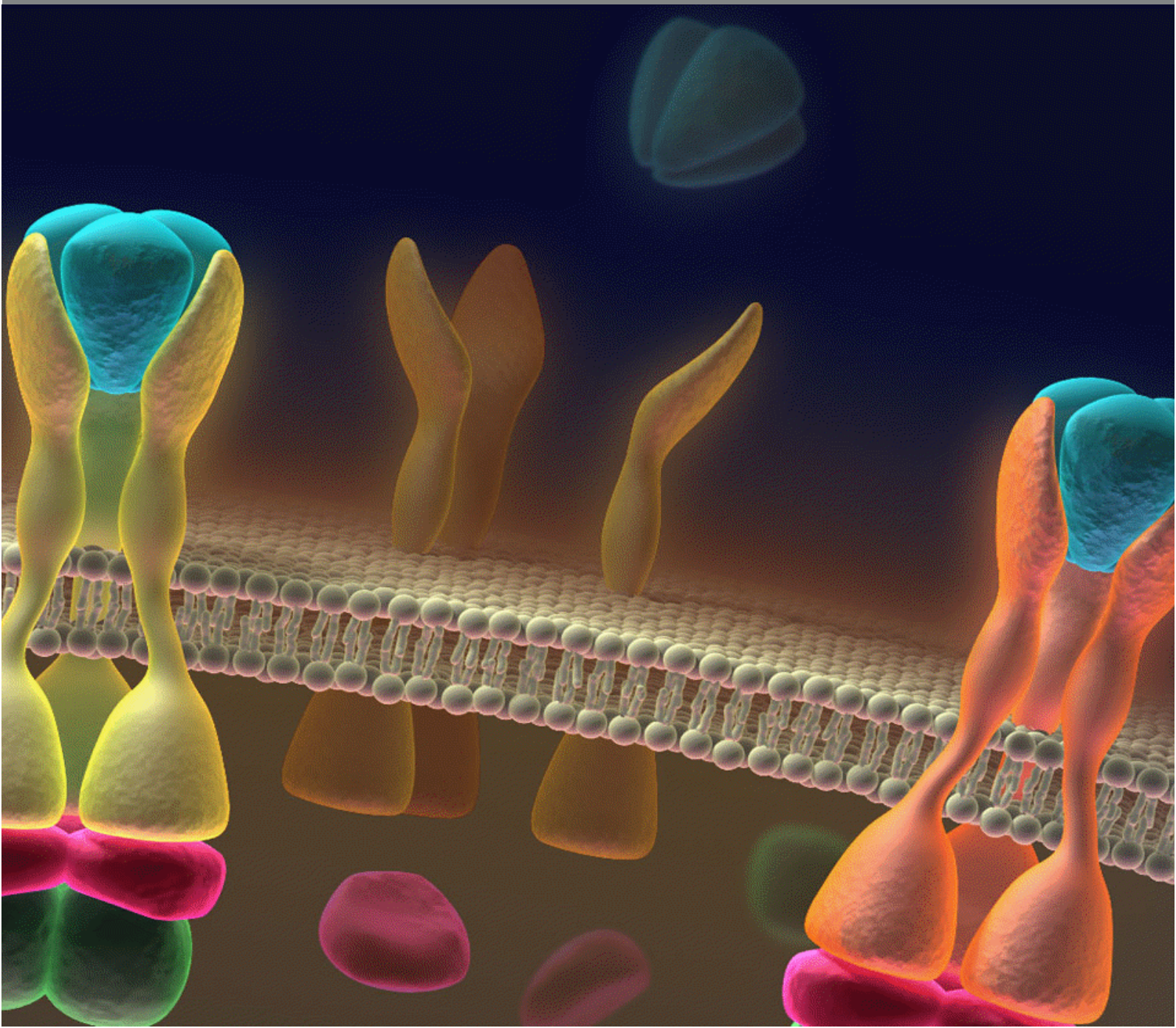
RECENT ADVANCES ON SIGNAL TRANSDUCTION

Neeraj Kaushik



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CHAPTER 1

RECENT DEVELOPMENTS IN VASCULAR DISEASE-RELATED CD47 SIGNAL TRANSDUCTION PATHWAYS

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ABSTRACT

Cardiovascular and brain conditions linked to atherosclerosis have a high rate of disability and decrease population quality of life. The development of atherosclerosis and the emergence of conditions that are closely related to atherosclerosis may thus be slowed by knowledge of its causes and ways to prevent them. TSP-1 is a known antiangiogenic factor, and CD47, which serves as TSP-1's receptor, can play a role in the regulation of atherosclerosis' antiangiogenesis. TSP-1/CD47, a crucial regulator of angiogenesis, regulates the expression of VEGF and the genes that are downstream from it. Therefore, a considerable involvement for the TSP-1, CD47, VEGF, and VEGFR2 signal in atherosclerosis is possible. Additionally, IL-1 and NLRP3 are examples of inflammatory compounds that might affect atherosclerosis. This review will focus on the pathophysiology and contributing factors of atherosclerosis.

KEYWORDS

Atherosclerosis, Cardiovascular, Infiltration, Pathophysiology.

INTRODUCTION

The prevalence of stroke has risen, making it a significant problem that has an impact on people's longevity and quality of life. Understanding the causes of stroke and how to prevent it is so crucial. Atherosclerosis plays a significant role in the development of ischemic stroke, and one of its key contributors is thrombosis, which results from the rupture of a susceptible plaque and can result in artery-artery embolization. A thin fibrous cap, a substantial lipid core, neovascularization, inflammatory infiltration of the plaque envelope and plaque, dilated remodeling, etc. are typical pathological characteristics of susceptible plaques. The theories surrounding the mechanics of atherosclerosis include the theories of lipid infiltration, endothelial damage, smooth muscle cell growth, chronic inflammation, and mononuclear macrophages. According to all ideas, chronic inflammation is the key factor in the development of atherosclerosis. A number of biological processes that affect the vulnerability of plaques have a significant impact on atherosclerosis. By combining several receptors and ligands, the CD47 pathway can produce proinflammatory and antiinflammatory effects [1], [2].

The Mechanism of Atherosclerosis Formation

Lipids are crucial in the initiation of atherosclerosis, which is a persistent inflammatory disease. Toll receptor 2 (TLR-2) and TLR-4 pathways are activated by hyperlipidemia, activating the congenital and adaptive immune response. This results in inflammation and the expression of atherosclerosis-promoting genes in macrophages and endothelial cells, which can have a significant impact on the process of inducing atherosclerosis. Low-density lipoproteins (LDL) build up in the damaged artery wall as a result of atherosclerosis, which damages the arterial endothelium wall. After that, LDL is converted into oxidized LDL (ox-

LDL), which can cause a minimal amount of inflammation within the damaged endothelium and activate the body's immunological response, which is crucial for the early stages of atherosclerosis. Monocytes/macrophages, lymphocytes, and other inflammatory cells play a major role in the formation of atherosclerosis. Th1 cells, CD8+ cells, and natural killer cells (NK cells) are interferon-producing lymphocyte subpopulations that are linked to disease development, whereas regulatory T cells are linked to a lower plaque load.

Endothelial cell destruction and LDL infiltration into the endothelium are results of a number of risk factors, including hyperlipidemia, hypertension, diabetes, and other illnesses. Damage to endothelial tissue and the presence of ox-LDL cause proinflammatory factors to be released, which can increase the expression of cell adhesion molecules (CAM), including P selectin, vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1), which mediate the adhesion of circulating monocytes and lymphocytes. Monocyte chemokine-1 (MCP-1) and T cells, respectively, operate as chemokines that cause monocytes and lymphocytes to penetrate the endothelium after adhering to it. The macrophage colony stimulating factor (M-CSF), which is thought to be a crucial step in the formation of atherosclerosis, causes monocytes to differentiate into macrophages after they migrate into the endothelium.

In order to take in ox-LDL, macrophages express scavenger receptors including SR-A, CD36, and lectin-like oxidized LDL receptor-1 (LOX-1), which causes lipid buildup and the development of foam cells in the wounded vascular wall. Additionally, by the production of cytokines including interleukin-1 (IL-1), IL-6, and MCP-1, macrophages stimulate T cell activation and inflammation, which can accelerate the development of atherosclerosis. The collagen in the plaque fiber cap can be broken down by macrophages producing matrix metalloproteinase (MMP), which thins the fiber cap and increases plaque instability. Activation of macrophages, ox-LDL uptake, and vascular smooth muscle cell (SMC) migration are induced by cytokines released by T cells, such as interferon and TNF, which promote atherosclerosis and decrease plaque stability. Activated lymphocytes, vascular endothelium, and smooth muscle cells all secrete fibromediated factors, such as various cytokines and growth factors, that encourage the proliferation of smooth muscle cells and the proliferation of the substrates of atherosclerotic plaques as this inflammatory process progresses. Angiogenesis, C - reactive protein (CRP), and vascular endothelial growth factor (VEGF) are key players in the development of atherosclerotic plaques and are affected by IL-6 [3]–[5].

Immune Response Factors Involved in Atherosclerosis, Innate and Adaptive

An inflammatory response in the artery wall can be brought on by lipoprotein deposition on the intima. The body's recognition of some molecules as non-self, such as pathogen-associated molecular patterns (PAMPs) or autologous molecules of damage-associated molecular patterns (DAMP), sets off the innate immune response. TNF (tumor necrosis factor) produced by T cells or type I interferon (IFN) are associated to the adaptive immune response, and some inflammatory factors, such as IL-12, IL-23, and IL-18, can produce plaque-forming components and hasten the development of atherosclerosis . When paired with macrophage scavenger receptors including CD36, SR-A1 and SR-A2, SR-BI, MARCO, LOX-1, and PSOX, ox-LDL, which is the atherosclerosis-initiating molecule, can kick-start inflammation and promote atherosclerosis. There is no doubt about CD36's impact on atherosclerosis. While SR-A was adversely correlated with IL-8, high levels of CD36 and LX-1 expression have been positively tied to the level of IL-1, accelerating the progression of atherosclerosis. Atherosclerosis is also tightly correlated with key immunological regulators

of inflammation, including as transforming growth factor (TGF), IL-10, and lipid mediators such lipoxins, resolvins, protectants, methylene resins, and prostaglandins.

Proinflammatory and antiinflammatory mechanisms play a key role in the development and establishment of atherosclerosis. Atherosclerosis is inhibited in a significant way by anti-inflammatory cytokines. Therefore, understanding inhibitory agents is essential for developing new treatments that can halt the progression of atherosclerotic disease. The development of the illness is also aided by anti-inflammatory cytokines connected to CD4+ regulatory T cells (Treg), such as interleukin-35 (IL-35), interleukin-10 (IL-10), and transforming growth factor (TGF-). While endothelial cell activation can be inhibited by IL-35, which is produced by proinflammatory stimulation in the early stages of atherosclerosis, and by IL-37 and IL-10, which both function as anti-inflammatory factors with immunosuppressive effects, A cell surface receptor called CD47, commonly referred to as IAP and the "don't eat me" signal, is extensively expressed on many different types of cells. Anti-CD47 antibodies can inhibit cell proliferation and aggregation, prevent atherosclerosis, and slow the development of plaques, according to prior research, which has demonstrated that the level of CD47 significantly rises in atherosclerotic plaques and patients with cerebrovascular diseases like a stroke or transient ischemic attack (TIA). The immune monitoring system may become resistant to CD47. An essential signaling immunoglobulin that controls the inflammatory response in macrophages is the signal-regulating protein (SIRP). SIRP (CD172) can deliver the "don't eat me" signal by binding to the cytoplasmic area of the phosphotyrosine phosphatases SHP-1 and SHP-2, which are expressed in monocytes/macrophages and neutrophils. Most healthy cells that interact with SIRP express CD47, which is a ligand of this receptor [6], [7].

Tyrosine inhibitory motifs (ITIMs) are phosphorylated on the intracellular immunological receptors of SIRP by CD47, which causes the recruitment and activation of phosphotyrosine phosphatases like SHP-1 and SHP-2. Then, phosphoprotein substrates are dephosphorylated, which has an impact on downstream signaling pathways that send the message "don't eat me" to prevent macrophage phagocytosis. In order to facilitate the production of inflammatory molecules like IL-1, this procedure is accomplished by increasing the signal transduction of MAPK (mitogen-activated protein kinase) and MerTK. Atherosclerosis causes macrophages to phagocytose, which causes cell aggregation, cell death, and faulty cell proliferation that ultimately results in the creation of a necrotic core in atherosclerotic plaques, speeding up the progression of atherosclerosis and making plaques more vulnerable. Strokes are more likely to occur when atherosclerosis develops in the carotid artery or other major arteries. In order to prevent cell aggregation, CD47 also interacts with the signal-regulating protein (SIRP). When CD47 is activated by the protein thrombospondin-1 (TSP-1), which is secreted by platelets, NO is produced and signal transmission is inhibited. Vascular disorders are brought on by the CD47-TSP-1 complex, which encourages the generation of reactive oxygen species.

DISCUSSION

CD47 Cytokines' Function in Proliferation

Immune escape, which is mediated by CD47 and can stop macrophage phagocytosis, promotes cell proliferation and aggregation, which further promotes the aggregation of damaged cells. An essential component of atherosclerosis is apoptosis, and the degree of apoptosis changes as atherosclerosis progresses through its many stages. According to studies, healthy bodies have a 20-fold reduction in their capacity to create new cells in atherosclerotic plaques. Atherosclerosis, the development of necrotic lipid cores, and

susceptible plaques are all clearly linked to dead cells, apoptotic cells, and necrotic debris accumulation. The primary mechanism for the formation of necrotic cores and the progressive growth of susceptible plaques is thought to be secondary necrosis of apoptotic cells and foam cells. A process known as efferocytosis allows macrophages and other phagocytes to quickly eliminate apoptotic cells under normal physiological circumstances. According to recent research, efferocytosis is thought to be a key factor in the development of plaques in both humans and animals. This could help to explain why the necrotic core of cells in plaques builds up over time and eventually increases the inflammatory response. By balancing phagocytic "eat me" signals on apoptotic cells with antiphagocytic "don't eat me" signals like CD47 molecules, macrophages mediate efferocytosis. By encouraging cell aggregation, CD47, one of the antiphagocytic signaling molecules, has been identified as a potential therapeutic target for atherosclerosis. Tumor necrosis factor- (TNF-) and other factors whose expression is increased by nuclear factor-B (NF-B) activation slow down the inhibition of CD47 expression, boosting CD47 expression, decreasing phagocytosis, and increasing the necrotic core . In addition to contributing to atherosclerosis, CD47-induced cell aggregation is a crucial factor in the emergence of cancer. A novel strategy for the treatment of atherosclerosis and cancer involves suppressing CD47 expression and inhibiting it using ligands.

CD47 Cytokines' Function in Inflammation

Chronic, multifactorial disease of the artery wall known as atherosclerosis is characterized by immune system activation, oxidative stress, and inflammation. Inflammation, a major factor in atherosclerosis, and the regulation of cell aggregation are intimately connected. Plaques that are vulnerable to intraplaque hemorrhage are more likely to deposit erythrocytes and release hemoglobin. An additional instrument for preserving immunological homeostasis as well as an efficient method for oxidative stress resistance are red blood cells. Red blood cells, however, can have a prooxidant activity and lose their typical structure and functional properties when a strong generation of reactive chemicals takes place. The activation of red blood cells under the influence of prooxidants results in alterations that increase the production of oxidants and free radicals and hasten the susceptibility of plaques. The expression of CD47 on erythrocytes and the inhibition of the signal-regulating protein receptor on circulating dendritic cells can both prevent dendritic cells from maturing and weaken their capacity for an adaptive immune response, which can slow the progression of atherosclerosis and make atherosclerotic plaques less vulnerable. The expression of CD47 in aging erythrocytes during the late stages of atherosclerosis can decrease erythrocyte phagocytosis and result in cell aggregation, which speeds up atherosclerosis. It is clear that CD47 can interact with many ligands to play both pro- and anti-inflammatory roles in the development of atherosclerosis. Proinflammatory mediators have an advantage over anti-inflammatory mediators in the early stages of atherosclerosis, promoting the development of atherosclerotic plaques. The development of atherosclerosis is significantly aided by the presence of proinflammatory substances such as IL-1, IL-6, IL-18, c-reactive protein (CPR), tumor necrosis factor (TNF-), and others. Additionally, the modulation of these variables has also been made a focus for atherosclerosis treatment [8]–[10].

The Function of CD47 Cytokines in Atherosclerotic Plaque

The necrotic core of the plaque is where CD47 expression is concentrated and noticeably increased in atherosclerosis. Anti-CD47 antibodies can slow the progression of atherosclerosis, demonstrating the intimate connection between CD47 and the development of atherosclerotic plaques. Some inflammatory substances, such TNF-, can increase CD47 expression and hasten the development of plaque and atherosclerosis. Numerous prior

investigations have demonstrated that CD47 encourages atherosclerosis by expressing the "don't eat me" signal to control macrophage endocytosis. Recent research has proven that CD47 has an anti-atherosclerosis impact and that mice lacking CD47 experience increased plaque development. T cells, NK cells, and dendritic cells were all activated as a result of CD47 deletion. Although CD47-/- can cause T cell activation, this stimulation won't advance atherosclerosis because CD47-/- mice don't create more TNF- than wild-type mice when their T cells are activated. The proportion of CD4+ T cells that can produce IFN- does not change, but CD8+ T cells produce more of it. This finding implies that CD47 is detrimental to the development of atherosclerosis. In the meantime, CD47-/- mice can activate and upregulate CD90+ NK cell expression, which can create IFN- and further promote atherosclerosis.

TSP-1/CD47's Inhibitory Effect on Atherosclerotic Plaques

TSP-1, an extracellular matrix (ECM) glycoprotein released and adhered to by neutrophils, monocytes, macrophages, and T cells, is expressed more frequently under hypoxia as a result. Different inflammatory cells express different TSP-1 receptors, including CD36, CD47, and integrin V3. In atherosclerosis, TSP-1 is involved in a number of processes, such as vascular smooth muscle migration, the degradation of extracellular matrix, basement membrane, and matrix metalloproteinase 2 (MMP-2) while also increasing the expression of cell adhesion factors, encouraging monocyte recruitment to the vascular wall, and promoting migration to the subintima . TSP-1 induces both positive and negative modulations of endothelial cell adhesion, motility, and growth through its interaction with a plethora of cell adhesion receptors, including CD47, CD36, and CD51/CD61, so that TSP-1 can modulate cellular functions including platelet activation and adhesion, leukocyte adhesion, migration, and phagocytosis to have effects on atherosclerosis, thrombosis, angiogenesis, and antiangiogenesis . According to studies, the absence of TSP-1 causes atherosclerotic plaques to mature more quickly. According to a study, the lipid core and plaque volume considerably rise while atherosclerosis speeds up in TSP-1-deficient mice. Through the T cell receptor CD47, TSP-1 can mediate T cell death, suppress the inflammatory response, and prevent angiogenesis. The endpoints of TSP-1's C structure domain, which it shares with CD47, determine its antiangiogenic activity. TSP-1 controls the bioavailability and action of the vascular endothelial growth factor, increases endothelial cell death, and inhibits endothelial cell migration and proliferation. A low vascular density in tumor cells is caused by an increase in TSP-1 and a decrease in VEGF, according to certain research, which indirectly validates TSP-1's antivascular capabilities. TSP-1's N-terminal domain has the ability to stimulate angiogenesis. Through its C-terminal and N-terminal domains, TSP-1 has pro- and antiangiogenic functions, while CD47 functions pro-angiogenicly by fusing the C-terminal of TSP-1 [11]–[13].

TSP-1 interacts with VEGF to prevent neovascularization, and CD47 is the only known receptor that can block the TSP-1/VEGF signaling pathway. Neovascularization is prevented by CD47 binding to TSP-1 because it prevents VEGFR2 activation and downstream expression but does not prevent VEGF from binding to VEGFR2. By preventing important angiogenic indicators in NO/c-GMP in the endothelium, vascular smooth muscle, platelet, and endothelial cells as well as inhibiting angiogenesis generated by the vascular endothelial growth factor (VEGF), TSP-1/CD47 also prevent angiogenesis. To reduce the pro-inflammatory effects of the lipopolysaccharide-mediated response and to exert an anti-inflammatory effect via the IL-1 pathway, TSP-1 and its receptor CD47 can also prevent the activation of NF-B/AP-1 . While TSP-1 binds to CD47 to control the phosphorylation of VEGFR2 and its downstream expression, CD47 interacts directly with VEGF. In order to isolate CD47 from VEGFR2 without impacting VEGF binding to VEGFR2, TSP-1 must bind

CD47 by the C-terminus. This inhibits downstream AKT activation and activates the functional response of endothelial cells to VEGF, which is to perform an antiangiogenic role. Endothelial cells and inflammatory cells like T cells both highly express VEGF and VEGFR2, which act as regulators of angiogenesis. TSP-1 and CD47 then control the expression of VEGF and VEGFR2.

HIF-1/CD47 Atherogenesis Is Promoted by a Signaling Pathway

Oxygen is crucial for the development of atherosclerosis, and hypoxia can increase the expression of the oxygen-induced factor-1 (HIF-1) found in macrophages and foam cells derived from macrophages. HIF-1 promotes inflammation, smooth muscle cell proliferation, and migration while also increasing the expression of the vascular endothelial growth factor (VEGF), which can promote neovascularization. The surface of endothelial cells, platelets, and other cells are typically found to express the crucial angiogenic factor VEGF. The frequency of intimal arteries and intracellular bleeding in plaques are substantially linked with the positive area of VEGF. Hypoxia stimulates the production of HIF-1-dependent CD47, which interacts with VEGF to activate antimacrophage phagocytosis and cause hypercytosis. This accelerates the development of an atherosclerotic plaque necrotic core and atherosclerosis. Through the HIF-1/VEGF/VEGFR2 pathway, HIF-1, which regulates VEGF, can enhance angiogenesis and increase plaque susceptibility. HIF-1 also participates in innate and adaptive immune responses, which are crucial in malignancies and inflammation. Nuclear factor-B (NF-B) and HIF-1 are both expressed more when there is chronic inflammation and hypoxia. When NF-B is activated in response to inflammation, tumor-promoting genes such as IL-6, cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (NOS2), platelet endothelial cell adhesion molecule-1 (PECAM-1), VEGF, and MMP-9 are activated and translocated to the nucleus . Through the activation of the CD47 antiligand by SIRP, HIF-1/CD47 can block the antitumoral impact of macrophages in malignancies. Significantly higher amounts of HIF-1/VEGF are found in tumor cells, which stimulates cell division and is crucial for the growth of tumors. Consequently, the use of HIF-1 antagonists may open up new possibilities for the treatment of cancer..

CONCLUSION

Numerous investigations have demonstrated that CD47-/- mice dramatically progressed atherosclerosis at a faster rate than wild-type mice. A type of "don't eat me" signal, CD47 is extensively expressed on many different types of cells. It causes "cell aggregation," lowers macrophage phagocytosis, increases the necrotic core, and ultimately promotes atherosclerosis. The CD47 expression is considerably elevated and concentrated in the necrotic core during atherosclerosis development, as shown by the apoE-/- mice in atherosclerosis produced by angiotensin II (Ang II). RhoA-p-MLC signaling pathways can be constrained by CD47-blocking antibodies, which also encourage the phagocytosis of necrotic cells. Anti-CD47 antibodies therefore exhibit anti-atherosclerotic properties. Additionally, the effectiveness of methotrexate and monoclonal antibodies against IL-1 (canakinumab) in the treatment of atherosclerosis was validated. The CANTOS test shown that canakinumab reduces the expression of inflammatory factors such IL-1 and CPR. Atherosclerosis resistance is produced by inhibiting NLRP3, an activator of IL-1, which decreases the expression and release of inflammatory molecules like VCAM-1 and ICAM-1. Inhibiting the release of IL-6 and lowering its downstream expression can both have a significant antiatherosclerosis effect because IL-6 is a characteristic inflammatory factor in the progression of atherosclerosis. TSP-1, an antivascular growth factor, not only affects immune modulation but also the inflammatory response. When TSP-1 and CD36, CD47, or anti-CD47 mAb are combined or incubated together, Th17 cell differentiation is inhibited, resulting in

the differentiation of CD4+ T cells into Treg cells. It worsens the inflammatory response and associated symptoms in psoriasis sufferers to some extent. New therapeutic options for a range of disorders may be made possible by the creation and use of TSP-1 and CD47 inhibitors. The expression of VEGF can be controlled in a variety of ways by VEGF, which also controls angiogenesis, which in turn controls inflammation. Anoxia and inflammation are both tightly tied to HIF-1, which induces anoxia. T cells, other inflammatory cells, and inflammatory-related substances like VEGF can control inflammation, tumor proliferation, and migratory activities by modulating macrophage expression. TSP-1, HIF-1, CD47, and VEGF all contribute significantly to inflammation and tumorigenesis, as was already mentioned. The application of antagonists in this field of study may offer fresh perspectives on the management of tumor and inflammation..

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CHAPTER 2

PHOTO BIOMODULATION OF FUNCTION-SPECIFIC SIGNAL TRANSDUCTION PATHWAYS IS MICROENVIRONMENT DEPENDENT

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Abstract

It has been demonstrated that cellular photobiomodulation on a cellular function is homeostatic. In this work, the function-specific route mechanism will be covered in more detail. It is possible that there are normal function-specific signal transduction pathways (NSPs) because the signal transduction pathways preserving a normal function in its function-specific homeostasis (FSH), resisting the activation of many other irrelative signal transduction pathways. Low level laser irradiation or monochromatic light may encourage the activation of partially activated NSP and/or its redundant NSP so that it may induce the second-order functional phase transition of the normal function from low level to high level as well as the first-order functional phase transition of the normal function from its dysfunctional one far from its FSH.

Keywords

Cellular, Cell-autonomous, laser therapy, Transduction.

INTRODUCTION

Cellular photobiomodulation (PBM) is the control of monochromatic light (LI) or laser irradiation on cells in vitro, in vivo, or ex vivo to stimulate or inhibit cellular processes without causing irreparable harm. The LI intensity is between approximately 10 and 1000 mW/cm2. The LI used in PBM is always low intensity LI (LIL), 10 mW/cm2, which also includes the LI used in so-called ultra-low-level laser therapy. However, moderate intensity LI (MIL), 0.10–1.0 W/cm2, is of PBM if the irradiation time is not long enough to irreparably damage organelles or cells. LIL's and MIL's PBMs are referred to as LPBM and MPBM, respectively. Two well-known types of low level LI (LLL) are MIL with short irradiation time and LIL. Numerous studies have emphasized the cell-autonomous mechanisms of PBM that are mediated by signal transduction pathways. On the other hand, our hypothesis was that the cellular microenvironment determines how cellular signal transduction pathways react to LLL. LLL may influence a variety of cellular signal transduction routes, however it is yet unclear exactly which signal transduction pathway it will do so. Numerous studies made the case that the microenvironment in which cells live may affect the modified signal transduction pathway. In this paper, it would be examined [1], [2].

The second is Function-Specific Homeostasis

In biological systems, negative feedback is frequently present and works to maximize a circuit's activity when there are alleles present with altered activities, maintaining a system's stability to both internal and external disruptions. A biosystem's negative feedback response known as function-specific homeostasis (FSH) aims to preserve the circumstances necessary

for the function to be carried out to perfection inside the biosystem. An in/far from its FSH function is referred to as normal/dysfunctional. The normal function is locally the best performed function since it performs better than all the dysfunctional functions. The well-known "Arndt-Schulz Law" or the J-shaped curves are the phenomenon. The apex of the Arndt-Schulz Law, also known as the J-shaped curve, can be stretched to a plateau, giving rise to the Arndt-Schulz Plateau Law, also known as the U-shaped curve, since the normal function can withstand external perturbations. In 10% fetal bovine serum (FBS), it has been found that there are the normal glucose (nG) at about 22.5 mM, in which many cell lines such as C2C12 and C3H10 T1/2 proliferate at its optimal rate, and the low/high glucose (lG/hG) whose concentration was lower/higher than the one of nG and in which the cell lines proliferate at a rate lower than the optimal rate. In other words, the cells are in their respective proliferation-specific homeostasis (PlSH) in 10% FBS and nG, respectively.

Under its threshold, a normal function can withstand external or internal disturbance. In their respective PlSH, Straussman et al. investigated the effects of twenty-two cytokines at five concentrations on six melanoma cell lines. They discovered that only hepatocyte growth factor (HGF) improved normal proliferation, whereas none of the other twenty-one cytokines could. Accordingly, it is implied that only HGF was permitted to engage its signal transduction route, whilst all twenty-one other cytokines were not permitted to activate their respective pathways. In a PlSH, the ability to replicate experimental results is inherent. The measured drug response data for the two large-scale pharmacogenomic studies, the Cancer Genome Project (CGP) and the Cancer Cell Line Encyclopedia (CCLE), are very inconsistent, according to a recent analysis by Haibe-Kains et al. Roswell Park Memorial Institute (RPMI) or Dulbecco's Modified Eagle's media (DMEM)/F12 media with 5% and 10% FBS, respectively, were used to cultivate CGP and CCLE cells. This implied that each CGP cell line was far from its corresponding PlSH and that the reproducibility of the IC50 (concentration in micromolar at which the drug inhibited 50% of the maximum cellular growth) against a given antidrug was impossible. According to the CGP, measurements of camptothecin IC50 made at two different locations utilizing matching cell line collections and identical experimental procedures only had a decent amount of correlation. On the other hand, each CCLE cell line may be in its own PlSH and have a repeatable IC50 value against a single antidrug. This explains why each CGP cell line had several IC50 values versus each CCLE IC50 value, and why the vast majority of medicines and gene-drug relationships had poor IC50 and AUC (area under the activity curve showing dose response) concordance [3], [4].

