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G-PROTEIN AND G-PROTEIN COUPLED RECEPTORS: IMPLICATIONS IN REGULATION OF IMMUNE RESPONSE

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ABSTRACT: *The guanine nucleotide binding proteins (G proteins) act as molecular switches of 'on' and 'off' when bound to GTP and GDP respectively while the guanine protein coupled receptors (GPCRs) are membrane bound receptors whereby extracellular substances (ligands)communicate signals from these substances to an intracellular molecule the G-proteins which in turn bind and activate or inhibit downstream effect or molecules causing cellular responses. This review is aimed at exploring the concept and mechanism of G-proteins and GPCR and their implication in immune response. The GPCR can be activated by various physiological or pathological processes cellular metabolism, hormones, neuro-transmitters, chemokines, autocrines, paracrines, endocrine and exocrine secretions which play an important role in relaying or routing signals to several intracellular pathways. The signal transduction by the extracellular activation or inhibition of the GPCR mediate metabolic enzymes, ion channels, transporters, cellular gene transcription, migration, survival, activation, differentiation and cytokine secretion of immune cells resulting in the synthesis and regulation of embryonic development, gonadal development, learning /memory organismal homeostasis, hematopoiesis and immune dynamics. Therefore, G proteins and GPCRs signaling systems are key determinants in innate and adaptive immunity. The signal transduction of G-Protein and GPCR by cytokine chemotaxis as Chronic inflammatory mediators is associated with tumorigenesis, metastasis with potential antagonism for appropriate targeted therapy.*

KEYWORDS: G-proteins, GPCR, Signaling, Transduction, Immune system.

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INTRODUCTION

Guanine nucleotide binding proteins (G-protein) are Monomeric (small GTPases) or Heteromeric (G-protein complexes) consisting of three subunits termed alpha (α), beta (β), and gamma (γ) (Hurowitz et al., 2000). G-protein acts as molecular switches inside cells which are involved in transmitting signals from a variety of stimuli outside a cell to its interior. Their activities are regulated by factors that control their ability to bind and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP). When they are bound to GTP, they are "on" and when bound to GDP, they are "off". GTPases as proteins are part of bigger enzymes. Small GTPases are monomeric while larger GTPases are trimeric though they function by similar principles. Small GTPases are often anchored to the inner side of the cell membrane. When the G-protein binds the receptor, GDP is exchanged for GTP causing the G-protein to become activated. The activated G-protein subunits then activate multiple pathways throughout the cell such as motility, proliferation and changes in gene transcription eventually (Hamm, 1998).

Monomeric G-Protein have molecular masses from 20-40KDa (Luo et al., 2022). They are small G-proteins which can be classified structurally into five families, namely: the Ras, Rab, Rho, Sarl/Arf and Ran families (Luo et al., 2022). Ras proteins are crucially important molecules for biology and human health.

Heteromeric G-Proteins

The heteromeric G-proteins consist of three subunits, namely: alpha(α), beta(β) and gamma(γ) attached to the cytosolic face of the seven transmembrane (Hurowitz et al., 2000). They are classified into four families according to their subunits: Gαi,Gαs ,Gα12/13 and G αq. The Gs and Gi families regulate adenylyl cyclase activity while Gαq activates phospholipase Cβ and hydrolysing phosphatidylinositol 4,5 bisphosphate into diaglycerol (DAG) and inositol triphosphate and activating protein kinase C increasing calcium efflux from endoplasmic reticulum. Gα12/13 can activate small GTPase families (Neves et al., 2002).

STRUCTURAL CLASSIFICATION OF GPCRs

GPCRs are located in the transmembrane region of the cell surface; ligands attach to the GPCR and they transfer extracellular stimuli into intracellular signals that produce cellular responses. In humans, over 800 GPCRs have been identified in the genome (>3% of human genome) and are associated with various ligands, such as hormones, neurotransmitters, growth factors, chemokines, ions, odorant molecules, and even light photons (Pierce, Premont & Lefkowitz, 2002). Many of the remaining GPCRs are thought to be sensory in function (Foord et al., 2005). The ligands can bind only 200-300 GPCRs, the remaining are considered orphan receptors as no ligand or function has been identified. The GPCRs are very important in physiological activities, as uncontrollable expressions and signaling have been linked to various inflammatory diseases such as rheumatoid arthritis or diseases with certain inflammatory aspects such as cancer. GPCR has become a useful target for the development of novel therapeutics which account for over 35% of all clinical drugs in the market formulated and prepared to regulate their function. However, 3 registered drugs have only been produced for about 30–40 well-characterized GPCRs and therefore, there are many opportunities to validate and discover new drug targets and therapeutics from the remaining GPCRs (Hauser et al., 2017). GPCRs have a common structure of seven transmembrane a-helical segments (H1–H7)

