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# ROLE OF GPCR SIGNALING PATHWAY IN CANCER DEVELOPMENT- A REVIEW

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**Abstract—***Cancer is an irregular growth of cells brought about by multiple changes in gene expression. This results in a population of irregular cells that may invade tissues and metastasize to distant sites (Fidler,2003). Cancer causes due to a mutation in genes responsible for regulation of cell cycle, oncogenes, tumor suppressor genes, etc. G-protein coupled receptors(GPCR) are a large group of cell surface receptor associated with heterotrimeric signal transducing G-protein (Marinissen et al., 2001). GPCRs such as CXCR4, SDF1 and EP2, etc. plays an important role in the regulation of cell growth, differentiation, and gene transcription, three vital factors to the biology of cancer (Fidler,2003). Malignant cells often take over the normal physiological functions of GPCRs to survive, evade the immune system, surrounding tissues and disseminate to other organs, proliferate autonomously, increase their blood supply (Dorsam and Gutkind, 2007). Emerging experimental and medical knowledge indicate that GPCRs have a principal position in melanoma progression and metastasis. Many reports suggest that aberrant expression of GPCR lead to cancer (Wu et al., 2012).*

**Keywords***: Cancer, oncogenes, Tumor suppressor genes, G-protein coupled receptors (GPCR), Malignant cells.*

## Introduction

### Cell cycle

It is a series of events that prepares a cell to divide and finally divides. The cell cycle consists of two phases; Interphase and Mitosis. In interphase, the cell prepares itself for division. It again comprises of 3 phases; gap1 (G1) phase, synthetic (S) phase and gap2 (G2) phase(Figure 1). G1 phase represents the time interval between mitosis and initiation of next cell cycle DNA replication. Cells metabolically grow but does not replicate. mRNA and proteins required for replication are synthesized. In S-phase DNA replication takes place which is followed by G2 phase, whereby, cells prepare themselves for mitosis.

### Cell cycle regulation

The process of the cell cycle is highly regulated and is achieved by both extracellular signals as well as intracellular signals. The passage of a cell through the cell cycle is strickly regulated by cyclin and its corresponding cyclin-dependent kinase (Cdk) a serine/ threonine kinases. There are different types of cyclin and Cdks which functions in different phases of cell cycle, for example, Progression of G1 to S is regulated by Cdk2, Cdk4 and Cdk6 in association with cyclin D and E. Cdk2 and cyclin E are required for transition of cell from G1 to S and initiation of DNA replication.Cdk2/Cyclin A is necessary for progression through S phase and Cdk21/cyclinA and Cdk1/cyclinB is a requisite for transition of cell through S to G2 and G2 to M respectively. The cell cycle is regulated by Cdk/cyclin complex at certains points in the cell cycle. These points are known as cell cycle checkpoints. There are three checkpoints in the cell cycle *viz*., G1/S, G2/M and M. G1/S checkpoint is situated near the end of G1 phase. In this point the cell is checked for cell size, energy reserve and DNA damage. P53 and Rb, known as tumor suppressor gene functions at this point. P53 detects DNA damage and restrict cell cycle progression. It can also induce apoptosis if the cell is not fit for next step. Rbprotein restricts cell cycle by binding to the elongation factor E2F. In G2/M checkpoint, cell is scrutinized for complete and error free replication of the DNA, cell size and protein reserves. P53 function here in a similar manner as it does in G1/S checkpoint. Wee1 and cdc25 regulates the entry of cell into mitotic phase. It is found that decrease in Wee1 and cdc25 drives the cell toward mitosis. M checkpoint, also known as the spindle checkpoint occurs near the end of the metaphase stage of mitosis. At this point cell are checked for correct alignment of sister chromatids to the spindle microtubules. The function is performed by anaphase promoting complex.

