Gα₁₂ and Gα₁₃: 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 Gα₁₂ subfamily (Gα₁₂/Gα₁₃)-mediated signaling plays a crucial role in cellular function and various pathological processes. The current research on the physiological and pathological function of Gα₁₂/Gα₁₃ is constantly expanding. Changes in the expression levels of Gα₁₂/Gα₁₃ have been found in a wide range of human diseases. However, the mechanistic research on Gα₁₂/Gα₁₃ is scattered. This review briefly describes the structural sequences of the Gα₁₂/Gα₁₃ isoforms and introduces the coupling of GPCRs and non-GPCRs to Gα₁₂/Gα₁₃. The effects of Gα₁₂/Gα₁₃ 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 Gα₁₂/Gα₁₃ in cancer, inflammation, metabolic diseases, fibrotic diseases, and circulatory disorders are brought to focus.

Keywords: G protein-coupled receptor, Gα₁₂, Gα₁₃, cell pathophysiology, diseases

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: Gα_s (s stands for stimulation), Gα_i/o (i stands for inhibition), Gα_q/11, and Gα₁₂/₁₃ (Hilger et al., 2018; Yang et al., 2020). The function of Gα_q, Gα₁₁, and Gα₁₃ have been well documented. Meanwhile, the progress in understanding the function of the Gα₁₂/₁₃ 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 Gα₁₂/₁₃ in recent years (Worzfeld et al., 2008).
Ga_{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. Ga_{12} and Ga_{13} share 67% of their amino acid sequence and have many downstream signaling targets in common (Montgomery et al., 2014; Stecky et al., 2020). Some of the pathways that are triggered by both Ga_{12} and Ga_{13} include phospholipase C (PLC)-\(\epsilon\) 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, Ga_{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, adenylyl 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 secondarily messengers eventually lead to physiological responses (Jiang et al., 2008; Kalwa et al., 2015; Ayoub and Pin, 2013; Xie et al., 2016). Ga_{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 Ga_{12} and/or Ga_{13} (Yang et al., 2020; Rasheed et al., 2021). In this review, the structure of Ga_{12} and Ga_{13} is reviewed along with their roles in GPCR signal pathways, cell function, and disease pathogenesis.

### The Amino Acid Structure of Ga_{12} and Ga_{13}

The Ga_{12/13} subfamily consists of two \(\alpha\) subunits encoded by GNA12 and GNA13. The Ga_{12/13} subunits were originally discovered based on the amino acid sequence similarity with other Ga subunits and their insensitivity to pertussis toxin (Arang and Gutkind, 2020). The structure of Ga_{12/13} subunit consists of an amino-terminal \(\alpha\)-helical domain and a Ras-like GTPase domain. There is a link between these two domains involved in binding to GDP and GTP (Svrakovatikaj et al., 2016; Smrcka and Fisher, 2019). In response to activation of GPCR, the conformation of GDP-bound inactive Ga_{12/13} is transformed into the active form with GTP binding, triggering the dissociation of Ga_{12/13} from G\(\beta\)G\(\gamma\) and activation of downstream effectors (Arthofer et al., 2016). After dissociation, free G\(\beta\)G\(\gamma\) subunits transmit signals through regulating canonical effectors, including adenylyl cyclase, PLC, and various ion channels (Senarath et al., 2018). G\(\beta\)G\(\gamma\) 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 G\(\beta\)G\(\gamma\) subunits in mammal cells define much of the diversity that occurs within GPCR signaling with respect to spatial and temporal bias and are extensively involved in the pathogenesis of diseases (Masuho et al., 2021). G\(\beta\)G\(\gamma\) signaling has been previously well summarized.