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joined with each of the intracellular and extracellular loops, made up of an intracellular C-terminus and extracellular C-terminus respectively. Rhodopsin, ß1 adrenergic, ß2 adrenergic, A2A adenosine, glucagon, glucagon like peptide, corticotropin-releasing factor, activation by neurotransmitter glutamate ,signal transducer by phosphorylation regulation and ubiquitination in the Hedgehog pathway are structural analysis and crystalization of GPCRs. The structure and biological processes which control GPCR elaborates the concept of receptor activation and signal transduction . Based on earlier studies, the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification has assigned GPCRs into 5 distinct groups namely: class A (rhodopsin-like receptors), class B (secretin-like receptors), class C (glutamate- like receptors), frizzled, and other 7TM proteins (Foord et al., 2005). Class A also known as rhodopsin-like receptors is the largest and most diverse group amongst the families and consists of receptors for light, olfactory, biogenic amines, chemokines, prostanoids, adrenaline, and many others. Class B comprises receptors for the calcitonin, parathyroid hormone, and the varying group of gastrointestinal hormones such as secretin and glucagon. Class C GPCRs include the GABAB receptor, the group of metabotropic glutamate receptors and calcium-sensing receptor. Class C is relatively small and members generally contain a large extracellular amino terminus thought to be important for ligand capture (Foord et al., 2005). Despite the general sequence and structural similarities of members within each family (over 25%), 4 individual GPCRs have prominent differences in their extracellular and intracellular loops and these regions are important for ligand binding and interaction with downstream mediators (Venkatakrishnan et al., 2016). These distinctness make specific GPCRs to show peculiar signaling characteristics due to distinct receptor couplings to different G-proteins resultant in variance of signaling in the intracellular pathway and dissimilar of the G-protein independent pathway complex regulatory of the processes such as receptor desensitization, internalization, endocytosis, and re-sensitization (Venkatakrishnan et al., 2016).

GUANINE PROTEIN COUPLED RECEPTORS: (GPCR) are found in Eukaryotes and there are 1000 different unique types used in drugs ,hormones ,neurotransmitters, serotonin etc. Structurally a GPCR is made up of long protein that has three basic regions:an extracellular portion(the N-terminus), an intracellular portion (the C-terminus) and a middle segment containing seven transmembrane domains .Beginning at the N-terminus ,this long protein winds up and down through the cell membrane with the long middle segment transversing the membrane seven times in a serpentine pattern, the last of the seven domains is connected to the C-terminus. A GPCR binds a ligand (a molecule that possesses an affinity for the receptor),the ligand triggers a conformational change in the seven transmembrane and activates the C-terminus. The biggest class of GPCRs is A (rhodopsin-like class) that comprises about 90% out of all GPCRs (Schoneberg et al., 2004).

Receptors are special proteins which receive chemical signals in the form of small molecules that act as ligands, meaning that they interact with the active site of the receptor. They are specifically found in the cell membrane extracellular domain that translates recognition by a receptor into a biochemical action within the cell. Most are single trans-membrane proteins whose domain spans through the extracellular sensing by binding to a ligand which initiates a downstream signaling cascade and intracellular signaling. A ligand can be a sugar, lipid, another protein or peptide or even a nucleic acid which acts as agonist by producing signal or non-agonistic by not producing signal. A ligand can be free floating in the blood or interstitial fluid like soluble antigen or attached to the surface of another cell. Receptor/ligand pairings

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are extremely specific; the specificity allows the cell to have increased sensitivity in responding to changes in the molecular environment and allows it to be able to distinguish relatively subtle differences between similar types of molecules. After a receptor binds to an extracellular ligand, it causes signal transduction. The signal transduction involves conversion whereby the extracellular binding event into intracellular biochemical cues by equipping the intracellular of the receptor with enzymatic activity. When the ligand binds, the conformational change binding induces or activates the enzyme and kicks off a chain reaction signaling within the cell.

MECHANISM OF ACTION OF A G-PROTEIN COUPLED RECEPTOR

GPCR is a long protein that has three basic regions: an extracellular portion (the N terminus), an intracellular portion (the C terminus), and a middle segment containing seven transmembrane domains. Beginning at the N-terminus, this long protein winds up and down through the cell membrane with the long middle segment traversing the membanding a ligand which initiates a downstream signaling cascade and intracellular signaling (Kobilka, 2007).

