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**Adhesion G Protein–Coupled
Receptors as Drug Targets**

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Abstract

The adhesion G protein–coupled receptors (aGPCRs) are an evolutionarily ancient family of receptors that play key roles in many different physiological processes. These receptors are notable for their exceptionally long ectodomains, which span several hundred to several thousand amino acids and contain various adhesion-related domains, as well as a GPCR autoproteolysis–inducing (GAIN) domain. The GAIN domain is conserved throughout almost the entire family and undergoes autoproteolysis to cleave the receptors into two noncovalently-associated protomers. Recent studies have revealed that the signaling activity of aGPCRs is largely determined by changes in the interactions among these protomers. We review recent advances in understanding aGPCR activation mechanisms and discuss the physiological roles and pharmacological properties of aGPCRs, with an eye toward the potential utility of these receptors as drug targets.



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INTRODUCTION

G protein-coupled receptors (GPCRs) are highly amenable to modulation by pharmaceuticals, and it is estimated that one-third of currently approved drugs target GPCRs (1). However, these therapeutics are focused on only a small fraction of the GPCR superfamily, and no drugs have been approved to target any members of the second-largest GPCR family, the adhesion GPCRs (aGPCRs), which includes 33 members in humans. Thus, the aGPCR family possesses enormous potential for drug discovery, especially because aGPCRs have been linked to a wide variety of different diseases and regulate many important physiological processes throughout the body. In this review, we discuss the relatively brief history of aGPCR research and describe the many recent advances that have shed light on aGPCR ligands, activation mechanisms, and downstream signaling pathways. We also discuss the roles of aGPCRs in various aspects of physiology and how these receptors might be targeted by novel therapeutics to treat human diseases.

ADHESION GPCR FUNDAMENTALS

Traditionally, aGPCRs have been named for idiosyncratic reasons, dependent more on the circumstances of their initial characterization than on the fact that they belong to the aGPCR family. Recently, though, all aGPCRs were renamed with the ADGR prefix, followed by a letter indicating the receptor subfamily and a number for each receptor within that group (2). This new nomenclature has been adopted by the International Union of Basic and Clinical Pharmacology and is used as the primary identifier for receptors discussed here. **Table 1** lists the 33 human aGPCRs with their new and previous identifiers.

The first characterization of aGPCRs was in the area of immunology in the mid-1990s. A homolog of the mouse macrophage marker F4/80 was determined to be a seven-transmembrane-spanning (7-TM) protein and named EMR1 (for epidermal growth factor-like molecule containing mucin-like hormone receptor 1) (3). A few months later, work by a different group identified the leukocyte activation marker CD97 as a 7-TM receptor (4). These two receptors would later

Table 1 A summary of adhesion GPCR nomenclature and key signaling pathways^a

Subfamilies	New nomenclature	Previous identifier(s)	Signaling pathways	N-terminal fragment interactors
III	ADGRA1	GPR123	Not known	Not known
	ADGRA2	GPR124, TEM5	β -catenin (47), Cdc42 (99)	Heparin (71), $\alpha_v\beta_3$ integrin (71), WNT7 (47)
	ADGRA3	GPR125	Not known	Not known
VII	ADGRB1	BAI1	Rac1 (45, 46), $G\alpha_{12/13}$, RhoA (12, 19)	Phosphatidylserine (45), lipopolysaccharide (62), $\alpha_v\beta_5$ integrin (63)
	ADGRB2	BAI2	$G\alpha_{16}$, NFAT-Luc (21)	Not known
	ADGRB3	BAI3	Not known	C1ql1 (65), C1ql3 (64)
IV	ADGRC1	CELSR1	Rho kinase (51, 52)	Not known
	ADGRC2	CELSR2	Ca^{2+} (48)	C2 N-terminal fragment (48)
	ADGRC3	CELSR3	Ca^{2+} (48)	C3 N-terminal fragment (48)
V	ADGRD1	GPR133	$G\alpha_s$ (161), cAMP (42, 161)	Not known
	ADGRD2	GPR144	Not known	Not known

(Continued)

Table 1 (Continued)

Subfamilies	New nomenclature	Previous identifier(s)	Signaling pathways	N-terminal fragment interactors
II	ADGRE1	EMR1	Not known	Not known
	ADGRE2	EMR2	G α_{15} (42)	Chondroitin sulfate (68)
	ADGRE3	EMR3	Not known	Not known
	ADGRE4	EMR4	Not known	Not known
	ADGRE5	CD97	G $\alpha_{12/13}$, RhoA (20)	CD55 (66, 67, 135), chondroitin sulfate (68), Thy-1 (CD90) (69), $\alpha_5 \beta_1$ integrin (70)
VI	ADGRF1	GPR110	G α_q (27), G α_s cAMP (34, 77)	Synaptamide (77)
	ADGRF2	GPR111	Not known	Not known
	ADGRF3	GPR113	Not known	Not known
	ADGRF4	GPR115	G α_{15} (42)	Not known
	ADGRF5	GPR116, Ig-Hepta	G α_q /RhoA/Rac1 (128), G α_q /inositol monophosphate (23)	Surfactant protein D (79)
VIII	ADGRG1	GPR56	G $\alpha_{12/13}$, RhoA (12, 18, 27, 37, 75), G $\alpha_{q/11}$ (38)	Tissue transglutaminase (72, 73), collagen III (74, 75)
	ADGRG2	GPR64, HE6	cAMP (23, 24), MAPK, RhoA (14)	Not known
	ADGRG3	GPR97	G α_o (42), RhoA and Cdc42 (43)	Not known
	ADGRG4	GPR112	SRE-Luc (44)	Not known
	ADGRG5	GPR114	G α_s (42)	Not known
	ADGRG6	GPR126	cAMP (25, 26, 32, 39)	Collagen IV (25), laminin-211 (32), prion protein (76)
	ADGRG7	GPR128	Not known	Not known
I	ADGRL1	LPHN1, CIRL, CIRL1 CL1	G α_o (35, 36), G α_q (36)	α -Latrotoxin (35, 54, 55), neurexins (56), teneurins (58), FLRT1 and 3 (57)
	ADGRL2	LPHN2, CIRL2, CL2	Not known	Teneurins (58), FLRT3 (57)
	ADGRL3	LPHN3, CIRL3, CL3	Not known	Teneurins (58), FLRT1 and 3 (57), FLRT2 and Unc5 (60)
	ADGRL4	ELTD1	Not known	Not known
IX	ADGRV1	VLGR1, GPR98, MASS1	G α_i (28), G α_s , G α_q (53)	Not known

