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## XCI. Adhesion G protein-coupled receptors

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## Abstract

The Adhesion family forms a large branch of the pharmacologically important superfamily of G protein-coupled receptors (GPCRs). As Adhesion GPCRs increasingly receive attention from a wide spectrum of biomedical fields, the Adhesion GPCR Consortium, together with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification, proposes a unified nomenclature for Adhesion GPCRs. The new names have ADGR as common dominator followed by a letter and a number to denote each subfamily and subtype, respectively. The new names, with old and alternative names within parentheses, are: ADGRA1 (GPR123), ADGRA2 (GPR124), ADGRA3 (GPR125), ADGRB1 (BAI1), ADGRB2 (BAI2), ADGRB3 (BAI3), ADGRC1 (CELSR1), ADGRC2 (CELSR2), ADGRC3 (CELSR3), ADGRD1 (GPR133), ADGRD2 (GPR144), ADGRE1 (EMR1, F4/80), ADGRE2 (EMR2), ADGRE3 (EMR3), ADGRE4 (EMR4), ADGRE5 (CD97), ADGRF1 (GPR110), ADGRF2 (GPR111), ADGRF3 (GPR113), ADGRF4 (GPR115), ADGRF5 (GPR116, Ig-Hepta), ADGRG1 (GPR56), ADGRG2 (GPR64, HE6), ADGRG3 (GPR97), ADGRG4 (GPR112), ADGRG5 (GPR114), ADGRG6 (GPR126), ADGRG7 (GPR128), ADGRL1 (latrophilin-1, C1RL-1, CL1), ADGRL2 (latrophilin-2, C1RL-2, CL2), ADGRL3 (latrophilin-3, C1RL-3, CL3), ADGRL4 (ELTD1, ETL), and ADGRV1 (VLGR1, GPR98). This review covers all major biological aspects of Adhesion GPCRs, including evolutionary origins, interaction partners, signaling, expression, physiological functions, and therapeutic potential.

## I. Introduction

G protein-coupled receptors (GPCRs) consist of five main families in mammals, the largest being the Rhodopsin family, or class A, with about 284 members (plus about 380 olfactory receptors) in humans, followed by the Adhesion GPCR family with 33 members, and then the Glutamate family (class C), Secretin family (class B), and Frizzled family, with 22, 15, and 11 members, respectively (Civelli et al., 2013). Originally, the Adhesion GPCRs were suggested to belong to class B (Baud et al., 1995; Hamann et al., 1995; Hamann et al., 1996a), but evidence emerged that they are different from the Secretin receptors in many aspects, including their unique autocatalytic processing, their multitude of domains in the often long N-termini, their evolutionary conservation, and their roles in cell-to-cell and cell-to-matrix adhesion. This is in contrast to the Secretin GPCRs, which are not autocatalytically processed and often mediate hormonal responses.

Different groups of researchers commonly studying the Adhesion GPCRs with EGF domains within their N-termini started a series of workshops that was the foundation for the current larger Adhesion GPCR Consortium (<http://www.adhesiongpcr.org/>) and the biennial Adhesion GPCR Workshops (e.g., (Arac et al., 2012a)). The Adhesion GPCR Consortium has also worked to establish descriptions of the Adhesion GPCRs for the International Union of Basic and Clinical Pharmacology (IUPHAR)/British Society for Pharmacology (BPS) Guide to Pharmacology (<http://www.guidetopharmacology.org/>). Herein, general gene and protein information on all 33 human Adhesion GPCRs, including data on binding partners, transduction mechanisms, tissue distribution, functional assays, physiological functions, relevant mutations, and involvement in pathophysiology are provided. This review, written by members of the Adhesion GPCR Consortium, extends this effort towards a comprehensive description of the Adhesion GPCRs in relation to human health and disease, and their prospects for pharmacological intervention, which is a hallmark of the GPCR superfamily.

## II. Recommended nomenclature

Adhesion GPCR nomenclature has been highly diverse for many historical reasons. Initial names, like CELSR (cadherin EGF LAG seven-pass G-type receptor), EGF-TM7 (epidermal growth factor–seven-span transmembrane), BAI (brain-specific angiogenesis inhibitor), VLGR (very large GPCR), and others, were created by pioneers of this research field, but without harmonization with regard to nomenclature efforts. In collaboration with the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC), about half of the Adhesion GPCR genes were assigned GPR# names (Fredriksson et al., 2002; Fredriksson et al., 2003a), but these were regarded as temporary identifiers until more information could be elucidated about the protein products. Today, we know that the Adhesion GPCRs are a unique set of proteins that share fundamental structural properties. The research field has expanded, and the high use of genome-wide efforts (omics), including studies both on genomics/genetics, expression, and epigenetics, calls for a naming system that clearly illustrates the relationship between these proteins/genes to a wide range of researchers. The IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) has noted this high level of name diversity and ambiguity. Therefore, NC-IUPHAR took the initiative to develop a new nomenclature and contacted members of the Adhesion GPCR Consortium who subsequently worked on an alternative naming system, guided by the HGNC. We aimed to give the Adhesion GPCRs a prefix that identifies any Adhesion GPCR homolog, independent of species or subfamily. Such a coherent and systematic naming system will help to name orthologs and other genetic variants in different species in the future. This is particularly important as Adhesion GPCRs are found in wide range of species, where they have important biological functions (see chapter VIII).

The prefix that was found to be the most appropriate and unique was **ADGR**, standing for **Adhesion G** protein-coupled **Receptor**. Each subfamily was then assigned a letter to relate to previous names, such as **L** for the latrophilins, **E** for the EGF-TM7 receptors, **C** for the CELSRs, **B** for the BAIs, and **V** for VLGR, while the subfamilies with GPR# names have been given a letter in alphabetic order (**A**, **D**, **F**, **G**). These subfamilies, formerly indicated with Roman numerals I-IX, were defined based on previous phylogenetic classifications according to the molecular signature of the seven-span transmembrane (7TM) regions and extracellular regions (Bjarnadottir et al., 2004; Lagerström and Schiöth, 2008; Langenhan et al., 2013). The

members within each subfamily received a number in similar orders as in previous names. This nomenclature (**Table 1** and **Figure 1**) has been accepted by both the HGNC and NC-IUPHAR, and both organizations encourage the use of this nomenclature in all literature and databases. We suggest that the new nomenclature be used together with the old names, for example 'ADGRE5 (CD97)', until the new names are fully established. It is important that these new names are mentioned in abstracts of scientific papers to ensure that researchers outside of the field can easily identify the relevant literature.

While the full version of the new names may be somewhat cumbersome to pronounce, for example at conferences, it is likely that the shorthand versions, such as A1, B3, F6, V1, etc. will be widely used during oral presentations, when there is no doubt that it is the Adhesion GPCRs that are being addressed. Such shorthand versions may also be very useful for tables and figures where space is limited providing clarifications in the legends.

### III. Taxonomy and evolutionary origin

Adhesion GPCRs are of ancient origin and found in all vertebrates (Fredriksson and Schioth, 2005), the closest relatives to the vertebrates (Kamesh et al., 2008; Nordstrom et al., 2008), primitive animals (Putnam et al., 2007; Nordstrom et al., 2011), the most ancient metazoan phyla (Srivastava et al., 2010), and also in unicellular metazoan relatives such as *Capsaspora owczarzaki* and *Monosiga brevicollis* (Krishnan et al., 2012). Recently, Adhesion GPCRs with short extracellular regions have been identified in several basal fungi, indicating that the Adhesion family is likely to have evolved before the split of unikonts from the common ancestor of eukaryotes about 1,275 million years ago (Krishnan et al., 2012). Adhesion GPCRs, like other GPCR families, have been proposed to have evolved from a common ancestor with the ancient cyclic adenosine 3', 5'-monophosphate (cAMP) receptors (Nordstrom et al., 2011; Krishnan et al., 2012), typically found in *Dictyostelium discoideum*. Furthermore, analysis of metazoan GPCR data sets indicates that Adhesion GPCRs are ancestral to the Secretin family, as Secretin GPCRs probably diverged from a specific family of Adhesion GPCRs (Nordstrom et al., 2009). Intriguingly, Adhesion GPCR gene-mining studies revealed a vast array of N-terminal domains that includes both well-known domains, like cadherin, EGF, and immunoglobulin, as well as domains that are unusual to Adhesion GPCRs, such as SRCR (scavenger receptor cysteine-rich) and Kringle, that are possibly the evolutionary result of lineage-specific innovations. Interestingly, the GPCR-autoproteolysis inducing (GAIN) domain is evolutionarily well conserved among Adhesion GPCRs and seems to be present from tetrahymena to mammals (Arac et al., 2012b; Promel et al., 2013).

As described in the previous chapter, human Adhesion GPCRs are classified into nine distinct subfamilies (Bjarnadottir et al., 2004). From an evolutionary perspective, potential homologs for genes belonging to subfamilies ADGRL (latrophilins), ADGRA, ADGRC (CELSRs), ADGRD, ADGRG, and ADGRV (GPR98) are present in most invertebrates, including ascidians (Kamesh et al., 2008), lancelets (Nordstrom et al., 2008), acorn worms (Krishnan et al., 2013), and cnidarians (Nordstrom et al., 2009), whereas the subfamilies ADGRE (EGF-TM7), ADGRF, and ADGRB (BAIs) are likely restricted to vertebrates (see **Figure 1**) (Kwakkenbos et al., 2004; Kwakkenbos et al., 2006; Yona et al., 2008b; Strotmann et al., 2011). However, there are also Adhesion GPCR genes in the genomes of choanoflagellates and fungi that cannot be classified according to the metazoan specific families (Krishnan et al., 2012). These likely



represent ancestral versions of Adhesion GPCRs that acquired more specified functions during the course of metazoan multicellularity evolution. Several gene-mining studies have also delineated the early evolution and diversification of characteristic extracellular Adhesion GPCR motifs and domains, with as prime examples the emergence of the GPCR proteolysis site (GPS) and Calx\_beta domains in the unicellular filasterean *C. owczarzaki* and the appearance of EGF\_CA domains in free-living unicellular organisms, such as the choanoflagellate *Salpingoeca rosetta* (Krishnan et al., 2012).

Overall, Adhesion GPCRs have an ancient origin, and they are likely to be one of the evolutionary innovations that allowed cells to adhere to and communicate with one another during the evolution of metazoan multicellularity. At the same time, the evolution of ADGRE (EGF-TM7) subfamily members is a recent and still ongoing process. Human ADGRE2 (EMR2) and ADGRE3 (EMR3) have no murine orthologs (Kwakkenbos et al., 2006), whereas human ADGRE4 (EMR4) is probably a pseudogene due to a single nucleotide deletion acquired after divergence from the great apes (Hamann et al., 2003; Caminschi et al., 2006). Moreover, ADGRE2 (EMR2) arose in early placental mammals and has since coevolved with ADGRE5 (CD97) and ADGRE3 (EMR3) through regional gene conversion (Kwakkenbos et al., 2006). As a consequence, ADGRE2 (EMR2) is a chimeric molecule with a 7TM region highly similar to ADGRE3 (EMR3) and EGF-like domains nearly identical to ADGRE5 (CD97) (Lin et al., 2000).

## IV. Receptor terminology

As introduced above, Adhesion GPCRs display a peculiar molecular architecture. Besides the canonical 7TM domain, which is shared by all GPCRs, Adhesion GPCRs are distinguished from other GPCR families in that they mostly possess large N- and C-termini (Bjarnadottir et al., 2004) and a GAIN domain (Arac et al., 2012b). With reference to topological considerations regarding membrane-spanning proteins, Adhesion GPCRs can be divided into an extracellular domain (ECD), a 7TM domain, and an intracellular domain (ICD; **Figure 2**) (Langenhan et al., 2013; Liebscher et al., 2013).

The N-termini of most Adhesion GPCRs contain, in varying copy number, multiple types of protein domains that are associated with adhesive functions, which makes many Adhesion GPCRs exceptionally large membrane-bound proteins (**Figure 1**). Moreover, the combinatorial complexity of these domains within individual Adhesion GPCRs generates the high structural (and likely also functional) diversity of the receptor family.

Most intriguingly, the GAIN domain is the single extracellular structural feature shared by all family members (Arac et al., 2012a) with only one exception, ADGRA1 (GPR123). Due to the juxtamembranous position of the GAIN domain and its autoproteolytic function, Adhesion GPCR molecules can also be divided into an N-terminal fragment (NTF) and a C-terminal fragment (CTF; **Figure 2**) (Langenhan et al., 2013; Liebscher et al., 2013). The NTF contains all extracellular protein domains and the larger part of the cleaved GAIN domain, whereas the CTF harbors a small part of the proteolysed GAIN domain, a linker region, the 7TM domain, and the entire ICD. It is important to note that not all Adhesion GPCRs are predicted to be cleavable at the GAIN domain; therefore, some Adhesion GPCRs, including ADGRF2 (GPR111), ADGRF4 (GPR115), and presumably also ADGRE1 (EMR1), ADGRA1 (GPR123), ADGRA2 (GPR124), ADGRA3 (GPR125), ADGRC1 (CELSR1), and ADGRC3 (CELSR3), might be expressed as single-chain receptors (Promel et al., 2012b; Langenhan et al., 2013).

Given the complex molecular design of Adhesion GPCRs, it is important to precisely follow the topology- and cleavage-based receptor terminology agreed upon by the Adhesion GPCR Consortium (see <http://www.adhesiongpcr.org/>) in all publications.

## V. Autoproteolytic processing

A defining feature of Adhesion GPCRs is the presence of a highly conserved cysteine-rich GPS (GPCR proteolysis site) of ~50 amino acids, located immediately before the first TM helix (Stacey et al., 2000; Lin et al., 2010). The GPS motif is named due to a common proteolytic modification of Adhesion GPCRs (and polycystins), which cleaves the receptors into an extracellular NTF and a membrane-spanning/cytoplasmic CTF (Krasnoperov et al., 1997; Ponting et al., 1999). Thus, the majority of mature Adhesion GPCRs are cleaved and exist as a non-covalently attached NTF–CTF complex. GPS proteolysis has been suggested to be critical for the maturation, stability, trafficking, and function of Adhesion GPCRs (Yona et al., 2008b). However, recent studies indicate that for some Adhesion GPCRs, the GPS motif itself, but not protein cleavage, is probably more important for receptor signaling and function (Promel et al., 2012a; Langenhan et al., 2013).

Proteolysis at the GPS occurs between a conserved aliphatic residue (usually a leucine) and a threonine, serine, or cysteine (L↓T/S/C) (Stacey et al., 2000). Detailed analysis has revealed that proteolysis occurs as an auto-catalytic intramolecular reaction (Lin et al., 2004). A plausible mechanism was suggested in which a series of nucleophilic attacks and subsequent generation and hydrolysis of an ester intermediate facilitates cleavage (Lin et al., 2004; Lin et al., 2010). The autoproteolytic reaction proceeds in the lumen of the endoplasmic reticulum during receptor biosynthesis and is absolutely dependent on the GPS motif; however, the GPS motif alone is not sufficient to mediate proteolysis (Chang et al., 2003b).

