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## Evidence for discontinuous cyclical Wnt/beta-catenin signaling

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### Keywords

Wnt signaling mechanism disease development

### Abstract

Wnt/beta-catenin signaling is critically important during development and for stem cell maintenance. Dysregulation of the Wnt pathway is implicated in numerous diseases, most notably cancer. Appropriate manipulations for intervention and therapy require an accurate understanding of the Wnt signaling mechanism. The consensus model for the Wnt pathway is surprisingly straightforward: In the OFF state of the pathway, the central regulator in the pathway, termed the destruction complex (DC) targets beta-catenin for degradation, thereby preventing it from nuclear signaling. In the ON state, ligand activation of the Wnt receptor inhibits DC activity, leading to beta-catenin accumulation and transcription of Wnt target genes. The prevailing model of Wnt signaling is predicated on continuous pathway activation at a proportional level to ligand concentration ("Standard" model). We deployed bimolecular fluorescence complementation (BiFC), a novel technology that enables investigations of dynamic changes in components of the signaling mechanism, within intact developing organs and at a single cell resolution. Thus, we identified DCs for the first time  in vivo. Further, we detected catalytically active DCs in cells without pathway activity, which we distinguished from inactivated DCs in actively signaling cells. Our preliminary results reveal substantially different dynamics of the signaling pathway, leading us to propose a radically new model for Wnt signaling. We will present support for the hypothesis that Wnt/beta-catenin signaling is discontinuous and uses a cyclical mechanism.