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$G\alpha_{12}$ and $G\alpha_{13}$: Versatility in Physiology and Pathology

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G protein-coupled receptors (GPCRs), as the largest family of receptors in the human body, are involved in the pathological mechanisms of many diseases. Heterotrimeric G proteins represent the main molecular switch and receive cell surface signals from activated GPCRs. Growing evidence suggests that $G\alpha_{12}$ subfamily ($G\alpha_{12/13}$)-mediated signaling plays a crucial role in cellular function and various pathological processes. The current research on the physiological and pathological function of $G\alpha_{12/13}$ is constantly expanding, Changes in the expression levels of $G\alpha_{12/13}$ have been found in a wide range of human diseases. However, the mechanistic research on $G\alpha_{12/13}$ is scattered. This review briefly describes the structural sequences of the $G\alpha_{12/13}$ isoforms and introduces the coupling of GPCRs and non-GPCRs to $G\alpha_{12/13}$. The effects of $G\alpha_{12/13}$ on RhoA and other signaling pathways and their roles in cell proliferation, migration, and immune cell function, are discussed. Finally, we focus on the pathological impacts of $G\alpha_{12/13}$ in cancer, inflammation, metabolic diseases, fibrotic diseases, and circulatory disorders are brought to focus.

Keywords: G protein-coupled receptor, $G\alpha_{12}$, $G\alpha_{13}$, cell pathophysiology, diseases

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INTRODUCTION

G protein-coupled receptors (GPCRs) family are a superfamily of membrane receptors responsible for signal transduction in cells. GPCRs are extensively studied drug targets because they participate in a broad range of human physiological and pathological processes. There are currently 481 drugs (about 34% of all drugs approved by the FDA) acting on 107 unique GPCRs to treat different diseases, including neurological disorders, metabolic and cardiovascular diseases, cancer, and inflammation (Hauser et al., 2017; Wang et al., 2020). Heterotrimeric G proteins are sensors for GPCR active conformations and trigger intracellular signal transduction (Maziarz et al., 2020). Heterotrimeric G proteins are composed of Gα, Gβ, and Gγ subunits, which are mainly located on the inner leaflet of the plasma membrane (Bondar and Lazar, 2021). Gα proteins are divided into four categories based on sequence homology and downstream effectors: $G\alpha_s$ (s stands for stimulation), $G\alpha_{i/o}$ (i stands for inhibition), $G\alpha_{q/11}$, and $G\alpha_{12/13}$ (Hilger et al., 2018; Yang et al., 2020). The function of $G\alpha_s$, $G\alpha_{i/o}$, and $G\alpha_q$ have been well documented. Meanwhile, the progress in understanding the function of the $G\alpha_{12/13}$ family, which was discovered in the early 1990s, has been relatively slow (Kim et al., 2018a). Nevertheless, with the development of new research tools (for example, constitutively active mutants, fusion proteins, and gene knockout, etc.), progress has been made in further to understanding the function of $G\alpha_{12/13}$ in recent years (Worzfeld et al., 2008).

$G\alpha_{12/13}$ subunits are expressed in most cell types and are able to induce diversified cellular signaling and responses that are important players in health and disease. $G\alpha_{12}$ and $G\alpha_{13}$ share 67% of their amino acid sequence and have many downstream signaling targets in commm (Montgomery et al., 2014; Stecky et al., 2020). Some of the pathways that are triggered by both $G\alpha_{12}$ and $G\alpha_{13}$ include phospholipase C (PLC)-ε and phospholipase D, mitogen-activated protein kinase (MAPK), and Na/H-exchange which promote cytoskeletal alterations, carcinogenic responses, and apoptosis (Litosch, 2012; Dusaban et al., 2013; Xie et al., 2016). Moreover, $G\alpha_{12/13}$ interacts with specific guanine nucleotide exchange factors (GEFs) (e.g., p115RhoGEF, leukemia-related RhoGEF, and PDZ-RhoGEF) to activate downstream effectors, including ras homolog family member A (RhoA), PLC, adenylate cyclase, and a variety of ion channels (Mikelis et al., 2013). These effectors, in turn, regulate the concentration of secondary messengers in the cells, such as diglycerides, cyclic adenosine monophosphate (cAMP), sodium ions, and calcium ions. Together, the activated RhoA and sencodary messengers eventually lead to physiological responses (Jiang et al., 2008; Kalwa et al., 2015; Wang et al., 2019). Furthermore, $G\alpha_{12/13}$ subunits also regulate the activity of a variety of transcription factors, such as signal transducer and activator of transcription 3, serum response factor (SRF), activator protein 1 (AP-1), and activated T cell nuclear factor (NFAT) (Kumar et al., 2006; Lee et al., 2009; Song et al., 2018; Yagi et al., 2019). Abnormally elevated upstream stimuli promote the incidence and development of diseases by increasing the corresponding receptor coupling to $G\alpha_{12}$ and/or $G\alpha_{13}$ (Yang et al., 2020; Rasheed et al., 2021). In this review, the structure of $G\alpha_{12}$ and $G\alpha_{13}$ is reviewed along with their roles in GPCR signal pathways, cell function, and disease pathogenesis.

The Amino Acid Structure of $G\alpha_{12}$ and $G\alpha_{13}$

The $G\alpha_{12/13}$ subfamily consists of two α subunits encoded by *GNA12* and *GNA13*. The $G\alpha_{12/13}$ subunits were originally discovered based on the amino acid sequence similarity with other Gα subunits and their insensitivity to pertussis toxin (Arang and Gutkind, 2020). The structure of $G\alpha_{12/13}$ subunit consists of an amino-terminal α-helical domain and a Ras-like GTPase domain. There is a link between these two domains involved in binding to GDP and GTP (Syrovatkina et al., 2016; Smrcka and Fisher, 2019). In response to activation of GPCR, the conformation of GDP-bound inactive $G\alpha_{12/13}$ is transformed into the active form with GTP binding, triggering the dissociation of $G\alpha_{12/13}$ from Gβγ and activation of downstream effectors (Arthofer et al., 2016). After dissociation, free Gβγ subunits transmit signals through regulating canonical effectors, including adenylate cyclase, PLC, and various ion channels (Senarath et al., 2018). Gβγ subunits also regulate a series of non-canonical effectors, such as the nuclear import of the extracellular regulated protein kinases (ERK) 1/2, oxidative phosphorylation, and mRNA processing (Khan et al., 2016). The large number of Gβγ subunits in mammal cells define much of the diversity that occurs within GPCR signaling with resepect to spatial and temporal bias and are extensively involved in the pathogenesis of diseases (Masuho et al., 2021). Gβγ signaling has been previously well summarized.

Although Gβγ-mediated effects of GPCR signaling are diverse, the assorted isoforms of Gα also have a wide variety of influences. These varied functions are highly related to their structures. Under present consideration, $G\alpha_{12}$ has four isoforms, of which isoform 1 is the longest isoform containing 381 amino acids (**Figure 1**). Compared with isoform 1, the encoded isoform 2 (305 amino acids) and isoform 3 (322 amino acids) are shorter and have different N-termini. Both $G\alpha_{12}$ isoform 2 and 3 have distinct 5′ untranslated region and 5′ coding region for different N-termini. The isoform 4 of $G\alpha_{12}$ lacks in-frame exons in the 3′ coding region relative to the isoform 1; the encoded isoform 4 (364 amino acids) is also shorter than isoform 1. $G\alpha_{13}$ has two isoforms, of which isoform 1 is the longer isoform containing 377 amino acids. The isoform 2 of $G\alpha_{13}$ uses an alternative 5′ exons resulting in a downstream start codon AUG. Thus, the encoded isoform 2 of $G\alpha_{13}$ has a shorter N-terminus than the isoform 1. The isoform sequences of $G\alpha_{12}$ or $G\alpha_{13}$ show similar structural domains, including an adenylyl cyclase binding site, a β-γ complex binding site, a switch I region (one of two surface loops that undergo conformational changes upon GTP binding), a switch II region, and a putative receptor binding site, respectively, (Lambright et al., 1996; Sunahara et al., 1997; Tesmer et al., 1997). Additional difference in the amino acid sequence of each isoform may provide tissue specific expression and cellular localization to fulfill the broad functional roles of the $G\alpha_{12}$ or $G\alpha_{13}$.

While literature clearly show that $G\alpha_{12/13}$ has different functions from other Gα subtypes, the functional difference between the isoforms of $G\alpha_{12}$ and $G\alpha_{13}$ has not been reported. Future studies on the structure-functional relationship between these isoforms will help understanding their roles in cells and diseases.

Regulation Network of $G\alpha_{12/13}$

$G\alpha_{12/13}$ has been shown to couple to more than 30 GPCRs. Activated by various upstream stimuli, $G\alpha_{12/13}$ can transmit to divergent downstream signaling pathways and regulates cell function in pathophysiological processes (Ackerman et al., 2015; Yung et al., 2017; Yanagida et al., 2018; Spoerri et al., 2020). $G\alpha_{12}$ and $G\alpha_{13}$ are broadly expressed, yet gene deficiency in mice shows that they are not interchangeable (Yang et al., 2020). Some GPCRs preferentially couple to either $G\alpha_{12}$ or $G\alpha_{13}$ (Ayoub and Pin, 2013; Yung et al., 2017; Mackenzie et al., 2019). Moreover, non-GPCRs are also shown to couple to $G\alpha_{12}$ and $G\alpha_{13}$ (Shen et al., 2013; Shen et al., 2015; Piccinin et al., 2019) (**Table 1**).

GPCRs Triggered $G\alpha_{12/13}$ Signaling

Lysophosphatidic Acid Receptors

Lysophosphatidic acid (LPA) is a biologically active phospholipid, which mediates various biological functions through six homologous LPA receptors (LAPRs) (Plastira et al., 2020). Activated LPARs promote $G\alpha_{12}$, but not $G\alpha_{13}$, association with v-raf murine sarcoma viral oncogene homolog A which than activates ERK. The activated ERK promotes ring

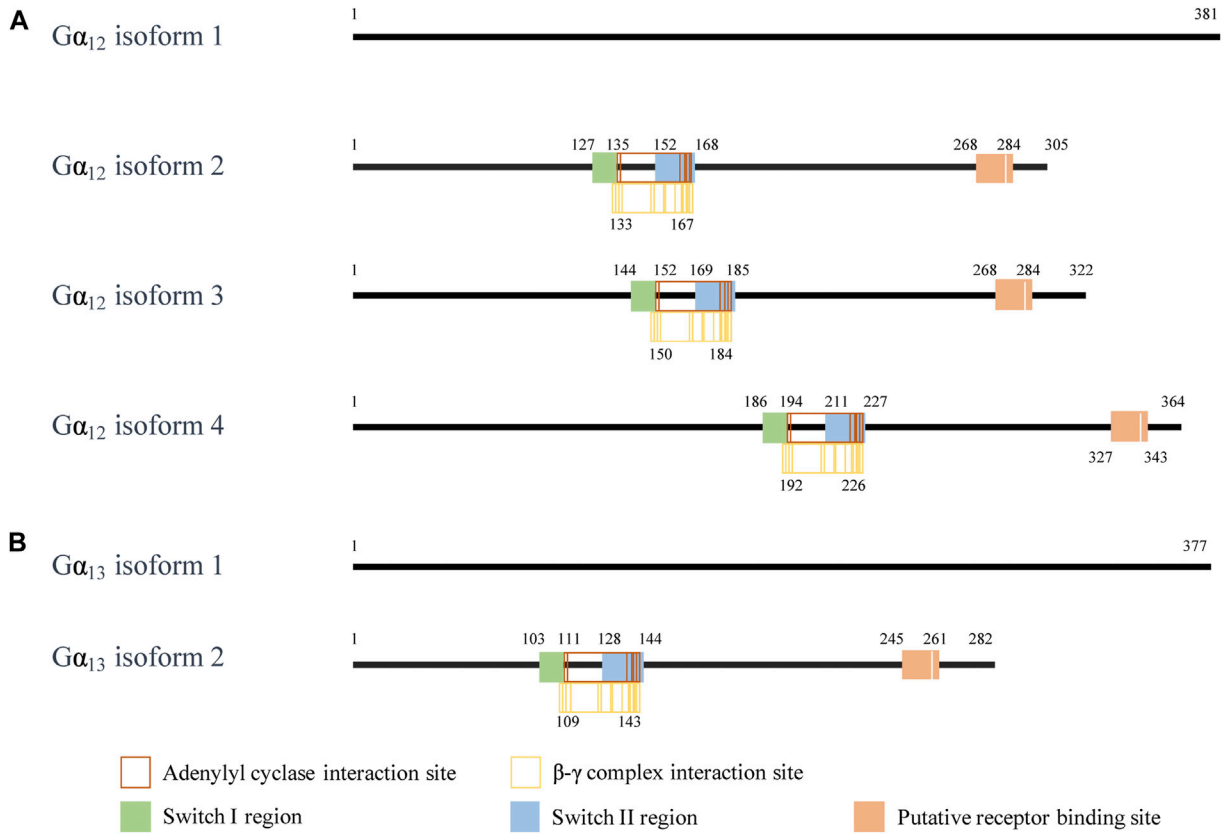

FIGURE 1 | The interaction site of the $G\alpha_{12/13}$ isoform. **(A)** The interaction sites on the amino acid fragment of $G\alpha_{12}$ isoforms. **(B)** The interaction sites on the amino acid fragment of $G\alpha_{13}$ isoforms. The information on the interaction sites of $G\alpha_{12}$ and $G\alpha_{13}$ is from NCBI. In NCBI reference sequence database, the human *GNA12* isoforms are NP_031379.2, NP_001269369.1, NP_001269370.1, and NP_001280021.1. (https://www.ncbi.nlm.nih.gov/gene/2768). The human *GNA13* isoforms are NP_006563.2 and NP_001269354.1. (https://www.ncbi.nlm.nih.gov/gene/10672).

finger and FYVE like domain-containing E3 ubiquitin protein ligase transcription and fibroblast migration (Gan et al., 2013). LPAR-$G\alpha_{12/13}$ signaling also plays an important role in embryonic blood vessel development (Tanaka et al., 2006). Additionally, LPAR1/2 couple with $G\alpha_{i/o}$, $G\alpha_{q/11}$, as well as $G\alpha_{12/13}$ to activate a variety of downstream pathways, such as protein kinase B (PKB, commonly known as AKT), RhoA, MAPK, and phosphatidylinositol 3-kinase (PI3K), and regulates cell proliferation, migration, and cytoskeleton rearrangement (Kihara et al., 2014). Previous studies have identified that LPAR4/6 can effectively couple to $G\alpha_{12/13}$ to stimulate Rho GTPase, which subsequently activates Rho-associated protein kinase (ROCK) I/II, leading to changes in the tension of the actin cytoskeleton (Noguchi et al., 2003; Yanagida et al., 2009). The LPAR4/6-activated $G\alpha_{12/13}$-Rho-ROCK signal also promotes nuclear translocation of Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) (Yasuda et al., 2019). YAP/TAZ promotes the proliferation of cancer cells (such as liver, bladder, and lung cancers) and accelerates the progress of cancer (Yagi et al., 2016; Maziarz et al., 2020). Activation of LPAR5 also induces axon retraction and stress fiber formation through an LPA-LPAR5-$G\alpha_{12/13}$ pathway (Lee et al., 2006). As of today, there is no evidence supporting a coupling between LPAR3 and $G\alpha_{12/13}$.

Frizzleds

Frizzled (FZD) receptors are unconventional GPCRs, which can be activated by the *Wingless/Int-1* lipoglycoprotein (WNT) family (Janda et al., 2017). FZD4 interacts with $G\alpha_{12/13}$ and does not interact with other subunits of the G protein family. The complex formed by FZD4 and $G\alpha_{12/13}$ is dissociated under WNT stimulation. The FZD4-$G\alpha_{12/13}$ signaling mediates cytoskeletal rearrangement and Rho signaling through p115RhoGEF, affecting angiogenesis in embryonic and tumor development (Arthofer et al., 2016). WNT5a/b and WNT3a bind to the receptor tyrosine kinase-like orphan receptor 1/2-FZD complex, activating Rho GTPases through $G\alpha_{12/13}$. The activated Rho inhibits the activity of large tumor suppressor 1/2 (LATS1/2), leading to YAP/TAZ dephosphorylation and nuclear translocation and promoting bone formation and cell migration (Park et al., 2015). Interestingly, a similar mechanism has been found in brain endothelial cells. The FZD10-$G\alpha_{13}$ complex dissociates under WNT5a/7a stimulation, and $G\alpha_{13}$ transmits a signal to YAP/TAZ through Rho family members (Hot et al., 2017). In osteoblasts, WNT family member 16 binds to

TABLE 1 | List of biologically significant $G\alpha_{12/13}$-associated receptors and their physiological functions.

