Adhesion Class G Protein-Coupled Receptors - Natural Chimeras with Unknown Cell Biological Functions

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Abstract:
G protein-coupled receptors (GPCR) constitute an expanded superfamily of receptors in metazoan genomes. Adhesion class G protein-coupled receptors (Adhesion-GPCRs) form the second largest class of GPCRs and are by far the most poorly understood GPCR class. Key to the structure and function of Adhesion-GPCRs is a juxtamembranous GPCR autoproteolysis-inducing (GAIN) domain. The GAIN domain in most Adhesion-GPCRs facilitates auto-catalytic processing into an extracellular N-terminal fragment (NTF) and a sevenpass-transmembrane (7TM)/cytoplasmic C-terminal fragment (CTF). The NTFs of Adhesion-GPCRs, which are very large in individual receptor homologs, express a wide variety of protein domains providing the ability for combinatorial interactions with cellular or matrix-associated molecules facilitating cell adhesion, orientation and positioning during development, immune responses and tumour growth.
It is neither known why proteolytic cleavage of Adhesion-GPCRs is conserved through evolution, nor why cleaved Adhesion-GPCRs fragments re-associate to almost unchanged appearance at the cell surface compared with uncleaved variants. Although the mode of Adhesion-GPCR signal transduction is still elusive, recent evidence implies that activity of Adhesion-GPCRs is regulated by the interaction between the GAIN and the 7TM domains. Physiological mechanisms that impinge on the proximity between both domains might thus be capable of modulating Adhesion-GPCRs activity and open the possibility to interfere with Adhesion-GPCR dysfunction.

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