

Galectin-3 Mediates Nuclear β -catenin Accumulation and Wnt Signaling in Human Colon Cancer Cells Through Regulation of GSK- β Activity

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Background: Wnt/beta (β)-catenin signaling plays essential roles in both development and carcinogenesis. More than 90% of colorectal cancers have an activating mutation in the canonical Wnt signaling pathway. One of the hallmarks of activating Wnt signaling is the accumulation of nuclear β -catenin. Galectin-3 (gal3), a β -galactoside-binding protein, has been recently implicated in Wnt signaling in breast cancer cells. Its role in regulating the Wnt pathway in colon cancer is unknown.

Methods: The human colon cancer cell line LiM6, derivatives stably transfected with gal3-antisense, and AG1, a cell line containing gal3-antisense under control of an inducible promoter, were used as model systems. Total β -catenin protein, its subcellular distribution, and the status of GSK-3 β phosphorylation/activation were determined by western blots. β -catenin/T-cell factor (TCF) transcriptional activity was measured using pTOPFLASH and pFOPFLASH TCF reporter plasmids. The effects of gal3 on TCF activity were examined by co-transfection with a pCNC10 plasmid containing full-length gal3 cDNA. LiCl, an inhibitor of GSK-3 β , was used to define the mode of action of gal3.

Results: Down-regulation of gal3 by stable introduction or induction (by doxycycline exposure) of gal3-antisense resulted in decreased total β -catenin protein levels and reduced nuclear distribution with concomitant dephosphorylation/activation of GSK-3 β . Basal β -catenin/TCF transcription activity and the expression of one of its target genes cyclin D1 were suppressed as well. Transfection of gal3 into low-level expressing gal3 cells (LS174T) and gal3-antisense cells augmented TCF luciferase reporter activity more than ten-fold. Exposure of these cells or LiM6 gal3-antisense clones to the GSK-3 β inhibitor, LiCl, led to β -catenin import into the nucleus and increased β -catenin/TCF transcriptional activity, mimicking the effects of gal3.

Conclusion: These results suggest that gal3 mediates Wnt signaling, in part, by regulating the phosphorylation/activity of GSK-3 β and therefore the ubiquitination/degradation of β -catenin in colon cancer cells.