Receptors	G proteins	Functions	References
		GPCRs	
LPA receptor	$G\alpha_{12}$	Migration of fibroblasts	Gan et al. (2013)
LPA receptor	$G\alpha_{12/13}$	Embryonic blood vessel development	Tanaka et al. (2006)
LPAR1	$G\alpha_{12}$	Proliferation of astrocytes	Loskutov et al. (2018)
LPAR1/LPAR2	$G\alpha_{12/13}$	Cell proliferation, migration, and cytoskeleton changes	Kihara et al. (2014)
LPAR4/LPAR6	$G\alpha_{12/13}$	Changes in the tension of the actin cytoskeleton	(Noguchi et al. (2003), Yanagida et al. (2009)
LPAR4/LPAR6	$G\alpha_{12/13}$	Angiogenesis	Yasuda et al. (2019)
LPAR5	$G\alpha_{12/13}$	Axon retraction and stress fiber formation	Lee et al. (2006)
FZD	$G\alpha_{12/13}$	Bone formation and cell migration	Park et al. (2015)
FZD	$G\alpha_{12/13}$	Bone homeostasis	Hendrickx et al. (2020)
FZD4	$G\alpha_{12/13}$	Angiogenesis	Arthofer et al. (2016)
FZD10	$G\alpha_{13}$	Angiogenesis	Hot et al. (2017)
PAR1/PAR2	$G\alpha_{13}$	Fibroblast adhesion maturation, spreading, and migration	Spoerri et al. (2020)
PAR1	$G\alpha_{12/13}$	Stress fiber formation	Regué et al. (2013)
PAR2	$G\alpha_{13}$	Smooth muscle contraction	Sriwai et al. (2013)
S1PR1/S1PR3/S1PR5	$G\alpha_{12}$	Inflammation	Ki et al. (2007)
S1PR2	$G\alpha_{12/13}$	Vascular smooth muscle cell migration and neointimal hyperplasia	Kim et al. (2011)
S1PR2	$G\alpha_{12/13}$	Myofibroblast contraction	Sobel et al. (2015)
S1PR2	$G\alpha_{13}$	Cardiomyocyte migration	Ye and Lin, (2013)
S1PR2/S1PR3	$G\alpha_{12/13}$	Stress fiber formation	Olivera et al. (2003)
S1PR2/S1PR3	$G\alpha_{12/13}$	Cardiac progenitor cell proliferation	Castaldi et al. (2016)
S1PR3	$G\alpha_{12/13}$	Inflammation	Dusaban et al. (2017)
S1PR3	$G\alpha_{13}$	Cardioprotection	Yung et al. (2017)
M1R	$G\alpha_{13}$	Impaired growth	Sabbir et al. (2018)
M3R	$G\alpha_{12}$	Human airway smooth muscle cells contraction	Yoo et al. (2017)
CXCR4	$G\alpha_{13}$	Tumor cell migration and adhesion	Scarlett et al. (2018)
CXCR4	$G\alpha_{13}$	Breast cancer metastasis	Yagi et al. (2011)
Calcium-sensing receptor	$G\alpha_{12/13}$	Gene expression, cytoskeleton, and cell shape	Leach et al. (2012), Leach et al. (2013)
AT_1R	$G\alpha_{12/13}$	Vasoconstriction	Lymperopoulos et al. (2021)
Thromboxane A2 receptor	$G\alpha_{12/13}$	Neointima formation and restenosis	Feng et al. (2016)
Ghrelin receptor	$G\alpha_{12}$	Food intake	Mende et al. (2018)
Dopamine D3 receptor	$G\alpha_{12}$	Inhibit inflammation	Wang et al. (2015)
5-HT_4R	$G\alpha_{13}$	Hippocampal synaptic function	Müller et al. (2021)
5-HT_4R	$G\alpha_{13}$	Angiogenesis	Profirovic et al. (2013)
Ull receptor	$G\alpha_{13}$	Tumor invasion	Lecointre et al. (2015)
Complement C5a receptor	$G\alpha_{12/13}$	Macrophage tail retraction	Raghavan et al. (2018)
GPR56	$G\alpha_{12/13}$	Myelination	Ackerman et al. (2015)
Purinergic receptor 6	$G\alpha_{13}$	Cell migration	Girard et al. (2020)
Gastrin type 2 cholecystokinin receptor	$G\alpha_{13}$	Cell migration	Masià-Balagué et al. (2015)
GPR40	$G\alpha_{12/13}$	Release of insulin vesicles	Rives et al. (2018)
GPR56	$G\alpha_{12/13}$	Muscle protein synthesis and myotube hypertrophy	White et al. (2014)
GPR91	$G\alpha_{12}$	Mitochondrial fission and cell migration	Ko et al. (2017)
ET-1 type A receptor	$G\alpha_{12/13}$	Formation of myofibroblasts	Nishida et al. (2007)
		Non-GPCRs	
Integrin β_1	$G\alpha_{13}$	Cell migration	Shen et al. (2013), Shen et al. (2015)
Integrin $\alpha_{IIb}\beta_3$	$G\alpha_{13}$	Cell retraction and migration	Gong et al. (2010)
Integrin $\alpha_{IIb}\beta_3$	$G\alpha_{13}$	Promote thrombosis	Pang et al. (2018)
PPARγ	$G\alpha_{13}$	Inhibit thrombosis	Unsworth et al. (2017)
Smoothened	$G\alpha_{12}$	Tumor growth and anti-apoptosis	Qu et al. (2013)

FZD receptors to activate canonical WNT signaling and non-canonical $G\alpha_{12/13}$ signaling and regulate bone homeostasis (Hendrickx et al., 2020).

Protease-Activated Receptors

Protease-activated receptors (PARs) consist of four subtypes (PAR1-4). PARs play an important role in blood vessel development, cell proliferation, tumorigenesis, and thrombosis (Chandrabalan and Ramachandran, 2021). In fibroblasts, PAR1/2 send signals to integrin $\alpha_5\beta_1$ through Gβγ and PI3K to induce fibronectin binding and initiate cell adhesion. PAR1/2 also send signals through $G\alpha_{13}$, $G\alpha_i$, ROCK, and Src to enhance integrin $\alpha_5\beta_1$-mediated adhesion (Spoerri et al., 2020). The PAR1-mediated $G\alpha_{12/13}$ activation stimulates RhoGEF and simultaneously activates the RhoA-ROCK pathway and myosin light chain (Flaumenhaft and De Ceunynck, 2017). Stimulation of PAR1 also initiates the assembly of F-actin through the $G\alpha_{12/13}$-RhoA pathway, which induces YAP dephosphorylation and nuclear translocation, thereby promoting cell migration and invasion (Regué et al., 2013). PAR2 couples with $G\alpha_q$, $G\alpha_i$, and $G\alpha_{13}$ to stimulate RhoA-ROCK activity independently of the cyclic adenosine

monophosphate-protein kinase A pathway to induce smooth muscle contraction (Sriwai et al., 2013). An earlier study found that in endothelial cells, PAR3 directly interacts with PAR1 to change the binding conformation of PAR1/$G\alpha_{13}$, induce the activation of downstream signaling pathways, and promote endothelial barrier dysfunction (McLaughlin et al., 2007). Presently, there is no clear evidence showing a direct interaction between PAR3/4 and $G\alpha_{12/13}$.

Sphingosine 1-Phosphate Receptors

Sphingosine 1-phosphate (S1P) is a natural biologically active lipid molecule that binds to five different S1P receptors (S1PR1-5). Activated S1PRs couple with $G\alpha_{12/13}$ to induce downstream signals (Zhang et al., 2020). An earlier study shows that S1PR2/S1PR3 couple to $G\alpha_{12/13}$ and send an "inside-out" signal to mediate the formation of stress fibers (Olivera et al., 2003). After binding to S1P, S1PR1/3/5 couple with $G\alpha_{12}$ and activate the c-Jun N-terminal kinase (JNK)-nuclear factor-kappa B (NF-κB) pathway to promote the expression of cyclooxygenase-2 and accelerate local inflammation (Ki et al., 2007). S1PR3 activates the $G\alpha_{12/13}$-RhoA pathway and promotes the expression of inflammatory gene in astrocytes (Dusaban et al., 2017). S1PR3 activates $G\alpha_{13}$-RhoA in cardiomyocytes and mediates cardio-protection during ischemia/reperfusion (I/R) (Yung et al., 2017). In vascular smooth muscle cells, S1PR2 couples to $G\alpha_{12/13}$ to activate AP-1-dependent induction of cysteine-rich protein 61 and promote the migration of vascular smooth muscle cells and neointimal hyperplasia (Kim et al., 2011). S1PR2 also induces the contraction of myofibroblasts through the $G\alpha_{12/13}$-Rho-ROCK pathway (Sobel et al., 2015). Moreover, $G\alpha_{12}$, activated by S1PR2, is recruited to E-cadherin to form a complex after mechanical stress. $G\alpha_{12}$ then recruits and activates p114RhoGEF, driving RhoA signaling and increasing the tensile strength of multicellular connections (Acharya et al., 2018).

Muscarinic Acetylcholine Receptors

Muscarinic acetylcholine receptors have five different subtypes (M1R-M5R) (Ruan et al., 2021). The increase of acetylcholine signal in neurons leads to the overexpression of M1R, promoting the polymerization of $G\alpha_{13}$ and Gβγ (Sabbir et al., 2018). $G\alpha_{13}$ disrupts the stability of tubulin polymer through the RhoA-ROCK signal, reducing mitochondrial transport and impairing growth in neurites (Sabbir et al., 2018). Early study has shown that M3R promotes the activity of phospholipase D through $G\alpha_{12}$ in HEK-293 cells (Rümenapp et al., 2001). It has also been found that $G\alpha_{12}$ binds to M3R in human airway smooth muscle cells. The M3R-$G\alpha_{12}$ signaling is important in promoting the contraction of human airway smooth muscle cells by inducing PI3K-mediated ROCK activation in a RhoA-dependent manner (Yoo et al., 2017).

Chemokine Receptors

The binding of chemokine C-X-C motif chemokine 12 (CXCL12) to C-X-C chemokine receptor 4 (CXCR4) activates RhoA through $G\alpha_{13}$, which leads to ROCK phosphorylation of myosin light chain and promotes cell migration and adhesion (Scarlett et al., 2018). In metastatic breast cancer cells, CXCR4 activates small Rho GTPases through $G\alpha_{13}$ to initiate cell motility and trans-endothelial migration (Yagi et al., 2011).

Non-GPCRs Triggered $G\alpha_{12/13}$ Signaling

Integrin "outside-in" signaling requires $G\alpha_{13}$ and monomeric small G proteins (i.e., Rho) to mediate cell retraction, migration, and spreading (Shen et al., 2012). $G\alpha_{13}$ directly binds to the ExE motif in the cytoplasmic domain of the integrin β_3 subunits, which is important in transducing the "outside-in" integrin signaling (Shen et al., 2013). $G\alpha_{13}$ also binds to the cytoplasmic domain of the integrin β_1 subunit in platelets, which mediates the Src-dependent transient inhibition of RhoA, activates the Rac1 and PI3K pathways, and promotes cell migration (Shen et al., 2013; Shen et al., 2015). Interfering with the expression of $G\alpha_{13}$ reduces $\alpha_{IIb}\beta_3$-dependent activation of c-Src, inhibits cell migration, and accelerates cell contraction, thereby spreading platelets on fibrinogen (Gong et al., 2010). Integrin $\alpha_{IIb}\beta_3$ also serves as a mechanical sensor that transmits "outside-in" signals through $G\alpha_{13}$-Src-Rac1-dependent pathways in platelets and facilitates coagulation *in vitro* and intravascularly *in vivo* (Pang et al., 2018). Therefore, the $G\alpha_{13}$-integrin interaction is important in thrombosis.

Additionally, peroxisome proliferator-activated receptor-γ (PPARγ), a member of the nuclear hormone superfamily, regulates lipid and glucose metabolism and homeostasis in many metabolic pathways (Piccinin et al., 2019). Treatment of platelets with PPARγ agonists leads to decreased binding between $G\alpha_{13}$ and integrin β_3, which prevents c-Src-dependent integrin β_3 phosphorylation and talin dissociation and weakens the downstream signal transduction of integrin $\alpha_{IIb}\beta_3$, thereby regulating platelet activation and reducing thrombosis (Unsworth et al., 2017). Moreover, in diffuse large B-cell lymphoma (DLBCL), smoothened recruits $G\alpha_i$ and $G\alpha_{12}$ and activates the protein kinase C (PKC)-caspase recruitment domain and membrane-associated guanylate kinase-like domain protein 1-dependent signaling cascade, which promotes activation of NF-κB, tumor growth, and anti-apoptosis (Qu et al., 2013).

$G\alpha_{12/13}$ and Biased Signaling

Traditionally, each GPCR is thought to initiate the "canonical" signal transduction through a single homologous G protein class (Seyedabadi et al., 2019). With the advances in the study of the ligand-receptor-effector relationship, it has been found that specific ligands induce a GPCR to selectively bind to a particular G protein subunit, transducing biased intracellular signaling toward one of many downstream pathways. This phenomenon is called "biased signaling"; and functionally selective ligands are called "biased ligands" (Tan et al., 2018).

Up to now, only a few GPCRs have shown biased signaling, but it is still the early days of understanding the biased signaling mechanisms. The characteristics of biased ligands, which have strong or weak activity in different pathways, may provide significant clinical advantages for developing new drugs. However, attention should be paid to testing conditions, ligand verification, and patient and disease selection to achieve successful biased ligand therapy (Seyedabadi et al., 2019). So far a few of the receptor types seen to produce biased signaling

involving Gα subunit switch include calcium-sensing receptors, angiotensin receptors, PARs, prostaglandin receptors, and ghrelin receptor.

The biased signaling can occur due to different underlying principles. The well-documented biased signaling is triggered by biased ligands. For instance, calcium-sensing receptor induces the activation of four G protein subfamilies ($G\alpha_{q/11}$, $G\alpha_{i/o}$, $G\alpha_{12/13}$, and $G\alpha_s$) (Abid et al., 2021). The ligands NPS-2143/NPS-R568 binds to a calcium-sensing receptor to specifically mediate the activation of $G\alpha_{12/13}$-RhoA signal, which in turn activates various other signal checkpoints that regulate gene expression, cytoskeleton, and cell shape (Leach et al., 2012; Leach et al., 2013). Similarly, the prostaglandin F2α receptor, a $G\alpha_q$-coupled GPCR, is activated by prostaglandin F2α (Pathe-neuschäfer-rube et al., 2005). PDC113.824 acts on the prostaglandin F2α receptor, which biasedly increases $G\alpha_q$-PKC-ERK1/2 signaling while inhibiting $G\alpha_{12}$-Rho-ROCK signaling, blocking cell contraction and skeletal reorganization, and inhibiting uterine contraction (Goupil et al., 2010). PAR2 is activated mainly by trypsin-like serine proteases and regulates various signaling pathways in coupling with $G\alpha_{i/o}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$ (Kim et al., 2018b). Among PAR2 antagonists, I-287 inhibits $G\alpha_q$, but biasedly activates $G\alpha_{12/13}$ without affecting $G\alpha_{i/o}$ signaling and β-arrestin recruitment, thereby attenuating the PAR2-mediated inflammatory response (Avet et al., 2020). Likewise, the ghrelin receptor in the arcuate nucleus of the hypothalamus, activated by Ghrelin, induces an intracellular signaling cascade through $G\alpha_q$, $G\alpha_{i/o}$, $G\alpha_{12/13}$, and β-arrestin (Hedegaard and Holst, 2020). The biased ligand YIL781 selectively activates $G\alpha_{q/11}$ and $G\alpha_{12}$ through the ghrelin receptor without intrinsic activity for β-arrestin recruitment, leading to an increased food intake and a reduced gastric emptying (Mende et al., 2018). However, other factors, including ionic strength, lipid environments, and downstream signaling partners, can also contribute to biased signaling observed in native cells and tissues. For instance, receptors can couple in a cell type-specific manner. The binding of angiotensin II (Ang II) to the Ang II type 1 receptor (AT_1R) causes AT_1R interaction with $G\alpha_{q/11}$, $G\alpha_{12/13}$, and $G\alpha_i$, depending on cell type (Forrester et al., 2018). When Ang II stimulates vascular smooth muscle cells, AT_1R binds to $G\alpha_{12/13}$ instead of $G\alpha_{q/11}$ to activate RhoA-ROCK and promote vasoconstriction (Lymperopoulos et al., 2021). Cleaving a receptor is another method that often leads to a change in downstream signaling. For PAR1, the endogenous ligand thrombin promotes PAR1 binding to heterotrimeric G proteins of the $G\alpha_{q/11}$, $G\alpha_{12/13}$, $G\alpha_i$, and $G\alpha_s$ families. The activation of matrix metalloproteinase-1 in platelets cleaves the N-terminal extracellular domain of PAR1, activating the $G\alpha_{12/13}$-Rho-MAPK signal instead of $G\alpha_{q/11}$, and promotes cell shape changes and platelet thrombosis (Trivedi et al., 2009).

$G\alpha_{12/13}$Signaling and Cell Function

As discussed above, the well-characterized downstream effector of active $G\alpha_{12/13}$ is the Rho GTPases through stimulating RhoGEF, which regulates the actin cytoskeleton and participates in various cellular functions, including cell proliferation, migration, contractility, and gene expression (Bodmann et al., 2017) (**Figure 2**).

Cell Growth and Apoptosis

$G\alpha_{12/13}$ was initially identified as an oncogene with the potential for tumor transformation of fibroblasts (Chan et al., 1993; Xu et al., 1993). Subsequent studies have shown that $G\alpha_{12/13}$ can promote mitogenic response and cell growth by transducing a RhoA-dependent signal, which increases YAP/TAZ-dependent gene expression (Goldsmith and Dhanasekaran, 2007; Syrovatkina and Huang, 2019).

Subsequent publications have revealed that $G\alpha_{12/13}$ coupling with several different receptor types promotes proliferation. S1P activates S1PR2/3 to trigger $G\alpha_{12/13}$-RhoA signaling, leading to the proliferation of mouse cardiac progenitor cells and regulating gene transcription in hearts (Castaldi et al., 2016). Stimulation of the thromboxane A2 receptor also promotes the activity of Rho GTPase through $G\alpha_{12/13}$. The activated Rho GTPase regulates actin cytoskeleton, increases nuclear translocation of YAP/TAZ, and promotes proliferation and migration of T/G HA-vascular smooth muscle cells (Feng et al., 2016). After the loss of primary cilia on human astrocytes, LPA promotes association between LPAR1 and $G\alpha_{12}/G\alpha_q$, augmenting mitogenic signaling and cell proliferation (Loskutov et al., 2018). Furthermore, the acetylcholine signaling via M1R activates $G\alpha_{13}$ protein to disrupt tubulin polymerization in axons and inhibit mitochondrial transport, thereby limiting the growth of neurites (Sabbir et al., 2018). G protein-coupled receptor 56 (GPR56) interacts with $G\alpha_{12/13}$ to mediate RhoA signaling and regulates zebrafish oligodendrocytes' development and subsequent myelination (Ackerman et al., 2015).