Cell cycle checkpoints and DNA repair mechanism correlates to cancer. Dysfunction of these two machineries linked to genome instability in cancer. Loss of ATM, a protein kinase helps in detection of DNA damage found to precede lymphoma (Shiloh and Kastan, 2001), single mutant inheritance of BRCA1 or BRCA2 in women is found be associated with breast and ovarian cancers (Neibergs, 2004).

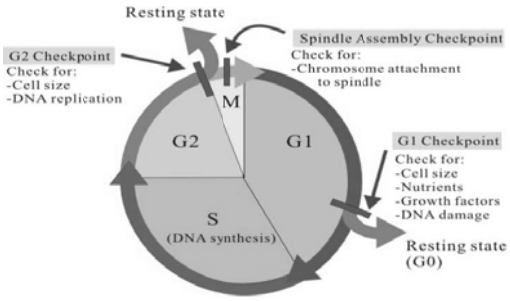


**Figure 1: Cell cycle regulation**

### 1.3 Cancer

According to Ruddon (2007) cancer be defined as abnormal growth of cells caused by multiple changes in gene expression that leads to a population of abnormal cells which can proliferate rapidly, forms new blood vessels and move to other organs (metastasis). It is a disease of multicellular organism. Abnormal cell growth leads to tumor formation. Tumor can be of two types: benign and malignant. Malignant tumors invade and destroy adjacent normal tissue, metastasize via lymphatic channels/ blood vessels to lymph nodes and other tissues ;Whereas, benign tumors do not invade surrounding tissue and are well differentiated as normal tissue.

### 1.4 Genetic basis of cancer

Two types of genes proto-oncogenes and tumor suppressor genes play an important role in cancer. Loss of function mutation in tumor suppressor gene and gain of function mutation in proto-oncogenes generally leads to cancer. Almost all human tumor have loss of function mutation of genes that acts at various cell cycle checkpoints to check cell cycle progression. For example loss of function mutation in p53 protein that acts as a DNA damage checkpoint in G1 phase is found to be associated with most number of cancers (Shiloh and Kastan, 2001). Gain of function mutation in proto-oncogene convert proto-oncogenes to oncogenes. Eg. Overexpression of c-myc, Ras genes is found to associated with cancer induction and proliferation. Other than mutation in proto-oncogenes and tumor suppressor genes, mutation in growth inhibitor, cell cycle controls, DNA repair mechanism also lead to cancer.

### 1.5 GPCR

GPCR are heptahelical cell surface receptors coupled with hetero-trimeric G-protein for signal transmission. It contains seven transmembrane α-helices with N-terminus on the exoplasmic face and C-terminus on the cytosolic face of the plasma membrane (Marinissen *et al.,* 2001). GPCR has four segments each on the exoplasmic (E1-E4) and cytosolic (C1-C4) face. The carboxyl-terminal segment (C4), the (C3) loops, and in some receptors, also the C2 loop are involved in interactions with trimeric G-protein. GPCR play a crucial role in multiple physiological functions as well as in tumor growth and metastasis (Marinissen *et al.,* 2001). For example, various biomolecules like hormones, lipids, peptides and neurotransmitters exert their biological effects by binding to GPCR coupled to heterotrimeric G-proteins, which are highly specialized transducers able to modulate diverse signaling pathways. Moreover, numerous responses mediated by GPCRs are not dependent on a single biochemical route; instead, result from the combination of a complex network of transduction cascades involved in many physiological activities and tumor development.

### 1.6 General mechanism of GPCR mediated signal transduction

The G-proteins contain three subunits designated as α, β and γ. During signalling the β and γ subunits remain bound together and are usually referred to as the Gβγ subunit. The Gα subunit is a GTPase protein that alternates between an active state with bound GTP and an inactive state with bound GDP. When ligand binds to receptor, it induces a conformational change in the receptor, which in turn activates the trimeric G-protein. The activated GPCR catalyzes exchange of GTP for GDP on the Gα subunit, as a result conformational changes takes place in the receptor, which leads to dissociation of Gβγ dimer from Gα . Activated Gα and Gβγ proteins then binds to various effectors and thereby switches it either on or off in different systems, and effectors continue to pass the signal to different kinds of second messengers such as Ca2+, cAMP etc. When the ligand dissociates from the receptor, an intrinsic GTPase activity convert bound GTP to GDP, which leads to the inactivation of G-protein cascade (Marinissen *et al.,* 2001).

