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Cell signaling: Role of GPCR

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ABSTRACT

The control and mediation of the cell cycle is influenced by cell signals. Different types of cell signaling molecules: Proteins (growth factors), peptide hormones, amino acids, steroids, retenoids, fatty acid derivatives, and small gases can all act as signaling molecules. G- protein coupled receptors(GPCR) are heptahelical, serpentine receptors and are multi functional receptors having lot more clinical implications. Many reports have been clarified the basic mechanism of GPCR signal transduction, numerous laboratories have published on the clinical implication/application of GPCR. To name a few, dysfunction of GPCR signal pathway plays a role in cancer, autoimmunity, and diabetes. In this report, we will review the role of GPCR in cell signaling and impact of GPCR in clinical medicine,

Key words: GPCR, Paracrine, Juxtacrine, Ligand binding, Oligomerisation, Translocation.

INTRODUCTION

Cell signaling is a complex system of communication, which controls and governs basic cellular activities and coordinates cell actions [1]. In biology point of view *signal transduction* refers to any process through which a cell converts one kind of signal or stimulus into another. Signal transduction involves sequences of biochemical reactions inside the cell, which are carried out by enzymes, activated by second messengers, resulting in a signal transduction pathway.

Signaling molecules

Multicellular organisms have diverse number of small molecules and polypeptides that coordinate cell's individual biological activity. These molecules have been functionally classified as:

- Peptide hormones (e.g., Melatonin[2], Glucagon)
- Proteins: Growth factors (e.g., Epidermal growth factor[3], Platelet derived growth factor)
- Steroids (e.g., Testosterone [4], Estrogen, Progestirone, Carticosteroids)
- Retenoids Synthesised from vit- A
- Neurotrophins (e.g., Nerve growth factor)[5]
- Neuropeptids (e.g., Enkephalins and Endorphins)[6]
- Small gases (e.g., Nitric oxide)
- extra-cellular matrix components (e.g., Fibronectin)[7]
- Neurotransmittors (e.g.,Acetylcholine[8],Dopamine[9],Adrenaline,5-HT[10],Histamine, GABA, Glutamate)
- Ecosanoids (e.g., Prostaglandins, Thromboxanes, Prostacyclines)
- Leukotrienes
- Vitamines (e.g., Vit- D₃)
- cytokines (e.g.,Interferon-gamma)[11]
- Chemokines (e.g.,RANTES)[12]
- Amino acid derivatives (e.g., epinephrine)[13]
- Poly peptides (e.g., Insulin)[14]
- Fatty acid derivatives

The classification of one molecule into one class of another is not exact. For example, epinephrine and norepinephrine secreted by the central nervous system act as neurotransmitters. However, epinephrine when secreted by the adrenal medulla acts as a hormone.

Unicellular organisms may also respond to environmental stimuli via the activation of signal transduction pathways. For example, slime molds secrete cyclic-AMP upon starvation, which stimulates individual cells in the immediate environment to aggregate [15]. Yeast also use mating factors to determine the mating types of other yeast and participate in sexual reproduction[16].

Cellular responses

Activation of genes[17], alterations in metabolism[18], the continued proliferation and death of the cell[19], and the stimulation or suppression of locomotion[20], few are of the cellular responses to extracellular stimulation that require signal transduction.

Classification of intercellular communication: cell signaling mechanisms

With in endocrinology (the study of intracellular signaling in animals) and the endocrine system, intracellular signaling is subdivided into the following classifications:

1. **Endocrine cell signaling:** Endocrine cells secrete a polypeptide or steroid hormone into blood vessel. The hormone is then carried to a target cell, which may be located at considerable distance from the secreting cell.

Example of a polypeptide hormone, secreted by the hypophysis and acting on thyroid gland. An example of a hormone is Estradiol, produced by the ovary and acting on endometrium.

2. **Paracrine cell signaling:** Paracrine cells secrete hormones or growth factors that act on adjacent steroid cells.

Examples are Glucagon and somatostatin acting on adjacent cells of the islets of Langernans which secrete insulin.

3. Autocrine cell signaling: Some hormones or growth factors such as prostaglandins and interlukins can act on the originating cell and excert an autocrine control.

An example for Autocrine signaling is found in immune cells.