$G\alpha_{12/13}$ is also very important in the proliferation of tumor cells. The activation of $G\alpha_{12/13}$ promotes cell growth and tumor development of hepatocellular, small cell lung carcinoma, and ovarian cancer cells, but not in breast and prostate cancer cells (Grzelinski et al., 2010; Rasheed et al., 2013; Yagi et al., 2016; Syrovatkina and Huang, 2019). The synthetic ligand, Clozapine N-oxide, stimulates GPCR-$G\alpha_{12/13}$ signaling and promotes the proliferation of ovarian cancer cells by activating YAP1 (Yagi et al., 2016). Bombesin secreted by small cell lung carcinoma cells activates the gastrin-releasing peptide receptor (GRPR)-$G\alpha_{12/13}$-Rho-NF-κB signaling cascade. Subsequently, the activated NF-κB increases the production of Sonic Hedgehog, which activates the Gli transcription factor and promotes cell proliferation, survival, blood vessel generation, and local invasion (Castellone et al., 2015).

Meanwhile, the combination of muscle-restricted coiled-coil protein and caveolin-1 promotes $G\alpha_{13}$-mediated p115RhoGEF activation, leading to subsequent activation of the Rho-ROCK signal and enhancing the proliferation and migration of human pulmonary artery smooth muscle cells (Nakanishi et al., 2016). Moreover, $G\alpha_{13}$ dynamically regulates the RhoA signaling through the combination of RhoGEF GTPase and integrin β_1, promoting integrin β_1-mediated proliferation of CHO cell lines (Shen et al., 2015). In addition to autophagy-mediated

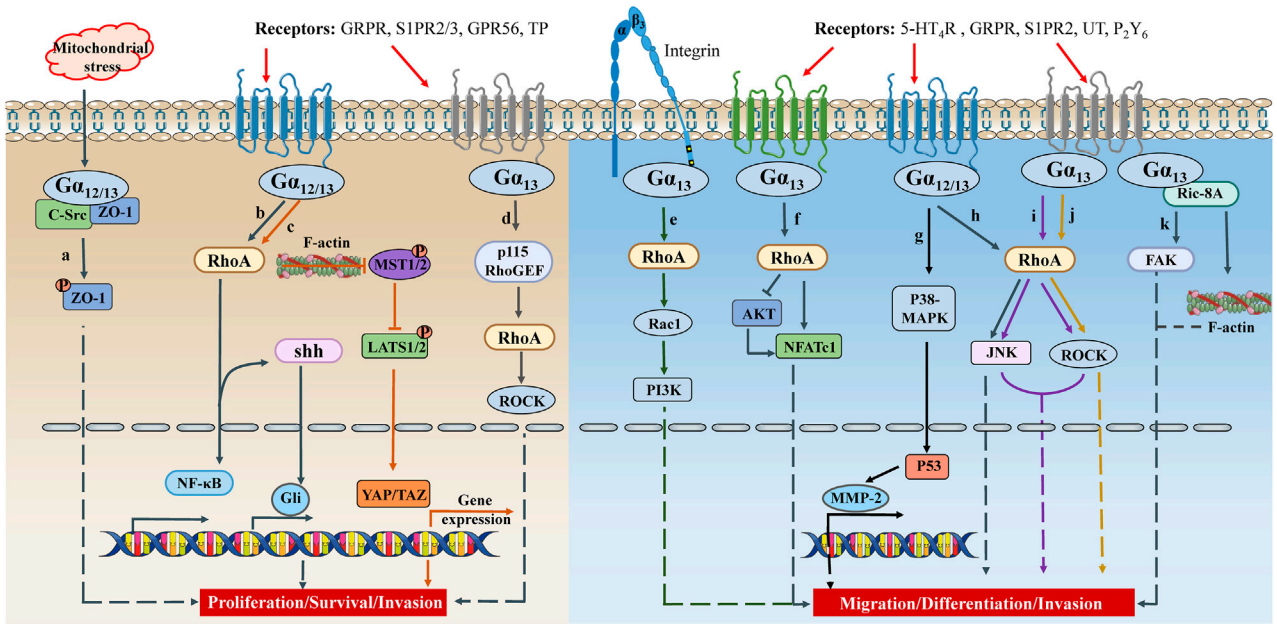

FIGURE 2 | The crosstalk between $G\alpha_{12/13}$ signaling and cell proliferation/migration. Under different physiological/pathological environments, GPCRs on the cell membrane receive different signals, couple $G\alpha_{12}$ or $G\alpha_{13}$, activate signal cascades, and promote synthesis of transcription factors or secretion of inflammatory factors. These signals ultimately lead to different cell activities, such as cell proliferation, survival, differentiation, migration, invasion, etc. TP, thromboxane A2 receptor; UT, urotensin II receptor; P_2Y_6, purinergic receptor 6; shh, sonic hedgehog; MST1/2, mammalian sterile 20-like kinases 1/2.

mitochondrial damage and oxidative stress, lysosomal dysfunction in cystopathy stimulates $G\alpha_{12}$/Src-mediated phosphorylation of zona occludin-1. The activated zona occludin-1-related signaling cascade promotes the proliferation of epithelial cells and disrupts the cell lining along the proximal tubules of mouse kidneys (Festa et al., 2018).

Studies have also found that $G\alpha_{12}$ and $G\alpha_{13}$ regulate apoptosis. In Madin-Darby canine kidney cells, the activation of endogenous $G\alpha_{12}$ and thrombin stimulation increase the activity of JNK1, inhibit the activity of NF-κB, and promote cell apoptosis (Yanamadala et al., 2007). In melanoma cells, US28, a GPCR encoded by human cytomegalovirus, is coupled with $G\alpha_{13}$ to induce cell apoptosis; silencing $G\alpha_{13}$ inhibits cell apoptosis driven by US28 (Joshi et al., 2015). Notably, this event has been only observed in human melanoma cell lines but not in murine cells. The emerging discovery of ligand-GPCR-$G\alpha_{12/13}$ signals will offer insight into the regulation of apoptosis on cancer cells.

Cell Migration

The ability of cell migration is essential for cell growth, proliferation, the inputs and outputs of nutrients and signal intermediates, and normal cell physiology. Cell movement also enhances tumor cell invasion and metastasis (Svitkina, 2018). The process of cell migration is usually accompanied by changes in the actin cytoskeleton. $G\alpha_{12/13}$ activates RhoA through their respective RhoGEF effectors and promotes the dynamic changes of cell shape controlled by actin cytoskeleton reorganization (Castillo-Kauil et al., 2020).

$G\alpha_{12/13}$ plays pivotal roles in cell migration that occurs during development. For instance, the 5-hydroxytryptamine type 4 receptor (5-HT_4R) triggers $G\alpha_{13}$-mediated RhoA signal transduction, promoting the reorganization of filamentous actin and the morphology of mouse astrocytes, and enhancing hippocampal synaptic function (Müller et al., 2021). The 5-HT_4R also mediates human endothelia cell migration and angiogenesis through the $G\alpha_{13}$-RhoA-ROCK pathway *in vitro* (Profirovic et al., 2013). In zebrafish development, the S1PR2-$G\alpha_{13}$-RhoGEF signal is necessary for the convergent movement of the endoderm by promoting myocardial migration at all stages of heart development (Ye et al., 2015). Disrupting the S1PR2-$G\alpha_{13}$-RhoGEF pathway jeopardizes the endoderm's convergence and the myocardium's migration during the segmentation process (Ye and Lin, 2013). With the high concentrations of urotensin II stimulation, urotensin II receptors recruit $G\alpha_{13}$ to activate the Rho-ROCK pathway and promote actin polymerization, which contributes to glioma cells invasion and new blood vessel formation (Lecointre et al., 2015). $G\alpha_{12}$ participates in cell differentiation through the nuclear factor of activated T-cell c1 (NFATc1) and regulates cell migration and resorption through RhoA in the process of osteoclast formation in mice (Song et al., 2018). Resistance to inhibitors of cholinesterase 8A (Ric-8A) is a guanine nucleotide exchange factor of Gα subunits and an important partner of $G\alpha_i$, $G\alpha_q$, and $G\alpha_{13}$ proteins (Papasergi-Scott et al., 2018). In *Xenopus* cranial neural crest cells, the Ric-8A-$G\alpha_{13}$-focal adhesion kinase (FAK) signal regulates focal adhesion dynamics and neurite formation to control cell migration (Toro-Tapia et al., 2018). The activated Ric-8A catalyzes the nucleotide exchange on $G\alpha_{13}$, induces the

reorganization of the actin cytoskeleton, and promotes the migration of mouse embryonic fibroblasts (Wang et al., 2011).

Cell migration that is mediated by $G\alpha_{12/13}$ is also important in metastasis. For example, the activated purinergic receptor 6 increases the number of filopodia and adhesions of human lung cancer cells (A549) and colorectal cancer cells (Caco-2) through both $G\alpha_q$-Ca^{2+}-PKCα and $G\alpha_{13}$-ROCK signals, regulating cell migration (Girard et al., 2020). The GRPR-$G\alpha_{13}$-RhoA-ROCK signaling is necessary for GRP to stimulate the migration of human colon cancer cells. This signaling also promotes the expression of COX-2, which contributes to cell migration (Patel et al., 2014). Similarly, $G\alpha_{12/13}$ signal facilitates the invasion of human cervical cancer cells through a RhoA-ROCK-JNK signal axis (Yuan et al., 2016). $G\alpha_{12/13}$ increases the gene expression of metalloproteinase-2 through p53, which is necessary for inducing the invasion and migration phenotypic changes of untransformed human breast epithelial cells (Kim et al., 2010). $G\alpha_{12}$, which is overexpressed in many hepatocellular carcinoma patients, relieves the regulation of p53-responsive miRNA and promotes the metastasis and invasion of tumor cells (Yang et al., 2015). The $G\alpha_{12}$-mediated pathway promotes metastasis and invasion of human nasopharyngeal carcinoma cells by regulating the reorganization of the actin cytoskeleton (Liu et al., 2009).

Increased $G\alpha_{12/13}$ mediated cell migration also greatly contributes to primary solid tumor growth. Take as example that $G\alpha_{13}$, which is up-regulated in breast cancer, inhibits the transcription of kallikreins through the RhoA-ROCK pathway and promotes the invasion and metastasis of breast cancer cells (Teo et al., 2016). The expression of *GNA13* in breast cancer cells is primarily regulated by MicroRNA (miR)-31, and the absence of miR-31 increases the expression of *GNA13* and the invasion of cancer cells (Rasheed et al., 2015). Similarly, $G\alpha_{13}$ is overexpressed in pancreatic ductal adenocarcinoma and enhances the invasion of human pancreatic cancer cells in three-dimensional collagen by destroying cell adhesion; however, this process does not go through ROCK signal transduction (Chow et al., 2016). $G\alpha_{13}$ is also involved in cell fusion (Carloni et al., 2013). Disintegrins and metalloproteinases stimulate $G\alpha_{13}$ to activate RhoA. The up-regulated RhoA activity causes dephosphorylation of ezrin/radixin/moesin proteins and destruction of plasma membrane-cortical actin interaction, promoting fusion of human metastatic colon cancer cells and cell acquisition of drug resistance (Carloni et al., 2013).

These observations highlight the importance of $G\alpha_{12/13}$-RhoA signaling in cell proliferation or migration. The expression of $G\alpha_{12/13}$ and the downstream signaling are often elevated in cancer cells. However, in some disease states (especially cancer), the upstream ligand and receptor of $G\alpha_{12/13}$ remain unknown.

Immune Cell Function

Due to the lack of specific inhibitors of $G\alpha_{12/13}$, the research of $G\alpha_{12/13}$ in immune cells was stagnant for many years. However, with various transgenic models, the studies on the role of $G\alpha_{12/13}$ in immune cells are accelerating.

T Cells

After naive T cells are activated, $CD4^+$ T cells differentiate into different effector subsets: T helper (Th) 1, Th2, Th17, and T follicular helper (Tfh) cells, which perform their specific auxiliary functions (Dong, 2021). During T cell activation, $G\alpha_{12/13}$ regulates actin polymerization and contributes to cell adhesion and migration (Wang et al., 2013). A recent study has found that $G\alpha_{13}$-RhoA-ROCK2 signaling plays a key regulatory role in the differentiation and function of early Tfh cells. The $G\alpha_{13}$-deficient Tfh cells impair the function of adhering B cells to form conjugates and stimulating B cells to produce immunoglobulins (Kuen et al., 2021). Morover, receptors coupled to $G\alpha_{12/13}$ have been demonstrated to be essential for T cell adhesion, differentiation, and retention in lymph nodes (Moriyama et al., 2014; Mathew et al., 2019). For example, S1PR2 promotes the maturation of Tfh cells by directing co-localization with B cells in the germinal center; and the deficiency of S1PR2 in Tfh cells inhibits the retention in lymph nodes (Moriyama et al., 2014). In response to the stimulation of CXCL12, the $G\alpha_{13}$-Rho signal in human T cells mediates the endosomal trafficking of CXCR4 (Kumar et al., 2011). CXCL12 also promotes the migration of Jurkat T cells through the CXCR4-$G\alpha_{13}$-Rho signal axis (Tan et al., 2006). Meanwhile, $G\alpha_{12/13}$ negatively regulates the activation state of integrin leukocyte-function-antigen-1 to modulate $CD4^+$T cells trafficking and proliferation and susceptibility to immune diseases (Herroeder et al., 2009). In response to the activation of T cell receptor signals, the interleukin-2 inducible T cell kinase directly interacts with $G\alpha_{13}$ to mediate the activation of SRF transcriptional activity (Huang et al., 2013). Conversely, $G\alpha_{12}$ is a key mediator of T cell receptor-mediated interleukin-2 production and controls the differentiation of Th2 and Th17 cells (Won et al., 2010). Additionally, $G\alpha_{13}$, but not $G\alpha_{12}$, mediated signal transduction is necessary for early thymocyte proliferation and survival (McNeil Coffield et al., 2004).

B Cells

Mature B lymphocytes express LPAR2/5, LPA negatively regulates B cell receptor signaling through the LPAR5–$G\alpha_{12/13}$–Arhgef1 pathway, inhibiting the release of calcium stored in the cell and the antibody response (Hu et al., 2014). $G\alpha_{12/13}$ also regulates the maturation, migration, and polarization of marginal zone B cells. In mice with depletion of $G\alpha_{12/13}$ in B cells, the number of zone B cells and zone B cell precursors are significantly reduced, but the formation of pseudopods is increased (Rieken et al., 2006).

Knockout of $G\alpha_{13}$ also results in the loss of restriction of B cells in the germinal center, thus spreading to lymph nodes and blood (Muppidi et al., 2014). Meanwhile, $G\alpha_{13}$ plays a direct role in the growth inhibition of B cells, affecting their survival and differentiation. It has been noted that the impaired phosphorylation of AKT at the Ser473 site is related to $G\alpha_{13}$ activity and may affect the growth and survival of B cells (Green et al., 2011; O'Hayre et al., 2016). The mechanism by which the $G\alpha_{12/13}$-RhoA axis inhibits the growth of B cells needs to be further explored.

Macrophages

In macrophages, complement C5a couples to $G\alpha_{12/13}$ to activate Rho GTPases and tail retraction in migrating cells. Macrophages without $G\alpha_{12/13}$ show complete chemotaxis but increased migration speed and a moderately impaired tail contraction (van den Bos et al., 2020). Thrombin, a major platelet activator, selectively induces the expression of CD36, a plasma membrane fatty acid transporter, and foam cell formation of RAW264.7 cells through PAR1-$G\alpha_{12}$ signaling and facilitates atherosclerosis (Raghavan et al., 2018). Thrombin also induces the migration of monocytes or macrophages through the PAR1-$G\alpha_{12}$ pathway (Gadepalli et al., 2013). The loss of Ric-8A in lymphocytes and bone marrow-derived macrophages leads to a decrease in the expression of $G\alpha_{i2/3}$, $G\alpha_q$, and $G\alpha_{13}$, but not $G\alpha_{12}$, leading to anemia and leukocytosis (Boularan et al., 2015).

The above studies suggest that dysregulation of $G\alpha_{12}$ or $G\alpha_{13}$ in immune cells may lead to pathophysiological consequences, such as cancer and autoimmunity. So far, the research of $G\alpha_{12/13}$ in immune cells is relatively scarce. More research is needed to bring new therapeutic targets for cancers and autoimmune diseases.

$G\alpha_{12/13}$ Signaling and Diseases

$G\alpha_{12/13}$ plays an important role in multiple stages of disease development in different tissues and organs. An increasing number of cancers have shown overexpressed $G\alpha_{12/13}$, which is correlated to abnormal cell proliferation, metastasis, and invasion (Montgomery et al., 2014). The high abundance or constitutive activation of $G\alpha_{12}$ and $G\alpha_{13}$ are effective stimulators of oncogenic transformation. $G\alpha_{12/13}$ also interacts with cell surface GPCRs and participates in the inflammation regulation (Dusaban et al., 2013; Hou et al., 2021). Meanwhile, $G\alpha_{12/13}$ levels in metabolic organs, including liver and muscle, are altered in metabolic diseases (Koo et al., 2017; Kim et al., 2019). However, the mechanism by which $G\alpha_{12/13}$ regulates the progression of these diseases has not been fully elucidated.

$G\alpha_{12/13}$ and Cancer

$G\alpha_{12/13}$ are called the *gep* proto-oncogenes and are usually overexpressed in cancers (Yagi et al., 2016). Besides the functional roles in cancer cell migration and invasion, $G\alpha_{12/13}$ and Rho GTPases exert pro- or anti-cancer effects in a cancer type and background-dependent manner.

