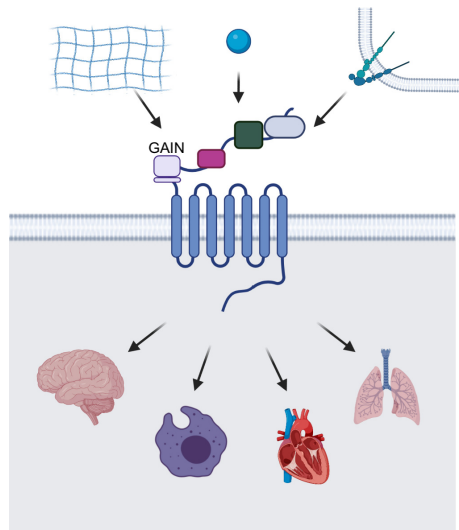# ADHESION G PROTEIN-COUPLED RECEPTORS: STRUCTURE, SIGNALING, PHYSIOLOGY, AND PATHOPHYSIOLOGY

Adhesion G Protein-Coupled Receptors: Structure, Signaling, Physiology and Pathophysiology

Adhesion GPCRs control diverse aspects of physiology and also play key roles in the pathophysiology of a variety of disorders by integrating heterogeneous signaling modailities. Elucidation of the signaling mechanisms and physiological actions of these receptors can lead to a better understanding of normal physiology and also promote the development of novel therapeutics for treating human disease.

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CLINICAL HIGHLIGHTS

This review article details key concepts and recent advances in adhesion GPCR (AGPCR) research. Dysfunction of AGPCRs has been implicated in a wide variety of human disorders. For example, mutations in ADGRV1 (VLGR1) underlie Usher syndrome type 2C, a common cause of deafness and blindness, and mutations in ADGRG1 (GPR56) result in bilateral frontoparietal polymicrogyria, a disease of cerebral cortex wiring. Additionally, dysregulation of AGPCR expression has been linked to a variety of human cancers. Thus, investigations into the fundamental physiology of AGPCRs may shed light on novel treatment avenues for AGPCR-linked disorders. Relevant to this goal, the past few years have witnessed the development of the first-ever small-molecule drugs targeting AGPCRs. Unraveling the mysteries of the AGPCR family will provide insights into many different aspects of normal physiology while also paving the way for novel therapeutic approaches in the treatment of human disease.

ADHESION G PROTEIN-COUPLED RECEPTORS: STRUCTURE, SIGNALING, PHYSIOLOGY, AND PATHOPHYSIOLOGY

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Abstract

Adhesion G protein-coupled receptors (AGPCRs) are a family of 33 receptors in humans exhibiting a conserved general structure but diverse expression patterns and physiological functions. The large NH_2 termini characteristic of AGPCRs confer unique properties to each receptor and possess a variety of distinct domains that can bind to a diverse array of extracellular proteins and components of the extracellular matrix. The traditional view of AGPCRs, as implied by their name, is that their core function is the mediation of adhesion. In recent years, though, many surprising advances have been made regarding AGPCR signaling mechanisms, activation by mechanosensory forces, and stimulation by small-molecule ligands such as steroid hormones and bioactive lipids. Thus, a new view of AGPCRs has begun to emerge in which these receptors are seen as massive signaling platforms that are crucial for the integration of adhesive, mechanosensory, and chemical stimuli. This review article describes the recent advances that have led to this new understanding of AGPCR function and also discusses new insights into the physiological actions of these receptors as well as their roles in human disease.

brain; cancer; cardiovascular; diabetes; immune

CLINICAL HIGHLIGHTS

This review article details key concepts and recent advances in adhesion GPCR (AGPCR) research. Dysfunction of AGPCRs has been implicated in a wide variety of human disorders. For example, mutations in ADGRV1 (VLGR1) underlie Usher syndrome type 2C, a common cause of deafness and blindness, and mutations in ADGRG1 (GPR56) result in bilateral frontoparietal polymicrogyria, a disease of cerebral cortex wiring. Additionally, dysregulation of AGPCR expression has been linked to a variety of human cancers. Thus, investigations into the fundamental physiology of AGPCRs may shed light on novel treatment avenues for AGPCR-linked disorders. Relevant to this goal, the past few years have witnessed the development of the first-ever small-molecule drugs targeting AGPCRs. Unraveling the mysteries of the AGPCR family will provide insights into many different aspects of normal physiology while also paving the way for novel therapeutic approaches in the treatment of human disease.

1. INTRODUCTION

G protein-coupled receptors (GPCRs) are the largest superfamily of cell surface receptors, featuring >750 members in mammalian genomes. Mammalian GPCRs have typically been classified as either Rhodopsin-like, Secretin-like, Glutamate-like, or Frizzled-like (1). In this classification system, adhesion GPCRs (AGPCRs), marked by their large NH_2 termini containing various adhesion domains, are part of the Secretin-like family. Evolutionary studies have revealed that AGPCRs are an ancient family, predicted to have appeared ~1,275 million years ago, although these prehistoric AGPCRs generally had shorter NH_2 termini (2). Elongation of the receptors' NH_2 termini may have been prompted by a need for increased interactions with the

extracellular environment, necessitating receptors with larger extracellular domains (3). These evolutionary studies on AGPCRs have prompted suggestions that AGPCRs should represent their own family of GPCRs, as in the "GRAFS" classification system, which divides GPCRs into Glutamate, Rhodopsin, Adhesion, Frizzled, and Secretin families (4).

There are 33 AGPCR genes expressed in humans, and the traditional names for many of these receptors are idiosyncratic, relating to details associated with the initial discovery of each receptor. Several years ago, the Human Gene Nomenclature Committee worked with

the International Union of Basic and Clinical Pharmacology (IUPHAR) and the Adhesion GPCR Consortium to develop a unified nomenclature for AGPCRs. In this official nomenclature, the name of each family member begins with "ADGR," a unique prefix referring to "adhesion G protein-coupled receptor" (**TABLE 1**). ADGR is then followed by letters and numbers relating to the receptors' subfamilies (5). In situations where a receptor's name is used repeatedly in written articles or oral presentations, the "ADGR" can be dropped and the last letter and number can be used alone for ease of reference (i.e., ADGRB1 can be referred to simply as "B1"). This nomenclature is used in this review, along with references to the receptors' traditional names at the first mention of each receptor in each section.

The general structural features of most AGPCRs include an extracellular NH_2-terminal domain, a GPCR autoproteolysis-inducing (GAIN) domain, the seven-transmembrane (7TM) domain common to all GPCRs, and a cytoplasmic COOH terminus (**FIGURE 1**). The domain architectures of the large NH_2 termini of AGPCRs have led to the categorization of the 33 family members into nine subfamilies based on the conserved domains: ADGRL (group 1, latrophilins; LPHNs), ADGRE (group 2, EMRs), ADGRA (group 3), ADGRC (group 4, CELSRs), ADGRD (group 5), ADGRF (group 6), ADGRB (group 7, BAIs), ADGRG (group 8), and ADGRV (group 9, GPR98). Although this classification system is based on sequence homology and domain conservation, recent analyses have questioned whether this system might need to be reevaluated (6).

2. STRUCTURE OF ADHESION GPCRs

Most AGPCRs possess large extracellular NH_2-terminal domains hundreds to thousands of residues in length, in addition to membrane-spanning seven-transmembrane (7TM) domains and intracellular COOH-terminal domains (7). Almost all AGPCRs contain GPCR autoproteolysis-inducing (GAIN) domains in the juxtamembrane region of their NH_2 termini, and these domains possess intrinsic autoproteolytic activity (8). After self-cleavage of the GAIN domain, adhesion GPCRs exist as two fragments that remain noncovalently associated for at least some period: an NH_2-terminal fragment (NTF), which consists of the NH_2 terminus up to the site of GAIN domain cleavage, and a COOH-terminal fragment (CTF), which comprises the 7TM region plus the intracellular domains and the small extracellular NH_2-terminal stalk that remains after cleavage of the GAIN domain.

Over the past decade, there has been a major push to understand the structures of AGPCRs in greater detail. In 2012, X-ray crystal structures of the GAIN

domains from several adhesion GPCRs provided the first high-resolution look at the structures of these domains (9). Subsequent X-ray crystallography studies provided novel insights into the structures of the extracellular regions (GAIN domains plus other NTF domains) from ADGRG1 (GPR56) (10) and ADGRG6 (GPR126) (11). X-ray crystallography experiments have also visualized the associations of portions of the ADGRL1–3 (latrophilin-1 to -3) NTFs with their binding partners FLRT2 (12) and teneurin-2 (13), and, independently, cryo-electron microscopy (cryo-EM) studies have provided a look at the interaction of ADGRL3 (latrophilin-2) with teneurin-2 (14).

Most recently, cryo-EM studies have yielded new insights into the structure of full-length ADGRG3 (GPR97), including images of the receptor coupled to its preferred G protein, $G\alpha o$, with this work representing the first-ever view of an AGPCR-G protein complex (15). One interesting aspect of this structure was that all three intracellular loops of G3 were found to have extensive interactions with the G protein heterotrimer, which is unusual relative to other GPCR-G protein structures that have been solved to date (16). Interestingly, it is known from previous biochemical studies that adhesion GPCRs form surprisingly stable complexes with their cognate G proteins, such that AGPCR-G protein complexes often can be easily immunoprecipitated together without the need for chemical cross linking (17, 18). The recent ADGRG3-$G\alpha o$ structure provides insight into the remarkably robust associations of active AGPCRs with the G proteins to which they couple.

Many important questions remain to be answered in future AGPCR structural studies. For example, the ADGRG3-$G\alpha o$ cryo-EM experiments were performed using a version of G3 with a mutation in the GAIN domain to prevent autoproteolysis (15). Furthermore, the conditions of these experiments did not allow for high-resolution visualization of the ADGRG3 NTF. Thus, no insights can be obtained from these studies about the relationship between the receptor's NTF and CTF after GAIN domain cleavage. Additionally, the palmitoylation on the COOH terminus of $G\alpha o$ was found in these studies to be inserted directly into the ADGRG3 7TM core, a feature of the ADGRG3-$G\alpha o$ complex that has not been observed for other GPCR-G protein interactions (15). Most $G\alpha$ subunits have lipid modifications, but these lipid groups do not typically make direct contacts with receptors. Future work will be necessary to determine whether this unusual mode of receptor-G protein association is common to other AGPCRs or unique to the ADGRG3-$G\alpha o$ complex.

2.1. Autoproteolysis of AGPCRs

Adhesion GPCRs can autoproteolytically cleave themselves at the GPCR proteolysis site (GPS), which is part

Table 1. *Annotated names and chromosomal locations of AGPCRs*

ADG Nomenclature Name	Alternative Name(s)	Human Gene ID	Location (chromosome)	Exon Count
ADGRA1	GPR123	84435	10q26.3	9
ADGRA2	GPR124	25960	8p11.23	19
ADGRA3	GPR125	166647	4p15.2	21
ADGRB1	BAI1	575	8q24.3	35
ADGRB2	BAI2	576	1p35.2	32
ADGRB3	BAI3	577	6q12-q13	32
ADGRC1	CELSR1	9620	22q13.31	38
ADGRC2	CELSR2	1952	1p13.3	34
ADGRC3	CELSR3	1951	3p21.31	35
ADGRD1	GPR133/PGR25	283383	12q24.33	30
ADGRD2	GPR144/PGR24	347088	9q33.3	21
ADGRE1	EMR1/TM7LN3	2015	19p13.3-p13.2	23
ADGRE2	CD97/VBU/EMR2/CD312	30817	19p13.12	24
ADGRE3	EMR3	84658	19p13.12	17
ADGRE5	CD97/TM7LN1	976	19p13.12	20
ADGRF1	PGR19; GPR110; KPG_012; hGPCR36	266977	6p12.3; 6	16
ADGRF2	GPR111, PGR20, hGPCR35	222611	6p12.3	12
ADGRF3	GPR113, PGR23	165082	2p23.3	19
ADGRF4	GPR115, PGR18	221393	6p12.3	10
ADGRF5	GPR116, KPG_001	221395	6p12.3	25
ADGRG1	BFPP, BPPR, GPR56, TM7LN4, TM7XN1	9289	16q21	23
ADGRG2	CBAVDX, EDDM6, GPR64, HE6, TM7LN2	10149	Xp22.13	32
ADGRG3	GPR97, PB99, PGR26	222487	16q21	13
ADGRG4	GPR112, PGR17, RP1-299I16	139378	Xq26.3	28
ADGRG5	GPR114, PGR27	221188	16q21	13
ADGRG6	APG1, DREG, GPR126, LCCS9, PR126, PS1TP2, VIGR	57211	6q24.2	28
ADGRG7	GPR128	84873	3q12.2	16
ADGRL1	CIRL1, CL1, LEC2, LPHN1	22859	19p13.12	27
ADGRL2	CIRL2, CL2, LEC1, LPHH1, LPHN2	23266	1p31.1	39

Table 1.—*Continued*

ADG Nomenclature Name	Alternative Name(s)	Human Gene ID	Location (chromosome)	Exon Count
ADGRL3	CIRL3, CL3, LEC3, LPHN3	23284	4q13.1	32
ADGRL4	ELTD1, ETL, KPG_003	64123	1p31.1	15
ADGRV1	FEB4; GPR98; MASS1; USH2B; USH2C; VLGR1; VLGR1b	84059	5q14.3	91

This table lists all 33 adhesion G protein-coupled receptors (AGPCRs) with their standardized and alternate names, along with their human gene ID and information about their chromosomal locations.

of the GAIN domain. The GAIN domain is conserved in all AGPCRs except for ADGRA1 (GPR123), which possesses a short NH_2 terminus devoid of any modular domains (19). The GPS is conserved in all other AGPCRs except for ADGRF2 (GPR111) and ADGRF4 (GPR115), which lack the consensus GPS motif and do not appear to undergo autoproteolysis (20). Other than ADGRA1, ADGRF2, and ADGRF4, however, the other 30 members of the human AGPCR family appear to possess intact GAIN domains and GPS motifs, and there is good evidence for most of these receptors that they undergo autoproteolysis as a part of their normal processing (8). This autoproteolysis occurs spontaneously, often during receptor trafficking to the plasma membrane, and there is little evidence that it can be modulated by ligand binding (8). However, the binding of ligands to AGPCRs can exert conformational forces that may lead to dissociation of the non-covalently-associated NTF and CTF regions that have already been cleaved by autoproteolysis (8).

