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Tobias Langenhan
Torsten Schöneberg *Editors*

# Adhesion G Protein-coupled Receptors

## Molecular, Physiological and Pharmacological Principles in Health and Disease

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## Molecular, Physiological and Pharmacological Principles in Health and Disease

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# Preface

The very first monograph that was dedicated to a general overview on the adhesion family of G protein-coupled receptors (aGPCRs) was published just in 2010 (Adhesion-GPCRs: Structure to Function. Yona and Stacey, Ed., Landes Bioscience and Springer). It was the earliest attempt by a small group of researchers to cast the scarce information on these enigmatic molecules into a general concept on what they do and how they do it.

The absence of such public face for the biology of aGPCRs was painfully felt by all colleagues who were actively researching aGPCRs in these days. Scepticism was high from many neighbouring fields why aGPCRs rise to such grotesque dimensions with thousands of residues dedicated to their extracellular tails alone. Also how their exotic functions during the development of organs could be accounted for by their peculiar bipartite adhesive/receptive structure was a constant source of doubt (and motivation for further investigation). Not least, whether aGPCRs are 'true' GPCRs and can thus be attacked by the immense technological armoury that has accumulated during the decades of research on other members of the GPCR superfamily was possibly the most pressing question we were confronted with. Next to the simple matter: what do these receptors sense, after all?

While many of these points could not be satisfactorily answered yet back then, the 2010 book project brought them on the map for the first time in a collective effort. Therefore, this venture from a group of adhesion GPCR aficionados was an incontestable sign of a growing community of researchers that had formed to pursue the inherent questions on aGPCRs with seriousness and persistence.

The roster of colleagues that have contributed their expertise, time and dedication to the current monograph bears testimony to that spirit, and we are immensely grateful for their support. We also wish to thank the Editorial Board of the *Handbook of Experimental Pharmacology* for allotting us an entire volume of this eminent book series to document our knowledge on aGPCRs. We are indebted to Susanne Dathe, Wilma McHugh, Rahila Nahid and Sumathy Thanigaivelu from *Springer Nature* for excellent editorial and technical support, and for generous funding from the Deutsche Forschungsgemeinschaft (DFG) to several chapter authors through a Research Unit Grant (FOR 2149), a first award of its kind to a coordinated scientific initiative dedicated to the study of aGPCRs.

The chapters of this volume are authored by renowned experts in the aGPCR field and chart the current state of aGPCR research. Following their contributions, the reader will learn that some of the pressing molecular issues of 2010 have begun to find answers:

- aGPCRs can signal via canonical signaling outlets and a credible mechanism on how they get activated has been recently devised (Liebscher et al., *Tethered agonism: a common activation mechanism of adhesion GPCRs*; Kishore et al., *Versatile signaling activity of adhesion GPCRs*).
- In some cases, the receptors' structural peculiarities have been experimentally matched with highly intriguing biochemical and biological phenomena such as in the case of the GAIN domain and other extracellular protein folds (Araç et al., *Understanding the structural basis of adhesion GPCR functions*).
- One such class of events regards the extensive proteolytic processing of aGPCRs and is discussed by Nieberler et al. (*Control of adhesion GPCR function through proteolytic processing*). Knapp et al. explore the central position of *adhesion GPCRs-related protein networks*, roles that are mainly relayed through their intracellular domains.
- Other vital components of their architecture such as the structure of the heptahelical transmembrane domain of aGPCRs have remained locked to our efforts, but it is clear that in the near future the focus will shift evermore into their direction and offer new vantage points to interfere with their activity. Nijmeijer et al. explored these possibilities in their chapter on *7TM domain structure of adhesion GPCRs*.
- Kovacs et al. review *the relevance of genomic signatures at adhesion GPCR loci* (specifically of human homologs), informing us about their role in phenotypic variation and disease aetiology, an overdue endeavour in the omics era that is aided by the novel harmonised nomenclature and classification system of the aGPCR family introduced by Krishnan et al. (*Classification, nomenclature and structural aspects of adhesion GPCRs*).

The second part of this book is dedicated to physiological and pathological aspects of aGPCRs:

- Scholz et al. describe the emerging concept of *adhesion GPCRs as a putative class of metabotropic mechanosensors*, which distinguishes them from the rest of the GPCR superfamily.
- Several chapters relate to this discovery with specialist focus on its implications in the nervous system (Harty et al., *Adhesion GPCRs as novel actors in neural and glial cell functions: from synaptogenesis to myelination*), in skeletal muscle (White et al., *Control of skeletal muscle cell growth and size through adhesion GPCRs*) and lung physiology (Ludwig et al., *Adhesion GPCR function in pulmonary development and disease*) and in the immune system (Hamann et al., *Adhesion GPCRs as modulators of immune cell function*). Musa et al. describe that *heart development, angiogenesis and blood-brain barrier*

*function are modulated by adhesion GPCRs*, adding further organ systems that require those receptors for their respective setups and daily operations.
- Finally, Strutt et al. discuss that *adhesion GPCRs govern polarity of epithelia and cell migration*, while the chapter of Aust et al. review the current state of knowledge on *adhesion GPCRs in tumorigenesis.*

We are certain that the research described in this book marks several milestones in the maturation of our understanding on how aGPCRs impact biology. It is to be hoped that the concepts on several aspects of aGPCRs unveiled in the last years are stepping stones to grasp their roles in human disease and therapeutic intervention. We are much looking forward to witness and participate in the exciting developments of this thriving area of biomedical research.

The book will start though with look back at the *History of the adhesion GPCR field* (Hamann and Petrenko), to record the path of our community and remark its scientific course throughout the last 20 years.

