Avri Ben-Ze'ev

Maralice Conacci-Sorrell
Nancy Gavert
Anna Kaplan
Shani Raveh

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

Department of Molecular Cell Biology

Tel. 972 8 934 **2202** **Fax.** 972 8 946 **5261**
E-mail: avri.ben-zeev@weizmann.ac.il
Web page: www.weizmann.ac.il/mcb/idcards/idben-zeev.html

β-catenin is a structural component of adherens junctions linking cadherin transmembrane receptors to the actin cytoskeleton. In addition, β-catenin is also a transcription factor, acting as a coactivator of LEF/TCF DNA binding proteins. The Wnt signaling pathway inhibits the degradation of β-catenin and induces its nuclear accumulation, interaction with LEF/TCF, and transcription of target genes. Mutations in components that regulate β-catenin turnover, prevalent in a variety of human cancers, promote the accumulation of β-catenin in the nucleus, resulting in aberrant transcriptional activation of target genes involved in cancer progression.

The projects in our laboratory focus on (1) The β-catenin-mediated cross-regulation of cell adhesion and LEF/TCF-mediated transcription; (2) The interplay between β-catenin and the tumor suppressor p53 and (3) 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, contributes to colon cancer development.
2. 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.
3. During colon cancer cell invasion there is an autoregulation of E-cadherin expression controlled by β-catenin and MAPK signaling that induce Slug, an inhibitor of E-cadherin transcription.
4. The neural cell adhesion molecules Nr-CAM and L1-CAM are novel target genes of β-catenin that are involved in motility and tumorigenesis of colon cancer and melanoma cells.
5. p53 can inhibit β-catenin signaling by accelerating its degradation, thus providing a protective cellular mechanism against the oncogenic activity of deregulated β-catenin.
6. Two components of nuclear bodies, PML and Sp100 (with tumor suppressor functions), are also transcriptional targets of β-catenin, and contribute to the anti-oncogenic cellular response to β-catenin signaling.

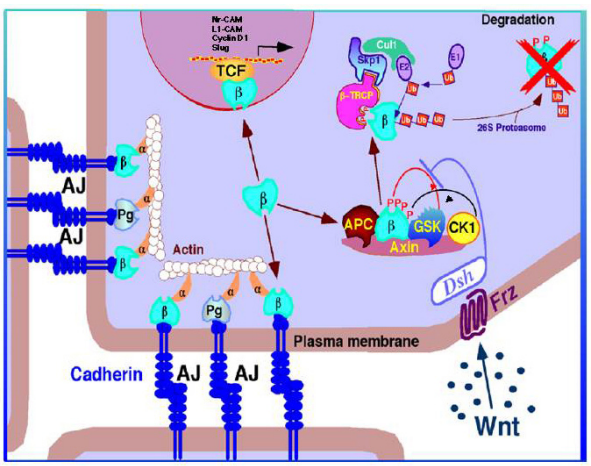

Fig. 1 *β-catenin (β) and plakoglobin (Pg) link cadherin receptors to the actin cytoskeleton via α-catenin (α) at cell-cell junctions (AJ). Wnt signaling inhibits the degradation of β-catenin by the ubiquitin proteasome systems, resulting in its accumulation in the nucleus, and activation of target genes such as cyclin D1, Nr-CAM, L1-CAM and Slug.*

Selected Publications

Levina, E., Oren, M., and Ben-Ze'ev, A. Downregulation of β-catenin by p53 involves changes in the rate of β-catenin phosphorylation and Axin dynamics. Oncogene In Press.

Conacci-Sorrell, M., Simcha, I., Ben-Yedidia, T., Blechman, J., Savagner, P., and Ben-Ze'ev, A. Autoregulation of E-cadherin expression by

