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Novel insights into G protein and G protein-coupled receptor signaling in cancer

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Abstract

G protein-coupled receptors (GPCRs) play a central role in signal transmission, thereby controlling many facets of cellular function. Overwhelming evidence now implicates GPCRs, G proteins and their downstream signaling targets in cancer initiation and progression, where they can influence aberrant cell growth and survival, largely through activation of AKT/mTOR, MAPKs, and Hippo signaling pathways. GPCRs also play critical roles in the invasion and metastasis of cancer cells via activation of Rho GTPases and cytoskeletal changes, and angiogenesis to supply the tumor with nutrients and provide routes for metastasis. Lastly, GPCRs contribute to the establishment and maintenance of a permissive tumor microenvironment. Understanding GPCR involvement in cancer malignancy may help identify novel therapeutic opportunities for cancer prevention and treatment.

Introduction

Agonist binding to G protein coupled receptors (GPCRs) results in rapid conformational changes that lead to the activation of heterotrimeric G proteins, comprised of $G\alpha$, β and γ subunits, and the recruitment of proteins responsible for receptor internalization and desensitization, including arrestins and GPCR kinases (GRKs) [1,2]. A novel family of highly evolutionarily conserved α -arrestins has recently received attention due their implicated roles in GPCR trafficking and degradation [3]. Most GPCRs will activate one or multiple $G\alpha$ proteins, which can be subdivided into 4 major families: $G\alpha_i$, $G\alpha_{12}$, $G\alpha_s$, and $G\alpha_q$, with each family activating distinct signaling pathways [4]. GPCRs can also trigger G protein-independent mechanisms, including signaling through β -arrestins and interactions with PDZ containing proteins and other GPCR-regulators/scaffolding proteins [5]. GPCRs act more as molecular rheostats rather than on-off switches, so the engagement of different G proteins and strength/duration of signaling may not only differ between GPCRs, but also for a given GPCR, depending on the ligand and cellular environment.

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Early indications that GPCRs could function as oncogenes include characterization of the transforming capacity of the *mas* proto-oncogene and other GPCRs in the presence of excess ligand availability, the identification of activating oncogenic mutations in thyroid stimulating hormone receptor (TSHR), and the association of virally-encoded GPCRs with tumorigenesis [4]. Since then, many GPCRs were shown to be overexpressed in a variety of cancer types and linked to tumor-cell growth when activated by circulating or locally produced ligands. Yet, despite the association of GPCRs with cancer progression and the fact that GPCRs represent one of the most “druggable” classes of molecules, representing approximately 25% of all therapeutics on the market, there are relatively few cancer treatments targeting GPCRs [6]. By better understanding the molecular mechanisms underlying GPCR function in cancer, we can identify the best therapeutic targets for cancer prevention and treatment.

GPCRs signaling in normal and cancer cell proliferation and survival

Cell growth promotion has been traditionally associated with the activation of tyrosine kinase growth factor receptors (RTKs) [7]. The discovery and use of bacterial toxins inhibiting G protein α_i subunits [8] established that multiple mitogens transduce proliferative signals through GPCRs, including thrombin and lysophosphatidic acid (LPA) [9-11]. Subsequent studies revealed that many mitogens act on GPCRs linked to the G_q and G_{12} G protein families, including many peptide hormones, bioactive lipid mediators, and neurotransmitters [4,12], supporting the involvement of GPCRs in cell proliferation in a variety of cell types [4,13,14]. The molecular mechanisms underlying cell growth promotion by GPCRs is still an active area on investigation, as it involves the coordinated activation of traditional second messenger generating systems with the regulation of protein-protein interaction based networks. Some of these signaling circuits may act in cell type specific manners to initiate or sustain cancer cell growth and the metastatic spread of primary tumor lesions.