The results of Gene Expression Omnibus and The Cancer Genome Atlas database analysis have shown that *GNA12* can be used as a biomarker for the personalized treatment of head and neck squamous cell carcinoma (HNSCC) patients and one of the prognostic genes for patients with HNSCC (Liu et al., 2021). *GNA13* is also a biomarker for the prognosis and metastasis of solid tumors, including HNSCC, ovarian cancer, lung cancer, and gastric cancer (Cerami et al., 2012; Gao et al., 2013; Cancer Genome Atlas, 2015). *GNA13* mutations are present at a high frequency in gastric cancer, nasopharyngeal cancer, prostate cancer, breast cancer, lymphoma, and bladder cancer (Muppidi et al., 2014; Wu et al., 2019; Arang and Gutkind, 2020).

The increased expression and activity of $G\alpha_{12/13}$ contribute to the pathogenesis of different cancers. The copy number of *GNA12* is significantly increased in ovarian cancer, which enhances the function of $G\alpha_{12}$ to promote cancer growth and metastasis (Wu et al., 2019). In two prostate cancer cell lines (C4-2B and PC3), both $G\alpha_{12}$ and $G\alpha_{13}$ are abundantly expressed (El-Haibi et al., 2013). The highly expressed *GNA13* also acts through Rho GTPase to drive the NF-κB transcription program and induce the expression of CXCL5 (Lim et al., 2019). A study on HNSCC has demonstrated that *GNA13* promotes the aggressive phenotype and drug resistance of tumor-initiating cells through the MAPK/AP-1 and NF-κB pathways (Rasheed et al., 2018). In bladder cancer, the Arg-200 (residue required to hydrolyze GTP) mutation of $G\alpha_{13}$ strongly activates YAP/TAZ-dependent TEAD and myocardin-related transcription factor-A/B-dependent SRF transcriptional activities through the RhoGEF-Rho GTPase cascade (Maziarz et al., 2020). Additionally, the low expression of MiR-30b-5p in renal cell carcinoma up-regulates the activity of $G\alpha_{13}$, which promotes cell proliferation, metastasis, and epithelial cell-mesenchymal transition (Liu et al., 2017). The reduction of regulators of G protein signaling protein (RGS) 12 promotes the $G\alpha_{12/13}$-RhoA-YAP pathway and Ezrin expression, which leads to the growth and progression of osteosarcoma and lung metastasis (Li et al., 2021). Moreover, $G\alpha_{13}$-mediated down-regulation of LATS1 promotes phenotypic changes of epithelial cell-mesenchymal transition in ovarian cancer cells (Yagi et al., 2019). These findings identify the $G\alpha_{13}$-Hippo signaling as a potential target for cancer therapeutic interventions.

A few GPCR ligands have been identified upstream of $G\alpha_{12/13}$ in cancers. LPA promotes the combination of $G\alpha_{12}$ and EFA6 through LPAR2 and activates the ADP-ribosylation factors 6 mesenchymal pathway, thereby promoting the invasion, metastasis, and drug resistance of renal cancer cells (Hashimoto et al., 2016). High concentrations of LPA are also accumulated in the ascites of patients with ovarian cancer (Yu et al., 2016). The heterodimerization of LPAR1 and CD97 amplifies the LPA-mediated $G\alpha_{12/13}$-Rho signal transduction and promotes the invasion of prostate cancer cells (Ward et al., 2011). Gastrin induces the activation of paxillin and FAK through the cholecystokinin B receptor-$G\alpha_{12/13}$-RhoA-ROCK signaling pathway, thereby promoting the redirection of the Golgi apparatus and the directional migration of pancreatic cancer cells (Mu et al., 2018). Gastrin also promotes the activation of $G\alpha_{13}$ through the gastrin type 2 cholecystokinin receptor in colon cancer cells. The recruitment of p190RhoGEF by $G\alpha_{13}$ enhances the phosphorylation of FAK and paxillin, leading to RhoA activation and promoting the migration of cancer cells (Masià-Balagué et al., 2015). In addition, the down-regulated GPR65 in a variety of hematological malignancies promotes $G\alpha_{13}$/Rho signal transduction, which leads to the decrease of c-myc oncogene expression and promotes growth, migration, and metastasis of blood cancer cells (Justus et al., 2017). $G\alpha_{13}$ binds to CXCR5 in response to CXCL13 treatment and promotes prostate cancer cell

movements; however, silencing $G\alpha_{13}$ does not affect CXCL13-dependent cell invasion (El-Haibi et al., 2013).

Interestingly, the $G\alpha_{13}$-Rho GTPase signaling has also been shown to alleviate hematological malignancies (Justus et al., 2017). In malignant tumors of the hematopoietic and lymphatic system, *GNA13* and RhoA mutations are present in B-cell lymphomas, mainly in DLBCL and Burkitt's lymphoma (Justus et al., 2017). The mutation of *GNA13* in germinal center B cells is resistant to programmed cell death (Healy et al., 2016). These B cells are differentiated, facilitating genetic instability through continuous somatic hypermutation (Muppidi et al., 2014). Over time, the accumulation of driver mutations in persistent germinal center B cells may cause lymphoma. Loss of $G\alpha_{13}$ facilitates germinal center B cells to spread to the lymph node and blood, leading to the pathogenesis of DLBCL (Healy et al., 2016). Moreover, in the absence of $G\alpha_{13}$ signaling, S1P acts through S1PR3 to promote mouse germinal center B cells migration into the circulation (Muppidi et al., 2015). S1PR2 signals through $G\alpha_{13}$ to induce tumor cell apoptosis and exert its tumor suppressor function (Flori et al., 2016). However, in DLBCL, the forkhead box protein 1 directly inhibits S1PR2 and promotes tumor cell survival (Flori et al., 2016). The restoration and activation of the $G\alpha_{13}$-Rho pathway help reduce tumor growth and progression, supporting that the $G\alpha_{13}$-RhoA axis has a tumor suppressor effect (Justus et al., 2017). Meanwhile, analyzing the genome of tumor tissues from patients with classical Hodgkin lymphoma has revealed that *GNA13* is one of the genes repeatedly mutated (Tiacci et al., 2018). *GNA13* variants are mostly heterozygous, including nonsense, frameshift, and missense mutations, like the mutation patterns in DLBCL and Burkitt's lymphoma (Muppidi et al., 2014; Justus et al., 2017).

Despite the emerging evidence supporting the critical roles of $G\alpha_{12/13}$ in cancers, many questions remain about how the ligands and receptors trigger $G\alpha_{12}$ or $G\alpha_{13}$ signaling in a cancer type-specific manner. A comprehensive understanding of these mechanisms may provide a promising prospect for targeting specific $G\alpha_{12/13}$ signaling processes in cancer therapies.

$G\alpha_{12/13}$ and Inflammation

$G\alpha_{12/13}$ has been implicated in both induction and suppression of inflammation. In the context of inflammation, thrombin, LPA, and S1P transmit signals through $G\alpha_{12/13}$-coupled receptors to amplify inflammatory responses (Gavard and Gutkind, 2008; Dusaban et al., 2017; Lee et al., 2019).

Early studies have found a direct connection between $G\alpha_{12/13}$ signaling and arachidonic acid in cells (Dermott et al., 1999; Mariggiò et al., 2006). NIH-3T3 cells transformed with $G\alpha_{12}$QL show increased secretion of arachidonic acid and transcriptional activation of cyclooxygenase-2 (Dermott et al., 1999). Thrombin stimulates CHO cells to activate the $G\alpha_{13}$-RhoA-ERK1/2 signaling through PAR1, leading to the phosphorylation of cytosolic phospholipase A2 and the increase of arachidonic acid (Mariggiò et al., 2006). The activation of LPAR and S1PR also promotes the expression of inflammatory genes (such as cyclooxygenase-2) and the proliferation of astrocytes through $G\alpha_{12/13}$-RhoA-PLCε-protein kinase D (PKD)-NF-κB signaling, which contributes to neuroinflammation (Dusaban et al., 2013).

Recent work has shown that S1P promotes the NLRP3 inflammasome-mediated inflammatory response and the secretion of pro-inflammatory cytokines such as interleukin-1β and interleukin-18 through the S1PR2-$G\alpha_{12/13}$-MAPK pathway (Hou et al., 2021). Meanwhile, a variety of pro-inflammatory ligands promote the interaction of $G\alpha_{13}$ to VE-cadherin, inducing Src activation and VE-cadherin phosphorylation, leading to the internalization of VE-cadherin, the loss of endothelial barrier function, and vascular inflammation (Gong et al., 2014). The deficiency of $G\alpha_{13}$ in leukocytes and platelets inhibits thrombosis and inflammation and significantly optimizes the survival rate of septic mice (Cheng et al., 2021).

$G\alpha_{12}$ and $G\alpha_{13}$ have opposite effects on osteoclasts. The silencing of $G\alpha_{13}$ enhances the AKT-GSK3β-NFATc1 signal cascade by inhibiting RhoA, strongly promoting the formation and size of osteoclasts (Wu et al., 2017). This observation depicts that $G\alpha_{13}$ is the main endogenous negative switch for osteoclast production. $G\alpha_{13}$ also protects against various bone loss disease models from inflammation (Wu et al., 2017; Nakano et al., 2019). In comparison, a study has shown $G\alpha_{12}$ is involved in the pathophysiology of bone diseases such as osteoporosis or rheumatoid arthritis (Song et al., 2018). Interestingly, the volume of trabecular bone increases in $G\alpha_{12}$ knockout mice, whereas the number of osteoclasts decreases, contrary to the phenotype of $G\alpha_{13}$ deletion (Song et al., 2018). The underlying mechanisms of these opposite phenotypes are unclear, possibly because that $G\alpha_{12}^{-/-}$ mice are whole body knocked out, whereas $G\alpha_{13}^{-/-}$ mice undergo an osteoclast lineage-specific conditional knockout.

$G\alpha_{12/13}$ and Metabolic Diseases

$G\alpha_{12}$ is extensively expressed in metabolic organs, for instance, the liver (Strathmann and Simon, 1991; Kim et al., 2018a). Fasting of normal mice for 24–48 h significantly enhances the expression of $G\alpha_{12}$ in the liver (Kim et al., 2018a). *GNA12*-knockout mice are prone to hepatic steatosis and obesity after being fed a high-fat diet due to reduced energy consumption (Kim et al., 2018a). A study using cDNA microarray analysis with the liver of *GNA12*-knockout mice has found that $G\alpha_{12}$ regulates mitochondrial respiration through the Sirtuin 1/PPARα network (Kim et al., 2018a). Sirtuin 1, a class III histone deacetylases activated by NAD^+, is an important regulator involved in the fatty acid oxidation transcription network (Kalliora et al., 2019). $G\alpha_{12}$ induces ubiquitin-specific peptidase 22 through HIF-1α to promote the stability of Sirtuin 1, controlling lipid metabolism and mitochondrial respiration (Kim et al., 2018a). Interestingly, $G\alpha_{12}$ also exists in the endoplasmic reticulum and participates in the endoplasmic reticulum export (Subramanian et al., 2019). With the coat protein II subunit Sec24 binds to the cargo, it acts as a GEF to activate $G\alpha_{12}$ at the export site of the endoplasmic reticulum, promoting cargo export and inhibiting protein synthesis (Subramanian et al., 2019).

The role of $G\alpha_{13}$ in energy metabolism has opposite effects in skeletal muscle (prodiabetic) and liver (antidiabetic) (Koo et al., 2017; Kim et al., 2019). $G\alpha_{13}$ is more highly expressed in skeletal muscle than other metabolic organs (Koo et al., 2017). The

knockout $G\alpha_{13}$ in skeletal muscles contributes to systemic energy homeostasis, increasing glucose metabolism and insulin sensitivity and inhibiting diet-induced obesity and hepatic steatosis (Koo et al., 2017). The level of $G\alpha_{13}$ in skeletal muscle is reduced by exercise but is increased under conditions of metabolic diseases. Loss of $G\alpha_{13}$ in skeletal muscle inhibits the RhoA-ROCK2 pathway and activates NFATc1, which induces the conversion of skeletal muscle fibers into oxidized form and enhances energy metabolism (Koo et al., 2017). On the contrary, the lack of $G\alpha_{13}$ in the liver of mice leads to the overproduction of inter-α-trypsin inhibitor heavy chain 1, which exacerbates systemic insulin resistance (Kim et al., 2019).

GPR40 is a clinically proven molecular target for the treatment of diabetes. A GPR40 allosteric full agonist promotes glucose-stimulated insulin secretion in pancreatic β cells through GPR40-mediated $G\alpha_{12}$ signaling (Rives et al., 2018). In response to mechanical overload, GPR56 elevates the expression of the mammalian target of rapamycin and insulin-like growth factor 1 through $G\alpha_{12/13}$ and promotes muscle protein synthesis and myotube hypertrophy (White et al., 2014). Succinate activates the $G\alpha_{12}$-PKC-p38-dynamin-related protein 1 signaling through GPR91 to increase mitochondrial fission, enhances ATP production and membrane potential of mitochondria, and promote the migration of human mesenchymal stem cells (Ko et al., 2017). LPA is a key product of fatty acid metabolism. LPAR4 is selectively coupled with $G\alpha_{12/13}$ in adipocytes to limit the remodeling and healthy expansion of white adipose tissue in high-fat diet mice (Yanagida et al., 2018). The above studies have shown that the GPCR-$G\alpha_{12/13}$ axis can be an attractive target for treating metabolic diseases.

$G\alpha_{12/13}$ and Fibrotic Diseases

$G\alpha_{12/13}$ has a pro-fibrotic effect mainly mediated by the RhoA-ROCK activation (Haak et al., 2020). Early studies have demonstrated that $G\alpha_{12/13}$ play a key role in regulating the phenotype of cardiac fibroblasts (Fujii et al., 2005; Nishida et al., 2007). The stimulation of Ang II induces the production of reactive oxygen species (ROS) through the AT_1R-$G\alpha_{12/13}$-Rac pathway. The ROS-mediated JNK activation promotes the activity of AP-1 and NFAT, leading to the proliferation of cardiac fibroblasts (Fujii et al., 2005). Recently, it has been found that targeted inhibition of the $G\alpha_{12/13}$-RhoA-ROCK pathway successfully alleviates Ang II-induced cardiac dysfunction and the fibrotic response of cardiac fibroblasts (He et al., 2017). Endothelin-1 activates the Endothelin-1 type A receptor-$G\alpha_{12/13}$ axis in cardiac fibroblasts and promotes the formation of myofibroblasts through Rac-dependent ROS production and JNK activation (Nishida et al., 2007). The osteoglycin in the heart binds to LPAR3 and mediates the $G\alpha_{12/13}$-Rho-ROCK signal to attenuate the transactivation of epidermal growth factor receptors, thus inhibiting the proliferation and migration of cardiac myofibroblasts and negatively regulating cardiac fibrotic remodeling (Zuo et al., 2018).

Among numerous G protein members, $G\alpha_{12}$ is expressed abundantly in hepatic stellate cells of the fibrotic liver, whereas $G\alpha_{13}$ is not (Kim et al., 2018c). The imbalance of miR-16 in hepatic stellate cells leads to the overexpression of $G\alpha_{12}$, which promotes autophagy through the transcription of JNK-dependent autophagy-related genes 12-5 and accelerates the progression of liver fibrosis (Kim et al., 2018c). Meanwhile, deficiency of $G\alpha_{12}$ significantly blocks bleomycin-induced pulmonary fibrosis in mice. LPA stimulates the phosphorylation and activation of PKC-δ through $G\alpha_{12}$ and the mammalian target of rapamycin complex 2, which is important for fibroblast migration and the development of pulmonary fibrosis (Gan et al., 2012).

In short, the role of $G\alpha_{12}$ or $G\alpha_{13}$ in fibrotic diseases is unclear. Using various omics (e.g., genomics, proteomics) to detect the expression of $G\alpha_{12/13}$ in specific tissues/cells of fibrotic diseases, exploring its upstream receptors and downstream signals may lead to a better understanding of the pathological mechanisms of the fibrotic diseases.

$G\alpha_{12/13}$ and Circulatory and Renal Disorders

$G\alpha_{13}$ is involved in heart remodeling induced by pressure overload and plays a central role in the transition to heart failure (Takefuji et al., 2012). The Ang II-AT_1R-$G\alpha_{13}$-RhoA-myocardin-related transcription factor signal cascade regulates the expression of hypertrophy and fibrosis genes in cardiomyocytes (Takefuji et al., 2012). In response to low concentrations of thrombin, disabled-2, a linker protein, regulates $G\alpha_{12/13}$-mediated RhoA-ROCK activation and enhances ADP release, which increases the activity of AKT and mammalian target of rapamycin and promotes platelet aggregation and thrombosis (Tsai et al., 2014). Thrombin also stimulates platelets to promote the interaction of $G\alpha_{13}$ and receptor-interacting protein kinase 3. Receptor-interacting protein kinase 3 participates in the integrin-$G\alpha_{13}$ signal to promote platelet activation and thrombosis (Zhang et al., 2017). The newly developed high-load ExE peptide nanoparticles, based on the $G\alpha_{13}$ binding ExE motif on the cytoplasmic domain of integrin β_3, inhibit thrombosis and protect mice from cardiac I/R injury (Pang et al., 2020). This study supports that the integrin-$G\alpha_{13}$-RhoA-YAP pathway can be targeted for anti-atherosclerosis therapy (Wang et al., 2016). Inhibiting proteins that specifically interact with $G\alpha_{13}$ is a promising approach for the treatment of diseases such as macular degeneration, atherosclerosis, and tumor angiogenesis (Wang et al., 2017). In the process of angiogenesis, RGS5 converts $G\alpha_{q/11}$-mediated calcium-dependent contraction to $G\alpha_{12/13}$-mediated RhoA activation, leading to the formation of stress fibers in the vascular smooth muscle cells of the artery and the process of vascular remodeling (Arnold et al., 2014). $G\alpha_{12/13}$ are also essential for blood vessel formation. $G\alpha_{13}$ interacts with Abl1 to form a complex, which regulates actin cytoskeleton reorganization, remodeling, and endothelial cell migration and promotes blood vessel formation (Wang et al., 2017).