Würzburg, Germany — Tobias Langenhan
Leipzig, Germany — Torsten Schöneberg

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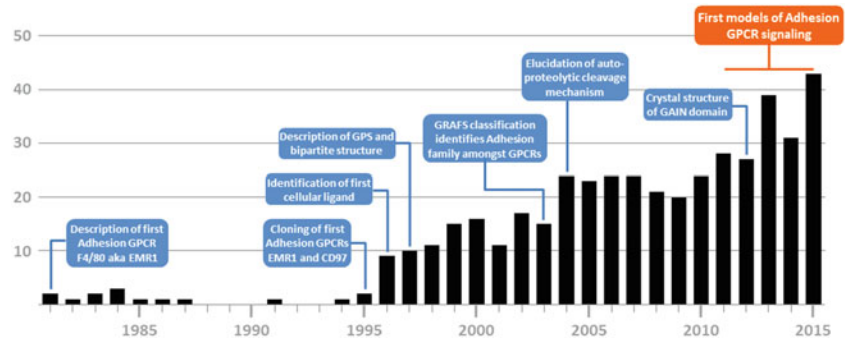
*Member of the DFG Research Unit FOR2149 *Elucidation of Adhesion GPCR Signaling*

# Introduction: History of the Adhesion GPCR Field

Jörg Hamann and Alexander G. Petrenko

**Graphical Abstract**




Development of the aGPCR scientific field based on PubMed-listed research articles and selected key findings

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**Abstract**

Since the discovery of adhesion G-protein-coupled receptors (aGPCRs) 20 years ago, reverse genetics approaches have dominated the elucidation of their function and work mechanisms. Seminal findings in this field comprise the description of aGPCRs as seven-transmembrane (7TM) molecules with an extended extracellular region, the identification of matricellular ligands that bind to distinct protein folds at the N-terminus, the clarification of an autoproteolytic cleavage event at a juxtamembranous GPCR proteolysis site (GPS), the elucidation of the crystal structure of the GPCR autoproteolysis-inducing (GAIN) domain that embeds the GPS and connects the receptor fragments, the demonstration that a short N-terminal sequence of the seven-transmembrane (7TM) region can serve as a tethered agonist, and, recently, the notification that aGPCRs can serve as mechanosensors. We here discuss how these discoveries have moved forward aGPCR research and, finally, linked the field to the GPCR field. We argue that crucial questions remain to be addressed before we can fully appreciate the biological nature of these fascinating receptors.

**Keywords**

Adhesion GPCRs • History • Biology • Structure • Signaling • Pharmacology

## 1 A Novel Type of Seven-Transmembrane Receptors

After the discovery of hormones as "first messenger" and cyclic adenosine monophosphate (cAMP) as a "second messenger" in the twentieth century, the search for molecules that transduce the "message" through the cell membrane led to the discovery of the first G proteins and then G-protein-coupled receptors (GPCRs). Forward biological approaches, searching for membrane-bound cognate receptors for biocative molecules, subsequently resulted in the identification of many GPCRs and the finding that seven-transmembrane (7TM) receptors possess the largest receptor family in nature. Yet, in contrast to rhodopsin, secretin, glutamate, and Frizzled GPCRs, members of the fifth GPCR family, the adhesion (a) GPCRs, were not discovered via their ligand molecules. Their identification about 20 years ago was the result of genetic approaches that became available through the development of cDNA cloning techniques in the late 1980s (Fig. 1). In 1995, the primary structure of the leukocyte surface molecules CD97 and EMR1 (EGF module-containing, mucin-like hormone receptor 1; in the mouse known as F4/80) was described [1, 2]. The mature proteins were found to comprise a 7TM region, the hallmark of all GPCRs. Most notable was the extended extracellular part, possessing several tandem epidermal growth factor (EGF)-like domains at the N-terminus. With reference to the binary molecule structure, the name EGF-TM7 was coined for these novel receptors [3].

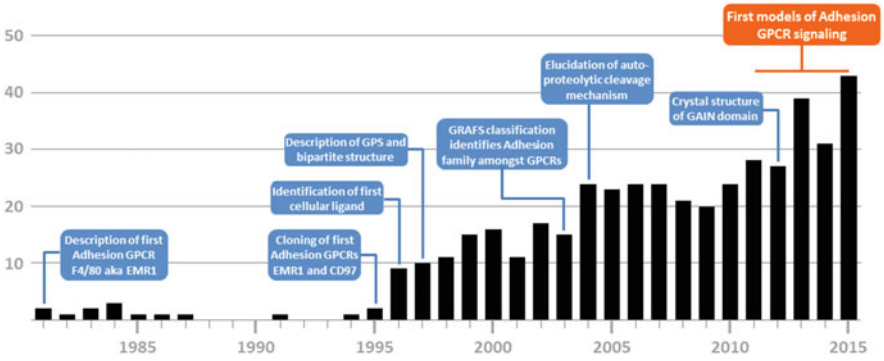


**Fig. 1** Development of the aGPCR scientific field. PubMed-listed research articles reporting on aGPCRs indicated per year throughout the last 35 years. Selected key findings are highlighted

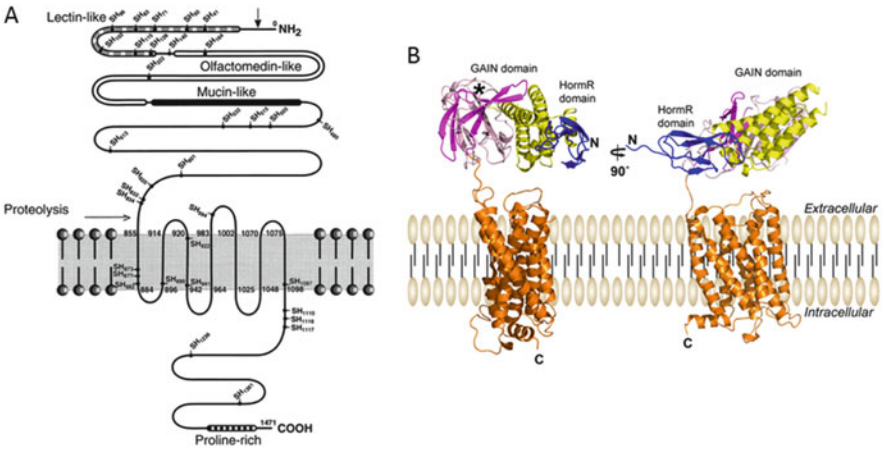


**Fig. 2** Progress in the structural understanding of aGPCRs. (**a**) Protein structure of CIRL-1/latrophilin 1 predicted in 1997 from the deciphered amino acid sequence of the mature polypeptide, with indicated the 7TM region, the extended extracellular region with several protein domains, and the juxtamembranous proteolysis site (reproduced from [4]). (**b**) Model of CIRL-1/latrophilin 1 suggested in 2012 based on crystal structures of the GAIN and hormone receptor domain and modeling of the 7TM moiety (reproduced from [6])