The GAIN domain is both necessary and sufficient for the autoproteolytic process in AGPCRs (9). The NH_2-terminal portion of the GAIN domain consists of six α-helices, whereas the COOH-terminal region closer to the transmembrane portion of the receptor consists of a twisted β-sandwich, including 13 β-strands and two small α-helices (21). The GPS motif, which consists of the last five β-strands of the portion of the NH_2 terminus proximal to the transmembrane domain of the receptor, is an integral part of this domain but is not functional by itself (21). Interestingly, the GAIN domain is also known to be the site of multiple human disease mutations (22). For example, mutations of the GAIN domain of ADGRG1 cause bilateral frontoparietal polymicrogyria (BFPP) (23). Additionally, mutations in the GAIN domains of ADGRL1 and ADGRB1 genes are hot spots for human cancers (21).

Beyond being found in AGPCRs, GAIN domains are also found in polycystin-1 (PKD1) and the PKD1-like family of related transmembrane proteins (8, 24). Mutations in PKD1 are responsible for most cases of autosomal dominant polycystic kidney disease, a leading cause of end-stage renal disease, and a number of the disease-
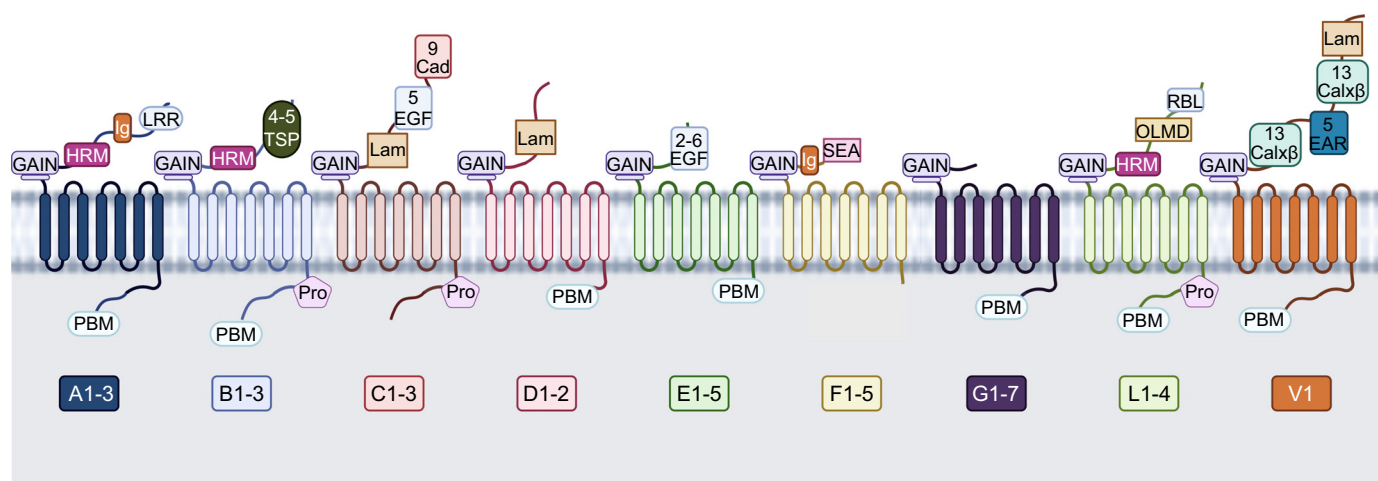

FIGURE 1. Adhesion G protein-coupled receptors (AGPCRs) exhibit great structural diversity. The various adhesion GPCR subfamilies are depicted with key motifs labeled. Cad, cadherin repeat; EAR, epilepsy-associated repeat; EGF, epidermal growth factor-like; GAIN, GPCR autoproteolysis-inducing domain; HRM, hormone receptor motif; Ig, immunoglobulin-like; Lam, laminin; LRR, leucine-rich repeat; OLMD, olfactomedin-like; PBM, PDZ binding motif; Pro, polyproline sequence; RBL, rhammose-binding lectin; SEA, sperm protein/enterokinase/agrin domain; TSP, type 1 thrombospondin repeats. Figure created, with permission, using BioRender.com.

causing mutations are located in the PKD1 GAIN domain (24). Interestingly, although PKD1 is not a GPCR, it has been shown to regulate G protein signaling in a manner that is influenced by cleavage of the GAIN domain (24). Along these same lines, GAIN domain cleavage also plays a key role in regulating signaling by AGPCRs, as described in sect. 3.

3. SIGNALING OF ADHESION GPCRs

Early work on AGPCRs, and early reviews of the field, focused on the ability of these receptors to mediate adhesive interactions (25, 26). Given that AGPCRs possess 7TM domains, which were known from work on other GPCR families to allow coupling to G proteins, there was speculation that AGPCRs may translate extracellular adhesive interactions into intracellular signaling cascades, but such signaling mechanisms were mostly hypothetical in the early years of the field (25, 26). However, the past decade has seen numerous advances in understanding the activation of AGPCR signaling, not only by adhesive interactions but also by mechanosensory forces and secreted small-molecule ligands.

3.1. Canonical G Protein-Dependent Signaling

GPCRs function via their 7TM regions as guanine exchange factors (GEFs) for heterotrimeric G proteins, promoting the exchange of GDP for GTP on the Gα subunit. The first evidence for G protein activation by an AGPCR came from work on ADGRL1, which was shown

to bind to alpha-latrotoxin (derived from black widow spiders) and stimulate increases in cyclic AMP and inositol (1,4,5)-trisphosphate (IP₃) levels in ADGRL1-transfected COS-7 cells treated with alpha-latrotoxin (27, 28). Further work determined that ADGRL1 couples to Gαo to regulate cAMP and IP₃ levels (27) and can also activate phospholipase C by coupling to Gαq (29). Subsequently, many AGPCRs have been shown to stimulate G protein-dependent pathways (30), and certain AGPCRs have even been shown to stimulate purified G proteins in vitro (31–34) and coimmunoprecipitate with their cognate G proteins from cells (17, 18), thereby providing strong evidence for G protein coupling.

The various members of the AGPCR family all preferentially couple to distinct subsets of G proteins (**FIGURE 2A**). This fact was vividly illustrated in screening assays performed in 2012 in which the G protein coupling preferences of a large number of AGPCRs were assessed by measuring second messengers such as cyclic AMP and inositol phosphate, which are traditionally downstream of G protein activation (35). These studies provided insights into the G protein coupling preferences of several AGPCRs, including ADGRG3, which exhibited a preference for coupling to Gαo (35). Almost a decade later, the aforementioned cryo-EM studies provided a high-resolution view of Gαo in association with the intracellular loops of ADGRG3 (15).

Most G protein-coupled receptors can couple to multiple G protein subtypes to activate a diverse array of signaling pathways (36), and AGPCRs are no exception. For example, the promiscuity of ADGRG2 (GPR64, "G2") has been well documented, with the receptor
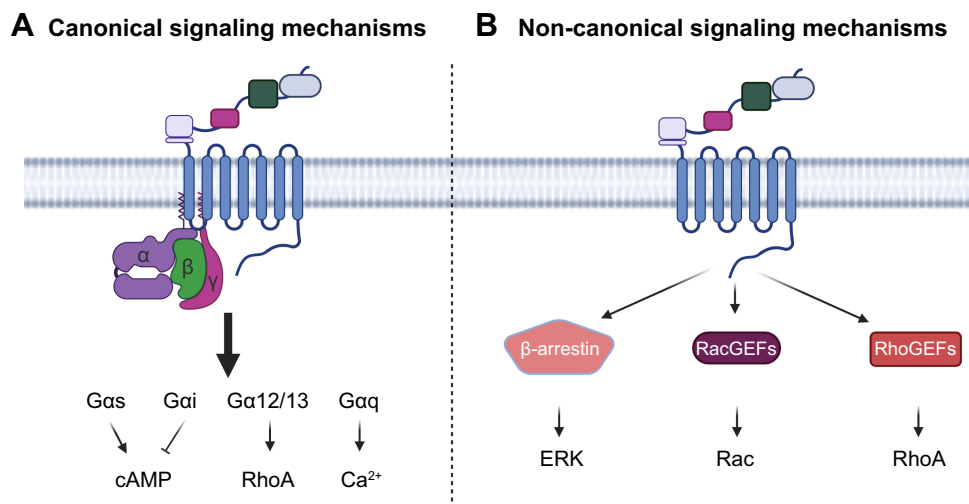

FIGURE 2. Adhesion G protein-coupled receptors (AGPCRs) engage in diverse signaling mechanisms. *A*: AGPCRs can engage in canonical G protein-mediated signaling pathways, wherein a receptor engages with heterotrimeric G proteins to trigger G protein-dependent signaling cascades. Shown here are Gαs, Gαi, Gα12/13, and Gαq, along with some of their downstream second messengers. *B*: AGPCRs can also engage in noncanonical signaling pathways that are independent of heterotrimeric G proteins. For example, AGPCRs can engage with β-arrestins, RacGEFs or RhoGEFs, among other signaling proteins, to activate various downstream pathways in a G protein-independent manner. Figure created, with permission, using BioRender.com.

coupling to Gαs (37–41), Gαq (37, 40–43), and Gα12/13 (40, 42). In the case of nonadhesion GPCRs that promiscuously couple to multiple G protein pathways, the strength of coupling often varies dramatically depending on cellular context because of the presence of cell-specific scaffold proteins that enhance certain pathways but not others (44). Many AGPCRs are known to bind to cytoplasmic scaffold proteins (45–52), and future studies in this area will undoubtedly shed light on the extent to which these receptor-scaffold interactions confer cell specificity to the receptors' G protein coupling preferences.

3.2. Noncanonical G Protein-Independent Signaling of AGPCRs

Many GPCRs can directly interact with signaling proteins other than heterotrimeric G proteins to mediate G protein-independent signaling (44). Several AGPCRs can mediate noncanonical signaling along these lines (FIGURE 2B). For example, ADGRB1 (BAI1) and ADGRB3 (BAI3) can regulate Rac signaling via interactions with two distinct Rac-GEFs: DOCK180, which associates with these receptors in complex with ELMO1 (53, 54), and Tiam1, which associates with ADGRB1 by binding to the receptor's distal COOH terminus (50). ADGRB1 has also been shown to associate with the RhoA-GEF Bcr to activate RhoA activity in hippocampal neurons (55). More generally, several AGPCRs, including ADGRG1, ADGRG2, ADGRB1, and ADGRB2 (BAI2), have been shown to robustly couple to β-arrestins (17, 40, 41, 43, 49, 56, 57). Activity-dependent GPCR interactions with β-arrestins are a common mode by which GPCRs can mediate G protein-independent signaling (58). For example, ADGRG2 signaling through β-arrestin-1 is essential for G2 regulation of fluid reabsorption in the testis (43). The capacity of AGPCRs to signal through G proteins, β-arrestins, and other signaling intermediates provides an opportunity for the development of "biased" ligands that preferentially activate one downstream signaling pathway but not others. Such biased ligands can serve as important research tools and also in some cases make for useful therapeutics (58). A summary of all known signaling pathways activated downstream of AGPCRs (including G protein-mediated and noncanonical signaling pathways) is shown in TABLE 2.

4. ACTIVATION OF ADHESION GPCRs

The earliest insights on the activation mechanisms of adhesion GPCRs came from the aforementioned studies on ADGRL1 demonstrating that engagement of the receptor's NH₂ terminus by alpha-latrotoxin could promote receptor signaling (27, 29, 59). Subsequent studies on several different AGPCRs, including ADGRG1 (56), ADGRG4 (GPR112) (60), ADGRB1 (49), ADGRB2 (61), and ADGRE5 (CD97) (62, 63), resulted in the surprising observation that truncation of the receptors' NH₂ termini, up the point of predicted GAIN domain cleavage, resulted in strong activation of receptor signaling. Taken together, these findings provided the underpinnings for the hypothesis (64) that the large NH₂-terminal regions of AGPCRs inhibit signaling by the receptors' 7TM regions, with NTF engagement resulting in either NTF removal or conformational rearrangement to remove inhibitory constraints and thereby activate receptor signaling.

4.1. Tethered Agonism

Other GPCRs that are known to become activated after removal of NH₂ terminal regions include the members of the protease-activated receptor (PAR) subfamily. For example, PAR1 can be cleaved by the secreted protease thrombin to unveil a cryptic agonist on the receptor's NH₂ terminus, resulting in receptor activation (65). Early work on ADGRL1 signaling led to suggestions that AGPCR signaling might have analogies to PAR signaling (66). This hypothesis was explicitly tested in studies on NTF-lacking versions of ADGRG6 (GPR126) and ADGRD1 (GPR133) (67). Similar to NTF-lacking versions of other AGPCRs, as described above, truncated versions of ADGRG6 and ADGRD1 exhibited high constitutive activation of Gαs to raise cyclic AMP levels, and, interestingly, removal of a portion of the postcleavage stalk (or stachel) greatly reduced the signaling activity of these truncated receptors (67). Moreover, exogenous administration of the stachel peptide rescued the activity of these mutant receptors (67). Similarly, independent studies demonstrated that the removal of portions of the postcleavage stalk of ADGRG1 and ADGRF1 abolished the activity of these receptors, with this activity being restored after treatment with peptides corresponding to the postcleavage stalk (31). Subsequently, similar findings were made in work on ADGRG2 (GPR64) (37, 41) and ADGRG5 (GPR114) (68).