4. Neurotransmitter cell signaling: [A specific form of paracrine signaling]

In response to a neural signal, neurans secrete neurotransmitters from the axon terminals to activate adjacent neurans.

5. Neuro endocrine cell signaling: [A specific form of endocrine signaling]

In response to a neural signal, neuroendocrine cells secret a hormone into the blood to travel to a target organ.

An example is norepinephrine acting on hepatocytes or adipocytes.

6. **Juxtacrine cell signaling:** signals are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.

G-protein-coupled receptors

G protein-coupled receptors (GPCRs), also known as seven transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptor, and G protein-linked receptors (GPLR), G-protein-coupled receptors (GPCRs) are a family of integral membrane proteins that possess seven membrane-spanning domains, and are linked to a guanine nucleotide-binding protein (or heterotrimeric G protein).

Examples of this family includes adrenergic receptors, olfactory receptors, chemokine receptors, neurotransmitter receptors, muscarinic cholinergic receptors, opioid receptors, and rhodopsin etc...

G protein-coupled receptors are found only in eukaryotes, including yeast, plants, choanoflagellates [21], and animals. The ligands that bind and activate these receptors include light-sensitive compounds, pheromones, neurotransmitters, odors, and hormones, and these vary in size from small molecules to peptides to large proteins. G protein-coupled receptors are involved in many diseases, and are also the target of almost half of all modern medicinal drugs [22].

Classification

GPCRs are grouped into 6 classes based on sequence homology and functional similarity [23, 24, 25].

- Class 1 (or A) (Rhodopsin-like)
- Class 2 (or B) (Secretin receptor family)
- Class 3 (or C) (Metabotropic glutamate/pheromone)
- Class 4 (or D) (Fungal mating pheromone receptors)

- Class 5 (or E) (Cyclic AMP receptors)
- Class 6 (or F) (Frizzled/Smoothened)

The very large rhodopsin A, group is further sub divided into 19 subgroups (A1-A19) [26]. An alternative classification system has been proposed recently called GRAFS (Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2, and Secretin) [27].

The human genome encodes around 350 G protein-coupled receptors, which detect hormones, growth factors and other endogenous ligands. Approximately 150 of the GPCRs found in the human genome have unknown functions.

Receptor structure





GPCRs are integral membrane proteins that possess seven membrane-spanning domains or tramsmembrane helices [Figure 1]. The extracellular parts of the receptor can be glycosilated. These extracellular loops also contain two highly-conserved cysteine residues that form disulfide bonds to stabilize the receptor structure.

GPCRs has weak analogy to bactereorhodopsin for which a structure had been determined by electron diffraction (PDB, 2BRD, 1AT9) [28, 29], and X-ray based cristallography(1AP9) [30]. In 2000, the first crystal structure of a mammalian GPCR, that of bovine rhodopsin(1F88), was solved[31]. In 2007, the first structure of a human GPCR was solved (2R4R, 2R4S) [32]. Then a higher resolution structure of the same receptor (2RH1) [33, 34]. This human β_2 -adrenergic receptor GPCR structure, proved to be highly similar to the bovine rhodopsin in relation to orientation of the seven transmembrane helices.

Mechanism:

G protein-coupled receptor is activated by an external signal in the form of a ligand or other signal mediator. This creates a conformational change in the receptor, causing activation of a G protein. Further effect depends on the type of G protein.

Ligand binding:

GPCRs include receptors for sensory signal mediators (e.g., light and olfactory stimulatory molecules); adenosine, bombesin, bradykinin, endothelin, melanocortins, neuropeptide Υ, γ-aminobutyric acid (GABA), opioid peptides, somatostatin, hepatocyte growth factor, 366

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vasopressin, opsins, vasoactive intestinal polypeptide family, and tachykinins, chemokines; lipid mediators of inflammation (e.g., prostaglandins, prostanoids, platelet-activating factor, and leukotrienes); peptide hormones (e.g., calcitonin, C5a anaphylatoxin, follicle-stimulating hormone (FSH), gonadotropic-releasing hormone (GnRH),glucagon, acetylcholine (muscarinic effect), and serotonin); and biogenic amines (e.g., dopamine, epinephrine, norepinephrine, histamine, glutamate (metabotropic effect), neurokinin, thyrotropin-releasing hormone (TRH), and oxytocin).