Microenvironments

Numerous tasks may be carried out by cells. Which function can be perfectly performed depends on the microenvironment in which cells dwell. It is hard to determine the effects of PBM on the proliferation, attachment, or migration of cells on a serum-free medium because they cannot proliferate, attach, or migrate despite the fact that they can experience apoptosis and be impacted by an LLL. But Straussman et al. found that the tumor microenvironment expressed intrinsic resistance to treatment. Numerous studies have focused on drug resistance's cell-autonomous causes. They found that stromal cell-produced HGF produced an immediate resistance to RAF inhibition, activated the HGF receptor MET, and reactivated the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-OH kinase- (PI3K-) AKT signaling pathways.

A cell can only perform that action in a microenvironment created for it. The proliferation of human dental pulp stem cells (DPSC) was examined by Eduardo et al. in four different concentrations of FBS: 5%, 10%, 12.5%, and 15%. After 24 hours, they found that the

proliferation in 10% FBS and that in 12.5% FBS, both of which were substantially less than that in 15% FBS but higher than that in 5% FBS, did not differ significantly from one another. It appeared that the PlSH, which was opposed to the transition of FBS, had multiplied in 10% to 12.5% of the FBS. Since many cell lines may only proliferate in 10% FBS, the medium is known as a proliferation-specific microenvironment (PSM). For many cell lines, the environment is referred to as a PlSH-specific microenvironment (PlSM) because proliferation in 10% FBS and nG is in its PlSH in nG (nPlSH). If the C3H10 T1/2 cells were grown in 10% FBS and lG such as 0 or 5 mmol/L glucose or hG such as 100, 200, or 300 mmol/L glucose for 3 or 6 hours, and then cultivated in a PlSM for 8 days, the modulated proliferation would change into the normal proliferation. A cell may experience apoptosis in a PSM or a differentiation-specific microenvironment (DSM). An LLL can stop apoptosis by promoting proliferation in a PSM or differentiation in a DSM. Other teams have studied the proliferation-mediated apoptosis inhibition; only Zhu et al. have investigated differentiation-mediated apoptosis inhibition. Furthermore, the second inhibition was more effective than the first. The majority of in vivo neurons are, in fact, differentiated. The role of PBM in the differentiation-mediated inhibition of apoptosis should be thoroughly investigated. [5], [6].

Pathways Depending on Function

Signals are required for all signal transduction pathways. When the cells are in their FSH, though, it might not function. Cancer cells are able to survive, spread, and thrive in "foreign" organs when their own PlSH inhibits numerous signaling pathways, particularly apoptotic. It was claimed that in addition to resisting internal and external disturbance, the cellular FSH's negative feedback also resisted the activation of numerous other irrelevant signal transduction pathways. The FSH is always destroyed through serum deprivation, fasting, or other stressors in order to identify the signal transduction pathways. Numerous signal transduction pathways have been partially activated in a cell that is far from its FSH. Alternately, one of them can be discovered, allowing for many signal transduction pathways to be available for a single signal. In this section, the signal transduction pathways were examined from the perspective of their functions.

Specific Signal Transduction Pathways for Normal Function

Both directly and indirectly, inhibiting the activation of other signal transduction pathways can promote the activation of one particular pathway. For instance, in serum-free media, dexamethasone (DEX) can boost IGF-1 promotion on skeletal muscle cell proliferation and the creation of rat hepatocytes' IGF binding protein (IGFBP) 1. Dexamethasone (DEX)-induced cardiac growth stop in rats can also be reversed by insulin-like growth factor (IGF) 1. The FSH of a cell may also stop the signal transduction pathway from being activated. The cellular FSH's negative feedback can stop many other unimportant signal transduction channels from activating, allowing other signal transduction pathways to continue to be fully active. It has been demonstrated that there are only a few effective strategies to improve a normal function or restore a malfunctioning function. Straussman et al. found that the regular proliferation was preserved by completely activating the platelet-derived growth factor (PDGF), BRAF, MAPK kinase (MEK), and extracellular signal-regulated kinase (ERK) pathways. This resistance to the signal transduction pathways of twenty-one cytokines, each at five concentrations, and their ability to induce proliferation. It is reasonable to presume that there may be typical function-specific signal transduction pathways (NSPs) given that the FSH prevents the activation of other signal transduction pathways that are not related to the NSPs while maintaining the complete activity of the NSPs. The six melanoma cell lines are said to develop normally via the PDGF pathway.

DISCUSSION

Multiple signaling pathways that are redundant

NSPs for a typical function might exist. Genes that perform the same function are said to be genetically redundant, and inactivating one of these genes has little to no impact on the biological phenotype. Genes that share the same function are referred to as redundant genes. In its NSP-specific microenvironment (NSM), each redundant gene may have its own NSP. Each NSP's complete activation can keep its NSM functioning normally. Duplicate NSPs (rNSPs) are NSPs that perform the same normal function as one another. According to Straussman et al. full activation of the HGF pathway, PI3K, AKT or RAF1, MEK, and ERK, as well as the synergistic full activation of the PDGF pathway and HGF pathway, were responsible for the proliferation enhancements of the six melanoma cell lines. The two NSPs of the regular proliferation of the six melanoma cell lines are the PDGF route and the HGF pathway [7]–[9].

The microenvironment determines whether NSP of a normal function truly preserves the normal function. Numerous signal transduction pathways have been partially activated for a defective function. Only a small number of signal transduction pathways remain fully activated while a malfunctioning function transforms into a normal one, whereas all other irrelevant signal transduction pathways are entirely blocked. There is always one NSP in the sparse signal transduction pathways. In their study of the effects of hG at 90 mM and LIL at 640 nm on the messenger ribonucleic acid (mRNA) of six genes in C2C12 cells, Liu et al. discovered that hG increased the mRNA expression of IGF-1, forkhead box O family (FOXO) 3a, Bcl-2 interacting mediator of cell death (Bim), and p27 while decreasing the proliferation and The mRNA for Bim is suppressed by IGF-1 . Although the nG activated NSP (nNSP) has not yet been discovered, the IGF-1 route is undoubtedly the hG activated NSP (hNSP) of C2C12 myoblasts. The normal proliferation of C2C12 myoblasts is maintained by both nPlSH and hPlSH, but nNSP/hNSP also maintains nPlSH/hPlSH in 10% FBS and nG/hG.

Functional Phase Transitions

The NSP of the 10% FBS controls the DPSC proliferation to a normal level. Eduardo et al. claim that while MIL could not alter the typical DPSC proliferation in 15% FBS, it could improve it in 10% FBS, and even this increased DPSC proliferation in 10% FBS was still considerably lower than that in 15% FBS. This suggested that the one in 15% FBS might at least be preserved by the synergistic combination of NSP and one of its rNSPs. Full activation is frequently used to maintain the first-order normal function in an NSP's NSM, while synergistic full activation of one NSP and its rNSPs is frequently used to maintain the third-order normal function in an NSP's NSM. The transition from a dysfunctional function to the first-order normal function is simply the second-order functional phase transition, as opposed to the phase transition from a th-order normal function to a th-order normal function, which is merely the first-order functional phase transition. In our research, serum-shocked C2C12 myoblasts were cultured in nG and FBS at different dosages. As the FBS concentration increases, the abnormal proliferation turns normal, and as a result, so does the order of the normal proliferation. FBS caused a transition from a second-order to a first-order proliferation phase in this instance. The second-order normal proliferation was maintained in the PDGF pathway-specific medium in the Straussman et al. experiments by the synergistic full activation of both the PDGF pathway and the HGF pathway, while the first-order normal proliferation was maintained in the PDGF pathway-specific medium. Here, HGF induced a

first-order proliferative phase shift in six melanoma cell lines in its PDGF pathway-specific media.

Pathway-Mediated Photobiomodulation

On the precise molecular mechanism of PBM, various theories exist. The cytochrome c oxidase (COX) idea was a favorite among them. The final stage of the electron transport chain, which is thought to be the rate-limiting reaction in mammals, is represented by cytochrome c and COX. Unique regulatory characteristics of cytochrome c and COX include allosteric modulation, isoform expression, and regulation via cell signaling pathways. Karu and Afanas'eva presented the COX theory of PBM. It was claimed that when cells were exposed to LLL, COX in the mitochondria served as the main photoacceptor, and PBM was facilitated by LLL-increased COX activity. The COX theory states that LLL can boost the generation of nitric oxide (NO) . However, a number of studies discovered that LIL might reduce NO generation. For instance, Montoro et al. discovered that LIL may reduce the NO generation of both FBS-deprived HDPCs with LPS and FBS-deprived HDPCs without lipopolysaccharide (LPS). Furthermore, Wu et al. showed that photosensitization of COX was the first reaction following the photon absorption of MIL, which inhibited COX's in-place enzymatic activity and resulted in a burst of reactive oxygen species (ROS). According to our homeostasis theory , Horvát-Karajz et al. discovered that the effects of one-time MIL irradiation, or MIL-induced stresses, were successful or self-limited at low dose but chronic at high dose. Cytarabine, paclitaxel, and vincristine are cytostatic drugs that may change the successful stress of MIL at low dose into chronic stress. In this situation, if COX was the main photoacceptor, LLL cannot boost COX activity [10]–[12].

According to Wu et al., MPBM is in fact mediated by COX-mediated ROS. Our homeostasis theory proposes that the primary photoreceptors of LIL were membrane receptors of cells or organelles, and that LPBM was mediated by receptor-activated signal transduction pathways. Protein kinase A and C, receptor tyrosine kinase, and inflammatory signaling are a few signaling pathways that have been found to target COX. Apoptosis, a mechanism that is overactive in stressed cells but inactive in cancer, is one of the cytochrome c's many roles, and four phosphorylation sites have been identified on it. In other words, pathways triggered by LIL may modify COX activity, which would account for LIL's enhanced COX activity. The LLL activation of a partially active NSP or/and its rNSP may operate as a mediator in the normalization of a malfunctioning function. According to Miyata et al. MIL did not influence the phosphorylation of p38 MAPK or c-Jun N-terminal kinase (JNK), but it did boost the phosphorylation of ERK 1/2 between 5 and 30 minutes after MIL irradiation. The C2C12 myoblast proliferation in our investigations is normal in the nPlSM, but dysfunctional in the 10% FBS and hG at 90 mmol/L. We discovered that hG enhanced the C2C12 myoblasts' IGF-1 mRNA expression, and that LIL further raised it until the IGF-1 pathway was fully activated and the hPlSH was created.

Photobiomodulation

Cellular processes are numerous. Typically, a cellular microenvironment only allows for one function to be performed. If the authorized function is dysfunctional, LPBM may promote the activation of its partially active NSP until it is fully engaged, rendering the dysfunctional function normal. For example, if the normal function has potential NSPs and is sustained by the synergistic complete activation of one NSP and its rNSPs in its NSM, the th-order normal function is the permitted function. If LPBM wants to upgrade the th-order normal function to the th-order normal function, it may stimulate the activation of its partially activated th rNSP until it is fully activated. The first and second PBMs are referred to as direct PBM (dPBM)

and indirect PBM (iPBM), respectively. In contrast to the dPBM, which causes a second-order functional phase transition from a dysfunctional function to the first-order normal function, the iPBM induces a first-order functional phase transition from the th-order normal function to the th-order normal function () if the normal function has potential NSPs..

Direct Photobiomodulation

There have been numerous research on dPBM's effects on cell proliferation, but few on its effects on various other cellular processes. Differentiation-specific homeostasis (DiSH) could exist. Brain-derived neurotrophic factor (BDNF) was revealed to be a mediator of the differentiation-mediated apoptosis inhibition of dPBM by Zhu et al. According to Saygun et al.'s research, basic fibroblast growth factor (bFGF) was a mediator of the dPBM-induced enhancement of human mesenchymal stem cells' (MSCs') osteoblast development. By causing apoptosis, amyloid (A) or 6-hydroxy dopamine may reduce the rate of proliferation, whereas LIL or the insect antibacterial peptide CopA3, a D-type disulfide dimer peptide known as LLCIALRKK, may suppress apoptosis by increasing proliferation. The neuron growth in Meng et al.'s research was resistant to LIL. It suggested that the multiplication of neurons might be normal. In order to establish the PlSH in A (aPlSH), for the human neuroblastoma cell line SH-SY5Y in its PlSH, LIL stimulated the defective proliferation until it became normal. BDNF has the ability to promote neuronal growth. According to Meng et al. , LIL raised BDNF levels. LIL elevated neuronal BDNF levels before encouraging defective proliferation up till the aPlSH was created [13], [14].

In the presence or absence of LIL at 810 nm, Huang et al. subjected primary cultured murine cortical neurons to oxidative stressors such as hydrogen peroxide, cobalt chloride, and rotenone. They discovered that the LIL raised ROS and MMP in nonoxidative neurons while increasing MMP while lowering high ROS levels and preventing cell death in cultured cortical neurons. The effects of LIL at 810 nm on glutamate, N-methyl-D-aspartate (NMDA), or kainate-induced excitotoxicity of primary murine cultured cortical neurons were also investigated by Huang et al. They discovered that the measurements can be classified into two groups: those where the effect of the LIL is similar in direction (both increased) regardless of whether the neurons are nonexcitotoxic or excitotoxic (these are viability, adenosine triphosphate (ATP), and mitochondrial membrane potential (MMP), and those where the direction of the LIL effect is opposite, raised for nonexcitotoxic neurons and decreased for excitotoxic neurons (these are intracelluar calcium). They provided a rather convoluted explanation based on the COX theory, as opposed to a relatively straightforward one based on NSPs. The viability, ATP, and MMP of either oxidative/excitoxic or nonoxidative/nonexcitoxic neurons have been promoted by LIL, but their mediated NSPs may be distinct from one another so that their intracellular Ca2+, ROS, and NO have been modulated by LIL in opposing ways even though the NSPs may be redundant with one another. In their study of LPBM on human skin fibroblasts in lG and 10% FBS, Esmaeelinejad and Bayat discovered that LIL increased the activation of the interleukin-6 (IL-6)/bFGF-mediated pathway. According to Jee et al. basal cell carcinoma cell line angiogenesis was stimulated by IL-6 via the JAK/STAT3 and PI3K/Akt pathways..

CONCLUSION

This research has made the argument that the microenvironment in which cells dwell determines which function of a cell may be carried out to perfection. The dependence could have thermodynamic roots. For dPBM or iPBM, a PSM may allow direct proliferation through its NSP, differentiation-mediated proliferation through its rNSP, or a combination of both. The differentiation was first encouraged for an iPBM in a PlSM, but eventually the

usual proliferation was upgraded. Direct differentiation via the NSP or proliferation-mediated differentiation via the rNSP are also examples of DSM-allowed differentiation. MSCs were taken from adult human bone marrow, separated, and cultivated in osteogenic medium in three-dimensional collagen scaffolds while being simultaneously exposed to LIL and complete medium. At day 7, the LIL encouraged both proliferation and differentiation, but at day 14, it only encouraged differentiation, according to Leonida et al. evidently, differentiation at day 14 was mediated by proliferation rather than differentiation at day 7, and vice versa.

An NSP in a dPBM may directly mediate normal differentiation in a DSM, and a rNSP of the NSP of the normal proliferation in an iPBM may indirectly mediate improved normal proliferation through differentiation in a PlSM. It was discovered that the bFGF/IGF-1/IGFBP3 mediated pathway was responsible for the promotion of LIL at 685 nm on both the osteoblast differentiation of human MSCs in osteogenic medium containing 10% FBS and 100 nM DEX in its dPBM and proliferation of human gingival fibroblasts in a PlSM containing 10% FBS in its iPBM . In the two main cell types of the hypothalamus, Pons and Torres-Aleman discovered that bFGF strongly affects IGF-1, its receptors, and its binding proteins.

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CHAPTER 3

COMPARATIVE ANALYSIS OF SIRT1 SIGNAL TRANSDUCTION EXPRESSION BY CAPSULE

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Abstract

In China, the Xuefuzhuyu capsule (XFZY) is frequently used to treat ischemic heart disease (IHD). XFZY has been shown to have a protective effect against apoptosis in Sprague-Dawley rat cardiomyocytes, while the exact chemical mechanism behind this action is yet unknown. Resveratrol (Res) has a similar effect. Through a long-term transcriptionally regulated mechanism, Silent Information Regulator of Transcription 1 (SIRT1) has been shown to be responsible for cardioprotection against ischemia-reperfusion injury Braunersreuther and Jaquet (2012). Therefore, the purpose of the current investigation was to determine if XFZY might protect ischemic myocardium cells brought on by ischemia through a signal transduction pathway mediated by SIRT1 utilizing electron microscopy, RT-PCR assay, and western blot test. All of the results indicated that SIRT1 might be transcriptionally controlled by the apoptotic pathway because P53, NF-kB, FOXO1, FOXO3, and FOXO4 were all considerably downregulated to SIRT1. Additionally, XFZ substantially enhanced the expression of SIRT1, which may indicate that SIRT1 is the target of XFZY's work on ischemic heart disease. Our results suggested that XFZY, which has the same pharmacological activity as Res, may protect myocardial cells and lessen myocardial injury through the SIRT1 signaling pathway.

Keywords

Disease, Heart disease, SIRT1 Signal, Transduction.

INTRODUCTION

One of the most dangerous conditions affecting people, ischemic heart disease (IHD) causes high mortality rates as well as permanent mobility impairment. Despite treating myocardial ischemia, it causes irreparable myocardial damage, which in turn causes cardiac remodeling marked by LV enlargement and decreased contractility. Ischemia/reperfusion (I/R) injury is still the main cause of heart failure and arrhythmia in this illness, and it has been demonstrated to be a major factor in myocyte necrosis and apoptosis. Although numerous therapies that reduced the severity of myocardial injury in animal models of I/R have been evaluated in patients, none of them have so far clearly outperformed the control, indicating the need for a new method of intervention. Modern biology places a high priority on elucidating the mechanisms governing aging and regulating organism lifespan, and it is generally acknowledged that myocardial oxygen delivery that is insufficient in comparison to myocardial oxygen demand is a significant factor in setting off the events that ultimately lead to cardiomyocyte death. According to a recent study, cardiac SIRT1 is markedly elevated in response to oxidative stress, and as a result, it can increase cardiac myocyte lifespan and restore cardiac myocyte function. Sirtuin 1 (SirT1) is a member of the sirtuin family of nicotinamide adenine dinucleotide NAD-dependent protein deacetylases that are involved in a number of cellular processes, including gene silencing, heterochromatin formation, cell

survival, metabolism, and development. SirT1 activation is thought to be advantageous for metabolic, neurodegenerative, and inflammatory diseases as well as to lengthen life [1], [2].

Numerous investigations have shown that Chinese medicine specifically protects against episodes of ischemia in the heart and brain. By raising SIRT1 and PGC-1a expression levels during ICA's neuroprotection against ischemia, Zhu et al. explored whether icariin (ICA) could protect the brain from ischemic injury . Chinese herbs or traditional medicine monomers are cardioprotective against ischemia, according to other investigations, but the underlying mechanism is yet unknown. The use of Chinese herbal compounds for myocardial ischemia was the subject of very few investigations, albeit. Resveratrol (Res) is well known for enhancing recovery from myocardial ischemia events and requires SIRT1 to mediate ischemic protection to lengthen lifespan . The Xuefuzhuyu capsule (XFZY), which shields cardiomyocytes from ischemia-induced injury, is frequently used in China to treat ischemic heart disease (IHD). However, the molecular mechanism underlying this protective action is yet unknown.

By using an electron microscope, we were able to see morphological changes in the ischemic myocardium of Sprague-Dawley rats in this investigation. We also looked at the expression levels of SIRT1, its target genes, and the protein in ischemic myocardium by RT-PCR assay and Western-blot analysis to investigate the mechanism of action of XFZY on antiapoptosis in IHD and to find a promising approach for the treatment of ischemia-induced injury. An experiment is a technique used to confirm or deny a hypothesis, as well as assess the likelihood or effectiveness of something that has never been tried before. Experiments show what happens when a specific factor is modified, which sheds light on cause-and-effect relationships. The purpose and scope of experiments vary widely, but they all rely on a repeatable process and a logical examination of the outcomes. Natural experimental experiments are also a thing.

While a youngster may conduct simple experiments to better grasp how objects fall to the ground, scientific teams may spend years conducting thorough research to increase their understanding of a phenomenon. In the scientific classroom, experiments and other hands-on activities are crucial to students' learning. When done often, experiments can improve exam scores as well as a student's engagement and interest in the content being studied. Experiments can range from highly controlled (such as tests needing complicated gear overseen by numerous experts that seek to learn information about subatomic particles) to personal and informal natural comparisons (such as tasting a variety of chocolates to determine a favorite). The ways in which experiments are used in the natural and human sciences differ greatly.

Controls are frequently used in experiments; they are intended to reduce the impact of variables other than the one independent variable. This improves the accuracy of the findings, frequently by contrasting the control measures with the other measurements. The scientific process includes scientific controls. The ideal experiment has no uncontrolled variables and all variables are regulated (accounted for by the control measurements). If all of the controls function as expected in such an experiment, it is possible to draw the conclusion that the experiment functioned as intended and that the observed findings were caused by the investigated variables. An experiment is an empirical approach used in the scientific method to settle disputes between competing models or hypotheses. Additionally, experiments are used by researchers to confirm or refute new or current theories [3]–[5].

A hypothesis, or an anticipation about how a certain process or phenomena operates, is typically the subject of an experiment. Without any preconceived notions about what the

experiment will disclose, an experiment may instead seek to answer a "what-if" question or to corroborate earlier findings. The outcomes of a correctly designed experiment typically confirm or refute the hypothesis. Some scientific theories contend that an experiment can never "prove" a hypothesis but can only contribute to its support. A theory can always be saved by proper ad hoc alterations at the sacrifice of simplicity, but an experiment that produces a counterexample can refute a theory or hypothesis.

Any elements that could compromise the experiment's accuracy, repeatability, or capacity to comprehend the data must be controlled in an experiment. Scientific controls and/or random assignment in randomized trials are two popular ways to remove confounding. Experiments are a key part of the scientific method in the physical sciences and engineering. They are used to test ideas and assumptions regarding how physical processes behave under specific circumstances (for instance, if a specific engineering procedure can generate the desired chemical molecule). In these domains, experiments frequently concentrate on repeating the same steps in the hopes of getting the same outcomes each time. It's rare to allocate tasks at random. The prevalence of experimental research varies greatly among fields in the social sciences and in medicine. However, when they are conducted, experiments normally take the form of clinical trials, in which the experimental units (often single humans) are allocated at random to a treatment or control condition where one or more outcomes are evaluated. In contrast to standards in the physical sciences, the average treatment effect—the variation in results between the treatment and control groups—or another test statistic derived from the experiment is often the subject of attention. Replications of the experiment are not normally included in a single research, although independent studies can be combined through systematic review and meta-analysis. Each of the scientific disciplines uses experiments differently in a number of ways. For instance, randomized experiments are frequently used in agricultural research (for instance, to compare the efficacy of various fertilizers), while experimental economics frequently uses experiments to test theorized human behavior without relying on random assignment of subjects to treatment and control conditions..

DISCUSSION

Experimental Animal Model

Rats' left coronary arteries are ligated using a simple left thoracotomy technique that involves wrapping a ligature around the intramyocardial segment of the artery that is located just ventral to the left atrium. While adult Sprague-Dawley rats are the most common species in our laboratory for coronary artery ligation, Fischer-344 and Brown Norway Fischer-344 cross rats have also been infarcted. The strategy employed in our lab is as follows. A left anterior thoracotomy is carried out under sterile circumstances after acepromazine maleate 50 mg/kg, xylazine 5 mg/kg, and ketamine He1 50 mg/kg intraperitoneally are used to induce anesthesia. A 7-0 synthetic ligature is wrapped securely around the proximal left anterior coronary artery after the heart is expressed via the incision. The muscle layer and skin are closed individually, and the lungs are inflated to lessen pneumothorax. Acetaminophen (67 rag/L) is added to the drinking water to provide postoperative analgesia. In most cases, a 50% acute survival rate is attained. The use of endotracheal intubation with ventilator support to give the surgeon additional time to complete the ligation and the administration of perioperative lidocaine to rats to lessen the likelihood of ventricular tachycardia and fibrillation are other modifications on this fundamental strategy [6], [7].

The Western-Blot Method

In molecular biology and immunogenetics, the western blot, also known as western blotting or protein immunoblotting, is a common analytical technique for identifying specific proteins

in a sample of tissue homogenate or extract. This method is used to view, separate, and quantify the various proteins in a complex protein combination in addition to detecting the proteins. The Western blot approach separates a particular protein from a complex utilizing three components: size separation, protein transfer to a solid substrate, and visual markering of the target protein with primary and secondary antibodies. To identify and bind to a particular target protein, a synthetic or animal-derived antibody is generated. This antibody is referred to as the primary antibody. Before any extra antibody is removed, the electrophoresis membrane is first washed in a solution containing the primary antibody. The primary antibody is then joined by a secondary antibody that recognizes and binds to it. The target protein can be indirectly detected by seeing the secondary antibody using techniques like staining, immunofluorescence, and radioactivity.

Dot blot analysis, quantitative dot blot, immunohistochemistry, immunocytochemistry, and enzyme-linked immunosorbent assay (ELISA) are further related techniques. Antibodies are employed in these procedures to detect proteins in tissues and cells by immunostaining. Western blot is a play on the Southern blot, a DNA detection method with the same name as its creator, English biologist Edwin Southern. Similar to this, RNA detection is known as a northern blot. Although the technique was independently developed in 1979 by Jaime Renart, Jakob Reiser, and George Stark at Stanford University and by Harry Towbin, Theophil Staehelin, and Julian Gordon at the Friedrich Miescher Institute in Basel, Switzerland, the term "western blot" was coined by W. Neal Burnette in 1981. It may still be the most used protein-analytical method, having been mentioned in the titles, abstracts, and keywords of more than 400,000 PubMed-listed papers between 1979 and 2019.

Applications

First two strips of a Western blot HIV test are positive and negative controls, followed by the genuine testing. For the qualitative detection of individual proteins and protein-modifications (such post-translational modifications), the western blot is widely employed in biochemistry. Western blots are thought to be used in at least 8–9% of all papers relating to proteins. It is employed as a generic technique to detect the presence of a particular single protein inside a complicated protein mixture. The size and color intensity of a protein band on the blot membrane can be used to estimate a protein's concentration semi-quantitatively. A pure protein with known quantities can also be diluted several times to provide a more accurate estimate of protein concentration. After cloning, protein synthesis is regularly checked using a western blot. Additionally, it is employed in medical diagnostics, such as the BSE-Test and HIV test.

A western blot is used in the confirmatory HIV test to find anti-HIV antibodies in a sample of human serum. Proteins from cells that are known to be infected with HIV are isolated and blotted on a membrane as described above. After washing away any free antibodies and adding a secondary anti-human antibody linked to an enzyme signal, the test serum is added in the primary antibody incubation step. The proteins to which the patient's serum carries antibodies are then shown by the stained bands. Additionally, a western blot is employed as the conclusive test for variant Creutzfeldt-Jakob Disease, a kind of prion illness connected to the ingestion of tainted beef from cattle with bovine spongiform encephalopathy (BSE, often known as "mad cow disease") (also known as BSE). A further use is in the tularemia diagnosis. The western blot's sensitivity is almost 100%, and its specificity is 99.6% when it comes to detecting antibodies against F. tularensis. Western blotting is used in several types of Lyme disease diagnostics. A western blot can also be used to establish the presence of HSV-2 (Herpes Type 2) and hepatitis B infections. A western blot may be utilized in veterinary medicine to validate a cat's FIV+ condition.

The World Anti-Doping Agency (WADA) uses the western blot technique among other things. Blood doping is the improper use of specific methods and/or drugs to enhance a person's mass of red blood cells, which enables the body to carry more oxygen to muscles and so improves performance and stamina. Erythropoietin (EPO), artificial oxygen carriers, and blood transfusions are the three well-known drugs or procedures for blood doping. According to WADA's List of Prohibited Substances and Methods, each is forbidden. In the anti-doping campaign for the 2014 FIFA World Cup, the western blot method was employed. Over 1000 samples in all were gathered and examined by Reichel, et al. in the Lausanne, Switzerland-based WADA recognized Laboratory. According to recent research using the western blot method, unique Velum SAR precast horizontal gels tailored for routine analysis allowed for a better identification of EPO in blood and urine. The ability of the rEPO micro-dose application to discriminate between different cell types was greatly improved with the use of the horizontal SAR-PAGE in conjunction with the precast film-supported Velum SAR gels [8], [9].

