The role of G-proteins and G-protein-coupled receptors in human disease

YunCheng Xian

Abstract:

In human diseases associated with G protein, changes in abnormal content and distribution of multiple signaling molecules and abnormal signaling pathways play critical roles in pathophysiological pathways. Abnormal information transmission and signaling pathways are common channels in the pathogenesis of G protein diseases. G protein-coupled receptors (GPCRs) are the largest group of membrane receptor proteins and represent the most common therapeutic targets for drugs. This paper uses liver injury, blood pressure regulation, Parkinson's disease, and some cancers to illustrate the pathogenic mechanism and pathway-related treatment of G-protein and GPCR.

1.INTRODUCTION

G protein-coupled receptors (GPCRs) is the largest class of membrane protein receptor family in the human genome, including class A rhodopsin-like receptor, class B secretin receptor, class C metabotropic glutamate receptor, class D fungal mating pheromone receptor, class E cyclic adenylate receptor and class F curli receptors (Frizzled / Smoothened family) [1,2]. They account for about 2% of the total protein encoded in the human genome. Approximately 34% of approved drugs act through GPCR, either activating or inhibiting the signal transduction cascade [3] by regulating GPCR activity in the drug.

The GPCR is a structurally monomer protein with the amino terminus on the outer surface of the membrane and the carboxyl terminus medial to the membrane. Its peptide chain repeatedly crosses the cell membrane heptad, making it a heptapeptide transmembrane receptor [4,5]. Because the peptide chain repeatedly passes through the membrane, several ring structures form the lateral and medial sides of the membrane, responsible for stimulating exogenous signals (chemical and physical signals) and intracellular signals, respectively, and part of the intracellular receptor can be associated with trimeric G proteins.

GPCRs are involved in several pathophysiological processes, activating and inactivating mutations of GPCR have implicated in various diseases such as malignancy [6]. Intervention with such receptors and their mediated signal transduction pathways may correct related diseases and cancers. This review provides an overview of the basic patterns of GPCR-mediated signal transduction pathway as well as different pathways for signaling. It also enumerates a portion of G protein-related human diseases and therapeutic pathways related to these pathways.

2.SIGNALING PATHWAY MEDIATED BY G-PROTEIN-COUPLED RECEPTORS

2.1 *G protein-coupled receptor-mediated signal transduction pathways have the same basic pattern*

Different combinations of αβγ G protein can form signal transduction pathways with different downstream molecules. GPCR mediated signaling can produce various different effects through different pathways, but the basic pattern of signal transduction pathway is roughly the same and includs the following steps or stages: First, extracellular signaling molecules bind to receptors, activating the receptor through allosteric effects. The effector molecules of G proteins transmit signals downstream mainly by catalyzing the production of small molecule messengers, such as cAMP production via AC and PLC production for DAG and IP3. Some effector molecules can alter the distribution of intracellular calcium by regulating ion channels, similar to IP3. Protokinases activate various cellular responses by phosphorylating some metabolic enzymes, gene expression-related transcription factors, and proteins related to cell motility. The process involves ligand-activated receptor binds to the G protein, causing a conformational change that decreases the affinity of the α subunit to GDP, releasing GDP and binding to GTP. The α subunit then binds GTP , dissociates from the β y subunit, and becomes activated. The downstream molecules can activate the GTP enzyme activity of the α subunit, hydrolyze GTP into GDP and return to the quiescent state.

2.2 *Different G protein-coupled receptors can transmit signals through different pathways*

Different extracellular signaling molecules bind to the

corresponding receptors and transmit signals through the G proteins, but the signals entering the cell are not the same due to different downstream signal transduction pathways formed by different G proteins. The three common pathways include:

2.2.1 ***The cAMP-PKA pathway***

This pathway is characterized by altered intracellular cAMP concentration and PKA activation in the target cells. Glucagon, adrenaline, and corticotropin can activate this pathway. Upon activation, PKA phosphorylates various protein substrates on their serine/threonine residues, changing their active state. There are three common roles for this pathway:

2.2.1.1 Regulation of metabolism

PKA can regulate different metabolic pathways by controlling the activity of key enzymes, such as activating glycogen phosphorylase b kinase, hormone-sensitive lipase, cholesterol lipase, thereby promoting the catabolism of glycogen, fat and cholesterol. PKA can also inhibit acetyl CoA carboxylase and glycogen synthase, inhibiting the synthesis of fat and glycogen [8].

2.2.1.2 Regulation of gene expression

PKA can modify and activate transcriptional regulators, thereby regulating gene expression. For instance, after activation, PKA translocated into the nucleus and phosphorylate the cAMP response element-binding protein (CREB). Phosphorylated CREB can then bind to the cAMP reaction element (CRE) and the CREB-binding protein (CBP). CBP, upon binding to CREB, acts on universal transcription factors, including TFIB, to promote their binding to promoters and activate gene expression [9,10].

2.2.1.3 Regulation of cell polarity

PKA can also regulate cell polarity by activating ion channels through phosphorylation, thereby regulating the cell membrane potential.