Although G\(\beta\)G\(\gamma\)-mediated effects of GPCR signaling are diverse, the assorted isoforms of Ga also have a wide variety of influences. These varied functions are highly related to their structures. Under present consideration, Ga_{13} 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 Ga_{12} isoform 2 and 3 have distinct 5’ untranslated region and 3’ coding region for different N-termini. The isoform 4 of Ga_{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. Ga_{13} has two isoforms, of which isoform 1 is the longer isoform containing 377 amino acids. The isoform 2 of Ga_{13} uses an alternative 5’ exons resulting in a downstream start codon AUG. Thus, the encoded isoform 2 of Ga_{13} has a shorter N-terminus than the isoform 1. The isoform sequences of Ga_{12} or Ga_{13} show similar structural domains, including an adenylyl cyclase binding site, a \(\beta\)-\(\gamma\) 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 Ga_{12} or Ga_{13}.

While literature clearly show that Ga_{12/13} has different functions from other Ga subtypes, the functional difference between the isoforms of Ga_{12} and Ga_{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 Ga_{12/13}

Ga_{12/13} has been shown to couple to more than 30 GPCRs. Activated by various upstream stimuli, Ga_{12/13} can transmit to divergent downstream signaling pathways and regulates cell function in pathophysiologial processes (Ackerman et al., 2015; Yung et al., 2017; Yanagida et al., 2018; Spoerri et al., 2020). Ga_{12} and Ga_{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 Ga_{12} or Ga_{13} (Ayoub and Pin, 2013; Yung et al., 2017; Mackenzie et al., 2019). Moreover, non-GPCRs are also shown to couple to Ga_{12} and Ga_{13} (Shen et al., 2013; Shen et al., 2015; Piccinin et al., 2019) (Table 1).

### GPCRs Triggered Ga_{12/13} Signaling

**Lysophosphatidic Acid Receptors**

Lysosphosphatidic acid (LPA) is a biologically active phospholipid, which mediates various biological functions through six homologous LPA receptors (LAPRs) (Plastira et al., 2020). Activated LAPRs promote Ga_{12}, but not Ga_{13}, association with v-raf murine sarcoma viral oncogene homolog A which than activates ERK. The activated ERK promotes ring
finger and FYVE like domain-containing E3 ubiquitin protein ligase transcription and fibroblast migration (Gan et al., 2013). LPAR-Gα12/13 signaling also plays an important role in embryonic blood vessel development (Tanaka et al., 2006). Additionally, LPAR1/2 couple with Gαi/o, Gαq/11, as well as Gα12/13 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 Gα12/13 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 Gα12/13-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-Gα12/13 pathway (Lee et al., 2006). As of today, there is no evidence supporting a coupling between LPAR3 and Gα12/13.

**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 Gα12/13 and does not interact with other subunits of the G protein family. The complex formed by FZD4 and Gα12/13 is dissociated under WNT stimulation. The FZD4-Gα12/13 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 Gα12/13. 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-Gα13 complex dissociates under WNT5a/7a stimulation, and Gα13 transmits a signal to YAP/TAZ through Rho family members (Hot et al., 2017). In osteoblasts, WNT family member 16 binds to...
FZD receptors to activate canonical WNT signaling and non-canonical Ga12/13 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 αβ1 through Gpβ and PI3K to induce fibronectin binding and initiate cell adhesion. PAR1/2 also send signals through Ga13, Gaα, ROCK, and Src to enhance integrin αβ-mediated adhesion (Spoerri et al., 2020). The PAR1-mediated Ga12/13 activation stimulates RhoGEF and simultaneously activates the RhoA-ROCK pathway and myosin light chain (Flaumenhaft and De Ceunynck, 2017).

