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Adhesion-GPCRs
Structure to Function

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PREFACE

Upon completion of the human genome project over 800 G protein-coupled receptor (GPCR) genes, subdivided into five categories, were identified. These receptors sense a diverse array of stimuli, including peptides, ions, lipid analogues, light and odour, in a discriminating fashion. Subsequently, they transduce a signal from the ligand–receptor complex into numerous cellular responses. The importance of GPCRs is further reflected in the fact that they constitute the most common target for therapeutic drugs across a wide range of human disorders. Phylogenetic analysis of GPCRs produced the GRAFS classification system, which subdivides GPCRs into five discrete families: glutamate, rhodopsin, adhesion, frizzled/taste and secretin receptors. The adhesion-GPCR family can be further subdivided into eight groups.

The field of adhesion-GPCR biology has indeed become large enough to require a volume dedicated solely to this field. The contributors to this book have made a courageous effort to address the key concepts of adhesion-GPCR biology, including the evolution and biochemistry of adhesion-GPCRs; there are extensive discussions on the functional nature of these receptors during development, the immune response and tumourgenesis. Finally, there are chapters dedicated to adhesion-GPCR signalling, an area of intense investigation.

This volume focuses on the recent advances in adhesion-GPCR biology. In Chapter 1, we learn about the evolution of the adhesion-GPCR genes in several species including mouse, rat, dog, chicken and the early vertebrate Branchiostoma. In Chapter 2, Formstone continues examining both invertebrate and vertebrate adhesion-GPCRs while discussing Flamingo/Starry Night (Drosophila) and Celsr (vertebrate). Both are of particular interest as core components of planar cell polarity during embryonic development. The roles of adhesion-GPCRs regarding embryogenesis and organogenesis are further analyzed in Chapter 3, in which Langenhan and Russ describe their recent observations concerning the adhesion-GPCR lat-1 as a new signalling receptor, which is essential to control long-range tissue polarity in the C. elegans embryo.

Structurally, the adhesion-GPCR family is defined by a large extracellular region linked to a TM7 moiety via a GPS (G protein-coupled receptor proteolytic site)-containing stalk region. In Chapter 4, Lin et al explore how this proteolytic cleavage was identified as an intrinsic protein modification process in the majority adhesion-GPCRs and dissect
its mechanism and functional consequences. Silva and Ushkaryov further develop the functional value of the GPS site through their description of Latrophilin. This neuronal adhesion-GPCR is the major brain receptor for the black widow spider toxin α-latrotoxin, which stimulates neuronal exocytosis in vertebrates. Chapter 5 presents the latest data regarding the function, signaling and ligands for latrophilin and its related receptors, in addition to dissecting the unusual aspects of post-translational cleavage and signalling by its receptor subunits.

The extended N-terminus region of adhesion-GPCRs often contain common structural domains including epidermal growth factor-like (EGF), thrombospondin repeats, leucine-rich repeats (LRR), lectin-like, immunoglobulin (Ig), cadherins and numerous others. In other proteins many of these domains are involved in protein–protein interactions and cell adhesion; hence the “adhesion-GPCR” nomenclature was conceived reflecting the potential dual roles in cellular adhesion and signaling. In Chapter 6, McMillan and White discuss the very large G protein-coupled receptor 1 (VLGR1) which is most notable for being the largest cell surface receptor in man. The large ectodomain of the protein contains several repeated motifs, including some 35-calcium binding, Calx-β repeats and seven copies of an epitempin repeat thought to be associated with the development of epilepsy. At least two spontaneous and two targeted mutant mouse lines are currently known. Mutant mice are sensitive to audiogenic seizures, have cochlear defects and significant, progressive hearing impairment. Mutations in VLGR1 in humans result in one form (2C) of Usher syndrome, the most common genetic cause of combined blindness and deafness.

Mutations in other adhesion-GPCRs, including the receptor GPR56, are also known to cause human disease. In Chapter 7, Strokes and Piao discuss how these mutations cause excess neuronal migration and a malformed cerebral cortex in the CNS in both primates and rodents. With the emerging effort in studying developmental processes, the vital roles in the development and function of the CNS of other members will be described. In Chapter 8, Xu explains other aspects of GPR56 biology, describing its binding to tissue transglutaminase, a major crosslinking enzyme in the extracellular matrix, and how its expression is suppressed in melanoma metastasis. The functions of GPR56 in cancer progression and the signalling pathways it mediates are also discussed. Further support of the potential importance of adhesion-GPCRs in tumorogenesis is discussed in Chapter 9. Aust profiles the expression of adhesion-GPCRs in tumors from databases and primary research articles and discusses their relevant roles in cell-cell communication, cell migration and angiogenesis.

The EGF-TM7 adhesion-GPCR subfamily are predominately expressed by leukocytes and are involved in coordinating both the innate and acquired immune responses. In Chapter 10, Yona et al highlight some recent immunological advances in relation to EGF-TM7 proteins and other members of the adhesion-GPCR family. Hamann et al, in Chapter 11, show how the use of specific antibodies towards the EGF-TM7 adhesion-GPCR CD97 inhibit the accumulation of granulocytes at sites of inflammation, thereby affecting innate immune responses. Spendlove and Sutavani expand on the role of CD97 through its interaction with the complement control protein DAF/CD55 in Chapter 12. The structural aspects of the CD55-CD97 complex are examined and its functional consequences in T-cell activation are also discussed. In Chapter 13, Lin et al review the historical and functional aspect of the macrophage specific adhesion-GPCR,
F4/80. The F4/80 antigen has now been used for over 30 years as an excellent marker for tissue macrophages. More recently, the receptor has been cloned and identified as an EGF-TM7 receptor critical for the induction of efferent CD8+ regulatory T cells responsible for peripheral immune tolerance.

Until recently, the signaling cascades of almost all adhesion-GPCRs have remained a mystery. In Chapter 14, Mizuno and Itoh review previous reports which suggest G protein-dependent and independent signaling pathways of adhesion-GPCRs and present successful approaches used to investigate the signal transduction of GPR56. In Chapter 15, Park and Ravichandran describe a signaling success story and review the phylogeny, structure, associating proteins, and proposed functions of BAI1. These include its role as a signaling phosphatidylserine receptor in the uptake of apoptotic cells by phagocytes.

Finally, Chapter 16 by Davies and Kirchhoff describes the expression of adhesion-GPCRs within the male reproductive tract and reviews their potential contribution in reproductive competence.

We would like to record our sincere thanks to all our contributors.

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