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Adhesion G protein–coupled receptors—Candidate metabotropic mechanosensors and novel drug targets

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Abstract

While a wide range of G protein-coupled receptors (GPCR) have emerged as prime targets for pharmacological intervention long ago, a distinct group of GPCR has only recently been identified and become a research subject to fundamental and clinical scientists. Adhesion-type GPCR (aGPCR) are exceptional members of the GPCR superfamily in many aspects: structurally, they appear as chimeric surface molecules that possess signature domains of heptahelical (7TM) and adhesion proteins, many aGPCR are autoproteolytically processed, and several homologues have lately been shown to operate as mechanosensors. Bound together by the recent discovery of tethered agonism in aGPCR, these molecular and functional features have entered first models on how aGPCR are activated. Here, I briefly review recent discoveries pertaining to the role of aGPCR as metabotropic mechanosensors that control a large variety of processes in all major tissue types.

KEYWORDS

adhesion GPCR, autoproteolysis, cancer, G protein-coupled receptors, monobodies

1 | COMPOSITION OF THE ADHESION FAMILY OF GPCR

The unravelling of signalling pathways has marked a major leap in the understanding of cellular, organ and organismic physiology. Surface receptors play a central role in this process, as they operate at the interface between the cell and its exterior. Transmembrane molecules of the adhesion G protein–coupled receptor (aGPCR) family denote an exception from the widespread interest that receptor molecules have received in the past. They are placed as a large group of over 30 human homologues within the seven transmembrane (7TM) receptor superfamily[1] (see Table 1 for previous and current receptor names) and exhibit characteristics that have rendered them a challenging research topic in the pre-genomics era.

Their existence as a family was not uncovered until bioinformatics efforts, based on whole genome sequencing datasets of a variety of organisms, could leverage the homology signatures of their 7TM domains to identify the set of aGPCR.[27] This process uncovered that the number and size of gene products derived from aGPCR genes are considerably large.[28] The aGPCR branch of 7TM receptors counts 33 homologues in the human genome,[1] which are further categorized in nine subfamilies based on the homology of their 7TM domains and the composition of their extracellular region (ECR).[28] Popular genetic models in aGPCR research possess receptor homologues only partially conforming to this initial classification. *Drosophila melanogaster* contains a single ADGRL and ADGRC ortholog, respectively,[29] and two additional functional aGPCR loci were recently identified in the fruit fly genome.[30] The gene set of the nematode *Caenorhabditis elegans* encodes two ADGRL paralogs and a sole ADGRC ortholog.[31] The genome of the zebrafish *Danio rerio*, another important model in the aGPCR field that has undergone a genome duplication during evolution, encodes at least 59 homologues from all subfamilies.[32]

TABLE 1 Evidence for GAIN domain-mediated autoproteolysis of adhesion GPCR

Receptor name		GPS tripeptide in human homologue	GPS cleavage for any homologue	References
Current	**Previous**			
ADGRA1	GPR123	GAIN domain absent	NA	
ADGRA2	GPR124	HLG	No	2
ADGRA3	GPR125	SLS	No	
ADGRB1	BAI1	RLS	Yes	3
ADGRB2	BAI2	HLS	Yes	4
ADGRB3	BAI3	RLS	Yes$^{\text{in vivo}}$ No$^{\text{in vitro}}$	5
ADGRC1	CELSR1	HTA	No	6
ADGRC2	CELSR2	HMT	Yes	7
ADGRC3	CELSR3	RTG	No	
ADGRD1	GPR133	HLT	Yes	8
ADGRD2	GPR144	HST	No	
ADGRE1	EMR1	QMA	No	
ADGRE2	EMR2	HLS	Yes	9,10
ADGRE3	EMR3	HLS	Yes	11
ADGRE4*	EMR4	HLS (mouse)	Yes	12
ADGRE5	CD97	HLS	Yes	13
ADGRF1	GPR110	HLT	Yes	14
ADGRF2	GPR111	LFT	No	
ADGRF3	GPR113	HLT	Yes	
ADGRF4	GPR115	VVM	No	15
ADGRF5	GPR116	HLT	Yes	16
ADGRG1	GPR56	HLT	Yes	17
ADGRG2	GPR64	HLT	Yes	18
ADGRG3	GPR97	HLT	Yes	19
ADGRG4	GPR112	HLT	Yes	20
ADGRG5	GPR114	HLT	No$^{\text{in vitro}}$	21
ADGRG6	GPR126	HFT	Yes	22
ADGRG7	GPR128	HTT	No	
ADGRL1	LPHN1	HLT	Yes	23
ADGRL2	LPHN2	HLT	Yes	
ADGRL3	LPHN3	HLT	Yes	
ADGRL4	ELTD1	HLT	Yes	24
ADGRV1	VLGR1	HMS	Yes	25

Asterisk indicates *ADGRE4P* as a pseudogene in humans.[26] If no reference is listed, GPS cleavability has not been experimentally documented to date but is inferred from the GPS tripeptide sequence.[9]

2 | THE 7TM-GAIN DOMAIN PAIR IS THE MOLECULAR HALLMARK STRUCTURE OF ADHESION GPCR

Apart from their distinct 7TM signature, their extensive assemblies of adhesion modules located in their ECR and large intracellular regions (ICR) (Figure 1A), aGPCR are characterized by another molecular feature that sets them apart from the rest of the 7TM superfamily. The extracellular GPCR autoproteolysis–inducing (GAIN) domain is positioned next to the heptahelical transmembrane unit of aGPCR, to which it is connected through a short linker[5] (Figure 1B). Before the discovery of the GAIN domain, several aGPCR homologues were already known to be autoproteolytically cleaved into a N- (NTF) and a C-terminal

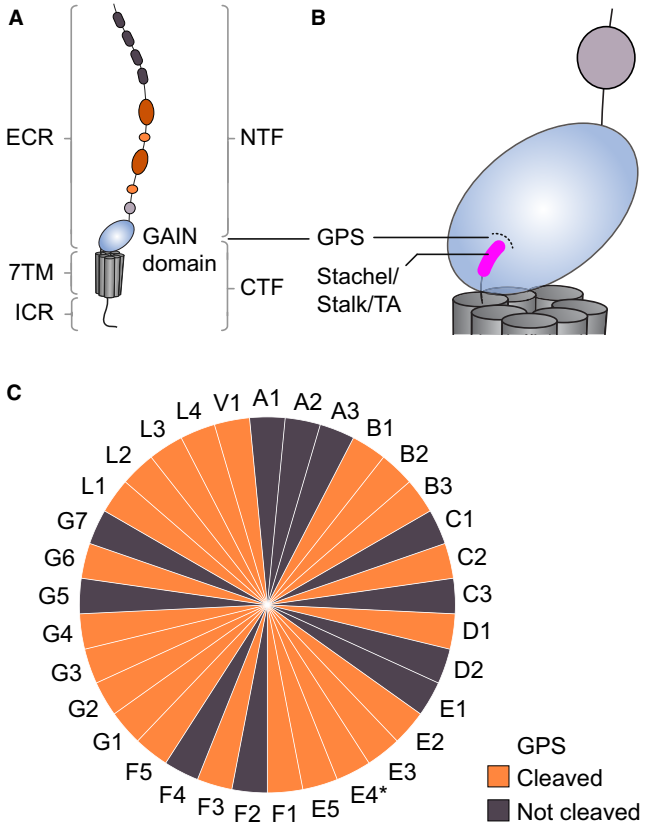

FIGURE 1 Molecular architecture of adhesion GPCR. A, The general layout of aGPCR distinguishes between a tripartite or bipartite architecture of the receptors depending on whether the protein topology or proteolytic cleavage fragments are considered, respectively. B, Position of the tethered agonist (in magenta) with respect to GAIN domain, GPS and 7TM domain. C, GPS cleavage of aGPCR processes many but not all receptor homologues. Pie chart is based on experimental data, or inferred from the presence/absence of a canonical GPS cleavage tripeptide ($H^{-2}L^{-1}T/S/C^{+1}$) of respective receptor homologues.[9,23,24] Asterisk indicates *ADGRE4P* as a pseudogene in humans.[26] Receptor numbering corresponds to the abbreviated revised nomenclature issued by the Adhesion GPCR Consortium (www.adhesiongpcr.org) and IUPHAR.[28] 7TM, heptahelical transmembrane domain; CTF, C-terminal fragment; ECR, extracellular region; GAIN, GPCR autoproteolysis–inducing domain; GPS, GPCR proteolysis site; ICR, intracellular region; NTF, N-terminal fragment; TA, tethered agonist

fragment (CTF) at an evolutionarily highly conserved GPCR proteolysis site (GPS)[9,33] (Figure 1B,C). The region necessary for this post-translational phenomenon was defined as the GPS motif encompassing approximately 50 amino acids before the beginning of the transmembrane unit.[33]

