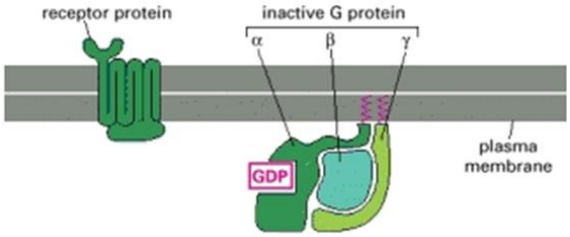
G Protein coupled receptors Gates of Life

Returning to normal cellular function by treatment of viral diseases.

Cellular Normal physiology dysfunction by viral organisms.

G Protein coupled receptors.



G protein-coupled receptors are the most abundant class of receptors in the human body. These receptors are exposed at the extracellular surface of the cell membrane, traverse the membrane, and possess intracellular regions that activate a unique class of signaling molecules called G proteins. (G proteins are so named because they bind the guanine nucleotides GTP and GDP.)

Multiple modules of working of the cell by G Protein Coupled receptors

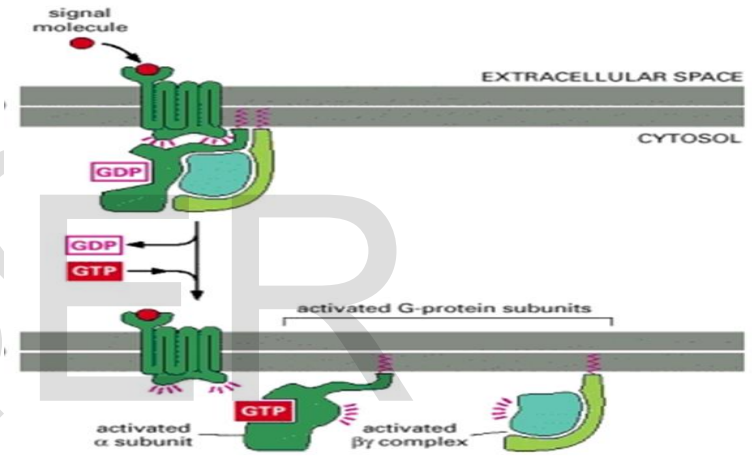
G protein-coupled receptors (GPCRs) are essential mediators of cellular communication.

The physiological role of GPCR activation ranges from gene transcription to cellular migration and proliferation.

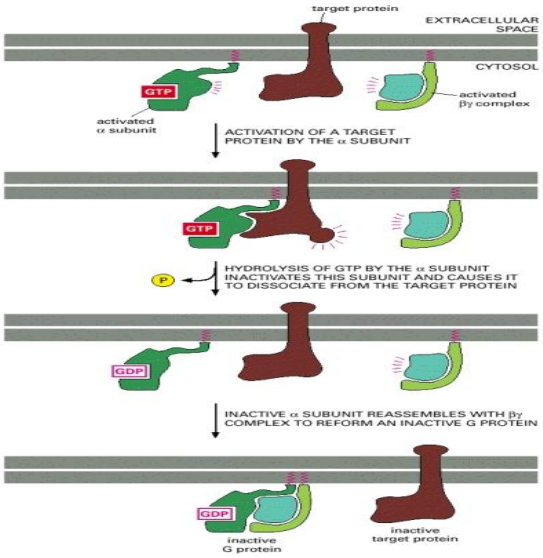
GPCRs can regulate an incredible range of bodily functions from sensation to growth to even hormone response.

Besides being activated by their cognitive ligands, GPCRs can signal independently from ligand activation. This so-called constitutive activity is the molecular basis of various pathologies (Smit et al., 2007).

Morphologic description of GPLRs



G protein-coupled receptors all have *7 transmembrane regions* within a *single polypeptide chain*. Each transmembrane region consists of a single α helix, and the α helices are arranged in a characteristic structural motif that is similar in all members of this receptor class. The extracellular domain of this class of proteins usually contains the ligand-binding region, although some G protein-coupled receptors bind ligands within the transmembrane domain of the receptor. In the resting (unstimulated) state, the cytoplasmic domain of the receptor is noncovalently linked to a G protein that consists of α and βγ subunits. Upon activation, the α subunit exchanges GDP for GTP. The α-GTP subunit then dissociates from the β,γ subunits, and the α or βγ subunit diffuses along the inner leaflet of the plasma membrane to interact with a number of different effectors.



Signals mediated by G proteins are usually terminated by the hydrolysis of GTP to GDP, which is catalyzed by the inherent GTPase activity of the α subunit.

