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Review Article

G Protein-Coupled Receptors (GPCRs) Mediated Signaling Pathway, An Essential Drug Targets in Tumor Regulation: An Overview

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Abstract

G protein-coupled receptors (GPCRs) are the integral membrane proteins used by the cell to convert the extracellular signals into intracellular responses. The GPCR stimulates signaling mediated by β-arrestins or G protein to exert forces of movement during metastasis and tumor cell. The GPCR mediated ERK/MAPK activation triggers multiple pathways that can regulate crosstalk between GPCR and receptor tyrosine kinase (RTK) signaling, which is responsible to many cellular functions with activated MAPK cascades. The components of ERK signaling cascade are attractive targets for drug development. ERK signaling cascade also enhanced inhibition of ERK signaling in the tumor, which is required for effective treatment of RAS/RAF mutant cancers. However, when ERK is activated, ERK is transported to the nucleus, and promotes a transcription of mitogenesis and proliferation related target genes. The activation of ERK via cytokines initiate expression level of transcription factors, protein kinase and regulatory genes, which is capable of regulating cell migration, differentiation, survival, proliferation, and apoptosis with rapidness and sequence. Furthermore, Wnt/β-catenin signaling pathway can regulate tumor progression via Wnt ligand interaction by promoting metastatic growth and resistance to chemotherapy in breast cancer. In this review, the significance of different GPCRs mediated signaling pathways capable of regulating cellular migration, differentiation, apoptosis, proliferation, cell survival, and tumor progression which helps to treat tumor cell.

Keywords: Cancer Progression; GPCR; Cytokines/ERK1/2 Signaling; GRK/β-arrestin Signaling; Wnt/ β-catenin Pathway; MAPK Pathway

Introduction

Cells in our body recognize and respond to external particle stimuli via the activation of signaling from a large class of receptors referred as G protein-coupled receptors (GPCRs). The GPCR is an integral membrane protein used by the cells to convert extracellular signals into intracellular responses such as neurotransmitters, taste signals, vision, and olfaction. They are also known as seven-transmembrane receptors or heptahelical receptors (7TMARs) that possess vital mechanisms of actions with a combination of signaling-transduction activities via G protein-dependent and G protein-independent signaling pathways, and regulatory functions [4]. The GPCR is widely regarded as the largest family of signaling protein, and is considered to be the largest cell surface receptors [8]. Cells processes information encoded in these chemical messages via GPCRs present in the plasma membrane [10-12], thereby enhancing biological switches that transmit both internal and external stimuli in the cell membrane [13]. Thus, GPCRs possess three parts of functional signaling system: receptor detecting ligands in the extracellular milieu, a heterotrimeric (αβγ) G protein which dissociates into α-subunits bound to guanosine triphosphate (GTP) [14].

GPCR are regulated by a small family of structurally conserved β-arrestin proteins, which must first be activated via interaction

with phosphorylated receptor C-terminus prior to their bindings. Several cellular and physiological processes such as metabolism, growth, homeostasis, cancer initiation and progression are regulated by GPCRs. Undoubtedly, they contribute to the establishment and maintenance of a microenvironment that is permeable for cell formation and growth, such as signaling molecules, the effect upon surrounding blood vessels, and the extracellular matrix [15]. Over 800 members of the GPCRs played a part in the tumoriogenesis and metastasis of many types of human cancers [18], including chemokine, endothelin and lysophosphatidic acid receptors.

The popularity of GPCRs as drug targets are vital to their physiological relevance which is responsible for cell proliferation, neurotransmission, differentiation, development and apoptosis. They are also believed to be the most successful drug target in numerous disorders/diseases such as inflammation, pains, metabolic and neurobiological disorders [18]. They are essentials for drug targeting [24] through the transduction of cellular responses including cell proliferation, differentiation, growth, and apoptosis [13].

Grushevskyi., *et al*. revealed that the sales of the GPCR drug target represent over 27% of global market share. Meanwhile, it has shown that the US Food and Drug Administration (FDA)-approved drug targets in the market targets at least 108 GPCRs. Reports further present that there are additional 66 receptor targets under clinical trials [25]. As of 2017, between 30%–40% of FDA-approved medications target GPCRs. The pharmacotherapeutic exploitation of GPCR signaling paradigm has created a drug-based field covering nearly 50% of the current pharmacopeia [14], and remain a major domain in the pharmaceutical drug discovery [26]. In this review, we briefly discussed the impacts of different signaling pathways of receptors in regulating cellular functions, such as cell proliferation, apoptosis, differentiation, and metastasis. Thus, this review will enrich our knowledge to deeply understand the signaling pathways that are involved in critical cellular processes and could help to design novel drugs for the treatment of tumors.

