Graduate Studies
Department of Physiology
MICHIGAN STATE UNIVERSITY

HORMONAL REGULATION OF NORMAL BREAST DEVELOPMENT and BREAST CANCER

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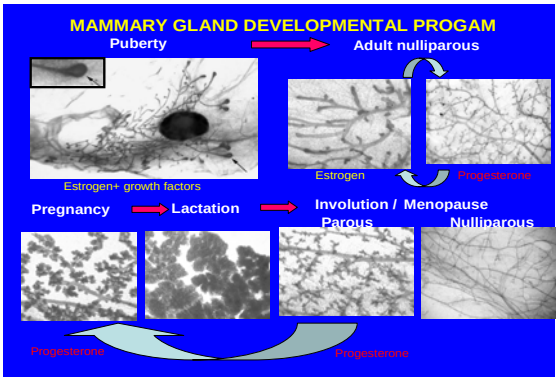
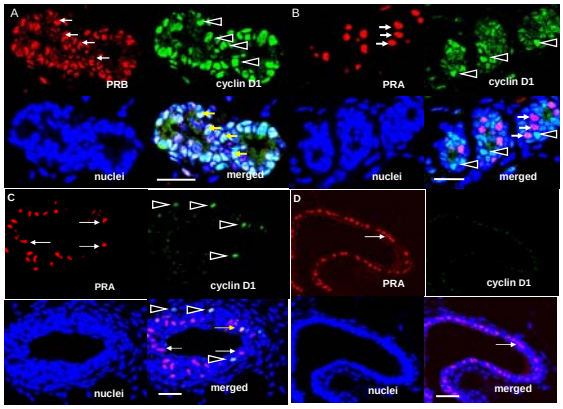
I. Endocrinology of normal breast growth and differentiation; steroid hormone- and growth factor-mediated growth control of normal breast cells.



PROGESTERONE RECEPTOR A OR B ISOFORM
COLOCALIZATION WITH CYCLIN D1 OR BrdU



Postnatal development of normal mammary gland from puberty to menopause is critically dependent upon two nuclear steroid hormones, estrogen and progesterone, a number of peptide hormones, and various growth factors. In the recent past there has been extensive focus on the role of estrogen as a growth regulator of normal breast tissue and breast cancer. However, progesterone is also a potent breast mitogen and recent epidemiological studies suggest that progesterone may play a greater role than estrogen in breast cancer. For this reason we are currently focused on understanding the molecular mechanism of action of progesterone in the normal mammary gland, using the mouse and rat mammary gland as model systems. Progesterone action is mediated through binding to the progesterone receptor. The progesterone receptor consists of two isoforms, PRA and PRB, which are expressed from a single gene in both humans and rodents. The two isoforms are believed to be functionally distinct based upon transgenic overexpression or gene deletion studies. However, their normal functions in vivo have not been identified. We are currently studying progesterone isoform function in vivo in mice at different developmental stages and known to have different functional responses to progesterone and in vitro in a novel primary culture model that recapitulates in vivo response to progesterone.

II. Breast Cancer and the Environment Research Center.

In humans, early onset of menstruation and late menopause are associated with increased breast cancer risk. One hypothesis to explain this observation is that early onset of menses and late menopause increase lifetime exposure of the breast to the mitogenic effects of progesterone. The Center's research focuses on testing this hypothesis in animal models. We will determine how environmental influences such as exposure to environmental and adolescent obesity affect the timing of sexual maturation, mammary gland development and the risk of developing breast later in life, i.e. adulthood, after exposure to known carcinogens. A specific focus of these studies is the integration of progesterone receptor function and mechanism of action into understanding pubertal vs adult breast development and breast cancer risk.

III. The role epithelial-stromal cell interactions and extracellular matrix molecules as modulators of hormone- and growth factor-mediated growth control in normal breast development and breast cancer.

The mammary gland is also unique in that most morphologic changes and tissue specific differentiation take place postnatally and require specific, appropriate epithelial-stromal cell interactions. Two mechanisms have been proposed to describe the molecular mechanisms underlying epithelial-stromal cell interactions: 1) by the production of growth factors/growth inhibitors which behave in paracrine ways, and/or 2) by modifying the composition of the extracellular matrix (ECM).. Estrogen and progesterone may also alter the composition of the ECM and/or the production of growth factors/inhibitors. We are currently investigating how epithelial-stromal cell interactions modulate proliferative responses of the normal and cancerous breast to estrogen and progesterone and growth factors/growth inhibitors. Using *in vivo* and *in vitro* approaches we are examining how stroma-derived growth factors such as HGF, EGF, IGF and ECM components such as collagen I, IV, laminin, and fibronectin can modulate responsiveness to estrogen and progesterone. With the development of breast cancer, a significant percentage of human tumors still exhibit some form of growth regulation by hormones and growth factors. The majority of tumors however, are no longer responsive to growth regulation and are classed as hormone-independent. The long term goal is the detailed analysis of the molecular mechanisms underlying epithelial-stromal cell interactions which result in the transition from a hormonally non-responsive to a responsive state and the development of new therapeutic strategies for the treatment of breast cancer.