

## **Progesterone Receptor A and B in rat mammary gland: Developmental Pattern of Expression and Relationship to Proliferation**

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Progesterone is a potent mitogen in the human breast and can increase breast cancer risk. Here we investigated expression pattern and functional roles of progesterone isoforms PRA and PRB in normal mammary gland development. Because the lobular development and histological organization of the rat mammary gland is very similar to the human breast the rat was used in these studies. We undertook an immunohistochemical approach using antibodies specific for only PRA or PRB in conjunction with analysis of the proliferation marker, BrdU. PRA expression appeared at 4-5 weeks, reached maximum in pubertal animals at 6-8 weeks and gradually declined in adulthood. During pregnancy PRA was strongly down-regulated in lobules compared to ducts. PRB expression was observed earlier at 3 weeks. The percentage of PRB expressing cells did not change substantially throughout development in both ducts and lobules; however, in lobules PRB was expressed at higher levels and in a greater proportion of cells than in ducts. In the pubertal gland PRA and PRB were often but not always co-expressed in the same cell. In adult virgin gland there were more cells expressing only PRB, particularly in lobules. In pregnant gland PRB was by far predominant isoform in lobules. The highest proliferation of mammary epithelium occurred in the end buds of 3-6 week old animals or in lobules in early pregnancy. In pubertal ducts and lobules proliferation rate was significantly lower and in adult virgin gland there were very few proliferating cells. PRA was rarely expressed in proliferating cells in pubertal or pregnant gland, whereas PRB was highly associated with proliferation in both pubertal and pregnant gland. Our results suggest that PRA-driven proliferation is mediated in PR negative cells through paracrine factors, while PRB may directly induce proliferation in PRB positive cells.

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