Soon after, CIRL-1 (calcium-independent receptor of α-latrotoxin 1)/latrophilin 1, a neuronal receptor for the black widow spider poison α-latrotoxin, was shown to possess a similar structure and strong homology to the 7TM cores of EGF-TM7 receptors [4, 5] (Fig. 2). However, instead of repetitive EGF-like domains, CIRL-1/latrophilin 1 contains singular lectin-like, olfactomedin, and hormone receptor motif domains in its extracellular part. Subsequent description of other homologous 7TM receptors, including latrophilins, EMRs, CELSRs (cadherin EGF LAG seven-pass G-type receptors), BAIs (brain-specific angiogenesis inhibitors), HE6 (human

epididymal 6), and VLGR1 (very large GPCR 1), confirmed the existence of a novel type of GPCR with a large extracellular part, differently composed of structural modules that are typically found in cell adhesion proteins, suggesting their role in coupling cell-to-cell interaction to intracellular signaling.

Right at the beginning, it became clear that these chimeric GPCRs undergo intensive posttranslational modifications and that CD97, CIRL-1/latrophilin 1, and several of their relatives consist of two noncovalently attached fragments that arise from cleavage of the full-length precursor molecules at a juxtamembranous GPCR proteolysis site (GPS) [4, 7, 8]. By pulse-and-chase labeling, it was shown that the cleavage at the GPS site takes place in the endoplasmic reticulum, rendering it fundamentally different from other proteolytic steps, such as furin processing, which occurs in the Golgi apparatus. In 2004, Hsi-Hsien Lin and colleagues showed that the cleavage is an autocatalytic event commonly employed by N-terminal nucleophile hydrolases [9]. The GPS motif appeared to be highly conserved in the aGPCRs family, representing essentially the eighth region of homology within the family. N-terminal to the GPS, larger regions with no sequence homology were found, linking the cell adhesion-like domains. Why the N-terminal protein adhesion-like domains in many aGPCRs are separated from the 7TM part by a large spacer sequence remained unclear for many more years.

Deciphering of the human genome finally disclosed the existence of 33 related receptors that, based on phylogenetic comparison of the 7TM part, assemble a distinct family of GPCRs. The original interest in these proteins was based primarily on their potential of linking cell-to-cell interactions to intracellular signaling. Helgi Schiöth and coworkers thus called them aGPCRs and subdivided them into nine subfamilies [10]. Their unique molecular design clearly sets the aGPCRs apart from other GPCR families, including the secretin GPCRs [11]. It is of note that in spite of their intricate structure, aGPCRs seem to be ancestral to most other GPCR families and have been found even in the most ancient metazoan phyla [12].

As aGPCRs increasingly received 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 (NC-IUPHAR), recently proposed a unified nomenclature [13]. The new names carry ADGR as a common dominator, followed by a letter and a number to denote each subfamily and subtype, respectively.

## 2 Receptor Biology Convenes a New Research Field

In line with the discovery of aGPCRs through genomic approaches, an interest in these molecules developed concurrently in different biomedical areas. In particular, immunologists, neuroscientists, and developmental biologists were among the first who studied these intriguing receptors. Far before any molecular structures were disclosed, Jon Austyn and Siamon Gordon had described in 1981 a monoclonal antibody directed against an antigen on mouse macrophages, called F4/80 [14]. This antigen, currently known as EMR1 (ADGRE1), has become widely

used as a macrophage marker, expressed during development and throughout adult life in a range of inflammatory, infectious, tumor, and other disease models. Other ADGREs (EMRs) are expressed in specific granulocyte populations [15]. More recently, also ADGRBs (BAIs) and ADGRGs have been identified in immune cells, and BAI1 (ADGRB1) attracted interest as a macrophage receptor for danger-associated molecular patterns [16, 17].

A link between aGPCRs and neuronal function was first established by the finding that α-latroxin evokes massive neurotransmitter release and hormone secretion upon binding to CIRL-1/latrophilin 1 (ADGRL1) [5, 18]. More recently, involvement of several ADGRLs (latrophilins) in high-affinity transsynaptic interactions has been reported, suggesting involvement in synaptic functions [19–21]. Another highly intriguing observation was the discovery that defects in the ADGRG subfamily member GPR56 (ADGRG1) cause a cortical malformation, known as bilateral frontoparietal polymicrogyria (BFPP) [22]. GPR56-associated BFPP, also studied in mouse models, has become a prime example for a monogenic disorder arising from aGPCR dysfunction. More recently, additional roles for GPR56 in gyral patterning and in neocortex evolution as well as in oligodendrocyte development have been described [23–25]. Furthermore, elegant studies in zebrafish and mice have linked GPR126 (ADGRG6) and GPR56 on Schwann cells and oligodendrocytes to myelination of peripheral and central nervous axons, respectively [24, 26, 27].

Investigation of invertebrate aGPCRs has helped to understand fundamental developmental processes in health and disease. The Drosophila CELSR (ADGRC) homolog Flamingo/Starry night governs planar cell polarity (PCP) through facilitating the asymmetric distribution of Frizzled and Disheveled [28–30], and chicken CELSR1 (ADGRC1) facilitates core-PCP signaling-mediated closure of the neural tube [31]. In a similar way, the latrophilin homolog LAT-1 organizes cell division planes across the anterior–posterior axis of the *C. elegans* embryo, acting in parallel with noncanonical Wnt/Frizzled signaling [32]. Moreover, CELSR homologs in *C. elegans* and mice regulate axon guidance and neural circuit development [33, 34]. Finally, CELSR1 and VLGR1 (ADGRV1) are required for the development of sensory epithelia; mutations in the latter are associated with the human Usher syndrome, a severe sensory-neuronal disorder that affects vision and hearing [35].