Second messenger generating systems

GPCR stimulation triggers the activation of heterotrimeric G proteins as GTP replaces GDP on the $G\alpha$ subunit, promoting its dissociation from $G\beta\gamma$ subunits. Both α -GTP bound and $G\beta\gamma$ subunit complexes then stimulate multiple downstream signaling cascades [4, 2], including the rapid generation of multiple second messengers. For example, $G\alpha_s$ stimulates adenylyl cyclases, increasing the cytosolic levels of cAMP, while $G\alpha_i$ inhibits adenylyl cyclases and hence decreases cAMP levels [15]. Members of the $G\alpha_q$ family activate phospholipase- $C\beta$, which cleaves PIP_2 into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3); the latter causes an increase in cytosolic calcium [16]. The targets of these diffusible second messengers include ion channels, calcium-sensitive enzymes, and kinases such as cAMP-dependent kinase (PKA), protein kinase C (PKC), cGMP-dependent kinase (PKG), and calcium-calmodulin regulated kinases (CAMKs), which are stimulated by cAMP, calcium/DG, cGMP, and calcium, respectively (Figure 1). Many of these kinases contribute to cancer progression and metastasis [17-22].

Small GTPases and MAPK cascades

In addition to the regulation of second messengers, GPCRs can control cell migration, survival, and growth by activating multiple mitogen activated protein kinase (MAPK) cascades. These include ERK1/2, JNK1-3, p38 α - δ MAPKs, and ERK5, which are a group of highly related serine/threonine kinases that link cell surface receptors to transcription factors [23]. In general, while Ras GTPases regulate ERK1/2, small GTPases of the Rho family, Rho, Rac, and Cdc42, control JNK and p38 MAPKs by a distinct kinase cascade [24] (Figure 1). These MAPKs play key roles in cell proliferation and metastasis, and their deregulation is a frequent event in human malignancies. Hence, how GPCRs regulate MAPKs, particularly through Ras and Rho GTPases, has been explored under multiple physiological and pathological conditions.

Specifically, many GPCRs coupled to G_i activate Rac and JNK through the direct interaction of G $\beta\gamma$ subunits with the P-REX1/2 family of Rac guanine nucleotide exchange factors (GEFs) [25,26]. G α_q activates Rho GTPases through p63-RhoGEF and Trio [27]. Receptors coupled to G α_{12} and G α_{13} activate Rho by stimulating a family of Rho GEFs, comprised of p115, PDZRhoGEF and LARG [28]. The JNK cascade is activated downstream of Rac and Cdc42 [24], which can mediate signaling from G $\beta\gamma$ dimers and G α_{12} , G α_{13} , G α_q and G α_i (reviewed in [4]). Activation of the ERK1/2 pathway by GPCRs is achieved in a highly cell-specific fashion (reviewed in [4]), promoted by Ras, tyrosine kinases, PI3Ks, PKCs, and/or arrestins. How GPCRs activate p38 and ERK5 is much less clear, but in general these MAPKs are activated primarily by G α_q , G $\alpha_{12/13}$, and G $\beta\gamma$ dimers [4]. Activation of MAPK pathways stimulates the expression of growth promoting early-immediate responsive genes, including those encoding the AP-1 family of transcription factors. MAPKs are involved in the regulation of both gene expression and transactivating activity of AP-1 members by a complex and not fully understood mechanism (Figure 1).

Activation of the PI3K, AKT, and mTOR pathway

Activation of the PI3K-AKT-mTOR pathway plays a central role in cell metabolism, migration, growth and survival [29,30]. PI3K generates PIP₃ inducing activation of AKT and mTOR [29,30]. PI3K γ exhibits restricted tissue distribution and is activated by the direct interaction of its catalytic (p110 γ) and regulatory subunit (p101) with G $\beta\gamma$ subunits [31]. PI3K γ is involved in chemokine-induced migration of leukocytes, and plays significant roles in innate immunity [32]. In cells lacking PI3K γ expression, GPCRs can utilize PI3K β to stimulate PIP₃ synthesis [33,34]. One of the most studied PI3K-regulated events is the activation of the kinases AKT and mTOR, which phosphorylate multiple substrates involved in cell migration, survival, and metabolism [33,34] (Figure 2).