The elucidation of the GAIN domain structure demonstrated that the GPS motif is a critical component of the fold and that the domain is sufficient and necessary to catalyse the cleavage reaction[5] (Figure 1B). It also showed that the cleavage reaction liberates the C-terminal β-strand of the domain while at the same time stabilizing its association with the rest of the GAIN domain through a network of hydrophobic interactions.[34] This unusual facility leads to the surface presentation of the full-length receptor as a NTF-CTF heterodimer even though both fragments are not connected through covalent bonds. Of note, several aGPCR are not autoproteolysed at all since their lack of the canonical tripeptide cleavage sequence or for yet unknown reasons[35] (Figure 1C).

3 | ADHESION GPCR CAN BE ACTIVATED THROUGH A TETHERED AGONIST

Drawing from the structural discoveries of the GAIN domain, its association with the 7TM domain, and the strong conservation of the amino acids representing the last β-strand of the GAIN domain, that is the receptor sequence C-terminal to the GPS (termed *Stachel* or *Stalk*), several investigations into the activation mechanism of aGPCR were launched.

A seminal experiment in this process was the artificial removal of the NTF of ADGRG1/GPR56, which resulted in a largely enhanced RhoA response leading to a model in which the NTF of an aGPCR suppresses the activity of its CTF.[36] This finding was corroborated by in vivo studies with the ADGRL/latrophilin homologue LAT-1 from *C. elegans* using intermolecular complementation experiments with truncated or chimeric receptor variants. These experiments showed that two non-functional LAT-1 variants either lacking a functional GPS motif or 7TM domain can reconstitute biological activity if co-expressed, extending the aGPCR activation model by suggesting that the GPS motif acts as a tethered endogenous ligand for the 7TM domain.[37] Incisive investigations into the exact nature of this process yielded molecular proof of the concept of tethered agonism in aGPCR. These experiments demonstrated that aGPCR versions lacking the NTF but retaining the complete CTF including the *Stachel* sequence (so-called ΔNTF receptors) display high constitutive activity. This activity is lost when the *Stachel* is removed (termed ΔECR receptors) or when it was spiked with point mutations. Conversely, signalling-defective ΔECR receptors could be stimulated with synthetic *Stachel* peptides showing that the *Stachel* sequence of aGPCR fulfils the functional criteria of a tethered agonist.[8,14] After this discovery, many more aGPCR homologues were demonstrated to use a tethered agonist for signal activation.[38] Based on the knowledge and consequential availability of synthetic activators of aGPCR signalling in form of *Stachel*-mimicking peptides, coupling analyses, which were only scarcely reported before, proceeded and led to the identification of canonical intracellular actuators, such as different Gα and β-arrestin for several aGPCR (Figure 2, Table 2).

However, observations of *Stachel*-independent signalling[45] require the consideration of different and more complex

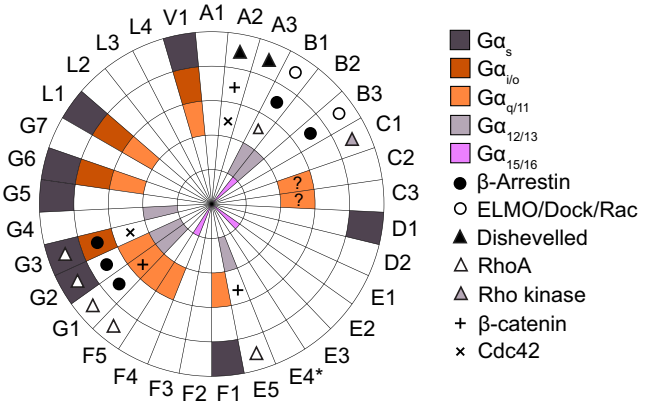

FIGURE 2 Adhesion GPCR signalling pathways. Receptor numbering corresponds to the abbreviated revised nomenclature issued by the Adhesion GPCR Consortium (www.adhesiongpcr.org) and IUPHAR.[28] ? indicates indirect evidence for coupling in this pathway. Asterisk indicates *ADGRE4P* as a pseudogene in humans[26]

activation scenarios for aGPCR.[76] This is supported by the discovery of non-canonical signal conduits directly engaging with individual aGPCR homologues.

Of note, it is intriguing that individual aGPCR seem to serve multiple downstream signalling pathways, a phenomenon referred to as biased signalling (Figure 2, Table 2). It will be both interesting and challenging to deduce whether the different signalling channels utilized by the same receptor correlate with discrete ligand and stimulus requirements (Table 3, see also next paragraph), an effort that will require close collaboration between pharmacologists and researchers that investigate the physiological context of each signalling pathway.

4 | MECHANOSENSING THROUGH ADHESION GPCR

The steps leading to tethered agonist exposure in a *Stachel*-dependent signalling model remain controversial. One obvious setting that may account for the liberation of the *Stachel* is the physical removal of the NTF through mechanical force since the lack of known covalent bonds between NTF and CTF. Interactions between the eponymous adhesion domains contained within the NTF of most aGPCR and matricellular or other membrane-exposed proteins are well documented and mark yet another exception of aGPCR from the rule (Table 3), as GPCR usually engage soluble ligands such as biogenic amines, peptides or hormones, to name a few ligand classes.[28,76,116] Forces transmitted through the interaction of aGPCR ECR and fixed ligand partners (Table 3) may prove strong enough to dislodge the *Stachel* from its GAIN domain encasing, although such forces have not been experimentally determined yet.

Indeed, several reports indicate that aGPCR homologues are involved in the perception of mechanical stimuli.[117] The intracellular anchoring of many aGPCR to cytoskeletal or scaffold proteins (Table 3) supports the mechanosensor model, which requires a *punctum fixum* (e.g. the intracellular fixation of the receptor to the cytoskeleton via its ICR) by which an aGPCR is stabilized against the motion of a *punctum mobile* within the same aGPCR molecule (e.g. the movement of the ECR or 7TM domain elicited by mechanical force).

For example, ADGRL/latrophilin/CIRL (calcium-independent receptor of α-latrotoxin), an aGPCR in *Drosophila*, accounts for a sizable fraction of the sensitivity of larval mechanosensory neurons towards proprioceptive, acoustic and tactile stimuli.[29] CIRL activation is *Stachel*-dependent and suppresses intraneuronal cAMP levels[118] (Figure 2). ADGRG6/GPR126, another aGPCR found highly expressed in the peripheral nervous system in Schwann cells, appears to register the stiffening of the basal lamina upon polymerization of its ligand laminin-211.[69] During Schwann cell development, this event marks the start signal for a myelination programme, which electrically insulates peripheral axons by spiralling of the Schwann cell membrane around them. This step depends on ADGRG6 in zebrafish and mouse models for myelination, involves $G\alpha_s$-coupling and thus initiates a rise in cAMP within the Schwann cell (Figure 2, Table 3).[70,119]

Also outside the nervous system, aGPCR partake in force-dependent biological functions. ADGRG1/GPR56, a receptor expressed in skeletal muscle, appears to regulate mechanical overload–induced muscle hypertrophy in mice and genetic removal of *ADGRG1* abrogates this pivotal growth programme.[120] ADGRF5/GPR116 is expressed in lung tissue, in particular in alveolar type II epithelial cells that secrete surfactant. The receptor acts as a chief regulator of the surfactant pool homeostat by suppressing surfactant uptake and/or secretion,[98,121,122] conceivably adapting lung compliance to mechanical stress inflicted by the respiratory inhalation/exhalation cycle. Genetic deletion of *ADGRF5* causes exuberant accumulation of surfactant in the lung of newborn mice, while treatment with $Stachel^{ADGRF5}$-derived peptides suppresses surfactant production in vivo in a $G\alpha_{q/11}$-dependent manner[123] (Figure 2).