³In most cases it remains unclear whether the N-terminal interacting molecules listed can exert effects on the signaling pathways listed. Abbreviations: cAMP, cyclic adenosine monophosphate; Luc, luciferase; NFAT, nuclear factor of activated T cell; SRE, serum response element.

be grouped in the same subfamily and renamed ADGRE1 and ADGRE5, respectively (2). The discovery of additional 7-TM proteins with long extracellular domains and similarity in their transmembrane cores resulted in a grouping of the receptors to a family called LNB-TM7 (long N-terminal domain 7-TM receptors with similarity to family B receptors) (5). In 2004, the family was renamed as the adhesion G protein-coupled receptors (6), the name that is still in widespread use today.

aGPCRs exhibit the classic 7-TM architecture that is common to all members of the GPCR superfamily, featuring an extracellular N terminus (NT) and a cytoplasmic C terminus (CT). The

NT regions of aGPCRs are quite large relative to most other GPCRs and possess a variety of conserved domains that can mediate adhesive interactions. The one NT domain that is common to almost all aGPCRs is the GPCR autoproteolysis-inducing (GAIN) domain (7), which contains a GPCR proteolysis site (GPS) motif (8). This domain is capable of autoproteolysis, resulting in two cleaved receptor protomers that have the ability to remain noncovalently associated with each other. By convention, the cleaved NT following GAIN domain proteolysis is referred to as the N-terminal fragment (NTF), and the rest of the receptor, including the short N-terminal stalk, 7-TM region, and cytoplasmic C terminus, is referred to as the C-terminal fragment (CTF).

ADHESION GPCR STRUCTURE

Adhesion receptors were named due to the presence of extracellular adhesion domains in the earliest-described members of the family (5, 9). However, the long amino acid termini of these proteins display a rich variety of protein domains, with many properties besides adhesion (**Figure 1**). For example, 13 of the 33 human aGPCRs have a hormone-binding domain reminiscent of the Secretin family of GPCRs (10). It is unclear whether these domains might mediate the binding of key ligands to aGPCRs. Of all the N-terminal domains found in aGPCRs, the GAIN domain is the archetypal structural feature of the aGPCR family and is present in each member except ADGRA1 (GPR123) (2). The approximately 300-amino acid domain is close to the start of the first transmembrane domain. Arac and colleagues (7) crystallized this domain from ADGRB3

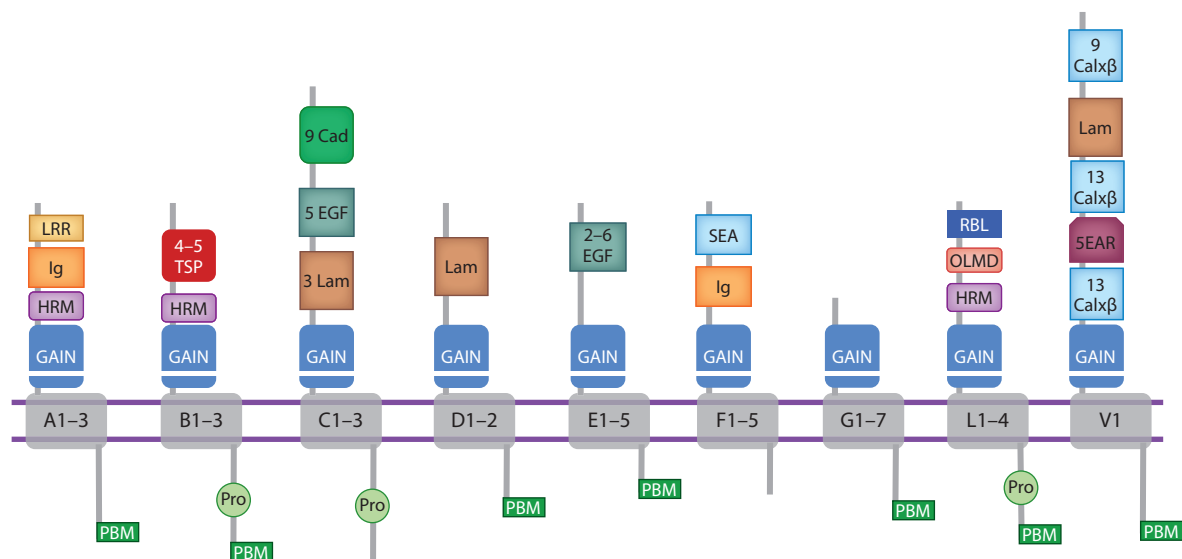


Figure 1

Adhesion GPCR subfamily structures. The nine adhesion GPCR subfamilies are listed alphabetically, with key protein domains depicted for each group. Some subfamily members have a slightly different structure from what is indicated in the figure. ADGRA1 has no GAIN, HRM, Ig, or LRR; ADGRA2 has no Ig; ADGRB3 has N-terminal CUB but no Pro; ADGRC1 and C3 lack Pro; ADGRF2–4 lack SEA; for ADGRG1–7, G1 has PLL, G6 has CUB and LAM, and PBM is found only in G1; and for ADGRL1–4, Pro is only in L1, and L4 has only EGF and GAIN. Abbreviations: Cad, cadherin repeat; EAR, epilepsy-associated repeat; EGF, epidermal growth factor-like (includes calcium-binding EGF-like domains); GAIN, GPCR autoproteolysis-inducing domain; GPCR, G protein-coupled receptor; HRM, hormone receptor motif; Ig, immunoglobulin-like; Lam, laminin; LRR, leucine-rich repeat; OLMD, olfactomedin-like; PBM, PDZ binding motif; Pro, polyproline sequence; RBL, rhamnose-binding lectin; SEA, sperm protein–enterokinase–agrin domain; TSP, type-1 thrombospondin repeat.