Western blot is used not only in fields of scientific study but also in fields of clinical research. Western blot is recognized as a potent diagnostic tool that is commonly utilized in the clinic environment since it may be used for the direct protein identification process. Finding illness biomarkers, such as particular proteins or antibodies, can be done using WB and protein detection techniques.It is regarded as an effective technique for locating specific proteins during the diagnosis of illnesses like cancer, autoimmune disease, and prion disorders. Western blotting is a typical process used to identify a number of biomarkers used in the diagnosis of neurological and oncological disorders. For instance, it is commonly accepted that the emergence of multidrug resistance (MDR) has significantly increased the difficulty of providing effective cancer therapy. Finding early, precise, and sensitive MDR mechanisms is therefore crucial, as is looking for more potent chemotherapeutic strategies to use in clinical settings. The WB approach is used to look at the expression of MDR-1/P-glycoprotein in the P388/ADR, P388 and HCT-15 cell lines. MRP1 levels have been found by WB as well.

The western blot, on the other hand, can be used to diagnose prion and protein isoform-related disorders, such as cancer, because it has the ability to discriminate between various protein isoforms. For instance, Creutzfeld-Jacob disease can be detected by a western blotting examination of the isoform pattern of 14-3-3 proteins in brain fluid. Additionally, research have shown that western blot may be a valuable method for detecting immunoreactive proteins connected to farmers lung disease, a pulmonary ailment brought on by breathing antigenic particles. Additionally, the western blot technique is utilized to detect proteins in synovial fluid and serum, allowing the clinical symptoms of osteoarthritis and rheumatoid arthritis to be diagnosed.As a potential biomarker of articular injury, western blot is performed to measure the levels of FSTL1 protein expression in people with knee osteoarthritis. In order to diagnose the clinical signs of osteoarthritis and rheumatoid arthritis, it is also utilized to identify proteins in synovial fluid and serum. It is used to evaluate the levels of the protein FSTL1, which may be a biomarker of articular injury, in people with knee osteoarthritis [10]–[12].

The western blot method includes gel electrophoresis to separate native proteins by 3-D structure or denatured proteins by the length of the polypeptide, electrophoretic transfer onto a membrane (typically PVDF or nitrocellulose), and immunostaining to identify a specific protein on the blot membrane. Protein denaturing electrophoretic separation typically uses SDS-PAGE. Since proteins might be positively, negatively, or neutrally charged, SDS is frequently used as a buffer (as well as in the gel) to give all proteins present a uniform negative charge. SDS-PAGE (SDS-polyacrylamide gel electrophoresis) is the name of this

type of electrophoresis. Protein samples are frequently boiled to denature the proteins before electrophoresis. As a result, proteases—enzymes that break down proteins—are prevented from degrading samples and proteins are segregated according to size. The proteins are transferred to a membrane (usually nitrocellulose or PVDF) after electrophoretic separation. The membrane is then frequently treated with Ponceau S to make the proteins visible on the blot and confirm that a proper transfer took place. To prevent non-specific antibody binding, the proteins are first blocked with milk (or another blocking agent) before being stained with target protein-specific antibodies. Finally, a secondary antibody that identifies the first antibody staining will be applied to stain the membrane, which may then be detected using a variety of techniques. To address the problem of antibody cross-reactivity, the western blot analysis procedure includes the gel electrophoresis step.

CONCLUSION

The muscle fiber structure was nearly completely absent in both the ischemia and L-NAME groups, and the myocardial cells were replaced by some collagen fiber clutter, mitochondrial enlargement, vacuolization, and disorderly cristae. With an uneven matrix, vacuolization, expanded week gap, and fuzzy intercalated disc shape, the nuclear membrane was ruptured. The findings in the normal and Res groups demonstrated that the myocardial cells were arranged in tidy rows, the gap was unobstructed, and just a few collagen fibers were present. The sarcomere was transparent and displayed the usual intercalated disc and mitochondrial membrane integrity components. There was no evidence of inflammatory cell infiltration, and the nuclear membrane and organelles were unharmed. Local myofilament was torn in the XFZY group, but the sarcomere's length was uniform, the mitochondrial swelling was minimal, and the crest was neatly structured. Similar pictures to those of the Res group were evident in the nuclear matrix, which was moderately cavitative and had nucleoli visible with normal intercalated disc structure.

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CHAPTER 4

PRESENCE OF LATENT AND ACTIVE MONOCYTE SIGNAL TRANSDUCTION RECEPTORS FOR TUBERCULOSIS

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Abstract
There is still a lack of knowledge on the processes that increase TB disease susceptibility or resistance. In order to understand the background of the differences between clinical and subclinical forms of M. tb infection, we compared the expression of cell signaling transduction receptors, CD14, TLR2, CD206, and 2 integrin LFA-1 on monocytes from patients with active TB or no mycobacterial lung disease, healthy individuals with M. tb latency, and uninfected controls. A prodrome of Met bacilli escaping immunological control in people with latent TB and no clinical symptoms may be the concurrent rise in expression of the membrane-bound mCD14 receptor and LFA-1 integrin in individuals with active TB. When a person has Mycobacterium tuberculosis infection but no active tuberculosis, it is referred to as latent tuberculosis, also known as latent tuberculosis infection. Latent tuberculosis is not communicable, whereas active tuberculosis is, hence it is impossible to contract TB from someone who has latent tuberculosis. The primary danger is that 10% of these persons will eventually acquire active tuberculosis. This is especially true, and there is an increased risk, in specific circumstances like taking immune-suppressing medicine or becoming older. Latent TB infection detection and therapy are crucial steps in the management of this illness. Latent TB is treated using a variety of methods. Usually, they have to be taken for a number of months.

Keywords

Lung disease, Monocytes, patients, Tuberculosis.

INTRODUCTION

The parameters that ensure protective immunity against Mycobacterium tuberculosis for persons exposed to this disease, including those who have received the attenuated M. bovis BCG vaccine, must be determined immediately. The profile of M. tb infections exhibits a striking degree of heterogeneity. M. tb is a disease that is distinguished by its propensity to survive for a long time inside people. However, despite being latently infected their entire lives, more than 90% of M.tb infected individuals never acquire active TB. Weak research has been done on the immunological response to M.tb during latency. As a result of compromised immunity or/and a pathogenic host inflammatory response to virulent mycobacteria, clinical TB symptoms appear years or even decades after M.tb infection. Additionally, despite having a prolonged high exposure to this virus, a tiny subset of individuals who are inherently resistant to TB remain M.tb-free. The global spread of M. tb bacilli is due to their capacity to persist inside host cells, particularly monocytes and macrophages. The first cells that come into contact with M. tb are macrophages, which are designed to kill microbes and phagocytose infections. However, by colonizing nondegradative phagosomes in macrophages, pathogenic TB bacteria are able to evade host defense [1], [2].

The moment M.tb makes contact with the macrophage receptors, macrophages begin to engage with it. Toll-like receptors, CD14 coreceptors, and C-type lectin receptors are important macrophage receptors that detect mycobacterial products. These receptors can detect endogenous signals brought on by necrosis and tissue injury. As a result of the signaling program started by macrophage receptors, transcription factors are activated, which causes the expression of inflammatory mediators, cytokines, and chemokines. Inhibitory feedback mechanisms are simultaneously activated by the signals elicited by CD14 and TLRs, limiting the intensity of inflammatory signaling. The immunological regulation of M. tb infection may depend on the kinetics of macrophage transition from an intracellular pathogen driven robust inflammatory signaling into a weak activated state. Lipoarabinomannan, lipomannan , phosphatidylinositol mannoside , and trehalose 6,6′-dimycolate , unique lipids that make up the cell envelope of pathogenic mycobacteria, interact with membrane CD14 and TLR2 on macrophages and activate signaling pathways that cause the innate immune response to infection . Although it also interacts with mycobacterial LAM, soluble plasma CD14 is known to sensitize host cells to LPS and increase endogenous CD14 gene expression. Through LAM-sCD14 complexes, soluble CD14 also stimulates the production of cytokines and adhesion molecules in CD14-negative cells including endothelium and epithelial cells. Studies showing that both anti-CD14 mAb and soluble CD14 could greatly decrease the uptake of M.tb bacteria by human microbial cells suggested that CD14 plays a role in the phagocytosis of nonopsonized M.tb.

However, complement receptors and mannose receptors have been implicated in a significant portion of mycobacterial absorption. It has been demonstrated that the mycobacterial LAM acts as a ligand, possibly mediating the absorption of M.tb via MRs on macrophages. Another crucial component of the innate immune response against mycobacteria is the serum mannose-binding lectin. MBL opsonizes M.tb and aids in phagocytosis. Patients with active TB had considerably higher serum MBL concentrations. Monocytes continuously move from the circulation into inflammatory sites during in vivo inflammatory response. The trafficking of M.tb-infected macrophages inside the host is significantly influenced by the integrin lymphocyte function associated antigen-1. LFA-1 expression and cell adhesion capabilities are increased in M.tb-infected human macrophages. Thus, altering LFA-1 on M.tb-infected cells may control homotyping cellular adhesion in granuloma formation and antigen presentation by modifying how M.tb-activated macrophages and T cells interact with one another. Ghosh et al. have shown that LFA-1 is a crucial component of protective immunity during pulmonary TB.

In our studies, we compared the serum concentration of sCD14 in healthy individuals with latent M.tb infection detected by the IFN-releasing assay and the uninfected IGRA negative subjects with the expression of mCD14 and TLR2 signaling receptors, mannose receptor CD206 and LFA-1 molecule, on blood monocytes, and patients with active pulmonary TB or nonmycobacterial lung diseases. Researchers have also looked at the connections between the expression of monocyte and serum signaling receptors, skin tuberculin hypersensitivity, and IFN- response to the M.tb specific antigens in patients with active TB and non-mycobacterial infectious lung illnesses.Only those with an active case of TB can transmit the bacteria... The TB skin test is frequently positive in persons who develop active pulmonary TB, commonly known as pulmonary tuberculosis. Additionally, they might spread the bacterium to others and exhibit all the symptoms and signs of TB disease. Therefore, other people nearby could inhale TB bacteria if a person with TB of the lungs sneezes, coughs, talks, sings, or does anything else that propels the bacteria into the air. According to statistics, one-third of those who are exposed to pulmonary TB contract the bacterium, yet only one in ten of these infected persons go on to develop active TB disease [3].

However, it is quite rare that someone would become infected with tuberculosis via brief social contact or exposure in a store. "In most cases, getting infected requires a long period of contact with a person who has active TB disease. After exposure, it typically takes 8 to 10 weeks for a TB test to reveal whether someone has contracted the disease. These minute droplets can hang in the air for several hours, depending on ventilation and other elements. If someone else inhales them, they could spread the TB infection to them. The likelihood of transmission will depend on the host's susceptibility, the context in which the exposure occurred, the length of the exposure, and the infectiousness of the TB patient. It is true that TB is difficult to contract. You require prolonged, regular contact with the infected person. Because of this, you are more likely to contract TB from a family member than a stranger.

A person does not have active or infectious tuberculosis if they had latent tuberculosis. People who have been exposed to TB frequently develop latent TB. The bacteria must become active for tuberculosis to progress to an active state. The person who contracts latent tuberculosis may never know who had the active case of tuberculosis that led to the diagnosis of latent tuberculosis for them because people in some countries, such as Canada, have medical privacy or "confidentiality" and are not required to disclose their active tuberculosis case to family, friends, or coworkers. Only mandatory testing or showing signs of active tuberculosis and going to a physician who does testing will allow a person to determine whether they have been exposed. Doctors might not suspect tuberculosis because it is uncommon in the United States; as a result, they might not test. It is wise to get tested if someone exhibits tuberculosis-like symptoms. An 18% probability exists for those with diabetes to get active TB. Patients with diabetes actually had a higher risk of dying from tuberculosis.A 10% risk exists for people with HIV and latent TB to become active each year.The greatest recognized risk factor for turning a latent M. tuberculosis infection into an active TB infection is HIV infection. Persons with HIV account for 30–60% of all new TB cases in several African nations, and TB kills more persons with HIV than any other disease worldwide.

DISCUSSION

The Bioethics Committee of the Medical University in Lodz approved the study that is being published here, and all study participants provided written informed consent. The study cohort consists of 218 Poles who were recruited at the Regional Specialized Hospital of Tuberculosis and Lung Diseases in Lodz, as well as 46 patients with non-mycobacterial lung diseases, 41 household contacts of TB patients, 48 work contacts of TB patients, and 43 patients with active pulmonary tuberculosis . The University of Lodz's Institute for Microbiology and Immunology staff members recruited 46 healthy people from their social networks who had no known TB contacts and no history of the disease. Clinical evaluation, a chest X-ray, sputum microscopy and culture on the Löwenstein-Jensen medium, and a tuberculin skin test were all performed on the patients. All TB patients exhibited typical chest X-ray features and verified TB bacteriology. The NMLD patients were admitted to the hospital for bronchitis, pneumonia, pleurisy, or a common lower respiratory tract infection. These patients had no prior TB exposure, and their TB bacteriology results were negative. Given the age range of the study participants and the fact that all newborns and school-age children in Poland are required to receive the antituberculosis BCG vaccine since 1950, there is a high likelihood that more than 98% of the participants have received the BCG shot [4]–[6].

QuantiFERON-TB Gold in Tube Assay

Blood was drawn from all participants' peripheral veins. They were gathered in the case of TB patients at the time of diagnosis and the start of therapy. The QFT-G test was carried out in accordance with the manufacturer's instructions. A mixture of M. tuberculosis antigens, PHA mitogen, or no stimulant was incubated with heparinized whole blood for 24 hours at 37°C in an environment enhanced with 5% CO2. The tubes were centrifuged at 2500 RCF for 15 minutes at room temperature following the incubation. Above the gel plug, plasma was collected, and it was kept at 20°C until the immunoenzymatic measurement of the IFN-level. QuantiFERON-TB Gold Analysis Software was used to calculate and interpret the results. An IGRA test was deemed positive if the IFN- concentration in blood cultures that had been stimulated with M.tb antigens and those that had not was 0.35 IU/mL and less than 25% of the Nil value. The quantitative IFN- findings from the TB Ag-Nil IGRA tests were also computed.

Analysis of mCD14, TLR2, CD206, and LFA-1 Expression by Flow Cytometry

All participants' heparinized blood samples were used for the flow-cytometry evaluation. On LSM 1077, the peripheral blood mononuclear leukocyte fractions were separated using density gradient centrifugation collected PBML at the interface were centrifuged at 250 RCF for 10 minutes at 20°C after being twice rinsed with RPMI-1640 media and collected. PBML were then dissolved in PBS, and the cell suspension's density was set to cells/mL. The mouse FITC-conjugated IgG2a anti-human CD14, PE-conjugated IgG2a anti-human TLR2, PE-conjugated IgG1 anti-human CD206, and PE-conjugated IgG1 anti-human LFA-1 monoclonal antibodies were used to incubate the cell samples . Antibodies of the isotype control served as a check for nonspecific binding. The cells were incubated with the relevant antibodies for 30 min, then washed twice with PBS, centrifuged, and then suspended in 200 L of PBS. Utilizing the FACScan and FlowJo software 7.2.2 for flow cytometry, the cells were examined. 10,000 cells in total were examined. The gated monocytes from PBML's forward and side scatter were used to analyze CD14 staining. In cells gated for CD14 monocytes, the expression levels of TLR2, CD206, and LFA-1 were calculated. The mean fluorescence intensity of samples treated with monoclonal antibodies was divided by the MFI value of isotype matched negative controls to determine the expression of the receptors on macrophages. Analysis was also done on the percentage of macrophages that were found to have the studied signal receptors.

Skin test for tuberculosis

The Mantoux test or Mendel-Mantoux test is a technique for both tuberculosis screening and tuberculosis diagnosis. It is also known as the Mantoux screening test, tuberculin sensitivity test, Pirquet test, or PPD test for pure protein derivative. It is one of the most widely used tuberculin skin tests, essentially taking the place of multiple-puncture tests like the tine test. In the UK, the Mantoux test took the place of the Heaf test, a type of tine test, in 2005. The American Thoracic Society and the Centers for Disease Control and Prevention support the Mantoux test. Although Soviet mantoux produced a lot of false positives because of children's allergic reactions, it was also employed in the USSR and is now common in most post-Soviet republics [7], [8].

48–72 hours later, the size of the induration is measured. Redness shouldn't be gauged through measurement. Mantoux test injection site in a healthy patient or in a high-risk group that was clinically determined to be negative after 50 hours. A glycerol extract of the tubercle bacillus is known as tuberculin. A species-neutral precipitate of molecules called purified protein derivative tuberculin is made from the filtrates of sterilized, concentrated cultures.

Robert Koch published the first account of the tuberculin reaction in 1890. German doctor Felix Mendel created and initially described the test in 1908. It is named for Charles Mantoux, a French physician who developed his test in 1907 and based on the work of Koch and Clemens von Pirquet. Due to tuberculin impurities that often led to misleading results, the test proved unreliable [9], [10].

Tuberculin contains a protein that Esmond R. Long and Florence B. Seibert determined to be its active ingredient. Then, for several years, Seibert worked on techniques for isolating and purifying the protein from Mycobacterium tuberculosis in order to produce pure protein derivative, which allowed for the development of a trustworthy tuberculosis test. In 1934, she published her first article on the purification of tuberculin. Seibert's PPD became the accepted method for tuberculin testing in the 1940s. M.A. Linnikova, a Russian, developed a modified version of PPD in 1939. The Soviet Union began mass producing PPD-L, which was named after Linnikova, in 1954. A person should be on the lookout for signs of active tuberculosis for the rest of their lives once they have been diagnosed with latent tuberculosis and a specialist has confirmed there is no active tuberculosis. There is no assurance that the tuberculosis bacteria have been eliminated even after the entire course of treatment has been taken."The signs of active tuberculosis, such as a cough, fever, night sweats, weight loss, etc., may be modest for many months. Delays in obtaining care may result, which increases the risk of the bacterium spreading.

Not all cases of tuberculosis result in lung involvement. The patient may have active tuberculosis for a long time before realizing they are active if the epidemic is in the brain, organs, kidneys, joints, or other regions. A person with TB disease "may feel completely healthy or may only occasionally cough." These signs may not necessarily indicate tuberculosis, and a patient may have active tuberculosis even if none of these symptoms are present. If you see any of the symptoms above, you should seek medical attention right away to prevent the spread of tuberculosis. Without seeking medical attention, a person with the aforementioned symptoms runs the risk of suffering from lung, eye, and organ damage as well as eventual death. The symptoms of tuberculosis may change from those seen when it affects the lungs when it settles in other organs or other regions of the body. So, even if a person doesn't have a cough or other flu-like symptoms, they could unknowingly have active tuberculosis. Other symptoms include those that would be present in other diseases, such as back pain, flank pain, PID symptoms, confusion, unconsciousness, difficulty swallowing, and many others. Therefore, when a patient has symptoms without a diagnosis of disease, consulting a doctor and requesting a tuberculosis test are extremely required to rule out tuberculosis.

Skin tests for tuberculosis

The Mantoux test, the original tuberculin skin test, was created in 1908. A standardized dead extract of cultivated tuberculin known as tuberculin is injected into the skin to gauge the body's immunological reaction to the bacterium. Therefore, if a person has previously been exposed to the bacteria, they should exhibit an immunological response to the injection, which is typically seen as a slight swelling or redness at the injection site. The Mantoux test and the Heaf test have been the two main TST techniques. The Heaf test, which was previously preferred in the UK because it was thought to require less training to administer and involve less inter-observer variation in its interpretation than the Mantoux test, was discontinued in 2005 because the manufacturer deemed its production to be financially unsustainable. In the US, the Mantoux test was the test of choice; now, it is the TST with the greatest global adoption. The WHO has now standardized the Mantoux test. Tuberculin, 100 units per milliliter, is injected intradermally into the lower forearm surface to deliver a dosage

of 5 units. The injection site is marked with waterproof ink to make it easier to locate it later if the level of reaction is mild. After 48 to 72 hours, the test is read. To the nearest millimeter, the forearm's area of induration is measured transversely from left to right, not up and down [11]–[13].

CONCLUSION

The study's second objective was to examine and contrast the expression of monocyte signaling receptors in people with active or latent tuberculosis and in those who were not infected with the disease. In order to identify latent M. tuberculosis infection in healthy volunteers without a history of the disease, the T-cell-based IFN-release assay was used on 46 community controls, 48 healthcare workers with a history of tuberculosis, and 41 household TB contacts. Additionally, patients with NMLD and TB underwent the IGRA. In both healthy Controls and NMLD patients, the prevalence of positive IGRA was reported to be 14%. The largest prevalence of latent TB infection was found among contacts at work, mostly women who had been in the TB field for a long time. Household contacts who were enrolled in the study soon after it was determined that one of their relatives had active TB had a lower prevalence rate. As a result, it was possible to suspect that family members with TB had recently been exposed to M. tb bacterium. The T-cell-based IFN-release assay was positive in 13% of NMLD patients and 65% of patients with active TB. As a result, the QuantiFERON-TB Gold In Tube assay had a 65% sensitivity and an 87% specificity for TB detection in patients with lung disorders. In comparison to TST, IGRA demonstrated better specificity, sensitivity, and positive and negative predictive values. Patients with TB had greater rates of positive TST and IGRA readings than those with NMLD. TST and IGRA values were negative for 26% of TB patients compared to 67% of NMLD patients. However, there was no discernible difference between the two patient groups in the frequency of inconsistent TST and IGRA values. Overall, all patients had a moderate level of agreement between the TST and IGRA. In TB patients, the concordance rate between TST and IGRA was likewise average.

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CHAPTER 5

RECENT DEVELOPMENTS IN COGNITIVE RADIO FREQUENCY DESIGN

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Abstract

As mobile data applications expand, there is a severe shortage of spectrum. Cognitive radio (CR) is currently regarded as a significant solution and is anticipated to be the main player in the future wireless technologies to reduce congestion and increase speeds. The introduction of cognitive radio systems will be followed by an examination of the difficulties in constructing an RF engine, as well as a look at its antennas, amplifiers, oscillators, and other parts that must function across a large frequency range. A cognitive radio (CR) is a radio that may be dynamically designed and adjusted to use the best nearby wireless channels to reduce user interference and congestion. In order to support more wireless communications in a particular spectrum band at a single place, such a radio automatically discovers available channels in the wireless spectrum and modifies its broadcast or reception characteristics as necessary. An example of dynamic spectrum management is this procedure. The cognitive engine is capable of configuring radio-system parameters in response to the operator's commands. "Waveform, protocol, operating frequency, and networking" are some of these parameters. In the communications environment, this performs as an autonomous unit, exchanging environmental data with the networks it accesses and other cognitive radios (CRs). In addition to "reading the radio's outputs," a CR also "monitors its own performance continuously." Using this data, a CR can "determine the RF environment, channel conditions, link performance, etc." and "adjust the radio's settings to deliver the required quality of service subject to an appropriate combination of user requirements, operational limitations, and regulatory constraints."

Keywords

Bandwidth, Cognitive radio, Environment, Frequency.

INTRODUCTION

Cognitive radio (CR) is viewed as a very promising solution to the rising demand for high data rates, which necessitates significant resources, such as energy and frequency bandwidth. A cycle of observation, analysis, and decision-making as well as opportunistic access to the available bandwidth are the fundamental tenets of CR devices' operation. As a result, a CR device, also known as a secondary terminal, must first detect the presence of a primary transmission before opportunistically transmitting anytime a frequency or time slot becomes available. The secondary terminal switches to a different band or modifies its transmission characteristics to avoid interfering with the authorized terminal's restarted transmission. In actual use, it is anticipated that cognitive radio devices will be able to detect channel occupancy on any band throughout the entire spectrum and automatically adjust to the principal transmission. The radio-frequency front-ends of the secondary terminal are subject to a variety of restrictions as a result of this continuous (or discontinuous) sensing procedure over such a wide bandwidth. These specifications, more specifically, place rigorous restrictions on antenna design, low noise amplification, frequency synthesizers that can

produce carrier frequencies ranging from tens of megahertz to around 10 GHz, mixing spurs, and spectrum sensing. To create software-defined cognitive radio equipment, baseband filters, RF filters, multiband amplifiers, broadband direct-conversion mixers, and ADCs/DACs are required. These RF components should work with a variety of frequencies [1], [2].

A reconfigurable radio front-end can be set up for cognitive radio so that it can transmit, steer to any band, tune to any channel with any bandwidth, and receive any suitable modulation scheme. In cognitive radio architectures, the capacity to build linear and spectrally agile components and designs in the radio-frequency front-end of the transceiver is seen as a fundamental technological concern. The main goals of the front-end design of a CR system, including the antennas, amplifiers, and oscillators, are revised in this study. Very few papers have examined the design difficulties of the CR front-end from beginning to end in the literature. A combined review of the various restrictions has also received very little attention. As an example of a first attempt to balance all these limitations, we mention the work in. Therefore, this document is a research piece that RF engineers working on CR may use as a reference. In order to finish this work, we outline and look into the difficulties that will need to be overcome in the upcoming years in order to develop a whole and easily configurable RF front-end for CR applications. A software-defined radio platform is seen to be evolving toward the concept of cognitive radio, which is a fully reconfigurable wireless transceiver that dynamically adjusts its transmission characteristics in response to network and user demands.

Traditional regulatory frameworks were not designed with cognitive radio in mind; instead, they were developed for an analog paradigm. The majority of radio frequency spectrum was found to be inefficiently used by regulatory agencies around the world, including the Federal Communications Commission in the United States and Ofcom in the United Kingdom. In most parts of the world, cellular network bands are overloaded, but other frequency bands (such as military, amateur radio, and paging frequencies) remain underutilized. That observation was supported by independent research carried out in various nations, which came to the conclusion that location and time affect spectrum usage. Furthermore, even when any unlicensed users would not significantly interfere with the allotted service, fixed spectrum allocation restricts the use of infrequently used frequencies (those assigned to specific services). If unlicensed users wouldn't interfere with licensed users, regulatory organizations around the world have been debating whether to let them use licensed bands. On dynamic spectrum access, these initiatives have centered cognitive radio research [3], [4].

The IEEE 802 LAN/MAN Standard Committee (LMSC) created and released IEEE 802.22, the first cognitive radio wireless regional area network standard, in 2011. For spectral awareness, this standard employs geolocation and spectrum sensing. Geolocation and a database of authorized transmitters in the region work together to discover open channels that the cognitive radio network can use. Through spectrum sensing, occupied channels are found by observing the spectrum. In order to make use of the unused frequencies or periods of time in a place, IEEE 802.22 was created. In the geolocated areas, this white space represents unused television channels. However, cognitive radio cannot consistently occupy the same open area. The network adapts as spectrum availability shifts to avoid interfering with authorized transmissionsThere are two primary categories of cognitive radio, depending on the criteria for broadcast and reception:

1. Full Cognitive Radio (Mitola radio), which takes into account all observable parameters by a wireless node (or network).

2. Spectrum-Sensing Cognitive Radio, which solely takes into account the radio frequency spectrum.

The portions of the spectrum that can be used for cognitive radio determine other types

Cognitive radio that can operate on licensed bands, with the exception of unlicensed bands like the U-NII band and the ISM band. The IEEE 802.22 working group is creating a wireless regional area network (WRAN) standard that will utilize TV white spaces, which are underutilized television channels. Cognitive radio that can only use unlicensed radio frequency (RF) spectrum is known as unlicensed-band radio. The IEEE 802.15 Task Group 2 specifications, which concentrate on the coexistence of IEEE 802.11 and Bluetooth, define one such system. Spectrum mobility is the process by which a user of a cognitive radio alters its operating frequency. By enabling radio terminals to function in the best frequency band that is currently available and preserving seamless communication requirements during transitions to better spectrum, cognitive-radio networks seek to exploit the spectrum in a dynamic way.

Cognitive radio networks that support spectrum sharing permit users of cognitive radio to share the licensed-band users' spectrum bands. However, cognitive radio users must limit their broadcast power in order to keep the interference to licensed-band users below a predetermined level. In networks with sensing-based spectrum sharing, cognitive radio users first listen to the spectrum allotted to licensed users to ascertain their current status. Users of cognitive radio choose their broadcast tactics based on the findings of the detection. Cognitive radio users will broadcast across certain bands if the licensed users are not using them. Cognitive radio users share the spectrum bands with licensed users by limiting their transmit power if the bands are in use by the licensed users. Users of cognitive radio are required to examine a white space database in this mode of spectrum sharing before being granted or refused access to the shared frequency. The white space database includes mathematical models, algorithms, and local restrictions that may be used to predict how much spectrum will be used in a given location and estimate the threat that a user of cognitive radio who accesses the shared spectrum poses to existing services. If the thought.

DISCUSSION

The Cognitive Radio Antennas

A new paradigm of approaches for improving the performance of radio communication systems through the effective use of radio spectrum is thought to be cognitive radio communication. The ability of reconfigurability in the underlying hardware and the related protocol suite is a crucial enabler for realizing a cognitive communication system and one of its primary problems. From the standpoint of antenna design, there is a rising demand for multiwideband antennas that are simple to integrate into the communication system. Modern architectures are primarily meant to be flexible and frequency agile in order to address broad frequency allocation and minimize the number of functional blocks. Antenna design for cognitive radio applications has undergone a lot of work. The research community has suggested using wideband antennas for spectrum sensing and narrowband antennas for transmission. The structure may also contain sensing and transmitting antennas. The term "software-defined radio" (SDR) refers to a radio communication system in which various components, such as mixers, filters, amplifiers, modulators/demodulators, detectors, etc., that are typically implemented in analog hardware, are now implemented using software on a personal computer or embedded system. Although the idea of SDR is not new, many operations that were before only theoretically feasible are now made possible by the rapidly developing capabilities of digital electronics [5]–[7].

