Ovarian Hormone Regulation of Stat5a Expression and its actions in Mammary Epithelial Cells

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Signal transducer and activator of transcription (Stat)5 is an important mediator of proliferation and differentiation in the mouse mammary gland and has also been implicated in mammary tumorigenesis. Mice lacking the Stat5a isoform exhibit a defect in pregnancy-dependent mammary gland development. Although the mechanisms of Stat5 signaling are well understood, very little is known about the regulation of its expression in the mammary gland. We hypothesized that the ovarian hormones, estrogen (E) and progesterone (P), control Stat5a expression during mammary gland development and tested this using immunohistochemistry. Stat5a expression was detected in the mammary epithelial cells of mature adult virgin, but not prepubertal mice. The increase in Stat5a expression correlates with increased E and P levels seen after the onset of puberty. When systemic E and P was removed from adult mice by ovariectomy, the levels of Stat5a fell significantly, and the addition of both E+P was necessary to restore its expression. Immunofluorescent staining revealed that Stat5a is expressed in the same cells as progesterone receptor (PR), suggesting it may be a direct target of P. One of the effects of E+P is increased proliferation of mammary epithelial cells, and this response is attenuated in Stat5 -/- mice, suggesting that Stat5 is required for this effect. Surprisingly, Stat5a was not present in the cells that were proliferating, revealing that it may act through a paracrine mechanism. In this model, an increase in Stat5a might result in the production of a secreted molecule, which then induces proliferation in neighboring, Stat5a negative cells. One potential candidate for such a molecule is receptor activator of NF-kB ligand (RANKL), which has been shown to be induced by Stat5a in other systems. We observed that Stat5a and RANKL are highly colocalized in the ductal epithelial cells, supporting the hypothesis that Stat5a induces RANKL expression in response to E+P treatment. In summary, we have shown that E+P treatment induces the expression of Stat5a in the mouse mammary gland. This results in a proliferative response which might be orchestrated indirectly by Stat5a through the upregulation of RANKL. Understanding the regulation of Stat5a expression and the mechanisms by which it functions in the normal mammary gland will shed light on its possible roles and regulation in breast cancer.