ADGRG2/GPR64 is an aGPCR expressed in efferent ductules of the testis and is required for male fertility.[124] Recent research exposed its course of action in this context by showing that ADGRG2 regulates fluid reabsorption and pH homeostasis $G\alpha_{q/11}$- and β-arrestin-1-dependently (Figure 2) through modulation of the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride-selective ion channel.[65] As fluid balance determines the transmural pressure in efferent ductules, it is conceivable that also in this instance the aGPCR converts information about the mechanical environment of its expression

TABLE 2 Evidence for coupling partners of adhesion GPCR

Receptor	Coupling	Reference
ADGRA2	Dishevelled	39
	β-catenin	40
	Cdc42	41
ADGRA3	Dishevelled	42
ADGRB1	ELMO/Dock/Rac	43,44
	$G\alpha_{12/13}$	By NFAT reporter assay[45]
	β-arrestin	45
	RhoA	46
ADGRB2	$G\alpha_{12/13}$	by NFAT reporter assay[4]
	$G\alpha_{15/16}$	4
ADGRB3	ELMO/Dock/Rac	47
	β-arrestin	48
ADGRC1	Rho kinase	49
ADGRC2	$G\alpha_{q/11}$	By calcium imaging[50]
ADGRC3	$G\alpha_{q/11}$	ba calcium imaging[50]
ADGRD1	$G\alpha_{s}$	51,52
ADGRE2	$G\alpha_{15/16}$	51,53
ADGRE5	$G\alpha_{12/13}$	54
	RhoA	54
	β-catenin	55
ADGRF1	$G\alpha_{s}$	56,57
	$G\alpha_{q}$	14
ADGRF4	$G\alpha_{q}$	57
	$G\alpha_{15}$	51
ADGRF5	$G\alpha_{q/11}$	57,58
	RhoA	58
ADGRG1	$G\alpha_{q/11}$	59
	$G\alpha_{12/13}$	14,36,45,60,61
	β-arrestin	45
	β-catenin	63
	RhoA	60
ADGRG2	$G\alpha_{s}$	57,64
	$G\alpha_{q}$	65,66
	$G\alpha_{12/13}$	66
	β-arrestin	65
	RhoA	66
ADGRG3	$G\alpha_{s}$	67
	$G\alpha_{i/o}$	51,67
	RhoA	19
	Cdc42	19
	β-arrestin	68
ADGRG4	$G\alpha_{12}$	20
ADGRG5	$G\alpha_{s}$	51
ADGRG6	$G\alpha_{s}$	8,69,70
	$G\alpha_{i/o}$	69
	$G\alpha_{q/11}$	69
ADGRL1	$G\alpha_{s}$	72
	$G\alpha_{o}$	73,74
	$G\alpha_{q}$	74
ADGRV1	$G\alpha_{s}$	75
	$G\alpha_{i}$	25
	$G\alpha_{q}$	75

(Continues)

TABLE 2 (Continued)

domain into a metabotropic response to equilibrate the tension by adjusting ion currents that drive fluid fluxes.

Finally, placed on the mast cell membrane ADGRE2/EMR2 tunes the release of histamine, a main actuator of the local inflammatory response. Patients suffering from a hereditary form of vibratory urticaria, a disorder characterized by dermal hives inflicted through mechanical stress to the skin, possess a point mutation in the ADGRE2 GAIN domain that was suggested to reduce the affinity between the receptor's NTF and CTF and consequently alleviates tethered agonist exposure.[125]

After all and even if *Stachel* dependence could be shown in some of the noted cases, it is unknown whether mechanostimulation actually removes the NTF from its CTF-base, thereby exposing the tethered agonist, or whether different conformational changes may allow for its interaction with the aGPCR transmembrane signal transduction unit. For example, ADGRL/CIRL-dependent mechanosensation in *Drosophila* sensory neurons remained unaffected even after receptor autoproteolysis was genetically abrogated. Unsettlingly, even though this situation precludes NTF-CTF dissociation mechanosensitivity continued to be *Stachel*-dependent.[118] Similar findings were obtained with engineered cleavage-defective aGPCR homologues in *C. elegans* development.[37] Not least, the existence of aGPCR that naturally lack the ability to self-cleave[28] yet likely also employ tethered agonism for signalling,[21] begs for a unifying model of *Stachel*-mediated receptor activation that accounts for its agonistic potential as convincingly as for its structural environment. This model may entail physiologically relevant stimulus modalities other than mechanical force that are registered by aGPCR, although no other has been brought forward yet.

5 | ADHESION GPCR ARE DEVELOPMENTAL REGULATORS

The physiological settings in which aGPCR operate are diverse, which is not surprising given the wide expression

TABLE 3 Evidence for extra- and intracellular binding partners of adhesion GPCR

Receptor	Extracellular interactors	References	Intracellular interactors	References
ADGRA2	Reck	77,78	DLG1	79
	Syndecan-1, -2	80		
	Integrin-$\alpha_v\beta_3$	2		
	Heparin	2		
ADGRB1	Phosphatidylserine	43	BAIAP1	81
	Lipopolysaccharide	82	BAIAP2	83
	Nogo receptor-like-2, -3	80	BAIAP3	84
			PAHX-AP1	85
ADGRB2			GIP3	86
ADGRB3	C1qL1-4	87		
	Stabilin-2	48		
ADGRC1	Vangl-2	88,89	LRRK2	90
	Frizzled-6	88		
ADGRC2	ADGRC2	50		
ADGRC3	ADGRC3	50	Frizzled-3	91
	Frizzled-3	91	SV2	91
	Dystroglycan	92	PSD-95	91
ADGRE2	Dermatane sulfate	93		
ADGRE5	CD55	94	DLG1	95
	CD90	96		
	Dermatane sulfate	93		
	Integrin-$\alpha_5\beta_1$, -$\alpha_v\beta_3$	97		
ADGRF1	Synaptamide	56		
ADGRF5	Surfactant protein D	98		
ADGRG1	Collagen-III	99,100		
	Tissue transglutaminase 2	101	Plectin	102
	Progastrin	103		
ADGRG6	Collagen-IV	71		
	Laminin-211	69		
	Prion protein PrP^C	104		
ADGRL1	Teneurin-2	105	Shank	106
	FLRT-1, -3	107	TRIP8b	108,109
	Neurexin-1α, -1β, -2β, -3β	110		
	Contactin-6	111		
ADGRL2	FLRT-3	107		
	Teneurin-2	112		
ADGRL3	Teneurin-3	107		
	FLRT-1, -3	107		
	UNC5A	113		
ADGRV1			Harmonin	114
			Whirlin	115

Intracellular signalling components listed in Table 2 are not included again.

landscape of receptor genes and gene products.[28] A common theme that is served by aGPCR functions though is the involvement in developmental phenomena. This is best documented for several aGPCR homologues, which function in the nervous system. Apart from their impact on sensory neurons and myelination through peripheral glia as discussed above, aGPCR homologues are involved in several aspects of the makeup of neural tissue,[126] where they control developmental aspects of the neuronal and the glial cell domain.