Working Description of active GPCRs

1. **Inside the Cell messengers:-** One major role of the G proteins is to *activate the production of second messengers*, that is, signaling molecules that convey the input provided by the first messenger—usually an endogenous *ligand or an exogenous drug* —to cytoplasmic effectors.

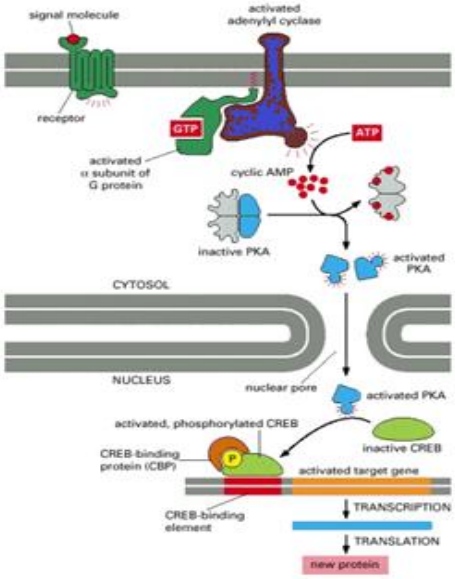
   Cytoplasmic effectors:-

   These effectors include Adenylyl cyclase (causing raised cAMP) , Phospholipase C (Phospholipd Hydrolysis), various Ion channels, and other classes of proteins.

2. **Activation of target proteins-** After a G-protein **α** subunit activates its target protein, it shuts itself off by hydrolyzing its bound GTP to GDP. This inactivates the **α** subunit, which dissociates from the target protein and reassociates with a **β-γ** complex to re-form an inactive G protein. Binding to the target protein or to a membrane-bound RGS protein (not

shown) usually stimulates the GTPase activity of the α subunit; this stimulation greatly speeds up the inactivation process shown here.

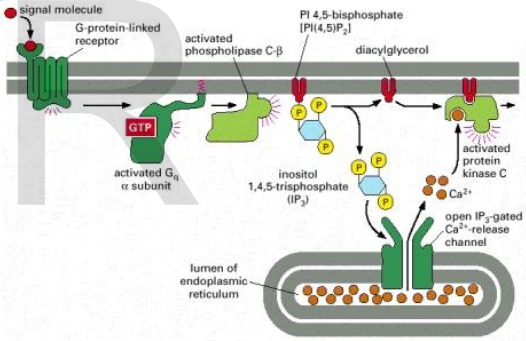
3. **Activation of Gene transcription by cAMP:-** The binding of an extracellular signal molecule to its G-protein-linked receptor leads to the activation of *adenylyl cyclase* and a rise in cyclic AMP concentration. The increase in cyclic AMP concentration activates protein kinase A (PKA) in the cytosol, and the released catalytic subunits then move into the nucleus, where they phosphorylate the CREB gene regulatory protein. Once phosphorylated, CREB recruits the coactivator CBP, which stimulates gene transcription. This signaling pathway controls many processes in cells, ranging from hormone synthesis in endocrine cells to the production of proteins required for long-term memory in the brain. Some kinases are activated by a rise in intracellular Ca2+ can also phosphorylate and thereby activate CREB.



Mammalian cells have at least two types of PKAs: ***type I*** is mainly in the cytosol, whereas ***type II*** is bound via its ***regulatory subunit*** and ***special anchoring proteins*** to the plasma membrane, nuclear membrane, mitochondrial outer membrane, and microtubules. In all cases, however, once the *catalytic subunits* are freed and active, they can migrate into the nucleus (where they can phosphorylate gene regulatory proteins), while the *regulatory subunits* remain in the cytoplasm.

Deregulated kinase activity is a frequent cause of disease, in particular cancer, wherein kinases regulate many aspects that control cell growth, movement and death. Drugs that inhibit specific kinases are being developed to treat several diseases, and some are currently in clinical use, including Gleevec (imatinib) and Iressa (gefitinib).

4. **Cancerous transformation:-** The activated receptor stimulates the plasma-membrane-bound enzyme phospholipase C-**β** via a G protein. Depending on the isoform of the enzyme, it may be activated by the **α** subunit of Gq as shown, by the **βγ** complex of another G protein, or by both. Two intracellular messenger molecules are produced when PI(4,5) P2 is hydrolyzed by the activated phospholipase C-**β**. Inositol 1,4,5-trisphosphate (IP3) diffuses through the cytosol and releases Ca2+ from the endoplasmic reticulum by binding to and opening IP3-gated Ca2+-release channels in the endoplasmic reticulum membrane. The large *electrochemical gradient* for Ca2+ across this membrane causes Ca2+ to escape into the cytosol. Diacylglycerol remains in the plasma membrane and, together with phosphatidylserine (not shown) and Ca2+, helps to activate the enzyme protein kinase C (phosphorylation of proteins), which is recruited from the cytosol to the cytosolic face of the plasma membrane. Of the 11 or more distinct isoforms of PKC in mammals, at least four are activated by diacylglycerol.