The studies on the tethered agonist regions of AGPCRs led to questions about how this sequence might get exposed to lead to receptor activation. Do the NTF and CTF regions of a cleaved AGPCR heterodimer need to dissociate to expose the tethered agonist? Studies on mutant versions of AGPCRs that lack intrinsic GAIN domain protease activity (and therefore do not undergo proteolysis) provided evidence against this idea, as such noncleavable receptors have been shown in many cases to exhibit levels of constitutive signaling activity comparable to wild-type (self-cleaving) receptors

Table 2. *AGPCR G protein-dependent and alternate signaling pathways*

Class	Receptor	Alt Name	G Protein Pathways Activated	Other Signaling Pathways Activated
A	ADGRA1	GPR123		
A	ADGRA2	GPR124		Wnt7/β-Catenin (209–211, 213, 214); cdc42 (205, 217)
A	ADGRA3	GPR125		Wnt/PCP/β-Catenin (333)
B	ADGRB1	BAI1	Gα12/13/RhoA (18, 49)	ELMO/Dock180/Rac (109); Tiam1/Rac (50); Bcr/RhoA (55); mdm2 (142, 277)
B	ADGRB2	BAI2	Gαz (17); Gα16 (61)	GABPγ (334)
B	ADGRB3	BAI3		ELMO/Rac1 (144)
C	ADGRC1	CELSR1		Wnt/PKC (300); Rho (160, 161)
C	ADGRC2	CELSR2	Gαq/Ca^{2+} (165)	
C	ADGRC3	CELSR3	Gαq/Ca^{2+} (165)	
D	ADGRD1	GPR133	Gαs/cAMP (35, 67, 71, 281)	
D	ADGRD2	GPR144		
E	ADGRE1	EMR1		
E	ADGRE2	EMR2	Gα12/Gα13/Gα14/Gαz/ Gαs/ Gαi/Gαq (63); Gα16/PLC (63, 104); Gα15 (35, 63)	
E	ADGRE3	EMR3		
E	ADGRE5	CD97	Gαz/Gα14 (63); Gα12/ Gα13/ RhoA (62, 63)	
F	ADGRF1	GPR110	Gαq/IP1 (31, 39); Gαs/cAMP (39, 80)	NF-κB (169)
F	ADGRF2	GPR111		
F	ADGRF3	GPR113		
F	ADGRF4	GPR115	Gα15 (35)	
F	ADGRF5	GPR116	Gαq/RhoA/Rac1 (313); Gαq/ Gα11/IP1 (204); Gαs/cAMP (234)	ERK1/2 (234)
G	ADGRG1	GPR56	Gα12/Gα13/RhoA (18, 31, 56, 172, 176, 180, 193); Gαq/Gα11 (335); Gαi (193)	
G	ADGRG2	GPR64	Gα12/Gα13/RhoA (40, 42); Gαs/cAMP (37–41); Gαq (37, 40–43)	β-Arrestin (41)
G	ADGRG3	GPR97	Gαo (15, 35)	RhoA/cdc42 (122)

Continued

Table 2.—Continued

Class	Receptor	Alt Name	G Protein Pathways Activated	Other Signaling Pathways Activated
G	ADGRG4	GPR112	Gα12/Gα14 (60)	
G	ADGRG5	GPR114	Gαs (68)	
G	ADGRG6	GPR126	Gαs/cAMP (39, 67, 184, 186, 336); Gαq/Gα12/α13 (336)	
G	ADGRG7	GPR128		ELMO (230)
L	ADGRL1	Lphn1/CIRL1	Gαq/Ca2+ (29, 136); Gαo (27, 29)	
L	ADGRL2	Lphn2/CIRL2	Gαs/cAMP (135)	
L	ADGRL3	Lphn3/CIRL3	Gαq/Gα12/α13 (34); Gαs/cAMP (135)	
L	ADGRL4	ETL		
V	ADGRV1	VLRG1	Gαq/PKC (241); Gαs/cAMP/ PKA (241); Gαi (242)	

This table displays the 33 adhesion G protein-coupled receptors (AGPCRs), organized by class, along with the documented G protein-dependent and alternate signaling pathways downstream of each receptor. This table highlights the diverse signaling capabilities of AGPCRs.

(18, 69–71). Recent studies employing bioorthogonal labels have revealed that the tethered agonist region can become exposed within the context of an NTF-CTF AGPCR heterodimer through intra-GAIN domain movements (72). These findings suggest a model in which the tethered agonist can become exposed through GAIN domain conformational changes, rather than strictly requiring NTF-CTF dissociation.

4.2. Beyond Tethered Agonism

In addition to masking cryptic tethered agonist sequences, AGPCR NTF regions can influence receptor signaling activity in other ways (**FIGURE 3**). In certain AGPCRs, for example, removal of the tethered agonist/stachel sequence does not appear to impair receptor signaling activity (18). Similarly, mutation of the tethered agonist/stachel sequence in ADGRG1 does not disrupt activation of the receptor by antibodies that bind to the NTF (73). These studies suggest that the NTF controls AGPCR signaling activity in at least two distinct ways: 1) modulation of the accessibility of the tethered agonist/stachel region and 2) interaction with other AGPCR regions (such as perhaps the extracellular loops) to mediate conformational changes that determine receptor signaling activity.

The ability to temporally control AGPCR signaling is crucial for probing the effects of AGPCRs on physiology. In theory, stachel peptides can be useful reagents for temporal control of AGPCR signaling, similar to how SFLLRN and related peptides from the PAR1 NH_2 terminus have been used for years as ligands to exert temporal control over the activity of PAR1 (65). However, the stachel peptides are fairly well conserved between different AGPCRs and therefore tend to exhibit a lot of cross-reactivity between receptors, especially at the high concentrations at which these peptides must be used (39). Moreover, stachel peptides often do not activate full-length AGPCRs, instead activating only highly truncated versions of AGPCRs that have had their stalk regions removed or mutated (31, 74). A different approach to temporal control of AGPCR signaling has been the development of mutant versions of AGPCRs with the PAR1 NH_2 terminus fused to the GPS cleavage site to allow for thrombin-dependent exposure of the AGPCR tethered agonist, leading to receptor activation (34). Such PAR/AGPCR chimeras can be useful tools in allowing for temporally controlled activation of AGPCR signaling pathways.

5. ADHESION GPCR LIGANDS

Beyond the use of stachel peptides and PAR/AGPCR chimeras, another way that temporal control over AGPCR signaling can be exerted is via the use of ligands. Most AGPCRs have massive NH_2 termini with multiple conserved domains, suggesting that each
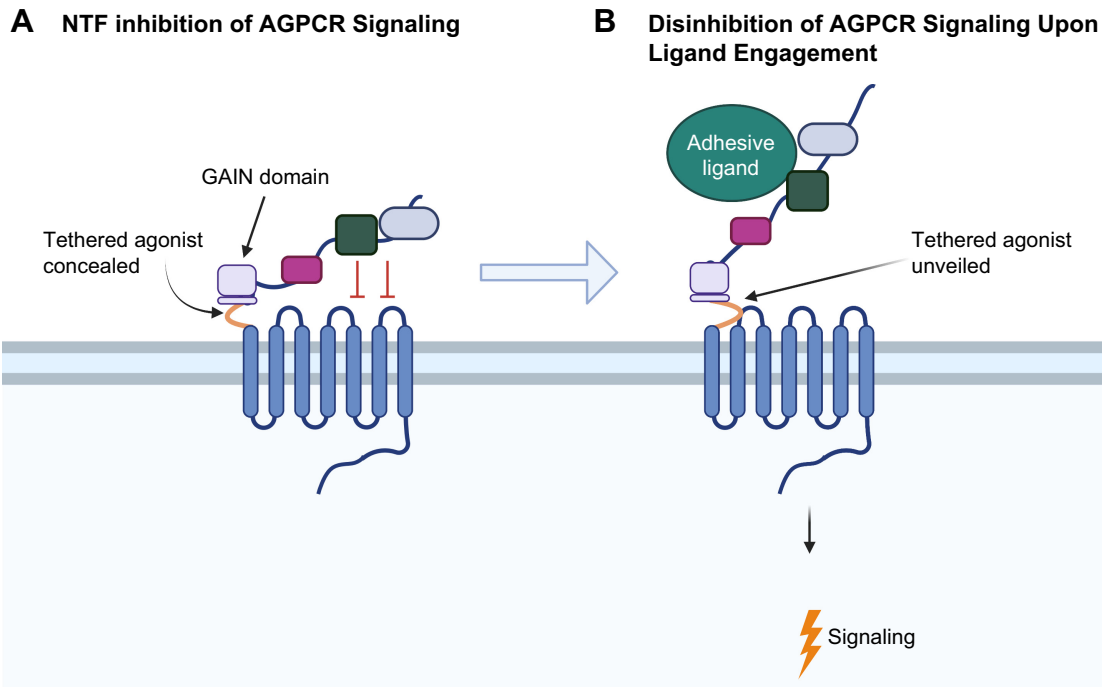
FIGURE 3. Adhesion G protein-coupled receptor (AGPCR) NH_2-terminal fragments suppress receptor signaling in multiple ways. *A*: for many (if not all) AGPCRs, the NH_2-terminal fragment (NTF) inhibits receptor signaling via concealment of the tethered agonist sequence, and for some receptors there is evidence that the NTF also exerts additional allosteric actions on the COOH-terminal fragment (beyond concealing the tethered agonist) that suppress receptor activity. GAIN, GPCR autoproteolysis-inducing domain. *B*: after engagement with an adhesive ligand, the NTF can change conformation such that multiple modes of inhibition are released. For example, the activated receptor may no longer experience allosteric inhibition by the NTF and additionally has an unveiled tethered agonist sequence that can fully activate receptor signaling. Figure created, with permission, using BioRender.com.

receptor possesses the capacity to bind to numerous extracellular partners. Indeed, various binding partners, mostly large adhesion proteins and/or components of the extracellular matrix, have been identified for many AGPCRs (**FIGURE 4**). Some of these binding partners modulate receptor signaling activity, whereas others seem to solely mediate adhesive interactions. In any case, the elucidation of a receptor's interacting partners can shed crucial light on that receptor's physiological effects. For this reason, the various AGPCR ligands/binding partners (summarized in **TABLE 3**) are discussed in the sections below in the context of understanding the physiological actions of AGPCRs.

5.1. Mechanosensory Signaling

The physical interaction of AGPCRs with extracellular adhesive ligands may, in many cases, not be enough to stimulate receptor signaling: the conveyance of mechanosensory force via these protein-protein associations may also be required. Indeed, over the past decade, multiple lines of evidence have emerged to suggest that detection of mechanosensitive stimuli is a primary physiological role of AGPCRs (**FIGURE 5A**). For example, the *Drosophila* ADGRL ortholog dCIRL is highly expressed in chordotonal neurons, the principal mechanosensory

cells in flies, and genetic deletion of dCIRL results in sharply diminished touch sensitivity of the flies as well as greatly reduced physiological responses of the chordotonal neurons to mechanosensitive stimuli (75). This mechanosensory action of dCIRL is dependent on the receptor's extracellular region, tethered agonist sequence, and G protein-dependent coupling to regulate cyclic AMP levels but is not dependent on autoproteolysis of the GAIN domain (70). In addition to the expression of dCIRL in the chordotonal neurons, the receptor is also expressed in the flies' nociceptive neurons that respond to much higher intensities of mechanical stimulation; interestingly, although dCIRL sensitizes the responses of the chordotonal neurons to low-intensity mechanical stimuli, the receptor dampens high-intensity mechanosensitive activation of the nociceptive neurons, thereby revealing a differential role of the receptor in detecting low- versus high-intensity mechanosensation (76).

In addition to the body of work from studies in *Drosophila*, there is also evidence that vertebrate AGPCRs serve as mechanosensors. G protein-dependent signaling by ADGRG6 (77) and ADGRG5 (GPR114, "G5") (68) can be greatly enhanced by mechanically stressing cultured cells that express these receptors. Similarly, knockdown or deletion of ADGRV1 (VLGR1, or "V1") from certain cell types
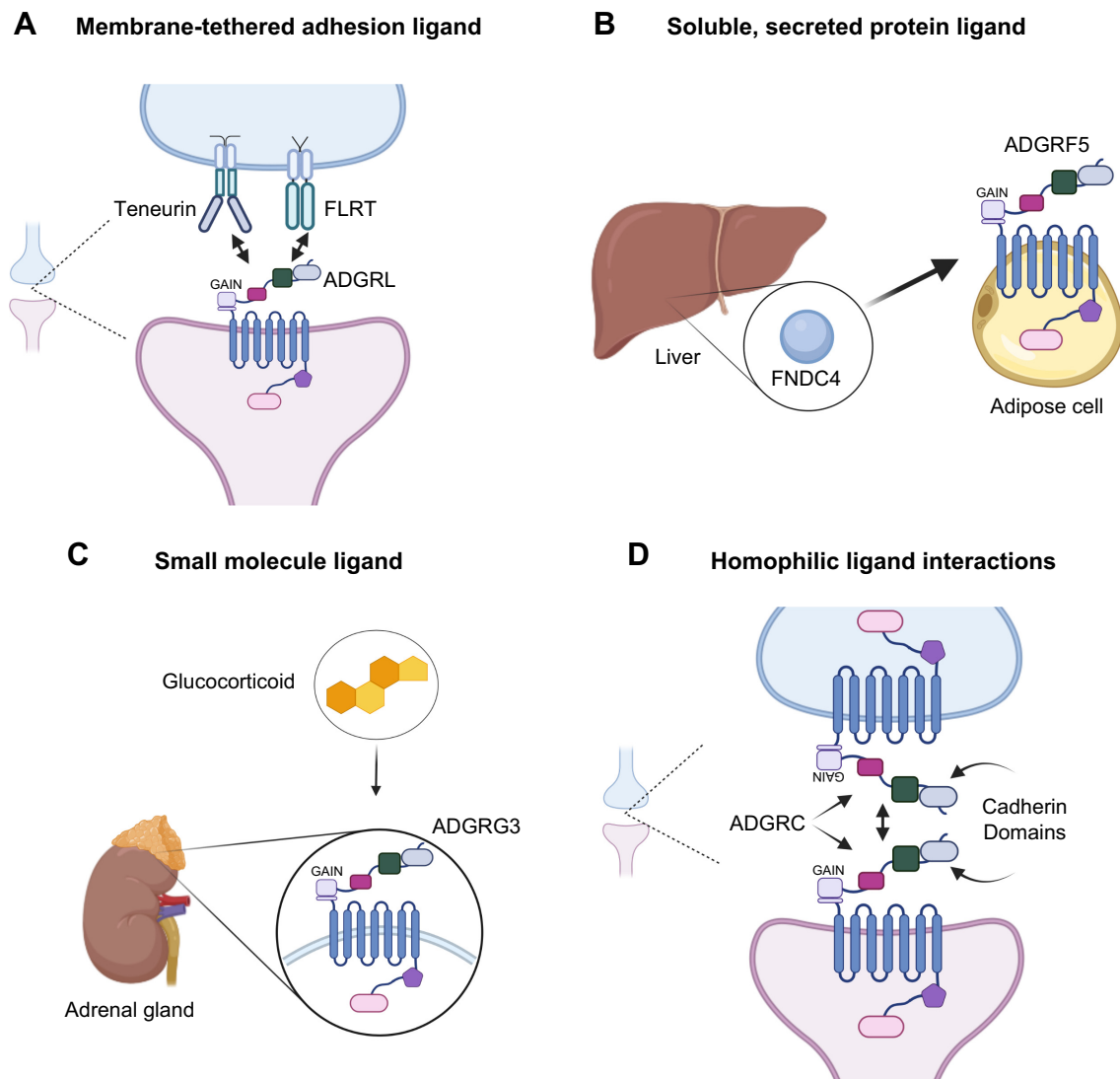
A   **Membrane-tethered adhesion ligand**

