

Meeting abstract

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The G protein-coupled receptor identity of the frizzled proteins

VL Katanaev* and S Buestorf

Address: University of Konstanz, Department of Biology, Konstanz, Switzerland

* Corresponding author

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Receptors of the Frizzled family initiate Wnt ligand-dependent signal transduction cascades controlling multiple steps in organism development and are highly conserved in animal evolution. Misactivation of the Wnt/Frizzled signaling underlies many cases of cancerogenesis. Frizzled receptors possess seven transmembrane domains and their signaling depends on trimeric G proteins in various organisms. However, as Frizzled proteins constitute a distinct group within the superfamily of G protein-coupled receptors (GPCR), and as Frizzled signaling can apparently be G protein-independent in some experimental setups, the GPCR nature of Frizzled receptors has been questioned. Here we demonstrate that human Frizzled receptors can directly bind the trimeric Go protein in a pertussis toxin-sensitive manner. Furthermore, addition of Wnt ligands elicits Frizzled-dependent guanine nucleotide exchange on Go. An excess of secreted Frizzled-related protein, a known antagonist of the Wnt/Frizzled pathways, inhibits Go activation, as does pretreatment of Go with pertussis toxin. These experiments provide a biochemical proof of the GPCR activities of Frizzled receptors. They also establish an in vitro assay of monitoring Frizzled activation by Wnt ligands, applicable for the high-throughput agonist/antagonist screening.