A basic SDR setup might include an analog-to-digital converter, such as a sound card, in a personal computer that is preceded by an RF front end of some kind. When compared to using electronic circuits or special-purpose hardware, the general-purpose processor handles a sizable portion of the signal processing. Such a design results in a radio that can transmit and receive a wide range of radio protocols (also known as waveforms), depending only on the software employed. For the military and mobile phone services, both of which must provide a wide range of constantly changing radio protocols, software radios are extremely useful. Long-term advocates like the Wireless Innovation Forum anticipate software-defined radios to overtake other radio communication technologies as the industry standard. SDRs and software defined antennas are what make cognitive radio possible.

Operational guidelines

Superheterodyne receivers adjust the desired signal to a standard IF (intermediate frequency) or baseband using a VFO (variable-frequency oscillator), mixer, and filter. This signal is then typically sampled by the analog-to-digital converter in SDR. However, in other applications, the radio frequency signal is immediately sampled by the analog-to-digital converter (after amplification) and no intermediary frequency tuning is required. Real analog-to-digital converters lack the dynamic range necessary to detect an antenna's sub-microvolt, nanowatt-power radio signals. As a result, the conversion stage must come before a low-noise amplifier, which has its own set of issues. For instance, within the dynamic range of the amplifier, if spurious signals are present (which is usual), they compete with the desired signals. They may entirely block the intended signals or add distortion to them. Placing band-pass filters between the antenna and the amplifier is the conventional option, although doing so limits the radio's adaptability. Real software radios frequently contain two or three analog channel filters with toggleable bandwidths.

Due to SDR's flexibility, it is no longer necessary to statically allocate limited spectral resources to a single fixed service. The phrase "digital receiver" was first used in 1970 by a researcher at a Department of Defense laboratory in the United States. A software baseband analysis tool named Midas was developed by the Gold Room at TRW in California. Its functioning was specified in software. Ulrich L. Rohde's team created the first SDR in 1982 at RCA while working on a project funded by the US Department of Defense and used the COSMAC (Complementary Symmetry Monolithic Array Computer) chip. The first speaker on this subject was Rohde, who delivered a speech titled "Digital HF Radio: A Sampling of Techniques" in February 1984 in London at the Third International Conference on HF Communication Systems and Techniques. As stated in their E-Team business newsletter, a group at the Garland, Texas, Division of E-Systems Inc. (now Raytheon) first used the term "software radio" to describe a digital baseband receiver in 1984. The E-Systems team created a "Software Radio Proof-of-Concept" lab to help spread awareness of Software Radio among different government entities. This Software Radio from 1984 used numerous array processors to access shared memory to allow customizable interference cancellation and demodulation for broadband transmissions, generally with thousands of adaptive filter taps [8], [9].

In 1991, Joe Mitola used the phrase "software radio" on his own to describe his idea for a GSM base station that would integrate a digital receiver from Ferdensi with digitally controlled communications jammers from E-Systems Melpar to create a real software-based transceiver. The US Air Force purchased the software radio concept from E-Systems Melpar. In 1990–1991 Melpar developed a prototype tactical terminal for commanders that made use of Harris digital receiver chip sets and Texas Instruments TMS320C30 CPUs. The Melpar prototype was short-lived because E-Systems ECI Division decided to "throw out those

useless C30 boards" when they produced the first units for limited production. They did this by switching to a digital baseband radio in place of the SpeakEasy-like IF ADC/DACs of Mitola's prototype. The Air Force refused to permit Mitola to publish the technical specifications of the prototype as well as Diane Wasserman to disclose associated software life cycle lessons gained because they believed it to be a "USAF competitive advantage". Instead, Mitola wrote "Software Radio: Survey, Critical Analysis and Future Directions" with permission from the USAF in 1991, which was the first IEEE publication to use the phrase. In this work, Mitola explained the design concepts without going into implementation details. Bob Prill of GEC Marconi opened his presentation after Mitola gave the paper presentation at the conference by saying, "Joe is absolutely right about the theory of a software radio and we are building one." SpeakEasy, the military software radio, was developed by Wayne Bonser, then of Rome Air Development Center (RADC), now Rome Labs; by Alan Margulies of MITRE Rome, NY; by then Lt Beth Kaspar, the original DARPA SpeakEasy project manager; and by others at Rome including Don Upmal. Prill presented a GEC Marconi paper on PAVE PILLAR, a SpeakEasy precursor. However, Mitola privately attributes the invention of the digital receiver technology—on which he based software radio once it was possible to transmit via software—to that DoD lab of the 1970s with its leaders Carl, Dave, and John, even though Mitola's IEEE publications produced the largest global footprint for software radio.

A few months after the National Telesystems Conference in 1992, a vice-president of E-Systems Garland Division protested to Melpar's (Mitola's) usage of the term "software radio" without giving Garland credit in an E-Systems corporate program assessment. Then-Melpar VP of marketing Alan Jackson questioned the Garland VP about whether their equipment or laboratory used transmitters. The Garland VP responded, "No, of course not—ours is a software radio receiver." That being the case, Al retorted, "Then it's a digital receiver, but without a transmitter, it's not a software radio." Al was supported by corporate leadership, therefore the publishing was accepted. The value of digitizing HF at RF and of processing it with Texas Instruments TI C30 digital signal processors (DSPs) and its predecessors was well understood by amateur radio operators and HF radio engineers in the 1980s and early 1990s. Radio engineers at Roke Manor in the UK and at a company in Germany had concurrently acknowledged the advantages of ADC at the RF. Mitola's publication of software radio in the IEEE introduced the idea to the larger radio engineering community. With hundreds of academic citations, his May 1995 special issue of the IEEE Communications Magazine with the cover story "Software Radio" was recognized as a breakthrough moment. Joao da Silva referred to Mitola as the "godfather" of software radio when he introduced him at the First International Conference on Software Radio in 1997, in large part due to his desire to offer such an important technology "in the public interest" [10], [11].

Peter Hoeher and Helmuth Lang created and put into action perhaps the first software-based radio transceiver in 1988 at the German Aerospace Research Establishment (DLR, formerly DFVLR) in Oberpfaffenhofen, Germany. The ideas of a software radio were used to create the transmitter and reception of an adaptive digital satellite modem, and a flexible hardware peripheral was suggested. Stephen Blust first used the phrase "software defined radio" in 1995. In 1996, the USAF and DARPA convened the first meeting of the Modular Multifunction Information Transfer Systems (MMITS) forum to discuss the commercialization of their SpeakEasy II program, and Bell South Wireless published a request for information at the meeting. Though Mitola initially disagreed with Blust's term, she eventually came around as a practical means of achieving the ideal software radio. Software-defined radios have their roots in the U.S. and European defense sectors of the late 1970s (for instance, Walter Tuttlebee described a VLF radio that used an ADC and an 8085

microprocessor), about a year after the First International Conference in Brussels. Although the concept was first implemented with an IF ADC in the early 1990s. The SpeakEasy military project, developed by the US DARPA and Air Force, was one of the earliest public software radio ventures. The main objective of the SpeakEasy project was to imitate more than ten current military radios that operate in frequency bands between 2 and 2000 MHz using programmable processing. Another SpeakEasy design objective was to make it simple to adapt to new coding and modulation standards in the future, enabling military communications to stay up with technological advancements in these areas.

Phase Speak Easy

The SpeakEasy program, which ran from 1990 to 1995, aimed to show off a radio for the tactical ground air control party of the U.S. Air Force that could operate between 2 MHz and 2 GHz and thus interoperate with ground force radios (frequency-agile VHF, FM, and SINCGARS), Air Force radios (VHF AM), Naval Radios (VHF AM and HF SSB teleprinters), and satellites (microwave QAM). Two specific objectives were to demonstrate a radio into which multiple contractors could plug parts and software and to produce a new signal format in two weeks from scratch. All of these objectives were achieved in a non-production radio during the project's demonstration during the TF-XXI Advanced Warfighting Exercise. There was some dissatisfaction with the early software radios' inability to appropriately filter out of band emissions, to use more than the most basic interoperable radio modes, and to suddenly lose connectivity or crash. Its cryptography processor was unable to switch context quickly enough to maintain multiple radio conversations at once. Despite being sufficiently practical, its software design was unique. Between 1996 and 1999, the MMITS Forum improved the SpeakEasy design, which encouraged the DOD’s integrated process team (IPT) for programmable modular communications systems (PMCS) to move forward with the Joint Tactical Radio System (JTRS) [12], [13].

The Texas Instruments C40s were the main components of the radio receiver's basic setup, which also included an antenna feeding an amplifier and down-converter (see Frequency mixer), an automatic gain control, and an analog-to-digital converter on a computer's VMEbus. On the PCI bus of the transmitter were digital-to-analog converters that fed an up converter (mixer), which in turn connected to a power amplifier and antenna. In order to feed the same analog to digital converters, the extremely large frequency range was segmented into a few sub-bands using various analog radio technologies. This is now the typical design approach for wideband software radios.

CONCLUSION

Typically, mechanical reconfigurability is attained by adding a rotational movement into the antenna structure. This approach has the benefit of not requiring biasing circuits for switch activation, which could impair antenna performance. provides a sample of this implementation. The antenna that is being presented is made up of two separate structures that are joined together on a single substrate: the first structure is an ultrawideband (UWB) antenna that covers the spectrum starting at 3.111 GHz for channel sensing, and the second structure is a triangular-shaped patch with reprogrammable frequency that is used to communicate with other RF devices. The spinning portion of the antenna is in charge of producing the necessary frequency tuning, and this rotational motion is used to achieve the frequency reconfigurability. Different resonances are created by rotating the antenna at various angles, which makes it possible to use the antenna for communication at the frequency designated by the "sensing" antenna. The construction of a cognitive radio front-

end with rotatable controlled reconfigurable antennas is used in as a further illustration of this technology. Another method of achieving frequency agility involves rotating the antenna patch under the control of a stepper motor installed on the antenna structure's rear. In Figure 4, this is displayed. An UWB detecting antenna is shown in with a partially grounded, slotted polygon patch on the back side. The triangular patch communicating antenna is rotated to create the desired frequency configuration..

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CHAPTER 6

THE FUNCTION OF RNA-BINDING PROTEINS IN THE MAPK SIGNALING PATHWAY

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Abstract

Mitogen-activated protein kinases (MAPKs), signaling enzymes required for a variety of biological processes including cell division, sexual differentiation, and death, are present in all eukaryotes. The MAPK signaling pathway is crucial for the regulation of gene expression because it phosphorylates transcription factors. Recent studies have identified numerous RNA-binding proteins (RBPs) as MAPK signaling regulators because they bind to the mRNAs encoding the MAPK pathway's components and regulate the stability of their transcripts. The fact that MAPKs phosphorylate and control RBPs' ability to bind and stabilize target mRNAs, which in turn controls a number of cellular processes, makes RBPs targets of MAPKs. This review adds to our understanding of the regulatory mechanism regulating gene expression by supplying evidence for the significance of MAPK signaling in the regulation of RBPs and their target mRNAs. The results that we present give more evidence for the therapeutic importance of the posttranscriptional modification of mRNA stability and its implications for drug discovery. RNA-binding proteins, or RBPs, are proteins that participate in the creation of ribonucleoprotein complexes by binding to double- or single-stranded RNA in living cells. The dsRNA binding domain, zinc fingers, and the RNA recognition motif (RRM), among other structural features, can be found in RBPs. They are cytoplasmic and nuclear proteins. However, because most mature RNA is quickly exported from the nucleus, the bulk of RBPs in the nucleus are found as protein and pre-mRNA complexes known as heterogeneous ribonucleoprotein particles (hnRNPs). RBPs are necessary for transport, localization, and cellular function, among other cellular processes. Splicing, polyadenylation, and mRNA stability are three post-transcriptional RNA control processes that they are particularly crucial for.

Keywords

Amino acid, Protein, Phosphorylation, RNA.

INTRODUCTION

A 70–75 amino acid domain known as the double-stranded RNA-binding motif (dsRM, dsRBD) is essential for RNA processing, RNA localization, RNA interference, RNA editing, and translational repression. The three domain structures that have been solved as of 2005 share common characteristics that explain why dsRMs only bind to dsRNA rather than dsDNA. It was discovered that the dsRMs communicate along the RNA duplex via both -helices and 1-2 loops. Additionally, all three dsRBM structures interact with the major groove's and one minor groove's sugar-phosphate backbones through the 1–2 loop and the alpha helix 2's N-terminal region. This interaction, which involves 2'-hydroxyls and phosphate oxygen, is a special adaption for the structure of an RNA double helix. Despite having similar structural characteristics, dsRBMs have unique chemical structures that allow them to be specific for a range of RNA topologies, such as stem-loops, internal loops, bulges, or helices with mismatches [1], [2].

Cartoon illustration of the protein's zinc-finger motif as "Zinc finger". Two histidine and two cysteine amino acid residues coordinate the zinc ion (green). The most prevalent DNA-binding domains in the eukaryotic genome are zinc-finger domains of the CCHH type. Several zinc fingers are used in a modular approach to achieve excellent sequence-specific DNA recognition. Zinc fingers display a protein structure in which a Zn2+ connects a -hairpin and a -helix. Additionally, the DNA sequence-specific identification is made possible by the interaction of the -helix protein side chains with the DNA bases in the main groove. Recent research has shown that zinc fingers can also identify RNA, despite their widespread recognition of DNA. Recent research has revealed that CCCH zinc fingers, in addition to CCHH zinc fingers, also use sequence-specific identification of single-stranded RNA through an interaction between intermolecular hydrogen bonds and Watson-Crick edges of the RNA bases. CCHH-type zinc fingers bind RNA using two different strategies. In the first mode, zinc fingers interact with a double helix's backbone in a non-specific way, whereas in the second mode, zinc fingers can detect individual bases that protrude specifically. The CCCH-type zinc finger, in contrast to the CCHH-type, exhibits a different method of RNA binding in which single-stranded RNA is recognized in a sequence-specific manner. In general, zinc fingers may directly detect RNA and DNA through their binding to ssRNA and dsDNA, respectively.

The transcriptional and post-transcriptional regulation of RNA by RNA-binding proteins plays a part in controlling the patterns of gene expression during development. RNA-binding proteins have been recognized as crucial elements throughout germline and early embryonic development as a result of extensive research on the nematode C. elegans. Their unique job entails timing cues for developmental events as well as the formation of somatic tissues (neurons, hypodermis, muscles, and excretory cells). However, because it is so difficult to identify the RNA targets of RBPs, it is very difficult to understand the process behind their role in development. This is due to the fact that many RBPs have numerous RNA targets. RBPs do, however, exhibit an unquestionable influence in the coordinated regulation of developmental pathways.

Embryonic development

Elav, Sxl, and tra-2 are RNA-binding protein-encoding genes in Drosophila melanogaster that play a crucial role in the early determination of sex and the maintenance of the somatic sexual state. These genes influence sex-specific splicing in Drosophila, which has implications at the post-transcriptional level. The feminizing gene tra is positively regulated by Sxl, resulting in the production of a functional tra mRNA in females. RNA-binding proteins such as FOG-1, MOG-1/-4/-5, and RNP-4 control the determination of somatic and germline sex in C. elegans. Additionally, a number of RBPs, including GLD-1, GLD-3, DAZ-1, PGL-1, and OMA-1/-2, perform their regulatory roles during the course of the meiotic prophase, gametogenesis, and oocyte maturation [3], [4].

The somatic process

Post-transcriptional regulation is crucial for somatic development in addition to RBPs' roles in germline development. RBPs working in somatic development regulate tissue-specific alternative splicing of the mRNA targets, in contrast to those working in germline and early embryo development. For instance, RRM domains in MEC-8 and UNC-75 localize to the hypodermis and nerve systems, respectively. EXC-7, another RRM-containing RBP, is also shown to localize throughout somatic development in the nervous system and in the cells of the embryonic excretory canal. Due to their enormous influence over a variety of physiological processes, RNA-binding proteins have drawn the attention of several

researchers. The potential of RNA-binding proteins has recently been the subject of numerous discoveries because of its significance in the biological sector. The number of RNA-binding proteins has greatly increased as a result of recent advancements in experimental identification of RNA-binding proteins.

Binding protein for RNA For optimal dendritic synaptic activity, Sam68 regulates the spatial and temporal compartmentalization of RNA metabolism. The absence of Sam68 causes aberrant posttranscriptional regulation, which in turn causes neurological conditions such fragile X-associated tremor/ataxia syndrome. Sam68 was discovered to interact with the mRNA responsible for producing -actin, which controls the cytoskeletal elements' role in the synaptic development of dendritic spines. Therefore, through controlling the metabolism of postsynaptic -actin mRNA, Sam68 is essential for controlling the number of synapses. The ACTB protein's structure is known as "beta-actin". The UNC-75 neuron-specific CELF family RNA-binding protein preferentially binds to the UUGUUGUGUUGU mRNA stretch in C. elegans neuronal cells using its three RNA recognition domains for the exon 7a selection. UNC-75 was discovered to exclusively trigger splicing between exon 7a and exon 8 only in the neuronal cells, whilst exon 7a is skipped due to its poor splice sites in non-neuronal cells.

Short-wavelength UV radiation, hypoxia, and hypothermia are just a few examples of the many physiological stressors that the cold inducible RNA binding protein CIRBP is involved in regulating. The findings of this study may have ramifications for the relationship between inflammation and disease states. The polarized growth of Candida albicans was revealed to be under the control of the serine-arginine family of RNA-binding protein Slr1. In comparison to Slr1 wild-type strains, mice with Slr1 mutations have longer survival rates because they have less filamentation and experience less damage to their epithelial and endothelial cells. As a result, this study shows that the SR-like protein Slr1 is involved in C. albicans pathogenicity and hyphal development [5], [6].

DISCUSSION

To effectively control gene expression and carry out biological processes, cells must react to a range of signals, such as extracellular stimuli, environmental pressures, developmental signals, and intrinsic information. Failure to coordinate various regulatory systems can contribute to the initiation and development of diseases like cancer because of the diversity and complexity of the regulation of gene expression. Regarding gene regulation, the focus has primarily been on gene transcription and its regulatory mechanisms, as well as more modern genome-wide techniques for gene transcription study. The control of mRNA degradation, stability, localization, and translation, among other posttranscriptional events, has emerged as a crucial stage in the gene expression cascade that necessitates sophisticated regulation by numerous intracellular signaling pathways. By binding to the specific mRNA species encoding proto-oncogenes, growth factors, cytokines, transcription factors, and other proteins in different cell types, RNA-binding proteins have been demonstrated to influence the expression of several proteins. Growing interest has been focused on the phosphoregulation of RNA-binding proteins by MAPKs and/or kinases downstream of MAPKs, which can regulate the translation or destruction of target mRNAs. The fission yeast Schizosaccharomyces pombe (S. pombe) is one of the most extensively researched model systems for the study of MAPK regulation. S. pombe is a fantastic model organism for the investigation of the mechanisms underlying signaling pathways in higher eukaryotes due to its robust genetics.

Numerous tumor-related signaling molecules, such as Ras, Rho, Protein Kinase C, and MAPK, as well as therapeutic targets, such as the phosphatase calcineurin (target of the immunosuppressant medication FK506) and TOR (target of Rapamycin), have highly conserved homologs in S. pombe. The homologs of mammalian p38 and ERK in S. pombe are called Spc1/Sty1/Phh1 and Pmk1, respectively. The goal of this review is to highlight the importance of several findings from studies in higher eukaryotes and the fission yeast model system that revealed a cross-talk mechanism between MAPKs and RNA-binding proteins (RBPs) in the control of biological processes, signal transduction mRNA localization, and translation. Diverse RBPs with distinct RNA-binding and protein-protein interactions are expressed by eukaryotic cells. The Eukaryotic RBP Database (EuRBPDB) lists 2961 human genes that code for RBPs. As the number of introns increased over evolution, so did the diversity of RBPs. In response to diversity, eukaryotic cells used RNA exons in varied configurations, resulting in a distinct RNP (ribonucleoprotein) for each RNA. Although post-transcriptional regulation of gene expression is a critical function of RBPs, only a small number of RBPs have undergone rigorous research.It is now obvious that RNA-RBP interactions are crucial for many biological functions carried out by organisms.

Structure

Many RBPs have modular structures and are made up of numerous repeats of only a few limited-sequence basic domains. These sequences are present in several RBPs and are ordered in various combinations. Through the reorganization of these few fundamental domains, the recognition of a specific RNA by a specific protein has emerged. Even though each fundamental domain can recognize RNA, many of these proteins need several copies of one of the numerous common domains in order to work.

Diversity

RNA-binding proteins cover RNA transcripts as soon as nuclear RNA leaves RNA polymerase. These proteins control many aspects of RNA metabolism and function, including RNA biosynthesis, maturation, transport, cellular localization, and stability. All RBPs have the ability to bind RNA, but because they do so with varied RNA-sequence specificities and affinities, the RBPs can have a wide range of targets and activities. These targets include several functional non-coding RNAs as well as mRNA, which codes for proteins. NcRNAs almost never operate as bare RNAs but rather as ribonucleoprotein complexes. These non-coding RNAs include small interfering RNAs (siRNA), small nuclear RNAs (snRNA), and microRNAs [7]–[9].

Differential splicing

The process of alternative splicing allows the same gene to produce many mature mRNA (messenger RNA) variants. It is a regulatory mechanism that increases the number of related proteins that can be produced as a result of changes in the integration of exons into mRNA, potentially expanding the genomic outputs. RBPs play a significant role in the control of this process. Some binding proteins, such as neuronal specific RNA-binding proteins, including NOVA1, recognize and bind to a specific sequence in the RNA (YCAY where Y signifies pyrimidine, U or C), controlling the alternative splicing of a subset of hnRNA. Splicesomal proteins are then attracted to this target location by these proteins. The splicesome is made up of the snRNPs U1 snRNP and U2AF snRNP, and SR proteins are well known for their role in alternative splicing through the recruitment of these snRNPs. RBPs, however, are also a component of the splicesome. The mechanism that eliminates introns and ligates the adjacent exons is known as the splicesome, which is a complex of snRNA and protein subunits. RBPs bind to the Cis-acting RNA elements that affect the inclusion or exclusion of exons during

splicing in addition to the core splicesome complex. Depending on where they bind, RBPs function as splicing enhancers or silencers at these locations, which are also known as exonic splicing enhancers (ESEs), exonic splicing silencers (ESSs), intronic splicing enhancers (ISEs), and intronic splicing silencers (ISSs).

An RNA-binding protein called ADAR is involved in RNA editing processes. The ADAR protein is used in the type of RNA editing that has received the most research. This protein alters the nucleotide composition of the RNA to modify mRNA transcripts post-transcriptionally. In an enzymatic reaction catalyzed by ADAR, adenosine is converted to inosine to do this. By efficiently altering the RNA sequence from that encoded by the genome, this mechanism increases the variety of gene products. The majority of RNA editing happens on non-coding sections of RNA, but it has been demonstrated that some protein-encoding RNA transcripts can undergo editing that alters the amino acid sequence of their proteins. The glutamate receptor mRNA is an illustration of this, where glutamine is changed to arginine, changing the way the protein functions [10], [11].

Localization of mRNA

By enabling spatially controlled protein creation, mRNA localization is essential for the regulation of gene expression. Proteins are translated in their intended target place of the cell by mRNA localization. This is crucial in the early stages of development when rapid cell cleavages produce a variety of mRNA combinations in different cells that might produce radically diverse cell fates. RBPs play a crucial role in the localization of this mRNA, ensuring that proteins are only translated where they are needed. ZBP1 is one of these proteins. At the transcriptional site, ZBP1 binds to beta-actin mRNA and follows it into the cytoplasm. This mRNA is subsequently localized to the lamella region of a number of asymmetric cell types, where it can be translated. In 2008, it was hypothesized that FMRP had a role in the location of a number of dendritic mRNAs in the neuronal dendrites of cultured hippocampal neurons in response to stimuli. Recent analyses of the FMRP-bound RNAs found in microdissected CA1 hippocampal neurons' dendrites showed no differences in their localization between FMRP-null and wild-type mouse brains.

RNA-protein interactions

In order to recognize their RNA targets, RNA-binding proteins must first recognize the sequences, structures, motifs, and RNA modifications of those targets. By controlling the production, maturation, and longevity of the RNA transcript, the RNA-binding proteins are able to differentiate their targets and govern a range of cellular processes. This connection starts during transcription, when some RBPs bind to RNA and stay there until they are degraded, while others only attach briefly to control RNA processing, transport, and localization. In a number of tissues and organisms, direct RNA binding sites of RNA-binding proteins are rigorously identified using cross-linking immunoprecipitation (CLIP) techniques. Three classes of the most extensively researched RNA-binding domains—the RNA-recognition motif, the double-stranded RNA-binding motif, and the zinc-finger motif—will be covered in this section.

RRM (RNA-recognition motif)

The most prevalent RNA-binding motif, the RNA recognition motif, is a short protein domain of 75–85 amino acids that forms a four-stranded -sheet in opposition to the two -helices. Numerous biological processes, including mRNA/rRNA processing, splicing, translation control, RNA export, and RNA stability, are affected by this recognition motif. NMR spectroscopy and X-ray crystallography have found ten RRM structural variants. These

structures demonstrate the complexity of protein-RNA recognition of RRM, which also involves protein-protein and RNA-RNA interactions. Even though they are intricate, all 10 structures share some characteristics. It was discovered that the four-stranded -sheet on the major protein surfaces of all RRMs interacts with the RNA, which typically contacts two or three nucleotides in a certain way. The inter-domain linker and the RNA as well as the RRMs themselves interact to produce significant RNA binding affinity and specificity toward variation. This RRM flexibility explains why the RRM is the most prevalent domain and why it is crucial for a number of biological processes.

CONCLUSION

In the MAPK (Mitogen-Activated Protein Kinase) signaling pathway, RNA-binding proteins play a critical and diverse function. These proteins help to regulate, fine-tune, and coordinate gene expression processes, which are required for cellular responses to extracellular signals and environmental stimuli. RNA-binding proteins have substantial effect on the MAPK pathway at several levels via their interactions with different RNA molecules. To begin, RNA-binding proteins play a role in post-transcriptional regulation by stabilizing or destabilizing mRNA transcripts encoding critical components of the MAPK pathway. This regulation ensures that the appropriate proteins are made at the appropriate moment in response to particular signals, allowing for precise control of pathway activation. Second, RNA-binding proteins often serve as mediators in the transport of certain mRNAs to subcellular compartments such as the cytoplasm or stress granules, where they may be effectively translated or stored until required. This subcellular localization is crucial for MAPK signaling spatiotemporal regulation. Furthermore, RNA-binding proteins may alter the stability and activity of MAPK-related kinases and phosphatases. RNA-binding proteins may fine-tune the phosphorylation and dephosphorylation processes that are typical of MAPK signaling by changing the amounts of these enzymes or their isoforms. Furthermore, several RNA-binding proteins act as adaptors or scaffolds, aiding the formation of MAPK-related protein complexes. These complexes are required for appropriate signal transduction and cellular responses.

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CHAPTER 7

SIGNAL TRANSDUCTION CONTROL AND PLATELET FUNCTION IN LIVER REGENERATION

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Abstract
The liver, of all organs, has a special capacity for tissue regeneration following damage or tissue loss, which is primarily brought on by mitosis in the normally dormant hepatocytes. Tumor necrosis factor alpha, interleukin-6, hepatocyte growth factor, and insulin-like growth factor are just a few of the cytokines and growth factors that stimulate the liver to regenerate. They also activate signaling pathways for nuclear factor b, signal transducer and activator of transcription 3, and phosphatidyl inositol 3-kinase. In a previous article, we discussed how platelets can influence hepatocytes directly as well as work in tandem with nonparenchymal liver cells like Kupffer cells and liver sinusoidal endothelial cells to promote liver regeneration through the release of various growth factors and cytokines. The functions of platelets and nonparenchymal cells in liver regeneration, along with the cytokines, growth factors, and signaling pathways connected to them, are discussed in this work. A lesion to a blood vessel can cause bleeding, and platelets, also known as thrombocytes from the Greek words for "clot" and "cell", react by clumping together to start a blood clot. Platelets are cytoplasmic fragments that are generated from megakaryocytes of the bone marrow or lung and enter the bloodstream. They have no cell nucleus. Only mammals produce platelets; in other animals such as birds and amphibians, thrombocytes circulate as whole mononuclear cells.

Keywords

Amphibians, Drug, Liver, Platelet.