Recent structural analysis revealed that the GPS motif is actually a part of a much larger (~320-residue) novel domain, termed the GAIN (GPCR autoproteolysis-inducing) domain (Arac et al., 2012b). The crystal structures of the GAIN domains of ADGRL1 (latrophilin 1) and ADGRB3 (BAI3) revealed that the GPS motif comprises the last five  $\beta$ -strands of subdomain B, and that cleavage occurs between the last two  $\beta$ -strands. Furthermore, the entire GAIN domain is necessary and, as opposed to the GPS motif, sufficient for autoproteolysis (Arac et al., 2012b).

Apart from a putative role for biosynthesis of Adhesion GPCRs, autoproteolysis at the GPS motif within the GAIN domain and subsequent reassociation of the NTF and CTF (homogeneous heterodimerization) has also been suggested to be ligand-dependent

(Volynski et al., 2004). In addition, Adhesion GPCRs may display promiscuity in NTF and CTF pairings, such that the NTF of one individual Adhesion GPCR can form a dimer with the CTF of another family member (heterogeneric heterodimerization) (Davies et al., 2007;Silva et al., 2009;Huang et al., 2012). Although this mechanism might not hold true for all Adhesion GPCR homologs in all species (Promel et al., 2012a), the implications for Adhesion GPCR signaling complexity and biological impact are vast (Langenhan et al., 2013;Liebscher et al., 2013;Promel et al., 2013).

## VI. Extracellular interaction partners

Several Adhesion GPCR interacting partners have been described over the years (**Figure 3**). The first molecule identified was CD55 (also known as decay-accelerating factor), which interacts with the EGF-like domains of ADGRE5 (CD97) (Hamann et al., 1996b). Later, chondroitin sulfate B (Stacey et al., 2003),  $\alpha_5\beta_1$  and  $\alpha_v\beta_3$  integrins (Wang et al., 2005), and CD90 (Wandel et al., 2012), were shown to bind distinct sites within the NTF of ADGRE5 (CD97). Chondroitin sulfate B also interacts with ADGRE2 (EMR2) (Stacey et al., 2003), which possesses an EGF-domain region very similar to ADGRE5 (CD97) (Lin et al., 2000). Similarly, ADGRG1 (GPR56) has different binding partners. Collagen III and tissue transglutaminase 2, a large calcium-dependent enzyme involved in cytoskeletal regulation, both interact with the NTF of GPR56 (Xu et al., 2006; Luo et al., 2011). Of note, the known binding partners of ADGRE5 (CD97), ADGRE2 (EMR2), and ADGRG1 (GPR56) are all widely expressed by stromal cells and may facilitate the positioning of motile cells that express these Adhesion GPCRs.

ADGRLs (latrophilins) are well studied with regard to interacting partner binding, and recently, teneurin-2 (also known as Lasso) was suggested to be an endogenous binding partner for ADGRL1 (latrophilin-1), which induces  $Ca^{2+}$  signals in cultured hippocampal neurons (Silva et al., 2011). Teneurin-2 interacts strongly and specifically with ADGRL1 (latrophilin-1) but binds very weakly to ADGRL2 (latrophilin-2) and does not bind to ADGRL3 (latrophilin-3) (Silva et al., 2011). However, ADGRL3 (latrophilin-3) does interact with teneurin-3 (O'Sullivan et al., 2012). In addition, all three mammalian latrophilins are known to interact with fibronectin leucine-rich transmembrane (FLRT) family members. The extracellular domains of ADGRL3 (latrophilin-3) and FLRT3 interact and promote glutamatergic synapse development (O'Sullivan et al., 2012). Both ADGRL1 (latrophilin-1) and ADGRL3 (latrophilin-3) interact with FLRT1 and FLRT3, whereas ADGRL2 (latrophilin-2) only interacts with FLRT3. Additionally, ADGRL1 (latrophilin-1) interacts with the pre-synaptically localized neurexin-1 $\alpha$ , -1 $\beta$ , -2 $\beta$ , -3 $\beta$  proteins forming a trans-synaptic adhesion complex (Boucard et al., 2012). Interestingly, all three distinct interacting partners of the latrophilins – teneurins, FLRTs, and neurexins – are single-span transmembrane molecules that have roles in axon guidance, neuronal connectivity, and synapse formation (Lise and El-Husseini, 2006; Tucker et al., 2007; Bottos et al., 2011; O'Sullivan et al., 2012). This suggests

that latrophilins have a general role in recognizing transmembranous molecules involved in neuronal biology and may function to signal during neuronal development mediated via interactions with these binding partners.

Members of subfamily ADGRB (BAIs) and ADGRF also have known interacting partners. In macrophages, the thrombospondin type 1 repeats of ADGRB1 (BAI1) bind phosphatidylserine, which enables both the recognition and subsequent internalization of apoptotic cells (Park et al., 2007). ADGRB1 (BAI1) also binds lipopolysaccharide of Gram-negative bacteria, resulting in Rac signaling and phagocytic uptake (Das et al., 2011). Moreover, ADGRB3 (BAI3) interacts with high affinity with C1q-like molecules and thereby might regulate synapse formation (Bolliger et al., 2011). Finally, surfactant protein D was recently suggested to be a binding partner for ADGRF5 (GPR116) (Fukuzawa et al., 2013), adding collectins to the list of potential molecules that interact with Adhesion GPCRs.

## VII. Signal transduction

The lack of a biological stimulus that induces receptor activity has been the major obstacle in elucidating the signal transduction mechanisms of Adhesion GPCRs. As discussed above, numerous interaction partners have been identified, but to date, none of these have been demonstrated to act as a pharmacological on/off signal. Nevertheless, Adhesion GPCRs clearly belong to the GPCR superfamily, since their common 7TM core has similarities with the other well-established GPCR families (Stacey et al., 2000; Lagerström and Schiöth, 2008). However, actual coupling and signaling via intracellular G proteins was not proven until recently.

### A. G protein-mediated intracellular signaling

Unfortunately, there is no known sequence motif that clearly identifies whether a given protein interacts with G proteins. Interactions between ADGRL1 (latrophilin-1) and  $G\alpha_o$  (Lelianova et al., 1997), as well as between ADGRG1 (GPR56) and  $G\alpha_{q/11}$  and  $G\alpha_{12/13}$  (Little et al., 2004) have been proposed using affinity chromatography and immunoprecipitation approaches. Additionally, an antibody against the extracellular domain of ADGRG1 (GPR56) activates the RhoA pathway (Iguchi et al., 2008). Furthermore, the binding of collagen III to ADGRG1 (GPR56) activates RhoA, which can be attenuated by dominant-negative  $G\alpha_{13}$ , supporting the notion that ADGRG1 (GPR56) couples to  $G\alpha_{12/13}$  upon stimulation. Mice lacking either GPR56 or collagen III display a malformed cerebral cortex, characterized by overmigration of neurons beyond the pial basement membrane (Li et al., 2008; Luo et al., 2011; Jeong et al., 2012). A very similar phenotype was found in mice lacking  $G\alpha_{12/13}$  (Moers et al., 2008), further supporting a model in which  $G\alpha_{12/13}$  is downstream of ADGRG1 (GPR56) activation. Mutant phenotypic analysis of another Adhesion GPCR, ADGRG6 (GPR126), also supported G-protein coupling for this receptor. Zebrafish (*Danio rerio*) *adgrg6* (*gpr126*) mutants exhibit myelination defects; these phenotypes were reversible through forskolin-induced cAMP increase (Monk et al., 2009), suggestive of  $G\alpha_s$  coupling. Additionally, in vitro analysis showed  $G\alpha_s$  and  $G\alpha_i$  coupling for ADGRG6 (GPR126) (Mogha et al., 2013).

More direct evidence of G-protein coupling was obtained for ADGRD1 (GPR133). Here, an overexpression strategy was applied to measure the basal activity of this Adhesion GPCR.

The basal activity of any GPCR results from an equilibrium between inactive and active conformations of receptors (Lefkowitz et al., 1993). Receptor overexpression does not change this equilibrium, but increases the number of receptors in both conformations, hence reaching a threshold at which the active conformation can be detected due to constitutive activation of signaling pathways. Using this approach, ADGRD1 (GPR133) showed a receptor concentration-dependent increase in cAMP levels, which is indicative of  $G\alpha_s$  coupling (Bohnekamp and Schoneberg, 2011) and  $IP_3$  levels when using a  $G\alpha_{qi}$  chimera, indicating  $G\alpha_i$  coupling (Liebscher et al., 2013). Using a similar approach, coupling to  $G\alpha_s$ ,  $G\alpha_q$ ,  $G\alpha_{i/o}$ , or  $G\alpha_{12/13}$  proteins was demonstrated for several other Adhesion GPCRs (ADGRE2 [EMR2], ADGRF1 [GPR110], ADGRF4 [GPR115], ADGRB1 [BAI1], ADGRG3 [GPR97], ADGRG5 [GPR114], ADGRG6 [GPR126]) (Gupte et al., 2012; Stephenson et al., 2013). In sum, multiple lines of direct and indirect evidence support the notion that most members of the Adhesion GPCR family can likely mediate signals by activation of G protein cascades.

## **B. G protein-independent intracellular signaling**

Experimental evidence suggests that Adhesion GPCRs are also capable of activating non-G-protein signaling cascades. This evidence is mainly based on interaction studies with intracellular proteins. For example, members of the ADGRB (BAI) subfamily present with a relatively long ICD, relative to most other Adhesion GPCRs, which is predisposed for such complex formation. Indeed, the ICD of ADGRB1 (BAI1) forms a complex with ELMO (engulfment and cell motility) and Dock180 (dedicator of cytokinesis), and mediates phagocytosis of apoptotic cells and Gram-negative bacteria as well as myoblast fusion via an ELMO/Dock180/Rac signaling module (Park et al., 2007; Das et al., 2011; Hochreiter-Hufford et al., 2013; Das et al., 2014). Similarly, BAI3 promotes myoblast fusion through ELMO/DOCK1 (Hamoud et al., 2014). A recent study showed that ADGRB1 (BAI1) also interacts with Par3/Tiam1 and recruits these proteins to synaptic sites for spinogenesis and synaptogenesis (Duman et al., 2013). However, unlike in phagocytosis and myoblast fusion, the ADGRB1 (BAI1)–ELMO/DOCK180 interaction is dispensable for the role of ADGRB1 (BAI1) in synapse development. Further, ADGRF5 (GPR116) was recently shown to engage a  $G\alpha_q$ -p63-RhoGEF-Rho GTPase pathway (Tang et al., 2013), and ADGRE3 (GPR97) signaling is involved Rho kinase activation (Valtcheva et al., 2013). Other examples come from planar cell polarity (PCP) signaling during embryonic development. During avian neural tube

Adhesion G protein-coupled receptors



closure, actomyosin-dependent planar-polarized contraction is mediated by ADGRC1 (CELSR1) via direct crosstalk to frizzled/dishevelled, DAAM1 (disheveled-associated activator of morphogenesis 1), and PDZ-RhoGEF, to upregulate Rho kinase (Nishimura et al., 2012). In the developing zebrafish gastrula, the intracellular C-terminus of ADGRA3 (Gpr125) directly interacts with dishevelled, and together, ADGRA3 (Gpr125) and dishevelled recruit a subset of PCP components into membrane subdomains (Li et al., 2013).

G protein-independent signaling via recruitment of PDZ domain- and SH3 domain-containing proteins, calmodulin, and arrestin is also common in other GPCR families (Magalhaes et al., 2012).  $\beta$ -arrestins were originally discovered to desensitize activated GPCRs. However, arrestins are now well-established mediators of receptor endocytosis, ubiquitylation, and G protein-independent signaling (Shukla et al., 2011). It is therefore interesting that recruitment of  $\beta$ -arrestin and ubiquitination has been demonstrated for the Adhesion GPCRs ADGRG1 (GPR56), ADGRG3 (GPR97), ADGRB1 (BAI1), and ADGRB3 (BAI3) (Paavola et al., 2011; Stephenson et al., 2013; Southern et al., 2013). Taken together, recruitment of G protein-independent cascades significantly contributes to the signaling repertoire of Adhesion GPCRs and probably accounts for the exceptional signaling complexity and specificity of Adhesion GPCRs.

### **C. Modes of signaling**

Although our knowledge of signaling pathways employed by Adhesion GPCRs has significantly increased in recent years, the molecular mode(s) whereby Adhesion GPCRs switch between active and inactive states is (are) still enigmatic. Despite a lack of agonists, several hypotheses describing distinct aspects of Adhesion GPCR activation and signaling mechanisms have recently emerged (Langenhan et al., 2013). One main paradigm, which dominates discussions about Adhesion GPCR signaling, is autoproteolysis at the GPS. Because most Adhesion GPCRs undergo autoproteolysis, it is hypothesized that this cleavage modulates receptor activity. Indeed, ADGRG1 (GPR56) and ADGRB1 (BAI1) receptor mutants without an NTF (mimicking the situation after GPS proteolysis and NTF release) have been found to display increased activity in studies on ADGRG1 (GPR56), ADGRB1 (BAI1), ADGRB2 (BAI2), and ADGRE5 (CD97) (Okajima et al., 2010; Paavola et al., 2011; Ward et al., 2011; Stephenson et al., 2013). How this is achieved in detail still remains elusive, but at least

two activation models of intracellular signaling cascades have been suggested (Paavola and Hall, 2012;Arac et al., 2012a;Langenhan et al., 2013;Promel et al., 2013;Liebscher et al., 2013): (1) a segment of the ECD functions as an inverse agonist of constitutive signaling by the 7TM, with this ECD-mediated inhibition being removed upon binding of a ligand, and (2) a segment of the ECD functions as a tethered agonist, which is exposed to the 7TM core following ligand binding. The second scenario might be more likely, since all other known GPCRs signal via an agonist-driven switch-on mechanism.

Evidence from various studies indicates that the GPS motif and the GAIN domain play vital roles in Adhesion GPCR function independent of receptor cleavage, potentially functioning as a hinge for receptor activity and signal transduction (Arac et al., 2012a). For example, human disease mutations in numerous Adhesion GPCRs map to the GAIN domain (Qian et al., 2002;Piao et al., 2004;Kan et al., 2010;Promel et al., 2013). A frequently discussed hypothesis proposes the GAIN domain as a potential interaction interface for ligands or even for intramolecular interactions (Arac et al., 2012a). Identification of such tethered ligands is one key future goal for the Adhesion GPCR field.

Another general question regarding Adhesion GPCR signaling concerns whether the NTF and CTF of a given receptor have separate functions. It has been shown for the *C. elegans* ADGRL (latrophilin) homolog LAT-1 that the complete ECD, anchored to the membrane, mediates a function independently from the CTF in vivo (Promel et al., 2012a). Moreover, when the GPS of *lat-1* is mutated such that the receptor is rendered entirely non-cleavable, this mutant remains capable of mediating both functions, the CTF-dependent mode and the CTF-independent mode. A further example is ADGRG6 (GPR126), which is required for heart and peripheral nervous system (PNS) development. Notably, ectopic expression of the NTF of GPR126 in a zebrafish knockdown model rescued defective trabeculation in the heart but not the myelination phenotype in the PNS, supporting a model in which the NTF of GPR126, in contrast to the CTF, plays an important role in heart development (Patra et al., 2013). The ECD also appears to be involved in homo- and heterodimerization of Adhesion GPCRs. For example, ADGRC1 (CELSR1) forms a homophilic trans interaction that is required for PCP signaling (Nishimura et al., 2012). Moreover, ADGRC2 (CELSR2), ADGRC3 (CELSR3), and ADGRG1 (GPR56) have also been reported to undergo homophilic trans interactions that influence receptor activity (Shima et al., 2007;Paavola et al., 2011).