For example, neural tube development involves planar cell polarity mechanisms, which are controlled through receptors of the ADGRC/CELSR (cadherin EGF LAG seven-pass G-type receptor) subfamily of aGPCR (reviewed in detail in Ref.[126]). Invertebrate CELSR homologues such as Flamingo/Starry night in *Drosophila* control the set-up of photoreceptor polarity in the eye and dendritic fields in the brain. In mammals, ADGRC1/CELSR1 is implicated in neural tube formation, while neuronal migration depends on ADGRC2/CELSR2 and ADGRC3/CELSR3 in mice, and the ADGRC homologue FMI-1 in *C. elegans*. Neuronally expressed ADGRG1 offers another compelling example of neurodevelopmental roles of aGPCR as missense or nonsense mutations of *ADGRG1* in humans cause severe defects in the set-up of the six-layered neocortex, a syndrome termed bilateral frontoparietal polymicrogyria (BFPP). Intriguingly, the importance of ADGRG1 signalling for brain development is underscored by the discovery that emergence of neocortical complexity through cortex gyration during evolution is at least accompanied if not driven by the expression of *ADGRG1* in distinct brain areas.[127] Several reports implicate aGPCR also in the architectural set-up of synapses, the communication interfaces between neurons and their target cells (reviewed in detail in Ref.[126]). For example, ADGRB3/BAI3 controls the formation of synapses in the cerebellum, while ADGRL2/latrophilin-2 participates in synapse assembly in the hippocampus, a brain region involved in the storage of episodic memories.[128]

Other organs that underlie developmental and functional control through aGPCR are the cardiovascular system, where ADGRG6 is necessary for heart formation,[129,130] and the haematopoietic system, which receives multiple differentiation and actuator signals, for example through the aGPCR ADGRG1,[131] ADGRG3/GPR97,[67] ADGRB1/BAI1[43] and ADGRE1/EMR1.[132]

6 | ADHESION GPCR AS DRUG TARGETS

Given the participation of aGPCR in developmental decisions, it is no surprise that the receptors have been found in association with numerous cancer types. This suspicion was nourished by the heavy load of aGPCR genes with somatic mutations in several metastatic cancers.[133,134] In some cases, this association was further investigated.

ADGRD1/GPR133 is a receptor, which is normally absent from brain tissue. However, under hypoxic conditions that occur in glioblastoma lesions the receptor becomes expressed and appears to support tumour growth explaining why ADGRD1 expression levels inversely correlate with patient survival. Reassuringly, genetic knockdown of *ADGRD1* mRNA in vitro and in a mouse xenograft model reduced the number of cancerous glioblastoma stem cells, curtailed tumour formation and benefitted survival of the xenograft host.[136] While ADGRD1 thus qualifies as a protumorigenic factor, ADGRB1 is an aGPCR that suppresses formation of another brain malignancy, medulloblastoma. Epigenetic silencing or experimental knockdown of *ADGRB1* leads to enhanced granule neuron precursors proliferation by reduction of p53 tumour suppressor levels in these cells.[137] ADGRG1 appears to serve a similar antitumorigenic function in several cancer types including glioblastomas, explaining why reduced ADGRG1 expression is associated with poor prognosis.[138] Also on haematologic malignancies, aGPCR have documented impact. Acute myeloid leukaemia (AML), a common blood cancer type with poor clinical outcome, is thought to arise from leukaemia stem cells. ADGRG1 is highly expressed in these cells and associated with high-risk genetic AML subgroups bearing a poor outcome. Therefore, ADGRG1 contributes to the molecular signature of leukaemia stem cells.[139]

aGPCR also seem heavily involved in the control of distinct immune cell functions as briefly suggested above and reviewed in detail in Refs.[140,141] For example, ADGRE1 is required for the mediation of peripheral immune tolerance, and at the same time mediates communication between natural killer (NK) cells and macrophages to orchestrate a potent immune response against certain bacterial invaders.[132] ADGRG3 serves in macrophages to mount their antimicrobial effector response.[67] In contrast, ADGRG1 suppresses human NK cell functions by preventing target cell killing through cytolytic proteins and inflammatory cytokines.[142]

Strategies to interfere with aGPCR signals in the context of neoplasias or immune functions are still scarce, also partly since the exact mechanisms of how receptor signalling, for example the involvement of metabotropic cascades as opposed to non-metabotropic effects, contributes to the respective immune or cancer biologies are unknown. However, recent efforts have yielded first compounds that interfere with aGPCR signals.

Based on the assumption that the events terminating in aGPCR activation can be mimicked or suppressed, small-molecule screens have discovered a few aGPCR modulators. Beclomethasone dipropionate was the first small molecule

identified in a high-throughput screen promoting [^{35}S]GTPγS binding by ADGRG3.[51] In an independent screen, three surrogate ligands, ezetimibe (an inhibitor of cholesterol absorption), flunarizine (a nonselective calcium channel blocker and histamine H1 receptor blocker) and the non-steroidal oestrogen zeranol, were found to activate β-arrestin recruitment through ADGRG3.[68] Later on, dihydromunduletone was shown to antagonize the tethered agonist activity of ADGRG1 and ADGRG5/GPR114,[143] while 3-α-acetoxydihydrodeoxygedunin and structurally related gedunin and khivorin derivatives were singled out as partial agonists for the same aGPCR.[144] Synaptamide, a docosahexaenoic acid metabolite, was reported to bind ADGRF1/GPR110 and activate a *Stachel*-independent cAMP response.[56] More screens are currently underway to add additional compounds to this list of pharmacological modulators of aGPCR function.

A different strategy to intersect with aGPCR signals uses antibodies or equivalent reagents that can allosterically modify aGPCR activity upon binding. The wide collection of interacting ligands and intracellular binding modules, which have been identified for about half of the aGPCR family (Table 3), offers a range of molecular targets for these approaches. For example, antibodies directed against the ECR of ADGRE2,[145] ADGRE5/CD97,[146,147] ADGRG1[60] and ADGRG3[67] impinge on their signalling behaviour. Lately, the screening of monobody libraries as a source for small, genetically encoded allosteric aGPCR modulators was successfully pioneered using the ECR of ADGRG1 as a target. Interestingly, both agonistic and inverse agonistic monobodies could be identified in the same screen.[148]

Taken together, although the research on artificial modulators of aGPCR signals is still in its infancy, several strategies tailored to the peculiarities of this large and important GPCR family—tethered agonists, large ECR, and matricellular or cell surface–resident binding partners—have started to emerge. Every new actuator on aGPCR signalling identified through these efforts will yield important tools to mechanistically dissect aGPCR activation, and curtail or replace their function in disease.

7 | CONCLUSION

Research on aGPCR remains highly topical, exciting and constitutes a dynamically expanding field that draws large interest from academic and industrial researchers. Their putative sensory function in mechanobiological feedback loops makes them attractive molecular actuators for physiological phenomena that require information about the force environment of a cell or tissue. This includes processes that unfold on short timescale (such as upon acute mechanical stimulation during neuronal mechanosensation) or in a longer time frame (as occurring during organ development) alike. Based on their suspected pharmacological tractability, aGPCR also begin to emerge as drug targets rendering them highly relevant molecular agents for future pharmaceutical endeavours.

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DISCLOSURE

Dr Langenhan has nothing to disclose.

REFERENCES

1. Bjarnadóttir TK, Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC, Schiöth HB. The human and mouse repertoire of the adhesion family of G-protein-coupled receptors. *Genomics*. 2004;84:23-33.
2. Vallon M, Essler M. Proteolytically processed soluble tumor endothelial marker (TEM) 5 mediates endothelial cell survival during angiogenesis by linking integrin alpha(v)beta3 to glycosaminoglycans. *J Biol Chem*. 2006;281:34179-34188.
3. Kaur B, Brat DJ, Devi NS, Van Meir EG. Vasculostatin, a proteolytic fragment of brain angiogenesis inhibitor 1, is an antiangiogenic and antitumorigenic factor. *Oncogene*. 2005;24:3632-3642.
4. Okajima D, Kudo G, Yokota H. Brain-specific angiogenesis inhibitor 2 (BAI2) may be activated by proteolytic processing. *J Recept Signal Transduct Res*. 2010;30:143-153.
5. Araç D, Boucard AA, Bolliger MF, et al. A novel evolutionarily conserved domain of cell-adhesion GPCRs mediates autoproteolysis. *EMBO J*. 2012;31:1364-1378.
6. Formstone CJ, Moxon C, Murdoch J, Little P, Mason I. Basal enrichment within neuroepithelia suggests novel function(s) for Celsr1 protein. *Mol Cell Neurosci*. 2010;44:210-222.
7. Beall SA, Boekelheide K, Johnson KJ. Hybrid GPCR/cadherin (Celsr) proteins in rat testis are expressed with cell type specificity and exhibit differential Sertoli cell-germ cell adhesion activity. *J Androl*. 2005;26:529-538.
8. Liebscher I, Schön J, Petersen S, et al. A tethered agonist within the ectodomain activates the adhesion G protein-coupled receptors GPR126 and GPR133. *Cell Rep*. 2014;9:2018-2026.
9. Lin H-H, Chang G-W, Davies JQ, Stacey M, Harris J, Gordon S. Autocatalytic cleavage of the EMR2 receptor occurs at a conserved G protein-coupled receptor proteolytic site motif. *J Biol Chem*. 2004;279:31823-31832.
10. Chang G-W, Stacey M, Kwakkenbos MJ, Hamann J, Gordon S, Lin H-H. Proteolytic cleavage of the EMR2 receptor requires both the extracellular stalk and the. *GPS Motif*. 2003;547:145-150.
11. Matmati M, Pouwels W, van Bruggen R, Jansen M, Hoek RM, Verhoeven AJ, et al. The human EGF-TM7 receptor EMR3 is a marker for mature granulocytes. *J Leukoc Biol*. 2007;81:440-448.