INTRODUCTION

In order to make up for the decreased hepatic volume and compromised function, the liver regenerates as a physiopathological event in a quantitative manner. The precise process of regeneration and the interaction between hepatocytes and cytokines are not entirely understood, despite the fact that multiple studies have demonstrated that a range of genes, cytokines, growth factors, and cells are involved in liver regeneration. A crucial problem with clinical morbidity and mortality in drug-induced liver injury and after surgery, such as hepatectomy or living-donor liver transplantation, is liver regeneration. Three phases can be used to describe the temporal evolution of the signaling pathways that are specifically activated during liver regeneration: a priming phase that involves the progression of dormant hepatocytes from the G0 to the G1 cell cycle; a proliferation phase that sees the progression of the entire hepatocyte population; and a termination phase where cell proliferation is suppressed and regeneration is stopped at a specific point. Hepatocytes are not terminally differentiated; instead, they are in proliferative quiescence (the G0 phase), but on stimulation, they can quickly initiate a cell division cycle. Tumor necrosis factor alpha (TNF)/nuclear factor b (NFB), interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3), activator protein-1 (AP-1), and mitogen-activated protein kinase

(MAPK)/extracellular signal-regulated protein kinase (ERK) are among the proteins and signaling pathways that are crucial during the priming phase of regeneration [1], [2].

Immediately after hepatectomy, phosphoinositide 3-kinase (PI3K)/Akt is also activated and has a significant antiapoptotic function in liver regeneration. Hepatocytes express a number of cell cycle proteins that direct the replication process during the proliferation phase, including hepatocyte growth factor (HGF) and epidermal growth factor (EGF). Transforming growth factor beta (TGF) and activins are essentially the key players in the termination phase. Hepatocytes make up 70% of the total number of cells in the liver and 80% of its volume. Nonparenchymal cells, such as Kupffer cells, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells, and lymphocytes, are made up of the remaining cells and are thought to be crucial in the release of cytokines. Kupffer cells are known to produce growth factors like insulin-like growth factor (IGF)-1 as well as inflammatory cytokines like TNF and IL-6 when activated . After hepatectomy, LSECs have also been shown to produce IL-6 and HGF, and activated hepatic stellate cells primarily produce HGF.

Although platelets are essential for thrombosis and hemostasis, a growing number of extrahemostatic activities of platelets have also been identified. Numerous growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), HGF, IGF, EGF, and TGF, as well as several cytokines, are found in platelets. Additionally, platelets play a few roles that stimulate or speed up hepatocyte proliferation. We recently discovered that platelets are crucial for the regeneration of the liver following hepatectomy and that platelet-derived HGF and IGF-1 are necessary for hepatocyte proliferation. In the course of liver regeneration, platelets work directly with hepatocytes as well as cooperatively with nonparenchymal cells in the liver. Platelets build up in the liver thanks in part to kupffer cells, which can then trigger liver regeneration. Additionally, the direct interaction between platelets and LSECs causes the release of sphingosine 1-phosphate (S1P) from the platelets, which then causes the LSECs to secrete IL-6. Through the STAT3 pathway, the IL-6 produced by LSECs stimulates the production of DNA in hepatocytes [3], [4].

Here, we discuss the cellular and molecular mechanisms of liver regeneration as well as the roles played by various important signaling pathways in the proliferation of hepatocytes. We pay special attention to platelet functions in liver regeneration. Platelets play a key role in hemostasis, the process of halting bleeding at the site of ruptured endothelium. Unless the obstruction is physically too big, they congregate at the location and seal the hole. First, adhesion occurs when platelets cling to objects outside the damaged endothelium. Second, they undergo a shape change, activate receptors, and release chemical messengers. Thirdly, they aggregate to form connections with one another over receptor bridges. The coagulation cascade is activated in conjunction with the formation of this platelet clog (primary hemostasis), resulting in fibrin deposition and linkage (secondary hemostasis). There may be overlap between these processes; the spectrum ranges from a mainly platelet plug, or "white clot," to a mostly fibrin plug, or "red clot," or the more common mixture. Some would add retraction afterward and platelet inhibition as the fourth and fifth steps to complete the process, while others would add wound repair as the sixth step. Additionally, platelets take involvement in innate and adaptive intravascular immunological reactions. Nitric oxide, endothelium-ADPase, and PGI2 (prostacyclin) are all produced by the intact endothelial lining to prevent platelet activation. The platelet activator ADP is broken down by endothelial-ADPase.

A cyclic AMP-activated calcium pump helps resting platelets maintain active calcium export. As the second messenger that causes platelet conformational change and degranulation, intracellular calcium concentration controls the status of platelet activation (see below). On

the surface of dormant platelets, prostanoid receptors are bound by endothelial prostacyclin. This action promotes calcium efflux and decreases intracellular calcium availability for platelet activation. It also stimulates the linked Gs protein to boost adenylate cyclase activity and cAMP generation.

Contrarily, ADP binds to purinergic receptors on the surface of platelets. ADP decreases platelet adenylate cyclase activity and cAMP synthesis because of the thrombocytic purinergic receptor P2Y12's coupling to Gi proteins. This causes calcium to build up inside the platelet by inactivating the cAMP calcium efflux pump. The other ADP-receptor, P2Y1, links to Gq and activates PLCB2, which produces inositol 1,4,5-triphosphate (IP3) and releases additional calcium into the cell. The combination of these causes platelet activation. This is avoided by ADP degradation by endothelial ADPase. Antiplatelet drugs like clopidogrel also function as purinergic receptor P2Y12 antagonists. According to data, a first wave of aggregation is caused by ADP activating the PI3K/Akt pathway, which causes the production of thrombin and the activation of PAR-1, both of which cause a second wave of aggregation.Only a few seconds after adhesion, platelet activation starts. It starts when the platelet's GPVI receptor and integrin 21 bind to the collagen from the subendothelium. GPVI is connected to the Fc receptor gamma chain and ultimately triggers the activation of PLC-gamma2 (PLCG2) and increased calcium release through the activation of a tyrosine kinase cascade.

Additionally, factor VII in the circulation is bound by tissue factor, starting the extrinsic coagulation cascade and increasing thrombin generation. Thrombin acts through Gq and G12 to activate platelets in a powerful way. These G protein-coupled receptors override the platelet's natural calcium efflux by activating calcium-mediated signaling pathways. For complete activation, three G protein families (Gq, Gi, and G12) work in concert. Additionally, thrombin encourages platelet plug secondary fibrin reinforcement. The coagulation cascade is accelerated by platelet activation, which in turn causes factor V and fibrinogen to be released and degranulate. Therefore, rather than happening in order, platelet plugging and coagulation actually happen concurrently, with one causing the other to result in the formation of the final fibrin-crosslinked thrombus [5]–[7].

DISCUSSION

Signaling Mechanism

Cell signaling, or cell communication in biology, is the capacity of a cell to receive, process, and transmit signals with its surroundings as well as with itself. In both prokaryotes and eukaryotes, cell signaling is an essential aspect of all cellular life. Extracellular signals are those that come from outside the cell and can be either physical such as mechanical pressure, voltage, temperature, or light or chemical such as tiny molecules, peptides, or gas. Cell signaling can be characterized as autocrine, juxtacrine, intracrine, paracrine, or endocrine depending on whether it occurs over short or long distances. As a result of cell injury or other biosynthetic routes, signaling molecules can also be produced and delivered passively or actively. Because they can recognize chemical messages or physical stimuli, receptors are essential for cell signaling. Proteins called receptors are typically found on the exterior of cells or inside them in places like the cytoplasm, organelles, and nucleus. Typically, extracellular signals (or ligands) attach to cell surface receptors, changing their conformation and causing them to start an enzyme's activity or open or close an ion channel. Some receptors are connected to enzymes or transporters rather than having enzymatic or channel-like domains. Nuclear receptors, for example, have a distinct process that involves altering their DNA-binding characteristics and cellular localization to the nucleus.

The first step in signal transduction is the conversion of an electrical signal (or transduction) into a chemical one. This chemical signal can then be used to either directly activate an ion channel (ligand-gated ion channel) or to start a second messenger system cascade that spreads the signal throughout the cell. A signal can be amplified through second messenger systems, in which activation of a few receptors causes the activation of several secondary messengers, magnifying the initial signal (the first messenger). Additional enzymatic processes including proteolytic cleavage, phosphorylation, methylation, and ubiquitinylation may occur as a result of these signaling pathways. The cornerstone for development, tissue repair, immunity, and homeostasis, each cell is programmed to react to particular extracellular signal molecules. Diabetes, autoimmune, and cancer are a few disorders that can be brought on by mistakes in signaling connections.

Taxonomic diversity

Quorum sensing allows individuals to start an action in many microscopic organisms like bacteria only when the population is large enough. When the population is dense enough, the marine bacteria Aliivibrio fischeri, which produces light, exhibits this cell-to-cell transmission. A signaling molecule is produced, detected, and the transcription of genes is then regulated as a result. Both gram-positive and gram-negative bacteria, as well as bacteria from different genera, use quorum sensing. In slime moulds, a chemical signal called an acrasin causes individual cells to group together to produce fruiting bodies and eventually spores. The individuals move by chemotaxis, or being drawn to a chemical gradient. Some species use the signal cyclic AMP, whereas others, like Polysphondylium violaceum, use the dipeptide glorin. In both plants and animals, signaling between cells takes place either through release into the extracellular space, which is further split into paracrine (over short distances) and endocrine (over long distances), or by direct contact, which is known as juxtacrine signaling and includes notch signaling. The ability of the secreting cell to react to the secreted signaling molecule distinguishes autocrine signaling from paracrine signaling. A specific instance of paracrine (for chemical synapses) or juxtacrine (for electrical synapses) signaling between neurons and target cells is synaptic signaling.

Creation and release

Molecules that are released by one cell and travel to establish contact with another carry several cell signals. Chemically speaking, signaling molecules might be classified as lipids, phospholipids, monoamines, amino acids, proteins, glycoproteins, or gases. TRH, Vasopressin, and Acetylcholine are a few examples of large, hydrophilic signaling molecules, while glucocorticoids, thyroid hormones, cholecalciferol, and retinoic acid are examples of small, hydrophobic signaling molecules that enter the cell. However, there are many significant exceptions to both of these generalizations, and the same molecule can act both via surface receptors and in an intracrine manner to different effects. Specialized cells in animal cells release these hormones, which are then transported to various body parts by the circulatory system. They subsequently enter target cells, which are able to detect the hormones, react to them, and generate a result. Also called endocrine signaling, this process. Plant growth regulators, also known as plant hormones, go to their targets by either diffusing through the air as a gas or passing through cells. Some cells in the human body create hydrogen sulfide in tiny concentrations, and it serves a variety of biological signaling purposes. There are now just two other similar gases that have been identified as signaling molecules in the human body [8], [9].

Exocytosis

A cell moves substances like neurotransmitters and proteins outside of the cell through a process called exocytosis. Exocytosis uses energy to move materials because it is an active transport process. All cells require exocytosis and its counterpart, endocytosis, to transport material into the cell since the majority of the chemical components that are crucial to them are big polar molecules that cannot cross the hydrophobic region of the cell membrane passively. Exocytosis is a type of bulk transport since it allows for the release of many molecules. Through porosomes, which are secretory gateways located in the cell plasma membrane, exocytosis occurs. At the cell plasma membrane, secretory vesicles transiently dock and fuse to discharge intra-vesicular contents from the cell. These formations are known as porosomes and are permanent cup-shaped lipoprotein structures. Membrane-bound secretory vesicles are transported to the cell membrane during exocytosis, when they dock and fuse at porosomes, releasing their contents water-soluble molecules into the extracellular space. The vesicle briefly merges with the plasma membrane, allowing for its secretion. Neurotransmitters can also be released by reverse transport through membrane transport proteins, which is how they are generally released from synaptic vesicles into the synaptic cleft in the setting of neurotransmission.

Paracrine

A cell can alter the activity of cells nearby by sending paracrine signals to those cells. Paracrine factors are signaling molecules that diffuse over extremely short distances (local action), in contrast to endocrine factors, hormones that travel over much larger distances via the circulatory system, juxtacrine interactions, and autocrine signaling. The generating cells release paracrine substances into the immediate extracellular environment. After the factors have traveled there, the gradient of the factor received in these nearby cells affects the result. How far paracrine factors can truly migrate, though, is unclear. Paracrine signals like retinoic acid only target cells nearby to the transmitting cell. Neurotransmitters are yet another example of a paracrine signal.

Some signaling molecules have both hormonal and neurotransmitter functions. Epinephrine and norepinephrine, for example, can function as hormones when produced from the adrenal gland and transported to the heart via the blood stream. Norepinephrine, a neurotransmitter in the brain, is another substance that neurons are capable of producing. Estrogen is a hormone that can be released from the ovary and act locally through paracrine or autocrine signaling. The majority of paracrine factors use a relatively simple set of receptors and pathways, despite the fact that paracrine signaling induces a wide range of responses in the stimulated cells. In fact, it is known that various bodily organs—even those of different species—use comparable sets of paracrine factors during differential development. Based on similar structural similarities, the highly conserved receptors and pathways can be divided into four major families: the fibroblast growth factor (FGF) family, the Hedgehog family, the Wnt family, and the TGF-superfamily. Binding of a paracrine factor to its associated receptor initiates signal transduction cascades that result in a variety of events [10], [11].

Receptors

A class of proteins known as receptors helps cells communicate with their neighbors. Receptors can interact with physical agents like light, mechanical temperature, pressure, and other molecules to form bonds with them (called ligands). Reception happens when a signal, typically in the form of a small, water-soluble molecule, binds to a receptor protein on the surface of the target cell. Alternatively, once inside the cell, the signaling molecule can bind

to intracellular receptors, other components, or stimulate enzyme activity (e.g. gasses), as in intracrine signaling.

As a ligand for cell surface receptors, signaling molecules interact with a target cell. They can also enter the cell through its membrane or endocytosis for intracrine signaling. Second messengers are typically activated as a result, having a variety of physiological impacts. Early embryonic cells communicate with uterine cells in several mammals. Bacteria and human epithelial and immune system cells communicate with one another and with each other in the human gastrointestinal tract. Some cells in the yeast Saccharomyces cerevisiae emit a peptide signal (mating factor pheromones) to signal to other cells that it is time to mate. Other yeast cells may bind to a cell surface receptor on the mating factor peptide and become stimulated to initiate mating.

G protein–coupled receptors

Cell surface receptors that detect substances outside the cell and trigger physiological responses are known as G protein-coupled receptors. They are a vast set of evolutionarily connected proteins. They are known as seven-transmembrane receptors because they couple with G proteins and traverse the cell membrane seven times. The binding site within transmembrane helices (Rhodopsin-like family) or the extracellular N-terminus and loops (such as glutamate receptors) are the two possible sites for ligand binding. Although a spontaneous auto-activation of an empty receptor can also be seen, they are all agonist-activated. Only eukaryotes, including yeast, choanoflagellates, and mammals, have G protein-coupled receptors. Light-sensitive substances, smells, pheromones, hormones, and neurotransmitters are among the ligands that bind to and activate these receptors. Their sizes range from tiny molecules to peptides to big proteins. There are numerous disorders that involve G protein-coupled receptors. [12].

The G protein-coupled receptors are involved in two main signal transduction pathways: the cAMP signal pathway and the phosphatidylinositol signal pathway. A ligand's binding to a GPCR changes its conformation, enabling it to function as a GEF (guanine nucleotide exchange factor). By trading the GDP attached to the G protein for a GTP, the GPCR can then activate a related G protein. Depending on the type of subunit, the G protein's subunit can then separate from the and subunits to further alter intracellular signaling proteins or directly target functional proteins..

CONCLUSION

The process of transduction, which can start with a single change in a sequence of molecules or with multiple modifications (referred to as a signal transduction pathway), is started when the receptor protein binds to the signaling molecule. Relay molecules are the molecules that make up these pathways. Activation of proteins through the addition or removal of phosphate groups, or even the release of additional small molecules or ions that can function as messengers, are frequent components of the multistep transduction stage process. One advantage of this multi-step process is the signal amplification. Other advantages include the ability to fine-tune the response in both unicellular and multicellular organisms, as well as greater options for regulation than simpler systems do.

In some circumstances, the cell's reaction to the ligand is directly associated with the receptor activation brought on by the ligand binding to a receptor. For instance, the neurotransmitter GABA has the ability to open an ion channel by activating a cell surface receptor. A chloride-selective ion channel that is a component of the receptor is opened when GABA binds to a GABAA receptor on a neuron. Chloride ions can enter the neuron when the GABAA receptor

is activated, which prevents the neuron from firing action potentials. The response of the cell is not always closely correlated with ligand-receptor interactions for many cell surface receptors, though. Before the ligand has its full physiological impact on the behavior of the cell, the activated receptor must first interact with other proteins within the cell. Following receptor activation, a chain of numerous interacting cell proteins frequently exhibits changed behavior. A signal transduction mechanism or route is the term used to describe the whole collection of cell changes brought about by receptor activation..

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CHAPTER 8

VARIETY OF ROLES IN PHYSIOLOGICAL AND PATHOLOGICAL SIGNAL TRANSDUCTION REGULATION

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Abstract

As a member of the sirtuin family, Sirtuin 2 possesses typical characteristics of evolutionarily well conserved deacetylase activity that depend on nicotinamide adenine dinucleotide. Furthermore, SIRT2, the only sirtuin protein that is colocalized with tubulin in the cytoplasm, has unique properties and functions. Through its post-translational modification of target genes, studies have increasingly demonstrated that SIRT2 can participate in the regulation of gene expression and regulate signal transduction in the metabolic pathway. As a result, SIRT2 has emerged as a key node in the metabolic pathway and contributes to the pathological process of diseases linked to metabolic disorders. The ability of SIRT2 to control all aspects of gene expression, including epigenetic modification, replication, transcription, and translation, as well as post-translational modification, is discussed in this paper. It is also made clear that SIRT2 is involved in signal transduction mechanisms that are specific to the metabolic process. As a result, SIRT2 may have a role in the inflammation and oxidative stress that accompany metabolic disorders, which in turn may lead to the development of diseases like neurodegenerative disorders, tumors, diabetes, and cardiovascular conditions. The many functions of SIRT2 in regulating physiological and pathological signal transduction have made it a crucial target for illness treatment, even though the involvement of SIRT2 in some diseases is still debatable. It is anticipated that as research progresses, SIRT2's clinical use will gain momentum.

Keywords

Cardiovascular, Mammals, Metabolic, Transduction.

INTRODUCTION

The type III histone deacetylases, also referred to as the silent information regulator family, are nicotinamide adenine dinucleotide -dependent deacetylases that are substantially conserved from bacteria to humans. Mammals have been found to contain seven distinct sirtuin types, each of which has a unique role and location within cells. SIRT1, SIRT6, and SIRT7 are mostly found in the nucleus, where SIRT1 controls energy metabolism, chromatin modification, and transcription. SIRT6 and SIRT7 are involved in DNA repair and rDNA transcription, respectively. SIRT3-5 are found in mitochondria, where they control the synthesis of ATP in response to caloric restriction and oxidative stress. The SIRT2 gene is distributed across metabolically active organs such the liver, heart, skeletal muscle, and brain. It is found on autosomal chromosome 19q13.2 and colocalizes with tubulin in the cytosol. Through its post-translational modification of target genes, studies have demonstrated that SIRT2 can engage in the regulation of gene expression and influence signal transmission in metabolic pathways. This paper focuses on the precise mechanism by which SIRT2 controls gene expression in all aspects and through post-translational modification of each target gene of synthetic metabolism and catabolism in lipid metabolism and glucose metabolism , and directly or indirectly affects the transduction of metabolic-related signals , leading to

crosstalk between metabolic signaling pathways; thus, SIRT2 has emerged as a crucial node [1], [2].

SIRT2 is a target for the therapeutic treatment of diseases because it can be implicated in inflammation and oxidative stress linked to metabolic disorders as well as the pathological process of diseases linked to metabolic disorders. In order to offer fresh perspectives and approaches for the treatment of diseases, this research first clarifies the precise mechanism of SIRT2 in the relationship between gene expression control and metabolic pathway signal transduction.The SIRT2 gene in humans encodes an enzyme called NAD-dependent deacetylase sirtuin 2. SIRT2 is a deacetylase that is regulated by NAD+ . Studies on this protein have frequently been inconsistent, illustrating how the cellular environment affects SIRT2's pleiotropic effects. Depending on whether they are healthy or malignant, brain cells respond differently to the natural polyphenol resveratrol. Like other members of the sirtuin family, SIRT2 exhibits a widespread distribution. SIRT2 has been shown to be expressed in a variety of tissues and organs, but it has been found to be especially prevalent in tissues that are relevant to metabolism, such as the brain, muscle, liver, testicles, pancreas, kidney, and adipose tissue of mice. Notably, the brain has far higher levels of SIRT2 expression than any other organs under investigation, particularly in the cortex, striatum, hippocampus, and spinal cord.

Function

Human sirtuins may serve as intracellular regulatory proteins with mono-ADP-ribosyltransferase activity, according to studies. SIRT2 has cytosolic roles in the modulation of gluconeogenesis, myelination in the central and peripheral nervous systems, and microtubule acetylation. There is mounting evidence that SIRT2 performs other roles in the nucleus. Nuclear SIRT2 is in charge of global H4K16 deacetylation during the G2/M transition, enabling H4K20 methylation and chromatin compaction in the process. Additionally, it was discovered that SIRT2 in vivo deacetylates H3K56 in response to DNA damage. Finally, SIRT2 deacetylates an automodification loop inside its catalytic domain to adversely inhibit the acetyltransferase activity of the transcriptional co-activator p300.A chemical or physical signal is transferred through a cell as a succession of molecular events through a process known as signal transduction. Protein kinases are most frequently responsible for the catalysis of protein phosphorylation, which ultimately causes a physiological response. Although in some instances the term sensor is used, generally speaking, proteins that detect stimuli are referred to as receptors. A biochemical cascade, or series of biochemical events known as a signaling pathway, is triggered by ligand binding in a receptor. Signaling pathways connect with one another to build networks that enable the coordination of cellular responses, frequently through combinatorial signaling events. At the molecular level, these responses can affect how genes are translated or transcribed, as well as how proteins are post-translationally altered and how they conform. The fundamental mechanisms governing cell growth, proliferation, metabolism, and many other functions are these molecular occurrences. Signal transduction pathways control cell communication in multicellular organisms in a wide range of ways [3], [4].

Each part of a signaling pathway is categorized based on the function it performs in relation to the initial stimulus. First messengers are ligands, and signal transducers are receptors, which in turn activate primary effectors. These effectors, which are primarily proteins, are frequently connected to second messengers, which in turn can activate further effectors. Signal gain is the idea that a signal can be amplified so that one signaling molecule can cause a reaction involving hundreds to millions of molecules depending on how effective the nodes are. Similar to other signal transduction, biological signal transduction is characterized by

delay, noise, signal feedback and feedforward, and interference, which can be minimal or severe. Analysis of signaling pathways and networks has become crucial to understanding biological processes and illness, including the signaling rewiring mechanisms driving acquired drug resistance. This is thanks to the development of computational biology.Most signal transduction pathways entail the attachment of signaling molecules, or ligands, to receptors that set off cellular activities. Receptor activation, which results from a change in receptor conformation brought on by the binding of a signaling molecule to a receptor, is a biological process. The majority of ligands that bind to cell surface receptors are soluble molecules from the extracellular media. These consist of neurotransmitters, cytokines, and growth factors. Fibronectin and hyaluronan, both of which are found in the extracellular matrix, can bind to these receptors. Additionally, some chemicals, like steroid hormones, are lipid-soluble and can pass through the plasma membrane to reach receptors in the cytoplasm or the nucleus. When steroid hormone receptors are stimulated, they bind to the promoter region of genes that respond to steroid hormones.

The chemical makeup of each class member is not taken into account in all classifications of signaling molecules. For instance, neurotransmitters, which range in size from tiny molecules like dopamine to neuropeptides like endorphins, as well as odorants, belong to a variety of molecular groups. In addition, some molecules may fall under more than one category. For instance, epinephrine is both a neurotransmitter and a hormone depending on where it is released from in the body. When overexpressed or altered, certain receptors, including HER2, can activate without the need for a ligand. As a result, the route becomes constitutively activated, which compensation mechanisms may or may not be able to reverse. Constitutive activation causes hyperproliferation and cancer in the instance of HER2, which functions as another EGFR in dimerization.

DISCUSSION

Controls Translation, Transcription, and Replication

A DNA fragment is copied into RNA during transcription. Messenger RNA is the term for DNA segments that are transcribed into RNA molecules that can encode proteins. Non-coding RNAs are RNA molecules that contain copies of additional DNA sequences. Only 1% to 3% of all RNA samples are mRNA. A minimum of 80% of mammalian genomic DNA can be actively transcribed, with the bulk of this 80% being ncRNA. In contrast, less than 2% of the human genome can be transcribed into mRNA. Nucleic acids which include DNA and RNA—use base pairs of nucleotides as a complementary language. An RNA polymerase reads a DNA sequence during transcription, creating a primary transcript, which is a complementary, antiparallel strand of RNA.for numerous cis-regulatory elements, such as core promoter and promoter-proximal elements that are situated close to the transcription start sites of genes, influence transcription in mammals. Although they typically have low basal activity, core promoters in combination with general transcription factors are adequate to direct transcription initiation. In DNA regions far from the transcription start sites, there are additional significant cis-regulatory modules. These include elements for enhancing, silencing, insulating, and tethering. Enhancers and the associated transcription factors play a key role in the start of gene transcription among this constellation of components. Some genes can experience up to a 100-fold increase in transcription as a result of an activated enhancer, even though it is located in a DNA region far from the gene's promoter [4]–[6].

Major gene-regulatory elements found in the genome are called enhancers. The majority of the time, enhancers govern cell type-specific gene transcription programs by traveling significant distances to reach close to the promoters of their target genes. Despite the fact that

there are hundreds of thousands of enhancer DNA regions, only a few enhancers are brought close to the promoters they control for a given type of tissue. 24,937 loops were discovered in a study of brain cortical neurons, connecting enhancers to their intended promoters. The promoters of their target genes are looped to by a number of enhancers, each of which is frequently hundreds or even millions of nucleotides away from its target gene. These enhancers can cooperate with one another to regulate the transcription of their shared target gene.

The graphic representation in this section depicts an enhancer looping around to be in close proximity to a target gene's promoter. A connector protein dimer, such as CTCF or YY1, stabilizes the loop by anchoring one member of the dimer to its binding motif on the enhancer and the other member to its binding motif on the promoter. A small group of these enhancer-bound transcription factors, which are typically bound to specific motifs on an enhancer, when brought close to a promoter by a DNA loop, regulate the level of transcription of the target gene. There are approximately 1,600 transcription factors in a human cell. The RNA polymerase II enzyme linked to the promoter receives regulatory signals from enhancer DNA-bound transcription factors directly through the mediator. When active, enhancers often cause RNA polymerases to work in two separate directions, resulting in the production of two enhancer RNAs. An inactive transcription factor may bind to an enhancer. The transcription factor may be phosphorylated to make it active, and once it is, the enhancer to which it is attached may also be activated. Before triggering the transcription of messenger RNA from its target gene, an active enhancer starts transcribed its own RNA [7], [8].

Methylation and demethylation of the CpG Island

The methylation of cytosines within CpG dinucleotides, where 5' cytosine is followed by 3' guanine or CpG sites, also regulates transcription at roughly 60% of promoters. The DNA nucleotide cytosine has a methylated version called 5-methylcytosine. An epigenetic marker called 5-mC is most frequently detected at CpG sites. Human DNA has about 28 million CpG dinucleotides. 70% to 80% of the CpG cytosines in the majority of mammalian tissues are typically methylated to create 5-methylCpG or 5-mCpG. CpG islands are collections of methylated cytosines that frequently occur in 5'-cytosine-guanine-3' sequences. CpG islands are present in around 60% of promoter sequences but just 6% of enhancer sequences. CpG islands are regulatory sequences because methylation of CpG islands in a gene's promoter can inhibit or silence gene transcription.

Through interactions with methyl binding domain proteins such MeCP2, MBD1, and MBD2, DNA methylation controls gene transcription. The CpG islands with the greatest methylation are where these MBD proteins bind most firmly. Both a transcription repression domain and a methyl-CpG-binding domain are present in these MBD proteins. They bind to methylation DNA and direct protein complexes that are involved in chromatin remodeling and/or histone modification to methylated CpG islands. MBD proteins often create a repressive chromatin environment by modifying the nucleosome and reorganizing the chromatin, or by accelerating the introduction of repressive histone marks. A schematic karyogram of a person demonstrates the human genome on G banding, with lighter parts often being more transcriptionally active and darker sections, such as non-coding DNA, being more inactive.

Karyotype

Transcription factors are proteins that bind to particular DNA sequences in order to control the expression of a gene, as was said in the preceding section. Typically, a transcription factor's DNA binding sequence is 10 or 11 nucleotides long. Approximately 1,400 distinct transcription factors are encoded in the human genome by genes that make up about 6% of all

human protein-coding genes, according to a 2009 summary by Vaquerizas et al. Only about 6% of the transcription factor binding sites connected to signal-responsive genes are found in promoters, compared to approximately 94% in enhancers. A specific transcription factor known as EGR1 protein is crucial for controlling the methylation of CpG islands. Enhancer or promoter sequences commonly contain an EGR1 transcription factor binding site. In the mammalian genome, EGR1 has around 12,000 binding sites, half of which are in promoters and the other half in enhancers. Cytosine methylation in the DNA has no effect on EGR1's ability to attach to its target DNA binding site [9], [10].