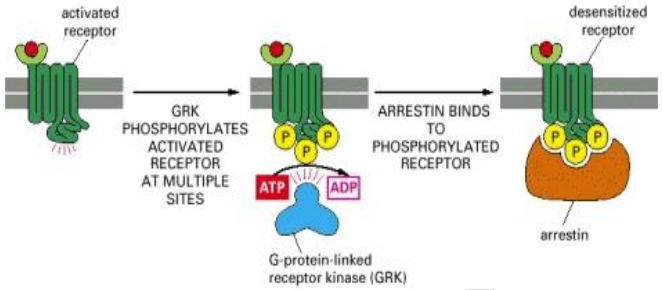
It is now clear that a number of catalytically active proteins bind arrestins and are recruited to agonist-occupied GPCRs Among them are

1. ***Src family tyrosine kinases*** (Luttrell et al., 1999; Barlic et al., 2000; DeFea et al., 2000a), components of the ERK1/2 and c-Jun N-terminal kinase 3 (JNK3) mitogen-activated protein (MAP) kinase cascades (DeFea et al., 2000b; McDonald et al., 2000; Luttrell et al., 2001),
2. ***Diacylglycerol kinase*** (Nelson et al., 2007), the inhibitor of nuclear factor (NF)κB, IκBα (Witherow et al., 2004), the ***Ral-GDP dissociation stimulator (GDS)***, Ral-GDS (Bhattacharya et al., 2002),
3. ***E3 ubiquitin ligase***, Mdm2 (Shenoy et al., 2001),
4. ***cAMP phosphodiesterases*** (PDE), PDE4D3/5 (Perry et al., 2002),
5. ***Ser/Thr protein phosphatase*** (PP)2A (Beaulieu et al., 2005).

It is via these interactions that arrestin-binding confers unique signaling properties upon agonist-occupied GPCRs, opening up a broad realm of previously unappreciated GPCR signal transduction.

Mode of deactivation of the GPCRs

The binding of an arrestin to the phosphorylated receptor prevents the receptor from binding to its G protein and can direct its endocytosis.

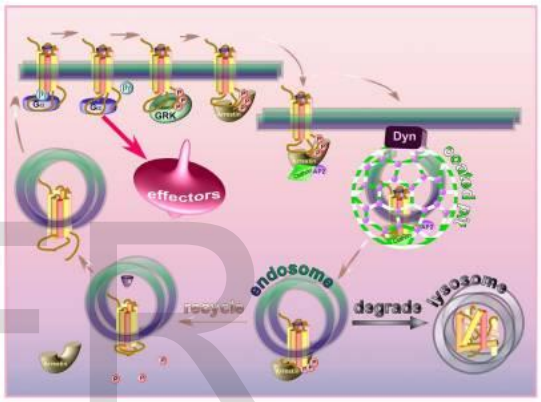


Arrestins terminate receptor interactions with G proteins, redirect the signaling to a variety of alternative pathways, and orchestrate receptor internalization and subsequent intracellular trafficking. The elucidation of the structural basis and fine molecular mechanisms of the arrestin–receptor interaction paved the way to the targeted manipulation of this interaction from both sides to produce very stable or extremely transient complexes that helped to understand the regulation of many biologically important processes initiated by active GPCRs.

Recycling of GPCRs

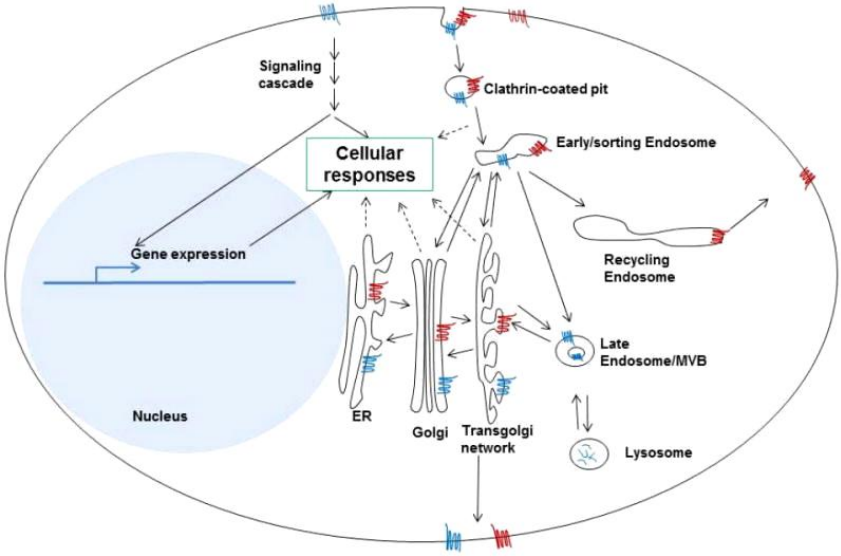
Phosphorylation of specific residues within the intracellular domains of the receptor by second messenger-dependent protein kinases like protein kinase (PK) A and (PK) C causes heterologous desensitization, so called because it is independent of ligand occupancy.