2.2.2 The G proteins activated by IP 3 / DAG-PKC pathway through

IP3 promotes the rapid release of Ca^{2+} in the cellular calcium reservoir and increases the Ca^{2+} concentration in the cytoplasm.DAG, phosphatidylserine at the plasma membrane, and Ca^{2+} act together on the regulatory domain of PKC, which makes the PKC undergo allosteric changes and expose the active center.

Proteins modified by PKC phosphorylation include some plasma membrane receptors, membrane proteins, and various enzymes. Therefore, PKC can be related to the regulation of various physiological functions. In addition, PKC can phosphorylate the transcriptional regulator of immediate-early gene and accelerate the expression of the early response genes. Most of the immediate-early genes are cellular proto-oncogenes, and their expression products are modified by phosphorylation to further activate the late response genes and promote cell proliferation[11].

2.2.3 The Ca^{2+}/ calmodulin-dependent protein kinase pathways

GPCR can increase intracellular Ca^{2+} concentrations in at least three ways: certain G proteins can directly activate calcium channels at the cell plasma membrane, or activate the cell plasma membrane through PKA to promote Ca^{2+} influx into the cytoplasm, or promote Ca^{2+} release from the cytoplasmic calcium pool through IP3.

After an increase in Ca^{2+} concentration in the cytoplasm, the signal is transmitted by binding calmodulin. The downstream signal transduction molecules of Ca^{2+} / CaM complexes are some protein kinases, whose common feature is that they can be activated by Ca^{2+} / CaM complexes [12], so they are collectively referred to as calmodulin-dependent protein kinases. Calmodulin-dependent kinases belong to protein serine/threonine kinases, such as phosphorylase kinase (PhK), calmodulin-dependent kinase (Cal-PK) I, among others. These kinases can activate various effector proteins and participate in various physiological processes, including contraction and movement, substance metabolism, neurotransmitter synthesis, cell secretion and division. For example, CaMK can modify and activate synapsin I, tyrosine hydroxylase, tryptophan hydroxylase, skeletal muscle glycogen synthase [13], among others, participating in the synthesis and release of neurotransmitters [14], and regulating various cellular functions such as glucose metabolism.

3. G PROTEIN WITH THE HUMAN DISEASE

3.1 *liver injury*

TGR5 is a G-protein coupled receptor that responds to different nonconjuaged and conjugated bile acids [6]. TGR5 mRNA is ubiquitously expressed in both human and mouse tissues, including the liver, gallbladder, and intestine [15,16]. Activation of TGR5 mediates choleretic, proliferative and antiapoptotic effects, suggesting a potential role in cholangiocyte function.[21]

TGR5 is maining activated by chenodeoxycholic acid, followed by deoxycholic acid, cholic acid, and lithocholic acid [22]. Studies have shown that TGR5 signals main through increasing intracellular cAMP levels, leading to the rapid phosphorylation of AMP-activated protein kinase, which is involved in anti-inflammatory responses and energy metabolism TGR5 can also directly regulate

bile acid and glucose and lipid metabolism to prevent liver steatosis [23,24,25].

Meanwhile, TGR5 also plays a crucial role in the treatment of liver injury. TGR5 can regulate liver microcirculation, inflammation, tissue regeneration, bile secretion, and gallbladder filling [26]. Studies have shown that TGR5-null mice are more prone to develop inflammatory liver injury, cholestatic liver injury, and liver fibrosis. Studies have shown that TGR 5-null mice are more prone to develop inflammatory liver injury, cholestatic liver injury, and liver fibrosis. In bile duct epithelial cells of patients with primary sclerosing cholangitis, reduced TGR5 levels may promote the development of a reactive biliary epithelial cell phenotype and aggravate biliary injury [27]. TGR 5 agonists can ameliorate inflammatory liver injury, cholestatic liver injury, non-alcoholic fatty liver disease, and improve extrahepatic complications of liver disease, such as cholestatic pruritus [26]. TGR5 inhibitors can delay the progression of polycystic liver disease and cholangiocarcinoma [26].

3.2 *nervous system disease*

3.2.1 *Role and possible mechanisms of GRKs in nervous system disease*

Alzheimer's disease (AD) and Parkinson's disease (PD) are typical neurodegenerative diseases of the nigrostriatal pathwayIn recent years, G protein-coupled receptor kinases (GRKs) have been increasingly studies in relation to PD. GRKs are a class of important soluble proteins that mediate receptor desensitization.

After sustained stimulation, GRKs phosphorylate the receptor, and arrestins binds to the phospho-receptor, causing desensitization of dopamine (DA) receptors. Upon binding to the receptor, arrestins inhibit signaling via the G protein and leads to receptor internalization. The binding and redistribution of GRKs and arrestins to signaling molecules in subcellular structures affect not only the strength but also the direction and timing of signal transduction [28]. Histological experiments have shown that GRK6 mRNA is higher than other GRKs in many parts of the brain. Immunohistochemical tests also found that GRK6 is expressed in dorsoventral striatum, indicating that GRK6 may be the main receptor kinase involved [29].

3.2.2 *Role and possible mechanisms of GRK6 in nervous system disease*

Evidence gathered over the last two decades suggests that GRK 6 is mainly expressed in the neurons of the D1 and D2 receptors, indicating that this kinase is involved in the regulation of DA receptor signaling [28-31].

