

ESTROGEN CONTROL OF HORMONE-RESPONSIVE BREAST CANCER CELL GROWTH AND FUNCTIONS

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Estrogen hormones 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 act as tumor promoters. The role of estrogens in neoplastic transformation of breast epithelial cells led to introduction of routine ER determination in breast cancer (BC) specimens as a molecular marker for the identification of estrogen-responsive tumors, more likely to respond to hormone-ablation therapy. ER expression status of the tumor, however, is an insufficient predictor of its responsiveness to such therapeutic regimens and many attempts have been made to find additional components of the estrogen signaling pathway that might allow more accurate identification of ER-positive BC subtypes. Gene expression profiling with DNA microarrays is holding the promise to provide a new molecular classification of BCs, provided that more knowledge of the gene expression 'signatures' that characterize the different BC cell phenotypes become available. This is particularly true concerning the cellular responses to physiologically relevant stimuli such as female sex hormones. To this aim, we thus carried out genome-scale gene expression profiling analyses with cDNA microarrays of human BC cells response to estrogens. Glass arrays including 9,000 cDNA elements were exploited to monitor changes in expression of the corresponding mRNAs in estrogen-responsive human BC cells at regular intervals during the first 32hrs stimulation with a mitogenic dose of 17-beta estradiol (E2), a timing that corresponds to completion of a full mitotic cycle in hormone-stimulated cells. 6,080 genes were found to be expressed at detectable levels in this ER-positive cell type, including 344 genes whose expression either increases or decreases following hormonal stimulation. Analysis of these estrogen-responsive genes, based on hierarchical clustering of mRNA expression profiles, identify discrete patterns of hormone-dependent gene activation and inhibition, including 3 kinetically distinct clusters of down-regulated genes, 3 gene clusters characterized by cell cycle phase-specific activation and 2, larger clusters reflecting estrogen, mitogen and/or BC specific gene activation events. Interestingly, estrogen-responsive genes do not appear randomly distributed in the genome, as chromosome 17 for example was found particularly rich in hormone-activated gene clusters. According to the functions initially assigned to the products of these newly identified hormone-regulated genes, estrogen stimulation enhances cell viability and growth, confers to the cell resistance to stress and affects its responsiveness to chemotherapy. The hormone-responsive genes identified here represent a new set of molecular markers exploitable to unravel estrogen actions in BC cells and to verify the existence of ER-positive BC phenotypes characterized by graded response to endocrine therapy. In this respect, initial evidence of the potential usefulness of the gene set hereby identified to allow discrimination between hormone-responsive and non-responsive human BC cell lines and for breast tumor sub-typing will be provided.

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