(BAI3) and ADGRL1 and called it the GAIN domain. Even though some aGPCRs undergo GAIN domain-mediated autoproteolysis in the endoplasmic reticulum (11), the N- and C-terminal protomers traffic together to the cell membrane and bind in a noncovalent manner (8). Receptor cleavage is not necessary for cell surface expression of aGPCRs (12–14). The aforementioned crystal structure of the GAIN domain provided insight into how the NTF and CTF protomers remain associated, with the postcleavage stalk tightly bound inside a hydrophobic groove in the cleaved GAIN domain (7).

The 7-TM core of aGPCRs most closely resembles that of the Family B secretin-like receptors (15). Many rhodopsin family (Family A) GPCRs have a DRY motif in the third intracellular loop that is important in G protein coupling, but adhesion receptors do not conform this model (16). However, most aGPCRs (21 of 33) have an E-X-X-X-Y motif in the third intracellular loop in which the position of the Y corresponds to that of the Y in the DRY motif of the rhodopsin-like receptors (15). In the extracellular loops, aGPCRs somewhat resemble the metabotropic glutamate receptors, with short first and third extracellular loops and conserved cysteine and tryptophan residues in the second extracellular loop (15). However, the functional contributions of these structural features are largely untested for aGPCRs.

ADHESION GPCR ACTIVATION MECHANISMS

For many years, no endogenous ligands for aGPCRs were known and relatively few specific tools, such as receptor antibodies, were available. Thus, initial progress in understanding the potential signaling activity of aGPCRs was slow. One idea was that the long, extracellular NTs might contain ligand binding sites analogous to those in Family C GPCRs and similar to the metabotropic glutamate receptors (17). This hypothesis was tested for ADGRG1 and ADGRB1 by removing the receptors' NTF regions at the site of predicted GAIN domain cleavage, leaving just the CTF protomer intact. Surprisingly, instead of resulting in inactive receptors, truncated forms of G1 (18) and B1 (19) were much more active than the full-length receptors. Truncated versions of ADGRE5 (20) and ADGRB2 (21) also had large increases in receptor signaling activity. These findings led to the proposal of a disinhibition model of signaling (**Figure 2c**) whereby the NTF regions of aGPCRs can inhibit the intrinsic signaling potential of the CTF (7-TM) region by locking the receptor in an inactive conformation (22). In addition to the receptors mentioned above, ADGRG2 (14, 23, 24), ADGRG6 (25), ADGRD1 (26), ADGRF1 (27), and ADGRV1 (28) are all highly active when the NTF is removed via truncation.

As early as 2002, the possibility was considered that aGPCR cleavage could play a role in receptor activation analogous to the activation of the protease-activated receptors (PARs) (8). However, it was not until 2014 that evidence emerged that exogenous peptides derived from the postcleavage stalk sequence could activate ADGRG6 and ADGRD1 (26). Soon thereafter, ADGRG1 and ADGRF1 were also shown to be activated by peptides derived from the postcleavage stalk region (27). This mechanism has been termed the tethered agonist model of aGPCR signaling, wherein the postcleavage stalk acts as a tethered agonist to push the receptor into an active conformation (**Figure 2a**).

The generality of the tethered agonist model is an issue being addressed in ongoing studies. A key hurdle for such experiments is that for almost all aGPCRs, the stalk, or Stachel (German for “stinger”), peptides derived from the postcleavage stalk are highly hydrophobic and therefore are difficult to work with in aqueous solutions. Moreover, in some cases, only certain lengths of peptide can agonize the receptor, and peptides that are even a single residue longer or shorter may exhibit no agonistic action or strongly inhibit activity by apparently acting as inverse agonists (27). A number of aGPCRs can be activated by postcleavage stalk (or Stachel) peptides (29), but

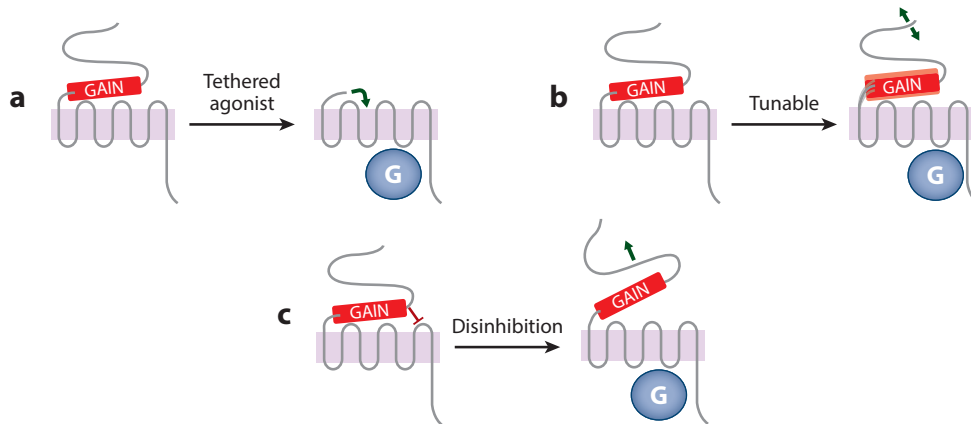


Figure 2

Models of the activation of aGPCR signaling. Generally speaking, aGPCR activation is governed by interactions between the NTF and CTF protomers. (a) The tethered agonist (e.g., stalk or Stachel) can be unmasked when the NTF is completely removed. (b) The stalk may also act as a lever, with its position being modulated by NTF movements to tune receptor activity. (c) In some cases, the NTF can also suppress signaling by the CTF protomer in ways that do not depend on the stalk, with disinhibition being achieved when the NTF is pulled away from the CTF by ligand interactions or shed completely from the protein complex. These mechanisms are not mutually exclusive, and in fact, all three mechanisms may occur for any given aGPCR, although the relative importance of each mechanism may vary from receptor to receptor. Abbreviations: CTF, C-terminal fragment; aGPCR, adhesion G protein-coupled receptor; GAIN, GPCR autoproteolysis-inducing domain; NTF, N-terminal fragment.

evidence has emerged that liberation of the postcleavage stalk is not required for activation of all aGPCRs. For example, a truncated version of ADGRB1 that lacks the postcleavage stalk exhibits no signaling deficits relative to a truncated version of ADGRB1 that mimics the GAIN-cleaved version of the receptor and possesses an intact stalk (12).

