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Review

Adhesion GPCRs in immunology

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ABSTRACT

Adhesion GPCRs (aGPCRs) form a subfamily of the large GPCR super family. Most aGPCRs are characterised by a non-covalent bipartite structure that consists of a large extracellular domain and a membrane-spanning 7 transmembrane domain. Typically, aGPCRs can combine cell adhesion by the large extracellular domain with intracellular signalling by the 7 transmembrane domain. Immune responses rely on cellular communication and subsequent defence reactions. Indeed, aGPCR ADGRB1 and members of the ADGRE class have been linked to processes like phagocytosis, leucocyte activation and migration. Nevertheless, research is hampered by absence of endogenous ligands, unknown activity of generated antibodies and non-identified signalling pathways. Yet, based on their membrane localisation and important function, aGPCRs could be novel drug targets to modulate leucocyte function.

Contents

Abbreviations: GPCR, G protein-coupled receptor; aGPCR, adhesion G protein-coupled receptor; ADGR, general adhesion GPCR name followed by class and subtype specific code; 7TM, 7 transmembrane; VLGR1, very large G protein-coupled receptor 1; ECD, extracellular domain; GPS, GPCR proteolysis site; GAIN, GPCR autoproteolysis inducing; NTF, N-terminal fragment; CTF, C-terminal fragment; HBD, hormone binding domain; FLRT, fibronectin leucine-rich repeat transmembrane; EGF, epidermal growth factor; PTX, pentraxin; Ig, immunoglobulin; LRR, leucine-rich repeat; RGD, arginine–glycine–aspartate; SEA, sperm protein–enterokinase–agrin module; TSR, thrombospondin repeat; CUB, Cs1 and Csr/Uegf/BMP-1; LPS, lipopolysaccharide; LAG, laminin A G-type; EAR, epilepsy-associated repeat; BAI, brain-specific angiogenesis inhibitor; CNS, central nervous system; ELMO, engulfment and cell motility protein; Dock180, dedicator of cytokinesis protein 180; GEF, guanosine exchange factor; GTPase, guanosine triphosphate; ROS, reactive oxygen species; TGFα, transforming growth factor α; ERK, extracellular signal-regulated kinase; SRF, serum response factor; NFAT, nuclear factor of activated T cells; IFNγ, interferon γ; IL, interleukin; MAPK, mitogen activated protein kinase; JNK, cJun N terminal kinase; TNFα, tumour necrosis factor α; GM-CSF, granulocyte–macrophage colony-stimulating factor; DC, dendritic cell; WT, wild type; PKB/Akt, protein kinase B; GSK-3β, glycogen synthase kinase 3β; mAb, monoclonal antibody; LPAR1, lysophosphatidic acid receptor 1; PDB, protein data bank.

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1. Introduction

1.1. aGPCRs, as special GPCR subfamily

Adhesion G protein-coupled receptors (aGPCRs) form a 33-membered subfamily of the large GPCR superfamily [1,2]. They share amino acid sequence similarity in their 7 transmembrane (7TM) region with the secretin-like GPCR subfamily, which is thought to have originated from ancestral aGPCRs [3,4].

aGPCRs feature unique subfamily-specific properties that couple (extracellular) cell adhesion to intracellular GPCR signalling (Fig. 1, Table 1, for recent reviews see Refs. [1,2]). Their large (~300–6000 residues) extracellular domains (ECDs) comprise multiple functional subdomains that facilitate interactions with extracellular proteins [1,2]. In fact, the average ECD is ~1.5–20 times the size of a 7TM domain and the height of the ADGRE2 (EMR2)/CD55 interaction protruding the cell surface has been estimated to be ~300 Å [5]. ECDs can bind extracellular proteins that are located on the same cell (cis) or on neighbouring cells (trans). Importantly, comparable ECD subdomain compositions do not result in similar binding properties due to conformational differences. Also, not all aGPCRs possess known functional subdomains in their ECD and not all functional subdomains are known to bind extracellular proteins. Consequently, most aGPCRs are still orphan receptors [1]. Of note, aGPCRs that have been paired with extracellular interaction partners are not necessarily modulated in signalling by these binding interactions. In fact, only a few binding partners are actual agonists, able to activate the aGPCR and evoke an intracellular response mediated by the 7TM domain. Preferably, a distinction should be made between a binding partner that mediates cellular adhesion through extracellular interactions and a binding partner that can affect aGPCR signalling as (inverse) agonist or antagonist.