Next to developmental effects in several organ systems, including the reproductive tract, the role of aGPCRs in tumorigenesis evoked interest in the clinical implication of the receptors. Gabriela Aust was the first who showed that expression of CD97 (ADGRE5) correlates with dedifferentiation and invasiveness in various carcinomas [36, 37]. Inversely, GPR56 controls melanoma growth and metastasis [38].

The examples of aGPCR research provided here are far from complete. However, they illustrate a research field that developed in parallel and fairly separated within different biomedical areas, resulting in a steadily growing number of publications (Fig. 1). It was Siamon Gordon who organized in 2002 a 1-day workshop for immunologists and tumor biologists working on EGF-TM7 receptors

**Table 1** Biennial adhesion GPCR workshops

| Date | Place | Organizers | Talks | Scientific highlights |
|---|---|---|---|---|
| April 4, 2002 | Oxford | Siamon Gordon | 16 | Identification of cellular ligands |
| March 19, 2004 | Leipzig | Gabriela Aust | 19 | Autoproteolytic cleavage at the GPS |
| March 24, 2006 | Amsterdam | Jörg Hamann | 22 | Interaction between receptor fragments |
| March 29, 2008 | Oxford | Martin Stacey | 15 | Adhesion GPCRs in development |
| May 1, 2010 | Leipzig | Gabriela Aust | 19 | In vivo models for Adhesion GPCRs |
| September 6–8, 2012 | Würzburg | Tobias Langenhan | 23 | Crystal structure of the GAIN domain; Autonomous signaling by the CTF; Tethered vs inverse agonist models |
| June 5–7, 2014 | Boston | Xianhua Piao | 33 | Stachel mechanism of receptor activation; Receptor triggering by mechanosensation |
| June 2–4, 2016 | Leipzig | Torsten Schöneberg; Tobias Langenhan | 38 | TBD |

*CTF* C-terminal fragment, *GAIN* GPCR autoproteolysis-inducing, *GPCR* G-protein-coupled receptor, *GPS* GPCR proteolysis site, *TBD* to be determined

in Oxford (Table 1). During the following events in Leipzig (2004), Amsterdam (2006), Oxford (2008), and Leipzig (2010), aGPCRs expressed outside the immune system, such as CIRL-1/latrophilin 1, GPR64 (ADGRG2), and VLGR1, slowly entered the stage. The more recent events in Würzburg (2012) and Boston (2014) dealt with all aspects of aGPCR biology and saw a strongly expanding audience [39, 40]. Yet, despite the transformation into 3-day events, the aGPCR Workshops are still informal gatherings, at which novel, unpublished work is presented, and open questions are discussed in an intimate setting. By catalyzing cross talk and collaboration between aGPCR researchers with a different scientific background, the aGPCR Workshops had a tremendous impact on the field. Currently, the community is looking forward to the next event in Leipzig in 2016.

A decisive step in the development of the field was the founding of the aGPCR Consortium (AGC; www.adhesiongpcr.org) in 2012. As an international, open network of academic and nonacademic laboratories interested in aGPCRs, the AGC currently connects more than 60 scientists from 15 countries. The AGC has become a meeting place for everyone interested in aGPCRs and organizes, currently, the biennial workshops. Moreover, the AGC provides information and visibility for the aGPCR community, works on terminology and nomenclature issues, and serves as a starting ground for collaborative research initiatives. The latter has led to the establishment of the Research Unit 2149—*Elucidation of*

*Adhesion GPCR signaling*—in 2015, which is supported by the Deutsche Forschungsgemeinschaft (www.adhesiongpcr.de).

## 3 From Molecular Structure to Pharmacology

While work on aGPCRs transcended different biomedical areas, the central question on the mechanism by which these receptors signal remained hard to answer for a long time. The existence of numerous protein domains implied that aGPCRs might engage in cell–cell interactions. A similar function of receptor tyrosine kinases has been very well described, with its importance in cancer biology and development. In 1996, Jörg Hamann demonstrated that CD97 binds decay-accelerating factor/CD55, a molecule associated with regulation of the complement cascade [41]. Since then, interacting partners, often matricellular molecules, have been identified for about ten aGPCRs. However, no comprehensive picture arose that would fit the concept of agonistic ligands as these have identified for other GPCR families [42].

Recently, the juxtamembrane part of the aGPCRs containing the GPS motif has been implicated in the receptor signaling. Demet Araç showed that the GPS is an integral part of a much larger domain that was termed GPCR autoproteolysis-inducing (GAIN) domain [6]. Crystal structures of GAIN domains from CIRL-1/latrophilin 1 and BAI3 (ADGRB3) revealed a conserved, novel fold that fine-tunes the chemical environment at the GPS to catalyze peptide bond hydrolysis (Fig. 2). Another key finding by the groups of Randy Hall and Lei Xu was the observation that the C-terminal fragment (CTF) of some aGPCRs shows intense metabotropic and biological activity, implying that the N-terminal fragment (NTF) controls receptor signaling [43, 44], and that the ectodomain of aGPCRs may act as a tethered ligand for their 7TM domain [45].

Building forth on these studies, the laboratories of Ines Liebscher, Torsten Schöneberg, and Gregory Tall have proposed a tethered agonist mechanism according to which displacement of the NTF exposes a short N-terminal sequence of the 7TM domain, designated *Stachel* (German for stinger), that is hidden within the GAIN domain [46, 47]. Synthetic peptides, comprising these *Stachel* sequences, have been shown to potently trigger various aGPCRs, in vitro and also in vivo. Finally, work from the groups of Bruce Spiegelman, Kelly Monk, and Tobias Langenhan uncovered that mechanical cues trigger the activity of aGPCRs under physiological conditions, adding mechanosensation to the sensory canon of the GPCR superfamily [27, 48, 49].