Another idea, termed the tunable model (27) (**Figure 2b**), is that the stalk can act more like a lever within the cleaved but associated NTF-CTF complex to tune signaling activity based on its position. In this model, the position of the stalk may be dictated by NTF interactions with extracellular adhesive ligands and by mechanosensory stimuli. Indeed, various lines of evidence suggest that aGPCRs might generally act as metabotropic mechanosensors (30). For example, ADGRG5 (GPR114) can be activated by mechanical stimulation *in vitro* in a manner that depends on a glutamine residue in the Stachel sequence, which might be necessary to place the Stachel in the appropriate position (31). In addition, the signaling activity of ADGRG6 in response to its ligand laminin-211 depends on stimulation dynamics: Under static conditions, laminin-211 inhibits activity, but it becomes agonistic with increasing frequency of vibration or shaking (32). Along these same lines, the *Drosophila* homolog of the ADGRL receptors is a mechanoreceptor for sensory modalities in the fly chordotonal organ (33). The localization of ADGRV1 in auditory hair cell stereocilia suggests that this receptor might also have a mechanosensory function, but this has not yet been shown (30). The unusual ectodomain architecture of aGPCRs and their intercellular interactions (see the section titled Adhesion GPCR Ligands) invite the hypothesis that aGPCRs may convey information related to external forces across the cell membrane (30).

The emerging consensus is that aGPCR signaling is activated by changes in the interactions between the NTF and CTF protomers. However, the specific changes in the NTF-CTF association necessary for activation may vary among members of the family (**Figure 2**), and ongoing

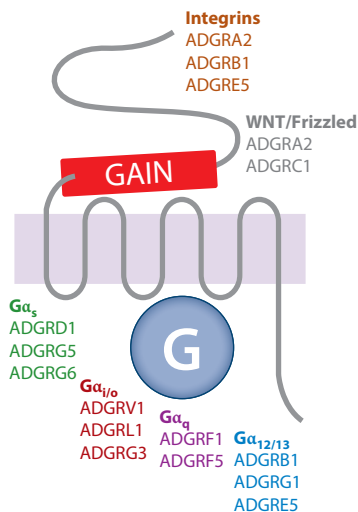


Figure 3

Adhesion GPCR signaling pathways. Adhesion GPCRs have been found to initiate a variety of downstream signaling cascades. This schematic summarizes the signaling pathways for which there is evidence of activation by more than one adhesion GPCR. Abbreviations: GAIN, GPCR autoproteolysis-inducing domain; GPCR, G protein-coupled receptor.

work is addressing how such activation occurs on a receptor-by-receptor basis. For aGPCRs activated by a tethered agonist-dependent mechanism, for example, there is interest in the specificity of their binding of tethered agonists. A consequence of the high degree of sequence homology across the aGPCR family at the GAIN cleavage site is that the agonistic portion of Stachel peptides from one receptor often closely or exactly matches that of another receptor. Indeed, activating peptides derived from ADGRF1 (GPR110) can activate F1 and the closely related receptor ADGRF5 (GPR116), as well as ADGRG2 (GPR64), which resides in a separate subgroup of aGPCRs (34). Interestingly, in some cases, only certain pathways can be activated by peptides from one receptor to another, for example, peptides from ADGRF4 (GPR115) and ADGRF5 stimulate inositol monophosphate accumulation but not cAMP (cyclic adenosine monophosphate) in cells expressing ADGRF1 (34).

ADHESION GPCR SIGNALING PATHWAYS

Understanding the signaling pathways downstream of aGPCRs is critical for drug discovery as well as for achieving a fundamental understanding of receptor function. Early signaling studies on ADGRL1 (35, 36) demonstrated G protein coupling, and now many aGPCRs have been found to couple to G proteins. Known G protein pathways [heterotrimeric and small guanosine triphosphatases (GTPases)] activated by each aGPCR are described here and summarized in **Table 1** and **Figure 3**.

ADGRG1 has been intensively studied, including its G protein coupling, due to its involvement in human disease (discussed below). An antibody directed at the G1 NTF was shown to activate Gα_{12/13}-mediated RhoA signaling, as evidenced by inhibition with the RGS domain of p115RhoGEF, C3 exoenzyme, and dominant negative RhoA (37). Later work established that a version of G1 truncated at the predicted site of GAIN domain cleavage strongly activates the

RhoA pathway (18), can be co-immunoprecipitated with $G\alpha_{13}$ (12), and can directly stimulate $G\alpha_{13}$ in reconstitution assays (27). Others have found that G1 can associate with $G\alpha_q$ (38), although G1-mediated activation of $G\alpha_q$ has not been observed (27).

ADGRG6 (GPR126), another ADGRG subfamily member, has been linked to both $G\alpha_s$ and $G\alpha_i$ (25, 26, 39), but G6 may couple differentially to these G proteins in a manner that depends on the mechanism of receptor activation, cellular context, or both. Other aGPCRs also may couple to multiple G proteins, for example, ADGRG2 to $G\alpha_s$, $G\alpha_i$, $G\alpha_{12/13}$, and $G\alpha_q$ (14, 23). Many traditional GPCRs couple to multiple proteins, with coupling often regulated by factors such as receptor phosphorylation (40) or association with scaffold proteins (41). In future studies, it will be interesting to explore whether such regulation also occurs for aGPCRs.

Signaling pathways downstream of several other ADGRG subgroup receptors have also been documented. ADGRG2 (GPR64) can activate both serum response element (SRE) and nuclear factor κ B luciferase reporters, depending on NTF cleavage events (14), and stimulates cAMP when treated with Stachel peptides (23). ADGRG3 (GPR97) couples to $G\alpha_o$ (42) and can activate the small GTPases Cdc42 and RhoA (43). Little is known about the function or activity of ADGRG4 (GPR112), but the truncated CTF of this receptor was reported to activate SRE-luciferase (44). ADGRG5 (GPR114) was found to stimulate cAMP, which was abolished by small interfering RNA directed at $G\alpha_s$ (42), and a similar result was reported for ADGRD1 (GPR133) (42), indicating that both of these receptors likely couple to $G\alpha_s$.