These studies indicate that Adhesion GPCRs can signal via at least two different modes, 'cis' (e.g., intracellular G-protein signaling) or 'second cis/trans', where second cis refers to co-reception in complex with a second transmembrane receptor and trans refers to interaction with extracellular partners. Importantly, the trans mode would be unique for Adhesion GPCRs among the other GPCR families. ADGRE5 (CD97) may serve as an example for the second *cis* interaction mode: in both prostate and thyroid cancer cell lines, ADGRE5 (CD97) amplifies (lysophosphatidic acid (LPA)-induced RhoA activation via interaction with LPA receptor 1 (Ward et al., 2011;Ward et al., 2012). These studies provide evidence for heterodimerization of an Adhesion GPCR with a canonical GPCR and the physiological consequence of this association.

Finally, Adhesion GPCR NTFs, upon shedding, can also initiate non-cell autonomous activities at distant locations. For example, soluble ADGRE5 (CD97) stimulates angiogenesis through binding to  $\alpha_5\beta_1$  and  $\alpha_v\beta_3$  integrins (Wang et al., 2005). Soluble ADGRA2 (GPR124) has an exposed cryptic RGD (arginine-glycine-asparagine) motif in the NTF that binds  $\alpha_v\beta_3$  integrin and supports the survival of endothelial cells (Vallon and Essler, 2006), and ADGRB1 (BAI1) similarly possesses an NTF RGD motif that inhibits angiogenesis by engaging with integrins (Koh et al., 2004).

There have been numerous reports of the shedding of a 120-kDa fragment from the NTF of ADGRB1 (BAI1) (termed 'vasculostatin') and the role it has in inhibiting angiogenesis (Koh et al., 2004;Kaur et al., 2005;Kaur et al., 2009;Hardcastle et al., 2010;Klenotic et al., 2010). However, these results are hard to reconcile with the solved structure of the GAIN domain, which suggests that the cleaved NTF will remain tightly bound to the CTF (Arac et al., 2012a). An elegant explanation for this conundrum was the discovery of an additional furin- and matrix metalloproteinase-dependent cleavage location in the NTF of ADGRB1 (BAI1) creating 'vasculostatin-40' (Cork et al., 2012). This smaller 40-kDa fragment of ADGRB1 (BAI1), which contains a single thrombospondin repeat, is capable of angiogenesis activity and therefore can reconcile the functional and structural studies. Additional cleavage sites close to the GAIN domain may be a common theme observed in Adhesion GPCRs that is not yet fully appreciated, as ADGRL1 (latrophilin-1), ADGRB2 (BAI2), and ADGRF5 (GPR116) have all been reported to possess such sites. (Fukuzawa and Hirose, 2006;Krasnoperov et al., 2009;Okajima et al., 2010). These findings indicate that that Adhesion GPCRs may easily have

at least two separate functions: one that is cell autonomous and another that is not, increasing the number of pathways that each family member may be involved in.

## VIII. Expression

Adhesion GPCRs are present on almost all mammalian cells. **Figure 4A/B** provides a summary of the available data on the expression of Adhesion GPCRs in humans and rodents (mice and rats), obtained by transcriptional profiling and protein analysis techniques.

Some Adhesion GPCR subfamilies have been initially described as enriched in distinct cell types or organs, like the immune system or the central nervous system (CNS). For example, cells of the immune system prominently express ADGRE (EGF-TM7) subfamily receptors as well as the ADGRG subfamily members ADGRG1 (GPR56), ADGRG3 (GPR97), and ADGRG5 (GPR114). The presence of ADGRE (EGF-TM7) subfamily receptors 1–4 (EMR1–4) is a defining feature of myeloid leukocytes. The tightly restricted expression of murine ADGRE1 (EMR1 or F4/80) has allowed its use as an excellent marker of resident murine tissue macrophages for over 30 years (Austyn and Gordon, 1981;Gordon et al., 2011). Human ADGREs (EMRs) are useful markers for granulocytes, with ADGRE1 (EMR1) found on eosinophils and ADGRE3 (EMR3) on mature polymorphogenic granulocytes (Hamann et al., 2007;Matmati et al., 2007;Legrand et al., 2014). In contrast, ADGRE5 (CD97) is not restricted to myeloid cells but also found on lymphoid, epithelial, muscle, and other cell types (Eichler et al., 1994;Jaspars et al., 2001;Aust et al., 2006;Veninga et al., 2008;Zyryanova et al., 2014).

Members of subfamilies ADGRL, ADGRC, and ADGRB (latrophilins, CELSRs, and BAIs) were first identified in the CNS (Krasnoperov et al., 1997;Lelianova et al., 1997;Hadjantonakis et al., 1997;Shiratsuchi et al., 1997;Shima et al., 2002;Stephenson et al., 2014). Later studies actually revealed that expression of these subfamilies is not restricted to the CNS, and in particular, human ADGRLs (latrophilins) and murine ADGRCs (CELSRs) have been identified in many cell types. Similarly, ADGRV1 (VLGR1) was originally reported to be selectively expressed in sensory cells of the eye and inner ear (van Wijk et al., 2006;Maerker et al., 2008;Zalocchi et al., 2012), but recent RT-PCR data suggest a more widespread expression for several short isoforms of this receptor, especially during tissue development (McMillan et al., 2002;Weston et al., 2004).

Some Adhesion GPCRs have been reported to be expressed in only few cell types or organs, including human ADGRE1 (EMR1) in eosinophils (Hamann et al., 2007;Legrand et al., 2014), and human and mouse ADGRF4 (GPR115) in the skin (Promel et al., 2012b;Gerber et al.,

2013). Many more Adhesion GPCRs are widely distributed, such as the above-discussed ADGRE5 (CD97) and the ADGRLs, ADGRCs, and ADGRBs (latrophilins, CELSRs, and BAIs). Likewise, ADGRG1 (GPR56), originally identified in melanoma cells, is also expressed by various progenitor cells and by cytotoxic lymphocytes (Zendman et al., 1999; Piao et al., 2004; Della Chiesa et al., 2010; Peng et al., 2011). Of note, extracellular interaction partners (see chapter V) have been ascribed mostly to Adhesion GPCRs that have a rather wide cellular distribution.

The presence of Adhesion GPCRs on stem and progenitor cells is an important theme and likely at the basis of their role in various developmental processes and in tumorigenesis (see chapter IX-C). For example, ADGRE5 (CD97) and ADGRG1 (GPR56) are expressed by hematopoietic stem and progenitor cells (van Pel et al., 2008a) (<https://www.immgen.org/>), ADGRG1 (GPR56) is found on neural stem cells (Bai et al., 2009), and ADGRA3 (GPR125) is a specific marker of adult spermatogonial progenitor cells, a source of multipotent stem cells (Seandel et al., 2007; Dym et al., 2009; Izadyar et al., 2011).

While the cellular distributions of some Adhesion GPCRs provide clues on their involvement in physiological processes, a substantial number of receptors are still poorly characterized. For example, expression of ADGRCs (CELSRs) has been studied in detail only in the mouse and zebrafish.

Marked differences in the expression of some Adhesion GPCRs between human and mouse have been observed, stressing the importance of a comprehensive investigation of expression patterns in different species. For example, the characteristic presence of ADGRE1 (EMR1) on resident tissue macrophages is mouse-specific, while the specific presence of ADGRG1 (GPR56) on cytotoxic lymphocytes is a human trait (<https://www.immgen.org/>). Future interpretations of the biological roles of Adhesion GPCRs based on model organism studies need to consider these potential differences.

## **IX. Physiology and Disease**

Cell biological effects of Adhesion GPCRs have been studied in great detail using a wide range of genetic models, including invertebrate and non-mammalian vertebrate species, and in vitro assays. This extensive body of work is covered within chapter IX.A and delineates fundamental structure–function relationships of Adhesion GPCRs at the cellular level. These models have helped to sketch a preliminary picture of Adhesion GPCR impact on individual organs described in chapter IX.B, and is the basis to understand clinical implications of Adhesion GPCR signals as discussed in chapter IX.C.

### **A. Molecular and cellular functions**

#### ***1. Cell size, shape control, and cytoskeleton***

The ability of many Adhesion GPCRs to mediate regulation of cytoskeletal organization has long been appreciated (Oda et al., 1999;Usui et al., 1999;Gao et al., 1999;Li and Gao, 2003). The known developmental functions of the ADGRB (BAI) and ADGRC (Flamingo/Starry night/CELSRs; also designated as 7TM-cadherins by developmental biologists (Hulpiau and van Roy, 2009)) subfamily members rely upon actin- and microtubule-based processes (Antic et al., 2010;Hashimoto et al., 2010;Park and Ravichandran, 2010). Although cadherin repeats are present, for example in Flamingo and ADGRC3 (CELSR3) (Berger-Muller and Suzuki, 2011), evidence of classic cadherin-mediated signaling cascade activation has not yet been obtained.

Elegant studies have recently revealed that members of ADGRC (CELSR) and ADGRB (BAI) subfamilies facilitate changes to the size and shape of cell membranes via actin reorganization downstream of signaling by Rho/Rac guanine-nucleotide exchange factors (GEFs) to Rho, Rac, and Cdc42 (Stephenson et al., 2014). These small GTPases link membrane receptors to the assembly/disassembly of the cytoskeleton via cell signaling. Apart from the previously discussed functions, ADGRB1 (BAI1) additionally regulates the size and shape of actin-rich protrusions (spines) on the dendrites of cultured neurons (Duman et al., 2013) through the spatial restriction of the RacGEF Tiam1 and the cell polarity protein Par3 (Suzuki

and Ohno, 2006). The observation that ADGRB1 (BAI1) also binds to integrins suggests an exciting potential link between ADGRB1 (BAI1), cell adhesion, and cell polarity.

Subfamily ADGRC (CELSR) receptors recruit RhoGEFs during PCP signaling (see next section) to control the size and shape of asymmetric epithelial membrane domains. In the insect tracheal system, anisotropic enrichment (asymmetric enrichment across opposing cell membranes) of components, including the *Drosophila melanogaster* Adhesion GPCR Flamingo, results in the associated planar polarity of RhoGEF2, leading to increased endocytosis of E-cadherin (Warrington et al., 2013). Rho signaling plays essential roles in endocytosis through cytoskeletal modulation (de Curtis and Meldolesi, 2012). Adherens junction turnover facilitates membrane shrinkage, which drives the cell rearrangements essential for tracheal tube morphogenesis. Asymmetric enrichment of adherens junction-associated ADGRC1 (CELSR1) and PDZ-RhoGEF was also observed within the ventral neural tube during avian neural tube closure (Nishimura et al., 2012). PDZ-RhoGEF forms part of a protein complex with frizzled/dishevelled/Daam1, which upregulates Rho kinase activity resulting in the contraction of planar polarized actin–myosin cables and apical constriction of neuroepithelial cells. Thus, the vital inward bending of the neural plate is facilitated by actin–myosin-mediated shrinkage of neuroepithelial cell apical membranes.

## **2. Planar cell polarity**

The *Drosophila* Adhesion GPCR Flamingo was originally identified because of its essential role in PCP signaling (Usui et al., 1999). PCP, which acts orthogonally to apico-basal polarity, was first recognized in insects (Lawrence, 1973; Lawrence and Shelton, 1975), but its effects can be visualized on the body surface of most animals by the orderly alignment of hairs on mammalian skin and insect cuticle (Seifert and Mlodzik, 2007; Devenport and Fuchs, 2008). Flamingo and its vertebrate homologue, ADGRC1 (CELSR1), function in a defined signaling pathway, called the core-PCP pathway, in which PCP information is locally propagated from one cell neighbor to another across epithelial/epidermal fields. First described for Flamingo (Shimada et al., 2001), the molecular signature of PCP signaling is the asymmetric distribution of pathway components. Studies in *Drosophila* have also revealed that asymmetry of core-PCP proteins is preceded by the uniform cell surface localization of Flamingo close to apical adherens junctions, followed by recruitment of the 7TM receptor



Frizzled and the multi-domain protein Dishevelled (Strutt et al., 2002). This core group alone can transmit local PCP but does so less efficiently than protein complexes, which include the transmembrane protein Vang (Struhl et al., 2012). It is generally believed that ADGRC (CELSR) proteins form homodimeric molecular bridges between neighboring cells. ADGRCs (CELSRs) are therefore fundamental to local PCP transmission, and their asymmetric enrichment at both interfaces of opposing cell membranes is unique (Strutt et al., 2002; Devenport et al., 2011). Frizzled and Vang each enrich to opposing cell membranes and are thought to interact *in trans*. It remains an open question whether the role of ADGRCs (CELSRs) in PCP signaling is instructive or merely one of stabilization of asymmetric protein complexes. Downstream of ADGRCs (CELSRs), small GTPase signaling elicits cytoskeleton alignment, cell junction turnover, and cell shape changes. Notably, mice mutant in gene homologs of *Drosophila* core-PCP components, including ADGRC (CELSR) homologs, exhibit severe developmental defects in multiple tissue and organ systems including the neural tube (Wansleeben and Meijlink, 2011).

Similar in effect to ADGRCs (CELSRs), the ADGRL (latrophilin) subfamily homolog LAT-1 organizes cell division planes across the anterior–posterior axis of the *C. elegans* embryo, acting in parallel with non-canonical Wnt/Frizzled signaling (Langenhan et al., 2009). The molecular requirements for LAT-1 function in this process argue for a role(s) involving intercellular interactions coupled to cell signaling, as has been proposed for ADGRCs (Flamingo and CELSRs). Thus, it is tempting to speculate that these Adhesion GPCRs may fulfill similar functions in PCP transmission in different tissue contexts.

### **3. Cell adhesion and migration (Xian)**

The long ECDs of most Adhesion GPCRs contain structural domains that are implicated in cell–cell and cell–matrix interactions, including EGF-like, thrombospondin, leucine-rich, lectin-like, immunoglobulin, and cadherin repeats (**Figure 1**). Indeed, the term ‘Adhesion’ was proposed for this family to reflect potential roles in cellular adhesion (Fredriksson et al., 2003b).

ADGRE5 (CD97) provides a model for Adhesion GPCR-mediated cell–cell and cell–matrix interactions. ADGRE5 (CD97) is expressed on almost all leukocytes, and the first-identified binding partner of ADGRE5 (CD97), CD55, is found on stromal cells in addition to its presence

on leukocytes (Hamann et al., 1996b). Interestingly, in the presence of arterial shear stress, the binding of leukocyte ADGRE5 (CD97) to stromal cell CD55 results in shedding of the NTF of ADGRE5 (CD97) and subsequent downregulation of the CTF (Karpus et al., 2013). This observation implies that the ADGRE5 (CD97)–CD55 interaction facilitates the engagement of adhesive contacts between ADGRE5 (CD97)-positive immune cells and CD55-positive stromal cells, possibly to enable the retention of leukocytes at specific tissue sites, while the shear stress-dependent downregulation of ADGRE5 (CD97) upon contact with CD55 prevents cell aggregation in the circulation.