B   **Soluble, secreted protein ligand**

C   **Small molecule ligand**

D   **Homophilic ligand interactions**

FIGURE 4. Adhesion G protein-coupled receptors (AGPCRs) can engage with a diverse array of ligands to exert their physiological actions. *A*: some AGPCR ligands are membrane-tethered adhesion ligands, for example, the teneurins and FLRTs that interact across synapses with postsynaptic ADGRL1–3 to regulate synapse formation. *B*: other AGPCR ligands are soluble, secreted proteins, for example, the hepatokine FNDC4, which can activate ADGRF5 to regulate adipose cell physiology. *C*: some AGPCRs bind to endogenous ligands that are small molecules, as in the case of glucocorticoids activating ADGRG3 to exert physiological effects in the adrenal cortex (15). *D*: certain AGPCRs can engage in homophilic or heterophilic interactions with other AGPCRs. For example, ADGRC receptors can interact with each other across cellular junctions via their cadherin-like domains. GAIN, GPCR autoproteolysis-inducing domain. Figure created, with permission, using BioRender.com.

dramatically reduces cellular responses to mechanical stretch, thereby providing evidence that V1 plays an important mechanosensory role (78). In studies on cells expressing ADGRE5 (CD97), it was found that the application of mechanical force provokes phosphorylation of a key serine residue on the receptor's cytoplasmic COOH terminus, with this phosphorylation event disrupting the receptor's interaction with the scaffold protein DLG1 and perturbing the receptor's ability to mediate cellular adhesion (51). The recently solved crystal structure of ADGRE5 in complex with its large extracellular ligand CD55 provides insight into how E5 can serve a mechanosensory role, as the antiparallel binding of the E5-CD55 complex suggests a mechanism

for the transmission of tensile force and the consequent force-dependent repositioning of the tethered agonist to modulate receptor activity (79).

5.2. Small-Molecule Ligands

Although the realization that AGPCRs can mediate mechanosensory signaling has been a surprising advance in recent years, an even more surprising insight has been that AGPCR signaling can be activated by small-molecule ligands (**FIGURE 5*B***). Some of these ligands are putative endogenous ligands, for example, the bioactive lipid synaptamide, which binds to the GAIN domain of ADGRF1 (GPR110) and agonizes receptor signaling (80, 81).

Table 3. *AGPCR-ligand binding and physiological significance*

Class	Receptor	Alt Name	AGPCR Ligands	Physiological Significance	Reference(s)
A	ADGRA1	GPR123			
	ADGRA2	GPR124	$\alpha_V\beta_3$-integrin	Adhesion and migration during angiogenesis	(208, 218)
			Glycosaminoglycans	CNS vascularization and BBB establishment	(207, 208)
	ADGRA3	GPR125			
B	ADGRB1	BAI1	$\alpha_V\beta_5$-integrin	Endothelial cell proliferation	(337)
			Phosphatidylserine	Macrophage engulfment	(109)
			Lipopolysaccharide	Macrophage engulfment	(111)
			RTNR4	Neuronal development	(145, 146)
			CD36	Inhibition of angiogenesis	(274, 279)
	ADGRB2	BAI2			
	ADGRB3	BAI3	C1q11–C1q14, C1q-like-3	Synapse formation; myoblast fusion; insulin secretion	(147–151, 231)
C	ADGRC1	CELSR1			
	ADGRC2	CELSR2	Homophilic interactions	Axon guidance; neurite growth	(165)
	ADGRC3	CELSR3	Homophilic interactions	Axon guidance; neurite growth	(165)
			Dystroglycan	Axon guidance; neurite growth	(168)
D	ADGRD1	GPR133			
	ADGRD2	GPR144			
E	ADGRE1	EMR1			
	ADGRE2	EMR2	Chondroitin sulfate	Adhesion	(96, 97)
	ADGRE3	EMR3			
	ADGRE5	CD97	Chondroitin sulfate	T and B cell interaction	(96–98)
			$\alpha_V\beta_3$-, $\alpha_5\beta_1$-integrins	Angiogenesis	(98)
			LPA receptor	Tumor invasion	(62)
			CD90	Leukocyte trafficking to inflammatory sites	(95)
			CD55	T cell activation	(79, 93, 94, 99–101)

Continued

Table 3.—Continued

Class	Receptor	Alt Name	AGPCR Ligands	Physiological Significance	Reference(s)
F	ADGRF1	GPR110	Synaptamide	Synaptogenesis	(80, 81)
	ADGRF2	GPR111			
	ADGRF3	GPR113			
	ADGRF4	GPR115			
	ADGRF5	GPR116	FNDC4	Glucose homeostasis	(234)
			Surfactant Protein-D	Pulmonary surfactant pool size regulation	(200, 201)
G	ADGRG1	GPR56	Collagen III	Cortical development and lamination; hemostatic plug formation	(82, 177, 180, 193, 247)
			Heparin	Cell adhesion and migration	(249)
			Transglutaminase-2	Central nervous system myelination and melanoma progression	(178, 179, 181, 225, 258)
			Progastrin	Colonic mucosal proliferation	(250)
			Phosphatidylserine	Synaptic pruning	(183)
	ADGRG2	GPR64			
	ADGRG3	GPR97	Glucocorticoids	Adrenal cortex secretion	(15)
	ADGRG4	GPR112			
	ADGRG5	GPR114			
	ADGRG6	GPR126	Collagen IV	Peripheral nerve development	(189)
			Laminin-211	Schwann cell development	(77)
			Cellular Prion Protein	Schwann cell function	(190)
	ADGRG7	GPR128			
L	ADGRL1	Lphn1/CIRL1	α-latrotoxin	Toxin docking with cells	(27–29, 59, 125, 126, 128)
			Teneurins	Neuronal pathfinding and synaptogenesis	(13, 136, 137, 140)
			Neurexins	Transsynaptic connection formation	(59)
			FLRT proteins	Synaptic development	(13, 139)
	ADGRL2	Lphn2/CIRL2	Teneurins	Axon guidance	(13, 133, 135, 137)
			FLRT proteins	Synaptic development	(13, 133, 139)

Continued

Table 3.—Continued

Class	Receptor	Alt Name	AGPCR Ligands	Physiological Significance	Reference(s)
	ADGRL3	Lphn3/CIRL3	Teneurins	Neuronal reshaping; synapse formation; axon guidance	(14, 133, 135, 137)
			FLRT proteins	Synaptic development	(12, 14, 133, 139)
	ADGRL4	ETL			
V	ADGRV1	VLGR1			

This table displays the 33 adhesion G protein-coupled receptors (AGPCRs) along with their known ligands and a brief summary of the physiological significance that has been elucidated for each receptor/ligand pair. The information contained in this table underscores the diverse range of ligands engaged by AGPCRs, including adhesion proteins, extracellular matrix components, secreted peptides, and small molecules. BBB, blood-brain barrier; CNS, central nervous system; LPA, lysophosphatidic acid.

Additionally, steroid hormones such as glucocorticoids have been shown to bind to the 7TM region of ADGRG3 and promote coupling of the receptor to G proteins (15). These observations that AGPCRs can be activated by small-molecule ligands have led to a paradigm shift in the field, away from the view that the core function of AGPCRs is the mediation of adhesion and toward a more inclusive model in which AGPCRs serve as massive signaling platforms that are crucial for the integration of adhesive, mechanosensory, and chemical stimuli.

Beyond the putative endogenous ligands mentioned above, other small-molecule ligands that have been recently identified for AGPCRs include druglike compounds found in high-throughput screening campaigns. For example, beclomethasone was identified in high-throughput screens as an agonist for ADGRG3 (35). Similarly, screens for ADGRG1 ligands identified 3-α-acetoxydihydrodeoxygedunin as an agonist (33, 82) and dihydromunduletone as an antagonist (32), whereas screens for ADGRG6 ligands identified apomorphine as an agonist (83). Interestingly, beclomethasone,
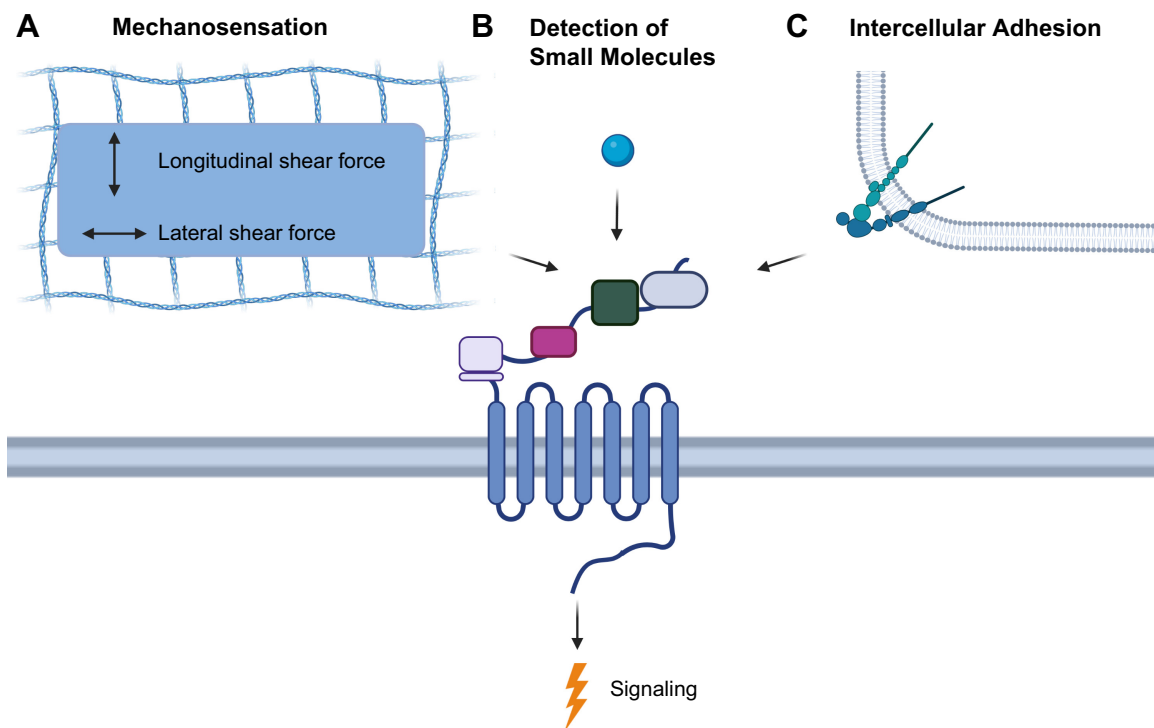

FIGURE 5. Adhesion G protein-coupled receptors (AGPCRs) can integrate heterogeneous signals. *A*: AGPCRs can detect shear forces via the extracellular matrix and transduce these forces into intracellular signaling. *B*: AGPCRs can also respond to secreted small molecules to induce signaling. *C*: AGPCRs can mediate adhesion signaling by sensing intercellular interactions with ligands that are large proteins or membrane lipids. The integration of all of these heterogeneous signals may be a central function of AGPCRs. Figure created, with permission, using BioRender.com.

3-α-acetoxydihydrodeoxygedunin, dihydromunduletone, and apomorphine all exhibit four-ring structures that are reminiscent of steroid hormones. Thus, the aforementioned recent report that ADGRG3 is activated by glucocorticoids ([15]) may be a harbinger of more reports to come about AGPCR stimulation by steroid hormones. Indeed, there exists extensive literature on the rapid, "nongenomic" actions of steroid hormones that are not mediated by traditional nuclear steroid receptors ([84, 85]). In many cases, these mysterious steroid hormone effects are mediated by unidentified G protein-coupled receptors ([84, 85]). Thus, given that the residues comprising the steroid hormone-binding pocket of ADGRG3 are highly conserved in many other AGPCRs ([15]), it is plausible that other AGPCRs may be activated by steroid hormones, with these steroid-AGPCR pairings accounting for some of the currently unexplained rapid physiological actions of steroid hormones.

6. PHYSIOLOGY OF ADHESION GPCRs

Adhesion GPCRs control many diverse physiological processes throughout the body. Physiological actions known to be mediated by AGPCRs are described below, subdivided by system and also by receptor subfamily. In cases where a specific AGPCR ligand or downstream signaling pathway has been identified as physiologically relevant, these ligands and/or signaling pathways are discussed in the context of the receptor's physiological effects.

6.1. Immune System

6.1.1. ADGRE subfamily.

The earliest studies on the physiological actions of AGPCRs came from work on the immune system ([86]). In 1981, the F4/80 receptor (now known as ADGRE1, EMR1, or "E1") was characterized as a cell surface marker for mouse macrophages ([87]). Subsequent work has demonstrated that the expression pattern of ADGRE1 varies dramatically between different species; in humans, for example, this receptor is expressed primarily in eosinophils ([88]). Genomic analyses have revealed that E1 is evolving rapidly, with large variations in NTF domain architecture between different species ([89]), suggesting a species-specific role in immune system physiology for this founding member of the AGPCR family.

Another member of the ADGRE subfamily that has garnered intense interest concerning immune function is ADGRE5 (CD97, "E5"). This receptor is expressed in a wide range of hematopoietic cells as well as in smooth muscle cells ([90]). Studies utilizing antibodies that block the function of E5 have shown that this receptor is critically important for controlling neutrophil migration and mediating antibacterial immunity ([91]). Insofar as E5 can dictate the localization and activity of immune cells such as neutrophils and macrophages, it also plays a critical role in inflammatory processes, as illustrated in studies demonstrating that both E5 neutralizing antibodies ([92]) and genetic deletion of E5 reduce inflammation in mouse models of rheumatoid arthritis ([93]).