The ability to activate aGPCRs enabled studies aiming at identifying downstream signaling modes. The demonstration that the receptors can couple to all subclasses of G proteins [46, 50] led to the recognition as bona fide GPCRs [55]. Consequently, established GPCR conferences currently discuss developments in aGPCR research. Yet, uncertainties remain (Table 2). Information concerning the ability of aGPCR binding partners to trigger G proteins is very scarce so far [27, 51], and we do not know whether the functioning of the receptors is confined to

**Table 2** Certainties and uncertainties about GPCRs

| What do we know | What we are not sure of |
|---|---|
| • GPCRs are bipartite molecules with a large extracellular region that is connected through a GAIN domain to a 7TM moiety | • A functional link between adhesive capacity and receptor signaling remains to be established |
| • The majority of aGPCRs undergo autocatalytic processing at a GPS embedded within the GAIN domain | • Lack of cleavage of some aGPCRs suggests that a bipartite structure is not a prerequisite for receptor function |
| • aGPCRs can be activated through a tethered agonist (*Stachel* sequence) | • Mechanisms allowing exposure of the *Stachel* need to be determined, in particular for solid tissues and non-cleavable receptors |
| • aGPCRs are widely distributed and cause distinct biological phenotypes | • It is not clear whether aGPCRs display cell type-specific or general cellular functions |

*7TM seven-transmembrane, aGPCR adhesion GPCR, GAIN* GPCR autoproteolysis-inducing, *GPCR* G-protein-coupled receptor, *GPS* GPCR proteolysis site

G-protein signaling. Early studies on PCP in Drosophila showed that the CELSR homolog Flamingo arranges in *trans* and in *cis* with other transmembrane molecules to execute its functions [28–30], possibly presenting another major working mechanism. In addition, CD97 has been shown to heterodimerize with the lysophosphatidic acid (LPA) receptor to amplify LPA-initiated Rho-dependent signaling and invasion in prostate cancer cells [52].

Another interesting possibility exists that the large NTF of aGPCRs may serve autonomously by interacting as a ligand with other receptors. In the original discovery of BAI1, its ectodomain soluble fragment had a role in the inhibition of brain-specific angiogenesis [53]. Also, the presence of a specifically cleaved soluble fragment of CIRL-1/latrophilin 1 was detected in the brain, comprising about 5 % of the total amount of the receptor expressed [54]. Finally, a genetic study uncovered a specific role of the N-terminal fragment of GPR126 in axon sorting [27].

Based on the anecdotal identification of most of its members, the aGPCR cohort is one of the prime examples of genome-sequencing effort-driven identification and definition of an entire molecule class. As a consequence, research on aGPCRs grows out of a "molecule-centered" rather than "biology-centered" history since almost two decades. This situation has recently changed with the advent of molecular models on the signaling paradigm of aGPCRs and their physiological mode of activation. The field has now entered a highly intriguing stage, and we predict that the pharmacological insight and tools that are currently developed will boost novel attempts to understand the biological functions of aGPCRs in health and disease.

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## References


1. Baud V, Chissoe SL, Viegas-Péquignot E, Diriong S, N'Guyen VC, Roe BA et al (1995) EMR1, an unusual member in the family of hormone receptors with seven transmembrane segments. Genomics 26:334–344
2. Hamann J, Eichler W, Hamann D, Kerstens HM, Poddighe PJ, Hoovers JM et al (1995) Expression cloning and chromosomal mapping of the leukocyte activation antigen CD97, a new seven-span transmembrane molecule of the secretion receptor superfamily with an unusual extracellular domain. J Immunol 155:1942–1950
3. McKnight AJ, Gordon S (1996) EGF-TM7: a novel subfamily of seven-transmembrane-region leukocyte cell-surface molecules. Immunol Today 17:283–287
4. Krasnoperov VG, Bittner MA, Beavis R, Kuang Y, Salnikow KV, Chepurny OG et al (1997) alpha-Latrotoxin stimulates exocytosis by the interaction with a neuronal G-protein-coupled receptor. Neuron 18:925–937
5. Lelianova VG, Davletov BA, Sterling A, Rahman MA, Grishin EV, Totty NF et al (1997) Alpha-latrotoxin receptor, latrophilin, is a novel member of the secretin family of G protein-coupled receptors. J Biol Chem 272:21504–21508
6. Araç D, Boucard AA, Bolliger MF, Nguyen J, Soltis SM, Südhof TC et al (2012) A novel evolutionarily conserved domain of cell-adhesion GPCRs mediates autoproteolysis. EMBO J 31:1364–1378
7. Gray JX, Haino M, Roth MJ, Maguire JE, Jensen PN, Yarme A et al (1996) CD97 is a processed, seven-transmembrane, heterodimeric receptor associated with inflammation. J Immunol 157:5438–5447
8. Krasnoperov V, Lu Y, Buryanovsky L, Neubert TA, Ichtchenko K, Petrenko AG (2002) Post-translational proteolytic processing of the calcium-independent receptor of alpha-latrotoxin (CIRL), a natural chimera of the cell adhesion protein and the G protein-coupled receptor. Role of the G protein-coupled receptor proteolysis site (GPS) motif. J Biol Chem 277:46518–46526
9. Lin HH, Chang GW, Davies JQ, Stacey M, Harris J, Gordon S (2004) Autocatalytic cleavage of the EMR2 receptor occurs at a conserved G protein-coupled receptor proteolytic site motif. J Biol Chem 279:31823–31832
10. Bjarnadóttir TK, Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC, Schiöth HB (2004) The human and mouse repertoire of the adhesion family of G-protein-coupled receptors. Genomics 84:23–33
11. Lagerström MC, Schiöth HB (2008) Structural diversity of G protein-coupled receptors and significance for drug discovery. Nat Rev Drug Discov 7:339–357
12. Nordström KJ, Lagerström MC, Wallér LM, Fredriksson R, Schiöth HB (2009) The Secretin GPCRs descended from the family of Adhesion GPCRs. Mol Biol Evol 26:71–84
13. Hamann J, Aust G, Araç D, Engel FB, Formstone C, Fredriksson R et al (2015) International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors. Pharmacol Rev 67:338–367
14. Austyn JM, Gordon S (1981) F4/80, a monoclonal antibody directed specifically against the mouse macrophage. Eur J Immunol 11:805–815
15. Gordon S, Hamann J, Lin HH, Stacey M (2011) F4/80 and the related adhesion-GPCRs. Eur J Immunol 41:2472–2476
16. Park D, Tosello-Trampont AC, Elliott MR, Lu M, Haney LB, Ma Z et al (2007) BAI1 is an engulfment receptor for apoptotic cells upstream of the ELMO/Dock180/Rac module. Nature 450:430–434
17. Das S, Owen KA, Ly KT, Park D, Black SG, Wilson JM et al (2011) Brain angiogenesis inhibitor 1 (BAI1) is a pattern recognition receptor that mediates macrophage binding and engulfment of Gram-negative bacteria. Proc Natl Acad Sci U S A 108:2136–2141
18. Lang J, Ushkaryov Y, Grasso A, Wollheim CB (1998) Ca2+-independent insulin exocytosis induced by alpha-latrotoxin requires latrophilin, a G protein-coupled receptor. EMBO J 17:648–657