Ahmed et al [33] found that virus-mediated overexpression of striatal GRK6 improved the rotation behavior of PD rats and alleviated abnormal apathy by promoting D1 receptor internalization and signal transduction. In contrast, GRK6 knockdown aggravated the rotation behavior and caused dyskinesia. In the monkey model, increased GRK6 inhibited dyskinesia but did not affect the anti-PD effect of levodopa, or even prolonged the anti-PD effect of low-dose levodopa. Therefore, GRK6 plays an important role in neurological diseases and may be a potential therapeutic target for treating PD.

There are countless treatments for G protein-related neurological diseases, and the therapeutic role of β -arrestin in CNS diseases is mainly described here. Initially, β-arrestins were considered as negative regulators of GPCRs, combining with GRK to cause receptor desensitization of GPCRs and terminate the signal transduction caused by agonists. In Alzheimer's disease, GPCRs recruited by β -arrestin2 interact through APH-1 and γ -secretase complex, which then transversely moves to the lipid raft, activating γ -secretase. β -secretase catalyzes APP, which is then hydrolyzed by γ-secretase to generate β-amyloid and β-amyloid precursor protein intracellular domain (APP intracellular domain, AICD). β amyloid can lead to the aggregation of extracellular β amyloid [34]. This provides a new idea for the treatment of Alzheimer's disease.

In the treatment of Parkinson's disease, Wu et al [35] developed a rat 6-hydroxydopamine (6-OH-DA) model and detected decreased expression of β-arrestin1 in the striatal region of PD rats using immunoblotting. However, the expression of β-arrestin1 in PD rats with concurrent dyskinesia was further decreased. After treatment with MK-801, an antagonist of the NMDA (N-methyl-D-aspartate) receptor, the expression of β-arrestin1 increased, indicating that the decrease of β-arrestin1 during the development of PD may cause the latter to be in a hypersensitive state. This may be one of the bases of dyactiopathy. Increasing the expression of β-arrestin1 may provide a new treatment for Parkinson's disease.

3.3 *blood pressure regulation*

The G protein family is an important molecule necessary for cardiovascular cell signaling and physiological activities. GPCRs mediate many neurotransmitter and hormone biological functions in the body, and have important regulatory roles for vasoconstriction, cardiac output and blood flow. The regulator of G protein signaling protein-2 (RGS2) is a selective and efficient inhibitor that acts on the q subunit of G protein, mediating the contraction and relaxation of in blood vessels, especially resistance vessels. RGS2-knockout mice exhibit a refractory hypertensive phenotype and persistent resistance vasoconstriction [36].

Studies have shown that some missense mutations in the RGS2 gene alter protein function, thereby affecting blood pressure levels in experimental animals [37]. Ethnic-specific missense mutation sites have been found in different populations around the world, and some of them have been shown to be associated with hypertension phenotype in animal experiments.

One of the most important causes of imbalanced blood pressure regulation (hypertension) and atherosclerosis is vascular calcification. Studies have shown that there are numerous GPCRs associated with vascular calcification. The harm of vascular calcification is that it may cause blood vessels to become brittle and hard, which often leads to imbalanced blood pressure regulation (hypertension) and atherosclerosis.

In the experiments on the mechanism of Intermedin$_{1}$-s$_{3}$ (IMD $_{1}$-s$_{3}$), it was found that IMD$_{1}$-s significantly down-regulated ER stress inducer Chitlamamycin (Tm) or dithiothreitol (DTT)-induced VSMCs ERS-response protein glucose-regulated protein 78 (GRP78), GRP94, and the activated transcription factor 4 (ATF4). IMD$_{1}$-s$_{3}$ significantly downregulated the expression of the calcification early and late ERS response protein molecules GRP78, GRP94, and ATF4, and its inhibition was blocked by the IMD receptor antagonist IMD$_{17}$ -47 and the PKA inhibitor H89.

Hoechst staining showed calcified VSMCs apoptosis. The expression of CCAAT/enhancer binding protein homology (CCAAT/CHOP) and cleaved active caspase-12 protein was increased 1.69 and 1.56 times, respectively, compared to the control group. IMD pretreatment significantly inhibited calcification VSMCs apoptosis and ERS apoptosis overexpression. Meanwhile, IMD$_{1}$-s$_{3}$ upregulated the expression of the calcified VSMCs contraction phenotype marker molecules α-actin, and SM22α -actin, and downregulated the protein expression of the osteoblast-like cell marker molecules OPN and osteocalcin. The calcified VSMCs alkaline phosphatase activity and calcium content in the IMD$_{1}$-s$_{3}$ treatment group were decreased by 39.7% and 52.8%, respectively, compared to the calcified group alone. Alizarin red staining showed a significant reduction in calcified nodules in the IMD$_{1}$-s$_{3}$ -treated group.

In conclusion, IMD$_{1}$-s$_{3}$ regulates ERS and its induced cell apoptosis by activating its receptor and cAMP/PKA signaling pathway, thus inhibiting VSMCs calcification [38,39].