ADGRG1 (GPR56) is also reported to mediate cell–matrix adhesion in developing neurons and hematopoietic stem cells. Loss of ADGRG1 (GPR56) resulted in decreased granule cell adhesion to laminin and fibronectin (Koirala et al., 2009). Moreover, knockdown of ADGRG1 (GPR56) decreased cellular adhesion of acute myeloid leukemia (AML) cells to fibronectin, laminin-1, and collagen III, corresponding with a significant decrease in the number of hematopoietic stem cells (HSC) in the bone marrow of *Adgrg1* (*Gpr56*) knockout mice and, conversely, an increase in HSC number the spleen, liver, and peripheral blood (Saito et al., 2013). These data suggest that ADGRG1 (GPR56) plays a role in the maintenance of HSCs and/or leukemia stem cells in the bone marrow niche.

Adhesion and migration are closely linked processes, especially in non-circulating cells. Several Adhesion GPCRs increase cell migration in vitro, probably via signaling to members of the Rho family of small GTPases (see chapter VII), which act to regulate cytoskeletal structure as well as cell or extracellular matrix contacts. Some examples include ADGRG3 (GPR97), regulating the migration of lymphatic endothelial cells to facilitate angiogenesis via RhoA and Cdc42 (Valtcheva et al., 2013), ADGRA2 (GPR124), mediating Cdc42-dependent directional migration of brain endothelial cells towards embryonic forebrain cell conditioned medium (Kuhnert et al., 2010), and, finally, ADGRE5 (CD97) overexpression, increasing single random tumor cell migration (Galle et al., 2006).

In most cases, the extracellular signals for Adhesion GPCR-regulated migration have not yet been identified; adhesive interactions, soluble molecules, such as LPA, or mechanical stress are likely candidates. Of note, an antibody directed to the ECD of ADGRE2 (EMR2) induced adhesion and CXCL12-directed migration of neutrophils in vitro (Yona et al., 2008a).

Finally, direct consequences on cell migration, such as guiding of cells in developmental processes (see chapter VIII.C.1), have been shown for several Adhesion GPCRs in vivo. The *C. elegans* ADGRC (CELSR) homolog FMI-1 appears to be involved in the navigation and shaping of neuronal processes during the development of gamma-aminobutyric-acid (GABA)ergic neurons (Steimel et al., 2010;Najarro et al., 2012;Huarcaya Najarro and Ackley, 2013). The instructive effects by a pioneer axon on follower axon movements were shown to rely on the ECD but not the 7TM nor ICD of FMI-1, indicating that the adhesion and/or trans signaling events figure prominently in this function (Steimel et al., 2010). Moreover, ADGRG1 (GPR56) inhibits migration of neural progenitors through coordinated action with  $\alpha_3\beta_1$  integrin (Iguchi et al., 2008;Luo et al., 2011;Jeong et al., 2013).

#### **4. Cell cycle, cell death, and differentiation**

Although there is no mechanistic data supporting a direct role for Adhesion GPCRs in controlling canonical cell cycle pathways, there is growing evidence that certain Adhesion GPCRs are important for the regulation of cell proliferation. In vitro, conditioned medium containing cleavage products of the ADGRB1 (BAI1) NTF suppresses proliferation of endothelial cells by blocking  $\alpha_v\beta_5$  integrin (Koh et al., 2004;Kaur et al., 2005;Cork et al., 2012). In vivo, hippocampal neuron proliferation increases in *Adgrb2* (*Bai2*) knockout mice relative to wildtype animals, although how ADGRB2 (BAI2) inhibits neurogenesis is unclear (Okajima et al., 2011). Similarly, conditional loss of *Adgrg6* (*Gpr126*) in Schwann cells causes increased proliferation of this cell type (Mogha et al., 2013). Moreover, proliferation of neuronal progenitors is modulated by ADGRG1 (GPR56), as indicated by opposing effects of loss- and gain-of-function studies in mice (Bae et al., 2014).

In addition, Adhesion GPCRs are regulators of cell survival. Overexpression of ADGRB1 (BAI1) causes increased clearance of apoptotic human umbilical vein endothelial cells (HUVECs) (Koh et al., 2004). Recently, ADGRCs (CELSRs) were shown to potentially regulate the inhibition of apoptosis during early brain development in mice. Although levels of apoptosis are not significantly affected in *Adgrc2* (*Celsr2*) and *Adgrc3* (*Celsr3*) single knockout mice, there is a considerable increase in apoptosis in medial rhombomeres 4/5 in *Adgrc2;Adgrc3* (*Celsr2;Celsr3*) double knockout embryos when compared to wildtype or single knockout embryos (Qu et al., 2010). The molecular basis of this observation has yet to be explored.

Furthermore, Adhesion GPCRs also regulate essential developmental transitions at both tissue and cellular levels. ADGRL2 (latrophilin-2) expression is required for normal epithelial–mesenchymal transition (EMT) of endothelial cells in the atrioventricular canal of the heart during early chick development; however it is unclear how ADGRL2 (latrophilin-2) controls this transition (Doyle et al., 2006). In zebrafish and mice, ADGRG6 (GPR126) signaling is required for Schwann cell differentiation as elevation of cAMP mediated by ADGRG6 (GPR126) is necessary for the terminal differentiation of myelinating Schwann cells (Monk et al., 2009; Monk et al., 2011; Glenn and Talbot, 2013; Mogha et al., 2013). Hence, Adhesion GPCRs appear also to figure in the regulation of cell differentiation.

Finally, Adhesion GPCRs have recently been implicated in promoting cell–cell fusion. ADGRB1 (BAI1), ADGRB3 (BAI3), and ADGRG1 (GPR56) promote myoblast fusion to form mature multinucleated skeletal muscle fibers (Hochreiter-Hufford et al., 2013; Wu et al., 2013; Hamoud et al., 2014). Apoptotic myoblasts expose phosphatidylserine, which activates ADGRB1 (BAI1) signaling on healthy myoblasts to promote fusion with myoblast and myotubes.

## B. Organ systems

### 1. Hematopoietic system and immunity

Members of subfamily ADGRE (EGF-TM7), ADGRB (BAI), and ADGRG are prominently expressed by cells of the immune system. The ADGRE (EGF-TM7) receptors ADGRE1–4 (EMR1–4) and ADGRE5 (CD97) have been studied in vitro and in vivo using antibodies and genetic mouse models. ADGRE5 (CD97) has been implicated in innate and adaptive immune processes through its role in cellular migration (Leemans et al., 2004), proliferation (Capasso et al., 2006), and mobilization from the bone marrow (van Pel et al., 2008b). Many of these effects are presumed to be either adhesion- or signaling-dependent, as they are also observed in mice lacking the binding partner CD55. Addition of F4/80 (mouse ADGRE1 [EMR1])-blocking antibodies to cell culture prevented NK cell–macrophage cellular contacts necessary for mediating a robust IFN $\gamma$  response towards the bacteria *Listeria monocytogenes* (Warschkau and Kiderlen, 1999). Moreover, in mouse models, ADGRE1 (EMR1) was essential for the induction of peripheral immune tolerance from eye-derived antigens (Lin et al., 2005). Elucidation of the function of other ADGRE (EGF-TM7) subfamily receptors is hampered by the absence of ADGRE2 (EMR2) and ADGRE3 (EMR3) orthologs in rodents. In vitro studies demonstrated a role of human ADGRE2 (EMR2) in enhancing neutrophil migration, degranulation, and cytokine secretion, as well as in suppressing lipopolysaccharide-induced neutrophil survival (Yona et al., 2008a; Huang et al., 2012).

Although not restricted to the hematopoietic lineage, BAI1 has been shown to bind phosphatidylserine and mediates the uptake of apoptotic cells by numerous cell types, including macrophages (Park et al., 2007; Elliott et al., 2010; Sokolowski et al., 2011). In macrophages, it also acts as a pattern recognition receptor binding to lipopolysaccharide of Gram-negative bacteria resulting in Rac signaling and phagocytic uptake (Das et al., 2011).

The presence of ADGRG1 (GPR56), ADGRG3 GPR97, and ADGRG5 GPR114 in leukocyte subsets (Della Chiesa et al., 2010; Peng et al., 2011) implies that these Adhesion GPCRs have immune-related functions, which need to be explored. These receptors may also mediate hematopoietic stem cell repopulation and retention of myeloid cells within the bone marrow niche (Saito et al., 2013). In mice, the highest expression of *Adgrg3* (*Gpr97*) mRNA was found in the bone marrow. Although a previous study failed to demonstrate defects in lymphocyte

development in *Adgrg3* (*Gpr97*) mutant mice (Sleckman et al., 2000), a more recent study showed altered follicular versus marginal zone B-lymphocyte fate decision in the spleen and decreased numbers of B220<sup>+</sup> lymphocytes in the bone marrow in an independently raised *Adgrg3* (*Gpr97*) mouse model (Wang et al., 2013a).

## **2. Cardiovascular system**

Several Adhesion GPCRs are associated with the cardiovascular system. ADGRL2 (Iatrophilin-2) is required for heart valve formation, acting as a component of the epithelial-mesenchymal transition in the atrio-ventricular canal (Doyle et al., 2006). ADGRL1 (Iatrophilin-1) expression has been detected during rat heart development, but its function is unclear (Ferrand et al., 1999). *Adgrg6* (*Gpr126*) knockout mice are lethal, with most dying in utero ~E12. Mutant embryos show signs of myocardial wall thinning, hypotrabeulation, defective mitochondrial function (Patra et al., 2013), and circulatory failure (Waller-Evans et al., 2010).

ADGRE5 (CD97) and ADGRL4 (ELTD1) regulate angiogenesis. The NTF of human ADGRE5 (CD97) is a chemoattractant for migration and invasion of HUVECs in vitro. ADGRE5 (CD97) binds to  $\alpha_v\beta_3$  and  $\alpha_5\beta_1$  integrins, and when overexpressed in tumor cells, soluble ADGRE5 (CD97)-NTF promotes angiogenesis after injection in mice (Wang et al., 2005). ADGRL4 (ELTD1) is expressed in endothelial cells of human renal and colorectal tumors, and is required for proper HUVEC sprouting and vessel formation in zebrafish (Masiero et al., 2013). *Adgrl4* (*Eltd1*) silencing in a mouse orthotopic ovarian cancer model markedly reduced tumor growth and metastatic dissemination, probably by reduction of microvessel density (Masiero et al., 2013).

The NTF of ADGRA2 (GPR124) is shed by cultured HUVECs, mediating cell survival by linking glycosaminoglycans of the ECM to integrin  $\alpha_v\beta_3$  (Vallon and Essler, 2006). In vivo, ADGRA2 (GPR124) functions autonomously in CNS endothelial cells to regulate sprouting and migration. *Adgra2* (*Gpr124*) knockout results in embryonic lethality due to CNS-specific angiogenesis arrest and hemorrhage (Kuhnert et al., 2010; Anderson et al., 2011; Cullen et al., 2011), whereas vascular overexpression results in CNS-specific hyperproliferative vascular malformations, suggesting relevance for ADGRA2 (GPR124) in various CNS-related vascular pathologies.

ADGRG3 (GPR97) is the most highly and specifically expressed GPCR in mouse intestinal lymphatic endothelium (Valtcheva et al., 2013). It regulates migration of human lymphatic endothelial cells in vitro via the small GTPases RhoA and Cdc42 (Valtcheva et al., 2013). Expression studies in human gliomas and ischemia models in rats identified ADGRBs1–3 (BAIs1–3) as anti-angiogenic (Nishimori et al., 1997;Kee et al., 2002;Kee et al., 2004), and BAI1 at least acts in a paracrine way through its NTF, called ‘vasculostatin’ (Kaur et al., 2005;Cork et al., 2012). Overexpression of ADGRB1 (BAI1) (Duda et al., 2002;Kudo et al., 2007) or vasculostatin (Kaur et al., 2005;Kaur et al., 2009) in mice drastically reduced tumor growth. Recent genome-wide association studies have also implicated Adhesion GPCRs in heart rate control (*ADGRD1* [*GPR133*]) (Marroni et al., 2009), brain arterio-venous malformation (*ADGRA2* [*GPR124*]) (Weinsheimer et al., 2012), stroke (*ADGRC1* [*CELSR1*]) (Yamada et al., 2009;Gouveia et al., 2011), and myocardial infarction (*ADGRC2* [*CELSR2*]) (Kathiresan et al., 2009;Qi et al., 2011).

### **3. Respiratory tract**

Although understudied in terms of Adhesion GPCR biology, the respiratory system displays a wide array of Adhesion GPCR expression patterns and phenotypes. Expression profiling shows that several Adhesion GPCRs, including ADGRE5 (CD97), ADGRF5 (GPR116), and ADGRG6 (GPR126), are present at high levels in lung tissue (Abe et al., 1999;Veninga et al., 2008;Promel et al., 2012b;Fukuzawa et al., 2013;Yang et al., 2013;Bridges et al., 2013). Moreover, ADGRC1 (CELSR1) expression is found in restricted spatial domains within the murine lung epithelium. In line with this observation, lung branching is perturbed in *Crash* (*Adgrc1* [*Celsr1*] mutant) mice, which results in disrupted lung development and defects in lung architecture (Yates et al., 2010b). The effect is regulated at least in part via Rho kinase-mediated regulation of the cytoskeleton. *Adgra2* (*Gpr124*)-deficient mouse embryos show reduced lung size (Anderson et al., 2011). To investigate lung hypoplasia, conditional knockout mice will be necessary, because *Adgra2* (*Gpr124*) deficiency results in embryonic lethality, caused by abnormal angiogenesis, as detailed above (Kuhnert et al., 2010;Anderson et al., 2011). *ADGRF5* (*GPR116*) mRNA is highly enriched in fetal and adult lung (Bridges et al., 2013;Fukuzawa et al., 2013;Yang et al., 2013). Gene targeting in mice revealed a critical role of ADGRF5 (GPR116) in lung surfactant homeostasis (Fukuzawa et al., 2013;Yang et al., 2013;Bridges et al., 2013); normally expressed by alveolar type II pneumocytes, ADGRF5

Adhesion G protein-coupled receptors

(GPR116) functions as a molecular sensor of alveolar surfactant pool sizes by regulating surfactant secretion. *Adgrf5* (*Gpr116*) deficiency results in progressive accumulation of surfactant lipids and proteins in the alveolar space in young mice, causing labored breathing and decreasing lifespan. These mice can serve as a model to understand human pulmonary alveolar proteinosis, which is characterized by an accumulation of lung surfactant. Finally, single nucleotide polymorphisms (SNPs) in *ADGRG6* (*GPR126*) are associated with impaired pulmonary function in humans, measured as ratio of forced expiratory volume in the first second/forced vital capacity (FEV<sub>1</sub>/FVC), in a meta-analysis of 28,890 participants (Hancock et al., 2010).