The ability of E5 to control the localization and activity of immune cells depends upon engagement of the receptor's NTF with various extracellular binding partners (**FIGURE 6A**). E5 has been shown to bind via its large extracellular NTF to two distinct GPI-linked surface proteins, CD55 (also known as the Decay-Accelerating Factor, or DAF) ([94]) and CD90 (also known as Thy-1) ([95]), as well as to chondroitin sulfate glycosaminoglycans ([96–98]) and $\alpha_5\beta_1$-integrin ([98]). The most intensively studied of these interactions is ADGRE5-CD55, with strong evidence for the in vivo importance of this interaction deriving from the fact that similar phenotypes (reduced inflammation in mouse models of rheumatoid arthritis) are observed upon genetic deletion of either E5 or CD55 ([93]). The E5-CD55 interaction can mediate adhesion between different cell types and also has physiological consequences for each partner: E5 modulates the ability of CD55 to affect T cell activation ([99, 100]), and reciprocally CD55 regulates the stability of ADGRE5 expression on leukocytes ([101]). Recent X-ray crystallography studies have provided a high-resolution view of CD55 in complex with the epidermal growth factor (EGF)-like domains of the E5 NTF and demonstrated that the two proteins bind antiparallel to one another ([79]). This work revealed that the E5-CD55 complex can withstand tensile force, thereby providing a potential mechanism for mechanosensitive activation of ADGRE5 ([79]).

As with ADGRE1 and ADGRE5, the other members of the ADGRE subfamily, ADGRE2 (EMR2, "E2"), ADGRE3 (EMR3, "E3"), and ADGRE4 (EMR4, "E4"), are also predominantly expressed in immune cells. E2 is highly expressed in neutrophils, and agonistic antibodies that stimulate the receptor can potentiate neutrophil activation in vitro ([26]). Increased ADGRE2 expression on neutrophils has been correlated in patients with systemic inflammation and cirrhosis of the liver ([102, 103]). E2 is also found in macrophages, with antibody-mediated stimulation of the receptor promoting macrophage differentiation as well as the expression of proinflammatory mediators ([104, 105]). E3 is a marker for granulocytes ([106]), but the receptor's function in this cell type is still not fully understood. E4 is a pseudogene that does not express as a functional receptor in humans but yet is expressed as a full-length receptor in activated
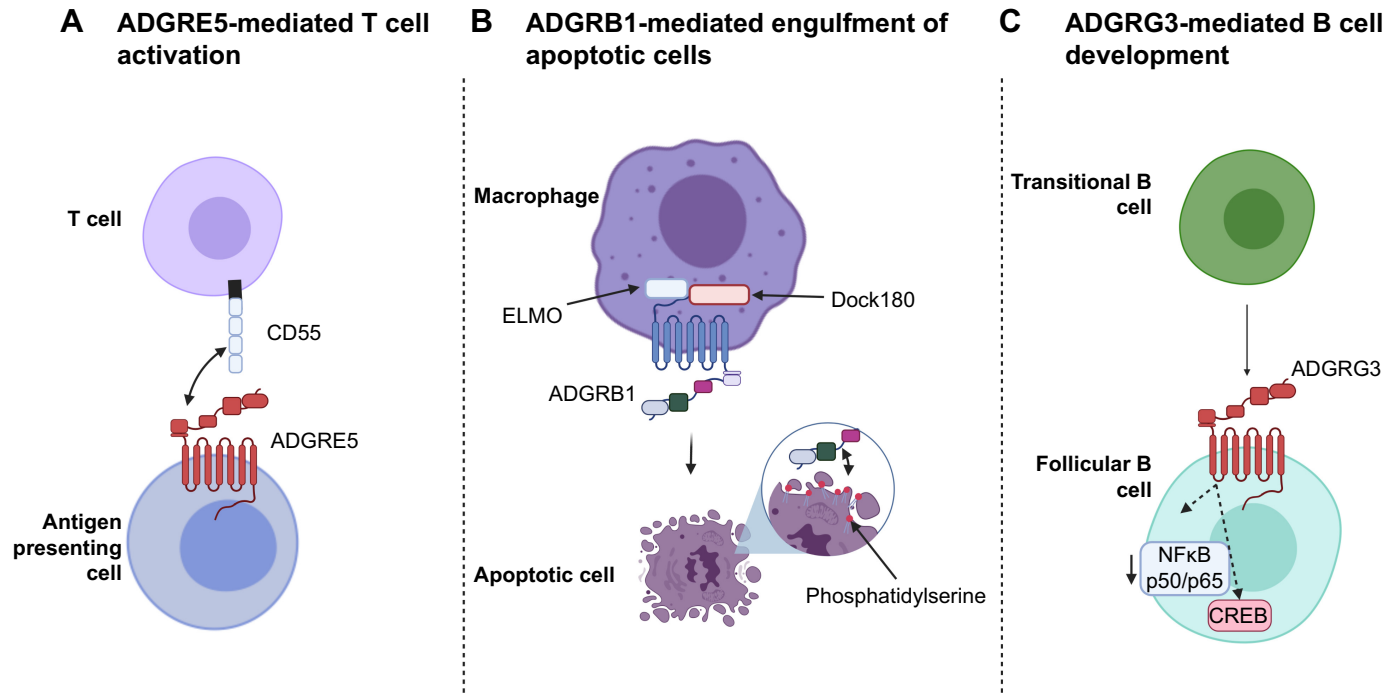
FIGURE 6. Adhesion G protein-coupled receptors (AGPCRs) have important roles in immune system physiology. *A*: ADGRE5 is expressed on antigen-presenting cells and recognizes CD55 on T cells to promote T cell activation. *B*: ADGRB1 in macrophages can interact via its thrombospondin repeats with exposed phosphatidylserine on apoptotic cells to induce engulfment. *C*: ADGRG3 is a key regulator of B cell fate, with the presence of ADGRG3 leading to decreased NF-κB signaling, cytoplasmic localization of CREB, and maintenance of follicular B cell populations. Figure created, with permission, using BioRender.com.

macrophages and other immune cells from apes, mice, and other species, suggesting an intriguing difference in immune cell physiology between humans and other animals (107, 108).

6.1.2. ADGRB subfamily.

Although members of the ADGRE subfamily were the first AGPCRs to be studied in the context of the immune system, AGPCRs from other subfamilies have also been found to exert striking effects on immune function. For example, ADGRB1 (BAI1, "B1") has been shown to play a key role in macrophage engulfment of apoptotic cells (109, 110) (**FIGURE 6*B***). B1 possesses multiple NH$_2$-terminal thrombospondin-like repeats, which can bind to externalized phosphatidylserine, a key signal of apoptosis (109, 110). In further work, the B1 NTF was also shown to recognize surface lipopolysaccharides on Gram-negative bacteria, with this association allowing for macrophage engulfment of the bacteria (111). The role of B1 in engulfment is facilitated by the interaction of the B1 COOH terminus with ELMO and DOCK proteins, which allow B1 to stimulate Rac pathways crucial for engulfment (109, 111). Interestingly, ADGRB1 also plays an important role in promoting the production of reactive oxygen species by macrophages (112), demonstrating that the receptor assists macrophages in their battle against bacteria both by enhancing macrophage microbicidal activity as well as by promoting engulfment. In addition to mediating macrophage antibacterial activity, B1 can also promote antiviral actions by macrophages (113). Recent work has shown that B1 can be difficult to detect in monocyte-derived macrophages (114), suggesting that the receptor's expression in these cells may be regulated in ways that are not yet defined.

6.1.3. ADGRG subfamily.

ADGRG1 (GPR56, "G1") exhibits high expression in CD56-null CD16+ natural killer (NK) cell subsets in the blood and inflamed peripheral tissues (115, 116). Overexpression of G1 in NK cells impairs this cell type's ability to migrate (116). G1 also negatively regulates other NK cell properties, including the production of inflammatory cytokines, degranulation, and target cell killing (117). In addition to G1 expression in NK cells, recent studies have demonstrated that this receptor can also be expressed in effector CD4+ memory T cells that reexpress CCR7 and CD45RA (118, 119), where its expression correlates with decreased TNF and IFN-γ production (119). Further work is needed to define the precise role(s) of G1 in T cells and compare/contrast the receptor's actions in this cell type to its more intensively studied activity in NK cells.

ADGRG3 (GPR97, "G3") has been shown to exert robust effects on B cell development (120). Mice lacking G3 exhibit a disorganized architecture of the spleen, including a sharply decreased follicular B cell population (120) (**FIGURE 6C**). Moreover, genetic deletion of G3 reduces macrophage migration into white adipose tissue, while simultaneously increasing macrophage migration into metabolic organs such as the liver and kidney (121). G3 has also been shown to be expressed in neutrophils, eosinophils, and mast cells (116, 122), although little is yet known about the receptor's actions in these cell types. The fact that G3 is robustly expressed in multiple immune cells is fascinating with regard to the recent revelation that G3 can be activated by glucocorticoids (15), as glucocorticoids are known to exert powerful effects on the physiology of many different cell types in the immune system, including a multitude of mysterious "nongenomic" actions that are not mediated via classical nuclear glucocorticoid receptors (123).

6.2. Nervous System

6.2.1. ADGRL subfamily.

Many adhesion GPCRs are highly expressed in the nervous system (124), with the earliest studies on AGPCRs in this system coming from work on ADGRL1–3. These receptors are also known as "latrophilins" because it was shown several decades ago that they can bind via their NTF regions to black widow spider alpha-latrotoxin (27, 125). Subsequent work demonstrated that the actions of alpha-latrotoxin on nervous system function (including the toxin's dramatic effects on neurotransmitter release) are mainly mediated via the formation of nonspecific cation channels by alpha-latrotoxin itself rather than through the toxin's activation of ADGRL signaling pathways (126, 127). Nonetheless, alpha-latrotoxin as an NH_2-terminal ligand capable of modulating ADGRL signaling proved to be a useful tool to elucidate some of the physiological actions of the members of this receptor subfamily.

Early studies on mice lacking ADGRL1 did not reveal any dramatic phenotypes (128). In vertebrates, ADGRL1 ("L1") and ADGRL3 ("L3") are largely expressed in the nervous system, whereas ADGRL2 ("L2") exhibits a wider pattern of expression (126, 129). Genetic deletion of ADGRL2 was found to result in embryonic lethality (130), demonstrating an essential function of the receptor in one or more organs in the body, similar to the essential role in development played by LAT-1, the *Caenorhabditis elegans* ortholog of ADGRL1–3 (131, 132). Although the embryonic lethality of L2-knockout mice made it difficult to discern the receptor's effects on brain physiology, mice with brain-specific deletion of L2 were found to be viable (130) and to exhibit decreased numbers of dendritic spines as well as input-specific impairments in the wiring of the stratum lacunosum moleculare in the CA1 region of the hippocampus (130, 133). Fascinatingly, mice lacking L3 were found to exhibit input-specific perturbations in distinct CA1 subfields, the stratum oriens and stratum radiatum (133), thereby demonstrating the exquisite specificity of ADGRL regulation of synaptic development. In related studies, L2 and L3 were found to play crucial roles in Purkinje cell formation of parallel fiber synapses in the cerebellum, with genetic deletion of both receptors together resulting in a dramatic loss in parallel fiber synaptic function (134). The effects of L2 and L3 on synaptic wiring have recently been shown to be dependent on the receptors' G protein-mediated signaling (135), which connects the receptors' signaling activity to their profound effects on synapse formation.

Many of the physiological actions of ADGRL1–3 are due to interactions with the receptors' extracellular binding partners. Specifically, these receptors have been shown to associate transcellularly via their NTF regions with teneurins (136–138) and FLRTs (139). Teneurin-2 is proteolytically shed during the course of synaptic development and can stimulate signaling by L1 on axonal growth cones to control axon attraction (140). Similarly, the aforementioned effects of L3 knockout on synaptic development in the hippocampal CA1 region cannot be rescued by mutant versions of L3 lacking the ability to interact with either FLRTs or teneurins, suggesting that ADGRL3 interactions with both classes of binding partners are essential for the ability of L3 to control synaptic wiring (133). Complementary in vivo studies have demonstrated that disruption of the ADGRL-teneurin association impairs excitatory synapse formation (14) and disruption of ADGRL-teneurin-FLRT complex formation perturbs the migration of neurons from cortical explants (13). Taken together, this body of work demonstrates that transcellular interactions of ADGRL1–3 with teneurins and FLRTs are critically important for dictating synapse formation in the brain.

6.2.2. ADGRB subfamily.

Another subfamily of adhesion GPCRs that exerts profound effects on synaptic function is ADGRB1–3 (BAI1–3, "B1–3"). Early work demonstrated that ADGRB1 is concentrated in the postsynaptic density (49, 50) and that knockdown of B1 both in cultured neurons (50) and in vivo (141) reduces dendritic spine formation in a manner dependent on the ability of the B1 COOH terminus to interact with Tiam1 to regulate Rac. ADGRB1 has also been shown to regulate dendritic arborization via association with the RhoGEF Bcr to control Rho signaling (55). These findings demonstrate that different signaling

pathways emanating from a single AGPCR can exert highly distinct physiological actions (**FIGURE 7**). Consistent with the idea that B1 is a key regulator of excitatory synapses in the brain, knockout mice lacking B1 were found to exhibit perturbations in postsynaptic density structure in addition to profound defects in synaptic plasticity and spatial learning (142).

Studies on B2 and B3 suggest that these receptors play roles similar to B1 in the nervous system, albeit at different populations of synapses. Mice lacking B2 have been shown to exhibit enhanced hippocampal neurogenesis and resistance to depressive phenotypes in mouse models of depression (143). B3 has been found to control dendritic arborization and branching both in vitro in cultured neurons and in vivo in Purkinje cells of the cerebellum (144). Further work in this area will likely clarify the synapse-specific actions of the various members of the ADGRB subfamily.