### 1.7 Gα and Gβγ mediated GPCR signalling

The effector molecule for Gαs and Gαi signalling is cAMP. In Gαs cytosolic ATP is converted into cAMP by Adenylyl cyclase whereas Gαi inhibit conversion of ATP into cAMP. The effector molecule for Gαq signalling is phospholipase C-β (PLCβ). PLCβ catalyzes the cleavage of phosphatidylinositol 4,5-biphosphate (PIP2) into the second messengers inositol (1,4,5) trisphosphate (IP3) and diacylglycerol (DAG), which further activates secondary effector molecules and signalling cascades (Marinissen *et al.,* 2001). The effectors molecules of the Gα12/13 pathway are three Rho-GEFs. The bound Rho-GEF activates small GTPase and Rho. The GTP bound Rho can further activates proteins for cytoskeleton regulation such as Rho-kinase (ROCK). The effector molecules of Gβγ are various ion channels, such as G-protein-regulated inwardly rectifying K+ channels (GIRKs) as well as some isoforms of AC and PLC along with some phosphoinositide-3-kinase (PI3K) isoforms.

### 1.8 GPCR and cancer

GPCRs have clear functional links to cancer. Many reports suggest that over expression of GPCR links to cancer. GPCRs have been found to be overexpressed in primary and metastatic melanoma, human colon carcinoma, squamous cell carcinoma (SCC) of the lung, basal cell carcinoma (BCC), hepatocellular carcinoma (HCC), and glioblastomamultiforme. Some of the GPCRs and ligands found to be involved in cancer. Orphan GPCRs such as GPR18, GPR48/LGR4, GPR49, GPR56, GPR87, and CXCR7/CMKOR1 are also

linked to the cancer phenotype. It was reported that GPR18 is overexpressed in melanoma GPR48 is involved incolon cancer invasion and metastasis (Wu et al., 2012).

**1.9 GPCR links inflammation cancer**

Cyclooxygenase (COX), also known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme that is responsible for synthesis of prostaglandin. Non-steroidal anti-inflammatory drugs (NSAID) such as aspirin and ibuprofen functions by inhibition of COX. COX1 and COX2 produce prostaglandin E2 (PGE2) that binds to its GPCR EP2. The binding of this ligand and receptor activates trimeric G protein. The Gαs subunit activates Adenylyl cyclase as a result of which CAMP concentration increases in the cytoplasm and Protein Kinase A get activated which phosphorylate CREB protein and increases the transcription of COX2 responsible for inflammation The Gβγ subunit stimulates Akt also known as protein kinase B through phosphatidylinositol-3 kinase (PI3K). Gαs subunit simultaneously binds to axin, a cytoplasmic protein through its regulator of G-protein signalling domain (RGS). This Gαs- axin binding releases glycogen synthase kinase 3β (GSK3β) from the complex (axin/APC/ GSK3β). The Akt stimulated by both Gβγ in turn phosphorylates the GSK3β inactivating the molecule. Inactivation of GSK3β leads to stabilisation, nuclear translocation and transcriptional activation of β-catenin. The β-catenin in turn binds to TCF/LEF transcription factor and transcription of MYC, cyclin D, IL8, MMPs VEGF occurs.