### Table 1: List of biologically significant Ga12/13-associated receptors and their physiological functions.

| Receptors | G proteins | Functions | References |
|-----------|------------|-----------|------------|
| LPA receptor | Ga12 | Migration of fibroblasts | Gan et al. (2013) |
| LPA receptor | Ga12/13 | Embryonic blood vessel development | Tanaka et al. (2006) |
| LPAR1 | Ga12 | Proliferation of astrocytes | Loskutov et al. (2018) |
| LPAR1/LPAR2 | Ga12/13 | Cell proliferation, migration, and cytoskeleton changes | Kihara et al. (2014) |
| LPAR4/LPAR6 | Ga12/13 | Changes in the tension of the actin cytoskeleton | (Noguchi et al., 2003, Yanagida et al. 2009) |
| LPAR5 | Ga12 | Angiogenesis | Yasuda et al. (2019) |
| LTA4 | Ga12/13 | Aneur retraction and stress fiber formation | Lee et al. (2006) |
| FZD | Ga12/13 | Bone formation and cell migration | Park et al. (2015) |
| FZD10 | Ga10 | Angiogenesis | Arthoe et al. (2017) |
| PAR1/PAR2 | Ga13 | Fibroblast adhesion maturation, spreading, and migration | Spoerri et al. (2020) |
| PAR1 | Ga12/13 | Stress fiber formation | Regué et al. (2013) |
| PAR2 | Ga13 | Smooth muscle contraction | Srivai et al. (2013) |
| S1PR1/S1PR3/S1PR5 | Ga12 | Inflammation | Ki et al. (2007) |
| S1PR2 | Ga12/13 | Vascular smooth muscle cell migration and neointimal hyperplasia | Kim et al. (2011) |
| S1PR2 | Ga12 | Myofibroblastic contraction | Sobel et al. (2015) |
| S1PR2 | Ga12 | Cardiomyocyte migration | Ye and Lin (2013) |
| S1PR2/S1PR3 | Ga12/13 | Stress fiber formation | Oliveira et al. (2003) |
| S1PR2/S1PR3 | Ga12/13 | Cardiac progenitor cell proliferation | Castaldi et al. (2016) |
| S1PR3 | Ga12 | Inflammation | Dusaban et al. (2017) |
| S1PR3 | Ga13 | Cardioprotection | Yang et al. (2017) |
| M1R | Ga13 | Impaired growth | Sabbir et al. (2018) |
| M3R | Ga12 | Human airway smooth muscle cells contraction | Yoo et al. (2017) |
| CXCR4 | Ga13 | Tumor cell migration and adhesion | Scarlett et al. (2018) |
| CXCR4 | Ga13 | Breast cancer metastasis | Yagi et al. (2011) |
| Calcium-sensing receptor | Ga12/13 | Gene expression, cytoskeleton, and cell shape | Leach et al. (2012), Leach et al. (2013) |
| AT1R | Ga12/13 | Vasoinhibition | Lymeropoulos et al. (2021) |
| Thromboxane A2 receptor | Ga12/13 | Neointima formation and restenosis | Feng et al. (2016) |
| Ghrelin receptor | Ga12 | Food intake | Mende et al. (2018) |
| Dopamine D3 receptor | Ga12 | Inhibit inflammation | Wang et al. (2015) |
| 5-HT4R | Ga13 | Hippocampal synaptic function | Muller et al. (2021) |
| 5-HT2A | Ga13 | Angiogenesis | Proftrovic et al. (2013) |
| Urt receptor | Ga13 | Tumor invasion | Lecomte et al. (2015) |
| Complement C5a receptor | Ga12/13 | Macrophage tail retraction | Raghavan et al. (2018) |
| GPR15 | Ga13 | Myelination | Ackerman et al. (2015) |
| Purinergic receptor 6 | Ga13 | Cell migration | Girard et al. (2020) |
| Gastrin type 2 cholecystokinin receptor | Ga13 | Cell migration | Masia-Balagué et al. (2015) |
| GPR40 | Ga12 | Release of insulin vesicles | Rives et al. (2018) |
| GPR56 | Ga12 | Muscle protein synthesis and myotube hypertrophy | White et al. (2014) |
| GPR91 | Ga12/13 | Mitochondrial fission and cell migration | Ko et al. (2017) |
| ET-1 type A receptor | Ga12/13 | Formation of myofibroblasts | Nishida et al. (2007) |

**Non-GPCRs**

| Receptors | Ga13 | Function | References |
|-----------|------|----------|------------|
| Integrin β1 | Ga13 | Cell migration | Shen et al. (2013), Shen et al. (2015) |
| Integrin αβ | Ga13 | Cell retraction and migration | Gong et al. (2010) |
| Integrin αβ | Ga13 | Promote thrombosis | Pang et al. (2018) |
| PPARγ | Ga13 | Inhibit thrombosis | Unsworth et al. (2017) |
| Smoothened | Ga12 | Tumor growth and anti-apoptosis | Qu et al. (2013) |
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/Gα13, 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 Gα12/13.

