

The Role of Wnt Signaling in Prostate Stem Cell Biology

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We propose that prostatic stem cells and prostatic tumor cells have many common features and that isolating and identifying the phenotype of normal stem cells will aid in defining and isolating prostate cancer stem cells. Knowledge of the phenotype of the cancer stem cell may result in new rational therapies to treat prostate cancer. The Wnt-signaling pathway promotes the self-renewal of stem cells from a number of origins and is implicated in tumor formation. We plan to isolate prostatic cells with active Wnt-signaling pathways to determine if cells with stem cell properties reside within the Wnt-signaling population. To this end, we have employed two Wnt-signaling reporter mouse models to determine the location of cells with active Wnt-signaling pathways and to examine the role of androgens in regulating this pathway.

Whole mounts of GFP and lacZ Wnt-signaling reporter mice show the presence of Wnt-active cells predominately in the lateral lobe of the prostate (LP) and to a significantly lesser extent in the ventral (VP) and dorsal lobes (DP). Reporter expression decreases in whole mounts of castrated animals and increases after androgen replenishment, indicating that Wnt-signaling is both androgen dependent and lobe specific. To quantitate the number of Wnt-active cells, cell digests from the LP, VP, and DP from intact, castrated and castrated, and androgen-replenished animals were examined by FACS analysis for GFP-expressing (Wnt-active) cells. Consistent with the whole mount studies, FACS analysis showed a significant percentage of Wnt-active (GFP-expressing) cells in the LP of intact mice (14.2%) and low levels in the VP (1.1%) and DP (1.7%). Castration diminished Wnt expression in the LP (2.1%) and androgen replenishment (for 7 days) increased it (7.1%). FACS analysis of the LP revealed cells with both high (Wnt hi; 6.9%) and low (Wnt lo; 7.7%) Wnt expression. After castration, most Wnt-detectable cells in the LP were Wnt lo (1.9%). Wnt hi (1.8%) and lo (5.5%) cells were evident again after androgen replenishment (7days).

As we have shown that prostate stem cells are concentrated in the proximal regions of ducts, we determined Wnt expression along the proximal-distal ductal axis. The proximal region of the LP contained 3.0% Wnt-active cells, and the remaining ductal regions had 6.4% Wnt-active cells. Very low numbers of Wnt-active cells were present proximally after castration, and remaining regions of ducts contained 2.3%, with most of these being Wnt lo cells. As noted above, androgen replenishment restored Wnt expression.

Our data indicate that the LP differs from the VP and DP in Wnt expression. The data also indicate that Wnt expression is modulated by androgens and that two populations of Wnt-expressing cells (hi and lo) are present in the prostate. We plan to characterize and isolate these populations of cells to determine whether Wnt-expressing cells have properties of prostatic stem and transit-amplifying cells.

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