12. Stacey M, Chang G-W, Sanos SL, et al. EMR4, a novel epidermal growth factor (EGF)-TM7 molecule up-regulated in activated mouse macrophages, binds to a putative cellular ligand on B lymphoma cell line A20. *J Biol Chem*. 2002;277:29283-29293.
13. Gray JX, Haino M, Roth MJ, et al. CD97 is a processed, seven-transmembrane, heterodimeric receptor associated with inflammation. *J Immunol*. 1996;157:5438-5447.
14. Stoveken HM, Hajduczok AG, Xu L, Tall GG. Adhesion G protein-coupled receptors are activated by exposure of a cryptic tethered agonist. *Proc Natl Acad Sci USA*. 2015;112:6194-6199.
15. Prömel S, Waller-Evans H, Dixon J, et al. Characterization and functional study of a cluster of four highly conserved orphan adhesion-GPCR in mouse. *Dev Dyn*. 2012;241:1591-1602.
16. Abe J, Fukuzawa T, Hirose S. Cleavage of Ig-Hepta at a "SEA" module and at a conserved G protein-coupled receptor proteolytic site. *J Biol Chem*. 2002;277:23391-23398.
17. Jin Z, Tietjen I, Bu L, et al. Disease-associated mutations affect GPR56 protein trafficking and cell surface expression. *Hum Mol Genet*. 2007;16:1972-1985.
18. Obermann H, Samalecos A, Osterhoff C, Schröder B, Heller R, Kirchhoff C. HE6, a two-subunit heptahelical receptor associated with apical membranes of efferent and epididymal duct epithelia. *Mol Reprod Dev*. 2003;64:13-26.
19. Valtcheva N, Primorac A, Jurisic G, Hollmén M, Detmar M. The orphan adhesion G protein-coupled receptor GPR97 regulates migration of lymphatic endothelial cells via the small GTPases RhoA and Cdc42. *J Biol Chem*. 2013;288:35736-35748.
20. Peeters MC, Mos I, Lenselink EB, Lucchesi M, IJzerman AP, Schwartz TW. Getting from A to B-exploring the activation motifs of the class B adhesion G protein-coupled receptor subfamily G member 4/GPR112. *FASEB J*. 2016;30:1838-1848.
21. Wilde C, Fischer L, Lede V, et al. The constitutive activity of the adhesion GPCR GPR114/ADGRG5 is mediated by its tethered agonist. *FASEB J*. 2016;30:666-673.
22. Moriguchi T, Haraguchi K, Ueda N, Okada M, Furuya T, Akiyama T. DREG, a developmentally regulated G protein-coupled receptor containing two conserved proteolytic cleavage sites. *Genes Cells*. 2004;9:549-560.
23. Krasnoperov VG, Bittner MA, Beavis R, et al. alpha-Latrotoxin stimulates exocytosis by the interaction with a neuronal G-protein-coupled receptor. *Neuron*. 1997;18:925-937.
24. Nechiporuk T, Urness LD, Keating M. ETL, a novel seven-transmembrane receptor that is developmentally regulated in the heart. ETL is a member of the secretin family and belongs to the epidermal growth factor-seven-transmembrane subfamily. *J Biol Chem*. 2001;276:4150-4157.
25. Hu Q-X, Dong J-H, Du H-B, et al. Constitutive Gαi coupling activity of very large G protein-coupled receptor 1 (VLGR1) and its regulation by PDZD7 protein. *J Biol Chem*. 2014;289:24215-24225.
26. Hamann J, Kwakkenbos MJ, de Jong EC, Heus H, Olsen AS, van Lier R. Inactivation of the EGF-TM7 receptor EMR4 after the Pan-Homo divergence. *Eur J Immunol*. 2003;33:1365-1371.
27. Fredriksson R, Gloriam D, Höglund PJ, Lagerström MC, Schiöth HB. There exist at least 30 human G-protein-coupled receptors with long Ser/Thr-rich N-termini. *Biochem Biophys Res Commun*. 2003;301:725-734.
28. Hamann J, Aust G, Arac D, et al. International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors. *Pharmacol Rev*. 2015;67:338–367.
29. Scholz N, Gehring J, Guan C, et al. The adhesion GPCR Latrophilin/CIRL shapes mechanosensation. *Cell Rep*. 2015;11:866-874.
30. Blanco Redondo B, Langenhan T. Parallel genomic engineering of two drosophila genes using orthogonal attB/attP Sites. *G3 (Bethesda)*. 2018;8:3109-3118.
31. Langenhan T, Prömel S, Mestek L, et al. Latrophilin signaling links anterior-posterior tissue polarity and oriented cell divisions in the *C. elegans* embryo. *Dev Cell*. 2009;17:494-504.
32. Harty BL, Krishnan A, Sanchez NE, Schiöth HB, Monk KR. Defining the gene repertoire and spatiotemporal expression profiles of adhesion G protein-coupled receptors in zebrafish. *BMC Genomics*. 2015;16:62.
33. Nieberler M, Kittel RJ, Petrenko AG, Lin H-H, Langenhan T. Control of adhesion GPCR function through proteolytic processing. *Handb Exp Pharmacol*. 2016;234:83-109.
34. Arac D, Sträter N, Seiradake E. Understanding the structural basis of adhesion GPCR functions. *Handb Exp Pharmacol*. 2016;234:67-82.
35. Prömel S, Langenhan T, Arac D. Matching structure with function: the GAIN domain of adhesion-GPCR and PKD1-like proteins. *Trends Pharmacol Sci*. 2013;34:470-478.
36. Paavola KJ, Stephenson JR, Ritter SL, Alter SP, Hall RA. The N terminus of the adhesion G protein-coupled receptor GPR56 controls receptor signaling activity. *J Biol Chem*. 2011;286:28914-28921.
37. Prömel S, Frickenhaus M, Hughes S, et al. The GPS motif is a molecular switch for bimodal activities of adhesion class G protein-coupled receptors. *Cell Rep*. 2012;2:321-331.
38. Liebscher I, Schöneberg T. Tethered agonism: a common activation mechanism of adhesion GPCRs. *Handb Exp Pharmacol*. 2016;234:111-125.
39. Eubelen M, Bostaille N, Cabochette P, et al. A molecular mechanism for Wnt ligand-specific signaling. *Science*. 2018;361:eaat1178-22.
40. Posokhova E, Shukla A, Seaman S, Volate S, Hilton M, Wu B, et al. GPR124 functions as a WNT7-specific coactivator of canonical β-catenin signaling. *Cell Rep*. 2015;10:123-130.
41. Kuhnert F, Mancuso Mr, Shamloo A, et al. Essential regulation of CNS angiogenesis by the orphan G protein-coupled receptor GPR124. *Science*. 2010;330:985-989.
42. Li X, Roszko I, Sepich DS, et al. Gpr125 modulates Dishevelled distribution and planar cell polarity signaling. *Development*. 2013;140:3028-3039.
43. Park D, Tosello-Trampont A-C, Elliott MR, et al. BAI1 is an engulfment receptor for apoptotic cells upstream of the ELMO/Dock180/Rac module. *Nature*. 2007;450:430-434.
44. Duman JG, Tzeng CP, Tu Y-K, et al. The adhesion-GPCR BAI1 regulates synaptogenesis by controlling the recruitment of the Par3/Tiam1 polarity complex to synaptic sites. *J Neurosci*. 2013;33:6964-6978.
45. Kishore A, Purcell RH, Nassiri-Toosi Z, Hall RA. Stalk-dependent and stalk-independent signaling by the adhesion G protein-coupled receptors GPR56 (ADGRG1) and BAI1 (ADGRB1). *J Biol Chem*. 2016;291:3385-3394.
46. Stephenson JR, Paavola KJ, Schaefer SA, Kaur B, Van Meir EG, Hall RA. Brain-specific angiogenesis inhibitor-1 signaling, regulation, and enrichment in the postsynaptic density. *J Biol Chem*. 2013;288:22248-22256.