Sphingosine 1-Phosphate Receptors
Sphingosine 1-phosphate (SIP) is a natural biologically active lipid molecule that binds to five different SIP receptors (SIPR1-5). Activated SIPRs couple with Gα12/13 to induce downstream signals (Zhang et al., 2020). An earlier study shows that SIPR2/SIPR3 couple to Gα12 and activate the c-Jun N-terminal kinase (JNK)-nuclear factor-kappa B (NF-kB) pathway to promote the expression of cyclooxygenase-2 and accelerate local inflammation (Ki et al., 2007). SIPR3 activates the Gα12/13-RhoA pathway and promotes the expression of inflammatory gene in astrocytes (Dusaban et al., 2017). SIPR3 activates Gα13-RhoA in cardiomyocytes and mediates cardioprotection during ischemia/reperfusion (I/R) (Yung et al., 2017).

In vascular smooth muscle cells, SIPR2 couples to Gα12/13 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). SIPR2 also induces the contraction of myofibroblasts through the Gα12/13-Rho-ROCK pathway (Sobel et al., 2015). Moreover, Gα13, activated by SIPR2, is recruited to E-cadherin to form a complex after mechanical stress. Gα12 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 Gα13 and Gβγ (Sabbir et al., 2018). Gα13 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 Gα12 in HEK-293 cells (Rümenapp et al., 2001). It has also been found that Gα12 binds to M3R in human airway smooth muscle cells. The M3R-Gα12 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 Gα13, 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 Gα13 to initiate cell motility and trans-endothelial migration (Yagi et al., 2011).

Non-GPCRs Triggered Gα12/13 Signaling
Integrin “outside-in” signaling requires Gα13 and monomeric small G proteins (i.e., Rho) to mediate cell retraction, migration, and spreading (Shen et al., 2012). Gα13 directly binds to the ExE motif in the cytoplasmic domain of the integrin β3 subunits, which is important in transducing the “outside-in” integrin signaling (Shen et al., 2013). Gα13 also binds to the cytoplasmic domain of the integrin β1 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 Gα13 reduces α5β3-dependent activation of c-Src, inhibits cell migration, and accelerates cell contraction, thereby spreading platelets on fibrinogen (Gong et al., 2010). Integrin α5β3 also serves as a mechanical sensor that transmits “outside-in” signals through Gα13-Src-Rac1-dependent pathways in platelets and facilitates coagulation in vitro and intravascularly in vivo (Pang et al., 2018). Therefore, the Gα13-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 Gα13 and integrin β3, which prevents c-Src-dependent integrin β3 phosphorylation and talin dissociation and weakens the downstream signal transduction of integrin α5β3, thereby regulating platelet activation and reducing thrombosis (Unsworth et al., 2017). Moreover, in diffuse large B-cell lymphoma (DLBCL), smoothened recruits Gα13 and Gα12 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-kB, tumor growth, and anti-apoptosis (Qu et al., 2013).