Most GPCRs fall into one of two classes based on their affinity for the two nonvisual arrestin isoforms, and the longevity of the receptor-arrestin interaction (Oakley et al., 2000). One class exhibits higher affinity for arrestin3 than arrestin2 and forms transient receptor-arrestin complexes that dissociate soon after the receptor internalizes. These receptors (e.g., the β2 and α1B adrenergic) tend to be rapidly resensitized and recycled back to the plasma membrane. The other class exhibits equivalent affinities for arrestin2 and -3 and forms more stable receptor-arrestin complexes that remain intact as the receptor undergoes endosomal sorting. These receptors (e.g., angiotensin AT1A and vasopressin V2) are sequestered in endosomes and tend to recycle slowly or undergo degradation.



Unlike the catalytic GPCR-G protein interaction, arrestin-bound GPCRs exist in a relatively stable complex that persists on a time scale of minutes to hours (Charest et al., 2005; Pfleger et al., 2006). It was the discovery that ***arrestins*** serve as adapters not only in the context of GPCR sequestration but also in linking activated GPCRs to other enzymatic effectors that prompted a re-envisioning of GPCR signal transduction (Miller and Lefkowitz, 2001; Perry and Lefkowitz, 2002; Maudsley et al., 2005; Shenoy and Lefkowitz, 2005a; Gesty-Palmer and Luttrell, 2008).

It is now clear that a number of catalytically active proteins bind arrestins and are recruited to agonist-occupied GPCRs, among them ***Src family tyrosine kinases*** (Luttrell et al., 1999; Barlic et al., 2000; DeFea et al., 2000a), components of the ERK1/2 and c-Jun N-terminal kinase 3 (JNK3) mitogen-activated protein (MAP) kinase cascades (DeFea et al., 2000b; McDonald et al., 2000; Luttrell et al., 2001), the ***E3 ubiquitin ligase***, Mdm2 (Shenoy et al., 2001), the ***cAMP phosphodiesterases*** (PDE), PDE4D3/5 (Perry et al., 2002), ***diacylglycerol kinase*** (Nelson et al., 2007), the inhibitor of nuclear factor (NF)κB, IκBα (Witherow et al., 2004), the ***Ral-GDP dissociation stimulator (GDS)***, Ral-GDS (Bhattacharya et al., 2002), and the ***Ser/Thr protein phosphatase*** (PP)2A (Beaulieu et al., 2005). It is via these interactions that arrestin-binding confers unique signaling properties upon agonist-occupied GPCRs, opening up a broad realm of previously unappreciated GPCR signal transduction.



Two different GPCRs (blue and red) are shown in this cartoon to illustrate the different membrane trafficking

pathways that they can go through. The blue GPCR goes through the lysosomal degradation pathway and the red GPCR goes through the recycling pathway. The two pathways can coexist for a given GPCR. Cells' responses to GPCRs can happen through external ligand-induced signaling cascades, as well as through internalized GPCRs.

Some Of the examples of dysfunctional GPCRs through ligands receptor interaction and or by signaling cascades.

1. **Activation of platelet function through G protein-coupled receptors**

Although primary adhesion of platelets to the vessel wall is largely independent of G protein-mediated signaling, the subsequent recruitment of additional platelets into a growing platelet thrombus requires mediators such as ADP, thromboxane A(2), or thrombin, which act through G protein-coupled receptors. Platelet activation via G protein-coupled receptors involves 3 major G protein-mediated signaling pathways that are initiated by the activation of the G proteins G(q), G(13), and G(i). This review summarizes recent progress in understanding the mechanisms underlying platelet activation and thrombus extension via G protein-mediated signaling pathways.