The striking effects of ADGRB1–3 in controlling dendritic growth and synaptic function are dependent on interactions of the receptors' NTF regions with various extracellular binding partners. For example, B1 has been shown to interact via its NH_2-terminal thrombospondin-like repeats with reticulon-4 receptors (RTN4Rs) (145, 146) in a manner that regulates dendritic arborization and synapse formation (145). Conversely, the thrombospondin-like repeats of ADRGB3 have been found to associate with the complement-like proteins C1ql1–4, with this association influencing synapse formation in cultured neurons (147). In vivo, C1ql1 promotes dendritic spine formation in Purkinje cells in a manner that depends upon the presence of B3 (148). Similarly, at a
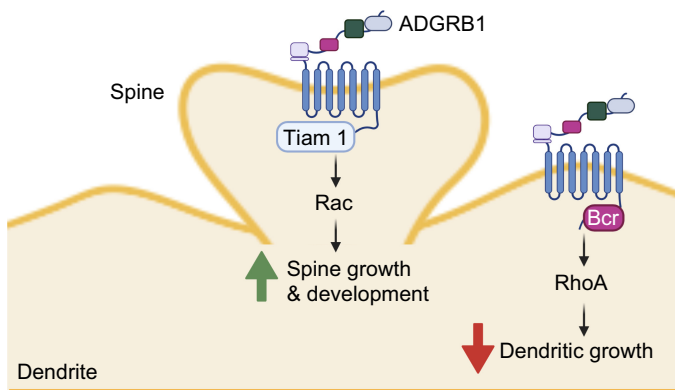
specific synaptic connection in the olfactory bulb, deletion of either C1ql3 or B3 results in a very similar phenotype (suppressed acquisition of the social transmission of food preference), thereby providing further evidence for the importance of the B3-C1ql interaction in vivo (149). Interactions of ADGRB3 with different members of the C1ql family have distinct effects on physiology, as, for example, that binding of B3 to C1ql4 inhibits secretion from pancreatic β-cells (150). The C1ql proteins most likely exert their effects on nervous system physiology by linking the ADGRB receptors to other key synaptic proteins, an idea advanced by recent work identifying the neuronal pentraxins NPTX1 and NPTXR as components of cell-cell adhesion complexes with C1ql3 and B3 (151).

6.2.3. ADGRC subfamily.

Similar to members of the ADGRB subfamily, ADGRC1–3 (Celsr1–3, "C1–3") have also been shown to play key roles in synapse formation. Knockout mice lacking C3 exhibit disrupted development of numerous axonal tracts, including a complete loss of the anterior commissure and internal capsule (152–156) (**FIGURE 8A**). C2 appears to be redundant with C3 at many synaptic connections, and dual deletion of both receptors can result in even more severe axonal pathfinding phenotypes than those observed in the individual knockouts (157). C2 and C3 also have important roles in controlling ciliogenesis, with the joint deletion of the two receptors resulting in a much more severe phenotype than either individual knockout (158).

The *Drosophila* ortholog of ADGRC1-3 is known as Flamingo, and this receptor exerts extensive cross talk with Frizzled to control planar cell polarity (PCP) in flies (159–161). Similar to the defects observed in flies with Flamingo mutations, mice lacking C1 exhibit a loss of PCP and severe neural tube defects early in development (162). Thus, analogous to Flamingo, C1 is considered a "core PCP" gene in vertebrates, whereas C2 and C3 are not considered core PCP genes even though they also exhibit cross talk with vertebrate Frizzled receptors (163). The molecular basis of this cross talk is still under investigation, as are the molecular mechanisms by which C2 and C3 exert their profound effects on axonal pathfinding and synapse formation. C2 and C3 are found both pre- and postsynaptically (164) and can interact in a *trans* fashion across junctions via the multiple cadherin-like repeats on their large NTF regions (165, 166), with ADGRC3, in particular, being essential for the formation of excitatory synapses in cultured neurons (164). Homophilic *trans* interactions (either C1-C1, C2-C2, or C3-C3) can stimulate the receptors' signaling activity (165) and also potentially serve to stabilize associations with other key proteins involved in the formation of
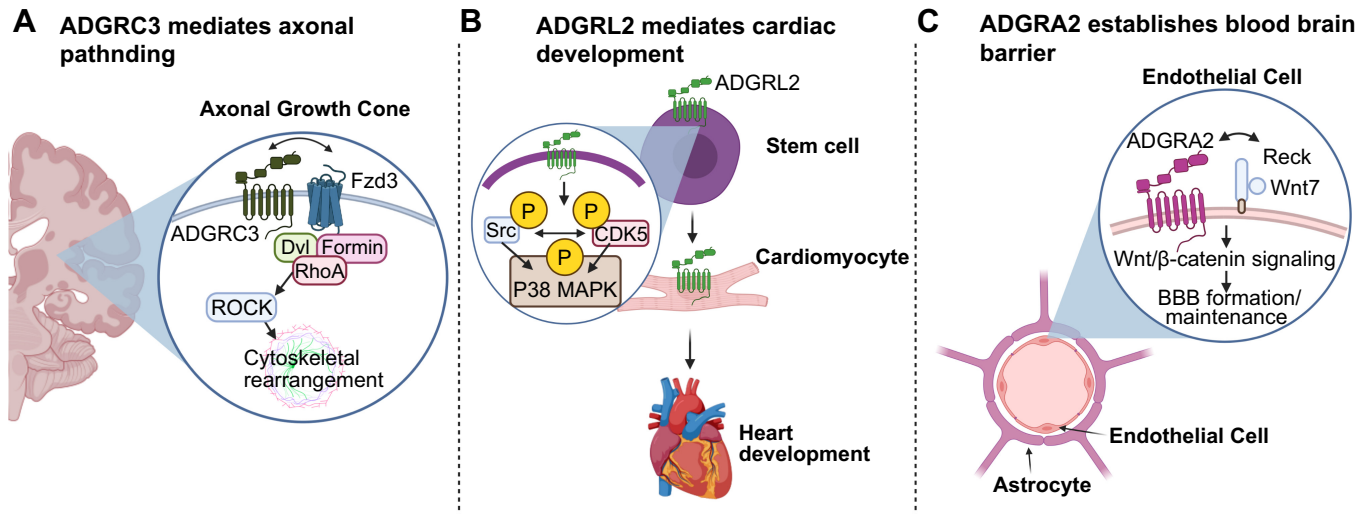
FIGURE 7. Adhesion G protein-coupled receptors (AGPCRs) can couple to multiple signaling pathways with differential effects on physiology. For example, ADGRB1 (B1) is known to associate with Tiam1 to stimulate Rac in a G protein-independent manner to promote dendritic spine growth and development. Conversely, B1 can also couple with Bcr to stimulate RhoA signaling via a completely distinct G protein-independent mechanism to inhibit dendritic growth. Thus, a given AGPCR can engage not only in multiple G protein-dependent pathways but also in multiple G protein-independent pathways that can exert differential effects on physiology. Figure created, with permission, using BioRender.com.

FIGURE 8. Adhesion G protein-coupled receptors (AGPCRs) are crucial in development. *A*: ADGRC3 is critical to axonal pathfinding during development, such that knockout of ADGRC3 results in loss of the ability to develop many essential axonal tracts. Mechanistically, ADGRC3 engagement of Fzd3 triggers RhoA signaling and subsequent cytoskeletal rearrangement to facilitate axonal pathfinding. *B*: ADGRL2 is critical for cardiac development. Normally, ADGRL2 signaling triggers phosphorylation of p38 MAPK to promote development of the heart. Loss of ADGRL2 results in dysfunctional cardiomyocytes, leading to abnormal heart development. *C*: ADGRA2 is key to the development of the blood-brain barrier (BBB). The interaction of ADGRA2 and Reck triggers β-catenin signaling to promote the formation of the BBB. Loss of ADGRA2, which normally engages in *cis* interactions with Reck on endothelial cells, results in defective BBB development. Figure created, with permission, using BioRender.com.

synapses and other types of cellular junctions (167). In addition, ADGRC3 can interact via its extracellular domain with dystroglycan, with this association being crucial for certain axon guidance decisions (168).

6.2.4. ADGRF subfamily.

Synaptamide (*N*-docosahexaenoylethanolamine) is a bioactive lipid known to exert several effects on nervous system physiology, and, as mentioned above, ADGRF1 (GPR110, "F1") has been identified as a receptor for this bioactive lipid (80). Synaptamide is so named because it can promote synaptogenesis in cultured neurons, but this effect is lost in neurons lacking F1; moreover, in vivo deletion of F1 from mice results in significant memory deficits (80). Another effect of synaptamide that is lost in F1-knockout mice is the ability of this lipid to attenuate brain inflammation following injection of mice with lipopolysaccharide (LPS) (169). An additional in vivo action of synaptamide is the promotion of recovery from nerve injury, and genetic deletion of F1 also blocks this effect (170). Interestingly, synaptamide has been reported to bind to the F1 GAIN domain (81), thereby raising the interesting question of whether other AGPCRs beyond F1 may bind via their GAIN domains to either synaptamide or related bioactive lipids.

6.2.5. ADGRG subfamily.

ADGRG1 (GPR56, "G1") plays an essential role in nervous system development that is distinct from the roles played by the various members of the ADGRL, ADGRB, ADGRC, and ADGRF subfamilies. G1 is expressed at high levels in neural progenitor cells (NPCs) (171, 172), and deletion of this receptor in mice causes the improper targeting of NPCs during early brain development, resulting in a cobblestone malformation of the cerebral cortex (173). G1 expression is lost in most differentiated cells in the central nervous system (CNS) but retained in oligodendrocyte precursor cells (OPCs), with loss of G1 function resulting in reduced numbers of mature oligodendrocytes and striking deficits in myelination in both mice (174, 175) and zebrafish (176). G1 is also expressed in Schwann cells, the myelin-producing cells of the peripheral nervous system, and loss of G1 function in zebrafish results in decreased myelination of peripheral nerves (177).

G1 exerts its profound actions on brain development and myelination via interaction with several key extracellular binding partners, including transglutaminase-2 (178, 179) and collagen III (180). Transglutaminase-2 released from microglia has been shown to interact with G1 on the surface of OPCs in a manner essential for the aforementioned effects of G1 on myelination (181), with these studies providing an intriguing example of glia-to-glia signaling. The physiological importance of the G1-collagen III interaction is suggested by observations that mice lacking collagen III exhibit a cobblestone malformation of the cerebral cortex that is nearly identical to the phenotype observed in mice lacking G1 (182). In addition to recognition of transglutaminase-2 and collagen III, one further way that ADGRG1 regulates brain

development is via its expression in microglia, where it facilitates microglial recognition of exposed phosphatidylserine on synaptic processes to mediate synaptic pruning (183).

Like ADGRG1, the related ADGRG6 (GPR126, "G6") can also regulate peripheral myelination, as shown in studies in both zebrafish (184) and mice (185). G6 modulates cyclic AMP levels in Schwann cells to control the migration and myelination activity of these cells (186). In addition to its role in development, G6 expression is maintained in adult Schwann cells, where the receptor promotes peripheral nerve regeneration after injury (187, 188).

G6 has several extracellular binding partners that are important in determining the receptor's physiological actions. These binding partners include collagen IV (189), lamin-211 (77), and the cellular prion protein PrP^C (190). The receptor's interaction with lamin-211 has been shown to influence G6-mediated cyclic AMP signaling and to be important for the aforementioned ability of G6 to control Schwann cell myelination activity (77). PrP^C can also promote G6-mediated cyclic AMP signaling to enhance G6-dependent myelination of peripheral nerves (190). Knockout mice lacking PrP^C exhibit late-onset peripheral neuropathy and demyelination (190), suggesting that the G6-PrP^C interaction may be a key determinant of peripheral myelin maintenance in vivo.

6.3. Cardiopulmonary and Cardiovascular Systems

6.3.1. ADGRG subfamily.

ADGRG6 (GPR126), which as discussed in sect. 6.2.5 plays an essential role in peripheral nerve myelination, is also critically important for cardiac development. Mice and zebrafish that lack G6 expression exhibit severe abnormalities in the development of the heart, including a pronounced thinning of the myocardial wall (191, 192). Intriguingly, this cardiac phenotype can be rescued in zebrafish by expression of just the NTF region of G6; in contrast, expression of the G6 NTF was not found to rescue the peripheral nerve myelination deficits of zebrafish lacking G6 (192). These findings suggest that G6 signaling is necessary for the receptor's effects on myelination but not its regulation of cardiac development, thereby providing a fascinating example of how the NTF and CTF domains of AGPCRs can have distinct physiological functions (**FIGURE 9**).

