ABSTRACT

REGULATION OF THE PROGESTERONE RECEPTOR IN THE MOUSE MAMMARY GLAND: CHARACTERISATION OF THE TRASCRIPTION UNIT, THE ROLE OF ACTIVATING PROTEIN-1 (AP-1), AND THE INFLUENCE OF OVARIAN HORMONES

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The mouse progesterone receptor (Pgr) gene contains tandem promoter regions that control expression of the two receptor isoforms, PRB and PRA. This locus also forms a cis-sense/antisense pair with a naturally occurring non-coding antisense transcript (PRantisense) whose expression is controlled by its own promoter. All three promoters respond to activating protein-1 (AP-1), but the sense PRA and PRB promoters were more responsive to c-Jun, while the antisense promoter was preferentially responsive to JunD or JunB. In cultured cells, as well as in tissues in vivo, the PRantisense transcript colocalized with the sense mRNA and with PRA protein. Both transcripts showed coregulation, rather than anti-regulation, and were co-expressed across mouse mammary gland development.

Expression of the mouse Pgr gene during mammary gland development is regulated by complex interplay between hormones and growth factors that affect growth and differentiation, many of which influence the activity of AP-1 family members and other transcription factors. We therefore examined the effect of steroid hormones and coexpression of Jun and Fos subunits on the activity of the mouse PR promoters, hypothesizing that differential regulation of PR isoform expression occurs at a

transcriptional level. Although the hormonal milieu of pregnancy supports increased PBR expression in the mouse, these studies did not support a prominent role of estrogen receptor (ER) or AP-1 in this regulation.

Additional experiments utilized an immunofluorescence approach with isoformspecific antibodies to examine the relationship between AP-1 and PR expression across development or following ovariectomy. The underlying hypothesis for these studies is that a change in the composition of AP-1 subunits may contribute to a shift from PRA to PRB expression during alveologenesis due to preferential effects of different AP-1 isoforms on the two promoters. These experiments establish that AP-1 alone cannot account for the appearance of PRB during pregnancy. However, the composition of AP-1 undergoes significant changes across development and, as noted above, AP-1 promotes transcription from both PR promoters. cJun correlated most highly with overall expression of PRA, and PRA expression invariably accompanied the expression of one Jun isoform or another. In ovariectomized mice expression of c-Fos disappeared entirely, while ovariectomy affected only the intensity of PRA staining.

In summary, these studies characterized the effects of hormone and phorbol ester treatment along with ER and AP-1 in transcriptional regulation of the mouse Pgr gene. Expression of AP-1 and PRantisense mRNA correlated positively with PRA expression across development in the mouse mammary gland. These correlations persisted in the pregnant mammary gland, failing to explain the appearance of PRB, but accounting for a subset of c-Jun+

/PRB+ cells that maintained their expression of PRA. Additionally,

experiments in ovariectomized mice supported the interesting finding that progesterone

and well as estradiol can stimulate mammary gland expression of both c-Fos and c-Jun.