**1.10 GPCR in cancer metastasis**

Stromal cell derived factor (SDF1), Lysophosphatidic acid (LPA), and thrombin promote the migration and invasion of cancer through its associated receptor, CXCR4, LPA1 and PAR1 respectively.COX2 expressed in tumor and stromal cells produces prostaglandin E2(PGE2) which binds to E2 receptor on cancer cell. The binding of PGE2 to cancer cell, releases MMP2 and MMP9, matrix metaloproteinases that degrades the extracellular matrix. In solid cancer cells, under hypoxic condition, hypoxia induced factor ( HIF1α) is activated; HIF1α enables the tumor cells to migrate from low O2 by migrating towards gradient SDF1 released by other organs. CXCR4, a chemokine receptor binds to SDF1 expressed on secondary organs. Thus, tumor expressing CXCR4 have affinity towards secondary organs expressing SDF1. The movement of cells results from contractile force at the back and side of cell that propel the cell towards chemo attractant (Wu et al., 2012). Stimulation of these GPCRs, such as CXCR4, LPA1, PAR1 and EP2, increases the release of vascular endothelial growth factor (VEGF), which promotes vascular permeability. Vascular permeability is required for extravasation and angiogenesis. Thus, tumor cell expressing these GPCRs move from primary organ to secondary organ in search of nutrient, oxygen, a process called metastasis. Tumor chemokine microenvironment helps evade immunosurveilance by stimulating less effective humoral response and inhibiting cell mediated immune response to tumor cells (Wu et al., 2012).

**1.11 GPCR in angiogenesis**

Tumor cell use strategies to complete their need for nutrient and oxygen. They produce angiogenic factors such as VEGF, bFGF, TGF-α, TGF-β, TNF-α, IL8 etc, by switching gene expression. Thrombin, a pro angiogenic molecule increases the expression of VEGF in cancer cell and its receptor in endothelial cells causing vascular permeability. It also acts on PAR1, leading to disassembly of endothelial adherence junction, thus inducing the vascular permeability. Thrombin cleaves fibrinogen to fibrin rich extracellular matrix. This creates a favourable environment for tumor endothelial cell adhesion, further blood vessel and tumor growth. IL8 is also a proangiogenic factor. It is released by endothelial cells in response to VEGF/NFkB. IL1 and VEGF promotes COX2, which in turn produces PGE2 that activate NFkB and ERK pathway. NFkB in turn releases IL8 and ENA78 and ERK pathway leads to increase in VEGF. Cancer also produces CC and CXC chemokines such as CCL2, CCL5 and IL8. These chemokines in turn recruits leukocyte, macrophage to tumor. These immune cells help to promote blood vessel growth, by releasing VEGF and other angiogenic factor. Cancer cells also upregulate COX2, which releases PGE2 and binds to E2 receptor on endothelial cell. It functions as a pro angiogenic factor.

**2. Future directions**

**2.1** Various evidence suggests that regulating GPCR function may delay or halt the progression of cancer. GPCRs for chemokines such as thrombin, COX2 are suitable targets for cancer treatments. There are reports to characterize SNPs in GPCR. This may be the key to study epidemiological studies in population based cancer. SNP might alter gene expression, ligand binding, etc. It was found that CCR5, CCR2, CCL5, SDF1, and CXCR6 has many polymorphism. Drug delivery, tumor imaging and biomarkers heralding are three emerging uses of GPCR

**2.2** GPCRs might also be valuable biomarkers for cancer diagnosis, as proven in malignant prostate cancer cases

**2.3** GPCRs have a well documented role in normal and aberrant mitogenic signalling and regulation of key molecular events implicated in cancer progression and invasion such as-

Upregulation of the activity and expression of matrix metalloproteinase and VEGF.

**3. Conclusion**

GPCRs are very important both physiologically and biologically. Their dysfunction are associated with development of various types of cancers such as breast, head and neck, prostate, colon cancer, basal cell carcinoma etc. It has been seen that GPCRs family can be used as therapeutic target in cancer research studies and control. Some limitations are visible in their role as potential drug targets which is

mainly due to the problems in the identification of their natural ligands. GPCRs deserve the most important attention in drug discovery programs.

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