4. G PROTEIN WITH CANCER

4.1 *mammary cancer*

Breast cancer (BC) is the most common cancer in women and a leading cause of cancer-related death among women. GPR116 is a member of the GPCR family. Tang [40] et al. found that GPR116 could regulate the metastasis of breast cancer. In addition, interfering with GPR116 was shown in breast cancer to produce a large number of neutrophils, and the upregulated MMP 8 led to the initial growth block of breast cancer cells by blocking the TGF-B signaling pathway. Finally, it was concluded that GPR116 affects the growth of breast cancer by regulating neutrophil polarity through the MMP 8 signaling pathway.

The somatostatin receptor (SSTR) belongs to an important member of the GPCR family, and has five different subtypes, namely SSTR 1-5. Different isoforms of SSTR can form heterologous dimers with each other, and the same isoform can form homodimers by themselves, all of which can affect the downstream signaling and regulate the entire signaling pathway. SSTR is expressed in normal tissues to varying degrees and in various tumors, including breast cancer. Finally, it was concluded that SSTR is mainly located in the cytoplasm and cell membrane of breast cancer, and both SSTR 1-5 is expressed in breast cancer, in which SSTR 1 and SSTR 4 are inversely correlated with the degree of breast cancer differentiation.

4.2 *renal carcinoma*

Renal cell carcinoma (RCC), also known as renal carcinoma, accounts for about 90% of all renal malignancies, and is the most mortality tumor [42] among genitourinary tumors. The early diagnosis of renal cell carcinoma is difficult, the prognosis of advanced patients is poor, and the incidence and mortality rates of renal cell carcinoma are still increasing year by year worldwide.

IL-6 is one of the most well-studied cytokines to date, and it has also been extensively studied in kidney cancer. Elevated levels of multiple inflammatory cytokines were detected in the blood at diagnosis, suggesting that metastatic [45,46] of RCC may have occurred. The most powerful indicator is the expression of IL-6 that accurately positions the metastatic status [46] at diagnosis. It has been suggested that IL-6 and IL-27 may play a role in RCC biology, and IL-6 together with IL-27 can predict survival and recurrence in RCC patients. Immunohistochemistry showed that IL-6 and its receptors are highly expressed in tumor cells and blood vessels of renal cancer patients and patients with high IL-6 levels have a poor prognosis. Currently, targeting IL-6 therapy has become a new therapeutic strategy for metastatic renal cell carcinoma.

Recently, the tumor-promoting role of IL-11 has been discovered. IL-11 stimulates tumor cell proliferation and invasion in colorectal adenocarcinoma through its downstream signaling cascade, and it also promotes the

migration of glioma cells and tumor-associated brain endothelial cells. Studies by Onnis et al [47] have shown that IL-11 increases anchorage-independent growth of renal cancer RCC4, prostate cancer PC3, and colon cancer HCT116 cells by activating oncogenic signaling pathways through STAT1 and STAT3. This suggests that IL-11 is a negative prognostic factor for renal cancer and incorporating IL-11 into the current prognostic system could improve risk stratification and clinical management of patients with ccRCC.

4.3 *carcinoma of colon*

Colon cancer is a common malignant tumor occurring in the colon, which accounts for the third highest number of gastrointestinal tumors. The most common types of colon cancer are adenocarcinoma, mucinous adenocarcinoma, and undifferentiated carcinoma. The G protein receptors linked with colon cancer are as follows:

4.3.1 *GPR126 with carcinoma of colon*

Recently reports have ddemonstrated that GPR126 was highly expressed in malignant colon cancer tissues and colon cancer cells. Many of the GPCRs highly expressed in tumor cells, when activated by ligands, regulate the growth of tumor cells. For example, protease-activated receptors (PARs), chemokine receptors (CXCRs), and bioactive lipid receptors have all been confirmed to be involved in the regulation of abnormal proliferation, angiogenesis, and tumor invasion of tumor cells [49]. Experimental result suggests a novel GPCR, GPR126, abnormally expressed in colon cancer tissues and regulates tumor proliferation, thereby enriching our understanding of the important role of GPCR in tumorigenesis and development. Previous reports have shown that GPR126 is induced by LPS that promotes the inflammatory response. Connecting the results, as a GPCR expressed in a specific cell population in the small intestine, GPR126 may be involved in the intestinal inflammatory response, and thus play a promoting role in the process of malignant intestinal lesions.

4.3.2 *RGS19 with carcinoma of colon*

RGS19 expression is an independent risk factor for poor prognosis in colon cancer patients. Sakaguchi et al [50] also reported similar findings in their study of sunitinib-resistant renal clear cell carcinoma. Patients with high RGS19 expression had lower overall survival time and recurrence-free survival time than those with low expression. RGS19 was identified as an independent risk factor for renal clear cell carcinoma using Cox analysis. It is well known that the factors affecting the prognosis of colon cancer include rapid tumor proliferation, invasion and metastasis. Patients with high expression of RGS19 have early distant metastasis, shorter survival time and poor prognosis. Therefore, detecting the expression level of RGS19 has certain clinical value in determining the invasion, metastasis and prognosis of colon cancer. The mechanism by which RGS19 promotes tumor invasion and metastasis has not been clearly defined. Wang et al. [51] found that RGS19 can bind the GIPC protein and activate the PI3K/Akt pathway. This pathway is a common signaling pathway mediating cell proliferation, survival and migration. furthermore, Akt phosphorylation transfers MDM2 from cytoplasm to nucleus, which inactivates p53 nucleus and further enhances the invasion and metastasis of tumor cells. It is here speculated that RGS19 may have a similar mechanism of action in colon cancer. These studies suggest that the upregulation of RGS19 in colon cancer may participate in the occurrence and metastasis of colon cancer and can become a potential indicator for the prognosis of colon cancer. Further studies at the molecular level, cellular level and clinical level are necessary to confirm this.

