Frizzled

Overview: Receptors of the Frizzled class (FZD, provisional nomenclature, see Foord *et al*., 2005), which also includes Smoothened (Smo, ENSG00000128602, not considered here), are 7TM receptors originally identified in *Drosophila* (Chan *et al*., 1992), which are highly conserved across species. FZD are activated by WNTs, which are palmitoylated, cysteine-rich glycoprotein hormones with fundamental functions in ontogeny and tissue homeostatis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription factor β-catenin (ENSG00000168036) 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, ENSG00000162337 and LRP6, ENSG00000070018), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β-catenin. β-Catenin, in turn, modifies gene transcription in concert 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 elevation of intracellular calcium (Slusarski *et al*., 1997), activation of cGMP-specific PDE6 (Ahumada *et al*., 2002) and elevation of cAMP (Hansen *et al*., 2009), which has been implicated to be mediated through heterotrimeric G proteins. FZD signalling can also occur through Dishevelled phosphoproteins (ENSF00000001536) to RAC-1 and JNK, as well as Rho and ROCK kinases. As with other 7TM receptors, members of the FZD family are functionally dependent on the β-arrestin scaffolding protein for internalization (Chen *et al*., 2003), β-catenin-dependent (Bryja *et al*., 2007) and independent (Kim and Han, 2007; Bryja *et al*., 2008) signalling. The pattern of cell signalling is complicated by the presence of additional ligands that can enhance (Norrin or R-spondin) or inhibit FZD function [secreted Frizzled-related proteins (sFRP), Wnt inhibitory factor (WIF), SOST or Dickkopf], as well as modulatory proteins with positive (Ryk, ENSG00000163785; ROR1, ENSG00000185483 and ROR2, ENSG00000169071) and negative (Kremen) regulatory features, which may also function as independent signalling proteins.

Nomenclature	Other names	Ensembl ID
FZD_1	Frizzled-1	ENSG00000157240
FZD_2	Frizzled-2	ENSG00000180340
FZD_3	Frizzled-3	ENSG00000104290
FZD_4	Frizzled-4, CD344	ENSG00000174804
FZD_5	Frizzled-5	ENSG00000163251
FZD_6	Frizzled-6	ENSG00000164930
FZD_7	Frizzled-7	ENSG00000155760
FZD_8	Frizzled-8	ENSG00000177283
FZD_9	Frizzled-9, CD349	ENSG00000188763
FZD_{10}	Frizzled-10, CD350	ENSG00000111432

There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration–response relationships (see Kikuchi *et al*., 2009).

Ligands associated with FZD signalling

WNTs: WNT1 (ENSG00000125084), WNT2 (ENSG00000105989, also known as Int-1-related protein), WNT2B (ENSG00000134245, also known as WNT-13), WNT3 (ENSG00000108379), WNT3A (ENSG00000154342), WNT4 (ENSG00000162552), WNT5A (ENSG00000114251), WNT5B (ENSG00000111186), WNT6 (ENSG00000115596), WNT7A (ENSG00000154764), WNT7B (ENSG00000188064), WNT8A (ENSG00000061492), WNT8B (ENSG00000075290), WNT9A (ENSG00000143816, also known as WNT-14), WNT9B (ENSG00000158955, also known as WNT-15 or WNT-14b), WNT10A (ENSG00000135925), WNT10B (ENSG00000169884, also known as WNT-12), WNT11 (ENSG00000085741) and WNT16 (ENSG00000002745).

Extracellular proteins that interact with FZDs: Norrin (ENSG00000124479), R-spondin 1 (ENSG00000169218), R-spondin 2 (ENSG00000147655), R-spondin 3 (ENSG00000146374), R-spondin 4 (ENSG00000101282), sFRP 1 (ENSG00000104332), sFRP 2 (ENSG00000145423), sFRP 3 (ENSG00000162998), sFRP 4 (ENSG00000106483), sFRP 5 (ENSG00000120057).

Extracellular proteins that interact with WNTs or LRPs: Dickkopf 1 (ENSG00000104901), WIF 1 (ENSG00000156076), SOST (ENSG00000167941), Kremen 1 (ENSG00000183762) and Kremen 2 (ENSG00000131650).

Abbreviations: FZD, Frizzled; **TCF/LEF**, ternary complex factor/lymphoid enhancer binding factor

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