Gα12/13 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 (Gαq/11, Gαi/o, Gα12/13, and Gαq) (Abid et al., 2021). The ligands NPS-2143/NPS-R568 binds to a calcium-sensing receptor to specifically mediate the activation of Gα12/13-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 Gαq-coupled GPCR, is activated by prostaglandin F2α (Pathe-neuschäfer-rube et al., 2005). PDCI13.824 acts on the prostaglandin F2α receptor, which biasedly increases Gαq-PKC-ERK1/2 signaling while inhibiting Gα12-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 Gαq/11, Gα12/13, and Gαq/11, Gα12/13 (Kim et al., 2018b). Among PAR2 antagonists, I-287 inhibits Gαq, but biasedly activates Gα12/13 without affecting Gαq/11 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 Gαq, Gαq/11, Gα12/13, and β-arrestin (Hedegaard and Holst, 2020). The biased ligand YIL781 selectively activates Gαq/11 and Gα12/13 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 (AT1, R) causes AT1, R interaction with Gαq/11, Gα12/13, and Gαi/o, depending on cell type (Forrester et al., 2018). When Ang II stimulates vascular smooth muscle cells, AT1, R binds to Gα12/13 instead of Gαq/11 to activate RhoA-ROCK and promote vasoconstriction (Lymeropoulos 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 Gαq/11, Gα12/13, Gαi/o, and Gαq families. The activation of matrix metalloproteinase-1 in platelets cleaves the N-terminal extracellular domain of PAR1, activating the Gα12/13-Rho-MAPK signal instead of Gαq/11, and promotes cell shape changes and platelet thrombosis (Trivedi et al., 2009).

Gα12/13 Signaling and Cell Function

As discussed above, the well-characterized downstream effector of active Gα12/13 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

Gα12/13 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 Gα12/13 can promote mitotic 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 Gα12/13 coupling with several different receptor types promotes proliferation. SIP activates S1PR2/3 to trigger Gα12/13-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 Gα12/13. 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 Gα12/13 augmenting mitogenic signaling and cell proliferation (Loskutov et al., 2018). Furthermore, the acetylcholine signaling via M1R activates Gα13 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 Gα12/13 to mediate RhoA signaling and regulates zebrafish oligodendrocytes’ development and subsequent myelination (Ackerman et al., 2015).

Gα12/13 is also very important in the proliferation of tumor cells. The activation of Gα12/13 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-Gα12/13 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)-Gα12/13-Rho-NF-kB signaling cascade. Subsequently, the activated NF-kB 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 Gα13-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, Gα13 dynamically regulates the RhoA signaling through the combination of RhoGEF GTPase and integrin β1, promoting integrin β1-mediated proliferation of CHO cell lines (Shen et al., 2015). In addition to autophagy-mediated
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-\(\kappa\)B, 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-Kaulil 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\(_7\)R) 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\(_7\)R 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 G\(\alpha\) subunits and an important partner of G\(\alpha_i\), G\(\alpha_q\), and G\(\alpha_{13}\) proteins (Papasegri-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 Ga12/13 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 Gaq–Ca2+–PKCa and Ga13–ROCK signals, regulating cell migration (Girard et al., 2020). The GRPR–Ga13–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, Ga12/13 signal facilitates the invasion of human cervical cancer cells through a RhoA–ROCK–JNK signal axis (Yuan et al., 2016). Ga12/13 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). Ga12, 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 Ga12-mediated pathway promotes metastasis and invasion of human nasopharyngeal carcinoma cells by regulating the reorganization of the actin cytoskeleton (Liu et al., 2009).

Increased Ga12/13 mediated cell migration also greatly contributes to primary solid tumor growth. Take as example that Ga13, 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, Ga13 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). Ga13 is also involved in cell fusion (Carloni et al., 2013). Disintegrins and metalloproteinases stimulate Ga13 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 Ga12/13–RhoA signaling in cell proliferation or migration. The expression of Ga12/13 and the downstream signaling are often elevated in cancer cells. However, in some disease states (especially cancer), the upstream ligand and receptor of Ga12/13 remain unknown.