GRK/β-arrestin signaling in cancer progression

G-protein-coupled receptor kinase (GRK) family has seven serine/threonine kinases, which are supposed to inhibit activated GPCRs. They are classified into three sub-groups based on sequence similarities such as rhodopsin kinase (GRK1[rhodopsin kinase] and GRK7 [cone opsin kinase]),β-ARK(β-adrenergic receptor kinase) subgroup (GRK2 and GRK3) and GRK4 subgroup (GRK4, GRK5, and GRK6). There are four members of GRK4 splice variants (GRK4, GRK- α, GRK4- β, GRK4- γ, and GRK4- δ) and three GRK6 splice variants (GRK6A, GRK6B and GRK6C) [31]. GRKs regulate the functionality of both GPCR and growth [32], and they are the first negative GPCR modulators identified, which can be phosphorylated.Its phosphorylation mechanism enhances the recruitment of β-arrestins resulting to an uncoupling from G-protein and GPCR internationalization. Whenever there are changes in GRK functionality, it can influence the balance/bias between the G-protein-independent and GRK/β-arrestins as parts of GPCR signaling and recruitment of arrestin interactors [34-39]. Thus, β-arrestins are recruited to the GPCR upon phosphorylation by GRKs, resulting in the termination of GPCR intracellular signal transduction and control G-protein subunit coupling. GRK phosphorylation of the intracellular regions of the target GPCR is dependent on GPCR inhibition mechanisms in which arrestin can bind to the phosphorylated GPCR domain to inhibit further G protein activation leading to GPCR internalization, desensitization, and recycling or degradation [31,40]. β-arrestins are not only capable of binding to the phosphorylated residues on the receptors but at the same time it binds to the region of the intracellular core which overlaps with heterotrimeric G protein binding site resulting to the blocking of G protein binding to the receptor [9].

On the other hand, β-arrestin mediates GPCR enhancing actin cytoskeleton remodeling by activation and localization of specific proteins for formation of necessary forces of movement during chemotaxis, cell invasion, cancer cell proliferation, metastasis and tumor cell migration [31], resulting in receptor endocytosis and desensitization. Receptor endocytosis and/or β-arrestin in the signaling of other families of cellular receptors and transporters has played a significant role in tumor regulation including non-receptor and RTK, non-classical 7TMARs such as smoothened and frizzled and cytokine receptor also known as TGFB receptors. The interaction of GPCRs with β-arrestins in a ligand or stimulus-dependent fashion regulates cellular proliferation, apoptosis, and differentiation.

PI3K/AKT signaling

Protein kinase B (AKT) is a serine/threonine kinase, which is the central regulator of the widely divergent cellular process, including migration, survival, differentiation, metabolisms, and proliferation. Phosphatidylinositol 3-hydroxy (P13K) is based on

structure, mechanism of activation, and distribution. AKT are classified into catalytic and regulatory subunits as class IAP13Ks and class IBP13Ks. Class IAP13Ks are activated by RTK, whereas class IBP13Ks are activated by GPCR [36,37]. Activated receptors can directly stimulate class 1A P13Ks and binds with regulatory subunit or adapter molecules such as the insulin receptor substrate proteins which on the other hand triggers activation of P13K by converting its catalytic domain of phosphatidylinositol (3,4)-bisphosphate (PIP_2) lipids to phosphatidylinositol (2,3,5)-triphosphate (PIP3) [38]. Meanwhile, different phosphorylation of phosphatidylinositol 3-hydroxy via P13K/AKT Pathway is frequently activated in human cancer which, regulates cell survival, proliferation, adhesion, invasion, migration, and metastasis downstream of several growth factor receptor. The AKT can be activated by numerous types of stimuli via growth factor receptors through phosphatidylinositol 3-kinase (P13K)-dependent manner, which are negatively regulated by the tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (PTEN). The Akt can regulate different cellular functions such as cell growth, metabolisms, transcription, proliferation, survival, protein synthesis, and apoptosis. The activation of Akt are regulated by multistep processes involving P13K [38].