A ligand can be a sugar, lipid, another protein, or peptide or even a nucleic acid which acts as agonist by producing signal or nonagonist by not producing signal. A ligand can be free floating in the blood or interstitial fluid like soluble antigen or attached to the surface of another cell. When a receptor binds to an extracellular ligand, it causes signal transduction which involves conversion whereby the extracellular binding event into intracellular biochemical cues by equipping the intracellular of the receptor with enzymatic activity.

Many immune receptors are linked to enzymes called kinases. Kinases covalently attach a phosphate group to serine, threonine or tyrosine. Amino acids reside in a reversible process called phosphorylation; phosphate group can change how a protein interacts with other proteins such as changing enzyme active sites, altering protein binding sites or changing how transcription factors behave by the addition of a phosphate group (Kobilka, 2007).

Signaling Cascade

When a ligand adaptor protein localized to the cytoplasmic tail of the receptor binds to a ligand thereby recruiting guanine –nucleotide exchange factor(GEF) to swap out bound GDP for GTP,which allows the GTPases to become activated and launch a cell signaling cascade. Ras, Rac and Rho are all common small GTPases that can have widespread cell signaling effects. Some of the ways that the signal carried by the ligand can propagate inside a cell. The signal then in response to the receptor activation depends on many factors such as levels of receptor expression and ligand concentration as well as which particular combination of receptors were activated and in what order. The end of a signaling cascade can lead to a huge range of possible outcomes including protein modifications like phosphorylation, transcription and translation of new proteins, changes in cell adhesion and motility, phagocytosis, antigen presentation, proliferation, apoptosis, survival and release of cytotoxic or microbicidal proteins.

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MECHANISMS OF IMMUNE CELL RESPONSES

Antigen receptors allow immune cells to sense the presence of infectious microbes and damaged diseased cells. Specific Lymphocyte Receptor T cell antigen receptors are found only in cell membranes.

Costimulatory receptors need more to bind and recognize microbial antigen. Many require costimulation from other cells to confirm that there is a threat and to give the cells permission to become fully activated and carry -out their various effector functions. A type of two signal system in which immune cells need to detect signals to become activated is present throughout the immune system. Costimulation is carried out by costimulatory receptors

Cytokines and cytokines receptors are soluble, small protein signals that immune cells use to communicate with one another. They can be released by immune cells or by cells in infected or damaged tissues and differ from classical hormones in that they are not produced by specialized glands.

Chemokines are a family of small molecular weight soluble protein messengers/signals like cytokines that promote (guide) directional migration of leukocytes (immune cells), endothelial and epithelial cells to the site of damage. They are classified into CXC,CC,CX3C or C Chemokines based on the positioning of the conserved Cysteine residues (Zlotnik & Yoshie, 2000).

GPCRs IN IMMUNE RESPONSE

G-proteins and GPCRs are expressed in haematopoietic stem and progenitor cells including chemokine receptors $CXCR_4$, the leukotriene receptor (CysLT1), the sphingosine1-phosphate receptor (S1P1) and identification of the various maturation stages in the hematopoietic clonal lineage populations. Functions mediated by GPCRs can both exacerbate inflammation and promote its resolution. GPCRs expressed in these cells play important roles in sensing the presence of chemoattractant, transducing signals that lead to the production of inflammatory cytokines, nociception, and regulation of intracellular and intercellular communications associated with increased blood flow and increased vascular endothelial permeability. These GPCRs act as gate-keepers in general and help in particular to shape immune responses of macrophages toward extracellular pathogens as well as injury related danger molecules. Large number of studies have demonstrated clearly that mammalian GPCRs feature prominently in the regulation of other aspects of macrophage biology including macrophage development, differentiation and activation. Phagocytes have the abilities to chase, capture and eventually eliminate invading bacteria. It was reported that phagocytes could respond to small molecules derived from invading bacteria and fungi (Harris, 1954). Chemokines are primarily responsible for the recruitment of neutrophils to the site of inflammation and tissue injury. Other classic chemoattractant receptors including those for platelet-activating factor (PAF) and leukotriene B4 (LTB4) and a large number of chemokines were subsequently identified as GPCRs (Yokomizo, 1997). GPR 56 and GPR 97 modulate the development and functions of Haemopoietic stem and progenitor cells (HSPC) and various immune cell types regulating innate and /or adaptive immune responses. Their uncontrolled expression and/or activity of these receptor molecules consequently lead to immune dysfunction and disorder. The identification of specific ligands development of receptor specific antibodies and agonists/antagonists makes it possible to manipulate the cellular functions of GPCRs in-vitro

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and in–vivo. The relationship of immune GPCRs with various autoimmune/inflammatory pathologies and hematopoietic malignancies has marked these receptors as attractive therapeutic targets of immune cell related diseases. The mouse embryo and adult bone marrow expresses significant levels of GPR 56 though the expression weakens significantly with cell differentiation. Kartalaei et al. (2015) also demonstrated GPR56 involvement in haematopoietic cluster formation during endothelial to hematopoietic cell transition of zebrafish and mouse. The movement of mature leukocytes to inflammatory sites and lymphocyte migration in-vivo are dependent on GPCR and delivered through pertussis toxin(Ptx) in mice elicited long lasting leukocytosis .

