Understanding Wnt/beta-catenin signaling in development and disease

Summary

Canonical Wnt/β-catenin signaling is initiated by the action of the Frizzled (Fz) receptor and its coreceptor LDL receptor-related-protein 6 (LRP6). Wnt signaling induces LRP6 phosphorylation at conserved PPPSPxS motifs, which serve as docking sites for the scaffolding protein Axin, thereby allowing the Wnt receptor complex to inhibit β-catenin phosphorylation and degradation. LRP6 phosphorylation is mediated via the action of glycogen synthase kinase 3 (GSK3) and casein kinase 1 (CK1), and requires the function of the Fz receptor and its downstream partner Dishevelled (Dvl).

I’ll discuss our study on the regulation of LRP6 phosphorylation, and the role of LRP6-Axin interaction in the initiation and amplification of Wnt signaling at the plasma membrane. I’ll also discuss some biochemical experiments aimed to understand the mechanism by which phosphorylated LRP6 leads to inhibition of β-catenin phosphorylation. Finally I’ll describe a novel transmembrane protein that appears to regulate the Wnt receptor complex.