**Immune Cell Function**

Due to the lack of specific inhibitors of Ga12/13, the research of Ga12/13 in immune cells was stagnant for many years. However, with various transgenic models, the studies on the role of Ga12/13 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, Ga12/13 regulates actin polymerization and contributes to cell adhesion and migration (Wang et al., 2013). A recent study has found that Ga13, RhoA–ROCK2 signaling plays a key regulatory role in the differentiation and function of early Th cells. The Ga13-deficient Th cells impair the function of adhering B cells to form conjugates and stimulating B cells to produce immunoglobulins (Kuen et al., 2021). Moreover, receptors coupled to Ga12/13 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 Th cells by directing co-localization with B cells in the germinal center; and the deficiency of S1PR2 in Th cells inhibits the retention in lymph nodes (Moriyama et al., 2014). In response to the stimulation of CXCL12, the Ga13–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–Ga13–Rho signal axis (Tan et al., 2006). Meanwhile, Ga12/13 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 Ga13 to mediate the activation of SRF transcriptional activity (Huang et al., 2013). Conversely, Ga13 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, Ga13, but not Ga12, 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–Ga12/13–Arhgef1 pathway, inhibiting the release of calcium stored in the cell and the antibody response (Hu et al., 2014). Ga12/13 also regulates the maturation, migration, and polarization of marginal zone B cells. In mice with depletion of Ga12/13 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 Ga13 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, Ga13 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 Ga13 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 Ga12/13–RhoA axis inhibits the growth of B cells needs to be further explored.
Macrophages
In macrophages, complement C5a couples to Ga12/13 to activate Rho GTPases and tail retraction in migrating cells. Macrophages without Ga12/13 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-Gα signaling and facilitates atherosclerosis (Raghavan et al., 2018). Thrombin also induces the migration of monocytes or macrophages through the PAR1-Gα12 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 Gaα12, Gaαq, and Gaα13, but not Gaα12, leading to anemia and leukocytosis (Boularan et al., 2015).

The above studies suggest that dysregulation of Ga12 or Ga13 in immune cells may lead to pathophysiological consequences, such as cancer and autoimmunity. So far, the research of Gaα12/13 in immune cells is relatively scarce. More research is needed to bring new therapeutic targets for cancers and autoimmune diseases.

Ga12/13 Signaling and Diseases
Ga12/13 plays an important role in multiple stages of disease development in different tissues and organs. An increasing number of cancers have shown overexpressed Ga12/13, which is correlated to abnormal cell proliferation, metastasis, and invasion (Montgomery et al., 2014). The high abundance or constitutive activation of Gaα12 and Gaα13 are effective stimulators of oncogenic transformation. Ga12/13 also interacts with cell surface GPCRs and participates in the inflammation regulation (Dusaban et al., 2013; Hou et al., 2021). Meanwhile, Gaα12/13 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 Gaα12/13 regulates the progression of these diseases has not been fully elucidated.

Ga12/13 and Cancer
Ga12/13 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, Gaα12/13 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 Ga12/13 contribute to the pathogenesis of different cancers. The copy number of GNA12 is significantly increased in ovarian cancer, which enhances the function of Ga12 to promote cancer growth and metastasis (Wu et al., 2019). In two prostate cancer cell lines (C4-2B and PC3), both Gaα12 and Gaα13 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 Gaα13 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 Gaα13, which promotes cell proliferation, metastasis, and epithelial cell-mesenchymal transition (Li et al., 2021). Moreover, Gaα13-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 Gaα13–Hippo signaling as a potential target for cancer therapeutic interventions.

A few GPCR ligands have been identified upstream of Ga12/13 in cancers. LPA promotes the combination of Gaα12 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 Gaα12-ROCK signaling 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-Gα12/13-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 Gaα13 through the gastrin type 2 cholecystokinin receptor in colon cancer cells. The recruitment of p190RhoGEF by Gaα13 enhances the phosphorylation of FAK and paxillin, leading to RhoA activation and promoting the migration of cancer cells (Masía-Balagué et al., 2015). In addition, the down-regulated GPR65 in a variety of hematological malignancies promotes Gaα12/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). Gaα13 binds to CXCR5 in response to CXCL13 treatment and promotes prostate cancer cell proliferation (Liu et al., 2013).
movements; however, silencing Ga13 does not affect CXCL13-dependent cell invasion (El-Haibi et al., 2013).