2. **γ-Herpesvirus-Encoded G Protein-Coupled Receptors →→→→ Oncogenic Function of the KSHV-Encoded Chemokine Receptor ORF74**

Lytic gene ORF74 that is expressed in KS lesions in humans (Cesarman et al., 1996). Shortly after its identification, this viral chemokine receptor was promptly identified as a constitutively active transforming viral gene in transfected cells in vitro and in xenograft models (Arvanitakis et al., 1997; Bais et al., 1998). Furthermore, numerous in vivo transgenic models confirmed the implication of ORF74 in the development of KS, and light has been shed on several mechanisms activated by this receptor for pathogenesis (Yang et al., 2000; Montaner et al., 2003; Sodhi et al., 2004; Jensen et al., 2005; Grisotto et al., 2006). ORF74 is able to activate various signaling pathways, mediated by a broad range of kinases and transcription factors, which results in the induction of proinflammatory and angiogenic genes. In particular, ORF74 constitutively couples to Gαq/11 and Gβγ subunits to activate the p44/42 mitogen-activated protein kinases (MAPKs) (Smit et al., 2002). In concert with p38 and Jun N-terminal kinase MAPK activation, the hypoxia-inducible transcription factor hypoxia-inducible factor-1α is subsequently triggered and mediates the transcription of the vascular endothelial growth factor (VEGF) gene, giving rise to an angiogenic phenotype (Sodhi et al., 2000). In addition, ORF74 expression in KSHV-negative KS-derived cells induces the constitutive activation of the NF-κB transcription factor and the expression and release of proangiogenic and proinflammatory factors such as interleukin-6, CXCL8, CCL5, granulocyte macrophage colony-stimulating factor, E-selectin, and vascular and endothelial adhesion molecules vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (Pati et al., 2001). Secretion of soluble factors by ORF74-expressing cells is able to subsequently induce NF-κB transcriptional activation in neighboring cells, confirming a paracrine mechanism of transformation for ORF74 (Martin et al., 2008).

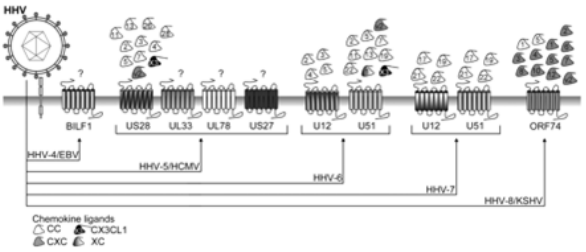


Fig. 1. HHV-encoded vGPCRs. HHVs infect cells by binding to specific cellular receptors. Upon transcription of the viral genome, vGPCRs are expressed and can bind various chemokines. Human chemokine ligands from the CC (open), CXC (gray), CX3C (filled) and XC (shadow) classes and the KSHV-encoded CXCL2 chemokine (gray, v2) bind to various vGPCRs. For some receptors, ligands still need to be determined

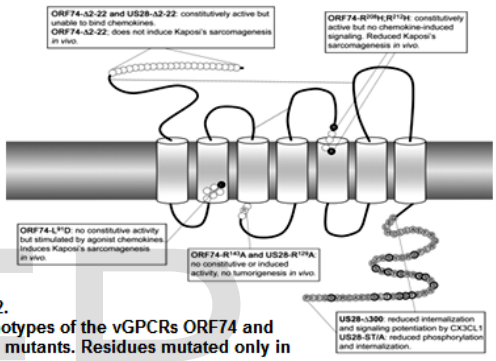


Fig. 2.
Phenotypes of the vGPCRs ORF74 and US28 mutants. Residues mutated only in ORF74 are highlighted in filled circles, whereas gray circles indicate US28-specific mutant residues. Mutated amino acids generated for both ORF74 and US28 are indicated with open circles. Dotted circles represent undefined amino acids and are used to visualize the position of mutated amino acids in transmembrane domains or intra/extracellular loops. Dotted lines represent the conserved disulfide bridges between the extracellular loops 2 and 3 in ORF74 and US28 vGPCRs.

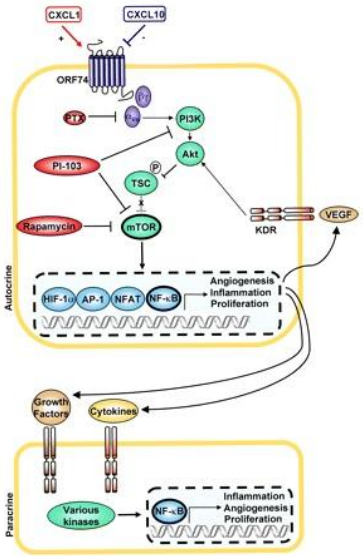


Fig. 3.
ORF74-induced autocrine and paracrine signaling during cellular transformation. ORF74 constitutively activates G protein subunits and the downstream PI3K/Akt kinases. In turn, the TSC protein is inactivated by phosphorylation and leads to the accumulation of mTOR. Various transcription factors are activated and promote angiogenesis, inflammation and proliferation. ORF74-expressing cells secrete various growth factors and cytokines that bind to their respective receptors and promote transformation in a paracrine manner. The single inhibition of mTOR with rapamycin reduces ORF74-induced KS development but is less effective than the dual inhibition of both PI3K and mTOR with PI-103 (Chaisuparat et al., 2008).