Two ADGRB subfamily members have been shown to couple to G proteins. ADGRB1 activates the Rho pathway in a manner sensitive to the RGS domain of p115RhoGEF, thereby providing evidence for coupling to $G\alpha_{12/13}$ (19). Furthermore, truncated, constitutively active versions of B1 can be co-immunoprecipitated with $G\alpha_{13}$ (12). Despite a high degree of similarity with the 7-TM structure of B1, ADGRB2 (BAI2) has a unique signaling profile, and its activation of a nuclear factor of activated T cell (NFAT) luciferase reporter was potentiated by the addition of $G\alpha_{16}$, a promiscuous G protein (21). This finding demonstrates the receptor's capacity for G protein coupling but not its specificity. The cognate G proteins for ADGRB3 have not been identified. In addition to the aforementioned coupling to heterotrimeric G proteins, ADGRB1 has also been shown to couple to guanine nucleotide exchange factors for Rac, including ELMO (45) and Tiam1 (46), and to stimulate Rac in a manner that does not depend on heterotrimeric G protein activation.

G protein coupling has yet to be shown for the ADGRA subfamily. Nonetheless, ADGRA2 (GPR124) can be coactivated (with Frizzled) by WNT7A to stimulate β -catenin signaling and, unlike G protein signaling of other aGPCRs, this activation depends on the presence of an intact NT (47). Members of the ADGRC subfamily can engage in homophilic interactions in *trans* (48) and are also involved in WNT/Frizzled signaling (49, 50), although it is not clear whether they function as coreceptors for WNT proteins, as does ADGRA2. ADGRC1 can signal to the Rho pathway (51, 52), although it is not known whether this occurs downstream of heterotrimeric G proteins or depends on other mechanisms, such as direct recruitment of Rho GEFs. ADGRC2 and 3 (CELSR2 and 3) can activate Ca^{2+} signaling in a phospholipase C- and endoplasmic reticulum calcium store-dependent manner, suggesting $G\alpha_{q/11}$ coupling, although it is unclear whether G proteins mediate this signaling activity (48). ADGRV1, the largest aGPCR, has been found to couple to $G\alpha_i$ (28) and signal to protein kinases A and C via $G\alpha_s$ and $G\alpha_q$ (53). Of note, G protein coupling has not been established for many aGPCRs (Table 1). Thus, there is enormous potential for basic discovery regarding these receptors.

ADHESION GPCR LIGANDS

Although most aGPCRs are still considered to be orphan receptors, a number of extracellular interacting proteins have been identified, some of which may be endogenous agonists for the

receptors (**Table 1**). Early on, ADGRL1 was found to be the calcium-independent receptor for the black widow spider venom neurotoxin α -latrotoxin (35, 54, 55). Endogenous ligands have been inferred for other ADGRLs: Presynaptic neuroligins (56), postsynaptic FLRT proteins (57), and teneurins (58, 59) bind with high affinity to ADGRL1 and ADGRL3 extracellular regions and are thought to promote intercellular, and perhaps transsynaptic, adhesion. Furthermore, ADGRL3 was recently found to engage in a ternary complex with the transmembrane cell guidance proteins Unc5 and FLRT2 (60). The binding of Lasso (teneurin-2) stimulates Ca^{2+} signaling in hippocampal neurons expressing ADGRL1 (59).

A number of interacting partners have been identified for the ADGRB (BAI) subfamily of aGPCRs, but they have unknown signaling effects. The N-terminal type-1 thrombospondin repeats of ADGRB1 bind to phosphatidylserine, thereby allowing the receptor to recognize and mediate the internalization of apoptotic cells (45). As noted above, this function has been linked to signaling by the Rac GEF ELMO–DOCK180. The role of B1 in macrophages includes recognition of gram-negative bacteria by surface lipopolysaccharide (LPS) interaction with thrombospondin repeats (61, 62). As with the ADGRL1–3 receptors, which share similar ectodomain structures, all three ADGRB proteins have at least four N-terminal type-1 thrombospondin repeats; it is unclear whether ADGRB2 and B3 also bind phosphatidylserine and LPS. A unique feature of the ADGRB1 NT is an integrin-binding RGD motif, which can interact with $\alpha_v\beta_5$ integrin (63). In the brain, ADGRB3 is a target of the C1q proteins, which are secreted proteins bearing the complement pathway–like C1q globular domain. B3 was first reported to bind to C1q13 (64) and was subsequently shown to bind to C1q11 in the cerebellum and to regulate synaptogenesis (65).

Another complement cascade protein, complement decay-accelerating factor (CD55), is a ligand for ADGRE5 (CD97) (66), although with relatively low affinity (67). The epidermal growth factor–like (EGF-like) domains of ADGRE2 and the longest form of ADGRE5 are nearly identical; both bind chondroitin sulfate, a glycosaminoglycan (68). Despite this high degree of ectodomain similarity, ADGRE2 only weakly interacts with CD55 (67), suggesting that aGPCRs with very similar ectodomains may still have highly specific interactomes (68). E5 has also been shown to bind to Thy-1 (CD90) (69) and $\alpha_5\beta_1$ integrin (see below) (70). Similarly, ADGRA2 also has a cryptic RGD motif that can interact with $\alpha_v\beta_3$ integrin when it is unveiled by matrix metalloproteinase cleavage (71).

ADGRG receptor family members can bind to multiple extracellular proteins. G1 was shown to inhibit melanoma growth and metastasis by interacting with a component of the extracellular matrix (ECM), tissue transglutaminase (TG2), via the G1 extracellular NT (72). Further work on this interaction revealed a unique paradigm: G1 prevents excess TG2-mediated ECM cross-linking by internalizing TG2 and degrading it, thereby retarding melanoma growth and progression (73). Additionally, G1 has been found to bind to collagen III in a manner that stimulates $\text{G}\alpha_{12/13}$ -mediated signaling to the Rho pathway (74, 75).