Interestingly, the Ga13-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 Ga13 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 Ga13 signaling, SIP acts through S1PR3 to promote mouse germinal center B cells migration into the circulation (Muppidi et al., 2015). S1PR2 signals through Ga13 to induce tumor cell apoptosis and exert its tumor suppressor function (Flori et al., 2016). However, in DLBCL, the forhead protein 1 directly inhibits S1PR2 and promotes tumor cell survival (Flori et al., 2016). The restoration and activation of the Ga13-Rho pathway help reduce tumor growth and progression, supporting that the Ga13-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 Ga12/13 in cancers, many questions remain about how the ligands and receptors trigger Ga12 or Ga13 signaling in a cancer type-specific manner. A comprehensive understanding of these mechanisms may provide a promising prospect for targeting specific Ga12/13 signaling processes in cancer therapies.

**Ga12/13 and Inflammation**

Ga12/13 has been implicated in both induction and suppression of inflammation. In the context of inflammation, thrombin, LPA, and SIP transmit signals through Ga12/13-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 Ga12/13 signaling and arachidonic acid in cells (Dermott et al., 1999; Mariggiò et al., 2006). NIH-3T3 cells transformed with Ga12/QL show increased secretion of arachidonic acid and transcriptional activation of cyclooxygenase-2 (Dermott et al., 1999). Thrombin stimulates CHO cells to activate the Ga13-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 Ga12/13-RhoA-PLCε-protein kinase D (PKD)-NF-κB signaling, which contributes to neuroinflammation (Dusaban et al., 2013).

Recent work has shown that SIP promotes the NLRP3 inflammasome-mediated inflammatory response and the secretion of pro-inflammatory cytokines such as interleukin-1β and interleukin-18 through the S1PR2-Ga12/13-RhoA-PLCε pathway (Hou et al., 2021). Meanwhile, a variety of pro-inflammatory ligands promote the interaction of Ga13 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 Ga13 in leukocytes and platelets inhibits thrombosis and inflammation and significantly optimizes the survival rate of septic mice (Cheng et al., 2021).

Ga12 and Ga13 have opposite effects on osteoclasts. The silencing of Ga13 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 Ga13 is the main endogenous negative switch for osteoclast production. Ga13 also protects against various bone loss disease models from inflammation (Wu et al., 2017; Nakano et al., 2019). In comparison, a study has shown Ga12 is involved in the pathophysioloogy of bone diseases such as osteoporosis or rheumatoid arthritis (Song et al., 2018). Interestingly, the volume of trabecular bone increases in Ga12 knockout mice, whereas the number of osteoclasts decreases, contrary to the phenotype of Ga13 deletion (Song et al., 2018). The underlying mechanisms of these opposite phenotypes are unclear, possibly because that Ga12/13 mice are whole body knocked out, whereas Ga13 mice undergo an osteoclast lineage-specific conditional knockout.

**Ga12/13 and Metabolic Diseases**

Ga12 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 Ga12 in the liver (Kim et al., 2018a). Ga12-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 Ga12 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). Ga12 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, Ga12 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 Ga12 at the export site of the endoplasmic reticulum, promoting cargo export and inhibiting protein synthesis (Subramanian et al., 2019).

The role of Ga13 in energy metabolism has opposite effects in skeletal muscle (prodiabetic) and liver (antidiabetic) (Koo et al., 2017; Kim et al., 2019). Ga13 is more highly expressed in skeletal muscle than other metabolic organs (Koo et al., 2017). The
knockout Ga\textsubscript{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 Ga\textsubscript{13} in skeletal muscle is reduced by exercise but is increased under conditions of metabolic diseases. Loss of Ga\textsubscript{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 Ga\textsubscript{13} in the liver of mice leads to the overproduction of inter-alpa-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 \( \beta \) cells through GPR40-mediated Ga\textsubscript{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 Ga\textsubscript{12/13} and promotes muscle protein synthesis and myotube hypertrophy (White et al., 2014). Succinate activates the Ga\textsubscript{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 Ga\textsubscript{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-Ga\textsubscript{12/13} axis can be an attractive target for treating metabolic diseases.

