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Stem cells and the origin of prostate cancer

Summary
Understanding the lineage relationship between normal progenitor cells and cell type(s) of origin for cancer may yield important molecular insights into prostate cancer prognosis and treatment response [1]. In our work, we have shown that a known regulator of prostate epithelial differentiation, the homeobox gene Nkx3.1, marks a luminal stem cell population that functions during prostate regeneration and is an efficient target for oncogenic transformation in prostate cancer [2]. Genetic lineage-tracing studies demonstrate that rare cells which express Nkx3.1 in the absence of testicular androgens (castration-resistant Nkx3.1-expressing cells, CARNs) are bipotential and can self-renew in vivo, while single-cell transplantation assays show that CARNs can reconstitute prostate ducts in renal grafts. Targeted deletion of the Pten tumor suppressor gene in CARNs results in rapid formation of carcinoma following androgen-mediated regeneration. In our ongoing studies, we are investigating the properties of CARNs as well as other epithelial cell types during prostate regeneration and as cells of origin for cancer in vivo. In particular, we have utilized CK5-CreERT2 transgenic mice for lineage-tracing of basal cells during androgen-mediated prostate regeneration and oncogenic transformation. I will discuss our recent findings with respect to elucidating the prostate epithelial lineage hierarchy and its relationship to cancer initiation.