While very little EGR1 transcription factor protein is present in unstimulated cells, translation of the EGR1 gene into protein is dramatically increased an hour after stimulation. Growth factors, neurotransmitters, hormones, stress, and damage can all increase the production of EGR1 transcription factor proteins in different types of cells. EGR1 proteins are up-regulated in the brain during neuronal activation and they bind to the pre-existing TET1 enzymes that are created in large quantities in neurons. 5-Methylcytosine can be demethylated by TET enzymes. TET1 enzymes can demethylate the methylated CpG islands at promoters when EGR1 transcription factors transport them to EGR1 binding sites. These promoters can then start the transcription of their target genes after demethylation. Through the engagement of TET1 by EGR1 to methylation regulatory regions in the promoters of several genes, hundreds of genes in neurons are differently expressed after neuron activation. The splice isoform DNMT3A2 has characteristics of a traditional immediate-early gene, such as being robustly and briefly generated in response to neural activity. Histone post translational changes appear to control where the DNA methyltransferase isoform DNMT3A2 binds and adds methyl groups to cytosines. However, brain activity results in DNMT3A1 degradation along with decreased methylation of at least one assessed targeted promoter.

Initiation

A eukaryotic protein-coding gene's regulatory sequence elements can be located upstream of the open read frame, right next to it, or many kilobases away . Transcriptional regulation from DNA to mRNA is up-regulated via promoter and enhancer regions. The 5' and 3' untranslated regions of that mRNA then control translation to produce the finished protein. Proteins coupled to the DNA can be brought close to one another during transcription initiation because the intervening DNA can loop back on itself. Thus, many kilobases upstream or downstream of the open reading frame, the basal transcription machinery can interact with far-off activators and repressors. An RNA polymerase-promoter "closed complex" is formed when RNA polymerase binds to a specific DNA sequence known as a "promoter" together with one or more generic transcription factors. The promoter DNA is still completely double-stranded in the "closed complex". The next step is for RNA polymerase to unwind about 14 base pairs of DNA to produce a "open complex" with the help of one or more general transcription factors. The promoter DNA is partially unraveled and single-stranded in the "open complex". The "transcription bubble" is the name given to the single-stranded DNA that is exposed. The RNA polymerase then chooses a transcription start site in the transcription bubble with the help of one or more general transcription factors, binds to an initiating NTP and an extending NTP, and catalyzes bond formation to produce an initial RNA product [11]–[13].

Five subunits make up the RNA polymerase holoenzyme in bacteria: two subunits, one subunit, one subunit's, and one subunit. A sigma factor is a single universal RNA transcription factor found in bacteria. The RNA polymerase core enzyme forms the RNA polymerase holoenzyme by joining with the bacterial general transcription factor before binding to a promoter. When the sigma subunit is connected to the core enzyme, which

consists of two subunits, one subunit, and one'subunit only, the RNA polymerase is referred to as a holoenzyme. The starting nucleotide of developing bacterial mRNA is not capped with a modified guanine nucleotide, in contrast to eukaryotes. Bacterial transcripts have a starting nucleotide that contains a 5′ triphosphate, which can be utilized to map transcription initiation locations across the whole genome [14], [15].

In addition to extra subunits, RNA polymerase in archaea and eukaryotes has subunits that are homologous to each of the five RNA polymerase subunits in bacteria. The actions of the bacterial general transcription factor sigma are shared by a number of cooperative general transcription factors in archaea and eukaryotes. TBP, TFB, and TFE are the three main transcription factors found in archaea. There are six general transcription factors found in eukaryotes that are involved in RNA polymerase II-dependent transcription: TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH. TFIIA is a multisubunit factor, while TFIIE is an ortholog of archaeal TFE. TBP's binding causes the TFIID to bind to DNA first, while TFIIH is the last component to be enlisted. The RNA polymerase-promoter closed complex in archaea and eukaryotes is frequently referred to as the "preinitiation complex". Additional proteins that control the formation and operation of the transcription initiation complex are known as activators, repressors, and, in some situations, related coactivators or corepressors.

CONCLUSION

After eating, the blood sugar level rises as a result of the small intestine's epithelial cells absorbing glucose. Consuming glucose after blood sugar levels have risen produces a significant quantity of energy needed to maintain normal physiological functions. Unused glucose is transformed into glycogen and then into fat by inducing the release of insulin after the energy demand has been satisfied. Additionally, Cha et al. showed that SIRT2 but not SIRT1 was responsible for controlling the acetylation levels and activity of glycolytic enzymes. SIRT2 is a crucial enzyme that controls the glycolytic process as a result. Additionally, to aid in the consumption of glucose via glycolysis, glucokinase can catalyze the conversion of glucose to 6-phosphate glucosamine. By deacetylating GCK-regulated protein, which separates GKRP from GCK, SIRT2 can activate GCK and facilitate hepatic glucose absorption. Studies have demonstrated that inhibiting SIRT2 can decrease glycolytic flux and inhibit glucose-stimulated insulin secretion by regulating the Akt/glycogen synthase kinase -3/-catenin pathway in beta cells. These studies also demonstrate that inhibiting SIRT2 can improve the stability of GKRP protein and promote the degradation of ALDOA.

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CHAPTER 9

ESTROGEN-MEDIATED SIGNAL TRANSDUCTION IN OSTEOCLAST FORMATION A PROTEOMIC ANALYSIS

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Abstract

Particularly in postmenopausal women, estrogen is crucial in preventing osteoclast development and preventing bone loss due to osteoporosis. The particular processes by which estrogen affects osteoclasts are not well understood. To assess the differential protein expression in receptor activator of nuclear factor-B ligand -induced osteoclasts in the presence and absence of estrogen, we conducted proteomics analysis and bioinformatics analysis in the current work. We discovered 6403 proteins, of which 124 were regulated, which calls for more research and confirmation. A collection of proteins called estrogen receptors is present inside cells. They are receptors that the estrogen hormone activates. There are two classes of ER: membrane estrogen receptors, ER-X, and Gq-mER), which are mostly G protein-coupled receptors, and nuclear estrogen receptors, which are members of the nuclear receptor family of intracellular receptors. The former is referred to in this article. positively and 231 negatively by estrogen. A bioinformatics research revealed that estrogen therapy disrupted 77 intracellular pathways, including both canonical and unverified canonical osteoclast production processes. Our research confirms that estrogen inhibits the production of osteoclasts by encouraging apoptosis and suppressing differentiation and polarization. However, it also raises the possibility that estrogen may reduce the formation of osteoclasts through additional mechanisms.

Keywords:

DNA, Estrogen, Osteoporosis, Receptors.

INTRODUCTION

The ER is a DNA-binding transcription factor that can translocate into the nucleus after being activated by estrogen and bind to DNA to control the activity of many genes. It also serves other purposes that are not related to DNA binding, though. Osteolytic illnesses such postmenopausal osteoporosis, which are caused by abnormal bone resorption by osteoclasts, are characterized by pathologically reduced bone mineral density. In postmenopausal osteoporosis, estrogen is an important regulator of bone mass. Osteoporosis is usually caused by estrogen shortage in postmenopausal women, and estrogen replacement therapy is a useful way to delay the loss of bone density. Osteoclast bone resorption is not permitted by estrogen, either directly or indirectly. The majority of estrogen's effects are mediated through estrogen receptors, especially in direct regulation. Inducing apoptosis in a dose- and time-dependent manner, estrogen activates ER but not ER, shortening the already brief lifespan of differentiated osteoclasts by activating the Fas cell surface death receptor /Fas ligand system. Additionally, estrogen inhibits the growth of osteoclasts by downregulating the enzymes cellular-Jun and Jun N-terminal kinase 1. Additionally, estrogen inhibits osteoclast adherence

by lowering the expression of the 3 integrin. However, it is still unknown exactly how estrogen controls osteoclasts [1], [2].

Induced by the receptor activator of nuclear factor-B ligand, osteoclasts the only bone-resorbing cells produced from hematopoietic stem cells go through differentiation and fuse to form enormous multinucleated cells. For osteoclast development and activation, RANKL and RANK interaction trigger intracellular cascades that are essential. Nuclear factor-B pathway activation by RANKL facilitates osteoclast differentiation. TNF receptor-associated factors are recruited in order to mediate RANK's downstream signaling. TRAF6 is essential for RANKL-induced osteoclast development among the TRAF family members. NF-B and mitogen-activated protein kinase are two signaling molecules that are activated by TRAF6. Additionally, RANKL promotes the phosphorylation of the transcription factor MITF, which is linked to osteoclastogenesis and another transcription factor associated with microphthalmia. By turning on c-Fos, a component of AP-1, RANK signaling also activates transcription factor activator protein-1. Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1 is induced by NF-B and c-Fos activation. Osteoclast-specific genes like cathepsin K and TRAP are stimulated to express by a transcription factor complex made up of transcription factors including NFATc1 and MITF. In mature osteoclasts, RANKL also lowers the degree of Fas expression, which in turn lowers Fas-mediated apoptosis.

Osteoclast polarization and bone matrix adherence are also necessary for the activation of bone resorption. Osteoclasts polarize to create a constricting, sealing zone where cathepsin K breaks down the organic matrix while protons break down bone minerals. Integrin-mediated recognition of the extracellular matrix is necessary for the formation of the sealing zone. The key involvement of v3 integrin in osteoclast attachment has been shown in numerous investigations. Additionally, it has been hypothesized that ITGB3 contributes to the creation of the osteoclasts' typical ruffled border and actin ring. Small guanosine triphosphatases, including as RhoA, Rac, and Arf6, are important regulators of the development of the sealing zone in addition to integrin [3]–[5].

Several cytokines that control osteoclast differentiation are regulated by estrogen. In order to thoroughly investigate how estrogen regulates differentiating osteoclasts, we performed proteomics analysis and bioinformatics analysis on the protein changes that take place when osteoclast precursor RAW 264.7 cells differentiate into mature osteoclasts after being induced by RANKL in the presence or absence of estrogen. The - or -subtypes of the receptor are preferentially bound by subtype-specific estrogen receptor modulators. Furthermore, different estrogen receptor combinations may react to diverse ligands differently, which could result in tissue-specific agonistic and antagonistic effects. It has been suggested that the ratio of - to - subtype concentration influences the development of several disorders.

The ability to facilitate ER interactions with various proteins, such as transcriptional coactivators or corepressors, is the basis for the idea of selective estrogen receptor modulators. Additionally, various tissues have variable ratios of coactivator to corepressor protein. As a result, a given ligand may behave as an agonist in some tissues and as an antagonist in others. As an antagonist in the breast, tamoxifen is utilized as a therapy for breast cancer. However, a partial ER agonist in the endometrium and an ER agonist in the bone. The - or -subtypes of the receptor are preferentially bound by subtype-specific estrogen receptor modulators. Furthermore, different estrogen receptor combinations may react to diverse ligands differently, which could result in tissue-specific agonistic and antagonistic effects. It has been suggested that the ratio of - to - subtype concentration influences the development of several disorders.

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The subsequent recruitment of additional proteins by the DNA/receptor complex results in the transcription of downstream DNA into mRNA, followed by the recruitment of protein that alters cell function. Both estrogen receptor subtypes feature a DNA-binding domain and can operate as transcription factors to control the synthesis of proteins. Estrogen receptors are also found in the cell nucleus. Through a number of coactivators, including PELP-1, the receptor also interacts with activator protein 1 and Sp-1 to stimulate transcription. Transactivation and hormone sensitivity are controlled by p300's direct acetylation of the lysine residues in the hinge region of the estrogen receptor alpha..

DISCUSSION

Culture of Cells

The technique through which cells are cultivated under controlled circumstances, typically away from their natural environment, is known as cell culture or tissue culture. American doctor Montrose Thomas Burrows is credited with coining the phrase "tissue culture". Another name for this method is micropropagation. The cells of interest can then be maintained under carefully monitored conditions after being removed from living tissue. In an incubator, they must be maintained at body temperature. The specifics of these conditions vary depending on the type of cell, but they typically include a suitable vessel with a substrate or rich medium that provides the necessary nutrients, growth factors, hormones, and gases, as well as controls the physio-chemical environment. The majority of cells must adhere to a surface or artificial substrate to form monolayers, but some can grow freely in a medium as suspension cultures. A liquid, semi-solid, or solid growth medium, such as broth or agar, is generally used to aid this. Animal cells and tissues are typically cultured using the term "tissue culture," while plants are cultured using the more precise term "plant tissue culture." The majority of cells have a genetically defined lifespan, however under the right circumstances, some cell-culturing cells have been "transformed" into immortal cells that will continue to divide eternally.

In contrast to other methods of culture that also produce cells, such as plant tissue culture, fungal culture, and microbiological culture, the phrase "cell culture" currently most commonly refers to the growing of cells obtained from multicellular eukaryotes, particularly animal cells. The methodology and historical development of cell culture are very similar to those of tissue and organ culture. Cells serve as the hosts for viruses in viral culture. In the middle of the 20th century, the laboratory technique of preserving live cell lines a population of cells descended from a single cell and possessing the same genetic makeup apart from their original tissue source became increasingly reliable. Sydney Ringer, an English biologist from the 19th century, created salt solutions with sodium, potassium, calcium, and magnesium chlorides that could keep an animal heart outside of its body beating. Wilhelm

Roux developed the fundamental idea behind tissue culture in 1885 when he cut a piece of an embryonic chicken's medullary plate out and kept it in a warm saline solution for many days. Ross Granville Harrison, a naturalist, documented the development of frog embryonic cells that would later give rise to nerve cells in a medium of clotted lymph in 1907. Vaccinia virus was developed in 1913 by E. Steinhardt, C. Israeli, and R. A. Lambert in guinea pig ocular tissue pieces. In 1996, a small length of urethra was replaced using regenerative tissue for the first time, which led to the realization that the technique of taking tissue samples, growing them outside the body without a scaffold, and then reapplying them can only be used for short distances of less than 1 cm. The results of studies conducted by Ross Granville Harrison between 1907 and 1910, while he was a student at Yale University and a faculty member at Johns Hopkins Medical School, were published, laying the foundation for tissue culture [8]–[10].

The first person to highlight the advantages of plant tissue culture was Gottlieb Haberlandt. He proposed that this method might be used to determine the potential of individual cells through tissue culture as well as the reciprocal effects of tissues on one another. Since Haberlandt made his first claims, techniques for tissue and cell culture have been developed, resulting in important biological and medical advancements. He first proposed the concept of totipotency in 1902, which states that "theoretically all plant cells are capable of giving rise to a complete plant." The 1940s and 1950s saw a substantial advancement in cell culture methods to aid virology research. Viral growth in cell cultures allowed for the creation of pure viruses for vaccine production. One of the first items produced in large quantities utilizing cell culture techniques was the injectable polio vaccine created by Jonas Salk. The cell culture work of John Franklin Enders, Thomas Huckle Weller, and Frederick Chapman Robbins—recipients of the Nobel Prize for their invention of a technique for producing the virus in monkey kidney cell cultures made it possible to develop this vaccine. Cell culture has helped with the creation of vaccines for a variety of diseases.

Preparing Samples and TMT Labeling

Tandem mass tags, which are chemical labels, facilitate sample multiplexing in the quantification and identification of biological macromolecules including proteins, peptides, and nucleic acids using mass spectrometry. TMT belongs to the family of reagents known as isobaric mass tags. This group of compounds all have the same mass, but when they break apart, they create reporter ions that have distinct masses. The relative ratio of the observed reporter ions represents the relative abundance of the tagged molecule, notwithstanding the fact that ion suppression has a negative impact on accuracy. Despite these problems, it has been shown that TMT-based proteomics' precision cannot be matched by label-free quantification. In addition to helping with protein quantification, TMT tags can increase the detection sensitivity of some extremely hydrophilic analytes, such as phosphopeptides, in RPLC-MS analysis.The tags consist of four sections: a mass reporter area, a cleavable linker region, a mass normalization region, and a protein reactive group. Even though each tag's mass reporter and mass normalization components have identical chemical structures and different isotope substitutions, their molecular masses differ. Because the combined M-F-N-R sections of the tags have the same total molecular weights and structures, distinct-tagged molecules cannot be distinguished during chromatographic or electrophoretic separation or in a single MS mode.

When fragmenting in MS/MS mode, the tag fragmentation produces quantification information and mass reporter ions, whereas the peptide backbone fragmentation produces sequence information.Mass spectrometry technologies like Mascot can account for the tag masses because the public has access to the structures of TMT tags through the unimod

database at unimod.org. Since version 2.2, Mascot can quantify using TMT and other isobaric mass tags without the requirement for additional software. The reliability of a protein measurement is intuitively determined by the comparability of ratios from different peptides and the signal strength of these measurements. The BACIQ technique is a rigorous mathematical approach that incorporates peptide intensities and peptide-measurement agreement into confidence intervals for protein ratios. The TKO standard should be used to assess interference. [11], [12].

Data analysis is the act of analyzing, filtering, modifying, and modeling data in order to uncover pertinent information, support conclusions, and help decision-making. Data analysis is utilized in several fields of business, science, and social science and has many dimensions and methodologies. It includes various techniques and goes by many different names. Data analysis contributes to more scientific decision-making and more efficient business operations in the modern business world. Data mining is a specific type of data analysis that concentrates on knowledge discovery and statistical modeling for predictive as opposed to just descriptive purposes. Business intelligence refers to data analysis that extensively relies on aggregation and is primarily concerned with business information. Data analysis can be broken down into three categories in statistical applications: descriptive statistics, exploratory data analysis, and confirmatory data analysis. While CDA focuses on validating or refuting existing hypotheses, EDA focuses on identifying novel features in the data. While text analytics combines statistical, linguistic, and structural techniques to extract and categorize information from textual sources, a type of unstructured data, predictive analytics focuses on the application of statistical models for predictive forecasting or categorization. These are all different types of data analysis. Data analysis is a step before data integration, and data integration and analysis are intertwined with data visualization and dissemination..

Data requirements.

The data is necessary as inputs to the analysis, which is specified based upon the requirements of those directing the analytics. The general type of entity upon which the data will be collected is referred to as an experimental unit. Specific variables regarding a population may be specified and obtained. Data may be numerical or categorical

Data cleaning

Once processed and organized, the data may be incomplete, contain duplicates, or contain errors. The need for data cleaning will arise from problems in the way that the datum are entered and stored. Data cleaning is the process of preventing and correcting these errors. Common tasks include record matching, identifying inaccuracy of data, and overall quality of existing data, deduplication, and column segmentation. Such data problems can also be identified through a variety of analytical techniques. For example; with financial information, the totals for particular variables may be compared against separately published numbers that are believed to be reliable. Unusual amounts, above or below predetermined thresholds, may also be reviewed. There are several types of data cleaning that are dependent upon the type of data in the set; this could be phone numbers, email addresses, employers, or other values. Quantitative data methods for outlier detection, can be used to get rid of data that appears to have a higher likelihood of being input incorrectly. Textual data spell checkers can be used to lessen the amount of mistyped words [13], [14].

Modeling and algorithms

Mathematical formulas or models, may be applied to the data in order to identify relationships among the variables; for example, using correlation or causation. In general

terms, models may be developed to evaluate a specific variable based on other variable contained within the dataset, with some residual error depending on the implemented model's accuracy. Inferential statistics includes utilizing techniques that measure the relationships between particular variables. For example, regression analysis may be used to model whether a change in advertising, provides an explanation for the variation in sales. In mathematical terms, Y is a function of X. It may be described as , where the model is designed such that and minimize the error when the model predicts Y for a given range of values of X. Analysts may also attempt to build models that are descriptive of the data, in an aim to simplify analysis and communicate results.

CONCLUSION

We used WebGestalt and Cytoscape for bioinformatics analysis to assess the impact of 17-estradiol on RANKL-induced osteoclast differentiation. Based on the WikiPathways database, enrichment analysis was carried out using WebGestalt: We found pathways confirmed to be involved in osteoclast differentiation, including pathways for TNF-/NF-B signaling, focal adhesion, estrogen signaling, apoptosis, MAPK cascade, senescence, autophagy, FAS, stress induction of heat shock protein regulation, and the osteoclast signaling. Of the 6403 proteins participating in 77 pathways, 2770 were mapped with high confidence. Additionally, we found pathways for Delta-Notch signaling, the urea cycle, and amino group metabolism that have not yet been confirmed to be related to osteoclasts. The differentially expressed proteins in the pathways identified by WebGestalt were then examined using Cytoscape in osteoclasts cultured with 17-estradiol and RANKL compared to osteoclasts cultured with only RANKL. When the proteins were mapped to WikiPathways, we saw that the expression of the proteins was changed along a number of routes. The markers of osteoclast differentiation, including TRAP, cathepsin K, and RANK, were clearly downregulated in cells grown with RANKL and 17-estradiol in the osteoclast signaling pathway. These results suggest that differentiation of osteoclasts was suppressed. H+-ATPase, on the other hand, was marginally elevated, which suggests increased bone resorption. In addition, we found that 17-estradiol reduced the activity of TNF receptor superfamily, member 11a, NF-B activator, which was a downstream target of Traf6. The Fas and apoptosis pathways were also examined, and we discovered that caspase-3, a protein that aids in apoptosis, was increased. In the well-known MAPK pathway, which is crucial for osteoclasts, CASP3 was similarly increased. Additionally, we examined the route involved in osteoclast polarization and discovered that RhoA was unmistakably increased. The fact that Jun was downregulated in practically all of the aforementioned pathways also caught us off guard. Our findings show that 17-estradiol modestly stimulates osteoclast bone resorption, but they also show that it promotes osteoclast death and inhibits osteoclast development and polarization.

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CHAPTER 10

RECENT DEVELOPMENTS IN WEARABLE FALL DETECTION SYSTEMS: A SURVEY

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Abstract

The average lifespan of a person has increased to over 80 years because to advancements in medicine and healthcare systems. As a result, by 2060, it is predicted that the demographic old-age dependence ratio the proportion of persons 65 and older to people in the 15–64 age range will rise from 28% to 50% in the European Union and from 33% to 45% in Asia. Therefore, it is anticipated that a greater proportion of people will require additional care. For instance, according to estimates by the National Program for Health Care of the Elderly, by 2025, 12% of India's population will be elderly, with 8% to 10% needing the highest level of care. Due to its impact on people's daily life, fall detection systems have received a lot of attention in the field of geriatric healthcare in recent years. A World Health Organization survey claims that as people age and become feebler, the likelihood of falling increases. Elderly residents in nursing homes have falls 40% more frequently than older residents of the community. Machine learning, particularly in FDSs, has found use in geriatric healthcare systems. In this essay, we look at typical FDS needs. Then, with a focus on the use of machine learning, we offer a summary of recent work in the field of fall detection systems. On the basis of the literature review, we also examine the difficulties with FDS systems.

Keywords

Detection, Health Care, Machine learning.

INTRODUCTION

Elderly assisted living systems powered by intelligent IoT have recently attracted a lot of academic attention. According to studies by the National Program for Health Care of the Elderly, by 2025, 12% of India's population would be elderly, with 8% to 10% needing the highest level of care. Therefore, the use of machine learning in AALS domains like fall detection has the potential to have a large social impact. In order to enable fall classification, detection, and prediction, a lot of work has been done on fall detection systems and the use of machine learning to such systems. We have been developing an FDS that uses a subject's biological profile to assign him to a risk category based on the likelihood that he will fall. We have outlined three categories: high danger, medium risk, and low risk. The classification thus created is then used with wearable sensor data and ML algorithms to identify falls. With an emphasis on the application of machine learning to wearable sensor-based techniques, the purpose of this paper is to present a thorough literature review of recent work in the domain of fall detection systems [1], [2].

The remainder of the essay is structured as follows. We start by looking at the ideal specifications for a wearable fall detection device. Finally, we give a brief review of FDSs based on wearable sensors, vision-based systems, and environmental sensors. Then, we delve a little deeper into the most recent developments in wearable technology-based FDS. We give a review of the literature on threshold-based methods and machine learning-based algorithms

for classifying and detecting falls in this article. We noticed that various articles looked at various ML algorithm performance parameters, and here we summarize the findings. Finally, research in the literature indicates that a subject's risk of falling is influenced by a variety of biological, physiological, and environmental factors. We report the findings of our investigation on the many biological variables that affect elderly people's risk of falling. The difficulties we found in the current fall detection solutions serve as the conclusion to our paper. Any technology that is intended to be utilized while being worn qualifies as wearable. Smartwatches and smartglasses are two popular examples of wearable technology. Wearable electronic devices are frequently placed next to or directly on the skin, where they can collect, process, and send data such as vital signs and/or environmental data and, in certain situations, provide the wearer with immediate biofeedback.

The Internet of Things, which enables objects to exchange data through the internet with a manufacturer, operator, and/or other connected devices without requiring human intervention, is exemplified by wearable devices like activity trackers. These "things" include electronics, software, sensors, and connectivity. Wearable technology has a wide range of potential applications, from communication and entertainment to enhancing fitness and health. However, because wearable devices have the potential to capture personal data, there are concerns about privacy and security. As the technology is improved and the market grows, there are more and more use cases for wearable technology. The most frequent form factors of wearables in consumer electronics include smartwatches, smart rings, and implants. In addition to commercial applications, wearable technology is being applied into healthcare, enhanced fabrics, and navigation systems. Like other technologies, wearable technology is examined for its dependability and security as it is recommended for use in important applications.German inventor Peter Henlein produced little watches that were worn as necklaces in the 1500s. Pocket watches gained popularity a century later as men's waistcoats gained in vogue. In the late 1600s, wristwatches were invented, but they were primarily worn as bracelets by ladies [3], [4].

1. The first wearable hearing aids were introduced in the late 1800s.
2. Pilot Alberto Santos-Dumont invented the wristwatch in 1904 and popularized its use today.
3. Calculator watches first became accessible in the 1970s, and their heyday was in the 1980s.
4. Wearable cameras have been employed as part of the expanding sousveillance trend from the early 2000s. Ilya Fridman hid a Bluetooth microphone into a pair of earrings in 2008.
5. Fitbit debuted its first step counter in 2010. The quantified self-movement includes wearable technology that monitors data like heart rate and walking.
6. 2013 saw the release of the first smart ring for consumers, manufactured by McLear.

The first extensively utilized cutting-edge wearable was introduced by McLear, also known as NFC Ring, in 2013. The smart ring might be used to send personally identifiable information, unlock other devices, accept bitcoin payments, and more. The initial patent, obtained by McLear in 2012 and covering all smart rings, was created by Joe Prencipe, a resident of Seattle, Washington. The Samsung Galaxy Gear was one of the first readily accessible smartwatches in 2013. The Apple Watch was released in 2015 by Apple.Rosalind Picard, Steve Mann, and Jennifer Healey were Rosalind Picard's students at the MIT Media Lab. They created "Smart Clothes" that continuously tracked the wearer's physiological data between 1991 and 1997. These "smart" clothing items, including "smart underwear," "smart shoes," and "smart jewelry," contained or controlled physiological sensors as well as ambient

sensors, including cameras and other gadgets. They also collected data relating to affective state.

At the same time, Thad Starner and Alex "Sandy" Pentland at the MIT Media Lab create augmented reality. Their smartglass prototype, which allows for quick web searches and instant chat, is featured on 60 Minutes in 1997. Although the prototype's glasses are almost as sleek as contemporary smartglasses, the processor was a computer worn as a backpack at the time, making it the lightest option. For a competition to design digital apparel in 2009, Sony Ericsson collaborated with the London College of Fashion. The winning cocktail dress uses Bluetooth technology to illuminate when a call comes in. During a "Fashion Hacking" session at a New York City creative collective, Zach "Hoeken" Smith of MakerBot fame created keyboard pants. A "remote non-intrusive patient monitoring" platform was created by the Tyndall National Institute in Ireland and used to assess the accuracy of the data produced by the patient sensors and the potential acceptability of the system among the end users. More recently, Katy Perry's costumes for stage performances and red carpet appearances, like the one she wore to the 2010 MET Gala in New York City, were designed by London-based fashion house CuteCircuit and featured LED lighting. Nicole Scherzinger, a singer, wore the first Tweet-featured dress ever made by CuteCircuit in 2012 [5], [6].

DISCUSSION

Fall Detection System Requirements

FDSs are designed to automatically detect falls and enable caregiver assistance when necessary. Because falls are more common and serious among the elderly, FDSs is most commonly used in geriatric care. It is crucial that falls are recognized in a nonintrusive manner since elderly people would use these systems. A wearable sensor that is cumbersome or inconvenient for the subject, for instance, could not be a common solution. The apparatus's power usage should be kept to a minimum because there's a chance the patient won't remember to recharge it. This demands that the system's sensors and network design be optimized for power usage. The subjects should be allowed to move about the region they choose without being constrained by an FDS. Wearable sensor-based systems give the subject more mobility than camera- or infrared-based systems, which may limit the subject to being in a certain region of interest. Multiple strategies, such as sweep coverage-based deployments, may be used by an IR- or camera-based system to enhance the coverage, although doing so would raise the system's cost.

The ability of an FDS to differentiate between falls and activities of daily living or near-fall situations is another crucial necessity. This will stop false positives from causing premature action to be taken and false negatives from leading to inadequate care being given. As a result, detection accuracy is a crucial consideration. It's also crucial to consider how triggers are produced after a fall is detected. Caregiver locations may be remote, hence an FDS should facilitate notifying remote personnel. The notice could be a brief note, similar to a message, or it could be a detailed report from the ROI, via photos taken by a camera. The former is simpler to put into practice, whereas the latter has the advantage of giving the observer a clear image of the impact before deciding on a course of action. Another element that should be taken into account while designing FDSs is latency. For the FDS to be effective, there should be as little time as possible between when falls are detected and when the caregiver is notified. This suggests that fall detection methods should be delay-sensitive. It also suggests that, in contrast to messages for keepalive or periodic reporting of sensor readings, the network design should offer excellent quality of service for data packets created as a result of fall detection.