$G\alpha_{12}$ also plays a key role in inducing renal I/R injury through various mechanisms, such as destruction of tight cell connections, oxidative stress, inflammation, and cell apoptosis. $G\alpha_{12}$ knockout mice are almost completely protected from I/R injury (Yu et al., 2012). In addition, kidney injury molecule-1 prevents tissue damage by blocking the binding of GTP to $G\alpha_{12}$ in renal I/R

(Ismail et al., 2015). $G\alpha_{12}$ is also necessary for the development of a mouse renal cyst model induced by polycystin-1 mutation. The lack of polycystin-1 promotes the activation of $G\alpha_{12}$, leading to alteration in the form of N-cadherin, destroying cell-matrix/cell adhesion, inhibiting FAK, but promoting the formation of stress fibers (Wu et al., 2016). The activation of $G\alpha_{12}$ in mouse podocytes also leads to the imbalance of collagen expression in glomeruli, age-dependent proteinuria, and focal glomerular sclerosis (Boucher et al., 2012). However, a study has found that the activation of the dopamine D3 receptor increases coupling to $G\alpha_{12}$, leading to the reduction in ROS production and inflammation, ultimately preventing renal I/R injury (Wang et al., 2015).

The coupling of different GPCRs to $G\alpha_{12/13}$ and the impacts on the pathophysiology have not been fully elucidated. The identification of the reciprocal binding domains of $G\alpha_{12/13}$ to related cellular proteins will facilitate the development of more specific inhibitors to selectively disrupt the interaction. A comprehensive understanding of the complex regulatory mechanisms of $G\alpha_{12/13}$ signaling may lead to novel therapeutics targeting specific functions of $G\alpha_{12}$ or $G\alpha_{13}$ in a disease-specific manner.

CONCLUSION

The mechanisms of signal transduction through $G\alpha_{12/13}$ are still one of the most enchanting problems in biology. Many crucial questions remain to be addressed: what determines the specificity of the receptor-$G\alpha_{12/13}$ interaction (Montgomery et al., 2014; Lymperopoulos et al., 2021)? What determines the specific selectivity of the receptor to $G\alpha_{12}$ or $G\alpha_{13}$ (Corbisier et al., 2015; Mackenzie et al., 2019)? Do receptor and $G\alpha_{12/13}$ form a pre-coupling complex (Ayoub et al., 2012; Zhang et al., 2017)? The importance of $G\alpha_{12/13}$ in mediating the complexity of signals, affecting the diversity of cell functions, and participating in the pathogenesis of diseases are continuously being explored. $G\alpha_{12/13}$ are pathologically relevant to cancer, bone diseases, liver steatosis, and pulmonary fibrosis. $G\alpha_{12/13}$ are considered an attractive biomarker and target for diagnosing and treating related diseases. However, it is unwise to directly stimulate or inhibit the activity of $G\alpha_{12/13}$ due to the complexity of its regulatory network, the diversity of functions, and the high likelihood of off-target effects. In comparison, stimulating/inhibiting the upstream receptor/downstream pathways of $G\alpha_{12}$ or $G\alpha_{13}$ in specific organs/cells may offer a chance of successful therapy. A better understanding of the ligand-receptor-$G\alpha_{12/13}$-downstream signaling networks may guide new drug development in the future.

AUTHOR CONTRIBUTIONS

PG wrote the manuscript; YT and MW drew the figures; HS made the table; LZ and WW gave comments; QW and YX gave instructions and revised the manuscript.

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REFERENCES

Abid, H. A., Inoue, A., and Gorvin, C. M. (2021). Heterogeneity of G Protein Activation by the Calcium-Sensing Receptor. *J. Mol. Endocrinol.* 67, 41–53. doi:10.1530/jme-21-0058

Acharya, B. R., Nestor-Bergmann, A., Liang, X., Gupta, S., Duszyc, K., Gauquelin, E., et al. (2018). A Mechanosensitive RhoA Pathway that Protects Epithelia against Acute Tensile Stress. *Developmental Cell* 47, 439–452. doi:10.1016/j.devcel.2018.09.016

Ackerman, S. D., Garcia, C., Piao, X., Gutmann, D. H., and Monk, K. R. (2015). The Adhesion GPCR Gpr56 Regulates Oligodendrocyte Development via Interactions with Gα12/13 and RhoA. *Nat. Commun.* 6, 6122. doi:10.1038/ncomms7122

Arang, N., and Gutkind, J. S. (2020). G Protein-Coupled Receptors and Heterotrimeric G Proteins as Cancer Drivers. *FEBS Lett.* 594, 4201–4232. doi:10.1002/1873-3468.14017

Arnold, C., Feldner, A., Pfisterer, L., Hödebeck, M., Troidl, K., Genové, G., et al. (2014). RGS 5 Promotes Arterial Growth during Arteriogenesis. *EMBO Mol. Med.* 6, 1075–1089. doi:10.15252/emmm.201403864

Arthofer, E., Hot, B., Petersen, J., Strakova, K., Jäger, S., Grundmann, M., et al. (2016). WNT Stimulation Dissociates a Frizzled 4 Inactive-State Complex with Gα12/13. *Mol. Pharmacol.* 90, 447–459. doi:10.1124/mol.116.104919

Avet, C., Sturino, C., Grastilleur, S., Gouill, C. L., Semache, M., Gross, F., et al. (2020). The PAR2 Inhibitor I-287 Selectively Targets Gαq and Gα12/13 Signaling and Has Anti-inflammatory Effects. *Commun. Biol.* 3, 719. doi:10.1038/s42003-020-01453-8

Ayoub, M. A., Al-Senaidy, A., and Pin, J.-P. (2012). Receptor-G Protein Interaction Studied by Bioluminescence Resonance Energy Transfer: Lessons from Protease-Activated Receptor 1. *Front. Endocrin.* 3, 82. doi:10.3389/fendo.2012.00082

Ayoub, M. A., and Pin, J.-P. (2013). Interaction of Protease-Activated Receptor 2 with G Proteins and β-Arrestin 1 Studied by Bioluminescence Resonance Energy Transfer. *Front. Endocrinol.* 4, 196. doi:10.3389/fendo.2013.00196

Bodmann, E. L., Krett, A. L., and Bünemann, M. (2017). Potentiation of Receptor Responses Induced by Prolonged Binding of Gα 13 and Leukemia-associated RhoGEF. *FASEB j.* 31, 3663–3676. doi:10.1096/fj.201700026r

Bondar, A., and Lazar, J. (2021). Optical Sensors of Heterotrimeric G Protein Signaling. *FEBS J.* 288, 2570–2584. doi:10.1111/febs.15655

Boucher, I., Yu, W., Beaudry, S., Negoro, H., Tran, M., Pollak, M. R., et al. (2012). Gα12 Activation in Podocytes Leads to Cumulative Changes in Glomerular Collagen Expression, Proteinuria and Glomerulosclerosis. *Lab. Invest.* 92, 662–675. doi:10.1038/labinvest.2011.198

Boularan, C., Hwang, I.-Y., Kamenyeva, O., Park, C., Harrison, K., Huang, Z., et al. (2015). B Lymphocyte-specific Loss of Ric-8A Results in a Gα Protein Deficit and Severe Humoral Immunodeficiency. *J.I.* 195, 2090–2102. doi:10.4049/jimmunol.1500523

Cancer Genome Atlas, N. (2015). Comprehensive Genomic Characterization of Head and Neck Squamous Cell Carcinomas. *Nature* 517, 576–582. doi:10.1038/nature14129

Carloni, V., Mazzocca, A., Mello, T., Galli, A., and Capaccioli, S. (2013). Cell Fusion Promotes Chemoresistance in Metastatic colon Carcinoma. *Oncogene* 32, 2649–2660. doi:10.1038/onc.2012.268

Castaldi, A., Chesini, G. P., Taylor, A. E., Sussman, M. A., Brown, J. H., and Purcell, N. H. (2016). Sphingosine 1-phosphate Elicits RhoA-dependent Proliferation and MRTF-A Mediated Gene Induction in CPCs. *Cell Signal.* 28, 871–879. doi:10.1016/j.cellsig.2016.04.006

Castellone, M. D., Laukkanen, M. O., Teramoto, H., Bellelli, R., Alì, G., Fontanini, G., et al. (2015). Cross Talk between the Bombesin Neuropeptide Receptor and Sonic Hedgehog Pathways in Small Cell Lung Carcinoma. *Oncogene* 34, 1679–1687. doi:10.1038/onc.2014.104

Castillo-Kauil, A., García-Jiménez, I., Cervantes-Villagrana, R. D., Adame-García, S. R., Beltrán-Navarro, Y. M., Gutkind, J. S., et al. (2020). Gαs Directly Drives PDZ-RhoGEF Signaling to Cdc42. *J. Biol. Chem.* 295, 16920–16928. doi:10.1074/jbc.ac120.015204

Cerami, E., Gao, J., Dogrusoz, U., Gross, B. E., Sumer, S. O., Aksoy, B. A., et al. (2012). The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data: Figure 1. *Cancer Discov.* 2, 401–404. doi:10.1158/2159-8290.cd-12-0095

Chan, A. M., Fleming, T. P., McGovern, E. S., Chedid, M., Miki, T., and Aaronson, S. A. (1993). Expression cDNA Cloning of a Transforming Gene Encoding the Wild-type G Alpha 12 Gene Product. *Mol. Cell. Biol.* 13, 762–768. doi:10.1128/mcb.13.2.762

Chandrabalan, A., and Ramachandran, R. (2021). Molecular Mechanisms Regulating Proteinase-Activated Receptors (PARs). *FEBS J.* 288, 2697–2726. doi:10.1111/febs.15829

Cheng, N., Zhang, Y., Delaney, M. K., Wang, C., Bai, Y., Skidgel, R. A., et al. (2021). Targeting Gα13-Integrin Interaction Ameliorates Systemic Inflammation. *Nat. Commun.* 12, 3185. doi:10.1038/s41467-021-23409-0

Chow, C. R., Ebine, K., Knab, L. M., Bentrem, D. J., Kumar, K., and Munshi, H. G. (2016). Cancer Cell Invasion in Three-Dimensional Collagen Is Regulated Differentially by Gα13 Protein and Discoidin Domain Receptor 1-Par3 Protein Signaling. *J. Biol. Chem.* 291, 1605–1618. doi:10.1074/jbc.m115.669606

Corbisier, J., Galès, C., Huszagh, A., Parmentier, M., and Springael, J.-Y. (2015). Biased Signaling at Chemokine Receptors. *J. Biol. Chem.* 290, 9542–9554. doi:10.1074/jbc.m114.596098

Dermott, J. M., Reddy, M. R., Onesime, D., Reddy, E. P., and Dhanasekaran, N. (1999). Oncogenic Mutant of Gα12 Stimulates Cell Proliferation through Cycloxygenase-2 Signaling Pathway. *Oncogene* 18, 7185–7189. doi:10.1038/sj.onc.1203345

Dong, C. (2021). Cytokine Regulation and Function in T Cells. *Annu. Rev. Immunol.* 39, 51–76. doi:10.1146/annurev-immunol-061020-053702

Dusaban, S. S., Chun, J., Rosen, H., Purcell, N. H., and Brown, J. H. (2017). Sphingosine 1-phosphate Receptor 3 and RhoA Signaling Mediate Inflammatory Gene Expression in Astrocytes. *J. Neuroinflammation* 14, 111. doi:10.1186/s12974-017-0882-x

Dusaban, S. S., Purcell, N. H., Rockenstein, E., Masliah, E., Cho, M. K., Smrcka, A. V., et al. (2013). Phospholipase Cε Links G Protein-Coupled Receptor Activation to Inflammatory Astrocytic Responses. *Proc. Natl. Acad. Sci. USA* 110, 3609–3614. doi:10.1073/pnas.1217355110

El-Haibi, C. P., Sharma, P., Singh, R., Gupta, P., Taub, D. D., Singh, S., et al. (2013). Differential G Protein Subunit Expression by Prostate Cancer Cells and Their Interaction with CXCR5. *Mol. Cancer* 12, 64. doi:10.1186/1476-4598-12-64

Feng, X., Liu, P., Zhou, X., Li, M.-T., Li, F.-L., Wang, Z., et al. (2016). Thromboxane A2 Activates YAP/TAZ Protein to Induce Vascular Smooth Muscle Cell Proliferation and Migration. *J. Biol. Chem.* 291, 18947–18958. doi:10.1074/jbc.m116.739722

Festa, B. P., Chen, Z., Berquez, M., Debaix, H., Tokonami, N., Prange, J. A., et al. (2018). Impaired Autophagy Bridges Lysosomal Storage Disease and Epithelial Dysfunction in the Kidney. *Nat. Commun.* 9, 161. doi:10.1038/s41467-017-02536-7

Flaumenhaft, R., and De Ceunynck, K. (2017). Targeting PAR1: Now what? *Trends Pharmacol. Sci.* 38, 701–716. doi:10.1016/j.tips.2017.05.001

Flori, M., Schmid, C. A., Sumrall, E. T., Tzankov, A., Law, C. W., Robinson, M. D., et al. (2016). The Hematopoietic Oncoprotein FOXP1 Promotes Tumor Cell Survival in Diffuse Large B-Cell Lymphoma by Repressing S1PR2 Signaling. *Blood* 127, 1438–1448. doi:10.1182/blood-2015-08-662635

Forrester, S. J., Booz, G. W., Sigmund, C. D., Coffman, T. M., Kawai, T., Rizzo, V., et al. (2018). Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. *Physiol. Rev.* 98, 1627–1738. doi:10.1152/physrev.00038.2017

Fujii, T., Onohara, N., Maruyama, Y., Tanabe, S., Kobayashi, H., Fukutomi, M., et al. (2005). Gα12/13-mediated Production of Reactive Oxygen Species Is Critical for Angiotensin Receptor-Induced NFAT Activation in Cardiac Fibroblasts. *J. Biol. Chem.* 280, 23041–23047. doi:10.1074/jbc.m409397200

Gadepalli, R., Kotla, S., Heckle, M. R., Verma, S. K., Singh, N. K., and Rao, G. N. (2013). Novel Role for P21-Activated Kinase 2 in Thrombin-Induced Monocyte Migration. *J. Biol. Chem.* 288, 30815–30831. doi:10.1074/jbc.m113.463414

Gan, X., Wang, C., Patel, M., Kreutz, B., Zhou, M., Kozasa, T., et al. (2013). Different Raf Protein Kinases Mediate Different Signaling Pathways to Stimulate E3 Ligase RFFL Gene Expression in Cell Migration Regulation. *J. Biol. Chem.* 288, 33978–33984. doi:10.1074/jbc.m113.477406

Gan, X., Wang, J., Wang, C., Sommer, E., Kozasa, T., Srinivasula, S., et al. (2012). PRR5L Degradation Promotes mTORC2-Mediated PKC-δ Phosphorylation and Cell Migration Downstream of Gα12. *Nat. Cell Biol* 14, 686–696. doi:10.1038/ncb2507

Gao, J., Aksoy, B. A., Dogrusoz, U., Dresdner, G., Gross, B., Sumer, S. O., et al. (2013). Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the cBioPortal. *Sci. Signal.* 6, pl1. doi:10.1126/scisignal.2004088

Gavard, J., and Gutkind, J. S. (2008). Protein Kinase C-Related Kinase and ROCK Are Required for Thrombin-Induced Endothelial Cell Permeability Downstream from Gα12/13 and Gα11/q. *J. Biol. Chem.* 283, 29888–29896. doi:10.1074/jbc.m803880200

Girard, M., Dagenais Bellefeuille, S., Eiselt, É., Brouillette, R., Placet, M., Arguin, G., et al. (2020). The P2Y 6 Receptor Signals through Gα Q/Ca 2+/PKCα and Gα 13/ROCK Pathways to Drive the Formation of Membrane Protrusions and Dictate Cell Migration. *J. Cell Physiol* 235, 9676–9690. doi:10.1002/jcp.29779

Goldsmith, Z. G., and Dhanasekaran, D. N. (2007). G Protein Regulation of MAPK Networks. *Oncogene* 26, 3122–3142. doi:10.1038/sj.onc.1210407

Gong, H., Gao, X., Feng, S., Siddiqui, M. R., Garcia, A., Bonini, M. G., et al. (2014). Evidence of a Common Mechanism of Disassembly of Adherens Junctions through Gα13 Targeting of VE-Cadherin. *J. Exp. Med.* 211, 579–591. doi:10.1084/jem.20131190

Gong, H., Shen, B., Flevaris, P., Chow, C., Lam, S. C.-T., Voyno-Yasenetskaya, T. A., et al. (2010). G Protein Subunit Gα 13 Binds to Integrin α IIb β 3 and Mediates Integrin "Outside-In" Signaling. *Science* 327, 340–343. doi:10.1126/science.1174779

Goupil, E., Tassy, D., Bourguet, C., Quiniou, C., Wisehart, V., Pétrin, D., et al. (2010). A Novel Biased Allosteric Compound Inhibitor of Parturition Selectively Impedes the Prostaglandin F2α-Mediated Rho/ROCK Signaling Pathway. *J. Biol. Chem.* 285, 25624–25636. doi:10.1074/jbc.m110.115196

Green, J. A., Suzuki, K., Cho, B., Willison, L. D., Palmer, D., Allen, C. D. C., et al. (2011). The Sphingosine 1-phosphate Receptor S1P2 Maintains the Homeostasis of Germinal center B Cells and Promotes Niche Confinement. *Nat. Immunol.* 12, 672–680. doi:10.1038/ni.2047

Grzelinski, M., Pinkenburg, O., Büch, T., Gold, M., Stohr, S., Kalwa, H., et al. (2010). Critical Role of Gα12 and Gα13 for Human Small Cell Lung Cancer Cell

Proliferation *In Vitro* and Tumor Growth *In Vivo*. *Clin. Cancer Res.* 16, 1402–1415. doi:10.1158/1078-0432.ccr-09-1873