The NT of ADGRG6 binds collagen IV (25) and laminin-211 (32), both of which may be key developmental signals that activate the receptor and increase cAMP levels. G6 expressed in Schwann cells is a target of the prion protein (76). The flexible tail of that protein contains a domain that is similar to the G6-interacting motif of collagen IV; indeed, the prion protein also stimulates cAMP signaling through interaction with G6 (76).

ADGRF1 (GPR110) and ADGRF5 (GPR116) are the only ADGRF subgroup members for which extracellular interacting molecules have been identified. Full-length ADGRF1 has been reported to be activated by synaptamide, a metabolite of the omega-3 fatty acid docosahexaenoic acid in brain tissue (77). Deletion of ADGRF5 and surfactant protein D in mice results in a similar phenotype in lung tissue, and surfactant protein D can interact with the ectodomain of F5 (78).

However, as for many of the interactions described in this section, the effect of this interaction on G protein signaling or other signaling downstream of F5 is not yet clear (79).

ADHESION GPCRS IN NERVOUS SYSTEM FUNCTION AND DISEASE

One criterion for assessing the therapeutic potential of a given drug target is the association of the target with genetic diseases in humans (80). By this criterion, aGPCRs stack up well as potential therapeutic targets because a number of aGPCRs have been associated with such diseases. The most intensively studied example has been ADGRG1, mutations of which cause bilateral frontoparietal polymicrogyria, a developmental disorder of the brain (81). G1 is highly expressed in neural stem cells and plays a key role in inducing neural stem cells to stop migrating once they find their proper position in the brain (37). Disease-associated mutations of G1 typically interfere with receptor folding, trafficking, signaling, or a combination of these; a number of disease-causing mutations have been described (82, 83). Patients with bilateral frontoparietal polymicrogyria also exhibit myelination deficits (81, 84). Recent work in mice has revealed that G1 is expressed in oligodendrocytes during development and that loss of G1 function results in deficient myelination (85, 86).

Mutations in ADGRV1 cause Usher syndrome type 2C, which is characterized by deafness and blindness (87). V1 is expressed at high levels in the stereocilia in the cochlea and in the ciliary membrane of photoreceptors (88, 89). This receptor appears to be important for aspects of ciliary function. Disease-causing mutations have been identified on the massive (>5,000 amino acid) V1 NT (90). Some of these mutations introduce stop codons, meaning that the expressed receptor would lack the 7-TM region that is necessary for signaling (90). However, at least one disease-associated mutation is found on the receptor's cytoplasmic CT and has been shown to modulate V1 coupling to G proteins (28).

Mouse, zebrafish, and human studies have established that ADGRC1 is required for neural tube closure (91, 92). Similarly, the other two CELSR (ADGRC) receptors are critical in neuronal migration and axon guidance (93), and CELSR3 (ADGRC3) is important for excitatory synapse formation (94). Other aGPCRs that are important in distinct aspects of nervous system development include ADGRG6, which is required for peripheral nervous system myelination (39, 95, 96), and ADGRA2 (GPR124), which regulates central nervous system angiogenesis. Knockout of A2 can result in embryonic death due to the disruption of angiogenesis and hemorrhage in the central nervous system (97–99). A2 is widely expressed in the vasculature (99), where it can promote WNT signaling to regulate angiogenesis (47, 100, 101). Conditional knockout of A2 in adult mice compromised blood-brain barrier integrity and resulted in hemorrhage in models of stroke and glioblastoma multiforme (GBM) (102).

The latrophilins (ADGRL1–3) and BAIs (ADGRB1–3) appear to be critical for synapse formation and strengthening. ADGRL1–3 receptors are found in both pre- and postsynaptic compartments (103). Human studies have linked ADGRL3 to attention deficit hyperactivity disorder (104, 105), and animal studies support this finding. Targeted deletion of L3 in mice results in hyperactivity and disrupted dopamine and serotonin transport (106), as well as significant changes in the relative strengths of connections among different layers of the neocortex (107). Deletion of L3 in zebrafish also results in hyperlocomotor behavior and other changes consistent with altered synaptic connections (108).

Parallel studies of ADGRB1 and -B3 have revealed that they are critical for dendritic maturation and stability. Knockdown of B1 in cultured neurons drastically alters dendritic spine morphology (46). Genetic deletion of B1 induces perturbations to the postsynaptic density regions of excitatory synapses *in vivo*, as well as impairments in synaptic plasticity and spatial memory (109). Less is

known about signaling by ADGRB3 compared with B1, but it has been genetically linked to schizophrenia (110) and is an important component of hippocampal and cerebellar synapses. In cultured neurons, C1ql3 decreases spine density through actions at B3 (64). Additional experiments have shown that B3 is critical for dendritic development in vitro (111) and through interactions with C1ql proteins, B3 is a necessary component of excitatory synapses on cerebellar Purkinje neurons (65). ADGRB2 is also enriched in the nervous system (112, 113) and contains these same Rac GEF-binding motifs, but it does not appear to be required for spine maturation and synaptic function. Compared with wild-type mice, those lacking B2 have no gross behavioral or anatomical defects but, surprisingly, have increased hippocampal neurogenesis and improved resilience in tests of mood disorder-related behavior (114).

ADHESION GPCRS IN CANCER

Members of the aGPCR family are among the most frequently mutated GPCRs in cancer (115, 116). Whole-genome analyses revealed that the *ADGRV1*, *ADGRB3*, and *ADGRL3* genes are among the most significantly mutated genes in tumors (116, 117). ADGRE5 and ADGRG1 are differentially expressed in various tumor cells: G1 is downregulated in most highly metastatic melanoma cell lines in comparison with lines with less metastatic potential (118), and E5 is undetectable in normal thyroid tissue but expressed in thyroid carcinomas, with the highest expression found in aggressive tumors (119). ADGRG1 can constrain melanoma growth and metastasis (72) by inhibiting angiogenesis via VEGF (vascular endothelial growth factor) suppression (120) and internalization of the tumor-promoting ECM enzyme TG2 (73).