In order to be able to anticipate falls before they happen, an FDS should additionally monitor a subject's biological characteristics and fall history. This would entail applying data analytics and machine learning approaches to the data gathered over time, as well as periodic reporting of the biological parameters by the sensor nodes [7]–[9].

Systems for detecting falls

Systems based on environmental sensing receive data from sensors positioned throughout the environment. Such systems include those that use passive infrared motion detectors and infrared sensors. By producing or detecting infrared radiation, measuring the heat being released by an object, or by detecting motion, infrared sensor-based devices recognize specific features of a ROI to detect a fall. Acoustic signals are used by microphone-based FDSs to identify the source of sound in a room and classify it as a fall or nonfall state. Based on the detection of motion inside a ROI, motion detector-based systems recognize falls. Taramasco et al.'s system uses very-low-resolution temperature sensors positioned on two horizontal planes along the floor to categorize falls as an example of an environmental sensing-based system. Three recurrent neural networks algorithms were compared: long short-term memory, gated recurrent unit, and bi-LSTM. Bi-LSTM had the highest accuracy. The developers of use the currently in place wireless infrastructure to detect falls. This was accomplished using the channel state information from WiFi deployments in the vicinity.

The CSI matrix was subjected to the Random Forest and Support Vector Machine algorithms for device-free fall detection. One individual at a time simulated falls during the experiments, which were carried out in controlled settings. This system has the benefit of being non-intrusive, which means it does not require its subjects to be carrying or wearing any monitoring equipment. Due to the impact of environmental factors like heat, the system may be prone to false positives. For instance, since the system relies on thermal sensors, the presence of other exothermic objects like heaters can affect how accurate it is. This study also shown that when numerous people are present in the experimented area, their combined movements affect the outcome's accuracy. Due to the short dataset utilized for training and testing in this study, false positive rates were also high, albeit being at acceptable levels. Using an RGB camera placed in a room and a low-cost mobile robot, Ciabattoni et al. present a system that generates a real-time video stream. Deep learning algorithms are used by the robot to detect users, estimate their positions to detect falls, take pictures and videos, and communicate with a Bot telegram. The stated fall detection accuracy was 93%.

Vision-based systems rely on image processing techniques on the video frames or photos taken by cameras around the ROI rather than performing any parameter monitoring of the subjects. To provide more precise fall detection, machine learning algorithms may be implemented atop image processing methods. Convolutional neural networks are trained on several optical flow image datasets in. This aids the network's ability to recognize various actions. The use of transfer learning from action recognition to fall detection follows. The experiment used three separate datasets, and it consistently produced results with accuracy levels above 95%. The method's vulnerability to errors brought on by changes in ambient lighting is one of its cited drawbacks. In their investigation of ML algorithms for fall detection using video sequences from various everyday activities and actual falls as input, Zerrouki et al. provide detailed comparison results. SVM outperformed Naive-Bayes, k-nearest neighbors, neural networks, and other algorithms in terms of accuracy, sensitivity, specificity, recall, F-measure, and area under the curve. In order to identify falls, Anishchenko uses deep learning and transfer learning techniques on data produced by security cameras under realistic situations. The goal was to go over the limitations of simulated datasets obtained in controlled settings [10], [11].

In order to determine whether a fall has occurred or not, Bhandari et al. analyze video frames in three steps: first, they identify interest points using the Shi-Tomasi algorithm, second, they determine the distance between interest points using the Lucas-Kanade algorithm, and third, they determine the speed and direction of motion. The technique is yet another instance of the use of unsupervised learning in the detection of falls. For nonfall activities, the reported accuracy is 95%, and for fall activities, it is 96.67%. A triaxial accelerometer and a Kinect camera were used to gather data for. During the training phase, the accelerometer data were classified as falls and nonfalls using the video input. On the data, time and frequency domain analysis utilizing lifting wavelet transform and SVM, respectively, was done. The SVM-based time domain analysis indicated 98.31% accuracy in detecting falls, compared to 100% for the frequency-based analysis. To identify falls and minimize false positives, Yanfei et al. process point cloud images and analyze feeds from a Kinect camera. Deep learning algorithms have recently been used to detect falls, and this field of study is now active. Utilizing video feeds from ambient data, Lu et al. apply CNN and LSTM to extract features. In addition to spatial information, the use of 3D CNN enables the extraction of motion properties from temporal sequences, and the regions of interest are located using an LSTM-based visual attention mechanism. The authors point out that this strategy excels while analyzing short datasets, but it will increase the system's computational expenses when analyzing lengthy motion sequences. While vision-based systems accurately depict abnormal circumstances to a remote caregiver via photos or video feeds, they frequently cost more, demand more computer power, take longer to process, and are a subtle invasion of the individuals' privacy [12], [13].

The sensors for fall detection in wearable device-based FDSs are built into a wearable item that the subject is wearing, like a wrist band. Heart rate variability, electrocardiogram, pulse oximetry, and kinematic properties measured by accelerometers, gyroscopes, and magnetometers are among the metrics tracked by such devices. In order to categorize and identify falls, wearable sensor data is provided as inputs to a threshold-based system or as feature sets to a machine learning-based system. Wearable sensor-based systems are less expensive, have minimal power consumption, which lowers the overheard when charging the system, and are typically in the shape of a band that can be worn around the wrist or thigh, which makes it less likely that the subjects will become separated from the system. Four wearable wristband-style gadgets that are currently on the market are summarized and compared by Kaewkannate and Kim in terms of their functionality and price. The configuration of the wearable gadget, the kind of sensors it uses, and the communication technology it employs all affect how much power it uses. Oletic and Bilas provide an analysis of the total power consumptions for various operation scenarios for specific wearable device designs. There are also methods where the sensors are integrated into smartphones or worn on other regions of the body instead of the wrist. Smartphone-based solutions require the user to take their device with them and charge it whenever necessary in order to detect falls, which is not a good requirement for geriatric healthcare systems. In several articles, an IoT-based end-to-end fall detection system is proposed. provides a case study of such a system in an indoor setting. Smart gadgets, big data, cloud computing, and low-power wireless sensor networks are all used in this concept. A 6LowPAN wearable with a 3D-axis accelerometer gathers movement data and uses decision tree algorithms to detect falls.

CONCLUSION

Geriatric healthcare has become increasingly important as a result of medical advancements and alterations in population demography. The use of technology in the healthcare industry has increased significantly in recent years. Applications of machine learning in elderly

healthcare include fall detection, sleep pattern analysis, vitals monitoring, and behavioral investigations. The main goal of these applications is to identify and/or anticipate anomalies. Based on a subject's activity patterns, machine learning in fall detection aids in intelligently identifying falls. While it might be simple for a fall detection system to sound an alarm whenever a change in activity pattern is noticed, doing so would lead to an excessive number of false alarms being set off. If the fall detection system is built to raise alarms cautiously, it might not raise alarms when actual falls take place. Therefore, it is crucial that false positives and false negatives in a fall detection system are reduced, and machine learning algorithms' ability to learn on its own plays a key part in this. The specificity, sensitivity, and recall of machine learning algorithms are additional performance metrics. The aim of this research is to enhance the performance characteristics of the algorithms when used for fall detection. Fall detection algorithms operate on datasets produced by cameras, ambient sensors, or wearable sensors..

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CHAPTER 11

RECENT DEVELOPMENTS IN HERPETIFORM DERMATITIS

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Abstract

An autoimmune bullous illness called dermatitis herpetiformis is linked to gluten intolerance, which commonly manifests as celiac disease. It is unclear how distinct pathogenetic processes may result in the dysregulation of immune responses in the skin and small bowel, respectively, as both illnesses are multifactorial disorders. Recent research has shown that epidermal transglutaminase 3 and IgA antibodies are crucial in the etiology of dermatitis herpetiformis. Here, we examine current immunopathological developments in dermatitis herpetiformis etiology. A chronic autoimmune skin disorder known as dermatitis herpetiformis is characterized by extremely irritating blisters filled with a watery fluid. Coeliac disease has a cutaneous symptom called DH, but the actual cause is unknown. The name of the condition, DH, refers to a skin irritation that resembles herpes in appearance, however it is not related to nor caused by the herpes virus. The average age of onset for DH is between 15 and 40, however it can also afflict young children and the elderly. Compared to women, men are slightly more affected. DH prevalence estimates range from 1 in 400 to 1 in 10,000. Patients with northern European and northern Indian ancestry are more likely to experience it, and celiac disease and gluten sensitivity are also linked to the human leukocyte antigen haplotypes HLA-DQ2 or HLA-DQ8.

Keywords

Antigen, Autoimmune, Dermatitis, Virus.

INTRODUCTION

Dermatitis herpetiformis is an autoimmune papulovesicular rash that commonly affects the scalp, buttocks, buttocks, elbows, and forearms. The histology, immunological, and presence of gastrointestinal disease identify the condition distinctly from other sub-epidermal blistering disorders. Subepidermal blisters with mostly neutrophil infiltrates at the tip of the papillary dermis are characteristic of the histopathological findings of the lesional skin of individuals with DH. Granular IgA deposition is seen by direct immunofluorescence in the papillary dermis. Celiac disease, a prevalent chronic small intestine disease, is the most common form in which gluten sensitivity manifests. Despite the fact that DH and CD are significantly correlated, the gastroenterological symptoms in DH are typically moderate or clinically nonexistent. However, even in the absence of clinical signs, inflammatory small intestinal alterations can frequently be detected by histological testing. The IgA class of autoantibodies is linked to both diseases. It has been demonstrated that there is a strong correlation between DH and HLA-DQ2 and HLA-DQ8. DH is linked to a number of illnesses, such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren syndrome, and thyroid disorders [1], [2].

Recent studies revealed that patients with DH who did not maintain a gluten-free diet had a larger risk for getting lymphoma, since individuals with DH have been shown to have an elevated risk of intestinal lymphoma. However, numerous investigations have been unable to show that patients with DH have a higher frequency of malignant neoplasms. Treatment with

dapsone is the usual therapy for DH. Here, we emphasize the most recent immunopathological discoveries related to the DH pathogenesis. Chronic papulovesicular eruptions that are extremely irritating and symmetrically distributed across extensor surfaces are the hallmark of dermatitis herpetiformis.616 The blisters range in size from extremely tiny to 1 cm in diameter. The disease is highly itchy, and you could feel like you need to itch all the time. Sometimes, in order to avoid having their blisters inspected by a doctor, the affected individual would scratch them off. Sometimes, before blisters develop in a specific place, there is intense itchiness or burning.

Although all ages may be affected, the signs and symptoms of DH often occur between the ages of 30 and 40. The smallest papules or vesicles, which typically resemble red bumps or blisters, are the first apparent indicators of dermatitis herpetiformis, despite the fact that the condition's initial signs and symptoms also include acute itching and burning. Except for the mouth and lips, the rash rarely affects other mucous membranes. The symptoms can range from moderate to severe, but if gluten consumption is prevented and the right treatment is given, they will probably go away. The amount of gluten consumed affects the recurrence of the chronic, cyclical symptoms of dermatitis herpetiformis, which are often experienced in brief intervals. These symptoms can occasionally coexist with celiac disease symptoms, which often include exhaustion, weight loss, bloating or loose stools, and abdominal pain. Even though there is related intestinal damage, people with DH frequently don't experience any gastrointestinal symptoms [3], [4].

Dermatitis herpetiformis produces a rash that develops and goes away in three stages. The patient can observe a slight skin darkening at the location of the lesions in the initial stage. The skin lesions progress to the next stage, where they become clear vesicles and papules that frequently appear in clusters. The final phase of symptom development—which is typically accompanied by a change in skin color—is the healing of the lesions. As a result, certain parts of the skin may change in color, becoming darker or lighter than the skin on the rest of the body. Patients typically scratch because to the acute itching, which might result in crusts.The initial pathological manifestations of the illness can be seen in the dermis. At this stage, edema, vascular dilatation, and cellular infiltration are possible modifications. Eosinophils and lymphocytes are frequently observed. The subepidermal bullae that are present in dermatitis herpetiformis-affected skin have rounded lateral margins.

The dermatitis herpetiformis-affected skin exhibits a collection of neutrophils when examined under a microscope. They are more common if the dermis and epidermis are in close proximity. Direct IMF examinations of unaffected skin reveal granular IgA in patches throughout the basement membrane and dermal papillae. Although there may be some partial villous atrophy in the jejunal mucosa, these changes are often less severe than in celiac disease. In terms of autoantigens, immunological investigations produced results that were comparable to those of celiac disease. Epidermal transglutaminase , a cytosolic enzyme involved in cell envelope construction during keratinocyte differentiation, is the primary autoantigen of dermatitis herpetiformis.

Numerous studies have identified various potential elements that might be more or less important in the dermatitis herpetiformis growth process. The discovery of eTG in skin-bound IgA precipitates from skin with this condition has led researchers to the hypothesis that dermatitis herpetiformis may be brought on by the deposition of both IgA and eTG within the dermis. These deposits may disappear after ten years of adhering to a gluten-free diet, according to estimates. Additionally, it has been proposed that this illness has a strong hereditary component. This idea is based on the claims that people who continue to consume foods containing gluten and have a family history of gluten sensitivity are more likely to

develop the condition as a result of the development of antibodies to gluten. These antibodies interact with eTG, and the resultant IgA/eTG complexes accumulate in the papillary dermis to produce the dermatitis herpetiformis lesions. After long-term abstinence of dietary gluten, these IgA deposits may go away [5]–[7].

Gluten contains gliadin proteins, which are absorbed by the gut and go into the lamina propria where tissue transglutaminase must deamidate them. Gliadin is changed by tTG to produce a more immunogenic peptide. The immunogenic peptide is endocytosed by classical dendritic cells, and if their pattern recognition receptors are activated by pathogen-associated molecular patterns or danger-associated molecular patterns , the danger signal will cause them to secrete IL-8 in the lamina propria, luring neutrophils. A very quick onset of inflammation follows the recruitment of neutrophils. Because memory B and memory T cells are produced in response to subsequent exposures to gluten, co-infection with microorganisms that carry PAMPs may not be necessary for the development of symptoms in gluten sensitivity.

Inflammation of the skin and intestines may be used to define dermatitis herpetiformis. Similar to and related to celiac disease is intestinal inflammation. Particularly in patients with specific HLA-DQ2 and HLA-DQ8 alleles and other atopy-causing gene variations, tTG is treated as an autoantigen. After the body has absorbed gluten, tTG is increased. Gliadin is only presented to CD4+ T cells on pMHC-II complexes by cDCs, who may also endocytose modified gliadin on its own or in complexes with tTG. These T cells become polarized into type I helper T cells after becoming activated. There are Th1 cells that are reactive to gliadin, but none that are reactive to tTG. Before they are endocytosed by cDCs in lymph nodes, tTG-modified gliadin complexes are removed off the surface of those cells by naive B cells. The B cell receptor, also known as the membrane-bound antibody or BCR, is unique to the complex's tTG region. In a procedure known as epitope spreading, the B cell endocytozes the complex and presents the changed gliadin to the TCR of the activated Th1 cell via pMHC-II. As a result, the B cell displays the foreign peptide while creating antibodies that are particular to the self-antigen. Once triggered, the B cell transforms into plasma cells that generate autoantibodies against tTG, which may also react with epidermal transglutanimase . IgA class antibodies accumulate in the intestines. Some might utilize their Fc region to attach to the CD89 receptor on macrophages. This will cause the tTG-IgA complex to endocytose, which will activate macrophages. More IL-8 is secreted by macrophages, which spreads the neutrophil-mediated inflammatory response.

DISCUSSION

IgA-Associated Pathogenesis in DH in Vivo

The immunopathological characteristic of DH is the accumulation of IgA in the papillary dermis. First, it was discovered that patients with DH have granular IgA deposition in the papillary dermis in both the perilesional and unaffected skin. Following the patient's adherence to a gluten-free diet, these IgA deposits either lessened in size or eliminated. Early research suggested that IgA was linked to bundles of microfibrils and anchoring fibrils beneath the basal lamina, but later research indicated that practically all IgA deposits were linked to nonfibrillar skin and other connective tissue components. Neutrophil infiltration into the papillary dermis and the development of basement membrane zone vesicles in the lamina lucida are both thought to be significantly influenced by IgA. It has been demonstrated that the epidermal IgA deposits in DH act in vitro as a ligand for neutrophil migration and adhesion. It has not yet been conclusively determined which specific IgA antibody causes granular deposition in the papillary dermis.

Tissue transglutaminase was recognized by Dieterich et al. as the autoantigen contributing to CD. Additionally, they demonstrated that patients with DH could be distinguished from those who had linear IgA bullous dermatosis by circulating autoantibodies to tTG . The clinical pattern exhibited in DH patients is frequently closely resembled by linear IgA bullous dermatosis . However, linear IgA bullous dermatosis can be distinguished from DH by the DIF observations of linear IgA deposits at the basement membrane. Patients with active CD have circulating anti-tTG and anti-gliadin IgA and/or IgG antibodies. The TG family, which includes nine unique proteins expressed in numerous cell types in humans, includes tTG. Members of the TG family exhibit conservation, particularly in a few domains with enzymatic relevance. Surprisingly, Sárdy et al. observed that sera from patients with DH had a higher affinity for TG3, but sera from patients with GSD interacted with both tTG and epidermal transglutaminase 3. Additionally, they showed that IgA deposition and TG3 colocalization were present in DH patients' papillary dermis [8]–[10].

Additionally, they demonstrated that tTG was not present in the TG3 and IgA complexes at the papillary dermis. So they suggested that TG3 might be the major autoantigen in DH rather than tTG. Regarding their enzymatically active domains, TG3 and tTG are similar. The cross-linking and preservation of the integrity of the cornified envelop are two tasks performed by TG3 in the epidermis. In normal skin, tTG is found in the basal layer keratinocytes, whereas TG3 is restricted to the top layer keratinocytes. In contrast, TG3 is present in the papillary dermis of DH skin and overlaps with the same IgA deposition locations. According to a theory put out by researchers, TG3 may be secreted from keratinocytes and bound in the papillary dermis by circulating IgA antibodies. Another possibility is that already-formed IgA and TG3 circulating complexes may be deposited in the papillary dermis. These circulating complexes were really discovered in the vessel walls of DH patients. The precise process by which IgA anti-TG3 deposits are localized in DH skin is unknown, though.

Patients with DH contain TG3 in the papillary dermis that overlaps with IgA deposits, according to Donaldson et al. They also discovered TG3 deposits in unaffected skin that was at least 5 cm away from the lesions. Additionally, IgA deposits were observed in every skin sample where TG3 was discovered, indicating that autoantibodies are the mechanism of TG3's deposition. Without IgA, TG3 was not detected in the dermis. IgA by DIF staining intensity and TG3 staining intensity were roughly associated. These results imply that other elements are required for the development of DH skin lesions in addition to these complexes.

IgA deposits that are granular or fibrillar in DH patients' skin

Although DH is most prevalent in Europe and the United States, it is extremely uncommon in Asians, especially Japan, and African Americans, possibly due to variations in the frequency of HLA antigens associated with DH. Although granular IgA deposits in the papillary dermis are frequently thought to be harmful for DH, the incidence of fibrillar patterns of IgA deposits in the papillary dermis of patients with DH has been documented. It's interesting to note that those patients appear to experience GSDs less frequently. Granular IgA deposits were present in the papillary dermis in 95.5% of Chinese patients with DH, but fibrillar IgA deposits were only present in one patient. Three DH patients were also documented in a recent study with fibrillar IgA deposition patterns in the papillary dermis, and two of the three patients lacked anti-TG and antiendomysial antibodies. It has been suggested that individuals with a fibrillar pattern of IgA deposits may exhibit more atypical symptoms than average, such as urticarial or psoriasiform skin lesions, the absence of GSD, or an HLA-B8/DR3/DQ2 haplotype, even though they frequently have other clinical findings that are consistent with DH . It is unclear if the decreased occurrence of GSD in patients with DH may be linked to this variation in IgA deposition.

DH-Specific Immunological Diagnostic Markers

First, Chorzelski et al. reported that IgA antibodies attach to the endomysium of smooth muscle, an intermyofibril material, in the skin of DH patients. Interestingly, Sárdy et al. demonstrated that these IgA antibodies have a specificity for TG, in particular epidermal-specific TGs, which were also detected in the sera of patients with DH and CD. IgA antibodies specific for TG3 and IgA antibodies that respond with both TG3 and tTG are both present in DH patients, as is now widely accepted. In a sizable cohort of DH patients, a recent study found that IgA anti-TG3 is more sensitive than any other marker linked with GSD in diagnosing DH. Serologic indicators for both DH and CD are serum IgA endomysial antibodies, which can be found by indirect immunofluorescence. Each muscle fiber is protected by a thin coating of connective tissue called an endomysium. Additionally, IgA anti-tTG, a significant endomysial antigen detectable by ELISA, shows a high degree of specificity and sensitivity in DH patients. The degree of small intestinal disease in CD correlates with anti-tTG and anti-TG3 IgA levels. Additionally, patients with DH and CD who strictly avoid gluten have low levels of anti-endomysial, anti-tTG, and anti-TG3 antibodies [10], [11].

Additionally, nearly 70% of CD and DH patients have positive blood IgA antibodies against gliadin. It has not been suggested that tTG or gliadin IgA antibodies may play a part in the pathophysiology of DH, though. No case of selective IgA deficiency in DH has been documented, despite the fact that selective IgA deficiency is around 10 to 15 times more common in individuals with CD. However, there have been reports of partial IgA insufficiency in DH, suggesting that pathogenically directed IgA antibodies were probably enough to cause cutaneous IgA depositions in DH . According to a recent study, intestinal injury may be linked to DH patients' production of IgA anti-tTG and IgA anti-TG3 antibodies. High levels of IgA anti-tTG and IgG anti-tTG antibodies have been linked to a more severe clinical manifestation of CD, according to research by Dahlbom et al. However, there is currently no information available on a potential association between any particular serological marker and the clinical severity of DH.

The Role of Neutrophils in DH Pathogenesis

Neutrophil infiltration and IgA deposition in the papillary dermis are characteristics of the skin lesions in DH patients. Circulating neutrophils in DH patients exhibit a high level of CD11b when DH activity is high. Additionally, neutrophils in skin lesions of DH patients displayed elevated CD11b expression, modestly decreased L-selectin expression, and elevated FcIgA receptor function, all of which suggest partial priming of the neutrophils. A chemokine called IL-8 is crucial for neutrophil inflammatory responses, upregulating CD11b expression on neutrophils and shedding L-selectin, which are required for strong adherence to endothelial cells and migration into tissue. Serum IL-8 levels in DH patients have been previously demonstrated to be elevated, and IL-8 levels are likewise elevated in patients who consume gluten. According to a recent study, the small bowel produces IL-8 as an immunological response to gluten consumption in the sera of DH patients.

DH Animal Models

The pathophysiology of gluten sensitivity has been better understood using animal models. A mouse model for DH was created by Marietta et al. They described a non-obese diabetic HLA-DQ8 transgenic mouse that, after receiving a gluten vaccination, develops neutrophilic skin lesions and cutaneous IgA deposition. Additionally, the skin lesions disappear after the following elimination of dietary gluten. Another fantastic DH model was just reported. Zone et al. inoculated recipient immunodeficient mice with human skin grafts with a goat anti-

human TG3 antibody. These animals had papillary dermal immune deposits, and both rabbit anti-TG3 and DH sera responded with these immune deposits. The papillary dermis of the human skin graft displayed granular deposition of the transferred IgG. A small amount of neutrophil infiltration did exist, though. If the sera have a high amount of anti-TG3 IgA, the transfer of sera from DH patients also led to deposits in the papillary dermis. Sera with the lowest levels of neutrophil infiltration at the basement membrane also had the highest amounts of anti-TG3 IgA. They were able to show that the passive transfer of an anti-TG3 antibody, as well as goat IgG and sera from DH patients, resulted in granular deposits in the papillary dermis [12].

CONCLUSION

Medication and a strict gluten-free diet work well to treat dermatitis herpetiformis in most cases. Due to the fact that DH is an autoimmune disorder, people who have it are also more susceptible to develop other autoimmune diseases such lupus erythematosus, diabetes mellitus, sarcoidosis, vitiligo, and alopecia areata. There has been a link between dermatitis herpetiformis and non-Hodgkin lymphoma, albeit a strict gluten-free diet reduces this risk to less than the population risk. Usually, dermatitis herpetiformis problems don't occur on their own, without being linked to another disorder. However, this condition's autoimmune nature makes it more likely to produce complications, as an overactive immune system is an indication that something is not functioning properly and may affect organs other than the digestive system. Concerns about potential consequences are increased by gluten intolerance and the body's response to it. This means that the consequences that could result from dermatitis herpetiformis are the same as those that could result from celiac disease, which include an increased risk of other autoimmune disorders like thyroid disease, osteoporosis, and some types of gut cancer.

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CHAPTER 12

THE MODIFICATION OF PROTEIN-PROTEIN INTERACTIONS IN AN ARCHAEAL LIGHT-SIGNAL TRANSDUCTION

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Abstract

In Natronomonas pharaonis, brief interactions between the photoreceptor and the transducer cause negative phototaxis to begin. The relationship between pharaonis phoborhodopsin and the cognate transducer protein, pHtrII, is somehow changed during the photocycle of ppR. Using low-temperature Fourier-transform infrared spectroscopy, we have investigated the signal transduction mechanism in the ppR/pHtrII system. In the study, vibrational bands were found by using isotope-labeling and site-directed mutagenesis, and spectral comparison in the presence and absence of pHtrII offered useful information in atomic details. These investigations allowed us to identify two routes by which light signals are converted from the receptor to the transducer: the retinal Lys205 of the ppR travels through Thr204 and Tyr199 to reach Asn74 of pHtrII, and the cytoplasmic loop area of pHtrII that connects Gly83 to Lys205 of the ppR. PPIs, or protein-protein interactions, are highly specialized physical contacts made between two or more protein molecules as a result of biochemical processes influenced by interactions such as electrostatic forces, hydrogen bonds, and the hydrophobic effect. In a cell or in a live creature, there are numerous physical connections with molecular associations between chains that take place in a particular biomolecular context. Since their actions are often controlled, proteins seldom ever act alone. Molecular machines that are composed of multiple protein components arranged by their PPIs carry out many molecular operations in a cell. The so-called interactomics of the organism is made up of these physiological interactions, and abnormal PPIs are the root cause of many aggregation-related disorders, including Creutzfeldt-Jakob and Alzheimer's diseases.

Keywords

Infrared, Organism, Protein, Spectroscopy.

INTRODUCTION

Protein-protein interaction and its fleeting alterations are the foundation of biological signal transduction. In some instances, a signal input causes two proteins that do not normally interact to form a brief protein-protein complex. Another scenario involves a complex formed by two proteins that changes in strength in response to a signal. It is difficult to experimentally capture these transitory changes since they are typically faint and unstable. What transient protein-protein complex should be studied next? Because the signal input is a light absorber of the photoreceptor, light-signal transduction, such as our eyesight and bacterial phototaxis, is very suitable to research transitory protein-protein interaction alterations. Light illumination is an excellent stimulus since it never disturbs the system and lasts for only a few femtoseconds. Thus, alterations in protein-protein interactions between their transducer proteins and the visual and archaeal rhodopsins have been examined. A retinal molecule is attached to a protein through a protonated Schiff base linkage acting as a

chromophore, and both ocular and archaeal rhodopsins contain a 7-transmembrane helical topology. Retinal photoisomerization causes structural changes in proteins that are used in the transmission of light signals. When light is activated in visual rhodopsin, the transducer, a hetero-trimeric G protein, forms a brief protein-protein complex without interfering with either other. It is thought that the mechanism of the transducer activation for the rhodopsin/G-protein system is shared by other G-protein coupled receptors and G-proteins. Light-induced protein-protein interaction is a crucial stage in our eyesight. In contrast, when exposed to darkness, archaeal rhodopsins establish a stable complex with their transducer protein in the membrane, and this protein-protein complex is temporarily altered by exposure to light [1], [2].

Which approach is then appropriate for examining brief changes in protein-protein interactions in rhodopsins? For this work, we employed Fourier-transform infrared spectroscopy. The atomic locations of proteins cannot be determined using vibrational spectroscopy, in contrast to X-ray crystallography and NMR. Analysis of the vibrational signals is made more challenging by the large protein and solvent water molecule absorptions that occur in the infrared frequency band. In contrast, because of structural changes brought on by stimuli, stimulus-induced difference FTIR spectroscopy can extract vibrational signals. In particular, light is the optimal stimulus due to its great temporal resolution and lack of system perturbation. Rhodopsin studies, which tracks intramolecular activities in rhodopsins, has widely used light-induced difference FTIR spectroscopy. We also applied similar technique to the protein-protein interaction between the transducer and visual rhodopsin, where we published the first study on both archaeal and visual rhodopsin in 2003 and 1997, respectively.