Regulation of the Hippo signaling pathway

GPCRs involved in cell proliferation stimulate the activity of the transcriptional co-activator YAP [35], which is a critical component of the Hippo signaling pathway that controls organ size in mammals [36-39]. YAP (and related TAZ), is active in proliferating cells, but cell confluence triggers the activation of the growth-inhibitory Hippo kinase cascade. This causes the activation of two kinases known as LATS1/LATS2, which phosphorylate and thereby inhibit YAP [40]. GPCRs linked to G $\alpha_{12/13}$ inhibit the activity of LATS, thus

relieving YAP from LATS-dependent inhibition [35], while receptors activating G α s promote LATS activation thus inhibiting YAP [35]. Recent work in our laboratory indicates that oncogenic mutations in the gene encoding G α_q activate YAP by a mechanosensing pathway initiated upon actin polymerization rather than by the inhibition of the Hippo pathway (unpublished results). YAP activation may represent a key pro-tumorigenic pathway activated by GPCRs, thereby representing a novel target for cancer treatment.

GPCR signal integration and crosstalk

While GPCRs can stimulate multiple diffusible second-messenger generating systems, their ability to promote normal and aberrant cell proliferation often relies on the persistent activation of PI3K/AkKT/mTOR, Ras and Rho GTPases, and MAPK cascades, thereby regulating the activity of nuclear transcription factors and co-activators, such as JUN, FOS and YAP [35,41]. Additionally, arrestin proteins contribute to G protein-dependent and G protein-independent events, initiating signaling and regulating receptor internalization and degradation/recycling kinetics [42,43]. β -arrestins are now believed to scaffold a wide variety of signaling complexes [44,45]. Some β -arrestin-biased GPCR agonists initiate intracellular signaling independently of the activation of heterotrimeric G proteins [45]. By forming multimeric signaling complexes with ERK1/2 and JNK, β -arrestins can retain these MAPKs in the cytosol, thus restricting their nuclear translocation and leading to interaction with cytosolic substrates instead [45].

A more global view of the general systems by which GPCRs exert their numerous physiological and pathological roles is necessary to appreciate the overall implications to tumorigenesis. In particular, extensive cross-talk and co-regulation may occur between GPCR- and RTK-initiated signaling pathways and through receptor transactivation [46,47]. Therefore, the final biological outcome of GPCR activation results from the integration of the network of GPCR-initiated biochemical responses in each cellular and environmental context. Such systems level understanding may provide a molecular framework for the development of novel approaches for therapeutic intervention in some of the most prevalent human diseases.

Viral GPCRs

Early studies of virally-encoded oncogenes provided the foundation of our current understanding of cancer biology. At least seven human viruses, Epstein-Barr virus (EBV/HHV- 4), hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV), human T-cell lymphotropic virus (HTLV-1), and Kaposi's associated sarcoma herpes virus (KSHV/HHV- 8), and Merkel cell polyomavirus, contribute to 10-15% of cancers [48,49]. Surprisingly, many human viruses harbor open reading frames encoding GPCRs in their viral genomes, indicating that these signaling circuits are required for replicative success [50]. For example, EBV encodes one GPCR (BILF1), and human cytomegalovirus (HCMV/HHV-5) expresses at least four GPCRs (US28, US27, UL33 and UL78). KSHV encodes a receptor commonly known as KSHV vGPCR (or ORF74), that resembles CXCR1 and CXCR2, the receptors for CXCL8/IL-8 and CXCL1/Gro- α chemokines [51]. KSHV vGPCR is constitutively active due to the presence of a several structural changes, and contributes to KS development due to its potent transforming and pro-angiogenic properties.

It promotes sarcomagenesis by increasing the activity of a complex signaling network, among which the activation of the PI3K γ /AKT/mTOR pathway represents a clinically relevant target for KS treatment (Figure 2). Ultimately, KSHV vGPCR-expressing cells act in a paracrine fashion to stimulate the unrestricted growth of surrounding and distant endothelial cells, thereby representing an excellent example paracrine neoplasia.

