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Regulation of Sox9 and Wnt Signaling by Galectin-3 in Human Colon Cancer Cells

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Background: Sox proteins constitute a large family of transcription factors characterized by a specific DNA-binding region named the high-mobility-group domain, and are involved in the control of many developmental processes. Sox9 has been identified as an intestine crypt transcription factor required for the differentiation of Paneth cells, and it has been proposed that Sox9 inhibits the transcriptional activity of β -catenin in the Wnt signaling pathway. Galectin-3 (Gal3), a β -galactoside-binding protein, is involved in the regulation of cancer-related gene expression and has also been recently implicated in the regulation of Wnt signaling. We hypothesize that galectin-3 may be a modulator of Sox9 expression in colon cancer cells where Wnt signaling plays an important role.

Methods: Human colon cancer cell lines LS174T and LiM6 stably transfected with galectin-3 sense or antisense and shRNA Gal3 knock-down clones were established and used as model systems. Total Sox9 and β -catenin protein were determined by western blots and immunohistochemistry. Sox9-dependent transcriptional activity and β -catenin/TCF transcriptional activity were measured using Col2a14x48 and pTOPFLASH, and pFOPFLASH TCF reporter plasmids respectively.

Results: Down-regulation of Gal3 resulted in up-regulation of Sox9 protein expression and decreased total β -catenin protein levels, while up-regulation of Gal3 dramatically

reduced Sox9 protein levels. Higher levels of Gal3 were associated with down-regulation of Sox9-dependent transcription and up-regulation of β -catenin/TCF4 transcriptional activity, while the opposite was observed in Gal3 knock-down clones. Co-transfection of Gal3 cDNA into colon cancer cells decreased Sox9-stimulated Col2a14x48 luciferase reporter activity and augmented TCF4 transcriptional activity. MG132, a proteasome inhibitor, blocked Gal3-mediated Sox9 down-regulation and Sox9-dependent Col2a14x48 promoter activity, suggesting that Gal3 may down-regulate Sox9 in part via the ubiquitin/proteasome pathway.

Conclusion: These results suggest that Gal3 down-regulates Sox9 expression and enhances β -catenin/Wnt signaling in colon cancer cells. This may have important implications for understanding the role of Gal3 in intestinal differentiation and neoplasia.