

Estrogen controls key cellular functions of responsive cells including the ability to survive, replicate, communicate and adapt to the extracellular milieu. Changes in the expression of 8400 genes were monitored here by cDNA microarray analysis during the first 32 h of human breast cancer (BC) ZR-75.1 cell stimulation with a mitogenic dose of 17beta-estradiol, a timing which corresponds to completion of a full mitotic cycle in hormone-stimulated cells. Hierarchical clustering of 344 genes whose expression either increases or decreases significantly in response to estrogen reveals that the gene expression program activated by the hormone in these cells shows 8 main patterns of gene activation/inhibition. This newly identified estrogen-responsive transcriptome represents more than a simple cell cycle response, as only a few affected genes belong to the transcriptional program of the cell division cycle of eukaryotes, or showed a similar expression profile in other mitogen-stimulated human cells. Indeed, based on the functions assigned to the products of the genes they control, estrogen appears to affect several key features of BC 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, the estrogen-responsive transcriptome does not appear randomly interspersed in the genome. In chromosome 17, for example, a site particularly rich in genes activated by the hormone, physical association of co-regulated genes in clusters is evident in several instances, suggesting the likely existence of estrogen-responsive domains in the human genome.