GPCRs in migration, invasion and metastasis

One of the most serious challenges facing cancer treatment is metastasis, the spread of cancer cells through blood or lymphatic vessels to distant organs [52]. Rather than spreading randomly, cancer cells metastasize preferentially to specific organs, with a greater incidence than would be expected from the circulatory pattern between the primary tumor site and secondary organs [53]. The GPCR family of chemokine receptors is centrally linked to the organ-specific metastasis of a number of cancers, in line with their normal immune cell function of directing receptor-bearing leukocytes towards sites of chemokine production. Similarly, tumor cells aberrantly expressing chemokine receptors can co-opt the migratory activity of chemokines, facilitating metastasis to other organs [54]. Chemokines locally released into the tumor microenvironment can also enhance the motility and survival of cancer cells in an autocrine and paracrine fashion [54]. Chemokines direct cell movement by inducing changes in cytoskeletal structure and dynamics of receptor-bearing cells. Actin polymerization leads to formation of protrusions, or pseudopods, and with the help of integrins, form focal adhesions with the extracellular matrix (ECM) to help propel the cell forward [55].

CXCR4 represents one of the best established chemokine receptors driving cancer metastasis. Tumor cells frequently exhibit aberrant CXCR4 expression, which has proliferative, pro-survival, and pro-migratory effects; additionally, the organs that are the most frequent sites of metastasis, including lymph nodes, lungs, bone marrow and liver, express its chemokine ligand, CXCL12/SDF-1 [53]. Several factors may contribute to the observed overexpression of CXCR4 in many tumors. For example, the HER2/Neu oncogene, which occurs in ~30% of breast cancers, limits the degradation of CXCR4, leading to its increased expression [56]. Additionally, hypoxia through activation of hypoxia-inducible factor-1 (HIF-1 α) induces transcription of CXCR4 [57]. As such, CXCR4 is highly expressed in breast cancer cells but not in normal breast tissues, and the inhibition of CXCR4 prevents the metastatic spread of breast cancer cells [53] and many other cancer types [52,54,58]. Although CXCR4 would represent an attractive target for therapeutic development, the use of CXCR4 inhibitors leads to the mobilization of stem cell progenitors from the bone marrow, thus limiting their use clinically for cancer treatment [59]. However, targeting molecules involved in the regulation of CXCR4 expression on cancer cells or their downstream signaling may offer alternative approaches for therapeutic intervention. In this regard, CXCR4 activates Rac1 through P-REX1, which plays a central role in metastasis in most breast cancer types [60]. CXCR4 can also couple to G_{12/13} in basal-like breast cancer cells, where G α_{13} protein expression is highly up-regulated, thus driving metastasis through a G_{12/13}-RhoA dependent manner [61], similarly to LPA and PAR-1 receptors (Figure 2), all of which can be considered potential targets for metastasis prevention and treatment.

Other chemokine receptors, including CCR7 and CCR10, have also been shown to play direct roles in metastatic homing of cancer cells types [62] and cancer cell survival and growth [63]. Local chemokine production in the tumor microenvironment can attract macrophages and leukocytes that may enhance the cytokine-rich microenvironment and induce the release of matrix metalloproteases (MMPs) that enable tumor cells to survive, proliferate and invade. In addition, recent functional screens demonstrated a role for GPR116, a member of the poorly characterized family of adhesion GPCRs, in invasion and migration of breast cancer cells, acting in a $G_{\alpha q}$ -RhoA/Rac1-dependent manner. Many new efforts are now focused on exploring the adhesion family of GPCRs, and their potential implications in tumor growth and metastasis [64].