Angiogenesis is critical for tumor growth (121). ADGRB1 and several other aGPCRs have been shown to regulate angiogenesis. For example, ADGRB1 inhibits angiogenesis through the release of N-terminal type-1 thrombospondin repeat fragments termed vasculostatins (122–124). The most N-terminal fragment is liberated by matrix metalloproteinase-14 cleavage to result in a 40-kDa protein (vasculostatin-40), whereas the entire NT (containing four additional thrombospondin repeat domains) can be released due to GAIN domain proteolysis. The ability of B1 to regulate angiogenesis may be especially important in brain tumors because, for example, B1 expression is decreased in GBM due to epigenetic silencing (125).

In contrast to ADGRB1, ADGRE5 is upregulated in GBM and increases the invasiveness of GBM cells (126). Rather than inhibiting angiogenesis, the NT of ADGRE5 can promote angiogenesis through the recruitment of endothelial cells, which is initiated by binding to integrins (70). ADGRE5 expression is induced in numerous cancer cell lines and correlates with metastatic aggressiveness (115). A possible mechanism linking ADGRE5 to invasiveness in prostate and thyroid cancer involves heterodimerization with the LPA receptor and signaling via $G\alpha_{12/13}$ and the Rho pathway (20, 127). Similarly, ADGRF5 can drive breast cancer metastasis through Rho pathway signaling, but it does so via $G\alpha_q/p63RhoGEF$ rather than $G\alpha_{12/13}$ (128).

ADGRL4 (ELTD1) is a proangiogenic aGPCR upregulated in GBM and endothelial cells (129–131). Little is known about its signaling activity, but ADGRL4 expression is regulated by multiple proangiogenic factors, including the Notch ligand DLL4, VEGF, and basic fibroblast growth factor (bFGF) (130). Importantly, small interfering RNA knockdown of ADGRL4 attenuates vascular endothelial cell sprouting in vitro and inhibits tumor growth in vivo, indicating that this receptor may be a therapeutic target for multiple human cancers (130).

Recently, ADGRD1 (GPR133) was implicated in GBM (132). D1 is expressed in hypoxic GBM cells, and its expression levels inversely correlate with patient survival. In addition, knockdown of D1 in mouse brain limited tumor growth and improved survival. These data suggest that ADGRD1

inhibitors could provide a novel therapeutic avenue for treating GBM by limiting the ability of GBM cells to survive in a hypoxic environment (132).

ADHESION GPCRS IN THE FUNCTION AND DISEASES OF THE IMMUNE, CARDIAC, PULMONARY, AND MUSCULOSKELETAL SYSTEMS

Expression in immune tissues is a common feature for all five members of the ADGRE family (EMR1–4, CD97), two ADGRG receptors (GPR56, GPR97), and ADGRB1 (133). ADGRE2/EMR2 is widely expressed in myeloid tissue including macrophages, monocytes, and mast cells. A recent study found that a missense mutation that switches a cysteine to tyrosine upstream of the cleavage site in ADGRE2 cosegregates in two large families with vibratory urticaria, a condition in which hives develop on the skin from typically innocuous stimuli (134). This study concluded that the loss of the cysteine residue destabilized the interactions between the extracellular NTF and the 7-TM domain, thereby lowering the threshold for mechanical stimulation that induces mast cell degranulation. As mentioned above, ADGRE5 can bind to CD55 on T cells (135), and macrophage-expressed ADGRB1 can recognize phosphatidylserine (45) and LPS on bacteria (62). In general, although aGPCRs appear to be involved in many immune functions, in most cases the relative contributions of receptor-mediated adhesion versus G protein-dependent signaling are not yet clear.

As described above, ADGRG6 is important for peripheral nervous system myelination, but the complete loss of G6 in mice also results in embryonic lethality due to cardiovascular failure (136). However, in zebrafish, the reintroduction of the G6 ectodomain up to the GPS motif rescued the cardiac defect but not myelination, indicating that the NTF is sufficient for cardiac functions but the CTF is required for myelination (137). Mice lacking ADGRL4 display exaggerated cardiac hypertrophy following pressure overload (138), which suggests that this receptor could be targeted in hypertrophic cardiomyopathy (139). Another ADGRL receptor, ADGRL2, is involved in the epithelial-to-mesenchymal transition in heart valve development (140).

Several aGPCRs are expressed in the lung (78), but only ADGRF5 (GPR116) has been studied in detail. Loss of functional F5 dramatically disrupts lung surfactant homeostasis in multiple mouse models (141, 142). In mice lacking F5, pulmonary surfactant, which is required for efficient respiration, accumulates in the lung (78, 141). Although mice lacking surfactant protein D and F5-null mice have similar phenotypes and these proteins co-immunoprecipitate, it is unclear whether surfactant protein D is an endogenous ligand for ADGRF5 (79).

Several aGPCRs can regulate the musculoskeletal system. For example, ADGRB1, ADGRB3, and ADGRG1 have key functions in skeletal muscle. B1 and B3 are critical for the fusion of myoblasts to form myofibers (143, 144), and G1 signaling is a key mediator of muscle hypertrophy (145). Mutations to ADGRG6 can result in a severe form of arthrogyriposis multiplex congenita, a disease characterized by a lack of normal joint flexibility and muscle strength in newborns (146). The disease-causing mutations in G6 impair cleavage of the receptor's GAIN domain, implicating GAIN autoproteolysis as essential for the receptor's function *in vivo*. Certain variants of G6 have also been associated with adolescent-onset idiopathic scoliosis, which is the most common skeletal disease in children (147, 148).

