Transcriptional Regulation of the Murine Progesterone Receptor

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Experiments in rodents point towards progesterone and its signaling pathways as important factors in normal mammary gland and the induction, progression and maintenance of tumors in the mammary gland. The progesterone receptor (PR) gene contains a tandem arrangement of two promoters, which give rise to transcripts encoding the two PR isoforms, PRA and PRB. PRA and PRB are believed to have specific and different functions in the mammary gland. Furthermore, during murine mammary gland development, expression of PRA and PRB are temporally and spatially dissociated. This project aims to characterize the transcriptional regulation of the PR gene in the mouse with a focus on potential mechanisms of differential regulation of PRA and PRB. We recently observed that a region upstream of the distal PR promoter appears to contain an AP1-dependent transcriptional enhancer based on its ability to stimulate promoter activity in response to phorbol ester treatment or AP-1 cotransfection. Phorbol ester (PMA, phorbol 12-myristate 13-acetate) mimics the function of the second messenger diacylglycerol (DAG), an activator of signaling kinases in the protein kinase C pathway that stimulate Jun-kinase (JNK) activation and AP-1 phosphorylation. MCF-7 cells were transiently transfected with different lengths of the murine PR promoter driving expression of the firefly luciferase gene. Measurement of luciferase activity shows that the tandem mPR promoter construct (containing sequences from –2494 to –444 bp upstream of the PRB transcription start site) supports significantly higher luciferase activity than the isolated distal or proximal promoter constructs that lack the region upstream of the distal promoter. This increased reporter gene activity depends on activation of AP-1, either by treatment of transfected cells with PMA or co-transfection of the tandem promoter with the AP-1 proteins, c-*jun* and c-*fos*. In contrast, all of these promoter constructs display an equivalent modest response to estradiol, reflecting the presence of multiple EREs dispersed throughout the PR promoter region. When combined with PMA, estradiol reduces, rather than augments the stimulatory activity of PMA on the tandem mPR promoter indicating that this element differs from many hormone-responsive AP-1 sites. Several copies of the AP-1 consensus sequence (TGAGTCA) are present in the –2494/-444 region of the mouse PR promoter, representing candidate TREs (phorbol ester or “TPA-response elements”). Data will be presented comparing the transcriptional activity of the various mPR promoter constructs in response to estradiol, phorbol ester, and their combined treatment.