

A Functional Requirement for the Oncogene β -catenin in Prostate Development

Brian Simons^{1,4}, Edward Schaeffer³, Luigi Marchionni² and David Berman^{1,2,3}

Departments of Pathology¹, Oncology², Urology³ and Molecular & Comparative Pathobiology⁴, Johns Hopkins University School of Medicine, Baltimore, MD

Developmental programs coordinate a variety of cellular processes including proliferation, invasion, and differentiation. During carcinogenesis, rather than randomly acquiring oncogenic mutations, uncontrolled reactivation of developmental pathways may provide a streamlined route to cancer. Abnormal expression or localization of Wnt pathway members are found in a significant minority of advanced prostate cancer. In rodent models, transgenic mice with activated Wnt signaling develop prostate cancer. The oncogene β -catenin is a transcriptional activator and the central mediator of Wnt signaling, but also plays key roles in E-cadherin mediated cell adhesion and androgen receptor function. Furthermore, microarray analysis identified multiple components of the Wnt pathway as components of the prostate development program in mouse embryos. To further address the role of β -catenin in prostate development, we used a novel organ culture system to efficiently delete β -catenin in the embryonic prostate. In vitro and in vivo development after β -catenin deletion yielded dramatically decreased organ size and strikingly abnormal morphology. Deletion of β -catenin in the adult prostate was less efficient and did not significantly affect organ homeostasis. These findings suggest that β -catenin and Wnt signaling play a key role in prostate development, and further study of this developmental program may give insight into its abnormal function in cancer. Our ability to efficiently target genes for deletion in developing prostate epithelium and mesenchyme should greatly accelerate our efforts to elucidate the mechanisms governing prostate growth and differentiation.