On Hormone Action in the Mammary Gland

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The importance of systemic reproductive hormones in mammary gland development and breast cancer has been known for more than a century. In fact, the first targeted therapy for cancer was the development of tamoxifen, as an estrogen receptor (ER) antagonist. Based on studies performed primarily in a few breast cancer cell lines, the textbook concept of steroid hormone action at present is that on ligand binding, steroid receptors translocate into the nucleus and stimulate proliferation, and that this effect is mediated by specific coregulators. More recently, as nicely discussed by Briskin and O'Malley (2011), the concepts of specific receptor-positive sensor cells for systemic hormones, and paracrine mediators regulating the development and proliferation of proximal cells has been elegantly shown by the use of genetically engineered mice and chimeric transplantation experiments. One key question raised by these studies is, "How is the patterning of hormone receptor-positive sensor cells established during normal development?" As described by Visvader and Smith (2011), mammary stem cells lack the estrogen and progesterone receptors, and these receptors are first expressed at a still-undefined stage of the mammary cell hierarchy following the appearance of ductal and alveolar progenitors. So how is this process regulated appropriately to provide the correct temporal and spatial expression of the receptor-positive ductal and alveolar cells needed

for normal ductal morphogenesis and alveolarogenesis? Furthermore, what happens when this process is inappropriately regulated during early breast cancer progression when there may be a switch from paracrine to autocrine signaling mechanisms?

Until recently, it was not possible to study these processes in primary mammary epithelial cells, because when these cells are grown under conventional cell culture conditions they rapidly lose the expression of steroid receptors. However, some recent success in culturing both primary mouse and human mammary cells in embedded 3D Matrigel cultures have provided at least a surrogate system to help dissect some of these paracrine mechanisms (Novaro et al. 2003; Graham et al. 2009). Still, it has not been possible to precisely mimic the patterning of receptor-positive cells observed in vivo in these surrogate in vitro models. So how can we specifically target steroid receptor-positive sensor cells to perform gain- and loss-of-function experiments in vivo? Recent advances using genetically engineered mouse models (Jeong et al. 2010; Mukherjee et al. 2010) may provide the key. In these models, Lydon, Demayo, and colleagues (Jeong et al. 2010) have inserted the Cre recombinase into the progesterone receptor gene allowing specific gene deletion only in that subset of mammary epithelial cells. Because the majority of ER positive cells are also progesterone receptor positive, this

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should facilitate loss-of-function studies of paracrine mediators for both steroid hormone receptors. Conversely, using a clever bigenic system for doxycycline-inducible expression, these same investigators have expressed one of the identified paracrine mediators, RANKL, in the mammary epithelium of progesterone receptor knockout mice exclusively in ER positive cells. Thus, this gain-of-function approach should help define the critical paracrine mediators of progesterone action and perhaps even the role of specific coregulators in this subset of cells.

Downstream from the nuclear receptors, hormonal signaling is regulated by different chromatin contexts and differential recruitment of coactivators as well as corepressors (Briskin and O'Malley 2011). Numerous posttranslational modifications also play key roles in modulating the effects of coregulators, but these have been studied primarily in the HeLa, and to a lesser extent in MCF7, cell lines. Thus, we still know very little about these coregulators and their modifications in normal mammary epithelial cells. Because cell context and architecture are critical, studies, therefore, should be performed in primary mammary epithelial cells to provide a better understanding of how these coregulators and their posttranslational modifications affect normal mammary gland development. No doubt, coregulators may differentially influence hormone receptor-positive cells as compared to the receptor-negative adjacent

cells, because most coregulators can also affect cells lacking steroid hormone receptors. Clearly, we are only at the tip of the iceberg when it comes to understanding the precise molecular mechanisms of hormone action in the normal mammary gland, and this will be critical for identifying alterations which occur during breast cancer progression.

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