The Possible Role for Progesterone Receptor A in Pregnancy Induced Protection Against Mammary Cancer

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Pregnancy before the age of 25 reduces breast cancer risk two-fold. In rodents, after pregnancy the mammary gland is less susceptible to carcinogen-induced mammary cancers. Progesterone and estrogens are involved in establishment of pregnancy-induced protection against mammary cancer, however, the contribution of progesterone receptor (PR) isoforms to the pregnancy-associated protection is not known. We investigated PR isoforms expression and it relationship to proliferation in the rat mammary gland after pregnancy compared with mammary glands treated with perphenazine (PPZ), (5 mg/kg of body weight, 5 injections/week, for a total of 3 week), which does not confer resistance to mammary cancer. PPZ treatment induces massive release of prolactin from the pituitary and produces mammary epithelium differentiation comparable to that observed during pregnancy. Immunofluorescence staining with PRB specific antibody showed that PRB expression level was similar in animals after pregnancy or PPZ treatment. Immunoperoxidase staining with PRA specific antibody revealed a significant decrease of PRA+ cells in lobular epithelium in late pregnancy but not immediately after PPZ treatment. Moreover, PRA levels was permanently decreased in glands that were involuted after pregnancy and lactation compared to age-matched virgin animals. In glands involuted after PPZ treatment, the PRA level was unchanged compared to age-matched virgin vehicle-control animals. Double labeling with PRA specific antibody and antibody against the proliferation marker, BrdU, revealed that in the late pregnant and PPZ-treated gland proliferation rate was high. However, in both cases PRA+ cells rarely colocalized with BrdU. In glands involuted after pregnancy and lactation, the proliferation rate was low and very few PRA+ cells colocalized with BrdU. In glands involuted after PPZ treatment, the proliferation rate was unexpectedly high and a significant proportion of PRA+ cells colocalized with BrdU. We speculate that the decrease in PRA+ cells and their low proliferative potential contribute to the protective effect of an actual pregnancy. Conversely, the maintenance and relatively high proliferative potential of PRA+ cells contribute to the lack of protection against mammary cancer after PPZ treatment. We hypothesize that there is a subpopulation of PRA+ cells that are progenitor cells and targets for transforming events leading to mammary cancer. Pregnancy results in a significant decrease in this putative PRA+ progenitor cell population, rendering the gland less susceptible to the development of mammary cancer.