Haak, A. J., Ducharme, M. T., Diaz Espinosa, A. M., and Tschumperlin, D. J. (2020). Targeting GPCR Signaling for Idiopathic Pulmonary Fibrosis Therapies. *Trends Pharmacol. Sci.* 41, 172–182. doi:10.1016/j.tips.2019.12.008

Hashimoto, S., Mikami, S., Sugino, H., Yoshikawa, A., Hashimoto, A., Onodera, Y., et al. (2016). Lysophosphatidic Acid Activates Arf6 to Promote the Mesenchymal Malignancy of Renal Cancer. *Nat. Commun.* 7, 10656. doi:10.1038/ncomms10656

Hauser, A. S., Attwood, M. M., Rask-Andersen, M., Schiöth, H. B., and Gloriam, D. E. (2017). Trends in GPCR Drug Discovery: New Agents, Targets and Indications. *Nat. Rev. Drug Discov.* 16, 829–842. doi:10.1038/nrd.2017.178

He, Z., Yang, Y., Wen, Z., Chen, C., Xu, X., Zhu, Y., et al. (2017). CYP2J2 Metabolites, Epoxyeicosatrienoic Acids, Attenuate Ang II-Induced Cardiac Fibrotic Response by Targeting Gα12/13. *J. Lipid Res.* 58, 1338–1353. doi:10.1194/jlr.m074229

Healy, J. A., Nugent, A., Rempel, R. E., Moffitt, A. B., Davis, N. S., Jiang, X., et al. (2016). GNA13 Loss in Germinal center B Cells Leads to Impaired Apoptosis and Promotes Lymphoma *In Vivo*. *Blood* 127, 2723–2731. doi:10.1182/blood-2015-07-659938

Hedegaard, M. A., and Holst, B. (2020). The Complex Signaling Pathways of the Ghrelin Receptor. *Endocrinology* 161, 161. doi:10.1210/endocr/bqaa020

Hendrickx, G., Boudin, E., Verbeek, M., Fransen, E., Mortier, G., and Van Hul, W. (2020). WNT16 Requires Gα Subunits as Intracellular Partners for Both its Canonical and Non-canonical WNT Signalling Activity in Osteoblasts. *Calcif Tissue Int.* 106, 294–302. doi:10.1007/s00223-019-00633-x

Herroeder, S., Reichardt, P., Sassmann, A., Zimmermann, B., Jaeneke, D., Hoeckner, J., et al. (2009). Guanine Nucleotide-Binding Proteins of the G12 Family Shape Immune Functions by Controlling CD4+ T Cell Adhesiveness and Motility. *Immunity* 30, 708–720. doi:10.1016/j.immuni.2009.02.010

Hilger, D., Masureel, M., and Kobilka, B. K. (2018). Structure and Dynamics of GPCR Signaling Complexes. *Nat. Struct. Mol. Biol.* 25, 4–12. doi:10.1038/s41594-017-0011-7

Hot, B., Valnohova, J., Arthofer, E., Simon, K., Shin, J., Uhlén, M., et al. (2017). FZD10-Gα13 Signalling axis Points to a Role of FZD10 in CNS Angiogenesis. *Cell Signal.* 32, 93–103. doi:10.1016/j.cellsig.2017.01.023

Hou, L., Zhang, Z., Yang, L., Chang, N., Zhao, X., Zhou, X., et al. (2021). NLRP3 Inflammasome Priming and Activation in Cholestatic Liver Injury via the Sphingosine 1-phosphate/S1P Receptor 2/Gα(12/13)/MAPK Signaling Pathway. *J. Mol. Med.* 99, 273–288. doi:10.1007/s00109-020-02032-4

Hu, J., Oda, S. K., Shotts, K., Donovan, E. E., Strauch, P., Pujanauski, L. M., et al. (2014). Lysophosphatidic Acid Receptor 5 Inhibits B Cell Antigen Receptor Signaling and Antibody Response. *J.I.* 193, 85–95. doi:10.4049/jimmunol.1300429

Huang, W., Morales, J. L., Gazivoda, V. P., Lai, J., Qi, Q., and August, A. (2013). The Zinc-Binding Region of IL-2 Inducible T Cell Kinase (Itk) Is Required for Interaction with Gα13 and Activation of Serum Response Factor. *Int. J. Biochem. Cell Biol.* 45, 1074–1082. doi:10.1016/j.biocel.2013.02.011

Ismail, O. Z., Zhang, X., Wei, J., Haig, A., Denker, B. M., Suri, R. S., et al. (2015). Kidney Injury Molecule-1 Protects against Gα12 Activation and Tissue Damage in Renal Ischemia-Reperfusion Injury. *Am. J. Pathol.* 185, 1207–1215. doi:10.1016/j.ajpath.2015.02.003

Janda, C. Y., Dang, L. T., You, C., Chang, J., de Lau, W., Zhong, Z. A., et al. (2017). Surrogate Wnt Agonists that Phenocopy Canonical Wnt and β-catenin Signalling. *Nature* 545, 234–237. doi:10.1038/nature22306

Jiang, L. I., Collins, J., Davis, R., Fraser, I. D., and Sternweis, P. C. (2008). Regulation of cAMP Responses by the G12/13 Pathway Converges on Adenylyl Cyclase VII. *J. Biol. Chem.* 283, 23429–23439. doi:10.1074/jbc.m803281200

Joshi, S., Wels, C., Beham-Schmid, C., Fukunaga-Kalabis, M., Holmen, S. L., Otte, M., et al. (2015). Gα13 Mediates Human Cytomegalovirus-Encoded Chemokine Receptor US28-Induced Cell Death in Melanoma. *Int. J. Cancer* 137, 1503–1508. doi:10.1002/ijc.29506

Justus, C. R., Sanderlin, E. J., Dong, L., Sun, T., Chi, J.-T., Lertpiriyapong, K., et al. (2017). Contextual Tumor Suppressor Function of T Cell Death-Associated Gene 8 (TDAG8) in Hematological Malignancies. *J. Transl Med.* 15, 204. doi:10.1186/s12967-017-1305-6

Kalliora, C., Kyriazis, I. D., Oka, S. I., Lieu, M. J., Yue, Y., Area-Gomez, E., et al. (2019). Dual Peroxisome-Proliferator-Activated-Receptor-Alpha/gamma Activation Inhibits SIRT1-PGC1alpha axis and Causes Cardiac Dysfunction. *JCI Insight* 5, e129556. doi:10.1172/jci.insight.129556

Kalwa, H., Storch, U., Demleitner, J., Fiedler, S., Mayer, T., Kannler, M., et al. (2015). Phospholipase C Epsilon (PLCε) Induced TRPC6 Activation: A Common but Redundant Mechanism in Primary Podocytes. *J. Cell. Physiol.* 230, 1389–1399. doi:10.1002/jcp.24883

Khan, S. M., Sung, J. Y., and Hébert, T. E. (2016). Gβγ Subunits-Different Spaces, Different Faces. *Pharmacol. Res.* 111, 434–441. doi:10.1016/j.phrs.2016.06.026

Ki, S. H., Choi, M. J., Lee, C. H., and Kim, S. G. (2007). Gα12 Specifically Regulates COX-2 Induction by Sphingosine 1-Phosphate. *J. Biol. Chem.* 282, 1938–1947. doi:10.1074/jbc.m606080200

Kihara, Y., Maceyka, M., Spiegel, S., and Chun, J. (2014). Lysophospholipid Receptor Nomenclature Review: IUPHAR Review 8. *Br. J. Pharmacol.* 171, 3575–3594. doi:10.1111/bph.12678

Kim, E.-S., Jeong, J.-B., Kim, S., Lee, K.-M., Ko, E., Noh, D.-Y., et al. (2010). The G12 Family Proteins Upregulate Matrix Metalloproteinase-2 via P53 Leading to Human Breast Cell Invasion. *Breast Cancer Res. Treat.* 124, 49–61. doi:10.1007/s10549-009-0697-2

Kim, K., Lee, J., and Ghil, S. (2018). The Regulators of G Protein Signaling RGS 16 and RGS 18 Inhibit Protease-activated Receptor 2/Gi/o Signaling through Distinct Interactions with Gα in Live Cells. *FEBS Lett.* 592, 3126–3138. doi:10.1002/1873-3468.13220

Kim, K. M., Han, C. Y., Kim, J. Y., Cho, S. S., Kim, Y. S., Koo, J. H., et al. (2018). Gα12 Overexpression Induced by miR-16 Dysregulation Contributes to Liver Fibrosis by Promoting Autophagy in Hepatic Stellate Cells. *J. Hepatol.* 68, 493–504. doi:10.1016/j.jhep.2017.10.011

Kim, T. H., Koo, J. H., Heo, M. J., Han, C. Y., Kim, Y. I., Park, S. Y., et al. (2019). Overproduction of Inter-α-trypsin Inhibitor Heavy Chain 1 after Loss of Gα13 in Liver Exacerbates Systemic Insulin Resistance in Mice. *Sci. Transl Med.* 11, eaan4735. doi:10.1126/scitranslmed.aan4735

Kim, T. H., Yang, Y. M., Han, C. Y., Koo, J. H., Oh, H., Kim, S. S., et al. (2018). Gα12 Ablation Exacerbates Liver Steatosis and Obesity by Suppressing USP22/SIRT1-Regulated Mitochondrial Respiration. *J. Clin. Invest.* 128, 5587–5602. doi:10.1172/jci97831

Kim, Y. M., Lim, S.-C., Han, C. Y., Kay, H. Y., Cho, I. J., Ki, S. H., et al. (2011). Gα 12/13 Induction of CYR61 in Association with Arteriosclerotic Intimal Hyperplasia. *Arterioscler Thromb. Vasc. Biol.* 31, 861–869. doi:10.1161/atvbaha.110.218552

Ko, S. H., Choi, G. E., Oh, J. Y., Lee, H. J., Kim, J. S., Chae, C. W., et al. (2017). Succinate Promotes Stem Cell Migration through the GPR91-dependent Regulation of DRP1-Mediated Mitochondrial Fission. *Sci. Rep.* 7, 12582. doi:10.1038/s41598-017-12692-x

Koo, J. H., Kim, T. H., Park, S.-Y., Joo, M. S., Han, C. Y., Choi, C. S., et al. (2017). Gα13 Ablation Reprograms Myofibers to Oxidative Phenotype and Enhances Whole-Body Metabolism. *J. Clin. Invest.* 127, 3845–3860. doi:10.1172/jci92067

Kuen, D. S., Park, M., Ryu, H., Choi, G., Moon, Y. H., Kim, J. O., et al. (2021). Critical Regulation of Follicular Helper T Cell Differentiation and Function by Gα13 Signaling. *Proc. Natl. Acad. Sci. U S A.* 118, 118. doi:10.1073/pnas.2108376118

Kumar, A., Kremer, K. N., Dominguez, D., Tadi, M., and Hedin, K. E. (2011). Gα13 and Rho Mediate Endosomal Trafficking of CXCR4 into Rab11+ Vesicles upon Stromal Cell-Derived Factor-1 Stimulation. *J.I.* 186, 951–958. doi:10.4049/jimmunol.1002019

Kumar, R. N., Shore, S. K., and Dhanasekaran, N. (2006). Neoplastic Transformation by the Gep Oncogene, Gα12, Involves Signaling by STAT3. *Oncogene* 25, 899–906. doi:10.1038/sj.onc.1209132

Lambright, D. G., Sondek, J., Bohm, A., Skiba, N. P., Hamm, H. E., and Sigler, P. B. (1996). The 2.0 Å crystal Structure of a Heterotrimeric G Protein. *Nature* 379, 311–319. doi:10.1038/379311a0

Leach, K., Wen, A., Cook, A. E., Sexton, P. M., Conigrave, A. D., and Christopoulos, A. (2013). Impact of Clinically Relevant Mutations on the Pharmacoregulation and Signaling Bias of the Calcium-Sensing Receptor by Positive and Negative Allosteric Modulators. *Endocrinology* 154, 1105–1116. doi:10.1210/en.2012-1887

Leach, K., Wen, A., Davey, A. E., Sexton, P. M., Conigrave, A. D., and Christopoulos, A. (2012). Identification of Molecular Phenotypes and Biased Signaling Induced by Naturally Occurring Mutations of the Human Calcium-Sensing Receptor. *Endocrinology* 153, 4304–4316. doi:10.1210/en.2012-1449

Lecointre, C., Desrues, L., Joubert, J. E., Perzo, N., Guichet, P.-O., Le Joncour, V., et al. (2015). Signaling Switch of the Urotensin II Vasoactive Peptide GPCR: Prototypic Chemotaxic Mechanism in Glioma. *Oncogene* 34, 5080–5094. doi:10.1038/onc.2014.433

Lee, C.-W., Rivera, R., Gardell, S., Dubin, A. E., and Chun, J. (2006). GPR92 as a New G12/13- and Gq-Coupled Lysophosphatidic Acid Receptor that Increases cAMP, LPA5. *J. Biol. Chem.* 281, 23589–23597. doi:10.1074/jbc.m603670200

Lee, J. H., Kim, D., Oh, Y. S., and Jun, H. S. (2019). Lysophosphatidic Acid Signaling in Diabetic Nephropathy. *Int. J. Mol. Sci.* 20. doi:10.3390/ijms20112850

Lee, S. J., Yang, J. W., Cho, I. J., Kim, W. D., Cho, M. K., Lee, C. H., et al. (2009). The Gep Oncogenes, Gα12 and Gα13, Upregulate the Transforming Growth Factor-β1 Gene. *Oncogene* 28, 1230–1240. doi:10.1038/onc.2008.488

Li, Y., Liu, M., Yang, S., Fuller, A. M., Karin Eisinger-Mathason, T. S., and Yang, S. (2021). RGS12 Is a Novel Tumor Suppressor in Osteosarcoma that Inhibits YAP-TEAD1-Ezrin Signaling. *Oncogene* 40, 2553–2566. doi:10.1038/s41388-020-01599-z

Lim, W. K., Chai, X., Ghosh, S., Ray, D., Wang, M., Rasheed, S. A. K., et al. (2019). Gα-13 Induces CXC Motif Chemokine Ligand 5 Expression in Prostate Cancer Cells by Transactivating NF-κB. *J. Biol. Chem.* 294, 18192–18206. doi:10.1074/jbc.ra119.010018

Litosch, I. (2012). Negative Feedback Regulation of Gq Signaling by Protein Kinase C Is Disrupted by Diacylglycerol Kinase ζ in COS-7 Cells. *Biochem. Biophysical Res. Commun.* 417, 956–960. doi:10.1016/j.bbrc.2011.12.037

Liu, B., Su, Q., Ma, J., Chen, C., Wang, L., Che, F., et al. (2021). Prognostic Value of Eight-Gene Signature in Head and Neck Squamous Carcinoma. *Front. Oncol.* 11, 657002. doi:10.3389/fonc.2021.657002

Liu, S.-C., Jen, Y.-M., Jiang, S. S., Chang, J.-L., Hsiung, C. A., Wang, C.-H., et al. (2009). Gα12-Mediated Pathway Promotes Invasiveness of Nasopharyngeal Carcinoma by Modulating Actin Cytoskeleton Reorganization. *Cancer Res.* 69, 6122–6130. doi:10.1158/0008-5472.can-08-3435

Liu, W., Li, H., Wang, Y., Zhao, X., Guo, Y., Jin, J., et al. (2017). MiR-30b-5p Functions as a Tumor Suppressor in Cell Proliferation, Metastasis and Epithelial-To-Mesenchymal Transition by Targeting G-Protein Subunit α-13 in Renal Cell Carcinoma. *Gene* 626, 275–281. doi:10.1016/j.gene.2017.05.040

Loskutov, Y. V., Griffin, C. L., Marinak, K. M., Bobko, A., Margaryan, N. V., Geldenhuys, W. J., et al. (2018). LPA Signaling Is Regulated through the Primary Cilium: a Novel Target in Glioblastoma. *Oncogene* 37, 1457–1471. doi:10.1038/s41388-017-0049-3

Lymperopoulos, A., Borges, J. I., Carbone, A. M., Cora, N., and Sizova, A. (2021). Cardiovascular Angiotensin II Type 1 Receptor Biased Signaling: Focus on Non-gq-, Non-βarrestin-dependent Signaling. *Pharmacol. Res.* 174, 105943. doi:10.1016/j.phrs.2021.105943

Mackenzie, A. E., Quon, T., Lin, L. C., Hauser, A. S., Jenkins, L., Inoue, A., et al. (2019). Receptor Selectivity between the G Proteins Gα 12 and Gα 13 Is Defined by a Single Leucine-to-isoleucine Variation. *FASEB j.* 33, 5005–5017. doi:10.1096/fj.201801956r

Mariggiò, S., Bavec, A., Natale, E., Zizza, P., Salmona, M., Corda, D., et al. (2006). Gα13 Mediates Activation of the Cytosolic Phospholipase A2α through fine Regulation of ERK Phosphorylation. *Cell Signal.* 18, 2200–2208. doi:10.1016/j.cellsig.2006.05.003

Masià-Balagué, M., Izquierdo, I., Garrido, G., Cordomí, A., Pérez-Benito, L., Miller, N. L. G., et al. (2015). Gastrin-stimulated Gα13 Activation of Rgnef Protein (ArhGEF28) in DLD-1 Colon Carcinoma Cells. *J. Biol. Chem.* 290, 15197–15209. doi:10.1074/jbc.m114.628164

Masuho, I., Skamangas, N. K., Muntean, B. S., and Martemyanov, K. A. (2021). Diversity of the Gβγ Complexes Defines Spatial and Temporal Bias of GPCR Signaling. *Cell Syst.* 12, 324–337. doi:10.1016/j.cels.2021.02.001

Mathew, D., Kremer, K. N., and Torres, R. M. (2019). ARHGEF1 Deficiency Reveals Gα13-Associated GPCRs Are Critical Regulators of Human Lymphocyte Function. *J. Clin. Invest.* 129, 965–968. doi:10.1172/jci125893