47. Hamoud N, Tran V, Croteau L-P, Kania A, Côté J-F. G-protein coupled receptor BAI3 promotes myoblast fusion in vertebrates. *Proc Natl Acad Sci USA*. 2014;111:3745-3750.
48. Hamoud N, Tran V, Aimi T, et al. Spatiotemporal regulation of the GPCR activity of BAI3 by C1qL4 and Stabilin-2 controls myoblast fusion. *Nat Commun*. 2018;9:4470.
49. Nishimura T, Honda H, Takeichi M. Planar cell polarity links axes of spatial dynamics in neural-tube closure. *Cell*. 2012;149:1084-1097.
50. Shima Y, Kawaguchi S-Y, Kosaka K, et al. Opposing roles in neurite growth control by two seven-pass transmembrane cadherins. *Nat Neurosci*. 2007;10:963-969.
51. Gupte J, Swaminath G, Danao J, Tian H, Li Y, Wu X. Signaling property study of adhesion G-protein-coupled receptors. *FEBS Lett*. 2012;586:1214-1219.
52. Bohnekamp J, Schöneberg T. Cell adhesion receptor GPR133 couples to Gs protein. *J Biol Chem*. 2011;286:41912-41916.
53. Kuan-Yu I, Huang Y-S, Hu C-H, et al. Activation of adhesion GPCR EMR2/ADGRE2 induces macrophage differentiation and inflammatory responses via Gα16/Akt/MAPK/NF-κB signaling pathways. *Front Immunol*. 2017;8:463.
54. Ward Y, Lake R, Yin JJ, et al. LPA receptor heterodimerizes with CD97 to amplify LPA-initiated RHO-dependent signaling and invasion in prostate cancer cells. *Cancer Res*. 2011;71:7301-7311.
55. Hilbig D, Dietrich N, Wandel E, et al. The interaction of CD97/ADGRE5 with β-catenin in adherens junctions is lost during colorectal carcinogenesis. *Front Oncol*. 2018;8:182.
56. Lee J-W, Huang BX, Kwon HeungSun, et al. Orphan GPR110 (ADGRF1) targeted by N-docosahexaenoylethanolamine in development of neurons and cognitive function. *Nat Commun*. 2016;7:13123.
57. Demberg LM, Winkler J, Wilde C, et al. Activation of adhesion G protein-coupled receptors: agonist specificity of stachel sequence-derived peptides. *J Biol Chem*. 2017;292:4383-4394.
58. Tang X, Jin R, Qu G, et al. GPR116, an adhesion G-protein-coupled receptor, promotes breast cancer metastasis via the Gαq-p63RhoGEF-Rho GTPase pathway. *Cancer Res*. 2013;73:6206-6218.
59. Little KD, Hemler ME, Stipp CS. Dynamic regulation of a GPCR-tetraspanin-G protein complex on intact cells: central role of CD81 in facilitating GPR56-Galpha q/11 association. *Mol Biol Cell*. 2004;15:2375-2387.
60. Iguchi T, Sakata K, Yoshizaki K, Tago K, Mizuno N, Itoh H. Orphan G protein-coupled receptor GPR56 regulates neural progenitor cell migration via a G alpha 12/13 and Rho pathway. *J Biol Chem*. 2008;283:14469-14478.
61. Wu MP, Doyle JR, Barry B, et al. G-protein coupled receptor 56 promotes myoblast fusion through serum response factor- and nuclear factor of activated T-cell-mediated signalling but is not essential for muscle development in vivo. *FEBS J*. 2013;280:6097-6113.
62. Luo R, Jeong S-J, Yang A, et al. Mechanism for adhesion G protein-coupled receptor GPR56-mediated RhoA activation induced by collagen III stimulation. *PLoS ONE*. 2014;9:e100043.
63. Shashidhar S, Lorente G, Nagavarapu U, et al. GPR56 is a GPCR that is overexpressed in gliomas and functions in tumor cell adhesion. *Oncogene*. 2005;24:1673-1682.
64. Balenga N, Azimzadeh P, Hogue JA, et al. Orphan adhesion GPCR GPR64/ADGRG2 is overexpressed in parathyroid tumors and attenuates calcium-sensing receptor-mediated signaling. *J Bone Miner Res*. 2017;32:654-666.
65. Zhang D-L, Sun Y-J, Ma M-L, et al. Gq activity- and β-arrestin-1 scaffolding-mediated ADGRG2/CFTR coupling are required for male fertility. *eLife*. 2018;7:27147-31658.
66. Peeters MC, Fokkelman M, Boogaard B, et al. The adhesion G protein-coupled receptor G2 (ADGRG2/GPR64) constitutively activates SRE and NFκB and is involved in cell adhesion and migration. *Cell Signal*. 2015;27:2579–2588.
67. Hsiao C-C, Chu T-Y, Wu C-J, et al. The adhesion G protein-coupled receptor GPR97/ADGRG3 is expressed in human granulocytes and triggers antimicrobial effector functions. *Front Immunol*. 2018;9:2830.
68. Southern C, Cook JM, Neetoo-Isseljee Z, et al. Screening β-arrestin recruitment for the identification of natural ligands for orphan G-protein-coupled receptors. *J Biomol Screen*. 2013;18:599-609.
69. Petersen S, Luo R, Liebscher I, et al. The adhesion GPCR GPR126 has distinct, domain-dependent functions in Schwann cell development mediated by interaction with laminin-211. *Neuron*. 2015;85:755-769.
70. Mogha A, Benesh Ae, Patra C, et al. Gpr126 functions in Schwann cells to control differentiation and myelination via G-protein activation. *J Neurosci*. 2013;33:17976-17985.
71. Paavola KJ, Sidik H, Zuchero JB, Eckart M, Talbot WS. Type IV collagen is an activating ligand for the adhesion G protein-coupled receptor GPR126. Science. *Signal*. 2014;7:ra76.
72. Müller A, Winkler J, Fiedler F, et al. Cell division in the *C. elegans* embryo is coordinated by G-protein signaling dependent on the adhesion GPCR LAT-1. *PLoS Genet*. 2015;11:e1005624.
73. Lelianova VG, Davletov BA, Sterling A, et al. Alpha-latrotoxin receptor, latrophilin, is a novel member of the secretin family of G protein-coupled receptors. *J Biol Chem*. 1997;272:21504-21508.
74. Rahman MA, Ashton AC, Meunier FA, Davletov BA, Dolly JO, Ushkaryov YA. Norepinephrine exocytosis stimulated by alpha-latrotoxin requires both external and stored Ca2+ and is mediated by latrophilin, G proteins and phospholipase C. *Philos Trans R Soc Lond B Biol Sci*. 1999;354:379-386.
75. Shin D, Lin S-T, Fu Y-H, Ptácek LJ. Very large G protein-coupled receptor 1 regulates myelin-associated glycoprotein via Gαs/Gαq-mediated protein kinases A/C. *Proc Natl Acad Sci USA*. 2013;110:19101-19106.
76. Purcell RH, Hall RA. Adhesion G protein-coupled receptors as drug targets. *Annu Rev Pharmacol Toxicol*. 2018;58:429-449.
77. Vanhollebeke B, Stone OA, Bostaille N, et al. Tip cell-specific requirement for an atypical Gpr124- and Reck-dependent Wnt/β-catenin pathway during brain angiogenesis. *eLife*. 2015;4:2807.
78. Cho C, Smallwood PM, Nathans J. Reck and Gpr124 are essential receptor cofactors for Wnt7a/Wnt7b-specific signaling in mammalian CNS angiogenesis and blood-brain barrier regulation. *Neuron*. 2017;95:1056-1073.e5.
79. Yamamoto Y, Irie K, Asada M, Mino A, Mandai K, Takai Y. Direct binding of the human homologue of the Drosophila disc large tumor suppressor gene to seven-pass transmembrane proteins, tumor endothelial marker 5 (TEM5), and a novel TEM5-like protein. *Oncogene*. 2004;23:3889-3897.
80. Chong Z-S, Ohnishi S, Yusa K, Wright GJ. Pooled extracellular receptor-ligand interaction screening using CRISPR activation. *Genome Biol*. 2018;19:205.