Figure 2: Signal transduction from a G-protein-linked receptor following interaction with its hormone ligand



GPCRs that act as receptors for stimuli that have not yet been identified are known as orphan receptors. For example, the physiologic agonists and functional role for a large number of orphan GPCR remain unknown, although such orphan receptors may prove to be as important—perhaps more so—than GPCR currently emphasized in physiologic and pharmacologic studies and in drug development [35-37]. Newly identified receptors (initially "orphans") in the cloning era have already yielded pharmacologically useful drugs, for example CaSR agonists (calcimimetics) and antagonists (calcilytics) as therapies for a variety of disorders [38].

Conformational change:

The transduction of the signal through the membrane by the recptor is not completely understood. It is identified that the inactive G protein is bound to the receptor in its inactive state. Once the ligand is recognized, the receptor shifts conformation and thus mechanically activates the G protein, which detaches from the receptor. The receptor can now either activate another G protein or switch back to its inactive state.

It is known that a receptor molecule exists in a conformational equilibrium between active and inactive biophysical states [39]. The binding of ligands to the receptor may shift the equilibrium toward the active receptor states. Three types of ligands exist: agonists are ligands which shift the equilibrium in favour of active states; inverse agonists are ligands that shift the equilibrium in favour of inactive states; and neutral antagonists are ligands that do not affect the equilibrium. It is not yet known how exactly the active and inactive states differ from each other.

Activation of G protein

If a receptor in an active state encounters a G protein, it may activate it [Figure 3, blue protein in part B]. Some evidence suggests that receptors and G proteins are actually pre-coupled. For example, binding of G proteins to receptors affects the receptor's affinity for ligands. Activated G proteins are bound to GTP.





Further signal transduction depends on the type of G protein. The enzyme adenylate cyclase [Figure 3, green protein in panel C] is an example of a cellular protein that can be regulated by a G protein, in this case the G protein G_s . Adenylate cyclase activity is activated when it binds to a subunit of the activated G protein [Figure 3, Panel D]. Activation of adenylate cyclase ends when the G protein returns to the GDP-bound state [Figure 3, panels D and A].

GPCR signaling without G proteins:

Some GPCRs are able to signal without G proteins. The ERK2 mitogen-activated protein kinase, a key signal transduction mediator downstream of receptor activation in many pathways, has been shown to be activated in response to cAMP-mediated receptor activation in the slime mold *D. discoideum* despite the absence of the associated G protein α - and β -subunits.

In mammalian cells, the much-studied β_2 -adrenoceptor has been demonstrated to activate the ERK2 pathway after arrestin-mediated uncoupling of G-protein-mediated signaling.

In kidney cells, the bradykinin receptor B2 has been shown to interact directly with a protein tyrosine phosphatase. The presence of a tyrosine-phosphorylated ITIM (immunoreceptor tyrosine-based inhibitory motif) sequence in the B2 receptor is necessary to mediate this interaction and subsequently the antiproliferative effect of bradykinin [40].

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Receptor regulation:

GPCRs become desensitized when exposed to their ligand for a prolonged period of time. There are two recognized forms of desensitization: 1) homologous desensitization, in which the activated GPCR is downregulated; and 2) heterologous desensitization, wherein the activated GPCR causes downregulation of a different GPCR. The key reaction of this downregulation is the phosphorylation of the intracellular (or cytoplasmic) receptor domain by protein kinases.

Phosphorylation by cAMP-dependent protein kinases:

Cyclic AMP-dependent protein kinases (protein kinase A) are activated by the signal chain coming from the G protein (that was activated by the receptor) via adenylate cyclase and cyclic AMP (cAMP). In a *feedback mechanism*, these activated kinases phosphorylate the receptor. The longer the receptor remains active, the more kinases are activated, the more receptors are phosphorylated. In β_2 -adrenoceptors, this phosphorylation results in the switching of the coupling from the G₀ class of G-protein to the G_i class. cAMP-dependent PKA mediated phosphorylation is also known as heterologous desensitisation, because it is not specific to ligand bound receptor. In fact any receptor causing an increase in PKA activity will cause increased amounts of this type of desensitisation of other receptors coupled to G₀ (*e.g.*, dopamine receptor D₂ activation may lead to β_2 -adrenoceptor desensitisation of this type)[41].