**Ga\textsubscript{12/13} and Fibrotic Diseases**

Ga\textsubscript{12/13} has a pro-fibrotic effect mainly mediated by the RhoA-ROCK activation (Haak et al., 2020). Early studies have demonstrated that Ga\textsubscript{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\textsubscript{1}R-Ga\textsubscript{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 Ga\textsubscript{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-Ga\textsubscript{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 osteoecytin in the heart binds to LPA3 and mediates the Ga\textsubscript{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, Ga\textsubscript{12} is expressed abundantly in hepatic stellate cells of the fibrotic liver, whereas Ga\textsubscript{13} is not (Kim et al., 2018c). The imbalance of miR-16 in hepatic stellate cells leads to the overexpression of Ga\textsubscript{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 Ga\textsubscript{12} significantly blocks bleomycin-induced pulmonary fibrosis in mice. LPA stimulates the phosphorylation and activation of PKC-\( \delta \) through Ga\textsubscript{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 Ga\textsubscript{12} or Ga\textsubscript{13} in fibrotic diseases is unclear. Using various omics (e.g., genomics, proteomics) to detect the expression of Ga\textsubscript{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.

**Ga\textsubscript{12/13} and Circulatory and Renal Disorders**

Ga\textsubscript{12} 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\textsubscript{1}R-Ga\textsubscript{12/13}-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 Ga\textsubscript{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 Ga\textsubscript{13} and receptor-interacting protein kinase 3. Receptor-interacting protein kinase 3 participates in the integrin-Ga\textsubscript{13} signal to promote platelet activation and thrombosis (Zhang et al., 2017). The newly developed high-load ExE peptide nanoparticles, based on the Ga\textsubscript{13} binding ExE motif on the cytoplasmic domain of integrin \( \beta 3 \), inhibit thrombosis and protect mice from cardiac I/R injury (Pang et al., 2020). This study supports that the integrin-Ga\textsubscript{13}-RhoA-YAP pathway can be targeted for anti-atherosclerosis therapy (Wang et al., 2016).

Inhibiting proteins that specifically interact with Ga\textsubscript{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 Ga\textsubscript{12/13}-mediated calcium-dependent contraction to Ga\textsubscript{12/13} mediated RhoA-ROCK 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). Ga\textsubscript{12/13} are also essential for blood vessel formation. Ga\textsubscript{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).

Ga\textsubscript{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. Ga\textsubscript{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 Ga\textsubscript{12} in renal I/R.
Coupling to Ga_{12/13} is also necessary for the development of a mouse renal cyst model induced by polycystin-1 mutation. The lack of polycystin-1 model promotes the activation of Ga_{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 Ga_{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 Ga_{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 Ga_{12/13} and the impacts on the pathophysiology have not been fully elucidated. The identification of the reciprocal binding domains of Ga_{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 Ga_{12/13} signaling may lead to novel therapeutics targeting specific functions of Ga_{12} or Ga_{13} in a disease-specific manner.

**CONCLUSION**

The mechanisms of signal transduction through Ga_{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-Ga_{12/13} interaction (Montgomery et al., 2014; Lymeropoulos et al., 2021)? What determines the specific selectivity of the receptor to Ga_{12} or Ga_{13} (Corbiser et al., 2015; Mackenzie et al., 2019)? Do receptor and Ga_{12/13} form a pre-coupling complex (Ayoub et al., 2012; Zhang et al., 2017)? The importance of Ga_{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. Ga_{12/13} are pathologically relevant to cancer, bone diseases, liver steatosis, and pulmonary fibrosis. Ga_{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 Ga_{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 Ga_{12} or Ga_{13} in specific organs/cells may offer a chance of successful therapy. A better understanding of the ligand-receptor-Ga_{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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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