

A Functional Requirement for the Oncogene Beta-Catenin in Murine Prostate Development

B. W. Simons^{1,4}, E. M. Schaeffer³, L. Marchionni², and D. M. 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. Reactivation of these signaling pathways during carcinogenesis may provide a streamlined route to cancer. Abnormal expression or localization of Wnt pathway members are found in a significant minority of advanced human prostate cancers, and transgenic mice with activated Wnt signaling develop prostate cancer. The central mediator of Wnt signaling is the oncogene beta-catenin, a transcriptional activator, which also plays key roles in E-cadherin mediated cell adhesion and androgen receptor function. Microarray analysis identified multiple components of the Wnt pathway as differentially expressed during prostate organogenesis in mouse embryos. To further address the role of beta-catenin in murine prostate development, we used a novel organ culture system to conditionally knockout beta-catenin in the embryonic prostate. Urogenital sinus development after beta-catenin deletion yielded dramatically decreased growth and a failure to adopt prostatic identity. This requirement for canonical Wnt signaling was limited to the initial stages of prostate identity specification and early invasion of epithelium into mesenchyme. Deletion of beta-catenin in the adult prostate did not significantly affect organ homeostasis. These findings suggest that beta-catenin and Wnt signaling play a key role in prostate induction and epithelial invasion, and further study of this developmental program may give insight into its abnormal function in cancer. Furthermore, 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.