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Class Frizzled GPCRs in GtoPdb v.2021.3

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Abstract

Receptors of the Class Frizzled (FZD, **nomenclature as agreed by the NC-IUPHAR subcommittee on the Class Frizzled GPCRs [175]**), are GPCRs originally identified in *Drosophila* [19], which are highly conserved across species. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it mediates effects in the Hedgehog signaling pathway [175]. FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription regulator β-catenin or being β-catenin-independent (often referred to as canonical *vs.* non-canonical WNT/FZD signalling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors *LRP5* (O75197) and *LRP6* (O75581), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β-catenin and subsequently its translocation to the nucleus. β-catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors. WNT/β-catenin-independent signalling can also be activated by FZD subtype-specific WNT surrogates [133]. β-catenin-independent FZD signalling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of heterotrimeric G proteins [33, 178, 150], the elevation of intracellular calcium [184], activation of cGMP-specific PDE6 [2] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [56]. Novel resonance energy transfer-based tools have allowed the study of the GPCR-like nature of FZDs in greater detail. Upon ligand stimulation, FZDs undergo conformational changes and signal *via* heterotrimeric G proteins [239, 240, 102, 174]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling towards planar-cell-polarity-like pathways. Importantly, FZDs exist in at least two distinct conformational states that regulate pathway selection [240]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [22], as well as for β-catenin-dependent [13] and -independent [89, 14] signalling. The pattern of cell signalling is complicated by the presence of additional ligands, which can enhance or inhibit FZD signalling (secreted Frizzled-related proteins (sFRP), Wnt-inhibitory factor (WIF), sclerostin or Dickkopf (DKK)), as well as modulatory (co)-receptors with Ryk, ROR1, ROR2 and Kremen, which may also function as independent signalling proteins.

Contents

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Class Frizzled GPCRs
https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=25
Introduction to Class Frizzled GPCRs
https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=25

Receptors

- FZD_1
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=229
- FZD_2
  https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=230
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