Phosphorylation by GRKs:

The G protein-coupled receptor kinases (GRKs) are protein kinases that phosphorylate only active GPCRs.

Phosphorylation of the receptor can have two consequences:

1. *Translocation*: The receptor is, along with the part of the membrane it is embedded in, brought to the inside of the cell, where it is dephosphorylated within the acidic vesicular environment [42] and then brought back. This mechanism is used to regulate long-term exposure, for example, to a hormone, by allowing resensitisation to follow desensitisation. Alternatively, the receptor may undergo lysozomal degradation, or remain internalised, where it is thought to participate in the initiation of signalling events, the nature of which depend on the internalised vesicle's subcellular localisation[41].

2. Arrestin linking: The phosphorylated receptor can be linked to arrestin molecules that prevent it from binding (and activating) G proteins, effectively switching it off for a short period of time. This mechanism is used, for example, with rhodopsin in retina cells to compensate for exposure to bright light. In many cases, arrestin binding to the receptor is a prerequisite for translocation. For example, beta-arrestin bound to β_2 -adrenoreceptors acts as an adaptor for binding with clathrin, and with the beta-subunit of AP2 (clathrin adaptor molecules); thus the arrestin here acts as a scaffold assembling the components needed for clathrin-mediated endocytosis of β_2 -adrenoreceptors[43-44].

Receptor oligomerization

The best studied example of receptor oligomerisation is the metabotropic $GABA_B$ receptors. These receptors are formed by heterodimerization of $GABA_BR1$ and $GABA_BR2$ subunits. Expression of the $GABA_BR1$ without the $GABA_BR2$ in heterologous systems leads to retention of the subunit in the endoplasmic reticulum. Expression of the GABA_BR2 subunit alone, meanwhile, leads to surface expression of the subunit, although with no functional activity (*i.e.*, the receptor does not bind agonist and cannot initiate a response following exposure to agonist). Expression of the two subunits together leads to plasma membrane expression of functional receptor. It has been shown that GABA_BR2 binding to GABA_BR1 causes masking of a retention signal [45] of functional receptors [46].

Physiological roles:

GPCRs are involved in a wide variety of physiological processes. Some examples of their physiological roles include:

1. **Regulation of immune system activity and inflammation:** chemokine receptors bind ligands that mediate intercellular communication between cells of the immune system; receptors such as histamine receptors bind inflammatory mediators and engage target cell types in the inflammatory response

2. Cell density sensing: A novel GPCR role in regulating cell density sensing.

3. **The sense of smell:** receptors of the olfactory epithelium bind odorants (olfactory receptors) and pheromones (vomeronasal receptors)

4. **The visual sense:** the opsins use a photoisomerization reaction to translate electromagnetic radiation into cellular signals. Rhodopsin, for example, uses the conversion of *11-cis*-retinal to *all-trans*-retinal for this purpose

5. **Autonomic nervous system transmission:** both the sympathetic and parasympathetic nervous systems are regulated by GPCR pathways, responsible for control of many automatic functions of the body such as blood pressure, heart rate, and digestive processes

6. **Behavioral and mood regulation:** receptors in the mammalian brain bind several different neurotransmitters, including serotonin, dopamine, GABA.

Impact of GPCRs in clinical medicine: genetic variants and drug targets

Widespread distribution and important roles in cell physiology and biochemistry, G-proteincoupled receptors (GPCR) play multiple important roles in clinical medicine. Most important are 1) Monogenic diseases of GPCR;

2) Genetic variants of GPCR; and

3) Clinically useful pharmacological agonists and antagonists of GPCR.

Diseases involving mutations of GPCR are rare, occurring in <1/1000 people, but disorders in which antibodies are directed against GPCR is more common. Genetic variants, especially single nucleotide polymorphisms (SNP), show substantial heterogeneity in frequency among different GPCRs but have not been evaluated for many therapeutic agonists and antagonists target GPCR and show inter-subject variability in terms of efficacy and toxicity.

