

NEW INSIGHTS ON THE ROLE OF ESTROGEN AND PROGESTERONE RECEPTORS IN MAMMARY GLAND BIOLOGY AND NEOPLASIA

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Female sex hormones (E and P) are direct mitogens for a subset of their target tissues, including the mammary gland where they induce growth of normal and transformed cells via specific intracellular receptors (ERs and PRs) and act as tumor promoters. Genome-wide gene expression profiling of hBC cell response to estrogens and antiestrogens identifies discrete patterns of hormone-dependent gene activation and inhibition and uncovers multiple gene pathways active in hormone-responsive human breast cancer (hBC) cells and potential target on novel therapeutic strategies. Indeed, based on the function assigned to the products of the genes it controls, E affects multiple key features of hBC cells, including their metabolic status, proliferation, survival, differentiation and resistance to stress and chemotherapy, as well as RNA and protein synthesis, maturation and turn-over rates. Interestingly, E target genes do not appear randomly distributed in the genome, as certain chromosomal regions are particularly rich in hormone-activated gene clusters, revealing collinear regulation of estrogen-responsive gene clusters in mammary gland epithelial cells. The patterns of expression of these newly identified estrogen-responsive gene and gene clusters differentiate hormone-dependent from -independent breast cancer cell lines and allow to classify primary breast tumors in distinct sub-groups, based on defined expression 'signatures' of specific gene sets.

In hormone responsive hBC cells, E and P promote G₁ phase progression by inducing expression of the cyclin D1 gene (*CCND1*) and phosphorylation of pRb. The region conferring *CCND1* responsiveness to E in hBC cells was recently mapped and shown to bind in vivo an AP-1 complex including the c-Jun/c-Fos heterodimer, which targets ER-alpha to this promoter. In this way, E induces formation of a multi-protein complex on the *CCND1* promoter that enhances transcription within 15 min of hormone challenge. These early events are followed by recruitment of the p36^{D1}/cdk4 holoenzyme to promoter via a constitutively bound E2F/pRb complex. This kinetic transcription factors interplay characterizes *CCND1* as the first known primary and secondary response gene. Interestingly, progesterone triggers similar regulatory events through its own NRs, suggesting that the gene regulation cascade uncovered here represents a cross-road for transcriptional control of G₁ phase by different classes of NRs.

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