

Effects of Progesterone on Inflammatory Processes in the Mammary Gland

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Progesterone (P) is a steroid hormone that promotes cell proliferation and development of the normal mammary gland. However, long term treatment with P, either alone or in combination with estrogen (E), promotes the development of mammary cancer in rodents and humans. The latter is evidenced by the increased risk of breast cancer in women receiving postmenopausal hormonal therapy that includes progestin. We recently showed that exposure to physiological levels of P causes an inflammatory response in the mammary glands of mice involving the production of inflammatory cytokines and chemokines, and resulting in the recruitment of leukocytes to the mammary peri-epithelial stroma. The role of hormones, P in particular, in mediating an inflammatory response in the mammary gland has not been previously recognized. Leukocyte populations including macrophages and eosinophils are known to be crucial for the tissue remodeling that takes place in normal mammary gland development. These same inflammatory processes that recruit leukocytes can promote tumorigenesis in the mammary gland and other tissues. The ability of P to mediate an inflammatory response in the mammary gland presents one plausible mechanism underlying the promotional effects of P in mammary tumorigenesis.

In order to investigate the role of P in recruiting specific types of leukocytes in the mammary gland, female adult BALB/c mice were ovariectomized and injected either with vehicle (C), E alone, P alone, or the combination of both E and P. Fixed sections of mammary glands from the various treatment groups were stained for leukocyte cell types that have previously been implicated in mammary gland development: macrophages were stained for F4/80 and eosinophils were stained with Vital New Red. Increased levels of macrophages and eosinophils were observed with P and E+P treatments relative to C and E, especially in the stroma near duct ends and small ducts, as well as near alveolar and lobular structures that develop after hormone treatment.

In summary, P treatment produced profound alterations in leukocyte populations in the peri-epithelial stroma of adult virgin mammary glands. The recruitment of macrophages and eosinophils, previously known to be involved in mammary ductal development, is consistent with P induction of inflammatory processes having a crucial role in mammary development.

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