Monogenic Diseases of GPCR

Monogenic diseases and genetic variants associated with those diseases are generally quite rare, occurring in <1% of the population and often variably among subjects of different ethnicities. Since GPCR comprise $\sim3\%$ of the human genome [47], it is perhaps not surprising that non-lethal mutations can occur in GPCR, especially those that are expressed in sensory and hormonal systems, where they serve as mediators of information transfer from the extracellular

environment to the cell interior. One such critical action is in the visual system where rhodopsin in photoreceptor-capturing neurons, retinal rods and color (red, blue and green) opsins in retinal cones, transduce the input from photons of light into electrical impulses that then travel to the brain and are decoded. A large number of monogenic mutations have been identified in rhodopsin, in particular in patients that have the disease retinitis pigmentosa; in addition, a number of hormonally responsive GPCR have been identified as pathologic entities in a variety of endocrine disorders [Table 1].

Receptor/Genename	ceptor/Genename Mutation Disease		
Calcium-Sensing (CaS)/CaSR	Multiple (e.g. Arg185Gln)	Autosomal Dominant Hypocalcemia (ADH) Sporadic Hypoparathyroidism Familial Hypoparathyroidism	[48,49]
CXCR4	Multiple (e.g. Ser338X)	WHIM syndrome	[50, 51]
Endothelin receptor B (ET _B)/EDNRB	Multiple (e.g. Trp276Cys)	Hirschsprung's disease	[52]
Follicle-stimulating hormone (FSH)/FSHR	Multiple (e.g. Ala189Val)	Female infertility	[53]
N-formyl-peptide (FPR)/FPR1	Phe110Ser, Cys126Trp	Juvenile periodontitis	[54]
Frizzled (FZD ₄)/FZD4	Multiple (e.g. Arg417Gln)	Familial exudative vitreoretinopathy (FEVR)	[55, 56]
Goandotropin-releasing hormone (GnRH)/GNRHR	Multiple (e.g. Arg262Gln)	Hypogonadotropic hypogonadism (HH)	[57,58]
GPR54/GPR54	Multiple (e.g. Cys223Arg)	Hypogonadotropic hypogonadism (HH)	[57,58]
GPR56/GPR56	Multiple (e.g. Cys223Arg)	Bilateral frontoparietal polymicrogyria (BFPP)	[59,60]
vGPCR/KSHV-GPCR	(constitutively active)	Kaposi's sarcoma (KS)	[61,62]
Relaxinfamilypeptidereceptor2(RXFP2)/LGR8	Multiple (e.g. Thr222Pro)	Cryptorchidism	[63-64]
MASS1 (also called VLGR1, USH2C)/MASS1	Multiple (e.g. Ser2652X))	Usher syndrome Febrile seizures (FS)	[65–69]
Melanocortin (MC ₄)/MC4R	Multiple (e.g. Pro78Leu)	Dominant and recessive obesity	[70,71]
Rhodopsin/RHO	Multiple (e.g. Pro23His)	Retinitis pigmentosa (RP)	[72-74]
Vasopressin receptor (V ₂)/AVPR2	Multiple (e.g. Arg113Trp)	Nephrogenic diabetes insipidus (NDI)	[75,76]

Table 1: Examples of rare mutants of GPCR that cause human diseases

Genetic variants of GPCR

Genetic variants/polymorphisms identified in GPCRs can influence receptor expression, targeting, function, and receptor turnover; as well as the ability of receptors to recognize and respond to pharmacologic agents. Below we describe selected GPCRs with polymorphisms involved in human diseases, in addition to elucidating their potential for serving as future therapeutic targets. [Table 2] lists sequence variants identified in human GPCR genes that relate to human diseases.

Receptor	Polymorphisms	Examples of disease associations	Ref
β_1 Adrenergic receptor	Arg389Gly	Heart failure	[77, 78]
β_2 Adrenergic receptor	Multiple	Hypertension, Asthma	[79,80]
β_3 Adrenergic receptor	Trp64Arg	Obesity	[81]
CC chemokine receptor 2 (CCR2)	Val64Ile	Delayed progression of AIDS	[82]
CC chemokine receptor 5 (CCR5)	Multiple	Associated with progression of AIDS	[83,84]
Dopamine receptor 2 (D ₂)	3'UTR52A/G	Associated with depression and anxiety	[85]
Dopamine receptor 3 (D ₃)	Ser9Gly, Promoter SNPs	Haplotype associated with schizophrenia	[86]
Muscarinic receptor subtype 3 (M ₃)	Promoter haplotype	Possible association with asthma and atopy	[87]
Neuropeptide S receptor (NPSR; also called GPR154, GPRA)	Haplotypes H1, H5 Asn107Ile, rs324981	Asthma susceptibility	[88,89,90]
P2Y ₁₂	CA deletion at Codon 240	Associated with bleeding diathesis	[91]

Table 2: Examples of polymorphisms of GPCR associated with human diseases.