81. Shiratsuchi T, Futamura M, Oda K, Nishimori H, Nakamura Y, Tokino T. Cloning and characterization of BAI-associated protein 1: a PDZ domain-containing protein that interacts with BAI1. *Biochem Biophys Res Commun*. 1998;247:597-604.
82. Das S, Owen KA, Ly KT, Park D, Black SG, Wilson JM, et al. Brain angiogenesis inhibitor 1 (BAI1) is a pattern recognition receptor that mediates macrophage binding and engulfment of Gram-negative bacteria. *Proc Natl Acad Sci USA*. 2011;108:2136-2141.
83. Oda K, Shiratsuchi T, Nishimori H, et al. Identification of BAIAP2 (BAI-associated protein 2), a novel human homologue of hamster IRSp53, whose SH3 domain interacts with the cytoplasmic domain of BAI1. *Cytogenet Cell Genet*. 1999;84:75-82.
84. Shiratsuchi T, Oda K, Nishimori H, et al. Cloning and characterization of BAP3 (BAI-associated protein 3), a C2 domain-containing protein that interacts with BAI1. *Biochem Biophys Res Commun*. 1998;251:158-165.
85. Koh JT, Lee ZH, Ahn KY, et al. Characterization of mouse brain-specific angiogenesis inhibitor 1 (BAI1) and phytanoyl-CoA alpha-hydroxylase-associated protein 1, a novel BAI1-binding protein. *Brain Res Mol Brain Res*. 2001;87:223-237.
86. Zencir S, Ovee M, Dobson MJ, Banerjee M, Topcu Z, Mohanty S. Identification of brain-specific angiogenesis inhibitor 2 as an interaction partner of glutaminase interacting protein. *Biochem Biophys Res Commun*. 2011;411:792-797.
87. Bolliger MF, Martinelli DC, Südhof TC. The cell-adhesion G protein-coupled receptor BAI3 is a high-affinity receptor for C1q-like proteins. *Proc Natl Acad Sci USA*. 2011;108:2534-2539.
88. Devenport D, Oristian D, Heller E, Fuchs E. Mitotic internalization of planar cell polarity proteins preserves tissue polarity. *Nat Cell Biol*. 2011;13:893-902.
89. Lei Y, Zhu H, Yang W, Ross ME, Shaw GM, Finnell RH. Identification of Novel CELSR1 Mutations in Spina Bifida. *PLoS ONE*. 2014;9:e92207.
90. Salašová A, Yokota C, Potěšil D, Zdráhal Z, Bryja V, Arenas E. A proteomic analysis of LRRK2 binding partners reveals interactions with multiple signaling components of the WNT/PCP pathway. *Mol Neurodegener*. 2017;12:54.
91. Thakar S, Wang L, Yu T, et al. Evidence for opposing roles of Celsr3 and Vangl2 in glutamatergic synapse formation. *Proc Natl Acad Sci USA*. 2017;114:E610-E618.
92. Lindenmaier LB, Parmentier N, Guo C, Tissir F, Wright KM. Dystroglycan is a scaffold for extracellular axon guidance decisions. *eLife*. 2019;8:e42143.
93. Stacey M, Chang G-W, Davies JQ, et al. The epidermal growth factor-like domains of the human EMR2 receptor mediate cell attachment through chondroitin sulfate glycosaminoglycans. *Blood*. 2003;102:2916-2924.
94. Hamann J, Vogel B, van Schijndel GM, van Lier RA. The seven-span transmembrane receptor CD97 has a cellular ligand (CD55, DAF). *J Exp Med*. 1996;184:1185-1189.
95. Hilbig D, Sittig D, Hoffmann F, et al. Mechano-dependent phosphorylation of the PDZ-binding motif of CD97/ADGRE5 modulates cellular detachment. *Cell Rep*. 2018;24:1986-1995.
96. Wandel E, Saalbach A, Sittig D, Gebhardt C, Aust G. Thy-1 (CD90) is an interacting partner for CD97 on activated endothelial cells. *J Immunol*. 2012;188:1442-1450.
97. Wang T, Ward Y, Tian L, et al. CD97, an adhesion receptor on inflammatory cells, stimulates angiogenesis through binding integrin counterreceptors on endothelial cells. *Blood*. 2005;105:2836-2844.
98. Fukuzawa T, Ishida J, Kato A, et al. Lung surfactant levels are regulated by Ig-Hepta/GPR116 by monitoring surfactant protein D. *PLoS ONE*. 2013;8:e69451.
99. Luo R, Jeong S-J, Jin Z, Strokes N, Li S, Piao X. G protein-coupled receptor 56 and collagen III, a receptor-ligand pair, regulates cortical development and lamination. *Proc Natl Acad Sci USA*. 2011;108:12925-12930.
100. Luo R, Jin Z, Deng Y, Strokes N, Piao X. Disease-associated mutations prevent GPR56-Collagen III interaction. *PLoS ONE*. 2012;7:e29818.
101. Xu L, Begum S, Hearn JD, Hynes RO. GPR56, an atypical G protein-coupled receptor, binds tissue transglutaminase, TG2, and inhibits melanoma tumor growth and metastasis. *Proc Natl Acad Sci USA*. 2006;103:9023-9028.
102. Ackerman SD, Luo R, Poitelon Y, et al. GPR56/ADGRG1 regulates development and maintenance of peripheral myelin. *J Exp Med*. 2018;215:941-961.
103. Jin G, Sakitani K, Wang H, et al. The G-protein coupled receptor 56, expressed in colonic stem and cancer cells, binds progastrin to promote proliferation and carcinogenesis. *Oncotarget*. 2017;8:40606-40619.
104. Küffer A, Lakkaraju AKK, Mogha A, et al. The prion protein is an agonistic ligand of the G protein-coupled receptor Adgrg6. *Nature*. 2016;536:464-468.
105. Silva J-P, Lelianova VG, Ermolyuk YS, et al. Latrophilin 1 and its endogenous ligand Lasso/teneurin-2 form a high-affinity transsynaptic receptor pair with signaling capabilities. *Proc Natl Acad Sci USA*. 2011;108:12113-12118.
106. Kreienkamp H-J, Zitzer H, Gundelfinger ED, Richter D, Bockers TM. The calcium-independent receptor for alpha-latrotoxin from human and rodent brains interacts with members of the ProSAP/SSTRIP/Shank family of multidomain proteins. *J Biol Chem*. 2000;275:32387-32390.
107. O'Sullivan M, de Wit J, Savas J, et al. FLRT proteins are endogenous latrophilin ligands and regulate excitatory synapse development. *Neuron*. 2012;73:903-910.
108. Popova NV, Plotnikov A, Deev IE, Petrenko AG. Interaction of calcium-independent latrotoxin receptor with intracellular adapter protein TRIP8b. *Dokl Biochem Biophys*. 2007;414:149-151.
109. Popova NV, Plotnikov AN, Ziganshin RK, Deyev IE, Petrenko AG. Analysis of proteins interacting with TRIP8b adapter. *Biochemistry Mosc*. 2008;73:644-651.
110. Boucard AA, Ko J, Südhof TC. High affinity neurexin binding to cell adhesion G-protein-coupled receptor CIRL1/latrophilin-1 produces an intercellular adhesion complex. *J Biol Chem*. 2012;287:9399-9413.
111. Zuko A, Oguro-Ando A, Post H, et al. Association of cell adhesion molecules Contactin-6 and Latrophilin-1 regulates neuronal apoptosis. *Front Mol Neurosci*. 2016;9:143.
112. Jackson VA, Meijer DH, Carrasquero M, et al. Structures of Teneurin adhesion receptors reveal an ancient fold for cell-cell interaction. *Nat Commun*. 2018;9:1079.
113. Jackson VA, Mehmood S, Chavent M, et al. Super-complexes of adhesion GPCRs and neural guidance receptors. *Nat Commun*. 2016;7:11184.
114. Reiners J, van Wijk E, Märker T, et al. Scaffold protein harmonin (USH1C) provides molecular links between Usher syndrome type 1 and type 2. *Hum Mol Genet*. 2005;14:3933-3943.

