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Activin Limits Progenitor Capability by Promoting Epithelial Cell Differentiation in the Mammary Gland

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Comments
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Activin limits progenitor capability by promoting epithelial cell differentiation in the mammary gland

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Transforming growth factor beta (TGF-beta) and activin utilize common signaling pathways, via smad2/3 and smad4, to mediate tumor suppression by effecting cell cycle arrest and apoptosis. Differences in temporal expression patterns suggest that each cytokine has specific roles in mammary gland development. Activin is expressed during pregnancy and lactation and is required for branching and lactogenesis, implying a role in mammary gland maturation. In contrast, TGF-beta is expressed during involution during mammary gland regression and functions to re-organize the mammary epithelial content to the non-lactating state. Previously, we found that TGF-beta and activin do share common signaling pathways allowing both cytokines to restrict the growth of mammary epithelial cells. However, extended exposure to TGF-beta (5ng/ml; 14 days) causes epithelial to mesencymal transition (EMT). The TGF-beta-treated cells were de-differentiated with loss of both luminal and basal markers. Activin treatment (50ng/ml; 14 days) did not activate EMT. Rather, activin promotes luminal epithelial differentiation with increased expression of prolactin receptor and luminal keratins. Therefore, to test the hypothesis that activin-treatment promotes luminal differentiation and decreases the proportion of progenitor cells in the epithelial population, we compared mammosphere forming capability in vitro and performed limiting dilution experiments in vivo by transplanting 50,000 or 500,000 pre-treated cells into cleared mouse mammary fat pads. The mammosphere assay showed that secondary mammospheres were significantly decreased in the activin-treated cells compared to both the control and TGF-beta treated cells. Tumor incidence between activin-treated and control cells were similar for transplants of 50,000 cells, but tumor incidence was significantly greater in TGF-beta-treated transplants. However, the activin-treated cells had poor outgrowth potential at both 50,000 and 500,000 cells relative to control. We conclude that activin may have the potential to reduce the stem cell population by promoting epithelial cell differentiation.