3. β-Herpesvirus-Encoded GPCRs

The β-HHV family consists of the human cytomegalovirus (HCMV also known as HHV-5), HHV-6, and HHV-7. All of these viruses present a broad cellular tropism and are involved in various pathologies. HCMV infects a broad range of cell types and is a known risk factor in immunocompromised patients. Immunosuppressed HCMV-infected transplantation patients are prone to graft rejection because of the development of cardiac allograft vasculopathy, resulting in cardiac allograft loss. Furthermore, ongoing HCMV infection is increasingly linked to the development of proliferative and cardiovascular pathologies. Several studies have shown the presence of HCMV in atherosclerotic lesions (Horváth et al., 2000; Chen et al., 2003) as well as in several neoplastic conditions such as colon, prostate, and breast cancers and in glioblastoma (Cobbs et al., 2002; Harkins et al., 2002; Samanta et al., 2003; Söderberg-Nauclér, 2008). As such, HCMV infection seems to be particularly detrimental in patients with an impaired immune system. HCMV encodes four GPCRs referred to as US27, US28, UL33, and UL78. Like other virus-encoded GPCRs, US28 and UL33 possess constitutive signaling abilities, whereas US27 and UL78 do not (Vischer et al., 2006a). Although US27, UL33, and UL78 have been shown to present sequence homology to chemokine receptors, so far no ligands were shown to bind these vGPCRs. As such, these receptors are still considered orphan receptors. So far, the most studied vGPCR is US28 (Vischer et al., 2006a). It presents homology to the CC and CX3C chemokine receptors and was shown to bind CC (CCL2, CCL3, CCL4, CCL5, CCL7, CCL11, CCL13, CCL26, and CCL28), CX3C chemokines (CX3CL1), and the viral chemokine vCXCL2 (Gao and Murphy, 1994; Billstrom et al., 1998; Kledal et al., 1998; Penfold et al., 2003) (Fig. 1). The CCL2, CCL5, CCL7, and CX3CL1 chemokines exhibit agonistic activity on the receptor (Gao and Murphy, 1994; Billstrom et al., 1998; Vomaske et al., 2009), whereas in other assays, CX3CL1 has also shown inverse agonistic activity (Casarosa et al., 2001). The chemokines CCL3 and CCL4, although binding US28 with high affinity, have not yet shown signaling abilities

4. US28 Ligand-Dependent Signaling as a Link to Atherosclerosis

Ligand-induced US28 signaling is cell type-specific, which may be of importance during atherogenesis, promoting the recruitment of macrophages and smooth muscle cells in the atherosclerotic plaques and inflamed lesions.

5. HCMV-Encoded US28 Function in Tumorigenesis

Based on the constitutive activation of the proinflammatory NF-κB transcription factor, US28 was suggested to promote inflammation and to potentially act as a viral oncogene (Maussang et al., 2006). Stable transfection of NIH-3T3 cells with US28 resulted in increased cellular proliferation without requiring any ligand stimulation (Maussang et al., 2006).

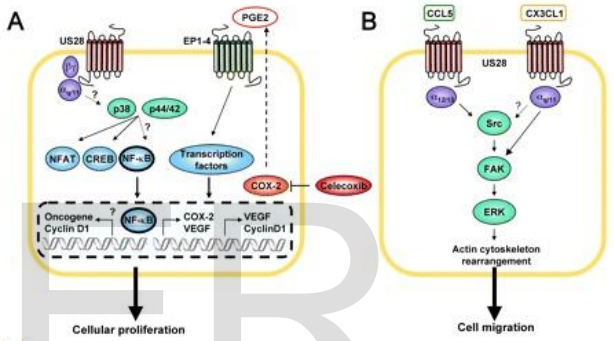


Fig. 4.
US28 signaling during cell proliferation and migration. A, US28 constitutively activates Gαq and Gβγ proteins and downstream MAPKs such as p38 and p44/42. In turn, transcription factors mediate the up-regulation of oncogenes and inflammatory factors (e.g., COX-2). PGE2 is produced by the up-regulated COX-2 and further activates transcription factors after binding to its cognate receptors EP1 to -4. This positive feedback loop further up-regulates angiogenesis (VEGF) and proliferation (cyclin D1). Celecoxib inhibits COX-2 activity and impairs tumor formation and angiogenesis in vivo (Maussang et al., 2009). B, stimulation of US28-expressing cells with CCL5 and CX3CL1 activates, respectively, Gα12/13 and Gαq proteins that both activate FAK and the downstream extracellular signal-regulated kinase (ERK). This leads to the rearrangement of actin cytoskeleton and cellular migration (Vomaske et al., 2009).