aGPCRs can be autoproteolytically cleaved at a L↓T/S/C site in the GPCR proteolysis site (GPS) [6,7]. This GPS is part of a larger (~320 residues) GPCR autoproteolysis inducing (GAIN) domain situated immediately N-terminal of the first TM helix [8,9]. Crystal structures of the ADGRL1 (LPHN1) and ADGRB3 (BAI3) GAIN domains reveal a conserved structure that consists of 6 α-helices and a twisted β sandwich including 2 small α-helices and 13 β strands [8] (Fig. 1). The GPS is formed by the last 5 β strands and the actual cleavage site is located between β strands 12 and 13 [8]. Although all aGPCRs (with exception of ADGRA1 (GPR123)) posses this GAIN domain, not all aGPCRs are currently thought to be cleaved due to absence of an ideal GPS consensus sequence [6] (Fig. 1). Whether these aGPCRs are truly non-cleaved in vivo and how this affects their function remains to be studied. Mutations in the GPS site of some aGPCRs lead to impaired trafficking to the cell surface and are a cause for aGPCR dysfunction, stressing the importance of autoproteolytic GPS cleavage for those aGPCR members. Moreover, GAIN domain mutations are linked to diseases such as bilateral frontoparietal polymicrogyria, breast and lung cancers [9].

Autoproteolytic cleavage results in a bipartite aGPCR structure: (1) an N-terminal fragment (NTF) consisting of the major part of the ECD and the GAIN domain without the last (13th) β strand and (2) a C-terminal fragment (CTF) comprising this 13th β strand and the 7TM domain [1,2] (Fig. 1). The NTF and CTF remain non-covalently attached on the cell surface, but can be disrupted by physical interactions with extracellular binders or shear stress [1,2]. Whether the NTF subsequently exists as soluble or membrane-anchored fragment, or and how NTF affects CTF function are still topics of debate and might also be different for aGPCR subtypes.

Interestingly, the isolated 7TM domain-containing CTF has been reported to possess constitutive activity [10], as many of the other GPCR family members [11]. The hydrophobic β-13 strand, originally named "Stachel" or "Stalk" sequence [12,13], is possibly exposed upon NTF removal and has been shown to function as a tethered agonist [12–15]. Yet, absence of this β-13 strand in ADGRG1 (GPR56) and ADGRB1 (BAI1) still results in an active receptor conformation able to affect downstream signalling, indicating that for some aGPCRs this tethered agonist is not essential for aGPCR activity [16]. Possibly, aGPCRs can have different receptor conformations that result in different signalling, a phenomenon known as biased signalling in other GPCR subfamilies. Indeed, full-length aGPCRs ADGRG2 (GPR64), ADGRG1 and ADGRB1 signal differently compared to NTF truncated variants [16,17]. Understanding the relation between extracellular NTF interactions and their effect on CTF function is key in understanding aGPCR signal transduction and modulation.

The rhodopsin GPCR subfamily includes many appreciated drug targets for a vast amount of our current drugs [18], whereas the aGPCR subfamily has not reach that milestone yet. This is mainly caused by the complex bipartite aGPCR structure. In fact, it is currently not clear which protein fragment (NTF or CTF) to target to elicit the preferred outcome. Agonists are rare and not all known binding partners evoke an aGPCR response. Also, not all human aGPCRs have a rodent ortholog for in vivo evaluation and downstream signalling events are often unknown. Finally, full-length proteins show considerable less (constitutive) activity in contrast to their NTF-truncated variants.

aGPCRs are important regulators that couple cellular adhesion towards intracellular events [1,2]. Two aGPCRs have been linked to diseases: ADGRG1 (GPR56) mutations result in the brain malformation bilateral frontoparietal polymicrogyria [19,20] and ADGRV1 (VLGR1) mutations are associated with Usher syndrome, a sensory-neuronal disorder, which affects both vision and hearing [21]. Importantly, no therapeutics have been identified to date that elicit their action via aGPCRs.

1.2. NTF-structure and possible function(s) of aGPCRs

aGPCRs are divided into nine distinct classes based on 7TM amino acid sequence overlap, nevertheless this 7TM division also correlates to some extent with aGPCR NTF compositions [22] (Fig. 1). This correlation hints at a conserved interplay between