

Differential Regulation of the Murine Progesterone Receptor

Emily Flynn, Richard Schwartz, and Richard Miksicek, Departments of Physiology and Microbiology & Molecular Genetics, Michigan State University, East Lansing, MI.

Experiments in rodents point towards progesterone and its signaling pathways as important factors in the induction, progression and maintenance of neoplastic tumors in the mammary gland. The progesterone receptor (PR) is comprised of two tandem promoters, which give rise to transcripts encoding two PR isoforms, A and B. Limited murine studies on the PR have largely been based on homology to defined elements in human or rat. This project aims to map the locations of the mRNA start sites for both PR-A and PR-B in mouse and to determine if the distal and proximal promoters are responsive to the presence or absence of progesterone and/or estrogen. An additional aim is to investigate the important transcription factor binding sites in the murine PR-A and PR-B promoters. The transcription factor sites under study are: Sp1, AP-1, EREs/Half EREs and C/EBP sites. Immunohistochemistry shows two distinct switches in PR regulation during mammary development. In pubertal mice, PR-A is high and PR-B is undetectable, while in the virgin adult PR-A levels are reduced and PR-B remains undetectable. On transition from virgin adult to pregnancy, PR-A levels are further reduced and PR-B levels increase. We propose four potential models to account for the differential regulation of PR observed during murine mammary development. The models invoke: (1) short acting factors binding in close proximity to each promoter, (2) long acting factors that act on A or B from distant enhancers, (3) promoter occlusion and (4) regulation through AP-1 sites analogous to those in the human PR gene. We have constructed PR-A only and PR-B only promoter-reporters to determine the activities of transcription factors upon these promoters in the presence of various hormone treatments. Preliminary data in different breast tumor cell lines shows an increase in PR-A expression in the presence of estradiol.

Emily Flynn
flynnem3@msu.edu
517-355-6475 x1386