19. Silva JP, Lelianova VG, Ermolyuk YS, Vysokov N, Hitchen PG, Berninghausen O et al (2011) Latrophilin 1 and its endogenous ligand Lasso/teneurin-2 form a high-affinity transsynaptic receptor pair with signaling capabilities. Proc Natl Acad Sci U S A 108:12113–12118
20. Boucard AA, Maxeiner S, Südhof TC (2014) Latrophilins function as heterophilic cell-adhesion molecules by binding to teneurins: regulation by alternative splicing. J Biol Chem 289:387–402
21. O'Sullivan ML, de Wit J, Savas JN, Comoletti D, Otto-Hitt S, Yates JR III et al (2012) FLRT proteins are endogenous latrophilin ligands and regulate excitatory synapse development. Neuron 73:903–910
22. Piao X, Hill RS, Bodell A, Chang BS, Basel-Vanagaite L, Straussberg R et al (2004) G protein-coupled receptor-dependent development of human frontal cortex. Science 303:2033–2036
23. Bae BI, Tietjen I, Atabay KD, Evrony GD, Johnson MB, Asare E et al (2014) Evolutionarily dynamic alternative splicing of GPR56 regulates regional cerebral cortical patterning. Science 343:764–768
24. Giera S, Deng Y, Luo R, Ackerman SD, Mogha A, Monk KR et al (2015) The adhesion G protein-coupled receptor GPR56 is a cell-autonomous regulator of oligodendrocyte development. Nat Commun 6:6121
25. Ackerman SD, Garcia C, Piao X, Gutmann DH, Monk KR (2015) The adhesion GPCR Gpr56 regulates oligodendrocyte development via interactions with Gα12/13 and RhoA. Nat Commun 21:6122
26. Monk KR, Naylor SG, Glenn TD, Mercurio S, Perlin JR, Dominguez C et al (2009) A G protein-coupled receptor is essential for Schwann cells to initiate myelination. Science 325:1402–1405
27. Petersen SC, Luo R, Liebscher I, Giera S, Jeong SJ, Mogha A et al (2015) The adhesion GPCR GPR126 has distinct, domain-dependent functions in Schwann cell development mediated by interaction with laminin-211. Neuron 85:755–769
28. Usui T, Shima Y, Shimada Y, Hirano S, Burgess RW, Schwarz TL et al (1999) Flamingo, a seven-pass transmembrane cadherin, regulates planar cell polarity under the control of Frizzled. Cell 98:585–595
29. Shimada Y, Usui T, Yanagawa S, Takeichi M, Uemura T (2001) Asymmetric colocalization of Flamingo, a seven-pass transmembrane cadherin, and Dishevelled in planar cell polarization. Curr Biol 11:859–863
30. Chen WS, Antic D, Matis M, Logan CY, Povelones M, Anderson GA et al (2008) Asymmetric homotypic interactions of the atypical cadherin flamingo mediate intercellular polarity signaling. Cell 133:1093–1105
31. Nishimura T, Honda H, Takeichi M (2012) Planar cell polarity links axes of spatial dynamics in neural-tube closure. Cell 149:1084–1097
32. Langenhan T, Prömel S, Mestek L, Esmaeili B, Waller-Evans H, Hennig C et al (2009) Latrophilin signaling links anterior-posterior tissue polarity and oriented cell divisions in the C. elegans embryo. Dev Cell 17:494–504
33. Steimel A, Wong L, Najarro EH, Ackley BD, Garriga G, Hutter H (2010) The Flamingo ortholog FMI-1 controls pioneer-dependent navigation of follower axons in C. elegans. Development 137:3663–3673
34. Tissir F, Goffinet AM (2013) Shaping the nervous system: role of the core planar cell polarity genes. Nat Rev Neurosci 14:525–535
35. Weston MD, Luijendijk MW, Humphrey KD, Möller C, Kimberling WJ (2004) Mutations in the VLGR1 gene implicate G-protein signaling in the pathogenesis of Usher syndrome type II. Am J Hum Genet 74:357–366
36. Aust G, Eichler W, Laue S, Lehmann I, Heldin NE, Lotz O et al (1997) CD97: a dedifferentiation marker in human thyroid carcinomas. Cancer Res 57:1798–1806
37. Steinert M, Wobus M, Boltze C, Schütz A, Wahlbuhl M, Hamann J et al (2002) Expression and regulation of CD97 in colorectal carcinoma cell lines and tumor tissues. Am J Pathol 161:1657–1667