GPCRs in tumor-induced angiogenesis

Solid tumors produce angiogenic factors promoting the migration and proliferation of endothelial cells, thus resulting in the formation of new vessels in response to the increasing nutrients and oxygen demands of the tumor cells. Many angiogenic factors act on GPCRs expressed on endothelial cells, including thrombin, prostaglandins, S1P, and chemokines [65-67]. Many chemokines, including CCL2, CCL5, and CXCL8/IL-8, recruit leukocytes and macrophages to the tumor site, which in turn can release VEGF and other angiogenic factors that contribute to the growth of new blood vessels [66]. In addition, inflammatory cytokines released in the tumor microenvironment promote the expression of COX-2 and the local release of prostaglandin E2 (PGE2), which increases the expression of pro-angiogenic VEGF, CXCL8 and CXCL5 by tumor and stromal cells [68].

Overall, GPCRs and their cognate ligands can promote angiogenesis directly by inducing proliferation of endothelial cells or indirectly by promoting release of VEGF and other angiogenic factors from stromal, immune, or cancer cells. Tumor vascularization provides nutrients to promote tumor outgrowth, and routes for invasion and metastasis.

Tumor microenvironment: Inflammation and immune cell evasion

Among the many mediators linking inflammation and cancer, the relationship between prostaglandin (PG) production and tumor progression is one of the best understood. PGs are a product of the cyclooxygenases COX-1 and COX-2, and their pro-inflammatory functions are initiated upon binding of PGs to their cognate GPCRs expressed in many cells. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit COX-1/2 can reduce the risk and incidence of numerous cancer types [69,70]. For example, COX-2 inhibition with NSAIDs reduces the overall number and size of adenomas in patients genetically predisposed to colorectal cancer, and represents an effective chemopreventive strategy for colon cancer in healthy individuals [69,70]. The contribution of PGE2 and signaling through its cognate GPCRs, EP1-EP4, to tumor progression has been extensively investigated [71-73]. EP1 is a G_q -coupled GPCR, whereas EP2 and EP4, which play a more prominent role in colon cancer, are coupled to G_s and stimulate cAMP accumulation [71] (Figure 1). In colon cancer cells, PGE2 can stimulate multiple signaling pathways, including β -catenin [74,75] and peroxisome proliferator activated receptor δ (PPAR δ), a nuclear hormone receptor.

Chemokines can also recruit macrophages to the site of the tumor. The role of CCL2 has been extensively studied for recruitment of CCR2-bearing tumor associated macrophages (TAMs), which play crucial roles in tumor vascularisation and growth. CCL5 has similarly been linked to macrophage recruitment [54,76]. On the other hand, some immune cells can facilitate killing of the tumor cells; in this case the tumor chemokine microenvironment may help evade the immune surveillance system, for example, by stimulating a less effective humoral response while inhibiting cell-mediated immune responses to tumor cells [54,76].

Widespread Mutations in GPCRs and G proteins in Cancer

Recent unbiased systematic approaches, including large-scale sequencing efforts, have highlighted an abundance of mutations in G proteins and GPCRs, and new studies are just beginning to explore the potential oncogenic effects of these mutations [77]. Initially, activating mutations in *GNAS* (encoding $G\alpha_s$) were shown to promote hyperplasia of endocrine cells, occurring in 28% of growth hormone-secreting pituitary tumors and 5% of thyroid adenomas [78,79]. Overall, mutations in *GNAS* occur in ~4.4% of tumor samples in a variety of different cancers [77]. The vast majority of these mutations cluster around two hotspot residues, R201 and Q227, which reduce the rate of GTP hydrolysis of the active GTP-bound $G\alpha_s$, resulting in constitutive signaling activity [78,80,81]. Similar hotspot mutations, Q209 and R183, occur in the $G\alpha_q$ family genes, *GNAQ* and *GNA11* (reviewed in 77). These mutations are mutually exclusive and activate the same signaling cascades, such that over 5.6% of all tumors sequenced in the COSMIC (v62) database are disrupted. In particular, most ocular melanomas harbor mutations in *GNAQ* or *GNA11*, which are considered to act as driver oncogenes, and ~6% of cutaneous melanomas. Recently, characterization of the $G_{q/11}$ signaling in uveal melanoma demonstrated that $G\alpha_q$ activates the GEF, Trio, and its regulated Rho GTPase signaling to promote tumorigenesis through the activation of MAPKs [41] and the transcriptional co-activator, YAP (unpublished observations), rather than depending solely on the stimulation of the best known PLC- β and PKC pathway.