ADGRG1 (GPR56) is a close relative of G6 that is not known to affect the heart but has been shown to exert powerful regulation over hemostasis. G1 is highly expressed in platelets, which play a key role in blood clotting, and mice lacking G1 exhibit delayed platelet responses and prolonged bleeding (193). Platelet interactions with collagens are known to be crucial for clot
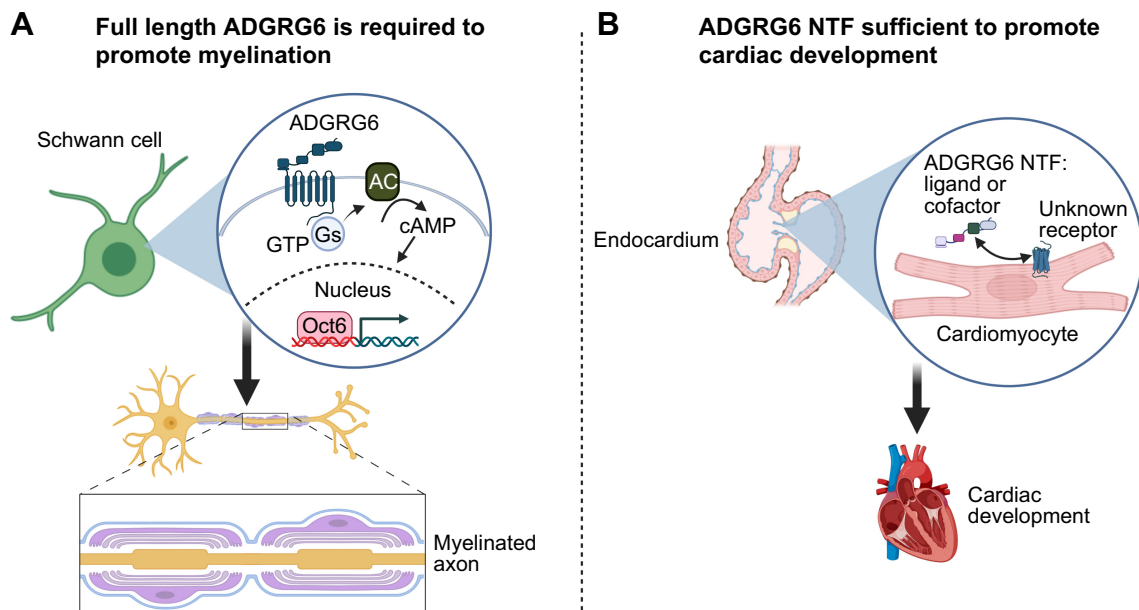

A **Full length ADGRG6 is required to promote myelination**

Schwann cell — ADGRG6 — AC — GTP Gs — cAMP — Nucleus — Oct6 — Myelinated axon

B **ADGRG6 NTF sufficient to promote cardiac development**

Endocardium — ADGRG6 NTF: ligand or cofactor — Unknown receptor — Cardiomyocyte — Cardiac development

FIGURE 9. Some adhesion G protein-coupled receptor (AGPCR) physiological effects are entirely due to the NH_2-terminal fragment (NTF), whereas others are not. A: loss of ADGRG6 (G6) results in disrupted myelination. This functional deficit can be rescued only by reexpression of the entire receptor, which allows for G6-stimulated cAMP production and changes in gene transcription to drive myelination of axons. B: loss of ADGRG6 also results in defective cardiac development. Remarkably, this phenotype can be rescued via expression of solely the receptor's NTF, revealing that the entire receptor is not required for the physiological effects of G6 in cardiac tissue. It is believed that the G6 NTF acts as a ligand or cofactor for an unknown cardiomyocyte receptor that promotes cardiac development. Figure created, with permission, using BioRender.com.

formation, and the aforementioned interaction of the G1 NTF region with collagen III (180) allows G1 on platelets to act as a sensor of shear force, activating platelet signaling pathways that contribute to hemostasis (193).

6.3.2. ADGRL subfamily.

As mentioned above, genetic deletion of ADGRL2 (Latrophilin-2, "L2") results in embryonic lethality (130). This phenotype can be explained, at least in part, by the fact that L2 is highly expressed in the heart (both myocardium and endothelium) and plays a role in the epithelial-mesenchymal transition (EMT) (194). L2 effects on cardiac development begin very early, as expression of the receptor is turned on during the differentiation of pluripotent stem cells into cardiac progenitor cells (195, 196) (**FIGURE 8B**). Indeed, genetic deletion of L2 prevents pluripotent stem cells from expressing any cardiac-specific genes whatsoever (196).

Another member of the ADGRL subfamily that is expressed in the heart is ADGRL4 (ELTD1, "L4"). Deletion of this receptor from mice results in aggravated cardiac hypertrophy and thickening of the heart's ventricular walls in response to pressure overload (197). Double knockout of both L4 and another AGPCR, ADGRF5 (discussed further in sect. 6.3.3), results in an even more dramatic phenotype characterized by malformations of the aortic arch arteries and perinatal lethality in most of the double-knockout mice (198).

6.3.3. ADGRF subfamily.

As mentioned in sect. 6.3.2, ADGRF5 (GPR116, "F5") is expressed in the heart and can influence cardiac development (198). However, the highest expression of F5 is in the lung, where it plays a crucial role in lung surfactant homeostasis (199–201) (**FIGURE 10A**). In addition to disrupted surfactant function, F5-knockout mice also display emphysema-like symptoms associated with an abnormal accumulation of alveolar macrophages (202, 203). The effects of F5 on pulmonary function are primarily due to G protein-dependent signaling by the receptor through $G\alpha q/11$; indeed, genetic deletion of $G\alpha q$ and $G\alpha 11$ phenocopies the effects of ADGRF5 knockout on lung surfactant homeostasis (204).

6.3.4. ADGRA subfamily.

ADGRA2 (GPR124, "A2") is highly expressed in the endothelium, and genetic deletion of A2 from mice results in a particularly dramatic disruption of angiogenesis in the brain marked by a complete loss of angiogenic sprouting into the neural tube and failure to establish the blood-brain barrier (205–208). A2 (and family member A3) is a necessary coactivator of the secreted ligand Wnt7 and works in concert with Frizzled receptors to mediate the effects of Wnt7 on angiogenesis (209, 210). This intriguing AGPCR-Frizzled cross talk involving A2 is reminiscent of the cross talk observed in *Drosophila* between Flamingo and Frizzled (159).

Further studies on A2 have shed light on how this receptor exerts its effects on vascular physiology. Mechanistic studies have revealed that the receptor's regulation of brain angiogenesis requires the interaction of the A2 NTF with the GPI-anchored extracellular protein RECK (211–216) (**FIGURE 8C**) as well as the interaction of the A2 CTF with cytoplasmic proteins from the

A **ADGRF5 maintains surfactant homeostasis**

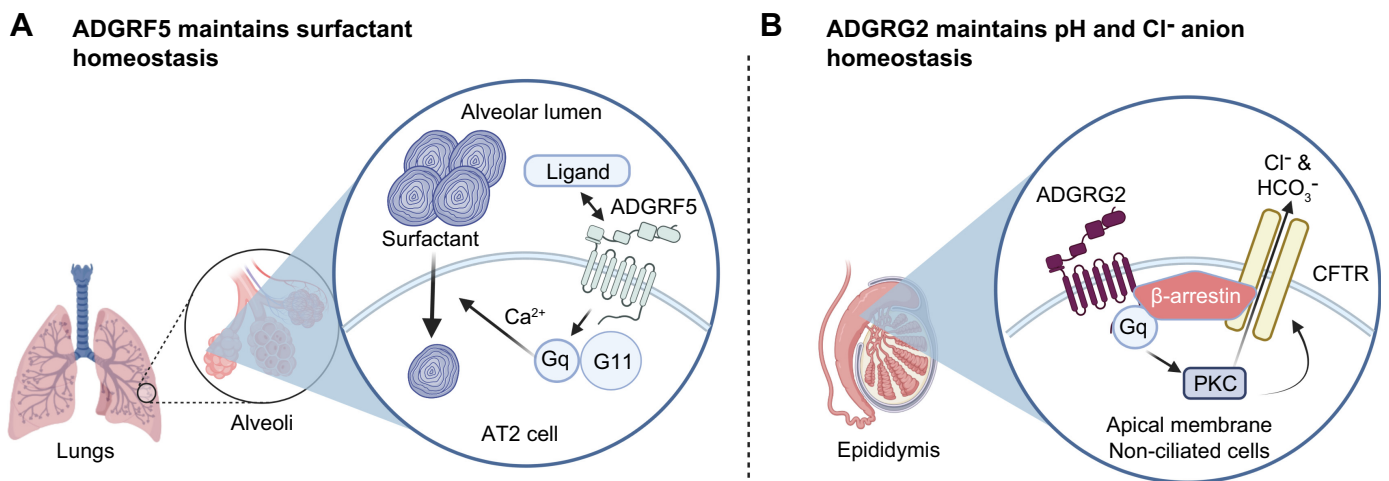**B** **ADGRG2 maintains pH and Cl⁻ anion homeostasis**

FIGURE 10. Adhesion G protein-coupled receptors (AGPCRs) regulate fluid homeostasis by coupling to G proteins. *A*: ADGRF5 is critical to the normal function of the lungs, where this receptor engages in signaling via $G\alpha q/G\alpha 11$ to maintain normal levels of surfactant critical to alveolar function. *B*: ADGRG2 is essential for the normal physiology of the epididymis. The receptor engages in G protein-dependent signaling via $G\alpha q$ and β-arrestin binding to control pH and ion homeostasis. Figure created, with permission, using BioRender.com.

Dishevelled (214), intersectin, and ELMO/DOCK families (217). ADGRA2 interactions with integrins also contribute to the receptor's regulation of angiogenesis (218). Experiments with conditional A2-knockout mice have demonstrated that loss of A2 from endothelial cells in adulthood results in disruption of the blood-brain barrier, revealing that the effects of A2 are not just essential in development but also continue to be important in the adult (219). Like A2, ADGRA1 (GPR123, "A1") is highly expressed in the central nervous system, although A1 is expressed in neurons rather than endothelial cells and influences energy expenditure and thermogenesis rather than regulating the blood-brain barrier (220).

6.4. Other Systems

6.4.1. ADGRG subfamily.

In addition to the physiological roles described above for ADGRG1 (GPR56, "G1") in the immune, nervous, and cardiovascular systems, this receptor has also been shown to play important roles in the pancreas and skeletal muscle. G1 is one of the most abundantly expressed GPCRs in pancreatic islets (221). Moreover, the G1 ligand collagen III stimulates pancreatic beta cell signaling pathways, promotes beta cell survival, and potentiates glucose-induced insulin secretion in a manner that is dependent on stimulation of G1 (221, 222). In muscle tissue, G1 promotes myoblast fusion (223) and regulates mechanical overload-induced muscle hypertrophy (224) in a manner dependent on interaction with the G1 ligand transglutaminase-2 (225).

ADGRG2 is most highly expressed in the epididymis, where it exerts striking effects on physiology (**FIGURE 10*B***). Male G2-knockout mice are infertile, exhibiting a buildup of fluid in the testis that perturbs normal sperm movement (226). G2 is specifically expressed in epididymal cell types that are known to be involved in fluid reabsorption (227), and in these cells G2 regulates the expression of several key epididymal genes (228). G2 also directly regulates ion flow via G protein-mediated signaling and arrestin-mediated complex formation with ion channels (43). Another cell type that exhibits significant G2 expression is the adipocyte, where the receptor has been found to regulate metabolism (229). In contrast, the related G6 was found in this same study to regulate adipocyte differentiation (229). G7 is highly expressed in intestinal tissues and has recently been shown to bind to the ELMO family of proteins (230), although the relevance of this interaction for gastrointestinal physiology remains to be explored.

6.4.2. ADGRB subfamily.

Like ADGRG1, ADGRB1 (BAI1, "B1") (54) and ADGRB3 (BAI3, "B3") (53, 231) are expressed in muscle tissue and promote myoblast fusion. B1 is especially highly expressed in cells of the Myo/Nog lineage, which are defined by coexpression of the skeletal muscle-specific transcription factor MyoD and the secreted protein Noggin (232). The regulation of myoblast fusion by B1 and B3, similar to some of the aforementioned actions of these receptors in the immune and nervous systems, is dependent on the interaction of the receptors' CTF regions with ELMO/DOCK proteins (53, 54). Interestingly, B1 and B3 are both essential for normal myoblast fusion and cannot functionally substitute for each other (53, 54), revealing that the receptors exert unique and nonredundant effects on myoblast physiology.

6.4.3. ADGRF subfamily.

Mice with adipose-specific deletion of ADGRF5 exhibit marked glucose intolerance and insulin resistance, revealing an important role for this receptor in the physiology of adipose tissue (233). More recent work has shown that F5 binds to the secreted hepatokine FNDC4 and mediates the ability of FNDC4 to promote insulin signaling and insulin-mediated glucose uptake in white adipocytes (234). The insulin-sensitizing effects of FNDC4 are due to its ability to stimulate F5 coupling to Gαs and promote downstream signaling through the cyclic AMP pathway (234). Beyond F5, there are several other AGPCRs that have recently been shown to be robustly expressed in various adipose cell types (229), and thus future studies in this area may reveal other fascinating examples of AGPCR regulation of adipose tissue physiology.

As mentioned above, mice lacking ADGRF5 exhibit cardiac defects, especially when ADGRL4 is also deleted, and it should be pointed out that these mice also exhibit defects in kidney function, notably the development of glomerular thrombotic microangiopathy (198). More recent studies have demonstrated high expression of F5 in the specialized acid-secreting A-intercalated cells (A-ICs) of the kidney (235). Moreover, F5-knockout mice exhibit a profound dysregulation of A-IC regulation of urine and blood pH (235).

Although F5 has been found to exert important physiological actions in lung, heart, adipose tissue, and kidney, as described above, the physiological importance of the related F4 has remained more elusive. However, recent studies have demonstrated that F4 is highly expressed in ameloblasts, the cell type that deposits enamel during tooth development (236). Indeed, genetic deletion of F4 from mice results in a dramatic hypomineralization of

tooth enamel due to the dysregulation of the expression of certain genes, such as carbonic anhydrase 6, that are known to be crucially important for tooth enamel mineralization (236).

7. PATHOPHYSIOLOGY OF ADHESION GPCRs

The clinical relevance of adhesion GPCRs is clear, given that mutation and/or dysfunction of many members of this family have been shown to underlie human disease. The frequent involvement of AGPCRs in pathophysiology contributes to the attractiveness of these receptors as therapeutic targets for treating disease and enhancing human health. In this section, we discuss the connections between various AGPCRs and human disorders.

7.1. ADGRV Subfamily

The first AGPCR to be recognized as a human disease gene was ADGRV1 (VLGR1 or "V1"). Mutations in V1 were found to be responsible for Usher syndrome type 2C (USH2C) (237). Usher syndrome is the most common cause of combined deafness and blindness, and there are multiple types of Usher syndrome caused by mutations to different genes. USH2C, which is caused by V1 mutations, is characterized by severe hearing loss and late-onset retinitis pigmentosa (237). The deaf-blindness that characterizes this condition is related to the tissue distribution of VLGR1, as the receptor is expressed at high levels in the stereocilia of the cochlea as well as in the ciliary membrane of visual photoreceptors (238, 239) (**FIGURE 11A**). Interestingly, V1 has been found to form a physical complex in stereocilia with the cytoplasmic scaffold protein harmonin, which is the product of the Usher syndrome type 1C gene (47), and the actin-binding protein myosin VIIA, which is the product of the Usher syndrome type 1B gene (240), thereby demonstrating physical complex formation between these three Usher syndrome gene products.