The regulation of cell differentiation, proliferation, migration and trafficking, and maintenance of glucose homeostasis are the basic functions of the P13K signaling pathway. The P13K expression increases the level of phosphatidyl-(3,4,5)-trisphosphate (PIP3) which aims in recruiting protein kinase B (Akt) to the cell membrane via binding to pleckstrin homology domains. For example, the activation of AKT promotes cell survival through several downstream prooncogenic pathways. This happens by preventing the release of cytochrome C and inhibits apoptosis via phosphorylating B cell lymphoma-associated death protein at Ser136, enhancing the release of its inhibition of B cell lymphoma xL (BCl-XL) [25]. Interestingly, the activation of the P13K/AKT pathway in tumor cells increases VEGF secretion by both hypoxia-inducible factor 1 (HIF-1) dependent and independent mechanisms. It can as well balance the expressions of other angiogenic factors such as nitric oxide and angiopoietins [40]. Generally, P13K/AKT regulates tumorigenesis due to its abilities to promotes cell proliferation, survival, and growth and this proved that the activation of the P13K/AKT signaling cascade is vital in medullary thyroid cancer [36].

MAPK Pathway

The effector cells activated by GPCRs are usually an extracellular-regulated kinase ERK, generally known as mitogen-activated protein kinase (MAPKs) [27]. MAPK is made up of c-Jun N-terminal kinases 1-3 (JNK1-3), ERK1/2, ERK5, and p38α-δ MAPKs, which are a group of highly related serine/threonine kinases that link cell surface receptors to transcription factors [28]. MAPK pathways convey the basic information across the membrane-bound receptors, which regulate the expressions of a gene and ERK cascade [31]. There are three subfamilies of MAPKs, such as c-Jun N-terminal kinases (JNKs) ERKs, and p38-MARKs. ERKs are important for cell survival while JNKs and p38-MARKs are responsive and thus regulate apoptosis. MAPK p38 consists of four isoforms [22,23]. ERK1/2 are the major components of MAPK pathways [16]. ERK1/2 share 85% sequence identity and perform identical functions such as regulating several tissues and cells expression [17,24,27,28]. They are ubiquitous in mammalian cells, which are regulated by the GTPase p21ras.

MAPK components play a significant role in targeting certain diseases through regulating, activating, and signaling transduction, which is used as promising tools for preventing, diagnosis, and treatment of diseases caused by parasites [10]. Several pathogens target numerous cells signaling pathways to modulate or inhibit the host's immune responses. Pathogens can utilize cell signaling such as MAPK, which regulates cellular function [10], includingcell proliferation, apoptosis, and differentiation. ERK family members possess a TGY motif present in the activation segment and subdivided into two kinases domain; ERK1 and ERK2 [14,22], others are ERK3/4, and ERK5/ERK7/8 [13].

MAPK pathways are made up of a phosphorylation cascade via a series of binary interactions that are organized for specific responses. MAPKs are regulated by dual phosphorylation of threonine and tyrosine residues within the activation loop and its phosphorylation binds on serine and threonine residues within a MAPK cascade. Thus, the MAPKs pathway is regulated at various levels such as kinase-kinase, and inhibition of cross-talk/output, colocalization of kinases by scaffold protein and kinase-substrate interactions [15]. Scaffold protein interacts with the MAPK pathway, thereby improving the effectiveness of MAPK signaling [34]. Although, the abnormal signaling of MAPK enhances cancer development

and progression [13,16,37]. Additionally, upon activation, MAPK translocate from the cytosol to the nucleus and then modulate its ability to perform the activities of several transcription factors via phosphorylation [14]. With regards to cellular function, the MAPK pathway has become an important signaling system such as cell development, division, cell growth, apoptosis, and synchronization of cellular processes [34]. The intracellular signaling pathways via MAPK inhibit immune responses. They can regulate the production of immunomodulatory cytokines such as TNFα, interleukin (IL)-1, IL-10, and IL-12, which are triggered through the activation of JNK, P38 MAPK, and ERK respectively. The activation of ERK including ERK1/2 through binding ligands to RTK at the plasma membrane (PM) as a result of small G-protein and Ras activation has been established. Ras plays a significant role by recruiting and activating the serine/threonine-protein kinase, Raf and, MAP3K which can further activate the MAP2K and MEK that are capable of phosphorylating the MAPK, and ERK1/2 at threonine and tyrosine residues within the TEY motif. However, activated Raf stimulates signaling cascade via MAPK phosphorylation, leading to the regulation of downstream proteins of ER1/2, which is necessary for a large number of Ras-induced cellular response [38].