115. van Wijk E, van der Zwaag B, Peters T, et al. The DFNB31 gene product whirlin connects to the Usher protein network in the cochlea and retina by direct association with USH2A and VLGR1. *Hum Mol Genet*. 2006;15:751-765.
116. Langenhan T, Aust G, Hamann J. Sticky signaling–adhesion class G protein-coupled receptors take the stage. *Sci Signal*. 2013;6:re3.
117. Scholz N, Monk KR, Kittel RJ, Langenhan T. Adhesion GPCRs as a putative class of metabotropic mechanosensors. *Handb Exp Pharmacol*. 2016;234:221-247.
118. Scholz N, Guan C, Nieberler M, et al. Mechano-dependent signaling by Latrophilin/CIRL quenches cAMP in proprioceptive neurons. *eLife*. 2017;6:1364.
119. Monk KR, Naylor SG, Glenn TD, et al. A G protein-coupled receptor is essential for Schwann cells to initiate myelination. *Science*. 2009;325:1402-1405.
120. White JP, Wrann CD, Rao RR, et al. G protein-coupled receptor 56 regulates mechanical overload-induced muscle hypertrophy. *Proc Natl Acad Sci USA*. 2014;111:15756-15761.
121. Yang M, Hilton M, Seaman S, et al. Essential regulation of lung surfactant homeostasis by the orphan G protein-coupled receptor GPR116. *Cell Rep*. 2013;3:1457-1464.
122. Bridges JP, Ludwig M-G, Mueller M, et al. Orphan G protein-coupled receptor GPR116 regulates pulmonary surfactant pool size. *Am J Respir Cell Mol Biol*. 2013;49:348-357.
123. Brown K, Filuta A, Ludwig M-G, et al. Gpr116 regulates pulmonary alveolar homeostasis via Gq/11 signaling. *JCI Insight*. 2017;2:93700.
124. Davies B, Baumann C, Kirchhoff C, et al. Targeted deletion of the epididymal receptor HE6 results in fluid dysregulation and male infertility. *Mol Cell Biol*. 2004;24:8642-8648.
125. Boyden SE, Desai A, Cruse G, et al. Vibratory urticaria associated with a missense variant in ADGRE2. *N Engl J Med*. 2016;374:656-663.
126. Langenhan T, Piao X, Monk KR. Adhesion G protein-coupled receptors in nervous system development and disease. *Nat Rev Neurosci*. 2016;17:550-561.
127. Bae B-i, Tietjen I, Atabay KD, et al. Evolutionarily dynamic alternative splicing of GPR56 regulates regional cerebral cortical patterning. *Science*. 2014;343:764-768.
128. Anderson GR, Maxeiner S, Sando R, Tsetsenis T, Malenka RC, Südhof TC. Postsynaptic adhesion GPCR latrophilin-2 mediates target recognition in entorhinal-hippocampal synapse assembly. *J Cell Biol*. 2017;216:3831-3846.
129. Waller-Evans H, Prömel S, Langenhan T, et al. The orphan adhesion-GPCR GPR126 is required for embryonic development in the mouse. *PLoS ONE*. 2010;5:e14047.
130. Patra C, van Amerongen MJ, Ghosh S, et al. Organ-specific function of adhesion G protein-coupled receptor GPR126 is domain-dependent. *Proc Natl Acad Sci USA*. 2013;110:16898-16903.
131. Saito Y, Kaneda K, Suekane A, et al. Maintenance of the hematopoietic stem cell pool in bone marrow niches by EVI1-regulated GPR56. *Leukemia*. 2013;27:1637-1649.
132. Lin H-H, Faunce DE, Stacey M, et al. The macrophage F4/80 receptor is required for the induction of antigen-specific efferent regulatory T cells in peripheral tolerance. *J Exp Med*. 2005;201:1615-1625.
133. Aust G, Eichler W, Laue S, et al. CD97: a dedifferentiation marker in human thyroid carcinomas. *Cancer Res*. 1997;57:1798-1806.
134. O'Hayre M, Vázquez-Prado J, Kufareva I, et al. The emerging mutational landscape of G proteins and G-protein-coupled receptors in cancer. *Nat Rev Cancer*. 2013;13:412-424.
135. Kan Z, Jaiswal BS, Stinson J, et al. Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature*. 2010;466:869-873.
136. Bayin NS, Frenster JD, Kane JR, et al. GPR133 (ADGRD1), an adhesion G-protein-coupled receptor, is necessary for glioblastoma growth. *Oncogenesis*. 2016;5:e263.
137. Zhu D, Osuka S, Zhang Z, et al. BAI1 suppresses medulloblastoma formation by protecting p53 from Mdm2-mediated degradation. *Cancer Cell*. 2018;33:1004-1016.e1005.
138. Moreno M, Pedrosa L, Paré L, et al. GPR56/ADGRG1 inhibits mesenchymal differentiation and radioresistance in glioblastoma. *Cell Rep*. 2017;21:2183-2197.
139. Pabst C, Bergeron A, Lavallee V-P, et al. GPR56 identifies primary human acute myeloid leukemia cells with high repopulating potential in vivo. *Blood*. 2016;127:2018-2027.
140. Hamann J, Hsiao C-C, Lee CS, Ravichandran KS, Lin H-H. Adhesion GPCRs as modulators of immune cell function. *Handb Exp Pharmacol*. 2016;234:329-350.
141. Lin H-H, Hsiao C-C, Pabst C, Hébert J, Schöneberg T, Hamann J. Adhesion GPCRs in regulating immune responses and inflammation. *Adv Immunol*. 2017;136:163-201.
142. Chang G-W, Hsiao C-C, Peng Y-M, et al. The adhesion G protein-coupled receptor GPR56/ADGRG1 is an inhibitory receptor on human NK cells. *Cell Rep*. 2016;15:1757-1770.
143. Stoveken HM, Bahr LL, Anders MW, Wojtovich AP, Smrcka AV, Tall GG. Dihydromunduletone is a small-molecule selective adhesion G protein-coupled receptor antagonist. *Mol Pharmacol*. 2016;90:214-224.
144. Stoveken HM, Larsen SD, Smrcka AV, Tall GG. Gedunin- and Khivorin-derivatives are small-molecule partial agonists for adhesion G protein-coupled receptors GPR56/ADGRG1 and GPR114/ADGRG5. *Mol Pharmacol*. 2018;93:477-488.
145. Yona S, Lin H-H, Dri P, et al. Ligation of the adhesion-GPCR EMR2 regulates human neutrophil function. *FASEB J*. 2008;22:741-751.
146. Veninga H, Becker S, Hoek RM, et al. Analysis of CD97 expression and manipulation: antibody treatment but not gene targeting curtails granulocyte migration. *J Immunol*. 2008;181:6574-6583.
147. de Groot Dm, Vogel G, Dulos J, et al. Therapeutic antibody targeting of CD97 in experimental arthritis: the role of antigen expression, shedding, and internalization on the pharmacokinetics of anti-CD97 monoclonal antibody 1B2. *J Immunol*. 2009;183:4127-4134.
148. Salzman GS, Zhang S, Gupta A, Koide A, Koide S, Arac D. Stachel-independent modulation of GPR56/ADGRG1 signaling by synthetic ligands directed to its extracellular region. *Proc Natl Acad Sci USA*. 2017;114:10095-10100.

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