38. Xu L, Begum S, Hearn JD, Hynes RO (2006) GPR56, an atypical G protein-coupled receptor, binds tissue transglutaminase, TG2, and inhibits melanoma tumor growth and metastasis. Proc Natl Acad Sci U S A 103:9023–9028
39. Araç D, Aust G, Calebiro D, Engel FB, Formstone C, Goffinet A, Hamann J et al (2012) Dissecting signaling and functions of adhesion G protein-coupled receptors. Ann N Y Acad Sci 1276:1–25
40. Liebscher I, Ackley B, Araç D, Ariestanti DM, Aust G, Bae BI et al (2014) New functions and signaling mechanisms for the class of adhesion G protein-coupled receptors. Ann N Y Acad Sci 1333:43–64
41. Hamann J, Vogel B, van Schijndel GM, van Lier RA (1996) The seven-span transmembrane receptor CD97 has a cellular ligand (CD55, DAF). J Exp Med 184:1185–1189
42. Langenhan T, Aust G, Hamann J (2013) Sticky signaling–adhesion class G protein-coupled receptors take the stage. Sci Signal 6:re3
43. Paavola KJ, Stephenson JR, Ritter SL, Alter SP, Hall RA (2011) The N terminus of the adhesion G protein-coupled receptor GPR56 controls receptor signaling activity. J Biol Chem 286:28914–28921
44. Yang L, Chen G, Mohanty S, Scott G, Fazal F, Rahman A et al (2011) GPR56 Regulates VEGF production and angiogenesis during melanoma progression. Cancer Res 71:5558–5568
45. Prömel S, Frickenhaus M, Hughes S, Mestek L, Staunton D, Woollard A et al (2012) The GPS motif is a molecular switch for bimodal activities of adhesion class G protein-coupled receptors. Cell Rep 2:321–331
46. Liebscher I, Schön J, Petersen SC, Fischer L, Auerbach N, Demberg LM et al (2014) A tethered agonist within the ectodomain activates the adhesion G protein-coupled receptors GPR126 and GPR133. Cell Rep 9:2018–2026
47. Stoveken HM, Hajduczok AG, Xu L, Tall GG (2015) Adhesion G protein-coupled receptors are activated by exposure of a cryptic tethered agonist. Proc Natl Acad Sci U S A 112:6194–6199
48. White JP, Wrann CD, Rao RR, Nair SK, Jedrychowski MP, You JS et al (2014) G protein-coupled receptor 56 regulates mechanical overload-induced muscle hypertrophy. Proc Natl Acad Sci U S A 111:15756–15761
49. Scholz N, Gehring J, Guan C, Ljaschenko D, Fischer R, Lakshmanan V et al (2015) The adhesion GPCR latrophilin/CIRL shapes mechanosensation. Cell Rep 11:866–874
50. Gupte J, Swaminath G, Danao J, Tian H, Li Y, Wu X (2012) Signaling property study of adhesion G-protein-coupled receptors. FEBS Lett 586:1214–1219
51. Paavola KJ, Sidik H, Zuchero JB, Eckart M, Talbot WS (2014) Type IV collagen is an activating ligand for the adhesion G protein-coupled receptor GPR126. Sci Signal 7:ra76
52. Ward Y, Lake R, Yin JJ, Heger CD, Raffeld M, Goldsmith PK et al (2011) LPA receptor heterodimerizes with CD97 to amplify LPA-initiated RHO-dependent signaling and invasion in prostate cancer cells. Cancer Res 71:7301–7311
53. Nishimori H, Shiratsuchi T, Urano T, Kimura Y, Kiyono K, Tatsumi K et al (1997) A novel brain-specific p53-target gene, BAI1, containing thrombospondin type 1 repeats inhibits experimental angiogenesis. Oncogene 15:2145–2150
54. Krasnoperov V, Deyev IE, Serova OV, Xu C, Lu Y, Buryanovsky L et al (2009) Dissociation of the subunits of the calcium-independent receptor of alpha-latrotoxin as a result of two-step proteolysis. Biochemistry 48:3230–3238
55. Monk KR, Hamann J, Langenhan T, Nijmeijer S, Schöneberg T, Liebscher I (2015) Adhesion G protein-coupled receptors: from in vitro pharmacology to in vivo mechanisms. Mol Pharmacol 88:617–623

# Part I

# Molecular and Pharmacological Properties of Adhesion GPCRs

# Classification, Nomenclature, and Structural Aspects of Adhesion GPCRs

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## Contents



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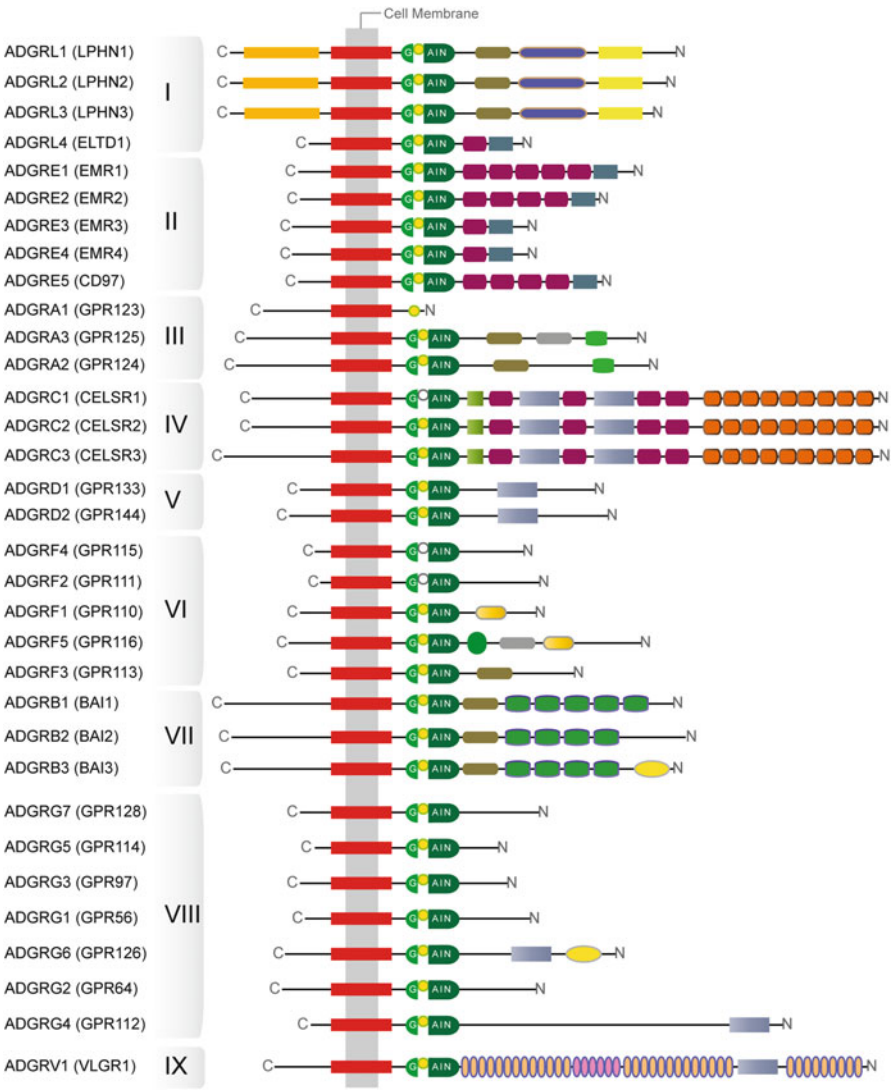
## Graphical Abstract