MAPK/ GRK2 pathway

GRK2 is a ubiquitous member of the GRK family and plays a vital role in the cellular process [34]. They belong to the subfamily of protein kinase A/G/C-like kinases [42]. GRK2 also possesses specific interaction with Gαq and Gβγ subunits that help to recruit GRK2 into the membrane, and also block the interaction of these G protein subunits with cellular effectors [41]. Furthermore, GRK2 are cytosolic enzymes that transport the plasma membranes when the receptors are activated, and its activities are regulated by interactions with proteins and lipids. GRK2 undergo signaling networks via direct interactions and/or phosphorylation of non-GPCR cellular partners such as RTK and several cytosolic or nuclear signaling proteins [34]. Apart from the phosphorylation-dependent processes/functions of GRK, it can contribute to the modulation of cellular responses in a phosphorylated-dependent manner, which enables its ability to effectively interact with a plethora of proteins involved in signaling and pathway [31]. MAPK cascade has an impact on the cardioprotective profile of GRK2 inhibition through the prevention of cardiomyocyte death. Whereas dual inhibition of RAF/MAPK and GRK2 by Raf kinase inhibitor protein (RKIP) induced cardiomyocyte apoptosis, signs of heart failure, and cardiac dysfunction. It is also reported that cardioprotective signaling induced by GRK2 inhibition appeared overlapping with tumor promotion [24]. When the activity of a particular GRKs is altered, it enhances modulation of proliferation, invasive or survival properties of tumor cells by acting as integrating signaling nodes [32]. No doubt that GRKs contributes to the cancer progression and tumor-specific pattern. For example, the culture of HEK cells with MEF feeder cell shows that GRK2 was able to reduce HEK cell proliferation and also in the dominant-negative GRK2-K220R promoted cell proliferation. Whereas MEF inhibitor PD0325901 prevented GRK2-mediated growth regulation which significantly indicating MAPK pathway-dependent function. The presence of the MAPK pathway and cell proliferation controlled by GRK2 is correlated with the regulation of the nuclear phosphor-ERK1/2 level [8].

Activation of ERK1/2 pathway for tumor regulation

ERK1/2 is a serine/threonine protein kinase belongs to the MAPK family and is present in eukaryotic cells. It plays a crucial role in signaling transduction from surface receptors to the cytoplasm or nucleus which in turn induces expression or activation of specific proteins resulting to the regulation of cell apoptosis, proliferation, differentiation, and metastasis in human malignancies [7]. During metastasis, ERK1/2 regulates invasion, resistance to therapy, and angiogenesis. ERK cascade regulates the apoptosis process by phosphorylation of various apoptotic regulating factors, e.g., caspase-9 [6].

The activation of the ERK signaling cascade enables both upstream activators and downstream targets of ERK1/2 [10]. OnceERK1/2 is activated in response to growth factor stimulation, its regulatory functions will be mimicked by the expression of active Ras resulting to subsequent ERKs phosphorylation via the action of the MAPK kinase, MEK1 and its phosphorylation by the known Ras effector RAF1 [39]. ERK1/2 are expressed hydrophilic non-receptor protein which can participate in the Ras-Raf-MEK-ERK signal transduction cascade found in numerous diseases such as cancer, pain, hypertrophy, and neuroinflammation [13]. The dysregulation of ERK signaling in human tumors causes mutations in RAS/BRAF. The components of ERK signaling cascade are attractive targets for drug development. However, RAF inhibitor has an effect in the treatment of BRAF mutant melanoma and resistance to treatment frequently developed due to an increased RAF dimerization and reactivation of ERK signaling. Therefore, sustained inhibition of ERK

signaling in the tumor may be required for effective treatment of RAS/RAF mutant cancers.