METHOD

In this systematized search following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines adopted (Tegegne et al., 2021), we used MEDLINE (www.ncbi.nih.gov/pubmed/) and search engines like Google scholar to find articles related to G-protein and GPCR and implications in regulation of immune response. The review is restricted to articles published in English up to the 10th of October, 2023. Records identified through MEDLINE(n=804)/Google scholar(1021) identifying (n=1825), after duplicates of (n=312) were removed. Furthermore, 1513 studies were screened for titles and abstracts involving eligibility of identified records on relevance, and 1,332 non-relevant studies were excluded after final assessment for eligibility. The 181 articles were selected for this systematic review.

DISCUSSION

GPR 56 as a surface marker and prognostic factor of acute myeloid leukemia(AML) and leukemia stem cells (LMCs) shows that GPR 56 modulates NK_1T and platelets as well as leukemic cells. Maghlto et al. (2021) also showed that GPR97 has functional compensation in haemopoiesis which indicated that GPR56 do not impair Hematopoietic Stem Progenitor Cells maintenance migration or function in steady-state or myeloablative stress–induced haemopoiesis. The role of the GPR97 associated receptor complex in pathologic inflammation was characterized by an increased GPR97 and MPR3 expression on the surface of Neutrophil and various inflammatory diseases including appendicitis, bacterial sepsis and granulomatosis with polyangiitis(GPA). Chemokines activate GPCR in both innate and adaptive immune cells and regulate their traffic between lymphoid organs and inflammatory sites. CXCL12 exerts its function by binding $CXCR_4$ a GPCR present on the surface of haematopoietic cell. This interaction is essential for the homing and maintenance of the Haemopoietic Stem Cell in the bone marrow. In 2008, FDA approved the use of $CXCR_4$-inhibitor Plerixafor (AMD3100 Mozobil) in association with granulocyte colony stimulating factor G-CSF) for the mobilization and collection of PBSC in patients with non-Hodgkin's lymphoma(NHL) and multiple myeloma (MM). Chemokines play key roles in the pathophysiology of inflammation and cancers. Active $CXCR_4$ have shown the stimulation of ovarian cancer cell growth through transactivation of the epidermal growth factor (EGF) receptors(Porcile et al., 2005). The activation of the chemokine receptors $CXCR_4$ and CCR_5 is documented to transactivate the JAK-STAT pathway. Janus kinase-signal transducer and activator of transcription (JAK-