Maziarz, M., Federico, A., Zhao, J., Dujmusic, L., Zhao, Z., Monti, S., et al. (2020). Naturally Occurring Hotspot Cancer Mutations in Gα13 Promote Oncogenic Signaling. *J. Biol. Chem.* 295, 16897–16904. doi:10.1074/jbc.ac120.014698

McLaughlin, J. N., Patterson, M. M., and Malik, A. B. (2007). Protease-activated Receptor-3 (PAR3) Regulates PAR1 Signaling by Receptor Dimerization. *Proc. Natl. Acad. Sci.* 104, 5662–5667. doi:10.1073/pnas.0700763104

McNeil Coffield, V., Helms, W. S., Jiang, Q., and Su, L. (2004). Gα13 Mediates a Signal that Is Essential for Proliferation and Survival of Thymocyte Progenitors. *J. Exp. Med.* 200, 1315–1324. doi:10.1084/jem.20040944

Mende, F., Hundahl, C., Plouffe, B., Skov, L. J., Sivertsen, B., Madsen, A. N., et al. (2018). Translating Biased Signaling in the Ghrelin Receptor System into Differential *In Vivo* Functions. *Proc. Natl. Acad. Sci. USA* 115, E10255–E10264. doi:10.1073/pnas.1804003115

Mikelis, C. M., Palmby, T. R., Simaan, M., Li, W., Szabo, R., Lyons, R., et al. (2013). PDZ-RhoGEF and LARG Are Essential for Embryonic Development and Provide a Link between Thrombin and LPA Receptors and Rho Activation. *J. Biol. Chem.* 288, 12232–12243. doi:10.1074/jbc.m112.428599

Montgomery, E. R., Temple, B. R. S., Peters, K. A., Tolbert, C. E., Booker, B. K., Martin, J. W., et al. (2014). Gα12 Structural Determinants of Hsp90 Interaction Are Necessary for Serum Response Element-Mediated Transcriptional Activation. *Mol. Pharmacol.* 85, 586–597. doi:10.1124/mol.113.088443

Moriyama, S., Takahashi, N., Green, J. A., Hori, S., Kubo, M., Cyster, J. G., et al. (2014). Sphingosine-1-phosphate Receptor 2 Is Critical for Follicular Helper T Cell Retention in Germinal Centers. *J. Exp. Med.* 211, 1297–1305. doi:10.1084/jem.20131666

Mu, G., Ding, Q., Li, H., Zhang, L., Zhang, L., He, K., et al. (2018). Gastrin Stimulates Pancreatic Cancer Cell Directional Migration by Activating the Gα12/13-RhoA-ROCK Signaling Pathway. *Exp. Mol. Med.* 50, 1–14. doi:10.1038/s12276-018-0081-6

Müller, F. E., Schade, S. K., Cherkas, V., Stopper, L., Breithausen, B., Minge, D., et al. (2021). Serotonin Receptor 4 Regulates Hippocampal Astrocyte Morphology and Function. *Glia* 69, 872–889. doi:10.1002/glia.23933

Muppidi, J. R., Lu, E., and Cyster, J. G. (2015). The G Protein-Coupled Receptor P2RY8 and Follicular Dendritic Cells Promote Germinal center Confinement of B Cells, whereas S1PR3 Can Contribute to Their Dissemination. *J. Exp. Med.* 212, 2213–2222. doi:10.1084/jem.20151250

Muppidi, J. R., Schmitz, R., Green, J. A., Xiao, W., Larsen, A. B., Braun, S. E., et al. (2014). Loss of Signalling via Gα13 in Germinal centre B-Cell-Derived Lymphoma. *Nature* 516, 254–258. doi:10.1038/nature13765

Nakanishi, N., Ogata, T., Naito, D., Miyagawa, K., Taniguchi, T., Hamaoka, T., et al. (2016). MURC Deficiency in Smooth Muscle Attenuates Pulmonary Hypertension. *Nat. Commun.* 7, 12417. doi:10.1038/ncomms12417

Nakano, S., Inoue, K., Xu, C., Deng, Z., Syrovatkina, V., Vitone, G., et al. (2019). G-protein Gα13 Functions as a Cytoskeletal and Mitochondrial Regulator to Restrain Osteoclast Function. *Sci. Rep.* 9, 4236. doi:10.1038/s41598-019-40974-z

Nishida, M., Onohara, N., Sato, Y., Suda, R., Ogushi, M., Tanabe, S., et al. (2007). Gα12/13-mediated Up-Regulation of TRPC6 Negatively Regulates Endothelin-1-Induced Cardiac Myofibroblast Formation and Collagen Synthesis through Nuclear Factor of Activated T Cells Activation. *J. Biol. Chem.* 282, 23117–23128. doi:10.1074/jbc.m611780200

Noguchi, K., Ishii, S., and Shimizu, T. (2003). Identification of p2y9/GPR23 as a Novel G Protein-Coupled Receptor for Lysophosphatidic Acid, Structurally Distant from the Edg Family. *J. Biol. Chem.* 278, 25600–25606. doi:10.1074/jbc.m302648200

O'Hayre, M., Inoue, A., Kufareva, I., Wang, Z., Mikelis, C. M., Drummond, R. A., et al. (2016). Inactivating Mutations in GNA13 and RHOA in Burkitt's Lymphoma and Diffuse Large B-Cell Lymphoma: a Tumor Suppressor Function for the Gα13/RhoA axis in B Cells. *Oncogene* 35, 3771–3780. doi:10.1038/onc.2015.442

Olivera, A., Rosenfeldt, H. M., Bektas, M., Wang, F., Ishii, I., Chun, J., et al. (2003). Sphingosine Kinase Type 1 Induces G12/13-Mediated Stress Fiber Formation, yet Promotes Growth and Survival Independent of G Protein-Coupled Receptors. *J. Biol. Chem.* 278, 46452–46460. doi:10.1074/jbc.m308749200

Pang, A., Cheng, N., Cui, Y., Bai, Y., Hong, Z., Delaney, M. K., et al. (2020). High-loading Gα13-Binding EXE Peptide Nanoparticles Prevent Thrombosis and Protect Mice from Cardiac Ischemia/reperfusion Injury. *Sci. Transl Med.* 12. doi:10.1126/scitranslmed.aaz7287

Pang, A., Cui, Y., Chen, Y., Cheng, N., Delaney, M. K., Gu, M., et al. (2018). Shear-induced Integrin Signaling in Platelet Phosphatidylserine Exposure, Microvesicle Release, and Coagulation. *Blood* 132, 533–543. doi:10.1182/blood-2017-05-785253

Papasergi-Scott, M. M., Stoveken, H. M., MacConnachie, L., Chan, P. Y., Gabay, M., Wong, D., et al. (2018). Dual Phosphorylation of Ric-8A Enhances its Ability to Mediate G Protein α Subunit Folding and to Stimulate Guanine Nucleotide Exchange. *Sci. Signal.* 11, eaap8113. doi:10.1126/scisignal.aap8113

Park, H. W., Kim, Y. C., Yu, B., Moroishi, T., Mo, J.-S., Plouffe, S. W., et al. (2015). Alternative Wnt Signaling Activates YAP/TAZ. *Cell* 162, 780–794. doi:10.1016/j.cell.2015.07.013

Patel, M., Kawano, T., Suzuki, N., Hamakubo, T., Karginov, A. V., and Kozasa, T. (2014). Gα13/PDZ-RhoGEF/RhoA Signaling Is Essential for Gastrin-Releasing Peptide Receptor-Mediated Colon Cancer Cell Migration. *Mol. Pharmacol.* 86, 252–262. doi:10.1124/mol.114.093914

Pathe-neuschäfer-rube, A., Neuschäfer-rube, F., and Püschel, G. P. (2005). Role of the ERC Motif in the Proximal Part of the Second Intracellular Loop and the C-Terminal Domain of the Human Prostaglandin F2α Receptor (hFP-R) in G-Protein Coupling Control. *Biochem. J.* 388, 317–324. doi:10.1042/bj20041321

Piccinin, E., Villani, G., and Moschetta, A. (2019). Metabolic Aspects in NAFLD, NASH and Hepatocellular Carcinoma: the Role of PGC1 Coactivators. *Nat. Rev. Gastroenterol. Hepatol.* 16, 160–174. doi:10.1038/s41575-018-0089-3

Plastira, I., Bernhart, E., Joshi, L., Koyani, C. N., Strohmaier, H., Reicher, H., et al. (2020). MAPK Signaling Determines Lysophosphatidic Acid (LPA)-induced Inflammation in Microglia. *J. Neuroinflammation* 17, 127. doi:10.1186/s12974-020-01809-1

Profirovic, J., Strekalova, E., Urao, N., Krbanjevic, A., Andreeva, A. V., Varadarajan, S., et al. (2013). A Novel Regulator of Angiogenesis in Endothelial Cells: 5-hydroxytriptamine 4 Receptor. *Angiogenesis* 16, 15–28. doi:10.1007/s10456-012-9296-7

Qu, C., Liu, Y., Kunkalla, K., Singh, R. R., Blonska, M., Lin, X., et al. (2013). Trimeric G Protein-CARMA1 axis Links Smoothened, the Hedgehog Receptor Transducer, to NF-κB Activation in Diffuse Large B-Cell Lymphoma. *Blood* 121, 4718–4728. doi:10.1182/blood-2012-12-470153

Raghavan, S., Singh, N. K., Gali, S., Mani, A. M., and Rao, G. N. (2018). Protein Kinase Cθ via Activating Transcription Factor 2-Mediated CD36 Expression and Foam Cell Formation of Ly6C Hi Cells Contributes to Atherosclerosis. *Circulation* 138, 2395–2412. doi:10.1161/circulationaha.118.034083

Rasheed, S. A. K., Leong, H. S., Lakshmanan, M., Raju, A., Dadlani, D., Chong, F.-T., et al. (2018). GNA13 Expression Promotes Drug Resistance and Tumor-Initiating Phenotypes in Squamous Cell Cancers. *Oncogene* 37, 1340–1353. doi:10.1038/s41388-017-0038-6

Rasheed, S. A. K., Subramanyan, L. V., Lim, W. K., Udayappan, U. K., Wang, M., and Casey, P. J. (2021). The Emerging Roles of Galpha12/13 Proteins on the Hallmarks of Cancer in Solid Tumors. *Oncogene* 41, 147–158. doi:10.1038/s41388-021-02069-w

Rasheed, S. A. K., Teo, C. R., Beillard, E. J., Voorhoeve, P. M., and Casey, P. J. (2013). MicroRNA-182 and MicroRNA-200a Control G-Protein Subunit α-13 (GNA13) Expression and Cell Invasion Synergistically in Prostate Cancer Cells. *J. Biol. Chem.* 288, 7986–7995. doi:10.1074/jbc.m112.437749

Rasheed, S. A. K., Teo, C. R., Beillard, E. J., Voorhoeve, P. M., Zhou, W., Ghosh, S., et al. (2015). MicroRNA-31 Controls G Protein Alpha-13 (GNA13) Expression and Cell Invasion in Breast Cancer Cells. *Mol. Cancer* 14, 67. doi:10.1186/s12943-015-0337-x

Regué, L., Mou, F., and Avruch, J. (2013). G Protein-Coupled Receptors Engage the Mammalian Hippo Pathway through F-Actin. *Bioessays* 35, 430–435. doi:10.1002/bies.201200163

Rieken, S., Sassmann, A., Herroeder, S., Wallenwein, B., Moers, A., Offermanns, S., et al. (2006). G12/G13 Family G Proteins Regulate Marginal Zone B Cell Maturation, Migration, and Polarization. *J. Immunol.* 177, 2985–2993. doi:10.4049/jimmunol.177.5.2985

Rives, M.-L., Rady, B., Swanson, N., Zhao, S., Qi, J., Arnoult, E., et al. (2018). GPR40-Mediated Gα12 Activation by Allosteric Full Agonists Highly Efficacious at Potentiating Glucose-Stimulated Insulin Secretion in Human Islets. *Mol. Pharmacol.* 93, 581–591. doi:10.1124/mol.117.111369

Ruan, Y., Patzak, A., Pfeiffer, N., and Gericke, A. (2021). Muscarinic Acetylcholine Receptors in the Retina-Therapeutic Implications. *Int. J. Mol. Sci.* 22, 4989. doi:10.3390/ijms22094989

Rümenapp, U., Asmus, M., Schablowski, H., Woznicki, M., Han, L., Jakobs, K. H., et al. (2001). The M3 Muscarinic Acetylcholine Receptor Expressed in HEK-293 Cells Signals to Phospholipase D via G12 but Not Gq-type G Proteins. *J. Biol. Chem.* 276, 2474–2479. doi:10.1074/jbc.m004957200

Sabbir, M. G., Calcutt, N. A., and Fernyhough, P. (2018). Muscarinic Acetylcholine Type 1 Receptor Activity Constrains Neurite Outgrowth by Inhibiting Microtubule Polymerization and Mitochondrial Trafficking in Adult Sensory Neurons. *Front. Neurosci.* 12, 402. doi:10.3389/fnins.2018.00402

Scarlett, K. A., White, E.-S. Z., Coke, C. J., Carter, J. R., Bryant, L. K., and Hinton, C. V. (2018). Agonist-induced CXCR4 and CB2 Heterodimerization Inhibits Gα13/RhoA-Mediated Migration. *Mol. Cancer Res.* 16, 728–739. doi:10.1158/1541-7786.mcr-16-0481

Senarath, K., Kankanamge, D., Samaradivakara, S., Ratnayake, K., Tennakoon, M., and Karunarathne, A. (2018). Regulation of G Protein βγ Signaling. *Int. Rev. Cell Mol Biol* 339, 133–191. doi:10.1016/bs.ircmb.2018.02.008

Seyedabadi, M., Ghahremani, M. H., and Albert, P. R. (2019). Biased Signaling of G Protein Coupled Receptors (GPCRs): Molecular Determinants of GPCR/transducer Selectivity and Therapeutic Potential. *Pharmacol. Ther.* 200, 148–178. doi:10.1016/j.pharmthera.2019.05.006

Shen, B., Delaney, M. K., and Du, X. (2012). Inside-out, Outside-In, and Inside-Outside-In: G Protein Signaling in Integrin-Mediated Cell Adhesion, Spreading, and Retraction. *Curr. Opin. Cell Biol.* 24, 600–606. doi:10.1016/j.ceb.2012.08.011

Shen, B., Estevez, B., Xu, Z., Kreutz, B., Karginov, A., Bai, Y., et al. (2015). The Interaction of Gα13 with Integrin β1 Mediates Cell Migration by Dynamic Regulation of RhoA. *MBoC* 26, 3658–3670. doi:10.1091/mbc.e15-05-0274

Shen, B., Zhao, X., O'Brien, K. A., Stojanovic-Terpo, A., Delaney, M. K., Kim, K., et al. (2013). A Directional Switch of Integrin Signalling and a New Anti-thrombotic Strategy. *Nature* 503, 131–135. doi:10.1038/nature12613

Smrcka, A. V., and Fisher, I. (2019). G-protein βγ Subunits as Multi-Functional Scaffolds and Transducers in G-Protein-Coupled Receptor Signaling. *Cell. Mol. Life Sci.* 76, 4447–4459. doi:10.1007/s00018-019-03275-2

Sobel, K., Monnier, L., Menyhart, K., Bolinger, M., Studer, R., Nayler, O., et al. (2015). FTY720 Phosphate Activates Sphingosine-1-Phosphate Receptor 2 and Selectively Couples to Gα12/13/Rho/ROCK to Induce Myofibroblast Contraction. *Mol. Pharmacol.* 87, 916–927. doi:10.1124/mol.114.097261

Song, M. K., Park, C., Lee, Y. D., Kim, H., Kim, M. K., Kwon, J. O., et al. (2018). Gα12 Regulates Osteoclastogenesis by Modulating NFATc1 Expression. *J. Cell Mol Med* 22, 849–860. doi:10.1111/jcmm.13370

Spoerri, P. M., Strohmeyer, N., Sun, Z., Fässler, R., and Müller, D. J. (2020). Protease-activated Receptor Signalling Initiates α5β1-integrin-mediated Adhesion in Non-haematopoietic Cells. *Nat. Mater.* 19, 218–226. doi:10.1038/s41563-019-0580-4

Sriwai, W., Mahavadi, S., Al-Shboul, O., Grider, J. R., and Murthy, K. S. (2013). Distinctive G Protein-dependent Signaling by Protease-Activated Receptor 2 (PAR2) in Smooth Muscle: Feedback Inhibition of RhoA by cAMP-independent PKA. *PLoS One* 8, e66743. doi:10.1371/journal.pone.0066743

Stecky, R. C., Quick, C. R., Fleming, T. L., Mull, M. L., Vinson, V. K., Whitley, M. S., et al. (2020). Divergent C-Terminal Motifs in Gα12 and Gα13 Provide Distinct Mechanisms of Effector Binding and SRF Activation. *Cell Signal.* 72, 109653. doi:10.1016/j.cellsig.2020.109653

Strathmann, M. P., and Simon, M. I. (1991). G Alpha 12 and G Alpha 13 Subunits Define a Fourth Class of G Protein Alpha Subunits. *Proc. Natl. Acad. Sci.* 88, 5582–5586. doi:10.1073/pnas.88.13.5582

Subramanian, A., Capalbo, A., Iyengar, N. R., Rizzo, R., di Campli, A., Di Martino, R., et al. (2019). Auto-regulation of Secretory Flux by Sensing and Responding to the Folded Cargo Protein Load in the Endoplasmic Reticulum. *Cell* 176, 1461–1476. doi:10.1016/j.cell.2019.01.035

Sunahara, R. K., Tesmer, J. J. G., Gilman, A. G., and Sprang, S. R. (1997). Crystal Structure of the Adenylyl Cyclase Activator G S α. *Science* 278, 1943–1947. doi:10.1126/science.278.5345.1943