The various ADGRV1 mutations that cause Usher syndrome are located throughout the receptor's domains. The majority of the pathological mutations are found on the receptor's massive extracellular NH_2 terminus, which is >5,000 amino acids in length (237). For example, a mutation in the ADGRV1 gene that truncates the receptor's NTF results in an autosomal-recessive, sound-induced seizure phenotype in the Frings mouse (241). However, some human-linked mutations are found on the V1 cytoplasmic regions, where they disrupt the receptor's interactions with key scaffold proteins and alter its coupling to G proteins (242). As mentioned above, there is recent evidence that ADGRV1 can act as a mechanosensor (78). Given that the primary job of cochlear hair cells is to detect auditory vibrations to mediate the sense of hearing, these observations of a mechanosensory role for V1 may shed light on the physiological role of V1 in hair cells that, when disrupted, leads to deafness.

7.2. ADGRG Subfamily

Alongside the link between ADGRV1 and Usher syndrome, the other most intensively studied connection
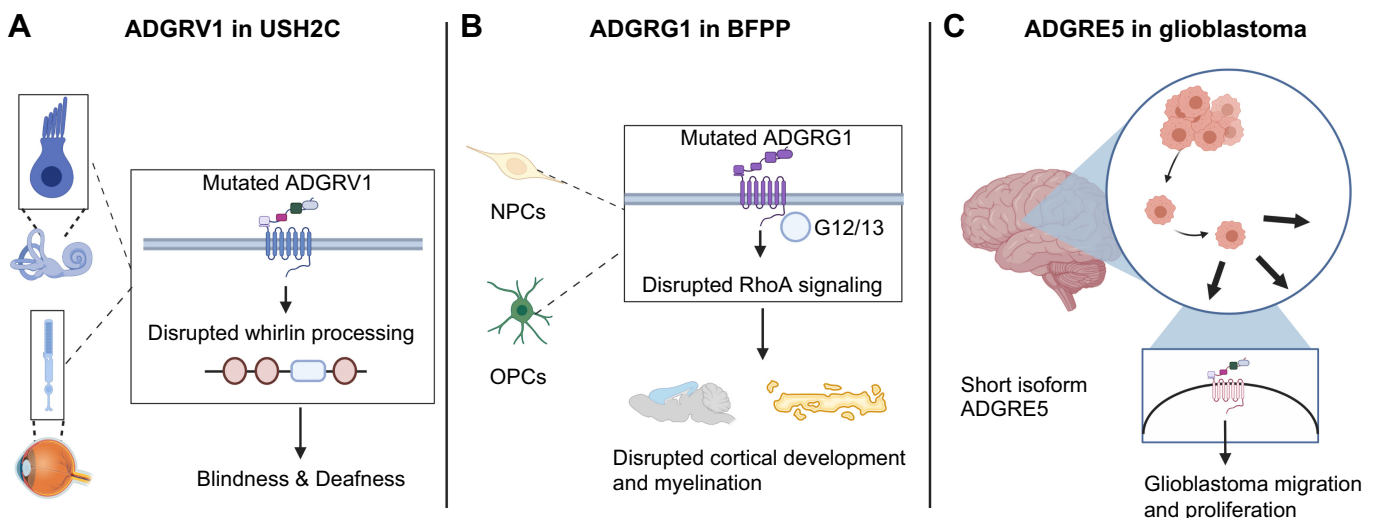

FIGURE 11. Adhesion G protein-coupled receptors (AGPCRs) can drive pathophysiology. *A*: mutations in ADGRV1 are associated with the development of Usher syndrome type 2C (USH2C). Dysfunction of this receptor can lead to deafness and blindness due to disrupted whirlin processing. *B*: mutations of ADGRG1 perturb RhoA signaling and cause bilateral frontoparietal polymicrogyria (BFPP), which is characterized by disrupted cortical development due to dysregulated neural progenitor cells (NPCs) and disrupted myelination due to altered activity of oligodendrocyte precursor cells (OPCs). *C*: ADGRE5 is upregulated in glioblastoma and associated with increased tumor invasiveness. Figure created, with permission, using BioRender.com.

between AGPCRs and human disease is the observation that mutations to ADGRG1 (GPR56, "G1") cause bilateral frontoparietal polymicrogyria (BFPP) (23, 171). BFPP is characterized by dysregulation of the wiring of the cerebral cortex and myelination deficits, with these clinical observations fitting well with the aforementioned studies in animal models revealing key roles for G1 in neural progenitor cell migration (173) and oligodendrocyte development (174) (**FIGURE 11*B***). The G1 mutations that lead to BFPP exert various effects on the receptor's function, including perturbation of receptor trafficking, signaling, and/or interaction with collagen III (243–248). Heparin is another extracellular ligand for G1 that exhibits altered binding to BFPP-associated G1 mutants (249). Additionally, G1 binding of the secreted peptide progastrin in colonic stem cells has been linked to colorectal carcinogenesis, thus marking G1 as a target for the treatment of this disorder as well (250).

Gene variants in another member of the ADGRG subfamily, ADGRG6 (GPR126, "G6"), have been shown to strongly contribute to the development of adolescent idiopathic scoliosis (AIS) (251, 252). G6 is highly expressed in cartilage, and zebrafish studies have demonstrated that genetic deletion of G6 leads to delayed ossification of the developing spine (251) in addition to the myelination (184) and cardiac (192) phenotypes described earlier. AIS is a polygenic disorder, and thus ADGRG6 variants do not entirely dictate the pathology as in the cases described above for ADGRV1/USH2C or ADGRG1/BFPP, but nonetheless the connection of AIS to G6 function has led to a better understanding of the disorder and new ideas for therapeutic approaches (253).

Members of the ADGRG subfamily have also been linked to human cancers. For example, G1 is overexpressed in gliomas and regulates glioma cell attachment, migration, mesenchymal differentiation, and radioresistance (254–256). In contrast, G1 is downregulated in metastatic melanoma and exerts effects on melanoma growth, migration, and angiogenesis (178, 257–260). G1 has additionally been identified as an important marker for leukemic stem cells in acute myeloid leukemia (AML) (261–263), and G1 deletion/knockdown has been found to greatly delay AML development in mouse models (261, 264). In terms of other members of the subfamily, G2 is overexpressed in Ewing's sarcoma (265) and parathyroid tumors (38), whereas G6 is overexpressed in colorectal cancer, where it promotes the growth of colorectal cancer cells (266).

7.3. ADGRB Subfamily

Consistent with the aforementioned important roles of the ADGRB subfamily in the brain (267, 268), genetic variation in these receptors has been linked to various psychiatric and neurological disorders. For example, B3 variants or changes in copy number have been linked in genetic studies to intellectual disability, cerebellar atrophy, and schizophrenia (269–272). Similarly, a B2 variant that encodes a receptor with increased constitutive signaling activity has been linked in genetic analyses to a rare neurodegenerative condition marked by severe spinal cord atrophy (17).

ADGRB receptors have also been implicated in human cancers. In glioblastoma, B1 acts as a tumor suppressor (273, 274), and its expression is lost during glioblastoma progression (275) due to epigenetic silencing (276). Similarly, in medulloblastoma, B1 also exerts a tumor suppressor action and again its expression is lost due to epigenetic silencing during cancer progression (277–279).

7.4. ADGRD Subfamily

Unlike ADGRB1, which as mentioned above is downregulated in glioblastoma, ADGRD1 (GPR133, "D1") is markedly upregulated in glioblastoma and promotes glioblastoma growth (280). Cleavage of the GAIN domain and dissociation of the NTF-CTF complex are essential for the regulation of glioblastoma signaling by D1 (281). Interestingly, D1 is most highly expressed in the hypoxic regions of glioblastoma tumors, where it promotes the survival of tumor cells under conditions of hypoxia (282). The observation that ADGRD1 is expressed at high levels in glioblastoma without being detectably expressed in normal brain tissue makes this receptor an attractive target for novel therapeutics aimed at treating glioblastoma (282).

7.5. ADGRE Subfamily

Another AGPCR that is overexpressed in glioblastoma and has been shown in multiple studies to promote the invasiveness of glioblastoma cells is ADGRE5 (283–286) (**FIGURE 11*C***). Similarly, E5 is also upregulated in other types of cancer beyond glioblastoma and has been demonstrated to promote the invasiveness of many of these cancer types (62, 287–291). Interestingly, E5 can also facilitate platelet interactions with tumors to promote metastasis (292).

In terms of other connections between ADGRE subfamily members and human disease, a missense mutation in ADGRE2 has been associated in multiple families with vibratory urticaria, a condition marked by hives in response to dermal vibration (293, 294). Interestingly, this disease-linked mutation in the E2 GAIN domain was found to promote dissociation of the receptor's NTF and CTF regions in response to vibration (293). Thus, the mutant receptor was hypersensitive to mechanical

stimuli, leading to sensitization of mast cells (which express high levels of ADGRE2) to vibration-induced degranulation and likely accounting for the skin pathology in the affected families. These findings demonstrate the clinical utility of prior basic research, discussed above, that shed light on both the mechanisms of AGPCR signaling (64, 74) and the ability of AGPCRs to serve as mechanosensors (295).

7.6. ADGRC Subfamily

ADGRC1–3 (Celsr1–3, "C1–3") are most abundantly expressed in the nervous system and have been linked to several nervous system disorders in humans. Notably, ADGRC1 mutations or copy number variations have been linked to human neural tube defects, including craniorachischisis and spina bifida (296–299). These clinical reports are consistent with the aforementioned studies in animal models demonstrating an essential role for C1 in neural tube development (162). Additionally, C1 has recently been linked to neuroprotection after cerebral ischemic injury through the promotion of Wnt/PKC signaling (300). In contrast, human mutations in ADGRC2 have been linked to the ciliopathy known as Joubert syndrome (301–303), which makes sense given that animal studies have revealed a major role for C2 in the control of ciliogenesis, as described above (158). ADGRC3 has several connections to pathophysiology, as its expression has been associated with hepatocarcinogenesis (304), and moreover C3 de novo and copy number variants have been strongly associated with Tourette disorder (305, 306), an observation that has generated interest given how few genes have been convincingly linked to Tourette disorder at this point despite intense research interest in this area.

7.7. ADGRF Subfamily

Several members of the ADGRF family have been shown to play significant roles in cancer development and progression. ADGRF1 (GPR110, "F1") is overexpressed in several different human cancers (307, 308) including glioma (309), breast cancer (310), osteosarcoma (311), and lung cancer (312). In both glioma and breast cancer cells, knockdown of F1 was shown to reduce the cells' invasiveness (308, 310), whereas in lung cancer cells F1 was found to accelerate proliferation and migration (312). Similarly, knockdown of the related ADGRF5 in breast cancer cells was found to suppress migration and invasion, and knockdown of F5 in vivo was observed to markedly reduce breast cancer metastasis in two mammary tumor metastasis mouse models (313).

7.8. ADGRL Subfamily

As mentioned above, the members of the ADGRL subfamily (Latrophilin 1–3, "L1–3") have been demonstrated in animal studies to control the wiring of specific synaptic connections in the brain, and, in a related vein, these receptors have also been linked in genetic studies to various nervous system disorders. For example, ADGRL3 variants have been connected in multiple large-scale studies to enhanced risk of developing attention deficit hyperactivity disorder (ADHD) (314–320). In contrast, variants in ADGRL2 have been associated with microcephaly (321) and cocaine use disorder (322).

With regard to human cancers, the member of the ADGRL subfamily that has been studied most intensively is ADGRL4 (ELTD1, "L4"). This receptor has been found to be overexpressed in gliomas (323) and to regulate glioma cell proliferation and migration (324). Further analyses have demonstrated that L4 is also overexpressed in several other types of cancer beyond glioma and powerfully promotes angiogenesis to facilitate cancer growth (325).

7.9. ADGRA Subfamily

As mentioned in sect. 6.3.4, another AGPCR that is known to exert dramatic effects on angiogenesis is ADGRA2 (GPR124, "A2") (205–207, 326, 327). Given these proangiogenic actions in normal physiology, it is not surprising that A2 has also been shown to play a role in cancer development. In fact, the receptor was originally identified as a cell surface marker for tumor endothelial cells, and therefore dubbed "tumor endothelial marker 5" or "TEM5" (328, 329). Subsequent work has demonstrated that ADGRA2 is overexpressed in several cancer cell types, including urothelial carcinoma (330) and lung adenocarcinoma (331). Moreover, A2 was recently shown to promote glioblastoma cell proliferation via mechanisms that go beyond the promotion of angiogenesis (332).

8. CONCLUDING THOUGHTS

The adhesion GPCRs are a diverse and fascinating family of receptors that play crucial roles in many different physiological processes. The importance of these receptors in human physiology is highlighted by the large number of clinical disorders that are associated with AGPCR dysfunction. The past decade has seen an explosion of interest in AGPCRs as well as a wide expansion in their perceived function. Early work on AGPCRs focused mainly on the ability

of these receptors to mediate adhesion, but the emerging view is that AGPCRs serve as large-scale signaling platforms that integrate and interpret multiple types of stimuli, including adhesive, mechanosensory, and chemical signals.

This paradigm shift raises many interesting questions. For example, in the case of AGPCRs that can be activated both by small-molecule ligands and mechanosensory forces, how exactly are these signals integrated to determine receptor activation state? Should one of these signals be viewed as the "orthosteric" agonist controlling receptor activity, with the other(s) considered as "allosteric" modulation? Or will a completely different model be required to understand the pleiotropic nature of AGPCR signaling?

Another set of mysteries driving future research in this area relates to the AGPCR GAIN domains. What is the physiological significance of GAIN domain autoproteolysis? Despite a decade of intense research in this area, including crystal structures of multiple GAIN domains and numerous studies on AGPCRs harboring mutant GAIN domains deficient in self-cleavage, there is still no definitive answer to this question. Do the NTF and CTF fragments of AGPCRs usually dissociate during receptor activation, or is it more typical for ligands (and/or mechanosensory forces) to merely alter the conformations of the two associated fragments to initiate receptor signaling? Future studies, including the elucidation of cryo-EM structures of active versus inactive AGPCRs, will likely provide critical insights into the structural changes that underlie AGPCR activation and the importance of GAIN domain autoproteolysis for this process.

Finally, further work in this emerging area will undoubtedly reveal many additional physiological roles for AGPCRs and also lead to new therapeutic approaches for targeting these receptors. The relatively limited number of small-molecule ligands currently known for AGPCRs (15, 32, 33, 35, 81–83) seems destined to expand dramatically in the coming years into a much more extensive armamentarium, which will create novel tools to facilitate research in this area while also providing exciting new avenues for the treatment of human disease.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

T.L. and R.A.H. prepared figures; drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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