It is important to emphasize that FTIR spectroscopy is a potent tool for keeping track of hydrogen-bonding interactions, which are essential in protein-protein complexes. By observing O-H and N-H stretching vibrations in the 4000-2000 range of the different FTIR spectra of rhodopsins , we have demonstrated this fact. One of the study's highlights is the detection of water stretching vibrations, and we recently discovered that rhodopsins need tightly hydrogen-bonded water molecules in order to have proton-pumping function. We present a summary of our FTIR research on the protein-protein complex in an archaea in this paper. Natronomonas pharaonis has a photoreceptor for negative phototaxis called pharaonis phoborhodopsin . Upon light absorption, pHtrII, the corresponding transducer protein, is activated by ppR. In the unphotolyzed state, ppR and pHtrII form a close 2: 2 complex, but the interaction changes in some way when ppR goes through its photocycle. Using low-temperature FTIR spectroscopy, we previously discovered structural alterations in ppR itself in 2001.

Unlike visual rhodopsins, ppR forms a stable complex with pHtrII in the membrane, allowing for the measurement of the same light-induced spectrum shifts in the ppR/pHtrII complex as for ppR. As a result, in 2003, we used FTIR spectroscopy to study the ppR/pHtrII complex for the first time. Since then, we have published a total of four studies. In order to inform what was known about the signal-transduction mechanism of the ppR/pHtrII complex system, this publication summarized these earlier investigations. The FTIR spectra of the major K-intermediate for the ppR/pHtrII complex were published in two articles in 2003, and are shown in chapter 3. The FTIR spectra of the M-intermediate, the active state in signal transduction, for the ppR/pHtrII complex are then shown in the following two chapters. The vibrational bands in the various FTIR spectra were identified in the research using isotope-labeling and site-directed mutagenesis. As a result, we were able to identify the signal-relay pathway that connects the retinal chromophore to the transducer protein's cytoplasm. The

crucial significance of an amino acid in function was discovered, which was completely unanticipated, and is now integrated with the structural information. PPIs have been investigated using a variety of techniques and viewpoints, including biochemistry, quantum chemistry, molecular dynamics, and signal transduction. With the help of all this knowledge, large protein interaction networks can be created, which are akin to metabolic or genetic/epigenetic networks and advance our understanding of disease molecular etiology, biochemical cascades, and potential protein targets for therapeutic intervention.A protein that serves as an electron carrier binds to an enzyme that serves as its reductase in numerous metabolic reactions. It dissociates after receiving an electron and then binds to the following enzyme, which serves as its oxidase. In order to maintain effective electron transfer, these interactions between proteins are dependent on extremely precise binding between proteins. Examples include the elements of the mitochondrial oxidative phosphorylation chain system. Microsomal and mitochondrial P450 systems; cytochrome c-reductase/cytochrome c/cytochrome c oxidase [3], [4].

Two basic Arg residues on the surface of the reductase and two acidic Asp residues on the adrenodoxin were shown to be crucial in the binding of the electron transfer protein adrenodoxin to its reductase in the case of the mitochondrial P450 systems. These residues involved in protein-protein interactions have been conserved throughout the evolution of this enzyme, according to more current research on the phylogeny of the reductase. Signals from outside the cell control how active it is. PPIs between the various signaling molecules are necessary for signal propagation within and/or along the interior of cells. Signal transduction, which is the recruitment of signaling pathways through PPIs, is crucial to many biological processes and many disorders, such as Parkinson's disease and cancer.

DISCUSSION

Complex of proteins between ppR and pHtrII

A collection of two or more connected polypeptide chains is referred to as a protein complex or multiprotein complex. In contrast to multidomain enzymes, which include numerous catalytic domains inside a single polypeptide chain, protein complexes are not multidomain enzymes. Quaternary structure is a type of protein complex. Non-covalent protein-protein interactions bind the proteins together in a protein complex. These complexes are the basis of the majority, if not all, biological processes. It is believed that the cell is made up of modular supramolecular complexes, each of which carries out a unique, distinct biological role. Higher cellular efficiency can result from proximity, which greatly increases the speed and selectivity of binding interactions between enzyme complexes and substrates. The process of identifying a complex's constituent parts is made more difficult by the fact that many of the methods used to penetrate cells and isolate proteins are inherently disruptive to such massive complexes.

The proteasome, which breaks down molecules, and the majority of RNA polymerases are two examples of protein complexes. Large hydrophobic interfaces between proteins usually bury surface regions larger than 2500 square s in stable complexes. In vivo, transitory protein complexes form and disintegrate momentarily, whereas permanent complexes have a lengthy half-life. While non-obligatory interactions have been discovered to be either permanent or transient, obligate interactions—protein-protein interactions in an obligate complex—typically last forever. It should be noted that there is no clear line between obligatory and non-obligate contact; instead, there is a continuum between the two that depends on a variety of factors, such as pH, protein concentration, etc. The characteristics of transitory and permanent/stable interactions, however, differ significantly. Stable interactions are highly

conserved, whereas transient interactions are much less so. Additionally, transient interactions are much less co-localized than stable interactions, and the interacting proteins on the two sides of a stable interaction have a higher tendency to be co-expressed than those of a transient interaction. Despite being fleeting by nature, transient interactions are crucial for understanding how cells function. The human interactome is enriched in these interactions, and proteins with intrinsically disordered regions regions in proteins that exhibit dynamic inter-converting structures in their native state have been found to be particularly rich in transient regulatory and signaling interactions.

Conversion of Light Signals in the K-Intermediate

The second level of the Chartered Accountancy programme in India is the CA Intermediate exam. In the nine months given for study, a student is expected to finish eight subjects and more than 7000 pages of readings. The group structure, which consists of four subjects in each group and requires passing all four tests in order to pass the group, is what makes this exam even more challenging. The student would fail in the subjects in which he has passed because failing one topic would result in the group failing as a whole right away. It should be noted that the average passing rate from 2010 to 2020 was only 16.76%, meaning that only 4 out of every 25 candidates passed the test. In spite of this, just 8.88% of candidates who attempted the November 2018 Chartered Accountancy Course in India passed.It is possible to split apart or create a modulated sinusoid from two amplitude-modulated sinusoids that are 90 degrees apart in phase. The same center frequency is shared by all three sinusoids. The terms "in-phase" and "quadrature" refer to the relationships between the two amplitude-modulated sinusoids and the amplitude- and phase-modulated carrier, respectively [5]–[7].

In other words, by combining two sine waves that are 90° out of phase in various ratios, it is possible to produce a sine wave that has been phase-shifted arbitrarily. The implication is that some signals' modulations can be handled independently of the signal's carrier wave. In numerous radio and signal processing applications, this is widely used. Independent of the carrier's frequency, I/Q data is used to represent the modulations of a particular carrier. The term "alternating current" refers to a sinusoidal voltage vs. time function with a frequency of f. It produces a sinusoidal current when applied to a conventional circuit or device. Any two sinusoids have a constant phase difference, in general. Typically, the input sinusoidal voltage is designated as having zero phase, which means that it was picked at random to serve as a handy time reference. The present function, such as sin, whose orthogonal components are sin cos and sin sin, as we have shown, is therefore responsible for the phase difference. The current and voltage sinusoids are said to be in quadrature, which implies they are orthogonal to one another, when occurs to be such that the in-phase component is zero. No typical electrical power is used in that scenario. It's important to keep in mind that the phrase "in quadrature" just suggests that two sinusoids are orthogonal, not that they are parts of another sinusoid.

Conversion of Light Signals in the Early M-Stat

An analog-to-digital converter in electronics is a device that transforms an analog signal into a digital signal, such as sound captured by a microphone or light entering a digital camera. An electrical device that transforms an analog input voltage or current into a digital number reflecting the magnitude of the voltage or current is an example of an ADC that can offer an isolated measurement. Although there are alternative options, the typical digital output is a two's complement binary value that is proportionate to the input. ADC architectures come in different forms. All but the most specialized ADCs are constructed as integrated circuits due to the complexity and requirement for perfectly matched components. These typically take

the form of metal–oxide–semiconductor mixed-signal integrated circuit chips that integrate both analog and digital circuits. The opposite process is carried out by a digital-to-analog converter , which transforms a digital signal into an analog signal.An ADC transforms an analog signal from continuous time and continuous amplitude to discrete time and discrete amplitude. The conversion involves quantization of the input, so it necessarily introduces a small amount of quantization error. Furthermore, instead of continuously performing the conversion, an ADC does the conversion periodically, sampling the input, and limiting the allowable bandwidth of the input signal.

The performance of an ADC is primarily characterized by its bandwidth and signal-to-noise ratio. The bandwidth of an ADC is characterized primarily by its sampling rate. The SNR of an ADC is influenced by many factors, including the resolution, linearity and accuracy, aliasing and jitter. The SNR of an ADC is often summarized in terms of its effective number of bits, the number of bits of each measure it returns that are on average not noise. An ideal ADC has an ENOB equal to its resolution. ADCs are chosen to match the bandwidth and required SNR of the signal to be digitized. If an ADC operates at a sampling rate greater than twice the bandwidth of the signal, then per the Nyquist–Shannon sampling theorem, near-perfect reconstruction is possible. The presence of quantization error limits the SNR of even an ideal ADC. However, if the SNR of the ADC exceeds that of the input signal, then the effects of quantization error may be neglected, resulting in an essentially perfect digital representation of the bandlimited analog input signal [8]–[10].

Resolution

The number of distinct, or discrete, values that the converter is capable of producing over the permitted range of analog input values is known as resolution. The greatest signal-to-noise ratio for an ideal ADC without the use of oversampling is thus determined by a certain resolution, which also dictates the size of the quantization error. The resolution is typically represented as the audio bit depth since the input samples are typically recorded electronically in binary form within the ADC. As a result, there are typically a power of two possible discrete values. An analog input can be encoded to one of 256 distinct levels, for instance, using an ADC with a resolution of 8 bits. Depending on the application, the values can represent the ranges from 0 to 255 or from 128 to 127. In terms of electricity, resolution can also be defined and expressed in volts. The least significant bit voltage is the change in voltage necessary to ensure a change in the output code level. The LSB voltage is the same as the ADC's resolution Q. An ADC's voltage resolution is determined by dividing its total voltage measurement range by the number of intervals..

CONCLUSION

Low-temperature the conversion of light signals from ppR to pHtrII, both of which form a complex in the unphotolyzed state, was demonstrated by Fourier-transform infrared spectroscopy. Only when pHtrII is present does retinal isomerization increase the O-H group of Thr204's hydrogen bond in ppR. The M intermediate recovers this structural disturbance, although pHtrII's Asn74 hydrogen bond is changed. The activation mechanism, which is hampered by the mutation of Gly83 in pHtrII, appears to involve numerous M states based on the temperature dependency of the amide-I vibration in ppR. This implies that the cytoplasmic domain's dynamic mobility is significant for protein-protein interactions. We identified two paths for converting light signals from the receptor to the transducer: one goes from Lys205 of ppR to Asn74 of pHtrII via Thr204 and Tyr199, and the other goes from Lys205 of ppR to the pHtrII cytoplasmic loop region that connects Gly83 . It should be noted that Bergo et al. had published time-resolved FTIR studies in 2003 and 2005 , which

essentially offered the same details on the protein structural changes in the complex. As a result, FTIR spectroscopy produced useful information on the alterations in protein structure.

The intermediate structures of the ppR/pHtrII complex for the K and M intermediates have recently been described , following the determination of the complex's X-ray crystallographic structure . Between the K and unphotolyzed states, very little structural changes were seen , and the same was true for the uncomplexed ppR . For the M intermediate, however, a number of structural changes were seen . The results of the spin-labeled EPR investigation may be in conflict with the intriguing fact that the opening of the F-helix was not detected . The mobility of the F-helix opening is likely impeded in the complex, as demonstrated by our FTIR investigation, albeit the degree of this impairment may vary depending on the sample conditions. In the signal transduction process, protein-protein interactions in the cytoplasmic aqueous phase must be crucial. As demonstrated in this paper, the disparity in When examining the protein-protein interaction and its momentary modifications for an archaeal light-signal transduction, FTIR spectroscopy is a potent technique. It will be possible to acquire a better understanding of the transient alterations of the protein-protein complexes by combining X-ray crystallographic structures and theoretical computations..

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CHAPTER 13

A QUICK REVIEW OF RECENT ADVANCES IN CARBON NANOSTRUCTURE-BASED SENSORS

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Abstract

An overview of recent developments in carbon nanostructured materials-based sensors is provided, covering newly published research. There are reviews and discussions of several publications that deal with experimental and theoretical data. For the discussion, the key findings for hybrid carbon-nanostructured devices, carbon nanotubes, nanodiamonds, fullerene, and graphene that exhibit sensing properties in many sectors were taken into consideration. The purpose of this research was to showcase sensor mechanisms, and the best outcomes thus far are laying the groundwork for future uses. A carbon tube having a diameter in the nanometer range is known as a carbon nanotube. They are one of the carbon allotropes. Single-walled carbon nanotubes are around 100,000 times smaller than the width of a human hair, with dimensions ranging from 0.5 to 2.0 nanometers. They can be imagined as hollow cylinder-shaped cuttings from a two-dimensional graphene sheet that has been folded up. Single-wall carbon nanotubes are nested in a tube-in-tube configuration to form multi-walled carbon nanotubes. MWCNT is a specific case of the double- and triple-walled carbon nanotubes. Exceptional tensile strength and thermal conductivity are only two of the extraordinary characteristics that carbon nanotubes can display due to their nanostructure and the strength of the connections between the carbon atoms. While some SWCNT structures are semiconductors, others have strong electrical conductivity. Carbon nanotubes can also be chemically altered. These characteristics are anticipated to be useful in a variety of technological fields, including electronics, optics, composite materials, nanotechnology, and other materials science-related applications.

Keywords

Carbon tube, Graphene, Nanotubes, Nanotechnology.

INTRODUCTION

The need to create novel sensors with more specialized properties has been growing recently. Some of the characteristics needed to create technological sensor devices are greater sensitivity and dependability, quicker reaction and recovery, cheap cost, decreased size, in situ analysis, and ease of operation . There are a huge variety of sensors available for tracking various variables, including pressure, humidity, biomolecules, and heavy metals. However, the majority of them lack the ideal limit of detection, sensibility, and/or selectivity, are expensive, require pretreatment, are difficult to operate and respond slowly. Regarding the above-mentioned parameters, nanotechnology has sponsored the most promising improvement in material properties, offering major advancements to get around previous constraints faced by conventional materials. Nanomaterials are made in the 1 to 100 nm size range, and due to their size, they differ dramatically in their characteristics from bulk materials and their equivalents with higher-order structures [1], [2].

The carbon-based substance is one of the most researched and used materials in the nanotechnology sector because of its exceptional features. When compared to other commonly used materials, carbonaceous structures have several advantages, particularly their exceptional physical-chemical characteristics. Simple manufacturing procedures can result in a sufficient volume of material with few densification flaws. Additionally, carbon-based materials, which exhibit good performance and are thought to be an environmentally acceptable material, can be considered an alternative to currently pricey electronic compounds. Since carbon nanostructures exhibit better physical and chemical parameters that result in high-quality sensing properties, they have been studied for application as potent sensor devices [3], [4].

Many carbon-based structures that were found many years ago are being researched and used in modern technology. The ND structure was created in the 1960s. NDs are essentially sp3 hybridized carbon structures that are nanosized. Their exceptional surface activity is attributed to structural flaws and unsaturated chemical bonds formed by carbon atoms, while their distinctive optical and electrical properties are caused by dopants found in the structure. In 1985, Fullerene was found thanks to the study of Kroto et al. Depending on the FLN size, FLNs are a molecular allotrope of carbon that are made up of a three-dimensional closed-cage composed of five- and six-membered rings with 12 pentagons and a varied number of hexagons. Carbon nanotubes, which are another carbon-based structure and members of the FLN family, have a quasi-one-dimensional structure. Following the release of Iijima's study and presentation of the tubular structure of CNTs in 1991, the number of CNT-related studies surged. The two-dimensional atomic crystal known as graphene was the first to be identified. It is made up of a single layer of carbon atoms organized in a honeycomb lattice structure. Some of the carbon-based structures employed in sensor applications are depicted in Figure 1. An ideal single-walled carbon nanotube has the shape of a regular hexagonal lattice drawn on an infinite cylindrical surface, with the carbon atom positions acting as its vertices. There are restrictions on the diameter of the cylinder and the arrangement of the atoms on it since the length of the carbon-carbon bonds is largely set [5], [6].

In the study of nanotubes, a zigzag path is described as a path that steps through each bond and then turns 60 degrees, alternating left and right. A common definition of an armchair path is one that takes four steps and then makes two left turns that are 60 degrees apart, followed by two right turns. On some carbon nanotubes, the tube is encircled by a closed zigzag route. One claims that the tube is a zigzag nanotube or that it is of a zigzag sort or configuration. The term "armchair type" or "armchair nanotube" is used to describe a tube that is surrounded by a closed armchair route. The closed zigzag routes that make up an infinite nanotube of this type are all connected to one another. A single-walled nanotube can have more types of structures than just the zigzag and armchair shapes. The structure of a general infinitely long tube can be described by picturing it being split open along its axis by a cut that passes through some atom A, and then being unrolled flat on the plane so that its atoms and bonds match those of an imagined sheet of graphene more specifically, with an infinitely long strip of that sheet. Over two graphene atoms A1 and A2 on the strip's opposite sides will be the two halves of the atom A. The circumference of the cylinder that passed through atom A will be represented by the line connecting points A1 and A2, which will also be perpendicular to the borders of the strip. Depending on the orientation of their three bonds, the atoms in the graphene lattice can be divided into two groups. The three bonds of half the atoms are pointed in the same direction, whereas the three bonds of the other half are 180 degrees rotated with respect to the first half. There must be a class difference between the atoms A1 and A2, which represent the identical atom A on the cylinder. Because they are restricted to

the lengths and directions of the lines that connect pairs of graphene atoms belonging to the same class, the circumference of the tube and the angle of the strip are therefore not arbitrary.

Let u and v represent two linearly independent vectors that link the graphene atom A1 to its two closest neighbors that share the same bond directions. In other words, if the carbons around a graphene cell are numbered from C1 to C6, then u can represent the vector from C1 to C3, and v can represent the vector from C1 to C5. The vector from A1 to A2 can then be expressed as a linear combination of n u + m v, where n and m are integers, for each additional atom A2 that belongs to the same class as A1. However, each pair of numbers defines a potential position for A2 in the opposite direction. By drawing the vector on the graphene lattice, cutting a strip of the latter along lines perpendicular to w via its endpoints A1 and A2, and rolling the strip into a cylinder in order to bring those two points together, one can reverse this theoretical procedure given n and m. A zigzag nanotube with 2k closed zigzag routes results from applying this construction to the pair. It produces an armchair tube with 4k closed armchair routes when applied to the pair.

DISCUSSION

Property Sensing

A sensor is a component that reacts to a chemical or physical stimulus by producing a signal that can be electronically examined. The sensor must respond quickly to external stimuli, be able to detect an analyte in a percentage as small as possible, have a quick recovery time, be able to distinguish the correct analyte from others, and be simple to use. Additionally, a cheap and environmentally friendly trait is desired. Therefore, it is essential to enhance currently employed systems and discover fresh, promising alternatives that permit replacing outdated technology. The utilization of carbonaceous nanoparticles is a viable option because of their unique features that make them appropriate for use as technological sensors. Different carbon architectures' high reactivity enables functionalization, which can improve an analyte's selectivity. Each carbon-based nanostructure has unique properties that make it suitable for use in a particular type of sensor. In biological contexts, for instance, sensors based on NDs with nitrogen-vacancy defect centers show promise. The delicate quantum structure of NV defects or NV centers makes them suitable for monitoring external perturbations like magnetic or electrical fields. These centers, which comprise of a nitrogen atom and an adjacent lattice vacancy and are one of the most prevalent defects in the diamond structure, cause NDs to glow. At room temperature, NDs sensing exhibits extremely high sensitivity. By detecting the magnetic resonance of one or more nuclear spins, NV centers found in the structure of NDs enable the conversion of physical properties into an optical transition that can be observed in the single photon range. The photoluminescence, chemical, and biological properties of fluorescent NDs are also affected by differences in size and form [7]–[9].

FLN has drawn a lot of interest in the creation of biosensors because of its improved electron-transfer kinetics, high surface-to-volume ratio, and biocompatibility. Nanocomposites based on FLN, or more precisely, C60, are capable of detecting a wide range of biological chemicals, including drugs, glucose, DNA, adenosine triphosphate, and many others. The optical and photoelectric properties of FLNs were also studied to develop materials for color sensing. In mechanical applications, FLNs offer tremendous impact strength and excellent resilience. Completely conjugated -electrons that are contained in zero dimension lead to strong redox activity and distinctive electrical characteristics. The icosahedral structure of FLN-truncated is a good electron acceptor. One of FLNs' key properties is their ability to interact with a variety of molecules and functional groups. Their application potential is increased by chemical functionalization, which increases their

solubility in various solvents and blends their properties with those of other substances. Although FLNs molecules are physically stable and have a strong affinity for electrons, they are chemically reactive, especially with free radicals..

CNTs have special properties because of their high surface-to-volume ratio and hollow structure. They are thought to make excellent candidates for creating chemical and biological sensors since they can electronically interact with a large number of molecules and adsorb them onto their surfaces. Excellent carrier mobilities, almost perfect quantum efficiency, and ultrathin body are just a few of the electrical characteristics of CNTs that enable applications at sub-8 nanometer scales, which is thought to be the limit for the development of traditional semiconductors. Tans et al. developed a CNT field-effect transistor in 1998 as a result of developments in CNT-based electronics, which was thought to be a potential replacement for nearly all existing metal-oxide semiconductor field-effect transistor applications [10], [11].

Due to its high mechanical strength, broad surface area, rapid heterogeneous electron transfer rates, and thermal and electrical conductivity, GPN and its derivatives have been exploited as a raw material for sensors in a variety of applications. Recent research have produced excellent outcomes, such as higher selectivity, low cost, simple operation, and quick response and recovery times. Determining variables, such as the ideal amount of graphene layers or the most effective method for gauging response and production routes, is still important. Quantifying gases is one of the most often used uses for graphene-based sensors. According to the intended function, each of the aforementioned structures possesses characteristics that can be utilised as sensing mechanisms. The following topics provide several examples of carbon-based structures used in sensor technology. At the conclusion of each topic, a table compares great reaction sensors to other previously reported ones. Studies from the previous two years that had a substantial applicability in the field of sensing were taken into consideration when developing the review's criteria [12], [13].

Multi-walled

The multiple wrapped layers that make up multi-walled nanotubes are called concentratic tubes of graphene. One of two methods can be used to predict the structures of multi-walled nanotubes. Graphite sheets are arranged in cylinders that are concentric to one another in the Russian Doll concept, for instance, a smaller single-walled nanotube inside a larger SWNT. One graphite sheet is folded inward and over itself to resemble a scroll of parchment or a rolled up piece of newspaper in the Parchment model. The gap between graphene layers in graphite is comparable to the interlayer distance in multi-walled nanotubes, which is around 3.4. The Russian Doll structure is more frequently observed. SWNTs can be used to describe each of its component shells and can be metallic or semiconducting. One of the shells, and hence the entire MWNT, is often a zero-gap metal due to restrictions on the relative diameters of the different tubes and statistical likelihood. Double-walled carbon nanotubes are a distinct type of nanotubes because they resemble single-walled carbon nanotubes in terms of appearance and attributes but are more resistant to chemical attacks. This is essential when it comes to grafting chemical functions onto the surfaces of nanotubes to functionalize them. Covalently functionalizing SWNTs causes certain C=C double bonds to break, producing "holes" in the structure of the nanotube and altering its mechanical and electrical properties. Only the outer wall is altered with DWNTs. The idea to selectively reduce oxide solutions in methane and hydrogen using the CCVD process to create DWNT on a gram-scale originally surfaced in 2003.

The telescopic motion capacity of inner shells and their unique mechanical properties will enable the use of multi-walled nanotubes as the main moving arms in next nanomechanical

systems. The retraction force of the telescopic motion is produced by the Lennard-Jones contact between the shells and has a value of about 1.5 nN.

Gas Detector

Due to their promising structure, which enables gas detection and quantification, carbon nanostructures are increasingly being used in gas sensor applications. The high surface-to-volume ratio and hollow design make them perfect for gas molecule adsorption and desorption. Additionally, the potential for functionalization raises gas selectivity. In order to meet the requirements for the effectiveness of gas sensors, such as high sensitivity and selectivity, quick reaction and recovery time, and stability, carbon nanostructures can be utilized in a variety of sensor systems. The fluctuation of applied voltage and current in relation to the quantity of gas molecules adsorbed onto the surface structure is typically the operational principle of these devices. When molecules and a sensor contact, an electrical signal is produced. The detection and quantification of harmful gases, particularly hydrogen sulfide , carbon monoxide , carbon dioxide , nitrogen oxide , ammonia , and methane , is one of the principal uses of carbonaceous materials as gas sensors. Controlling gas air pollutants is a particular priority since they have negative consequences on both the environment and human health. The primary allotropic forms of carbon employed in this kind of sensor include GPN, GO, CNTs, and most recently, FLN [14], [15].

In addition to being one of the causes of acid rain, NO2 gas, when its concentration exceeds the safe level, can be detrimental to human respiratory systems. The US Environmental Protection Agency recommends a 53 ppb yearly exposure limit for NO2. Therefore, a highly sensitive sensor system is required to detect low levels of NO2 gas in the atmosphere. A highly sensitive room-temperature gas sensor was created by Seekaew et al. by depositing a GPN bilayer onto Ni electrodes. The authors contrasted samples of monolayer and multilayer GPN with the performance of bilayer GPN gas sensors at room temperature. Researchers employed the Chemical Vapor Deposition technology to regulate the number of layers. The bilayer sensor displayed the highest sensitivity of the three samples, with a NO2 sensitivity of 1409 ppm1 throughout a concentration range of 1–25 ppm, more than twice that of the GPN monolayer sensor. Additionally, the bilayer sensor demonstrated strong selectivity to NO2 over CO, CO2, NH3, ethanol, and hydrogen gas. Ricciardella et al. looked into how different production processes for GPN affected the morphology, crystalline structure, and ultimately the effectiveness of NO2 sensors made from these materials. In comparison to the material produced by liquid phase exfoliation and CVD procedures, mechanical exfoliation produced less faulty material with the maximum amount of signal variation. They showed that a low defect level results in a faster interaction with the gas during exposure time.

Wu et al. created a superhydrophobic reduced GO for NO2 detection in a different study. In addition to reducing graphene's conductivity, the presence of functional groups like hydroxyl, epoxide, and carboxylic in GO renders GO-based gas sensors particularly susceptible to humidity because these groups are so hydrophilic. The high vacuum atmosphere, spark plasma created, and high temperature used in spark plasma sintering allowed authors to remove the majority of the oxygenated functional groups, which accelerated the reduction process. In addition to producing a superhydrophobic characteristic, the reduction of GO in rGO enhanced the surface regions with big flaws that encouraged gas adsorption. Sensitivity and gas adsorption are improved by increases in surface area and flaws sites, respectively. The NO2 sensor had a remarkable low limit of detection and high sensitivity. Superhydrophobicity, huge surface area, and a large number of fault sites are all credited with this performance.

To safeguard everyone from harm caused by air pollutants, harmful gases other than NO2 must be monitored in the environment. For instance, H2S can cause an abrupt collapse with loss of breathing and could cause mortality over the 100 ppm limit. Researchers created an H2S gas sensor based on graphene embellished with Ag nanoparticles in a recent study. The limit of detection of the doped graphene sensor was lower than the advised 100 ppm and it demonstrated selectivity in the presence of CH4, CO2, N2, and O2. Additionally, this new gadget had a rapid response time of 1 seconds and a brief recovery period of 20 seconds, enabling real-time H2S monitoring and prompt action.

CONCLUSION

Carbon nanostructure-based sensors have exceptional characteristics and offer a wide range of potential applications. The adaptable qualities of these materials used as sensor devices were discussed in this review. With a response as good as for those devices already described, various carbon allotropic forms can be applied in different sensing domains. Due to their excellent electric, thermal, mechanical, and chemical capabilities, nanodiamonds, fullerenes, graphene, nanotubes, and hybrid structures have been widely exploited. This review found that carbon nanostructures, particularly those that have been functionalized, exhibit a high degree of selectivity. Because the centers of nitrogen vacancies in nanodiamonds produce fluorescence responses, they are a great example of a carbon structure that has been used in a biological setting. Fullerenes are used in sensor systems that encourage interactions between the device and the analyte due of their cage structure, high reactivity, and biocompatibility. The identification of DNA, chlorambucil, and diazepam samples was made possible by recently published sensor systems that used fullerenes. Carbon nanotubes, like other allotropes, have a high degree of reactivity, but their mechanical qualities also have implications for the creation of sensors for measuring physical parameters like stress and strain. Their high surface-to-volume ratio also makes it possible to create gas sensors that are just as effective as those made with graphene structure. The sensors described in this review's devices represent the highest level of advancement now available for carbon nanostructure-based sensors, outlining the key areas of current study and outlining probable future directions. Regarding the carbon-based manufacturing, there are still many obstacles to overcome in order to optimize the functionalization process and phase out impurities. The selectivity of the sensor will be improved together with the control of defect densification, which is solely dependent on physical and chemical qualities and must be overcome.

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