Svitkina, T. (2018). The Actin Cytoskeleton and Actin-Based Motility. *Cold Spring Harb Perspect. Biol.* 10, a018267. doi:10.1101/cshperspect.a018267

Syrovatkina, V., Alegre, K. O., Dey, R., and Huang, X.-Y. (2016). Regulation, Signaling, and Physiological Functions of G-Proteins. *J. Mol. Biol.* 428, 3850–3868. doi:10.1016/j.jmb.2016.08.002

Syrovatkina, V., and Huang, X. Y. (2019). Signaling Mechanisms and Physiological Functions of G-protein Gα 13 in Blood Vessel Formation, Bone Homeostasis, and Cancer. *Protein Sci.* 28, 305–312. doi:10.1002/pro.3531

Takefuji, M., Wirth, A., Lukasova, M., Takefuji, S., Boettger, T., Braun, T., et al. (2012). G 13 -Mediated Signaling Pathway Is Required for Pressure

Overload-Induced Cardiac Remodeling and Heart Failure. *Circulation* 126, 1972–1982. doi:10.1161/circulationaha.112.109256

Tan, L., Yan, W., McCorvy, J. D., and Cheng, J. (2018). Biased Ligands of G Protein-Coupled Receptors (GPCRs): Structure-Functional Selectivity Relationships (SFSRs) and Therapeutic Potential. *J. Med. Chem.* 61, 9841–9878. doi:10.1021/acs.jmedchem.8b00435

Tan, W., Martin, D., and Gutkind, J. S. (2006). The Gα13-Rho Signaling Axis Is Required for SDF-1-Induced Migration through CXCR4. *J. Biol. Chem.* 281, 39542–39549. doi:10.1074/jbc.m609062200

Tanaka, M., Okudaira, S., Kishi, Y., Ohkawa, R., Iseki, S., Ota, M., et al. (2006). Autotaxin Stabilizes Blood Vessels and Is Required for Embryonic Vasculature by Producing Lysophosphatidic Acid. *J. Biol. Chem.* 281, 25822–25830. doi:10.1074/jbc.m605142200

Teo, C. R., Casey, P. J., and Rasheed, S. A. K. (2016). The GNA13-RhoA Signaling axis Suppresses Expression of Tumor Protective Kallikreins. *Cell Signal.* 28, 1479–1488. doi:10.1016/j.cellsig.2016.07.001

Tesmer, J. J. G., Sunahara, R. K., Gilman, A. G., and Sprang, S. R. (1997). Crystal Structure of the Catalytic Domains of Adenylyl Cyclase in a Complex with G Sα ·GTPγS. *Science* 278, 1907–1916. doi:10.1126/science.278.5345.1907

Tiacci, E., Ladewig, E., Schiavoni, G., Penson, A., Fortini, E., Pettirossi, V., et al. (2018). Pervasive Mutations of JAK-STAT Pathway Genes in Classical Hodgkin Lymphoma. *Blood* 131, 2454–2465. doi:10.1182/blood-2017-11-814913

Toro-Tapia, G., Villaseca, S., Beyer, A., Roycroft, A., Marcellini, S., Mayor, R., et al. (2018). The Ric-8A/Gα13/FAK Signalling cascade Controls Focal Adhesion Formation during Neural Crest Cell Migration in Xenopus. *Development* 145, 145. doi:10.1242/dev.164269

Trivedi, V., Boire, A., Tchernychev, B., Kaneider, N. C., Leger, A. J., O'Callaghan, K., et al. (2009). Platelet Matrix Metalloprotease-1 Mediates Thrombogenesis by Activating PAR1 at a Cryptic Ligand Site. *Cell* 137, 332–343. doi:10.1016/j.cell.2009.02.018

Tsai, H.-J., Huang, C.-L., Chang, Y.-W., Huang, D.-Y., Lin, C.-C., Cooper, J. A., et al. (2014). Disabled-2 Is Required for Efficient Hemostasis and Platelet Activation by Thrombin in Mice. *Arterioscler Thromb. Vasc. Biol.* 34, 2404–2412. doi:10.1161/atvbaha.114.302602

Unsworth, A. J., Kriek, N., Bye, A. P., Naran, K., Sage, T., Flora, G. D., et al. (2017). PPAR γ Agonists Negatively Regulate α II Bβ3 Integrin Outside-in Signaling and Platelet Function through Up-regulation of Protein Kinase A Activity. *J. Thromb. Haemost.* 15, 356–369. doi:10.1111/jth.13578

van den Bos, E., Ambrosy, B., Horsthemke, M., Walbaum, S., Bachg, A. C., Wettschureck, N., et al. (2020). Knockout Mouse Models Reveal the Contributions of G Protein Subunits to Complement C5a Receptor-Mediated Chemotaxis. *J. Biol. Chem.* 295, 7726–7742. doi:10.1074/jbc.ra119.011984

Wang, J., Hua, T., and Liu, Z.-J. (2020). Structural Features of Activated GPCR Signaling Complexes. *Curr. Opin. Struct. Biol.* 63, 82–89. doi:10.1016/j.sbi.2020.04.008

Wang, L., Guo, D., Xing, B., Zhang, J. J., Shu, H.-B., Guo, L., et al. (2011). Resistance to Inhibitors of cholinesterase-8A (Ric-8A) Is Critical for Growth Factor Receptor-Induced Actin Cytoskeletal Reorganization. *J. Biol. Chem.* 286, 31055–31061. doi:10.1074/jbc.m111.253427

Wang, L., Luo, J.-Y., Li, B., Tian, X. Y., Chen, L.-J., Huang, Y., et al. (2016). Integrin-YAP/TAZ-JNK cascade Mediates Atheroprotective Effect of Unidirectional Shear Flow. *Nature* 540, 579–582. doi:10.1038/nature20602

Wang, L., Wang, D., Xing, B., Tan, Y.-c., Huang, J., Liu, B., et al. (2017). G-protein Gα13 Functions with Abl Kinase to Regulate Actin Cytoskeletal Reorganization. *J. Mol. Biol.* 429, 3836–3849. doi:10.1016/j.jmb.2017.10.020

Wang, N., Huang, H., Xiong, Q., Chen, N., Xi, N., Wu, P., et al. (2019). GNAQ Negatively Regulates Antiviral Innate Immune Responses in a Calcineurin-dependent Manner. *J.I.* 203, 1288–1297. doi:10.4049/jimmunol.1900427

Wang, Y., Li, Y., and Shi, G. (2013). The Regulating Function of Heterotrimeric G Proteins in the Immune System. *Arch. Immunol. Ther. Exp.* 61, 309–319. doi:10.1007/s00005-013-0230-5

Wang, Z., Guan, W., Han, Y., Ren, H., Tang, X., Zhang, H., et al. (2015). Stimulation of Dopamine D3 Receptor Attenuates Renal Ischemia-Reperfusion Injury via Increased Linkage with Gα12. *Transplantation* 99, 2274–2284. doi:10.1097/tp.0000000000000762

Ward, Y., Lake, R., Yin, J. J., Heger, C. D., Raffeld, M., Goldsmith, P. K., et al. (2011). LPA Receptor Heterodimerizes with CD97 to Amplify LPA-Initiated RHO-dependent Signaling and Invasion in Prostate Cancer Cells. *Cancer Res.* 71, 7301–7311. doi:10.1158/0008-5472.can-11-2381

White, J. P., Wrann, C. D., Rao, R. R., Nair, S. K., Jedrychowski, M. P., You, J.-S., et al. (2014). G Protein-Coupled Receptor 56 Regulates Mechanical Overload-Induced Muscle Hypertrophy. *Proc. Natl. Acad. Sci.* 111, 15756–15761. doi:10.1073/pnas.1417898111

Won, H. Y., Min, H. J., Lee, W. H., Kim, S. G., and Hwang, E. S. (2010). Gα12 Is Critical for TCR-Induced IL-2 Production and Differentiation of T Helper 2 and T Helper 17 Cells. *Biochem. Biophysical Res. Commun.* 394, 811–816. doi:10.1016/j.bbrc.2010.03.079

Worzfeld, T., Wettschureck, N., and Offermanns, S. (2008). G12/G13-mediated Signalling in Mammalian Physiology and Disease. *Trends Pharmacol. Sci.* 29, 582–589. doi:10.1016/j.tips.2008.08.002

Wu, M., Chen, W., Lu, Y., Zhu, G., Hao, L., and Li, Y.-P. (2017). Gα13 Negatively Controls Osteoclastogenesis through Inhibition of the Akt-GSK3β-NFATc1 Signalling Pathway. *Nat. Commun.* 8, 13700. doi:10.1038/ncomms13700

Wu, V., Yeerna, H., Nohata, N., Chiou, J., Harismendy, O., Raimondi, F., et al. (2019). Illuminating the Onco-GPCRome: Novel G Protein-Coupled Receptor-Driven Oncocrine Networks and Targets for Cancer Immunotherapy. *J. Biol. Chem.* 294, 11062–11086. doi:10.1074/jbc.rev119.005601

Wu, Y., Xu, J. X., El-Jouni, W., Lu, T., Li, S., Wang, Q., et al. (2016). Gα12 Is Required for Renal Cystogenesis Induced by Pkd1 Inactivation. *J. Cell Sci* 129, 3675–3684. doi:10.1242/jcs.190496

Xie, S., Mason, F. M., and Martin, A. C. (2016). Loss of Gα12/13 Exacerbates Apical Area Dependence of Actomyosin Contractility. *MBoC* 27, 3526–3536. doi:10.1091/mbc.e16-05-0305

Xu, N., Bradley, L., Ambdukar, I., and Gutkind, J. S. (1993). A Mutant Alpha Subunit of G12 Potentiates the Eicosanoid Pathway and Is Highly Oncogenic in NIH 3T3 Cells. *Proc. Natl. Acad. Sci.* 90, 6741–6745. doi:10.1073/pnas.90.14.6741

Yagi, H., Tan, W., Dillenburg-Pilla, P., Armando, S., Amornphimoltham, P., Simaan, M., et al. (2011). A Synthetic Biology Approach Reveals a CXCR4-G13-Rho Signaling axis Driving Transendothelial Migration of Metastatic Breast Cancer Cells. *Sci. Signal.* 4, ra60. doi:10.1126/scisignal.2002221

Yagi, H., Asanoma, K., Ohgami, T., Ichinoe, A., Sonoda, K., and Kato, K. (2016). GEP Oncogene Promotes Cell Proliferation through YAP Activation in Ovarian Cancer. *Oncogene* 35, 4471–4480. doi:10.1038/onc.2015.505

Yagi, H., Onoyama, I., Asanoma, K., Hori, E., Yasunaga, M., Kodama, K., et al. (2019). Gα13-mediated LATS1 Down-Regulation Contributes to Epithelial-Mesenchymal Transition in Ovarian Cancer. *FASEB J.* 33, 13683–13694. doi:10.1096/fj.201901278r

Yanagida, K., Igarashi, H., Yasuda, D., Kobayashi, D., Ohto-Nakanishi, T., Akahoshi, N., et al. (2018). The Gα12/13-Coupled Receptor LPA4 Limits Proper Adipose Tissue Expansion and Remodeling in Diet-Induced Obesity. *JCI Insight* 3, e97293. doi:10.1172/jci.insight.97293

Yanagida, K., Masago, K., Nakanishi, H., Kihara, Y., Hamano, F., Tajima, Y., et al. (2009). Identification and Characterization of a Novel Lysophosphatidic Acid Receptor, p2y5/LPA6. *J. Biol. Chem.* 284, 17731–17741. doi:10.1074/jbc.m808506200

Yanamadala, V., Negoro, H., Gunaratnam, L., Kong, T., and Denker, B. M. (2007). Gα12 Stimulates Apoptosis in Epithelial Cells through JNK1-Mediated Bcl-2 Degradation and Up-Regulation of IκBα. *J. Biol. Chem.* 282, 24352–24363. doi:10.1074/jbc.m702804200

Yang, Y. M., Kuen, D.-S., Chung, Y., Kurose, H., and Kim, S. G. (2020). Gα12/13 Signaling in Metabolic Diseases. *Exp. Mol. Med.* 52, 896–910. doi:10.1038/s12276-020-0454-5

Yang, Y. M., Lee, W. H., Lee, C. G., An, J., Kim, E.-S., Kim, S. H., et al. (2015). Gα12 Gep Oncogene Deregulation of P53-Responsive microRNAs Promotes Epithelial-Mesenchymal Transition of Hepatocellular Carcinoma. *Oncogene* 34, 2910–2921. doi:10.1038/onc.2014.218

Yasuda, D., Kobayashi, D., Akahoshi, N., Ohto-Nakanishi, T., Yoshioka, K., Takuwa, Y., et al. (2019). Lysophosphatidic Acid-Induced YAP/TAZ Activation Promotes Developmental Angiogenesis by Repressing Notch Ligand Dll4. *J. Clin. Invest.* 129, 4332–4349. doi:10.1172/jci121955

Ye, D., and Lin, F. (2013). S1pr2/Gα13 Signaling Controls Myocardial Migration by Regulating Endoderm Convergence. *Development* 140, 789–799. doi:10.1242/dev.085340

Ye, D., Xie, H., Hu, B., and Lin, F. (2015). Endoderm Convergence Controls Subduction of the Myocardial Precursors during Heart-Tube Formation. *Development* 142, 2928–2940. doi:10.1242/dev.113944

Yoo, E. J., Cao, G., Koziol-White, C. J., Ojiaku, C. A., Sunder, K., Jude, J. A., et al. (2017). Gα12facilitates Shortening in Human Airway Smooth Muscle by Modulating Phosphoinositide 3-Kinase-Mediated Activation in a RhoA-dependent Manner. *Br. J. Pharmacol.* 174, 4383–4395. doi:10.1111/bph.14040

Yu, W., Beaudry, S., Negoro, H., Boucher, I., Tran, M., Kong, T., et al. (2012). H2O2 Activates G Protein, 12 to Disrupt the Junctional Complex and Enhance Ischemia Reperfusion Injury. *Proc. Natl. Acad. Sci.* 109, 6680–6685. doi:10.1073/pnas.1116800109

Yu, X., Zhang, Y., and Chen, H. (2016). LPA Receptor 1 Mediates LPA-Induced Ovarian Cancer Metastasis: an *In Vitro* and *In Vivo* Study. *BMC Cancer* 16, 846. doi:10.1186/s12885-016-2865-1

Yuan, B., Cui, J., Wang, W., and Deng, K. (2016). Gα12/13 Signaling Promotes Cervical Cancer Invasion through the RhoA/ROCK-JNK Signaling axis. *Biochem. Biophysical Res. Commun.* 473, 1240–1246. doi:10.1016/j.bbrc.2016.04.048

Yung, B. S., Brand, C. S., Xiang, S. Y., Gray, C. B. B., Means, C. K., Rosen, H., et al. (2017). Selective Coupling of the S1P 3 Receptor Subtype to S1P-Mediated RhoA Activation and Cardioprotection. *J. Mol. Cell Cardiol.* 103, 1–10. doi:10.1016/j.yjmcc.2016.12.008

Zhang, L., Dong, Y., Wang, Y., Hu, W., Dong, S., and Chen, Y. (2020). Sphingosine-1-phosphate (S1P) Receptors: Promising Drug Targets for Treating Bone-related Diseases. *J. Cell Mol Med* 24, 4389–4401. doi:10.1111/jcmm.15155

Zhang, Y., Zhang, J., Yan, R., Tian, J., Zhang, Y., Zhang, J., et al. (2017). Receptor-interacting Protein Kinase 3 Promotes Platelet Activation and Thrombosis. *Proc. Natl. Acad. Sci. USA* 114, 2964–2969. doi:10.1073/pnas.1610963114

Zuo, C., Li, X., Huang, J., Chen, D., Ji, K., Yang, Y., et al. (2018). Osteoglycin Attenuates Cardiac Fibrosis by Suppressing Cardiac Myofibroblast Proliferation and Migration through Antagonizing Lysophosphatidic Acid 3/matrix Metalloproteinase 2/epidermal Growth Factor Receptor Signalling. *Cardiovasc. Res.* 114, 703–712. doi:10.1093/cvr/cvy035

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GLOSSARY

5-HT4R 5-hydroxytryptamine type 4 receptor
AKT protein kinase B
Ang II angiotensin II
AP-1 activator protein 1
AT1R Ang II type 1 receptor
CXCL12 C-X-C motif chemokine 12
CXCR4 C-X-C chemokine receptor 4
DLBCL diffuse large B-cell lymphoma
ERK extracellular regulated protein kinases
FAK focal adhesion kinase
FZD Frizzled
GEF guanine nucleotide exchange factors
GPCRs G protein-coupled receptors
GRP gastrin-releasing peptide
GPR56 g protein-coupled receptor 56
HNSCC head and neck squamous cell carcinoma
I/R ischemia/reperfusion
JNK c-Jun N-terminal kinase
LATS1/2 large tumor suppressor 1/2
LPA lysophosphatidic acid
LPAR LPA receptor
MAPK mitogen-activated protein kinase
MRTF myocardin-related transcription factor
NFAT activated T cell nuclear factor
NFATc1 nuclear factor of activated T-cell c1
NF-κB nuclear factor-kappa B
PARs protease-activated receptors
PI3K phosphatidylinositol 3-kinase
PKC protein kinase C
PLC phospholipase C
PPARγ peroxisome proliferator-activated receptor-γ
RGS regulators of G protein signaling
RhoGEF Rho guanine nucleotide exchange factor
RhoA ras homolog family member A
Ric-8A resistance to inhibitors of cholinesterase 8A
ROCK Rho-associated protein kinase
ROS reactive oxygen species
S1P sphingosine 1-phosphate
SRF serum response factor
Tfh T follicular helper
Th T helper
WNT Wingless/Int-1 lipoglycoprotein
YAP/TAZ yes-associated protein/transcriptional coactivator with PDZ-binding motif