A surprising finding from recent mutation analyses of cancer genomes indicates that GPCRs are also mutated in approximately 20% of all cancers [77,82], including mutations in TSHR in thyroid cancer, and luteinizing hormone receptor (LHCGR) and follicle stimulating hormone receptor (FSHR) in breast, lung, and colon cancers [77]. One of the most frequently mutated seven transmembrane domain receptors in tumors is smoothened (SMO), which is negatively regulated by the twelve-transmembrane receptor Patched (PTCH) [83,84]. This inhibition of SMO is relieved when Hedgehog (HH) family members bind to PTCH and leads to downstream activation of the transcription factor GLI [83,84]. Mutations in PTCH and SMO have been linked to initiation of sporadic basal cell carcinoma [85,86]. Additionally, SMO is mutated in cancers arising in the colon and central nervous system among others. Frequent mutations are also observed in the family of GPCR adhesion receptors, the majority of which are still orphan, and the glutamate family of GPCRs. The adhesion receptors are thought to play roles in cell-to-cell and cell-to-matrix interactions, and includes GPR98 and brain-specific angiogenesis inhibitor (BAI) members [87]. Mutations in the glutamate receptors, *GRM8*, *GRM1* and *GRM3* have been implicated in squamous non-small cell lung cancer (NSCLC), NSCLC adenocarcinomas, and melanomas,

respectively (reviewed in [77]). Yet more studies are needed in order to fully understand the molecular consequences of these mutations and their ultimate effects on tumor progression.

Tumor Suppressor functions of some GPCRs

Although this review is focused on the pro-tumorigenic capacity of GPCRs and G proteins, not all function as oncogenes. In certain malignancies, some GPCRs and G proteins may actually play tumor suppressive roles and mutations may reflect inactivation of the respective genes. For example, inactivating mutations in the melanocortin 1 receptor (MC1R), which is important for pigment production, increase the risk of melanoma development [88]. CXCR3 ligands can indirectly mediate anti-angiogenic effects to suppress tumor progression, while the cannabinoid receptors CB1 and CB2 display tumor suppressive roles in several cancers, including gliomas and breast, colorectal, and skin cancer [89]. Additionally, SIP2 receptor signaling through $G\alpha_{13}$ in diffuse large B cell lymphoma (DLBCL) may exert tumor suppressive functions [90]. Although $G\alpha_{13}$ signaling has implications in tumor progression and metastasis, in the case of DLBCL, reduced expression or inactivating mutations in SIP2 and/or $G\alpha_{13}$ may instead enhance tumor progression. Lastly, GPR54/Kiss1-derived peptide receptor can function as a metastasis suppressor in melanoma and breast cancer cells [91]. Although GPR54 couples to G_q , the molecular basis of its anti-metastatic signaling mechanisms are still unknown. These are certainly not the only GPCR/G protein signaling pathways that may exhibit anti-tumorigenic effects in different cancers, and many yet are likely to be discovered in the future.

Concluding remarks

Activation of GPCRs elicits an array of signaling pathways including second messengers, GEFs, Ras and Rho GTPases, MAP kinases, PI3Ks, and their numerous downstream cytosolic and nuclear targets. These signaling pathways contribute to normal cell functions of growth, survival, differentiation, and migration; however, cancer cells can exploit these pathways through aberrant expression and regulation of GPCRs/G proteins and their ligands to enhance tumor growth, promote angiogenesis, invade and metastasize to distant sites, and evade the immune system (Figure 3). By directly targeting GPCRs or more selectively targeting particular downstream signaling components, there are many avenues for potential therapeutic development for cancer treatments.