ERK/RTK pathway

ERK pathway is linked to the activation of RTKs. GPCR mediated ERK activation, initiates multiple targets that can regulate crosstalk between GPCR and RTK signaling. GPCR can as well activate the ERK pathway via both G protein-dependent and independent pathways. ERK cascade reactions are activated by numerous stimuli RTK and GPCR. Activation of RTK and GPCR regulates cell differentiation, apoptosis, proliferation, cell survival, migration, and growth. The ability of ERK to be regulated by diverse feedback loops at different levels of the signaling cascade, which governs the temporal dynamics of ERK activity. The ERK activities duration is controlled by various mechanisms such as inactivation by specific phosphatases, internationalization and degradation of RTKs, and inhibition of adaptor protein recruitment by Sprouty (SPRY) family. Therefore, whenever there is inactivation of the RTK/ERK pathway enhances the progression of human cancer. The constitutive activation of RTK/ERK pathway reveals a proliferative advantage, and the malignant phenotypes on the cancer cells. The level of RTK activity under normal physiological conditions are tightly regulated by the mechanisms, including tyrosine phosphatases. RTK requires a transforming ability via mechanisms to maintain the disruption consequences between cell growth/proliferation and cell death. Constitutive RTK activation possesses oncogenic properties upon normal cells and can possibly trigger RTK-induced oncogenesis. Du, Z. and C.M., *et al*. had shown that abnormal RTK activation in human cancers is mediated by several mechanisms such as genomic amplification, gain-of-function mutations chromosomal rearrangements and/or autocrine activation [17].

Interestingly, the oncological activation of the RTK/ERK pathway is often mediated by mutations in the upstream RTK genes, underlies a large proportion of human tumors. This mutation drives aberrant activation of ERK, leading to inappropriate proliferation of tumor cells. On the other hand, the mutation could alter the kinetics of ERK signaling activation in tumor cells e.g., the oncogenic B-RAF mutations slow down both the activation and inactivation rates of ERK activity resulting in slow ERK kinetics. When there is a change in ERK activity kinetics such as activation and inactivation or reactivation, it enhances cancer cells with these mutations to proliferate in response to transient upstream inputs that are not sufficient to induce proliferation of normal cells. In contrast, ERK generated by transient inputs could be prolonged enough to induce cell proliferation.

Cytokine/ERK1/2 pathway for tumor regulation

MAPK p38 is among the three subfamilies of MAPKs, which are essential in regulating the expression of numerous cytokines activated in immune cells by inflammatory cytokines that are very vital in the activation of host immune response [18]. Cytokines, growth factors and ligands are capable of activating the ERK pathway mainly by GPCR [20]. Additionally, the activated ERK by cytokines initiates expression levels of transcription factors, protein kinase, and regulatory genes, thereby modulating cell migration, differentiation, survival, proliferation, and apoptosis with rapidness and sequence [27]. Reports showed that cytokine is among different stimuli that can activate the ERK1/2 pathway, which involves in the regulation of mitosis, meiosis, and post-mitotic functions in numerous cells [18]. On the other hand, cytokines are molecules that are actively released in response to infection, inflammation, or immunity that can inhibit cancer development and progression. Cytokine mainly transfers their signals via Janus kinase (JAKs), signal transducer, and activator of transcriptions (STAT) pathway [21]. They can trigger cellular effects and functions across signaling through JAK and signaling transducer and activator of (JAK/STAT) molecules [23]. JAK/STAT pathway is a principal signaling pathway for the signal transduction of many key cytokines involved in sepsis, which regulates cellular processes including differentiation, secretion of cytokines, or proliferation, and apoptosis in inflammatory bowel diseases in both adaptive and innate immune cells [23]. JAK/STAT signal is essential for the development and regulation of immune response [25]. The binding of cytokines to corresponding receptors can activate JAK, which can as well selectively phosphorylate STATs in which the activated STATs, in turn, translocate to the nucleus for the transcription of targeted genes [24]. The binding of specific ligands to cytokines induces conformational changes in the receptor leading to the activation of JAKs. The activated JAKs subsequently induce phosphorylation of specific tyrosine-based motifs in the cytokine receptors, which provides docking sites for Src homology 2 (SH2)-containing STATs [21].

Wnt/β-catenin signaling pathways in tumor regulation

The Wnt pathway mediates the biological process by a canonical or non-canonical pathway depending on the involvement of

β-catenin in signaling transduction. Wnt is originated from a fusion of the name of the Drosophila segment polarity gene wingless and the name of the vertebrate homolog [26-28]. The activation ofWnt/β-catenin signaling of the cascade is triggered by the binding of a Wnt ligand (Wnt1, Wnt2, Wnt3, Wnt3a, Wnt7a, Wnt7b, Wnt8a, Wnt10b or Wnt16) to its respective Fzd family of proteins [29,31]. In fact, Wnt ligands can reprogramed tumor cells metabolically. Thus, once there is a change in Wnt signaling, it can regulate the metabolic flexibility within tumors, which has presented a significant research interest in the role of Wnt signaling in tumorigenesis [31]. Wnt/β-catenin signaling is a highly conserved pathway which can regulate apoptosis, genetic stability, differentiation, growth, migration, stem cell renewal, and proliferation [43] and polarization. Furthermore, upon changes in the signaling, it has a significant effect on the physiological processes, including sustaining and cancer stem cell (CSC) proliferation in tumors [34]. Wnt/β-catenin signaling pathways also regulates the self-renewal and migration of cancer stem cells (CSCs), thereby promoting tumor growth and metastasis in breast cancer.

