Abstract:

The class Frizzled of G protein-coupled receptors (GPCRs), consisting of ten Frizzled (FZD_{1-10}) paralogs and Smoothened, remains one of the most enigmatic GPCR families. This class mediates signaling predominantly through Disheveled or heterotrimeric G proteins. However, the mechanisms underlying pathway selection are elusive. The predominant dogma of WNT-induced and FZD-mediated signal initiation is based on a signalosome model that depends on receptor heterodimerization in response to agonist stimulation, rather than ligand-induced conformational dynamics in the WNT-sensing receptors, the FZDs. However, focusing on understanding the receptor activation mechanisms in detail, we have identified dynamic structural rearrangements in FZDs, which reach from receptor dimer dissociation, over conformational rearrangements within the receptor TM bundle to dynamics of the N-terminal cysteine rich domain relative to the receptor core. In addition, we have employed a structure-driven mutagenesis approach in combination with an extensive panel of functional signaling readouts to investigate the importance of conserved state-stabilizing residues in FZD_5 for signal specification. In conclusion, we find that FZDs indeed are molecular machines requiring conformational dynamics for receptor activation and signal specification.