#### **4. Gastrointestinal tract**

ADGRE5 (CD97) is located in lateral cell contacts of human intestinal epithelial cells (Aust et al., 2013). Its overexpression in intestinal epithelial cells in transgenic mice attenuated experimental colitis, probably by strengthening adherens junctions (Becker et al., 2010). Furthermore, *Adgre5* (*Cd97*) transgenic mice show a massive enlargement of the small intestine. This megaintestine phenotype develops after birth, before weaning, with a normal microscopic anatomy and provides a unique model for studying postnatal cylindrical intestinal growth (Aust et al., 2013).

#### **5. Urinary system (kidney, urinary bladder)**

Only a handful of Adhesion GPCRs are expressed in the urinary system, and the functional consequences of their presence are unknown. *ADGRF1* (*GPR110*) gene expression was localized in the papilla-ureter transition zone in humans, i.e. the region of the renal pelvis where the tip of the papilla and the ureter meet, yet no obvious defects were observed in *Adgrf1* (*Gpr110*) knockout/*LacZ* knockin animals (Promel et al., 2012b). Moreover, murine ADGRC1 (CELSR1) protein was noted in collecting duct stalks and S-shaped bodies, just below the nephrogenic zone, and in proximal tubule and podocyte epithelia in E18.5 kidneys (Yates et al., 2010a).



## **6. Endocrine system and metabolism**

For a few Adhesion GPCRs, there is a clear indication of an essential function in endocrine organs and metabolism in general. In mice with adipose tissue-specific absence of *Adgrf5* (*Gpr116*), a pronounced glucose intolerance and insulin resistance developed (Nie et al., 2012). Mice deficient for *Adgrc2/3* (*Celsr2/3*) had severe defects in pancreatic beta-cell differentiation, resulting in decreased glucose clearance (Cortijo et al., 2012). Finally, in humans, a genetic association was identified for *ADGRC2* (*CELSR2*), for which SNPs correlate with decreased low-density lipoprotein levels (Kathiresan et al., 2008; Kathiresan et al., 2009).

## **7. Reproductive organs**

While key reproductive functions in both sexes are under the control of GPCR signaling, evidence is sparse to this point for roles of Adhesion GPCRs in the reproductive system. As yet, only ADGRG1 (GPR56) and ADGRG2 (GPR64), also named HE6 (human epididymis 6), both members of subfamily ADGRG, have been shown to be essential. ADGRG1 (GPR56) is expressed in peritubular myoid cells, Sertoli cells, and germ cells of the testis (Chen et al., 2010). ADGRG2 (GPR64) is mainly expressed in the non-ciliated principal cells of the proximal excurrent ducts (Kirchhoff et al., 2008), which are primarily implicated in testicular fluid reabsorption and sperm concentration. Targeted disruption of either of the encoding genes led to severe subfertility or complete infertility in homozygous knockout males (Davies et al., 2004; Chen et al., 2010). Female reproductive functions, in contrast, were unaffected. Hormonal levels in either of the knockout males were not significantly different from those in wildtype males, suggesting that both receptors exert their functions immediately in a tissue or cell type of the male genital tract. Male subfertility in *Adgrg1* (*Gpr56*) knockout males originated in defects in basal lamina formation during testis development, finally leading to seminiferous tubule disruption (Chen et al., 2010). Targeted disruption of *Adgrg2* (*Gpr64*) led to sperm stasis and duct obstruction, due to dysregulation of fluid reabsorption (Davies et al., 2004). Consequences of loss-of-function mutations in human orthologs of these Adhesion GPCRs in male fertility remain unknown.

## 8. Skeletal muscle and bone

Mounting evidence indicates pivotal functions for Adhesion GPCRs in the musculoskeletal system. Two laboratories recently made exciting discoveries regarding the functions of ADGRB1 (BAI1) and ADGRB3 (BAI3) in this system (Hochreiter-Hufford et al., 2013; Hamoud et al., 2014). Both proteins were reported to be expressed by myoblasts and to promote myoblast fusion into muscle fibers in vitro, but there appear to be differences regarding the in vivo context in which each protein functions, and these differences will be an interesting area for future study.

ADGRG1 (GPR56) was shown to be upregulated during early differentiation of human cultured myoblasts (Wu et al., 2013). In line with these findings, *Adgrg1* (*Gpr56*)-deficient myoblasts showed decreased myoblast fusion in vitro, but *Adgrg1* (*Gpr56*) knockout mice exhibited no overt skeletal muscle phenotype (Wu et al., 2013). Recently, ADGRE1 (CD97) was detected not only in the sarcolemma as other Adhesion GPCRs, but also in the sarcoplasmic reticulum of myocytes. *Adgre5* (*Cd97*)-knockout mice showed a dilated sarcoplasmic reticulum; yet, despite this severe ultrastructural alteration, the mice had no overt skeletal muscle phenotype (Zyryanova et al., 2014), which is similar to as *Adgrb1* (*Bai1*)- and *Adgrg1* (*Gpr56*)-deficient mice (Hochreiter-Hufford et al., 2013; Wu et al., 2013) and may indicate compensatory mechanisms.

Human height and weight, and thus body stature, are polygenic quantitative traits. Several studies support an association of the locus around *ADGRD1* (*GPR133*) with human height (Tonjes et al., 2009; Kim et al., 2012a; Kim et al., 2012b). In parallel, *Adgrd1* (*Gpr133*) has been identified as a positional candidate gene controlling body weight in mice in selection experiments for extreme body weight (Chan et al., 2012). *ADGRG6* (*GRP126*) SNPs are also coupled to human skeletal frame size. The SNP rs6570507 has the potential to regulate transcriptional activity and is associated inversely with trunk length (Soranzo et al., 2009) and adolescent idiopathic scoliosis, the most common pediatric skeletal disease (Kou et al., 2013). These data suggest that alterations in *ADGRG6* (*GRP126*) levels result in abnormal skeletal growth. Finally, *ADGRV1* (*VLGR1*) is involved in bone turnover. An increased risk of fractures, a clinical sign of osteoporosis, is associated with SNPs in the 3'-flanking region of *ADGRV1* (*VLGR1*) in postmenopausal women (Urano et al., 2012). Correspondingly, *Adgrv1* (*Vlgr1*) null mice (Yagi et al., 2005) showed decreased femoral bone mineral density and

trabeculae/cortical thickness resulting in increased fragility, which are probably caused by increased osteoclast activity (Urano et al., 2012).

### **9. Skin (including hair, nails, and mamma)**

Adhesion GPCRs can also be found in epidermal epithelia, where most expression studies have been performed in murine tissues. Besides ADGRC1 (CELSR1), ADGRF2 (GPR111), ADGRF4 (GPR115), and ADGRF5 (GPR116) are, amongst other tissues, also localized to epidermis in the mouse (Bjarnadottir et al., 2004; Devenport and Fuchs, 2008; Promel et al., 2012b). While ADGRC1 (CELSR1) has been identified as a key player in hair follicle polarization and PCP in mice (see chapter VIII.A), the function of the other Adhesion GPCRs in the skin remains elusive. Screens for novel skin-associated genes (Gerber et al., 2013) as well as for glucocorticosteroid response genes (Wang et al., 2004) showed ADGRF4 (GPR115) localization to keratinocytes. The appearance of ADGRF2 (GPR111) and ADGRF4 (GPR115) in vertebrate genomes is coincident with terrestrial evolution, suggesting the hypothesis that these Adhesion GPCRs play a function in skin specialization that is essential for life on land (Promel et al., 2012b). In mouse, both are expressed in stratified squamous epithelium with onset of expression very early during development of the epidermis in embryogenesis. ADGRF2 (GPR111) and ADGRF4 (GPR115) are highly homologous, suggesting a level of functional redundancy, which might be one reason why no phenotype in knockout mice lacking either gene has yet been detected (Promel et al., 2012b).

### **10. Nervous system and behavior**

Cell-surface interactions play a vital role in the development and function of the nervous system. Most Adhesion GPCRs are present in nervous tissues, and some are especially highly expressed in the brain (Haitina et al., 2008; Regard et al., 2008). While not critical for the survival of individual neurons per se, these Adhesion GPCRs seem to jointly control various high-level functions that are characteristic of the brain as an organ.

ADGRL1 (latrophilin-1) is involved in control of spontaneous exocytosis in neurons: on binding an exogenous agonist, the  $\alpha$ -latrotoxin of black widow spiders, it activates  $G\alpha_q$  and phospholipase C, leading to the release of stored  $Ca^{2+}$  and massive exocytosis (Davletov et

al., 1998; Ashton et al., 2001; Capogna et al., 2003; Volynski et al., 2004). Presynaptic ADGRL1 (latrophilin-1) strongly binds postsynaptic teneurin-2, and this interaction regulates presynaptic  $Ca^{2+}$  dynamics (Silva et al., 2011). Deletion of *ADGRL1* (*LPHN1*), together with five other genes, leads to a neuropsychiatric syndromic disorder in humans (Bonaglia et al., 2010). *Adgrl1* (*Lphn1*) knockout mice are viable, but demonstrate abnormal maternal behavior (Tobaben et al., 2002). ADGRL3 (latrophilin-3) interacts with FLRT3, and this affects the formation and regulation of excitatory synapses (O'Sullivan et al., 2012). SNPs in *ADGRL3* (*LPHN3*) are a risk factor for attention deficit/hyperactivity disorder (ADHD) (Arcos-Burgos et al., 2010; Ribasés et al., 2010; Domene et al., 2011). Loss of *Adgrl3* (*Lphn3*) function in mice and zebrafish disturbs dopaminergic brain circuits, leading to a hyperactive/impulsive phenotype, which can be rescued by anti-ADHD drugs (Wallis et al., 2012; Lange et al., 2012).

ADGRC subfamily members (Flamingo/Starry night/CELSRs) influence neural tube closure, the subcellular distribution of ependymal cilia, axon guidance, dendritic morphogenesis, and neuronal migration (Steimel et al., 2010; Berger-Muller and Suzuki, 2011; Boutin et al., 2012). ADGRC1 (CELSR1) facilitates neural tube closure via core-PCP signaling (Nishimura et al., 2012). However, this process also requires ADGRC3 (CELSR2) and ADGRC3 (CELSR3), hinting at a complex functional network that may involve long-range PCP in conjunction with shorter-range interactions and/or cell adhesion. That ADGRCs (CELSRs) influence neuronal cell adhesion is apparent from studies of axon guidance in insects (Chen and Clandinin, 2008). In distinct organisms, ADGRCs (CELSRs) differentially interact, either genetically or directly, with various proteins, such as Frizzled, Gogo, Espinas, Vangl2, and RhoA, to control axon outgrowth and targeting, as well as dendritic self-avoidance (Berger-Muller and Suzuki, 2011; Matsubara et al., 2011; Hakeda and Suzuki, 2013; Huarcaya Najarro and Ackley, 2013). These studies give credence to the idea that the function of 7TM-cadherins could be defined by their binding partners in cis (Berger-Muller and Suzuki, 2011). Notably, in mammals, ADGRC3 (CELSR2) and ADGRC3 (CELSR3) regulate dendrite morphogenesis in opposite ways, but also interact homophilically to trigger intracellular  $Ca^{2+}$  release, suggesting an involvement of G-protein signaling (Shima et al., 2007). *Adgrc3* (*Celsr3*) mutant mice exhibit severe defects in neural circuit development within the CNS, similar to *frizzled3* and *vangl2* mouse mutants (Wang et al., 2002; Tissir et al., 2005; Shafer et al., 2011).

As detailed above, in the CNS, ADGRB (BAI) proteins may contribute to synapse formation and/or function. In neurons, the ADGRB1 (BAI1) and ADGRB3 (BAI3) proteins are localized

postsynaptically, and ADGRB1 (BAI1) expression levels can regulate synaptogenesis (Duman et al., 2013; Lanoue et al., 2013; Stephenson et al., 2013). This function may involve the interaction of ADGRB (BAI) proteins with secreted C1q-like proteins, which strongly bind ADGRB3 (BAI3) and regulate synapse density in vitro (Bolliger et al., 2011). SNPs in *ADGRB3* (*BAI3*) significantly associate with schizophrenia and addiction predisposition (Liu et al., 2006a; DeRosse et al., 2008), and *Adgrb2* (*Bai2*) mutant mice display antidepressant-like behavior (Okajima et al., 2011).

ADGRG1 (GPR56) is likely responsible for mediating the interaction between early-born neurons and the pial basement membrane (Singer et al., 2013). Its binding to collagen III in basement membrane activates the  $\text{G}\alpha_{12/13}$ -RhoA pathway, inhibiting neuronal migration. Lack of ADGRG1 (GPR56) leads to breaches in basement membrane and neuronal ectopias during cerebral cortical development, resulting in bilateral frontoparietal polymicrogyria (BFPP) in humans and similar brain malformations in mice (Piao et al., 2004; Li et al., 2008; Luo et al., 2011). Recently, a role for ADGRG1 (GPR56) in gyral patterning and, potentially, neocortex evolution has been described (Bae et al., 2014). ADGRG6 (GPR126) signaling is required in Schwann cells to elevate cAMP and activate protein kinase A to initiate myelination (Monk et al., 2009; Glenn and Talbot, 2013; Mogha et al., 2013). In *Adgrg6* (*Gpr126*) mouse and zebrafish mutants and conditional knockouts, Schwann cells arrest in development and cannot generate a myelin sheath (Monk et al., 2009; Monk et al., 2011; Mogha et al., 2013).

Studies on the *Frings* mouse indicated that deficiency in *Adgrv1* (*Vlgr1*) is associated with audiogenic seizures and epilepsy (Skradski et al., 2001). More recently the expression of *Adgrv1* (*Vlgr1*) in oligodendrocytes has also been described, and myelin-associated glycoprotein levels were reduced in the *Frings* mutant, suggesting a potential role in regulating myelination for this Adhesion GPCR (Shin et al., 2013).

## **11. Sensory organs**

Although some Adhesion GPCRs are strongly expressed in rodent sensory organs (Haitina et al., 2008; Regard et al., 2008), relatively little is known about their role in sensory function. However, ADGRF3 (GPR113) has been shown to be selectively expressed in a subset of taste receptor cells (LopezJimenez et al., 2005), whereas ADGRCs1–3 (CELSRs1–3) are expressed in

the developing murine olfactory epithelium and cochlea (Shima et al., 2002). *Adgrc1* (*Celsr1*) mouse mutants exhibit defects in PCP of the inner ear sensory epithelium, revealed by misorientation of the outer but not inner hair cells (Curtin et al., 2003). Furthermore, zebrafish mutant for *adgrg6* (*gpr126*) have semicircular canal vestibular morphogenesis defects and thus vestibular dysfunction of the inner ear (Geng et al., 2013).