6. EBV-Encoded BILF1 Contributes to Immune Escape

Upon viral infection, double-stranded RNA binds to PKR, leading to its phosphorylation and activation. As a result, the overall cellular translational machinery is stopped, prohibiting viral replication, and only a few specific apoptotic genes are transcribed (García et al., 2006). This mechanism serves to prevent viral spreading by elimination of the infected cells. Thus, the inhibition of PKR by BILF1 may serve EBV to prevent cellular antiviral response. In addition, it was demonstrated recently that BILF1 expression also serves in immune escape by down-regulating antigen-presenting MHC class I cells of epithelial and melanoma cells (Zuo et al., 2009). BILF1 protein physically associated with MHC class I complexes, increasing their lysosomal degradation and down-regulating their surface expression. This mechanism was independent of constitutive G protein coupling because the BILF1 mutant K122A, unable to constitutively activate NF-κB, down-modulated MHC I surface expression to a similar extent than the WT receptor (Zuo et al., 2009). As such, BILF1 expression was shown to evade CD8+ T-cell response, preventing recognition by the host immune system.

7. EBV-Encoded BILF1 Contributes to Immune Escape

Upon viral infection, double-stranded RNA binds to PKR, leading to its phosphorylation and activation. As a result, the overall cellular translational machinery is stopped, prohibiting viral replication, and only a few specific apoptotic genes are transcribed (García et al., 2006). This mechanism serves to prevent viral spreading by elimination of the infected cells. Thus, the inhibition of PKR by BILF1 may serve EBV to prevent cellular antiviral response. In addition, it was demonstrated recently that BILF1 expression also serves in immune escape by down-regulating antigen-presenting

MHC class I cells of epithelial and melanoma cells (Zuo et al., 2009). BILF1 protein physically associated with MHC class I complexes, increasing their lysosomal degradation and down-regulating their surface expression. This mechanism was independent of constitutive G protein coupling because the BILF1 mutant K122A, unable to constitutively activate NF-κB, down-modulated MHC I surface expression to a similar extent than the WT receptor (Zuo et al., 2009). As such, BILF1 expression was shown to evade CD8+ T-cell response, preventing recognition by the host immune system.

The role of human herpesvirus-8 in the pathogenesis of multiple myeloma.

Human herpesvirus-8 has been strongly implicated in the pathogenesis of KS, BCBL, and multicentric Castleman's disease. Evidence for its role in the pathogenesis of multiple myeloma is accumulating. Human herpesvirus-8 is detectable in the nonmalignant bone marrow dendritic cells from most myeloma patients. In addition, HHV-8 is also detected in the peripheral blood of most myeloma patients. In contrast, this virus is rarely detected in close contacts of myeloma patients, healthy individuals, or patients with other malignancies. Furthermore, only about one fourth of patients with MGUS are infected with HHV-8. Sequencing of HHV-8 DNA isolated from myeloma patients shows both minor differences among patients and a conserved deletion unique to myeloma compared with HHV-8 in other malignancies. Consistent expression of both the viral homologues of IRF and IL-8R in myeloma suggests a possible role for these transforming viral genes in the pathogenesis of this disease. Although the described association between multiple myeloma and HHV-8 implies a causal role in the pathogenesis of this disease, no cause-and-effect relationship is yet demonstrated. Evidence may be obtained directly by fulfilling Koch's postulate in an animal model and indirectly through therapeutic interventions with antiviral agents or through extensive epidemiological studies. Such epidemiological studies would be greatly facilitated by the development of antibodies directed against the HHV-8 viral proteins uniquely present in myeloma. A direct or indirect causal effect of HHV-8 has potentially enormous implications for the therapeutic benefit of antiviral agents and preventative strategies using vaccines. There is, indeed, preliminary evidence that antiviral therapy in HIV-infected patients reduces the risk or development of KS. Clinical improvement in patients with KS treated with antiviral agents has also been reported. These observations suggest that future treatment strategies to combat multiple myeloma may include antiviral agents.

