

Microarray analysis of the estrogen-regulated transcriptome as a new tool for breast cancer prognosis and prediction of treatment response

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Estrogen control a number of cellular functions of responsive cells in normal physiology and represent a key factor in the development and progression of breast cancer (BC). Understanding the complex of genes whose expression is controlled by estrogen will have a relevant impact for BC diagnosis, staging and treatment. We have monitored changes in gene expression in BC cells at different periods of time after treatment with estrogen or antiestrogens, using genome-wide microarray analysis on different platforms. Hierarchical clustering revealed several hundreds of genes whose expression either increases or decreases significantly in response to estrogen/antiestrogen. Kinetic analysis reveals that the genetic program activated by the hormone in BC cells includes 8 main patterns of gene activation/inhibition. Based on the functions assigned to the encoded proteins, this newly identified estrogen responsive transcriptome (ERT) indicates that estrogen affect several features of BC cells, including proliferation, survival, differentiation, metabolic status and resistance to stress and chemotherapy, as well as RNA and protein synthesis, maturation and turnover rates. A bioinformatic metanalysis of the microarray data available at different websites on primary breast tumors revealed that a small subset of our ERT ensemble can correctly identify estrogen receptor-positive tumors, when data on ER α expression are taken out, and this represents a proof of concept for the study we have undertaken. RT-PCR analysis of the expression of few, newly identified estrogen-regulated genes, in an independent series of breast tumors performs well in discriminating ER+ from ER- tumors, as well. Further functional genomics analysis is under way, as well as studies on larger independent series of tumors, to unveil the possible prognostic and predictive value of our ERT.

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