5. G PROTEIN-RELATED TUMOR THERAPY

Tumor occurrence is not only the result of the activation of oncogenes and the inactivation or loss of tumor suppressor genes, but also related to the change of the activity of a series of factors in the cell cycle regulation, resulting in the formation of uncontrolled cycle operation. In most tissue cells, the transformation or malignant evolution of tumors leads to the cycle of uncontrolled operation, which shorten the cell cycle and accelerated the proliferation. Currently, the regulation of tumor cells to inhibit their unrestricted proliferation has become a new direction for clinical tumor treatment and research. Cell cycle turnover, growth, and differentiation are regulated by various intracellular signaling systems. Among them, the cAMP cell signaling system is the most well-established model for cell signaling today, which is considered to play a negative role on the proliferation cycle of cells.

After tumor initiation, cAMP concentrations in tumor tissues and peripheral blood tend to be lower than normal conditions. The results of many anti-tumor drugs have shown that the concentration of cAMP in the tumor tissue and in the blood of patients is significantly higher than before medication [52]. Exogenous cAMP and its numerous derivatives, such as 8-chloroadenosine and 8-bromine-cyclic nucleotide, have been shown to inhibit the proliferation of tumor cells and induce their differentiation [53].

Soybean isoflavones are a class of plant-derived active substances, which have been shown to have inhibitory

effects on a variety of tumors, such as breast, colon, and prostate cancer. The effects of daidzein and genistein on the proliferation of SHZ-88 rat breast cancer cells in vitro have been investigated [54]. Both compounds were found to significantly inhibit the growth of cancer cells, with dose and time-depensent effects, although genistein was more potent than daidzein. This may be because the hydroxyl group is the active group for their function, and daidzeone (4', 7-dihydroxoflavone) is one less hydroxyl than genistein (4',5,7-trishydroxoflavone), thus reducing its inhibition potency. A more detailed mechanism needs to be further investigated. Experimental results show that both substances can activate the cAMP/PKA signaling pathway by transiently increasing the intracellular cAMP concentration by inhibiting the activity of phosphodiesterase in cancer cells.

The main effect of cAMP signaling is the activation of target enzymes and gene expression, which cAMP achieves through the activation of the major receptor protein PKA mediating its effects. The activation of target enzyme is a rapid response process of target cells to cAMP signal, which can show the biological effect of cAMP signal in a short time, after PKA activation, enzymes involved in the regulation of sugar, protein and fat metabolism affect cell cycle, and some cyclin kinases such as cyclin dependent kinase 2 (CDK2) are involved in the regulation of cell cycle through phosphorylation, thus exerting the influence of cell cycle progression. The effect on gene expression is a slow response process. After PKA activation, it phosphorylates certain phosphoption factors, which then bind to specific regulatory sequences of genes regulated by cAMP, thereby regulating the expression of these genes. CREB has been the most intensively studied among these transcription factors.

Ahn et al [55] found that the effect of NGF induced differentiation of PC12 cells could be blocked by the CREB repressor - A-CREB, and its mechanism of action was to prevent the binding of CREB to DNA and inhibit CREB-mediated gene transcription. This indicates that CREB is able to regulate the gene expression of some factors that induce cell differentiation, thus promoting the production of corresponding proteins to induce differentiation. As a downstream factor of the cAMP/PKA signaling pathway, CREB regulates numerous target genes, including its own genes. The increase in CREB mRNA expression in the experiment may be due to the increased content of phosphorylated CREB in the nucleus after elevated PKA activity, which enhancing the transcription of its own genes. The increase of CREB mRNA expression may increase the intracellular CREB content, and play a role in regulating the cell growth, differentiation and cell cycle progression for a long time. However, these are only speculation. The mechanism of PKA and CREB regulating the changes in cyclin, its kinases and some cell differentiation factors, and then inhibiting tumor cell proliferation has not been clarified, and it remains to be further studied.

6. CONCLUSION AND OUTLOOK

Since the 20th centry, G protein and GPCRs have been a research direction for the treatment of acute and chronic diseases, as well as cancer. In clinical aspects, the treatment related to G protein-related diseases have been developed, but the involvement of many related cells, cellular factors and other complex regulation mechanism and signaling pathway have made the research difficult. However, with the discovery of various G protein receptors and pathways, the idea of incurable diseases and cancers is gradually abandoned. With the progress of research and clinical trials, it is believed that humans will be able to overcome the problem of G protein-related diseases and bring good news to patients.

REFERENCES

[1] Venkatakrishnan AJ, Deupi X, Lebon G, Tate CG, Schertler GF, Babu MM. Molecular signatures of G-protein-coupled receptors. Nature. 2013 Feb 14;494(7436):185-94. doi: 10.1038/nature11896. PMID: 23407534.

