Avri Ben-Ze'ev

Tamar Ben-Yedidya
Maralice Conacci
Uta Jatzwauk
Elina Levina
Michael Shtutman
Jacob Zhurinsky

The roles of β-catenin and plakoglobin in cell adhesion, transcription and oncogenesis

Department of Molecular Cell Biology

Tel. 972 8 934 2422 **Fax.** 972 8 946 5261
E-mail: avri.ben-zeev@weizmann.ac.il

β-catenin and plakoglobin are homologous proteins linking cadherin adhesion receptors at cell-cell adhesion sites to the actin cytoskeleton. In addition, β-catenin is also a transcription factor, acting as a coactivator of LEF/TCF DNA binding proteins. The pool of β-catenin involved in signaling is regulated by the Wnt signaling pathway that inhibits the proteasomal degradation of β-catenin, thereby inducing its nuclear accumulation, interaction with LEF/TCF, and transcription of LEF/TCF-responsive target genes (Fig. 1). Aberrant transcriptional activation by β-catenin is involved in cancer progression. The projects in our laboratory are focused on:

(1) The β-catenin-mediated cross-regulation of cell adhesion and LEF/TCF-mediated transcription; (2) The differences between the activities of β-catenin and plakoglobin in signaling; (3) The cross talk between β-catenin and the tumor suppressor p53; and (4) Discovery and functional studies of novel β-catenin-LEF/TCF target genes.

Our recent findings have shown that:

(1) Transcriptional activation of cyclin D1 (a major positive regulator of the cell cycle) by the β-catenin-LEF/TCF complex,

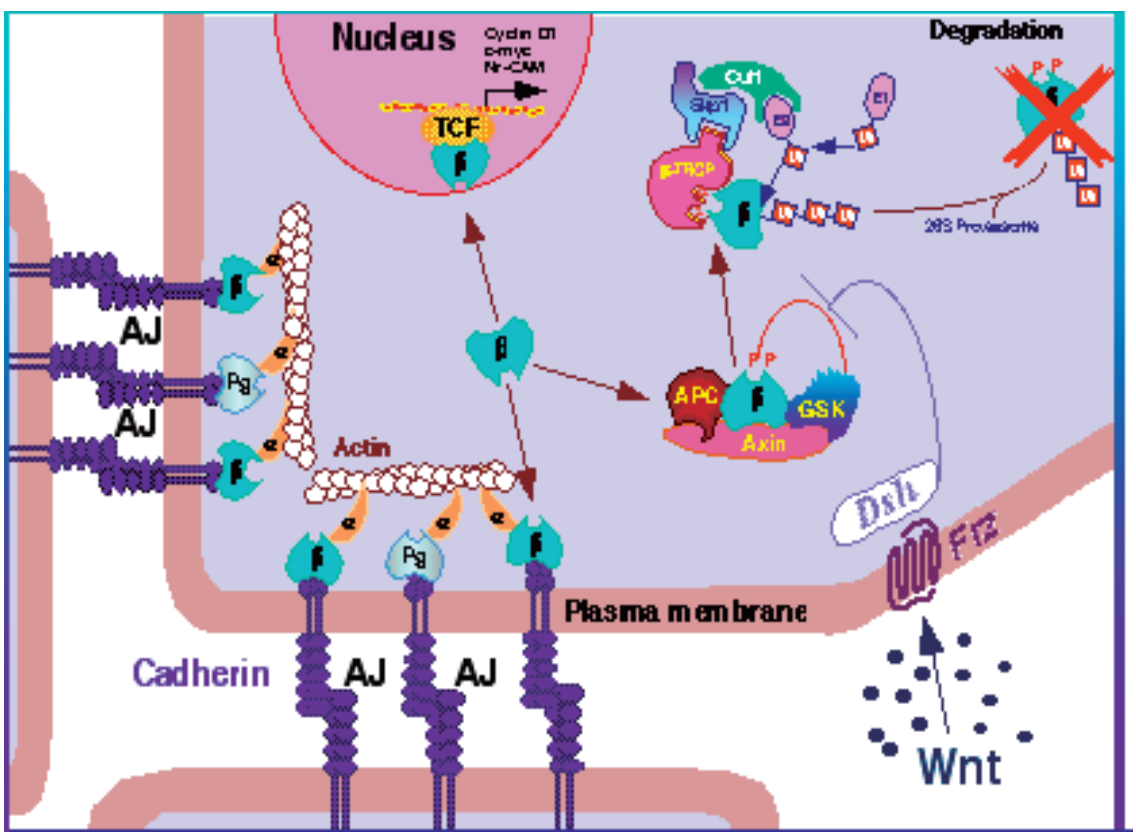

Fig.1 *β-catenin (β) and plakoglobin (Pg) link cadherin adhesion receptors to the actin cytoskeleton via α-catenin (α) at cell-cell junctions (AJ). Wnt signaling inhibits the degradation of β-catenin by the ubiquitin proteasomal systems, resulting in its accumulation in the nucleus, and activation of target genes such as cyclin D1, Nr-CAM or c-myc.*

contributes to colon cancer development.

(2) The degradation of β-catenin and plakoglobin by the proteasome depends on their conjugation to ubiquitin by an E3 ubiquitin ligase complex containing β-TrCP.

(3) Overexpression of cadherin, a partner of β-catenin in cell adhesion, inhibits β-catenin transcription by relocating β-catenin from the nucleus to cell-cell junctions, and short (23-27 a.a.) segments of the cadherin cytoplasmic domain can inhibit β-catenin-mediated transactivation in cancer cells.

(4) p53 can inhibit β-catenin signaling by accelerating its degradation, thus providing a protective cellular response to the oncogenic activity of deregulated β-catenin.

(5) The cell adhesion molecule Nr-CAM is a novel transcriptional target of β-catenin, it enhances cell motility, and induces cell transformation and tumorigenesis in nude mice.

(6) Two major components of nuclear bodies, PML and Sp100, are other potential transcriptional targets of β-catenin and plakoglobin and PML, enhance β-catenin-driven transcription.

We are currently addressing the molecular mechanisms, biological significance and relevance for tumorigenesis of these potential target genes of β-catenin and plakoglobin.

Selected Publications

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