cadherin-cadherin interactions: the roles of β-catenin signaling, Slug and MAPK. J. Cell Biol. 163,847-857 (2003).
Conacci-Sorrell, M., Ben-Yedidia, T., Shtutman, M., Feinstein, E., Einat, P., and Ben-Ze'ev, A. Nr-CAM is a target gene of the β-catenin/LEF-1 pathway in melanoma and colon cancer and its expression confers enhanced motility and tumorigenesis. Genes Dev. 16, 2058-2072 (2002).
Shtutman, M., Zhurinsky, J., Oren, M., Levina, E., and Ben-Ze'ev, A. PML is a target gene of β-catenin and plakoglobin and coactivates β-catenin-mediated transcription. Cancer Res. 62, 5947-5954 (2002).
Sadot, E., Conacci-Sorrell, M., Zhurinsky, J., Shnitzer, D., Lando, Z., Zharhary, D., Kam, Z., Ben-Ze'ev, A. and Geiger, B. Regulation of S33/S37-phosphorylated β-catenin in normal and transformed cells. J. Cell Sci. 115, 2771-2780 (2002).
Conacci-Sorrell, M., Zhurinsky, J. and Ben-Ze'ev, A. The cadherin-catenin adhesion system in adhesion, signaling and cancer. J. Clin. Invest. 109, 987-991 (2002).
Damalas, A., Kahan, S., Shtutman, M., Ben-Ze'ev, A. and Oren, M. Deregulated β-catenin induces a senescence-like phenotype and cooperates with Ras in transformation in a p53- and ARF-dependent manner. EMBO J. 20, 4912-4922 (2001).
Simcha, I., Kirkpatrick, C., Sadot, E., Shtutman, M., Polevoy, G., Geiger, B., Peifer, M., and Ben-Ze'ev, A. Cadherin sequences that inhibit β-catenin signaling: a study in yeast and mammalian cells. Mol. Biol. Cell. 12, 1177-1188 (2001).
Sadot, E., Geiger, B., Oren, M., and Ben-Ze'ev, A. Downregulation of β-catenin by activated p53. Mol. Cell. Biol. 20, 6768-6781 (2001).
Galbiati, F., Volonte, D., Brown, A.M.C., Weinstein, D., Ben-Ze'ev, A., Pestell, R. and Lisanti, M. Caveolin-1 expression inhibits Wnt/ β-catenin/Lef-1 signaling by recruiting β-catenin to caveolae membrane domains. J. Biol. Chem. 275, 23368-23377 (2000).
Sadot, E., Simcha, I., Iwai, K., Ciechanover, A., Geiger, B. and Ben-Ze'ev, A. Differential interaction of plakoglobin and β-catenin with the ubiquitin-proteasome system. Oncogene 19, 1992-2001 (2000).
Zhurinsky, J., Shtutman, M. and Ben-Ze'ev, A. Differential mechanisms of LEF/TCF family-dependent transcriptional activation by β-catenin and plakoglobin. Mol. Cell Biol. 20, 4238-4252 (2000).
Shtutman, M., Zhurinsky, J., Simcha, I., Albanese, C., D'Amico, M., Pestell, R., and Ben-Ze'ev, A. The cyclin D1 gene is a target of the β-catenin/LEF-1 pathway. PNAS USA. 96, 5522-5527 (1999).
Damalas, A., Ben-Ze'ev, A., Simcha, I., Martinez Leal, J. F., Zhurinsky, J., Shtutman M., Geiger, B. and Oren, M. Excess β-catenin promotes accumulation of transcriptionally active p53. EMBO J. 18, 3054-3063 (1999).
Ben-Ze'ev, A. and Geiger, B. Differential molecular interactions of β-catenin and plakoglobin in adhesion, signaling and cancer. Curr. Opin. Cell Biol. 10, 629-639 (1998).
Sadot, E., Simcha, I., Shtutman, M., Ben-Ze'ev, A. and Geiger, B. Inhibition of catenin-mediated transactivation by cadherin derivatives. PNAS USA. 95, 15339-15344 (1998).
Simcha, I., Shtutman, M., Salomon, D., Zhurinsky, J., Sadot, E., Geiger, B. and Ben-Ze'ev, A. Differential nuclear translocation and transactivation potential of β-catenin and plakoglobin. J. Cell Biol. 141, 1433-1448 (1998).
Salomon, D., Sacco, P., Guha Roy, S., Simcha, I., Johnson, K. R., Wheelock, M. J. and Ben-Ze'ev,A. Regulation of β-catenin levels and localization by overexpression of plakoglobin and inhibition of the ubiquitin-proteasome system. J. Cell Biol. 139,1325-1335 (1997).
Ben-Ze'ev, A. Cytoskeletal and adhesion proteins as tumor suppressors. Curr. Opin. Cell Biol. 9, 99-108 (1997).
Simcha, I., Geiger, B., Yehuda-Levenberg, S., Salomon, D. and Ben-Ze'ev, A. Suppression of tumorigenicity by plakoglobin: an augmenting effect of N-cadherin. J. Cell Biol.133, 199-206 (1996).

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