Meanwhile, about 80% of sporadic colonic cancers reportedly have stable β-catenin mutations and continuous activation of canonical Wnt signaling enhanced the initiation and development of colorectal cancer [37]. The role of canonical Wnt signaling in triple-negative breast cancer development has been fully established, and its self-renewal potential of cancer cells by the cancer stemness models became a strategic tool used to constructively explain numerous malignant phenotypes. This maybe as a result that stem cells have the ability to maintain long telomeres through the function of the TERT gene. TERT expression can be directly enhanced by binding of β-catenin to its promoter region, which also on the other hand, links telomerase activity to Wnt signaling [40,41]. At present, Wnt signaling is activated in 50% of breast tumor-related cases with a reduction rate in overall patient survival. Although Wnt/β-catenin signaling have been implicated in triple-negative breast cancer (TNBC). Interestingly, nuclear β-catenin can be overexpressed by other subtypes of breast cancer [30,42,43]. Therefore, activation of Wnt/β-catenin signaling by the pluripotent mesenchymal stem cells recruited to the tumor site enhances tumor development by promoting metastatic growth and resistance to chemotherapy in cholangiocarcinoma. For example, the M2-polarized tumor-associated macrophages (TAMs) in the surrounding stroma regulates the highly activated Wnt pathway in the tumor [43]. Though, Wnt/ β-catenin signaling in pancreatic cancer chemoresistance and subsequently targeting the signaling improves the sensitivity of chemotherapy in pancreatic cancer which, require a full mechanistic understanding of Wnt/ β-catenin signaling pathway in angiogenesis, relates cell cycle, maintaining highly resistant CSCs and apoptosis in pancreatic cancer [15]. Additionally, high activity of the Wnt pathway through hepatocyte growth factor (HGF) can activate β-catenin-dependent transcription, which can maintain CSC clonogenicity and restores the CSC phenotype in more differentiated tumor cells both *in vitro* and *in vivo*.

Types of Wnt/ β-catenin pathway

The extracellular Wnt signal stimulates several intracellular signal transduction cascades, such as the canonical or Wnt/β-catenin dependent pathways and the non-canonical or β-catenin-independent which consists of Wnt planar cell polarity (Wnt/PCP) pathway and the Wnt/Ca^{2+} pathway [26]. Non-canonical Wnt signaling plays a significant rolein transducing signaling either via intracellular Ca^{2+} levels or by small GTPases, which is capable of regulating cytoskeletal improvement. These signaling mechanisms are termed Ca^{2+} and planar cell (PCP) pathways [42]. Wnt/β-catenin dependent pathway is generally associated with cell polarity, differentiation, and migration [14].

Planar cell polarity (PCP) pathway in tumor regulation

PCP mediates the polarity cue in both Drosophila and vertebrates [20]. PCP signaling is required for the planar polarization of epithelial cells, e.g., during hair orientation and gastrulation in vertebrates. PCP pathways originated from genetic studies in Drosophila in which its mutations in Wnt signaling components such as Dishevelled (Dsh) and Frizzled (Fz) was established [41]. PCP pathway is referred to as a non-canonical Wnt/PCP pathway because of the presence of Dvl homologs and Fz receptors in the βcatenin-independent signaling pathway [39]. Fz and Dsh are the only two components known to be involved in both Wnt/β-catenin and PCP signaling [38]. Signaling via Fz/PCP is a conserved mechanism that polarizes cells along specific axes in a tissue. They depend on complex interactions between core components resulting in their asymmetric distribution and ultimately polarized activity in a cell [30].