Many aGPCRs are not ubiquitously expressed throughout the body, but instead are selectively distributed in a limited number of tissues, and some aGPCRs appear to play highly specific physiological roles. For example, the expression of ADGRG2 (GPR64) is restricted to the epididymis (this receptor is also known as HE6 for human epididymis protein 6), and male mice lacking the gene for this receptor are infertile (149). The discrete tissue expression of certain aGPCRs is

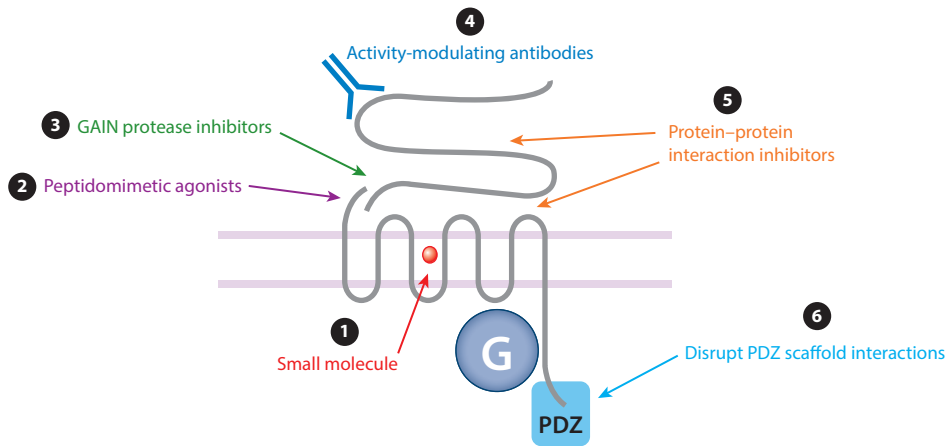


Figure 4

Targeting adhesion GPCRs with therapeutics. Adhesion GPCRs offer many opportunities for targeted drug development, including **1** small-molecule agonists, antagonists, or allosteric modulators (*red*); **2** peptides or peptidomimetic agonists (*purple*) that act at the tethered agonist interaction site; **3** modulators of GAIN proteolysis (*green*); **4** antibodies that modulate receptor activity (*dark blue*); and **5** regulators of protein–protein interactions, both extracellularly (*orange*) and intracellularly, for example, **6** with small molecules that disrupt binding to PDZ scaffold proteins (*light blue*). Abbreviations: GAIN, GPCR autoproteolysis–inducing domain; GPCR, G protein–coupled receptor; PDZ, PSD95/Dlg1/Zo-1 domain.

another feature that makes them attractive drug targets because they have the potential to facilitate the development of drugs with tissue-specific actions.

TARGETING ADHESION GPCRS WITH DRUGS

Due to their large size and complexity, aGPCRs present a variety of opportunities for therapeutic targeting (**Figure 4**). Similar to rhodopsin-like Family A GPCRs, the 7-TM domains of aGPCRs can be modulated by small molecules. Two examples demonstrate the feasibility of this approach; beclomethasone dipropionate was identified as a small-molecule agonist of ADGRG3 (GPR97) (42), and dihydromunduletone was found to be an antagonist of G1 (150). As more pathways downstream of aGPCRs are elucidated, it is likely that additional aGPCR family members will be identified through drug screening efforts as targets of small molecules.

The long ectodomains of aGPCRs provide opportunities for interventions that could alter receptor activity. The sizeable surfaces of aGPCR ectodomains are potential sites for antibody interaction. As mentioned above, a polyclonal antibody directed at the ectodomain of G1 can activate heterotrimeric G protein signaling (37). Similarly, ADGRE2 (EMR2)-mediated signaling in neutrophils is enhanced by antibodies recognizing the ADGRE2 NT (151, 152). Presumably this agonistic action of anti-aGPCR antibodies occurs by inducing a rearrangement in the NTF to relieve its inhibition on signaling by the 7-TM domain, by promoting ectodomain shedding, by changing the orientation of the tethered agonist peptide, or a combination of these. Beyond the concept of antibodies acting as agonists or antagonists, antibody–drug conjugates have been successful specifically in delivering cytotoxic compounds to target cells in cancer (153). In such cases, an anti-aGPCR antibody that does not alter receptor activity could be useful as a therapeutic agent.

Many of the ligands identified thus far for aGPCRs are large transmembrane or ECM proteins, for example, neurexins (56) and teneurins (59) for ADGRL1 and collagens and laminins for

ADGRG1 (74) and ADGRG6 (25, 32). Molecules that disrupt these protein–protein interactions could potentially regulate receptor activity. The disinhibition model of aGPCR activity posits that the NTF exerts an inhibitory constraint on the 7-TM region, possibly through NTF interactions with the extracellular loops. Disrupting these interactions could lead to receptor activation. Protein–protein interactions with large interfaces can be challenging to target therapeutically, but drugs that disrupt protein–protein interaction interfaces have entered clinical trials, and a number of advances have been made in this area (154). Progress in obtaining crystal structures of aGPCR ectodomains should aid these efforts (7, 155). Moreover, intracellular protein–protein interactions could also be targeted by molecules that can cross the plasma membrane. One possible target for such molecules would be the disruption of PDZ scaffold protein interactions at the CT of aGPCRs. Approximately half of human aGPCRs have C-terminal PDZ-binding motifs, and a number of aGPCRs interact with PDZ proteins (19, 46, 156, 157). PDZ interactions are some of the most feasible protein–protein interfaces to target with small molecules because only the final few amino acids of the receptor CT are involved and act as a ligand in the binding pocket of the PDZ protein (158, 159).

The GAIN domain provides other ways to target aGPCRs. Because this domain acts as a protease, it may be possible to inhibit or enhance ectodomain proteolysis. Protease inhibitors have been used in the clinical setting since the early 1980s and are widely used to treat disorders such as hypertension, cancer, and HIV infection (160). Also, a number of aGPCRs can be activated by peptides derived from the postcleavage receptor stalk (Stachel) sequence, and peptidomimetic drugs could presumably be developed to agonize these receptors as well. Further design of these molecules might also provide greater receptor specificity than can be attained with peptides, which have been shown to have extensive crossover activity at multiple receptors (34).

CONCLUSIONS

aGPCRs have enormous potential as drug targets. Their large ectodomains and complex structural dynamics create many drug targeting possibilities, in addition to their canonical 7-TM domains. Work during the past two decades has established that this receptor family is important in a wide range of physiological functions, yet no drugs specifically target these proteins. Recent advances in understanding both the physiological functions of many aGPCRs and the molecular dynamics that control their activation have brought the therapeutic targeting of these receptors closer to reality.

DISCLOSURE STATEMENT

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