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Class Frizzled GPCRs (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

Receptors of the Class Frizzled (FZD, **nomenclature as agreed by the NC-IUPHAR subcommittee on the Class Frizzled GPCRs [156]**), are GPCRs originally identified in *Drosophila* [17], 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 [156]. 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. 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 [28, 159, 135], the elevation of intracellular calcium [164], activation of cGMP-specific PDE6 [2] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [48]. 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 [213, 214]. Furthermore, the phosphoprotein Dishevelled constitutes a key player in WNT/FZD signalling. Importantly, FZDs exist in at least two distinct conformational states that regulate the pathway selection [214]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [19], as well as for β-catenin-dependent [12] and -independent [80, 13] 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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