

TGF- β Maintains Dormancy of Prostatic Stem Cells in the Proximal Region of Ducts

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We have previously reported that quiescent cells with high proliferative potential, namely stem cells, are located in the proximal region of mouse prostatic ducts. We now show that there are regional differences in TGF- β activation and signaling within prostatic ducts. We propose a model showing that under physiological conditions, TGF- β is a crucial regulator of prostatic tissue homeostasis, maintaining the stem cell-containing population of the proximal region in a dormant state in the intact prostate. We show that proximal cells in the intact prostate produce significantly more TGF- β than distal cells (61.0 ± 3.1 and 52.8 ± 2.9 pg TGF- β /10³ cells respectively) and activate nearly 9-fold more TGF- β than distal cells (19.7 ± 3.5 and 2.3 ± 1.2 pg TGF- β /10³ cells respectively). In addition we find that cells in the proximal region are less sensitive to the inhibitory effects of this cytokine, with 1.0 ng/mL TGF- β inhibiting the growth of proximal cells by 57.5% while that of distal cells is inhibited by 85.6%.

As TGF- β signaling is mediated by phosphorylation of SMADS 2 and 3 we determined the incidence of nuclear pSMAD in cells in different regions of prostatic ducts in intact and castrated animals. We show that there is a proximal-distal TGF- β signaling gradient in intact animals and that TGF- β signaling is modulated by androgens. In the intact prostate, pSMAD levels are 5-fold higher in the proximal region than in the distal region. During castration-induced involution, TGF- β signaling increases 6-fold distally, resulting in apoptosis of cells in this region and involution of the gland. At the same time TGF- β signaling decreases proximally, thereby priming these cells to respond to mitogenic growth factors after androgen administration, resulting in regeneration of the gland. We find that the cells in the proximal region of ducts express high levels of Bcl-2, which protects them from apoptosis induced by the high levels of active TGF- β present in this region. In contrast low levels of Bcl-2 are present in distal cells thus permitting apoptosis and involution of this region after the castration-induced increase in TGF- β mediated signaling in this region. A physiological TGF- β signaling gradient (high proximally, low distally) and its functional correlates are restored following androgen replenishment. In addition to highlighting the regulatory role of androgens and TGF- β in normal prostate physiology, these findings may have important implications for the deregulation of the stem cell compartment in the etiology of proliferative prostatic diseases.