Fz/PCP signaling regulates cell motility in the contexts of convergent extension and ommatidial rotation where these polarizing signals might regulate cell adhesive contacts by the recycling of E-

cadherin. They can as well regulate cell migration events during development. It is also used to generate movement in cells. Wnt5a ligands downstream of general mechanisms for many vertebrate PCP such as PCP-dependent cell movement. For example, the neural crest is a multipotent cell population formed through the neural and non-neural ectoderm enhances neural cells to migrate through the whole process of embryo response to chemotropic cues and enhance various neural and non-neural tissues [13,19]. PCP signaling can regulate neuronal migration and cell development, especially during vertebrate development, which has since become a notable research question [14]. Thus, PCP signaling involvement in cancer development still not properly established and remain controversial. Though, PCP signaling triggers tumor metastasis, invasion, and angiogenesis through the action of Wnt5a and as well involves in tumor suppression of Fat [24].

Wnt/Ca^{2+} pathway in tumor regulation

Wnt/Ca^{2+} signaling pathways are associated with tumor formation, and its activation are mainly through the binding of the Wnt ligand to the Fzd family of proteins. On the hands, it can activate phospholipase C (PLC) in which the secondary messengers enhance the release of intracellular calcium, and activation of calpain-1 and calcineurin (Cn) occurred due to calcium-dependent kinases [27]. Calcium-dependent kinases such as calcineurin (Calcin), calmodulin-dependent kinase II (CamKII), phosphatase, and protein kinase C (PKC) mediate varieties of effects in animal tissue. For example, CamKII and PKC can control dorsoventral in the embryo by regulating cell adhesion, differentiation, migration regulated through transcription factor known as nuclear factor of activated T cells (NFAT) [16].

Noncanonical Wnt-Ca^{2+} pathway process enhancing ligand Wnt5a tointeracts with Fzd receptors with co-receptor ROR1 or ROR2 causes the release of Ca^{2+} from the endoplasmic reticulum and activating phospholipase C via G-protein and SEC14-like protein 2 (SEC14L2) for the formation of 1,2-diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3) [30]. Furthermore, the reaction of Wnt5a with Fzd receptor via ROR2 is capable of mediating lamellipodia formation, cell invasion, increase cell migration, and promotion of metastasis. Thus, the activation of Wnt/Ca^{2+} signaling in a cancer cell by Wnt ligand via Wnt5a and its expression is associated with both tumor-prooncogenic and suppressive. In breast and colon cancers, the expression of Wnt5a correlates with a good patient prognosis with poor survival in melanoma and gastric cancer [17]. For example, in breast cancer cells, the effect of Wnt5a on reprogramming cancer cell metabolism is highly dependent. It can alter energy metabolism in distinct ways between melanoma breast cancer cells, thereby increasing the oxidative phosphorylation (mitochondrial respiration). This show that Wnt5a can considerably increase basal respiration and ATP turnover in breast cancer cells.

Future prospective

GPCRs signaling has been well implicated in cell differentiation, apoptosis, proliferation and control tumor progression. The chemotherapeutic approach in cancer treatment has gained much ground in the area of specific drug targeting. For this fact, there is need to further study the toxicity effects of each GPCRs mediated signaling pathways with respect to the chemotherapeutic methods of cancer treatment especially in breast cancer.

Conclusion

The GPCR is an integral membrane protein used by the cells to convert extracellular signals into intracellular responses. Currently, the use of different GPCR influenced signaling pathways as therapeutic targeting in regulating cancer progression, and metastasis has been fully established. In this article, we briefly discuss the progressive studies conducted previously on different signaling pathway and its effects on cancer growth, metastasis, and progression. These investigative studies provided an insight on the regulation of several signaling pathways including β-arrestin/GRK, PI3K/AKT, MAPK Pathway, Wnt/β-catenin, ERK1/2/Cytokines, ERK1/2, ERK/RTK, MAPK/ GRK2 especially for cellular function, and tumor progression.β-arresting -dependent ERK activation is slower and has a more sustained duration, and very sensitive to the use of β-arrestins, but an interaction with β-arrestins restricts activation of ERKs to the cytoplasm in several cases, and this has become a significant challenge. The ERK cascade remain the central signaling pathway which is responsible for the regulation of several types of cellular processes such as migration, growth, differentiation, survival, growth arrest, apoptosis, and proliferation.

Author Contribution

Muhammad Mehran Mouzam contributed in designing, writing, analyze the article. Aamna Bibi contributed in proofreading, evaluate revised. Watiba Danish and Noman Haider gave approval of the version to be submitted. Ayiza Sulaiman and Fatima Naveed

contributed in proofreading, analyze the article, evaluate revised version of the article, and approve its submission.

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