Just a study:- Detection of persistent measles virus infection in Crohn's disease: current status of experimental work

Epidemiological studies linking persistent measles virus infection to Crohn's disease generated a hypothesis6 for confirmation or rejection by searching for measles virus in Crohn's affected tissue.

Measles related antigen was present not only in colons affected with Crohn's disease but also in colons affected with ulcerative colitis and in non-IBD colitis.

Based on the sequence data provided by Kawashima et al, the sequence derived from a Crohn's disease patient differed by only two nucleotides from the vaccine strain while the sequences derived from cases of autism, which theoretically should be identical to the vaccine strains, differed by 3–5 nucleotides. There is also evidence to suggest the possibility that mixed DNA fragments were present in the PCR products that are usually produced by cross contamination with more than one template.40
http://gut.bmj.com/content/48/6/748

How Can a Better Understanding of GPCRs Lead to New Treatments for Diabetes?

Researchers are seeking to understand which (as well as how) GPCRs are involved in normal and diabetic islet function, as this knowledge has the potential to suggest new approaches to treat diabetes. Given the importance of GPCRs in transmitting signals from the extracellular environment and potential as drug targets, scientists have sought to understand their role in pancreatic islet cell biology. A first step in this process was to understand which GPCRs are expressed in islets. Shaun Coughlin and colleagues recently reported that mouse islets express high levels of at least 28 different GPCRs (Regard et al. 2007). Table 1 lists some of the GPCRs expressed by beta cells that are known to affect insulin secretion and their natural ligands. As the ligands and function of additional GPCRs are defined, more GPCRs that influence insulin secretion will likely be identified.

Table 1

GPCRs	Full name	Ligand	Alpha subunit	Cell type	Insulin secretion
ADRB2	Beta-2 adrenergic	Epinepherine	Gs	beta	+
ADRA2A	Alpha-2 adrenergic (A)	Norepinepherine	Gi	beta	-
MTNR1A	Melatonin 1A	Melatonin	Gq/Gi	beta	?
MTNR1B	Melatonin 1B	Melatonin	Gq/Gi	beta	?
HTR2B	Serotonin-2B	Serotonin	Gq	beta	+
HTR1D	Serotonin-1D	Serotonin	Gi	beta	-
M3	Muscarinic-3	Acetylcholine	Gq	beta	+
SSTR2	Somatostatin-2	Somatostatin	Gi	beta	-
GLP1R	Glucagon-like Peptide 1	Glucagon-like Peptide 1	Gs	beta/alpha?	+
GPR40	G-protein receptor40	Free fatty acids	Gq	beta	+
GPR119	G-protein receptor119	Free fatty acids	Gs	beta	+
GCGR	Glucagon	Glucagon	Gs/q	beta/alpa	+

Although glucose levels are a primary regulator of insulin secretion, signaling through different GPCRs can have positive or negative effects on insulin secretion through their regulation of intracellular signaling pathways. Identifying the downstream signaling partners for GPCRs has improved our understanding of this regulation of insulin secretion. There are some generalizations that can be made about the effects of GPCRs on insulin secretion based on their Gα subunit coupling preferences (Figure 3). GPCRs that signal through the Gαq and Gαs pathways tend to increase insulin secretion, whereas GPCRs that signal through the Gαi pathway generally inhibit insulin secretion. It is important to remember, however, that GPCRs couple to a complex of Gαβγ, so activation of GPCRs results in the release of Gβγ as well as Gα subunits. One of the unanswered questions is what role, if any, different Gβγ complexes play in insulin secretion. What has also become apparent to investigators in the field is that individual GPCRs often interact with more than one type of Gα subunit. Thus, the effects of any one type of GPCR on insulin secretion may be quite complex.

Conclusion

By this latest understanding of GPCRs and their natural existing ligand (different hormones, serotonin, adrenalin, other autoimmune substances or signal molecules) that make them to function in normal physiologic mannerisms will make control of most of the diseases originated by viruses and resulting dysfunction of GPCRs and then later appearance of the complications in the form of autoimmune dysfunction and or cancer or as one component of other chronic diseases.

References:

https://www.ncbi.nlm.nih.gov/books/NBK26912/
http://molpharm.aspetjournals.org/content/76/4/692
http://molpharm.aspetjournals.org/content/90/5/620
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628546/figure/F2/
https://www.ncbi.nlm.nih.gov/pubmed/17158345
https://www.ncbi.nlm.nih.gov/pubmed/17158345
https://www.ncbi.nlm.nih.gov/pubmed/10626142
https://www.nature.com/scitable/topicpage/g-protein-coupled-receptors-pancreatic-islets-and-14257267#