[2] Davenport AP, Scully CCG, de Graaf C, Brown AJH, Maguire JJ. Advances in therapeutic peptides targeting G protein-coupled receptors. Nat Rev Drug Discov. 2020 Jun;19(6):389-413. doi: 10.1038/s41573-020-0062-z. Epub 2020 Mar 19. PMID: 32494050.

[3] Lee SM, Booe JM, Pioszak AA. Structural insights into ligand recognition and selectivity for classes A, B, and C GPCRs. Eur J Pharmacol. 2015 Sep 15;763(Pt B):196-205. doi: 10.1016/j.ejphar.2015.05.013. Epub 2015 May 14. PMID: 25981303; PMCID: PMC4584177.

[4] Flor PJ, Acher FC. Orthosteric versus allosteric GPCR activation:The great challenge of group-III mGluRs.Biochem Pharmacol, 2012, 84(4):414–424.

[5] Herraiz C, JournéF, Abdel-Malek Z, Ghanem G, JiménezCervantes C, García-Borrón JC. Signaling from the human melanocortin 1 receptor to ERK1 and ERK2 mitogenactivated protein kinases involves transactivation of cKIT.Mol Endocrinol, 2011, 25(1):138–156.

[6] Schöneberg T, Liebscher I. Mutations in G Protein-Coupled Receptors: Mechanisms, Pathophysiology and Potential Therapeutic Approaches. Pharmacol Rev. 2021 Jan;73(1):89-119. doi: 10.1124/pharmrev.120.000011. PMID: 33219147.

[8] Zhang MY, Zhu L, Zheng X, Xie TH, Wang W, Zou J, Li Y, Li HY, Cai J, Gu S, Yao Y, Wei TT. TGR5 Activation Ameliorates Mitochondrial Homeostasis via Regulating the PKCδ/Drp1-

HK2 Signaling in Diabetic Retinopathy. Front Cell Dev Biol. 2022 Jan 14;9:759421. doi: 10.3389/fcell.2021.759421. PMID: 35096809; PMCID: PMC8795816.

[9] Karkoulias G, McCrink KA, Maning J, Pollard CM, Desimine VL, Patsouras N, Psallidopoulos M, Taraviras S, Lymperopoulos A, Flordellis C. Sustained GRK2-dependent CREB activation is essential for α-adrenergic receptor-induced PC12 neuronal differentiation. Cell Signal. 2020 Feb;66:109446. doi: 10.1016/j.cellsig.2019.109446. Epub 2019 Oct 31. PMID: 31678682.2

[10] Zhang H, Yang S, Wang J, Jiang Y. Blockade of AMPK-Mediated cAMP-PKA-CREB/ATF1 Signaling Synergizes with Aspirin to Inhibit Hepatocellular Carcinoma. Cancers (Basel). 2021 Apr 6;13(7):1738. doi: 10.3390/cancers13071738. PMID: 33917483; PMCID: PMC8038809.

[11] Bahrami S, Drabløs F. Gene regulation in the immediate-early response process. Adv Biol Regul. 2016 Sep;62:37-49. doi: 10.1016/j.jbior.2016.05.001. Epub 2016 May 13. PMID: 27220739.

[12] Nairn AC, Picciotto MR. Calcium/calmodulin-dependent protein kinases. Semin Cancer Biol. 1994 Aug;5(4):295-303. PMID: 7803766.

[13] Williams JP, Micoli K, McDonald JM. Calmodulin-an often-ignored signal in osteoclasts. Ann N Y Acad Sci. 2010 Mar;1192(1):358-64. doi: 10.1111/j.1749-6632.2009.05242.x. PMID: 20392260; PMCID: PMC2940234.

[14] Soderling TR. CaM-kinases: modulators of synaptic plasticity. Curr Opin Neurobiol. 2000 Jun;10(3):375-80. doi: 10.1016/s0959-4388(00)00090-8. PMID: 10851169.

[15] Maruyama T, Tanaka K, Suzuki J, Miyoshi H, Harada N, Nakamura T, Miyamoto Y, Kanatani A, Tamai Y. Targeted disruption of G protein-coupled bile acid receptor 1 (Gpbar1/M-Bar) in mice. J Endocrinol. 2006 Oct;191(1):197-205. doi: 10.1677/joe.1.06546. PMID: 17065403.

[16] Vassileva G, Golovko A, Markowitz L, Abbondanzo SJ, Zeng M, Yang S, Hoos L, Tetzloff G, Levitan D, Murgolo NJ, Keane K, Davis HR Jr, Hedrick J, Gustafson EL. Targeted deletion of Gpbar1 protects mice from cholesterol gallstone formation. Biochem J. 2006 Sep 15;398(3):423-30. doi: 10.1042/BJ20060537. PMID: 16724960; PMCID: PMC1559456.

[21] Keitel V, Häussinger D. TGR5 in cholangiocytes. Curr Opin Gastroenterol. 2013 May;29(3):299-304. doi: 10.1097/MOG.0b013e32835f3f14. PMID: 23429467.