GPCR polymorphisms can affect functional responses to some but not other ligands, e.g. with β_3 adrenergic receptors [89-91]. Such concepts may apply not only to acutely measured GPCR responses but also to receptor regulation, especially because certain GPCR polymorphisms alter such regulation [92]. In the following we illustrate these principles based upon examples from several drug classes acting on GPCR that are frequently used in clinical medicine [Table 3].

Table 3:	GPCR as	s drug tar	gets: some	examples	of the imp	act of rece	ptor po	lymorphisms.

Receptor	Drugs and some key indications	Polymorphism	Relevance	Ref
AT ₁ angiotensin II receptor	Antagonists (e.g. losartan) in the treatment of essential hypertension or congestive heart failure	A1166C SNP in untranslated part of exon 5	Inconclusive data for drug responses where multiple studies have been done	[93- 99]
α_{1A} - adrenergic receptor	Antagonists (e.g. tamsulosin) to treat micturition (bladder emptying) disorders associated with enlarged prostate glands	C1475T	Short- and long-term antagonist effects apparently not affected	[100]
β_1 - adrenergic receptor	Antagonists (e.g. propranolol, atenolol, metoprolol, carvedilol) to treat essential hypertension or congestive heart failure	Ser49Gly Arg389Gly	Arg389 linked to increased antagonist effect	[96,1 01- 103, 104,1 05]
β_2 - adrenergic receptor	Agonists (e.g. terbutaline, salbutamol, formoterol, salmeterol) for treatment of obstructive airway disease or premature labor	Arg16Gly Gln27Glu Thr164Ile	Possibly reduced responses with Ile164 otherwise no consistent association with drug responsiveness	[92]
D ₂ dopamine receptor	Antagonists (e.g. haloperidol and clozapine) to treat schizophrenia Agonists (e.g. levodopa) for the treatment of Parkinson's disease	-141C Ins/Del Taq1A	Reduced antagonist response with Del or homozygous A2 allele No consistent associations with therapeutic response or side effects of agonists	[106- 108]

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D ₃ dopamine receptor	Antagonists (e.g. haloperidol) in the treatment of schizophrenia	Ser9Gly	Increased risk of tardive dyskinesia with Gly allele	[106, 107]
5-HT _{2A} receptor	Antagonists (e.g. clozapine) to treat schizophrenia Indirect agonists (e.g. fluvoxamine) for the treatment of depression	T102C	Reduced response to clozapine with C allele Possibly reduced response to agonists with homozygous T allele	[107, 109]
5-HT _{2C} receptor	Antagonists (e.g. clozapine) to treat schizophrenia	Multiple polymorphisms in promoter and coding region in linkage disequilibrium	Genotypes associate with therapeutic response and with side effects such as tardive dyskinesia and weight gain	[110, 111]

CONCLUSION

GPCR is a multi-functional receptor that has numerous clinical implications. GPCR are physiologically important in maintaining homeostasis, in particular via their ability to mediate responses to circulating hormones and neurotransmitter input in the central, peripheral and autonomic nervous systems. The cloning and characterization of GPCR and of components involved in mediating receptor responses and in regulating receptor expression has provided a number of new insights, Because the ability of cells to precieve and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homiostasis. Neverthless, significant progress has been made in the last few years by many investigators. Further clarification of the precise role of GPCR in different biological context will likely lead to new and novel therapeutic stratagies for various diseases such as cancer, autoimmunity, and diabetes. In addition, further insights into GPCR biology may reveal novel, unexpected therapeutic targets that influence the GPCR life cycle or "ligand directed signaling". The existence of a large number of orphan GPCRs provides a treasure trove of possibilities.

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