Mutations in the *ADGRV1* (*VLGR1*) gene are associated with a severe sensory-neuonal disorder, the human Usher syndrome (USH) that affects vision and hearing (Weston et al., 2004). In the mouse inner ear, *ADGRV1* (*VLGR1*) is essential for the correct organization of signal-uptaking hair bundles during the differentiation of the mechanosensitive hair cells. There, *ADGRV1* (*VLGR1*) was identified as a component of the transient ankle-links, spanning between neighboring stereocilia (McGee et al., 2006; Michalski et al., 2007; Yagi et al., 2007). These links stabilize the growing stereocilia during the differentiation of the hair bundle. In murine retinal photoreceptor cells, *ADGRV1* (*VLGR1*) is also associated with adhesions fibers. The analysis of *Adgrv1* (*Vlgr1*)-deficient mice revealed that *ADGRV1* (*VLGR1*) is an integral component of fibrous links between the membranes of the apical inner segment and the connecting cilium at the base of the photosensitive outer segment (Maerker et al., 2008). In both cell types, *ADGRV1* (*VLGR1*) is part of protein networks composed of other USH proteins (Reiners et al., 2005; van Wijk et al., 2006). In photoreceptor cells, *ADGRV1* (*VLGR1*) is a component of a periciliary USH protein network, which is crucial for the transport of cargo from the inner to the outer segment (Maerker et al., 2008). In addition, *ADGRV1* (*VLGR1*) is found at synapses of cochlear and retinal cells (Reiners et al., 2005; Specht et al., 2009; Zallocchi et al., 2012); however, its synaptic function remains to be elucidated.

## C. Clinical aspects

### 1. Developmental defects

The most intensively-studied human disorder associated with loss of an Adhesion GPCR is BFPP (bilateral frontoparietal polymicrogyria), which is caused by mutations in *ADGRG1* (*GPR56*), as discussed above (Piao et al., 2004;Piao et al., 2005). BFPP is an autosomal recessive disorder (Piao et al., 2002;Chang et al., 2003a;Piao et al., 2004;Piao et al., 2005). Affected individuals present with moderate to severe intellectual disability, motor developmental delay, seizures, ataxia, and abnormal eye movement. Magnetic resonance images of BFPP brains reveal bilateral polymicrogyria with an anterior to posterior gradient, decreased white matter volume with associated bilateral signal changes, as well as brainstem and cerebellar hypoplasia. Histological studies in a *Adgrg1* (*Gpr56*) knockout mouse model and a human postmortum BFPP forebrain demonstrate that BFPP is a cobblestone-like cortical malformation, characterized by neuronal overmigration through a breached pial basement membrane (Li et al., 2008;Bahi-Buisson et al., 2010). Studies in *Adgrg1* (*Gpr56*) knockout mice further demonstrated that ADGRG1 (GPR56) is essential for proper morphogenesis of the rostral cerebellum by regulating the external granule cell adhesion to the extracellular matrix proteins (Koirala et al., 2009). Collagen III (gene symbol: *Col3a1*) is the ligand of ADGRG1 (GPR56) in the developing brain (Luo et al., 2011), and mouse *Col3a1* mutants phenocopy *Adgrg1* (*Gpr56*) mutants in cortical malformation (Jeong et al., 2012).

As noted above, mutations in the *ADGRV1* (*VLGR1*) gene cause human Usher syndrome (USH) type 2C (Weston et al., 2004). USH is the most common form of combined hereditary deaf-blindness (Wolfrum, 2012), and USH type 2 is characterized by congenital moderate to severe hearing impairment and onset of retinal dysfunction (*retinitis pigmentosa*) in the first or second decade of life. In contrast to USH type 1, the vestibular system is not affected. *Vlgr1/del7TM* mice lack the fibrous links between membranes of neighbouring stereocilia of hair cells and in the periciliary region of photoreceptor cells (McGee et al., 2006;Michalski et al., 2007;Maerker et al., 2008). In the inner ear, the lack of ankle links results in the disturbance of the organization of the hair bundles leading to profound deafness by 3 weeks of age, phenocopying the symptoms found in USH2C patients. In retinal photoreceptor cells,

the loss of the homologous fibrous links associated with photoreceptor cilia causes only a mild age-related phenotype in mouse models (Michalski et al., 2007), indicating that ADGRV1 (VLGR1) has a more crucial role in human photoreceptor cells. Furthermore, *Adgrv1* (*Vlgr1*) mutations in mice are associated with audiogenic seizures (Skradski et al., 2001) and defects in the human ortholog are possibly related to febrile seizures (Nakayama et al., 2002; Deprez et al., 2006). Interestingly, *ADGRV1* (*VLGR1*) has also been shown to be associated with osteoporosis susceptibility (Urano et al., 2012), suggesting additional crucial roles of the receptor in non-neuronal cell types.

In humans, *LPHN1* gene deletion has been linked to mental retardation, language delay, hyperactivity, hearing impairment, and cranial malformation (Bonaglia et al., 2010). Members of the ADGRB (BAI) subfamily have also been associated with human disease. As described above, the ADGRB1 (BAI1) and ADGRB3 (BAI3) proteins are localized postsynaptically in neurons, and ADGRB1 (BAI1) expression levels have been shown to regulate synaptogenesis (Selimi et al., 2009; Stephenson et al., 2013; Duman et al., 2013). ADGRB (BAI) proteins may regulate synaptogenesis by interacting with the secreted C1q-like proteins, which were shown to be high-affinity binding partners for the previously orphaned ADGRB3 (BAI3) receptor and to regulate synapse density in vitro (Bolliger et al., 2011). Consistent with a function for the ADGRB (BAI) proteins at synapses, SNPs in *ADGRB3* (*BAI3*) significantly associate with schizophrenia and addiction predisposition in genome-wide association studies (Liu et al., 2006b; DeRosse et al., 2008), and *Adgrb2* (*Bai2*) mutant mice display antidepressant-like behavior (Okajima et al., 2011).

Loss-of-function mutations in *ADGRCS1–3* (*CELSRs1–3*) are associated with several human disorders. Mutations in *ADGRC1* (*Celsr1*) cause neural tube defects as well as caudal agenesis in humans (Robinson et al., 2012; Allache et al., 2012). Similarly, mice with missense mutations in *Adgrc1* (*Celsr1*) show craniorachischisis, a severe neural tube defect (Curtin et al., 2003). Furthermore, improperly oriented hair cells in the inner ear and disorganized fur patterning have been reported (Curtin et al., 2003; Ravni et al., 2009). *Adgrc2* (*Celsr2*) knockout and *Adgrc2;Adgrc3* (*Celsr2;Celsr3*) double knockout mice exhibit impaired development of epidymal cilia resulting in hydrocephalus due to defective cerebrospinal fluid dynamics (Tissir et al., 2010), whereas *Adgrc3* (*Celsr3*) knockout mice have defects in the development of the anterior-posterior axon tract organization in the brainstem



(Fenstermaker et al., 2010). All three ADGRC (CELSR) proteins are essential for hindbrain neuron migration (Qu et al., 2010).

## **2. Tumorigenesis**

Cancer genome sequencing has identified putative driver mutations in numerous Adhesion GPCR genes (Wood et al., 2007;Greenman et al., 2007;Jones et al., 2008;Kan et al., 2010;Kang et al., 2013;Weischenfeldt et al., 2013). Notably, missense mutations in *ADGRL3* (*LPHN3*) and *ADGRB3* (*BAI3*) in lung cancer have been predicted to result in loss-of-function of these receptors (Kan et al., 2010). This and the high 'frequency of copy loss' to 'frequency of copy gain' ratio are consistent with a role of these Adhesion GPCRs as tumor suppressors. However, none of the cancer-associated mutations in Adhesion GPCRs have been studied in detail, and thus their impact in cancer progression is not understood.

ADGRE5 (CD97) was the first Adhesion GPCR identified to be involved in cancer (Aust et al., 1997). Widely distributed in normal cells, ADGRE5 (CD97) is regularly upregulated or posttranslationally modified in corresponding malignancies (Aust et al., 1997;Steinert et al., 2002;Aust et al., 2002;Wobus et al., 2004;Aust et al., 2006;Ward et al., 2012;Wu et al., 2012;Safaei et al., 2013;Mirkowska et al., 2013;Zyryanova et al., 2014). In thyroid cancer, ADGRE5 (CD97) expression levels correlate with dedifferentiation (Aust et al., 1997;Ward et al., 2012), and in colorectal cancer, this Adhesion GPCR is overexpressed at the invasion front (Steinert et al., 2002;Galle et al., 2006). Moreover, in gall bladder carcinoma and glioblastoma, ADGRE5 (CD97) expression is inversely related to overall survival (Wu et al., 2012;Safaei et al., 2013). Correspondingly, in mouse models of colorectal and gastric cancer, ADGRE5 (CD97) supported local tumor growth and promoted metastatic spread (Galle et al., 2006;Liu et al., 2012).

Further evidence for a role of ADGRE5 (CD97) in tumorigenesis comes from screening studies demonstrating that ADGRE5 (CD97) is a direct target of the tumor suppressor microRNA-126 in MDA-MB-231 cells (Lu et al., 2014). Gene expression studies and characterization of the leukemia cell surface proteome identified ADGRE5 (CD97) as a marker for minimal residual disease in ALL (acute lymphoblastic leukemia) (Coustan-Smith et al., 2011). ADGRE5 (CD97) expression also accounts for the most informative differences between normal and malignant cells in this leukemia (Mirkowska et al., 2013) and ADGRE5 (CD97) has been

identified as a leukemic stem cell marker in acute myeloid leukemia (AML) (Bonardi et al., 2013).

The function of ADGRG1 (GPR56) in cancer seems to be cell- and/or context-specific. On one hand, expression levels of ADGRG1 (GPR56) were found to be inversely correlated with the metastatic potential of melanoma cell lines (Zendman et al., 1999; Xu et al., 2006), and reexpression of the receptor led to a reduction in melanoma growth and metastasis (Yang et al., 2011). On the other hand, ADGRG1 (GPR56) was found to be upregulated in various cancer types (Shashidhar et al., 2005; Kausar et al., 2011) and in tumor cell lines (Ke et al., 2007), compared to normal samples.

In melanoma, the regulatory mechanisms of ADGRG1 (GPR56) appear to involve PKC $\alpha$  activation, VEGF secretion, and tumor angiogenesis (Yang et al., 2011). Overexpression of full-length ADGRG1 (GPR56) versus variants missing the NTF or those parts of the NTF that bind tissue transglutaminase 2 (Xu et al., 2006) had opposing downstream effects in tumor models (Yang et al., 2011). Recently, the mechanism by which ADGRG1 (GPR56) inhibits melanoma growth has been clarified: the tumor-promoting function of tissue transglutaminase 2 and its extracellular matrix-modifying activity is antagonized by ADGRG1 (GPR56) via receptor-mediated internalization and degradation (Yang et al., 2014).

Expression of ADGRF5 (GPR116) is associated with progression, metastasis, and poor prognosis in breast cancer patients (Tang et al., 2013). In breast cancer cell lines, ADGRF5 (GPR116) modulates motility and morphology via the G $\alpha_q$ -p63RhoGEF-Rho-GTPase pathway (Tang et al., 2013).

ADGRB1 (BAI1) expression is absent or down-regulated in glioblastoma (Nishimori et al., 1997; Kaur et al., 2003), colorectal cancer (Fukushima et al., 1998), metastatic brain tumors derived from lung (Zohrabian et al., 2007), renal cell carcinoma (Izutsu et al., 2011), and astrocytoma (Wang et al., 2013b). Further, ADGRB1 (BAI1) expression levels are inversely correlated with tumor vascularization (Fukushima et al., 1998; Hatanaka et al., 2000; Duda et al., 2002; Kang et al., 2006; Kudo et al., 2007; Hardcastle et al., 2010), suggesting anti-angiogenic functions. Changes in ADGRB1–3 (BAI1–3) expression levels in the experimental focal ischemia model in rodents further suggest a role for these proteins in neovascularization (Koh et al 2000, Kee et al 2002, Kee et al 2004, Jeong et al 2006). Indeed, proteolysis of ADGRB1 (BAI1) releases 120- or 40-kDa fragments from the NTF, named

'vasculostatin' or 'vasculostatin-40', respectively, which inhibit migration of endothelial cells in vitro and angiogenesis and/or tumor growth in vivo (Koh et al., 2004;Kaur et al., 2005;Kaur et al., 2009;Cork et al., 2012).

In summary, conventional clinical and biological research as well as genomic and proteomic analyses highlight the importance of Adhesion GPCRs in tumorigenesis.

## **X. Perspectives on pharmacological opportunities**

There are no marketed drugs known to act at Adhesion GPCRs, and we are not aware of any current clinical trials targeting these receptors with new drug compounds (Rask-Andersen et al., 2014). However, there is a growing interest in Adhesion GPCR pharmacology, and the structural features of the Adhesion GPCRs (i.e., having multiple extracellular epitopes) can be effectively targeted by antibodies. Numerous studies demonstrate a direct involvement of Adhesion GPCRs in immune reactions and tumor pathogenesis, providing perhaps the best current foundation for their therapeutic potential.

The selective expression of several Adhesion GPCR genes may provide opportunities for immune cell-ablation strategies. A recent study showed that afucosylated monoclonal antibodies directed against ADGRE1 (EMR1) dramatically enhanced natural killer cell-mediated cytotoxicity of human eosinophils and induced rapid and sustained depletion of eosinophils in monkeys (Legrand et al., 2014), providing promise as treatment for eosinophilic disorders. Notably, monoclonal antibodies directed against different EGF domains of the related ADGRE5 (CD97) receptor have been shown to deplete neutrophils specifically under inflammatory conditions (Veninga et al., 2011), with ameliorating consequences in experimental inflammatory disease models (Hamann et al., 2010). These findings indicate that targeting subfamily ADGRE (EGF-TM7) members may have potency for the treatment of inflammatory conditions caused by polymorphonuclear granulocytes.

As summarized in chapter IX.2, Adhesion GPCRs are involved in several aspects of tumorigenesis. Targeting angiogenesis during solid tumor growth may provide potential (onco)therapeutic benefits. ADGRA2 (GPR124) was first described as tumor-endothelial marker 5 (TEM5) because it is present in endothelial cells of the tumor stroma but not of the corresponding normal colonic tissue (Carson-Walter et al., 2001). ADGRA2 (GPR124) is required for VEGF-induced tumor angiogenesis in vivo (Wang et al., 2014). Moreover, in vitro knockdown of ADGRA2 (GPR124) overcomes resistance to gefitinib (Gao et al., 2014), an EGF receptor tyrosine kinase inhibitor that is a clinically effective treatment for non-small cell lung cancer (NSCLC). Thus, ADGRA2 (GPR124) might serve as a potential therapeutic target for overcoming NSCLC gefitinib resistance.

Moreover, modulation of Adhesion GPCR functionality in tumors, either by specific antibodies or drugs, may be an effective approach for preventing tumor progression. Indeed, ectopic expression of ADGRE5 (CD97) was found in human thyroid carcinomas (Aust et al., 1997;Ward et al., 2012), whereas the corresponding normal thyrocytes were ADGRE5 (CD97)-negative. The levels of ADGRE5 (CD97) protein correlated strongly to tumor dedifferentiation, and targeting this Adhesion GPCR might plausibly provide therapeutic benefit. Similarly, ADGRF5 (GPR116) protein levels increased in breast cancer with progression through clinical stages and was highest in tumors with distant metastases (Davies et al., 2011;Tang et al., 2013). However, as described in chapter VIII, the tumor-associated Adhesion GPCRs ADGRE5 (CD97), ADGRF5 (GPR116), and ADGRG1 (GPR56) are widely expressed and not restricted to a specific cell-type or tissue. Thus, their pharmacological targeting will require carefully designed preclinical safety studies and perhaps cell- and/or tissue-specific application of the therapeutic compounds.