[22] Wang C, Zhu C, Shao L, Ye J, Shen Y, Ren Y. Role of Bile Acids in Dysbiosis and Treatment of Nonalcoholic Fatty Liver Disease. Mediators Inflamm. 2019 Jun 24;2019:7659509. doi: 10.1155/2019/7659509. PMID: 31341422; PMCID: PMC6613006.

[23] Liu H, Pathak P, Boehme S, Chiang JL. Cholesterol 7α-hydroxylase protects the liver from inflammation and fibrosis by maintaining cholesterol homeostasis. J Lipid Res. 2016 Oct;57(10):1831-1844. doi: 10.1194/jlr.M069807. Epub 2016 Aug 17. PMID: 27534992; PMCID: PMC5036364.

[24] Lee YS, Lee C, Choung JS, Jung HS, Jun HS. Glucagon-Like Peptide 1 Increases β-Cell Regeneration by Promoting α- to β-Cell Transdifferentiation. Diabetes. 2018 Dec;67(12):2601-2614. doi: 10.2337/db18-0155. Epub 2018 Sep 26. PMID: 30257975.

[25] Shapiro H, Kolodziejczyk AA, Halstuch D, Elinav E. Bile acids in glucose metabolism in health and disease. J Exp Med. 2018 Feb 5;215(2):383-396. doi: 10.1084/jem.20171965. Epub 2018 Jan 16. PMID: 29339445; PMCID: PMC5789421.wssss

[26] Keitel V, Häussinger D. Role of TGR5 (GPBAR1) in Liver Disease. Semin Liver Dis. 2018 Nov;38(4):333-339. doi: 10.1055/s-0038-1669940. Epub 2018 Oct 24. PMID: 30357770.

[27] Reich M, Spomer L, Klindt C, Fuchs K, Stindt J, Deutschmann K, Höhne J, Liaskou E, Hov JR, Karlsen TH, Beuers U, Verheij J, Ferreira-Gonzalez S, Hirschfield G, Forbes SJ, Schramm C, Esposito I, Nierhoff D, Fickert P, Fuchs CD, Trauner M, García-Beccaria M, Gabernet G, Nahnsen S, Mallm JP, Vogel M, Schoonjans K, Lautwein T, Köhrer K, Häussinger D, Luedde T, Heikenwalder M, Keitel V. Downregulation of TGR5 (GPBAR1) in biliary epithelial cells contributes to the pathogenesis of sclerosing cholangitis. J Hepatol. 2021 Sep;75(3):634-646. doi: 10.1016/j.jhep.2021.03.029. Epub 2021 Apr 17. PMID: 33872692.

[28] Hanson SM, Cleghorn WM, Francis DJ, Vishnivetskiy SA, Raman D, Song X, Nair KS, Slepak VZ, Klug CS, Gurevich VV. Arrestin mobilizes signaling proteins to the cytoskeleton and redirects their activity. J Mol Biol. 2007 Apr 27;368(2):375-87. doi: 10.1016/j.jmb.2007.02.053. Epub 2007 Feb 22. PMID: 17359998; PMCID: PMC1904837.

[29] Erdtmann-Vourliotis M, Mayer P, Ammon S, Riechert U, Höllt V. Distribution of G-protein-coupled receptor kinase (GRK) isoforms 2, 3, 5 and 6 mRNA in the rat brain. Brain Res Mol Brain Res. 2001 Nov 1;95(1-2):129-37. doi: 10.1016/s0006-8993(01)03046-3. PMID: 11687284.

[30] Greengard P. The neurobiology of slow synaptic transmission. Science. 2001 Nov 2;294(5544):1024-30. doi: 10.1126/science.294.5544.1024. PMID: 11691979.

[31] Aubert I, Ghorayeb I, Normand E, Bloch B. Phenotypical characterization of the neurons expressing the D1 and D2 dopamine receptors in the monkey striatum. J Comp Neurol. 2000 Feb 28;418(1):22-32. PMID: 10701753.

[33] Gainetdinov RR, Bohn LM, Sotnikova TD, Cyr M, Laakso A, Macrae AD, Torres GE, Kim KM, Lefkowitz RJ, Caron MG, Premont RT. Dopaminergic supersensitivity in G protein-coupled receptor kinase 6-deficient mice. Neuron. 2003 Apr 24;38(2):291-303. doi: 10.1016/s0896-6273(03)00192-2. PMID: 12718862.

[35] Wu N, Song L, Yang X, Yuan W, Liu Z. NMDA receptor regulation of levodopa-induced behavior and changes in striatal G protein-coupled receptor kinase 6 and β-arrestin-1 expression in parkinsonian rats. Clin Interv Aging. 2013;8:347-52. doi:

10.2147/CIA.S41464. Epub 2013 Mar 26. PMID: 23569367; PMCID: PMC3615843.

[36] Feldman RD, Gros R. Regulator of G-protein signaling-2 as a candidate gene: the road to hypertension or just another roadside marker? Hypertension. 2006 Mar;47(3):337-8. doi: 10.1161/01.HYP.0000200748.73303.a6. Epub 2006 Jan 23. PMID: 16432040.