Representation of the nine distinct aGPCR subfamilies and their unique N-terminal domain architecture. The illustration also shows the extracellular structural feature shared by all aGPCRs (except ADGRA1), known as the GPCR autoproteolysis-inducing (GAIN) domain, that mediates autoproteolysis and subsequent attachment of the cleaved NTF and CTF fragments

**Abstract**

The adhesion family of G protein-coupled receptors (aGPCRs) is unique among all GPCR families with long N-termini and multiple domains that are implicated in cell–cell and cell–matrix interactions. Initially, aGPCRs in the human genome were phylogenetically classified into nine distinct subfamilies based on their 7TM sequence similarity. This phylogenetic grouping of genes into subfamilies was found to be in congruence in closely related mammals and other vertebrates as well. Over the years, aGPCR repertoires have been mapped in many species including model organisms, and, currently, there is a growing interest in exploring the pharmacological aspects of aGPCRs. Nonetheless, the aGPCR nomenclature has been highly diverse because experts in the field have used different names for different family members based on their characteristics (e.g., epidermal growth factor-seven-span transmembrane (EGF-TM7)), but without harmonization with regard to nomenclature efforts. In order to facilitate naming of orthologs and other genetic variants in different species in the future, the Adhesion-GPCR Consortium, together with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification, proposed a unified nomenclature for aGPCRs. Here, we review the classification and the most recent/current nomenclature of aGPCRs and as well discuss the structural topology of the extracellular domain (ECD)/N-terminal fragment (NTF) that is comparable with this 7TM subfamily classification. Of note, we systematically describe the structural domains in the ECD of aGPCR subfamilies and highlight their role in aGPCR-protein interactions.

**Keywords**

Adhesion GPCRs • Nomenclature • Classification • Pharmacology • Drug targets • Homologs • Mammals • Vertebrates • Model organisms • GAIN domain

## 1 Introduction

The G protein-coupled receptor (GPCR) superfamily is the largest family of cell surface receptors and is grouped into five major families: glutamate, rhodopsin, adhesion, frizzled, and secretin [1, 2]. Among all classes, the adhesion GPCRs (aGPCRs) comprise the second largest family with 33 members in the human genome [1, 2]. Prior to the release of the human genome, aGPCRs were not considered as a separate family of GPCRs. Indeed, at that time, only a few genes were identified that constituted a long extracellular region and a seven transmembrane segment (7TM) characteristic to GPCRs. One of the first aGPCRs cloned was the epidermal growth factor (EGF)-like molecule containing mucin-like hormone receptor 1 and later similar molecules were identified [3–6]. This paved the way for the recognition of these molecules as EGF-TM7-like receptors because of the presence of EGF-like domains in their extracellular region [6]. Similarly, other names that were initially termed for aGPCRs include LN-7TM [7] (for the presence of long N-terminal regions), LNB-7TM [8] (for their similarity to family B secretin-

like GPCRs), or family B2 receptors [9]. Shortly after the release of the human genome, several novel genes were identified, and subsequent gene mining showed that at least 30 GPCR-like sequences exist with a long extracellular region and GPCR proteolysis site (GPS) motif that induce autocatalytic processing [10]. Some of these receptors were often initially denoted or thought as secretin-like GPCRs and were placed in proximity to family B receptors [9]. Nonetheless, the large-scale effort to comprehensively classify the GPCRs in the human genome showed convincing phylogenetic evidence that aGPCRs constitute a separate family of GPCRs [1]. This made clearer that adhesion and secretin families are indeed distinct from each other, although these molecules share vague similarities and are often placed together as family B GPCRs [9]. This view is strengthened as the largest of differences were observed in their extracellular region and in particular aGPCRs are also distinct from secretin GPCRs in molecular function. For example, most aGPCRs contain the GPS motif, which is found in close proximity to the 7TM region (for review see [11]). Moreover, it is currently understood that the GPS motif is a part of a much larger GPCR autoproteolysis-inducing (GAIN) domain, which induces the autocatalytic processing of aGPCRs into an N-terminal fragment (NTF) and a C-terminal fragment (CTF) [12]. In addition, the NTF of aGPCRs contains numerous protein domains implicated in cell and matrix interactions [11, 13], and, thus, the established name of "adhesion" family GPCRs was initially coined to refer this feature. Conversely, the secretin GPCRs do not undergo such autocatalytic processing in their N-termini, however, contains a hormone-binding domain (HBD) to mediate hormonal responses [13, 14]. In this chapter, we review the classification of aGPCRs into nine families in the human genome and briefly discuss the classification and potential homologs of these families in other vertebrate and invertebrate genomes. Of note, we address the recently recommended nomenclature of aGPCRs [15] that aim to provide a coherent and systematic naming system independent of the species and subfamily names. Also, we discuss the similarities between aGPCR subclasses with respect to the organization of their structural topology (e.g., olfactomedin, cadherin, EGF-like and thrombospondin type 1 domain). The analysis nevertheless indicates remarkable differences that demonstrate the structural diversity of aGPCRs, but could also hint at potential interaction partners for orphan aGPCRs or provide information on NTF–CTF interactions. We therefore systematically describe the unique (sub) family-specific structural features and their protein interactions.

## 2 Classification of aGPCRs

### 2.1 Human aGPCR Subfamilies

Based on phylogenetic criteria, the human aGPCR repertoire is categorized into nine distinct subfamilies (considering ADGRV1 (VLGR1) as subfamily IX) according to the molecular signature of their 7TM region [1]. The number of genes belonging to the subfamilies I to VIII vary from two genes in "subfamily