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STAT) pathway activation enhances the recruit of STAT by tyrosine kinase family which causes it to dimerize and translocate to the nucleus and regulate the expression of cellular response, such as cellular proliferation, differentiation, survival and self- renewal like in Haematopoietic Stem Cells. Jaks are receptor-associated protein tyrosine kinases, and STATs are latent cytoplasmic transcription factors that are activated by tyrosine phosphorylation (Wong & Fish, 2003). The chemokine receptor $CXCR_4$ and $CXCR_7$ and their ligand $CXCl_{12}$ also mediate and shape their migratory pattern of primordial stem cell however interference with the chemokines or receptors mis-target the migratory patterns of progenitor cells resulting in developmental abnormalities (McGrath et al., 1999). The $CXCL_{12}/CXCR_4$ axis is also involved in lymphoma- and myelopoiesis in the bone marrow, hematopoietic stem cell homing to sites of vascular expansion and cardiac development (Ceradini et al., 2004). Chronic inflammatory conditions have been associated with the development of cancer and unresolved chronic inflammation leads to tumorigenesis. The tumor progression is influenced by the production of chemokines by tumor and stromal cells. Cancer is a key component of the tumor microenvironment, inflammation and cancer are connected by the extrinsic pathway being predisposed by chronic conditions like ulcerative colitis, the intrinsic pathway characterized by the production of inflammatory mediators being promoted by genetic events necessary for transformation. Prolonged oxidative stress results in the formation of free radicals responsible for chronic inflammatory environments which can predispose the host to diabetes, cancer, cardiovascular, neuronal and pulmonary diseases. Oxidative stress can lead to the activation of the following transcription factors, namely: NF-Kb,AP-1,p53,HIF-1a,PPAR-g,b-catenin/wnt and Nrf2 (Reuter et al., 2010). The role of inflammation is clearly shown by reducing the inflammation in the tumor microenvironment in a mouse tumor model. The reduction of inflammation leads to delayed accumulation of Myeloid –Derived Suppressor Cells (MDSC) thereby reducing primary and metastatic tumor progression (Bunt et al., 2007). These MDSCs link inflammation and cancer (Ostrand, Rosenberg & Sinha, 2009). Many non-communicable disease types have increased expression of chemokines and their receptors leading to aberrant chemokine receptor signaling and expression depending on type and extent of leukocyte infiltration into tumor microenvironment (Lazennec & Richmond, 2010). MDSCs and Tumor Associated Macrophages(TAMs) relate chronic inflammation to cancer and in the tumor microenvironment, increased production of reactive oxygen specie (ROS), reactive nitrogen specie (RNS) and arginase 1 produce active states for MDSCs and TAMs (Gabrilovich & Nagaraj, 2009). A number of GPCRs have been found to participate in transcriptional regulation. NF-KB, are closely associated with the expression of genes that encode inflammatory factors. Subsequent studies identified both PTX-sensitive and PTX-insensitive mechanisms by which GPCRs activate $NF\text{-}_KB$ (Yang et al., 2001). Several intracellular signaling molecules that were initially identified for immune cell functions, including CARMA3 and Bcl10, were found to regulate GPCR signaling leading to $NF\text{-}_KB$ activation (Wang et al., 2007). Viruses such as KSHV, HHV8, and RCMV encode GPCRs that are constitutively active, and when expressed in mammalian cells, activate $NF\text{-}_KB$. Like agonist-induced GPCRs, these viral GPCRs couple to more than one G-protein for signaling.

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CONCLUSION

This class of surface molecules, the G-Protein coupled receptors (GPCRs), are crucial in most immune processes. The G- protein–coupled receptor (GPCR) signaling is essential for the spatiotemporal control of leukocyte dynamics during immune responses. Many leukocyte cells express more than one GPCR on their surfaces and perceive extensive chemokines and chemoattractants which underlies the leukocyte movement. Polymorphonuclear leukocytes (PMN), monocytes and macrophages which are inflammatory cells express many GPCRs necessary in chemoattractants and chemokines. These receptors are essential in phagocytes' journey and their gathering at the inflammation sites where the cells aggravate inflammation but also ensure its clearance. Besides chemoattractant GPCRs, protease activated receptors (PARs) such as PAR1 are involved in the regulation of vascular endothelial permeability. Bradykinin pro-inflammatory and neuromodulator have multiple pathophysiological functions such as induction of vascular permeability and mitogenesis and it also triggers the release of other mediators like nitric oxide in inflammatory and cancer tissues. Thus, bradykinin antagonists may have applications in the modulation of cancer growth and in paraneoplastic syndromes (Howl et al., 2003; Wu et al., 2002). Prostaglandin receptors can intervene in both pro and anti-inflammatory activities, most GPCR involved in inflammatory cells interfere in transcription factor activation leading to the production and release of inflammatory factors and in some cases molecules that inhibit inflammation. An understanding of the signaling paradigms of GPCRs in inflammatory cells is likely to facilitate translational research and development of improved anti-inflammatory therapies. The knowledge of pathogenesis of most non-communicable diseases and tumors, a multi-pronged anti-tumor therapeutic approach is essential for effective remedy. The reduction or elimination of inflammation, oncogene inactivation and polarization of immune cells to T helper 1 type. The various approaches in the reduction or removal of inflammation include: lowering of stress level, chronic low dose employment of anti-inflammatory drugs, removal or blocking the accumulation of the chemokines (Galzi et al., 2010), removal or differentiation of MDSCs and conversion of TAMs (M2) to M1 macrophages. The reduction of chronic inflammation will produce a positive effect on cancer therapy.

RECOMMENDATION

Further research on how the G-Protein Coupled Receptor plays a specific role in the regulatory system that controls the metabolic response to non-communicable diseases should be done.

An understanding of the signaling paradigms of GPCRs in inflammatory cells and how it is likely to facilitate translational research and development of improved anti-inflammatory therapies should be promoted.

Declarations

Ethical Approval: The manuscript being a review article did not require Institutional ethical approval for publication.

Competing interest: The authors declare that there are no conflicts of interest.

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