[37] Yang J, Kamide K, Kokubo Y, Takiuchi S, Tanaka C, Banno M, Miwa Y, Yoshii M, Horio T, Okayama A, Tomoike H, Kawano Y, Miyata T. Genetic variations of regulator of G-protein signaling 2 in hypertensive patients and in the general population. J Hypertens. 2005 Aug;23(8):1497-505. doi: 10.1097/01.hjh.0000174606.41651.ae. PMID: 16003176.

[38] Duan X, Zhou Y, Teng X, Tang C, Qi Y. Endoplasmic reticulum stress-mediated apoptosis is activated in vascular calcification. Biochem Biophys Res Commun. 2009 Oct 2;387(4):694-9. doi: 10.1016/j.bbrc.2009.07.085. Epub 2009 Jul 19. PMID: 19622343.

[39] Chang JR, Duan XH, Zhang BH, Teng X, Zhou YB, Liu Y, Yu YR, Zhu Y, Tang CS, Qi YF. Intermedin1-53 attenuates vascular smooth muscle cell calcification by inhibiting endoplasmic reticulum stress via cyclic adenosine monophosphate/protein kinase A pathway. Exp Biol Med (Maywood). 2013 Oct;238(10):1136-46. doi: 10.1177/1535370213502619. Epub 2013 Sep 4. PMID: 24006303.

[40] Tang X, Jin R, Qu G, Wang X, Li Z, Yuan Z, Zhao C, Siwko S, Shi T, Wang P, Xiao J, Liu M, Luo J. GPR116, an adhesion G-protein-coupled receptor, promotes breast cancer metastasis via the Gαq-p63RhoGEF-Rho GTPase pathway. Cancer Res. 2013 Oct 15;73(20):6206-18. doi: 10.1158/0008-5472.CAN-13-1049. Epub 2013 Sep 5. PMID: 24008316.

[42] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul;70(4):313. PMID: 30207593.

[45] Kamińska K, Czarnecka AM, Escudier B, Lian F, Szczylik C. Interleukin-6 as an emerging regulator of renal cell cancer. Urol Oncol. 2015 Nov;33(11):476-85. doi: 10.1016/j.urolonc.2015.07.010. Epub 2015 Aug 18. PMID: 26296264.

[46] Gudbrandsdottir G, Aarstad HH, Bostad L, Hjelle KM, Aarstad HJ, Bruserud Ø, Tvedt THA, Beisland C. Serum levels of the IL-6 family of cytokines predict prognosis in renal cell carcinoma (RCC). Cancer Immunol Immunother. 2021 Jan;70(1):19-30. doi: 10.1007/s00262-020-02655-z. Epub 2020 Jul 3. PMID: 32621022; PMCID: PMC7838134.

[47] Onnis B, Fer N, Rapisarda A, Perez VS, Melillo G. Autocrine production of IL-11 mediates tumorigenicity in hypoxic cancer cells. J Clin Invest. 2013 Apr;123(4):1615-29. doi: 10.1172/JCI59623. Epub 2013 Mar 15. PMID: 23549086; PMCID: PMC3613900.

[50] Sakaguchi T, Yoshino H, Sugita S, Miyamoto K, Yonemori M, Osako Y, Meguro-Horike M, Horike SI, Nakagawa M, Enokida H. Bromodomain protein BRD4 inhibitor JQ1 regulates potential prognostic molecules in advanced renal cell carcinoma. Oncotarget. 2018 May 1;9(33):23003-23017. doi: 10.18632/oncotarget.25190. PMID: 29796168; PMCID: PMC5955408.

[51] Wang L, Lau JS, Patra CR, Cao Y, Bhattacharya S, Dutta S, Nandy D, Wang E, Rupasinghe CN, Vohra P, Spaller MR, Mukhopadhyay D. RGS-GAIP-interacting protein controls breast cancer progression. Mol Cancer Res. 2010 Dec;8(12):1591-600. doi: 10.1158/1541-7786.MCR-10-0209. Epub 2010 Oct 27. PMID: 21047775; PMCID: PMC3850212.

[52] Deeble PD, Murphy DJ, Parsons SJ, Cox ME. Interleukin-6- and cyclic AMP-mediated signaling potentiates neuroendocrine differentiation of LNCaP prostate tumor cells. Mol Cell Biol. 2001 Dec;21(24):8471-82. doi: 10.1128/MCB.21.24.8471-8482.2001. PMID: 11713282; PMCID: PMC100010.

[53] Anderson KC, Dalton WS. Synopsis of a research roundtable presented on cell signaling in myeloma: regulation of growth and apoptosis--opportunities for new drug discovery. Mol Cancer Ther. 2002 Dec;1(14):1361-5. PMID: 12516971.

[54] Lin CZ, Ma HT, Zou SX, Wang GJ, Chen WH, Han ZK. [Effect of soy isoflavones on cAMP/PKA pathway in breast cancer cells of the rat.]. Sheng Li Xue Bao. 2005 Aug 25;57(4):517-22. Chinese. PMID: 16094502.

[55] Ahn S, Olive M, Aggarwal S, Krylov D, Ginty DD, Vinson C. A dominant-negative inhibitor of CREB reveals that it is a general mediator of stimulus-dependent transcription of c-fos. Mol Cell Biol. 1998 Feb;18(2):967-77. doi: 10.1128/MCB.18.2.967. PMID: 9447994; PMCID: PMC108809.