There are other burgeoning fields in which Adhesion GPCRs may have a therapeutic role. As mentioned earlier, *Adgrf5* (*Gpr116*) deficiency in mice has been shown to result in progressive accumulation of surfactant lipids and proteins in the alveolar space (Fukuzawa et al., 2013;Yang et al., 2013;Bridges et al., 2013), thus enabling a better understanding of human pulmonary alveolar proteinosis, which is characterized by an accumulation of lung surfactant. Thus, ADGRF5 (GPR116) may provide an opportunity to pharmacologically manipulate pathways that modulate surfactant pool sizes and to achieve therapeutic benefit.

While most of the focus in Adhesion GPCR drug discovery to this point has been related to targeting the receptors' extracellular domains with antibodies, the potential modulation of these receptors with low molecular compounds is also an area of interest. Recently, the first high-resolution structures of the related Secretin GPCRs were published (Hollenstein et al., 2013) in complexes with small molecule drugs. This development may prompt novel means of drug discovery for the Adhesion GPCRs as well. It has been shown that Adhesion GPCRs with a truncated NTF can be expressed at the cell surface, showing basal activity in cAMP assays (Bohnekamp and Schoneberg, 2011), and such truncated receptors could be used for small molecule screening. Beclomethasone dipropionate was recently identified to specifically induce G-protein activation via binding to ADGRG3 (GPR97) (Gupte et al., 2012). The availability of low molecular weight substances would likely facilitate approaches to

target the wide range of Adhesion GPCRs that are expressed in the brain, a tissue that cannot easily be accessed by peripherally administered antibodies due to the presence of the blood–brain barrier. As mentioned earlier, numerous Adhesion GPCRs of clinical interest are found in the brain, with ADGRL3 (LPHN3) and ADGRB3 (BAI3) being two members of the family that have been associated with psychiatric disorders (Liu et al., 2006a;DeRosse et al., 2008;Arcos-Burgos et al., 2010;Ribasés et al., 2010;Domene et al., 2011).

In sum, Adhesion GPCRs possess novel extracellular elements, which can be targeted by antibodies serving as diagnostic and therapeutic tools, while their common features of ‘classical’ GPCRs also have potential in the development of low molecular weight drugs. Moreover, the cell-specific expression of several Adhesion GPCRs may extend our diagnostic repertoire to identify cell subpopulations, with the largest progress in this area so far being made for immune and tumor cells. Given the large number of important physiological processes that Adhesion GPCRs have been shown to regulate, it seems likely that interest in the therapeutic targeting of this receptor family will continue to escalate in the years to come.

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## **Author contribution**

Wrote or contributed to the writing of the manuscript: Hamann, Aust, Araç, Engel, Formstone, Fredriksson, Hall, Harty, Kirchhoff, Knapp, Krishnan, Liebscher, Lin, Martinelli, Monk, Peeters, Piao, Prömel, Schöneberg, Schwartz, Singer, Stacey, Ushkaryov, Vallon, Wolfrum, Wright, Xu, Langenhan, Schiöth

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## Figure legends

### **Figure 1 Schematic representation showing phylogenetic relationships of Adhesion GPCRs and their N-terminal domain architecture.**

Adhesion GPCRs can be subdivided into nine distinct subfamilies with 33 homologs in the human genome based on phylogenetic analysis of the conserved 7TM domain region. Each subfamily has a unique combination of N-terminal domains and varies widely in length of their N-termini. The conserved sequence motif within the GPS, found within the GAIN domain of most Adhesion GPCRs, mediates autoproteolysis and subsequent attachment of the cleaved NTF and CTF fragments. All subfamilies share a GAIN and 7TM domain (Adhesion GPCR signature), whereas the depicted N-terminal functional domains are not present in every homolog of the subfamilies. GPR123 is exceptional as it is the only mammalian adhesion GPCR that does not contain a GAIN domain. The domain abbreviations include: 7TM, seven-span transmembrane; CA, cadherin; CALX $\beta$ , calnexin- $\beta$ ; CUB, Cs1 and Csr/Uegf/BMP1; EGF, epidermal growth factor; EPTP/EAR, epitempin/epilepsy-associated repeat; GAIN, GPCR autoproteolysis-inducing; GPS, GPCR proteolytic site; HRM, hormone receptor motif; IG, immunoglobulin; LAM, laminin; LRR, leucine-rich repeat; OLF, olfactomedin; PTX, pentraxin; RBL, rhamnose-binding lectin; SEA, sperm protein, enterokinase, agrin module; TSP, thrombospondin.

### **Figure 2 Cleavage- and topology-based compartmentation of Adhesion-GPCR architecture.**

Most Adhesion GPCRs undergo autoproteolysis at the GPS within their GAIN domain resulting in a two-partite structure containing the NTF and the CTF (left). Alternatively, the protein layout of all Adhesion GPCRs is marked by a three-partite structure consisting of an ECD, a 7TM domain, and an ICD. The abbreviations include: 7TM, seven-span transmembrane; CTF, C-terminal fragment; ECD, extracellular domain; GAIN, GPCR autoproteolysis-inducing; GPS, GPCR proteolytic site; ICD, intracellular domain; NTF, N-terminal fragment.

### **Figure 3 Schematic representation of Adhesion GPCR interactions within the N-terminal fragments (NTFs).**

Each Adhesion GPCR that undergoes autoproteolysis is marked by a two-partite structure containing the NTF (dark green) and the CTF (light green) regions. The

interactions of the binding partners with the receptors are shown in 'cis' and 'trans' configurations. The interaction between the N-terminal domains of the Adhesion GPCR and binding partners are shown with grey–black gradient arrowheads, where known interaction towards the receptor is shown in black, and the putative interaction towards the ligand is shown in grey. The figure also shows some of the solved 3D structures of protein domains including RBL domain (2JX9) and tissue transglutaminase 2 (1KV3) obtained from the PDB database. The 3D structure of chondroitin sulfate B (a glycosaminoglycan) is obtained from the Pubchem compound database (Compound ID: 32756). The glycosylphosphatidylinositol anchor of CD55 and CD90 are highlighted in blue. Note: EMR2 interacts only with the chondroitin sulfate B, whereas the CD97 also interacts with the integrins  $\alpha 5\beta 1$  and  $\alpha v\beta 3$ , CD55, and CD90. The domain abbreviations include: 7TM, seven-span transmembrane; EGF, epidermal growth factor; EPTP/EAR, epitempin/epilepsy-associated repeat; GAIN, GPCR autoproteolysis-inducing; GPS, GPCR proteolytic site; HRM, hormone receptor motif; LAM, laminin; LRR, leucine-rich repeat; LRRCT, leucine-rich repeat C-terminal domain; LRRNT, leucine-rich repeat N-terminal domain; OLF, olfactomedin; PTX- pentraxin; RBL - rhamnose-binding lectin.

**Figure 4 Expression of Adhesion GPCRs.** Summary of available published data on the expression of Adhesion GPCRs in (A) humans and (B) mice and rats, obtained by transcriptional profiling and protein analysis techniques. For additional information and references, see the descriptions of individual Adhesion GPCRs at <http://www.guidetopharmacology.org/>.

**Figure 5 Functional involvement of Adhesion GPCRs.** Summary of available published data on the function of Adhesion GPCRs, obtained in vitro and in vivo from humans and mouse models.



## Tables

**Table 1. Proposed new nomenclature for Adhesion GPCRs**

Subfamily		Receptor		
Current number	Proposed new name	Current gene name	Current protein name (alternative names)	Proposed new name
I	L (Letrophilin)	<i>LPHN1</i>	Letrophilin 1 (CIRL-1, CL1, LEC2)	<i>ADGRL1</i>
		<i>LPHN2</i>	Letrophilin 2 (CIRL-2, CL2, LPHH1, LEC1)	<i>ADGRL2</i>
		<i>LPHN3</i>	Letrophilin 3 (CIRL-3, CL3, LEC3)	<i>ADGRL3</i>
		<i>ELTD1</i>	ELTD1 (ETL)	<i>ADGRL4</i>
II	E (EGF-TM7)	<i>EMR1</i>	EMR1 (F4/80)	<i>ADGRE1</i>
		<i>EMR2</i>	EMR2 (CD312)	<i>ADGRE2</i>
		<i>EMR3</i>	EMR3	<i>ADGRE3</i>
		<i>EMR4</i>	EMR4 (FIRE, GPR127)	<i>ADGRE4</i>
		<i>CD97</i>	CD97 (BL-Ac(F2))	<i>ADGRE5</i>
		<i>GPR123</i>	GPR123	<i>ADGRA1</i>
III	A	<i>GPR124</i>	GPR124 (TEM5)	<i>ADGRA2</i>
		<i>GPR125</i>	GPR125	<i>ADGRA3</i>
		<i>CELSR1</i>	CELSR1	<i>ADGRC1</i>
IV	C (CELSR)	<i>CELSR2</i>	CELSR2 (MEGF3)	<i>ADGRC2</i>
		<i>CELSR3</i>	CELSR3 (MEGF2, Fm1, EGFL1)	<i>ADGRC3</i>
		<i>GPR133</i>	GPR133	<i>ADGRD1</i>
V	D	<i>GPR144</i>	GPR144	<i>ADGRD2</i>
		<i>GPR110</i>	GPR110	<i>ADGRF1</i>
VI	F	<i>GPR111</i>	GPR111	<i>ADGRF2</i>
		<i>GPR113</i>	GPR113	<i>ADGRF3</i>
		<i>GPR115</i>	GPR115	<i>ADGRF4</i>
		<i>GPR116</i>	GPR116 (lg-Hepta)	<i>ADGRF5</i>
		<i>BAI1</i>	BAI1	<i>ADGRB1</i>
VII	B (BAI)	<i>BAI2</i>	BAI2	<i>ADGRB2</i>
		<i>BAI3</i>	BAI3	<i>ADGRB3</i>
		<i>GPR56</i>	GPR56 (TM7XN1)	<i>ADGRG1</i>
VIII	G	<i>GPR64</i>	GPR64 (HE6)	<i>ADGRG2</i>
		<i>GPR97</i>	GPR97 (Pb99)	<i>ADGRG3</i>
		<i>GPR112</i>	GPR112	<i>ADGRG4</i>
		<i>GPR114</i>	GPR114	<i>ADGRG5</i>
		<i>GPR126</i>	GPR126 (VIGR, DREG)	<i>ADGRG6</i>
		<i>GPR128</i>	GPR128	<i>ADGRG7</i>
		<i>GPR98</i>	VLGR1 (GPR98, MASS1, USH2C, FEB4)	<i>ADGRV1</i>
IX	V			

BAI, brain-specific angiogenesis inhibitor; CD, cluster of differentiation; CELSR, cadherin EGF LAG seven-pass G-type receptor; CIRL, calcium-independent receptor of  $\alpha$ -latrotoxin; CL, CIRL/latrophilin; DREG, developmentally regulated GPCR; EGFL, epidermal growth factor-like; EGF-TM7, epidermal growth factor–seven-span transmembrane; ELTD, EGF, latrophilin and seven trans-membrane domain-containing protein; EMR, EGF-like molecule containing mucin-like hormone receptor; ETL, EGF-TM7-latrophilin-related protein; FEB, febrile seizures gene disease locus; FIRE, F4/80-like receptor; Fm, flamingo; GPR, G protein-coupled receptor; HE, human epididymal; LEC, lectomedin; LPHH, latrophilin homologue in humans; MASS, monogenic audiogenic seizure susceptibility; MEGF, multiple epidermal growth factor-like domains; TEM, tumor endothelial marker; USH, Usher syndrome; VIGR, vascular inducible GPCR; VLGR, very large GPCR.