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Figure 1. Activation of growth and survival pathways by GPCRs

Stimulation of GPCRs results in the activation of multiple signaling pathways including second messenger generating systems, guanine nucleotide exchange factors (GEFs) for Ras and Rho GTPases, MAP kinases, PI3Ks, and their numerous downstream cytosolic and nuclear targets. This signaling network contributes to normal cell growth, survival, differentiation, and migration, but aberrant activation of GPCRs/G proteins and their downstream targets can result in tumor initiation, progression, and metastasis. In general, most mitogens acting on GPCRs stimulate $G_{\alpha_{q/11}}$, while others activate $G_{\alpha_{12/13}}$ and G_{α_i} G_{α} subunits, which initiate intracellular signaling together with multiple pathways regulated by $G_{\beta\gamma}$ subunits. In turn, these signaling routes converge in the nucleus to regulate the expression of growth promoting genes by the prolonged stimulation of transcription factors including c-FOS and c-JUN AP1 family members, YAP/TAZ, and c-MYC, among others. In parallel, activation of PI3K and AKT can induce cell proliferation by regulating cell cycle proteins, and promote cell survival through inactivation of pro-apoptotic proteins. AKT also activates an atypical kinase known as mTOR, which regulates protein synthesis, cell growth, and proliferation. In certain cancer cells, including colon cancer, activation of G_{α_s} by COX-2 derived prostaglandins promotes cell proliferation by multiple mechanisms, including PKA-dependent regulation of multiple transcription factors and G_{β_s} and $G_{\beta\gamma}$ -initiated pathways controlling the accumulation of transcription factors such as β -catenin. See text for details.

Figure 2. Signaling by virally-encoded oncogenic GPCRs, and metastasis-related signaling pathways elicited by chemokine receptors

In general, chemokine receptors, such as CXCR4, drive cell migration primarily by acting on G_i and the stimulation of G α_i and G $\beta\gamma$ -initiated pathways controlling actin remodeling through PI3K and Rac GEFs, as well as the expression of pro-invasive gene programs. This is well exemplified by the role of CXCR4 in breast cancer metastasis. CXCR4 can also couple to G_{12/13} in basal-like breast cancer cells, where G α_{13} protein expression is highly up-regulated, thereby driving metastasis in a G $\alpha_{12/13}$ -RhoA dependent manner. Similarly, LPA receptors and PAR-1 can activate G $\alpha_{12/13}$ -RhoA signaling in addition to G α_i . PI3K, Rac, and Rho signaling promotes the assembly of focal adhesions and actin polymerization important for inducing changes in cell shape and contraction, which are required for cell movement, thereby facilitating cancer cell migration, extravasation, and metastasis. Human

oncogenic viruses, such as the Kaposi's sarcoma associated virus (KSHV/HHV8) express constitutively active GPCRs (vGPCRs) from their viral genome. Emerging evidence indicates that KSHV vGPCR initiates Kaposi's sarcoma, a highly angiogenic malignancy, by activating multiple intracellular signaling networks resulting in upregulation of expression and release of pro-angiogenic cytokines, such as VEGF, IL6, and IL8/CXCL8 and Gro- α /CXCL1, thus initiating paracrine neoplasia. Among these multiple pathways, the activation of AKT and mTOR through PI3K γ represents a central pro-angiogenic and transforming mechanism deployed by KSHV-vGPCR, which has been successfully targeted in the clinic. The transforming effects of KSHV vGPCR also involves the activation of multiple MAPKs and their regulated transcription factors, including HIF-1 α , AP-1, NF- κ B, CREB, and NFAT transcription factors, all of which promote the expression and release of multiple KS-associated cytokines. Ultimately, KSHV vGPCR-expressing cells act in a paracrine fashion to stimulate the unrestricted growth of surrounding endothelial cells. See text for details.

Figure 3. GPCRs contribute to multiple facets of cancer progression

Cartoon depicting the involvement of GPCRs in cancer cell proliferation and survival, angiogenesis, invasion and metastasis, and inflammation and immune tolerance; short lists highlight some of the GPCRs involved in these processes.