**Figure 1: Schematic representation Adhesion GPCRs**

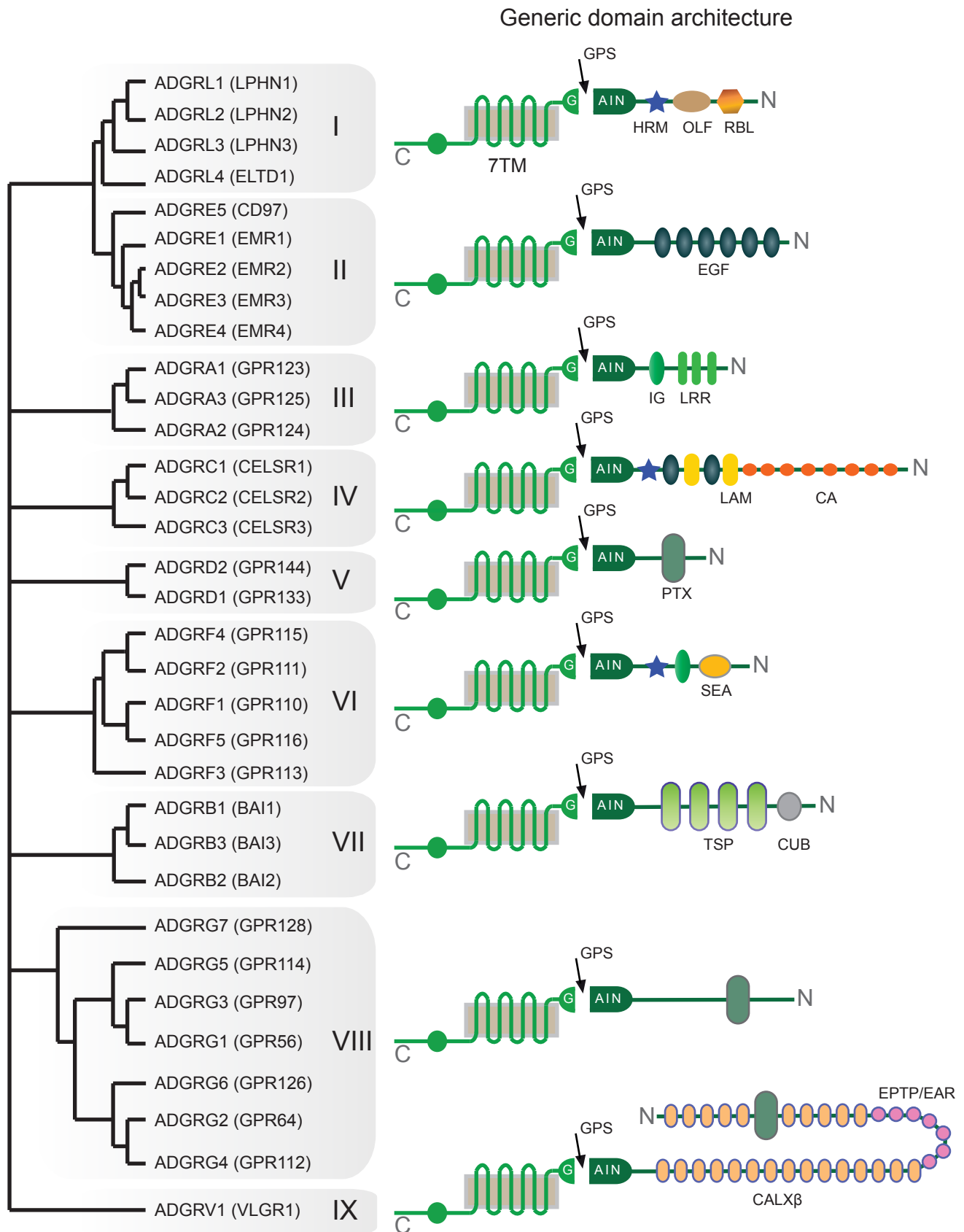


Figure 2: Adhesion-GPCR architecture

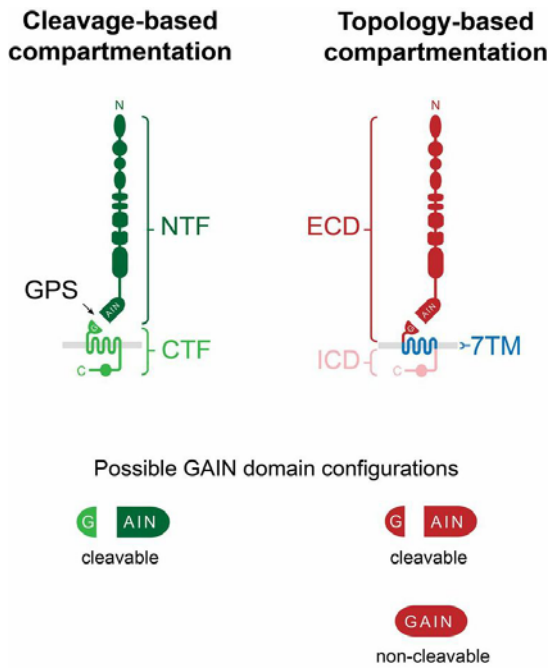


Figure 3: Adhesion-GPCR interactions

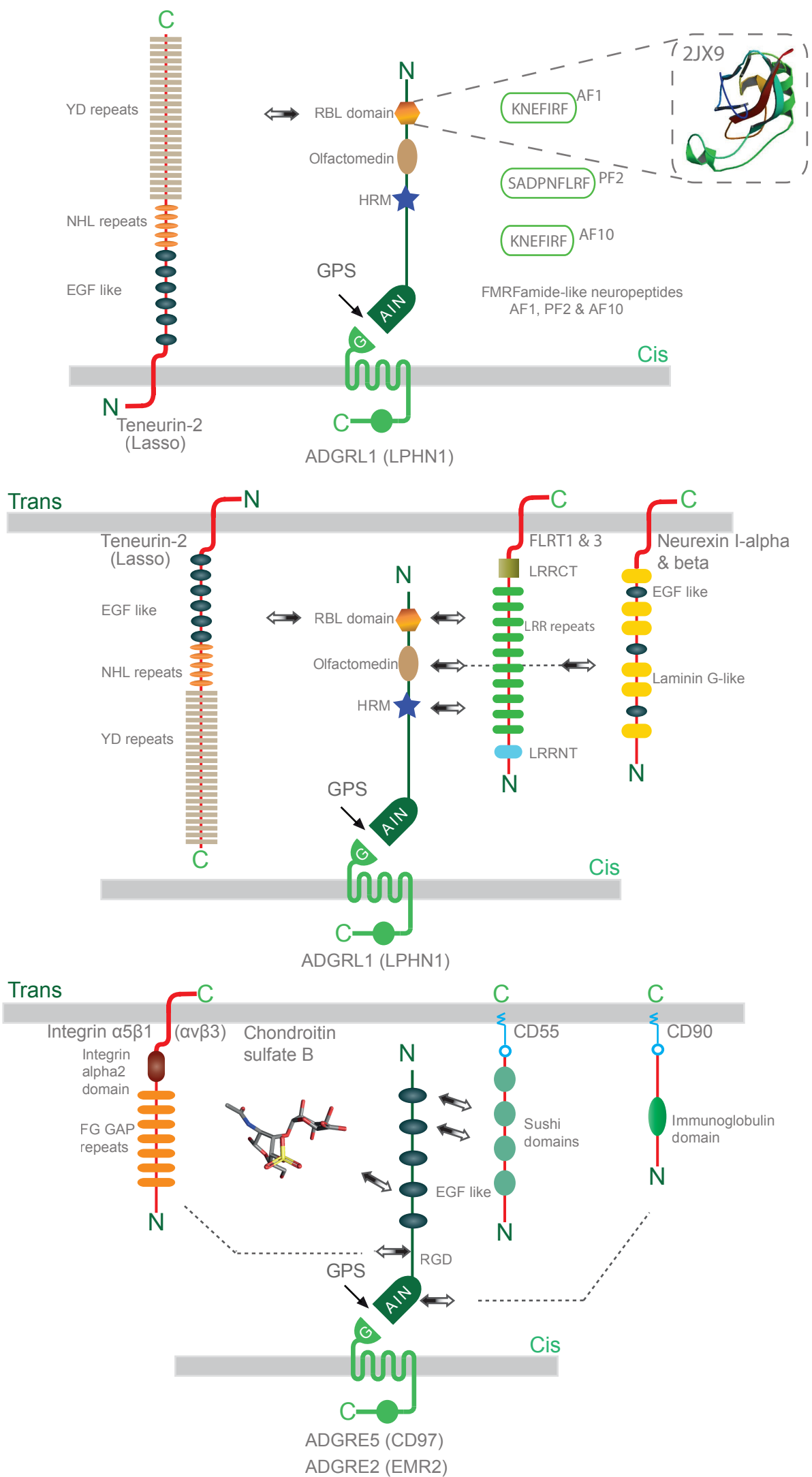
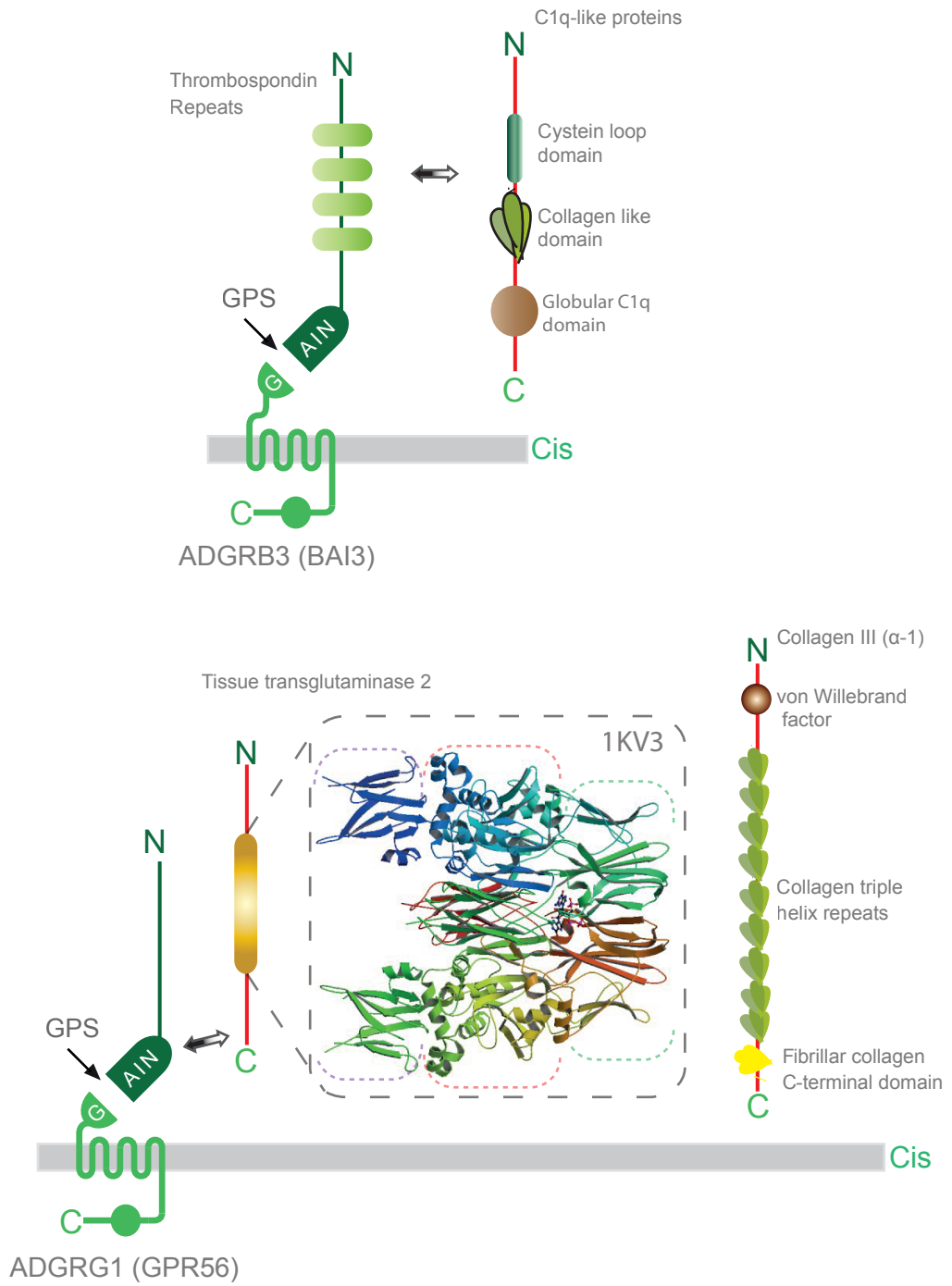


Figure 3 cont..





**Figure 4B: Expression of mouse/rat Adhesion GPCRs**

System	Subfamily	Gene																															
		I	I	I	I	II	II	II	III	III	III	IV	IV	IV	V	V	V	VI	VI	VI	VII	VII	VII	VIII	VIII	VIII	IX						
		ADGRL1 (LPHN1)	ADGRL2 (LPHN2)	ADGRL3 (LPHN3)	ADGRL4 (ELTD1)	ADGRE5 (CD97)	ADGRE1 (EMRL1)	ADGRE4 (EMRA4)	ADGRA1 (GPR123)	ADGRA2 (GPR124)	ADGRA3 (GPR125)	ADGR1 (CELSR1)	ADGR2 (CELSR2)	ADGR3 (CELSR3)	ADGRD1 (GPR133)	ADGRD2 (GPR144)	ADGRF1 (GPR110)	ADGRF2 (GPR111)	ADGRF3 (GPR113)	ADGRF4 (GPR115)	ADGRF5 (GPR116)	ADGRB1 (BA11)	ADGRB2 (BA12)	ADGRB3 (BA13)	ADRG1 (GPR56)	ADRG2 (GPR64)	ADRG3 (GPR97)	ADRG4 (GPR112)	ADRG5 (GPR114)	ADRG6 (GPR126)	ADRG7 (GPR128)	ADGRV1 (VLGR1)	
Structure/cell	Bone marrow – Hematopoietic stem/progenitor cells																																
	Circulation – Erythrocytes																																
Hematopoietic	Circulation – Platelets																																
	Circulation – Lymphocytes																																
	Circulation – Granulocytes																																
	Circulation/tissue – Monocytes/macrophages/DCs																																
	Heart – Myocytes																																
Cardiovasc	Vasculature – Endothelial cells																																
	Vasculature – Smooth muscle cells																																
	Vasculature – Pericytes																																
Resp	Trachea, bronchi – Epithelial cells																																
	Lung – Pneumocytes (alveolar cells)																																
Digestive	Salivary gland – Epithelial cells																																
	Stomach – Epithelial cells																																
	Intestine – Epithelial cells (resorptive, goblet, Paneth cells)																																
	Liver – Hepatocytes																																
	Pancreas – Exocrine and duct cells																																
Urinary	Kidney – Glomerulus mesangial cells																																
	Kidney – Tubules (proxima, distal, collecting)																																
	Urinary bladder – Urothelium																																
Urinary	Urinary bladder – Smooth muscle cells																																
	Thyroid – Thyrocytes																																
Endocrine	Thyroid – C cells																																
	Parathyroid																																
	Adrenal gland – Cortex and medulla																																
	Anterior pituitary gland																																
	Pancreas – Endocrine cells (islets of Langerhans)																																
	Intestine – Entero-endocrine cells																																
	Lung – (Neuro)endocrine cells																																
	Testis – Spermatoocytes																																
	Testis – Leydig cells																																
	Testis – Sertoli cells																																
Reproductive	Epididymis – Epithelial cells																																
	Prostate – Epithelial cells																																
	Ovary – Oocytes																																
	Ovary – Follicular epithelial cells																																
	Uterus – Endometrium																																
	Uterus – Myometrium																																
	Placenta																																
Skin	Skin – Epidermis – Keratinocytes																																
	Skin/whisker – Hair follicles																																
	Breast – Mammary gland epithelial cells																																
Musculoskeletal	Adipocytes (fat cells)																																
	Fibroblasts																																
	Skeletal muscle – Myocytes																																
	Bone – Osteocytes/-blasts																																
	Teeth – Odontocytes/-blasts																																
Nervous	Cartilage – Chondrocytes																																
	CNS – Neural stem/ progenitor cells																																
	CNS – Neurons																																
	CNS – Neuroepithelial cells																																
	CNS – Astrocytes																																
	CNS – Oligodendrocytes																																
	CNS – Radial glia cells																																
	CNS – Microglia																																
	PNS – Neurons																																
	PNS – Schwann cells																																
Sensory	Nose – Olfactory cells																																
	Tongue – Taste sensory cells																																
	Skin – Sensory cells																																
	Eye – Retina (CNS)																																
	Ear – Cochlea, vestibular system																																

*EMR2* and *EMR3* are not present in murids. Cardiovasc, cardiovascular; DC, dendritic cells; CNS, central nervous system; HSC, hematopoietic stem cells; PNS, peripheral nervous system; Resp, respiratory

unknown absent mRNA Protein+ Protein++ Protein+++

### Figure 5: Functional involvement of Adhesion GPCRs

Subfamily		I			II				III		IV			V		VI			VII			VIII			IX																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
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		ADGRL1 (LPHN1)	ADGRL2 (LPHN2)	ADGRL3 (LPHN3)	ADGRL4 (ELTD1)	ADGRE5 (CD97)	ADGRE1 (EMR1)	ADGRE2 (EMR2)	ADGRE3 (EMR3)	ADGRE4 (EMR4)	ADGRA1 (GPR123)	ADGRA2 (GPR124)	ADGRA3 (GPR125)	ADGRC1 (CELSR1)	ADGRC2 (CELSR2)	ADGRC3 (CELSR3)	ADGRD1 (GPR133)	ADGRD2 (GPR144)	ADGRF1 (GPR110)	ADGRF2 (GPR111)	ADGRF3 (GPR113)	ADGRF4 (GPR115)	ADGRF5 (GPR116)	ADGRB1 (BAI1)	ADGRB2 (BAI2)	ADGRB3 (BAI3)	ADGRG1 (GPR56)	ADGRG2 (GPR64)	ADGRG3 (GPR97)	ADGRG4 (GPR112)	ADGRG5 (GPR114)	ADGRG6 (GPR126)	ADGRG7 (GPR128)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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Human EMR4 is a pseudogen. Mol/Cell, molecular/cellular; Clin, clinical

unknown	assumed	shown
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