

## **MOLECULAR MECHANISMS OF FEMALE SEX HORMONE ACTION ON PROLIFERATION**

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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. In hormone responsive human breast cancer (hBC) cells these steroids promote G<sub>1</sub> progression by inducing expression of the cyclin D1 gene (*CCND1*) and phosphorylation of pRb. The mechanism by which E and P control *CCND1* expression, a key process in both normal mammary gland physiology and breast carcinogenesis, still awaits elucidation. The region conferring responsiveness of the *CCND1* gene to E in hBC cells binds *in vivo* the *c-Jun/c-Fos* heterodimer, which targets the ER to the promoter. In this way, E promotes 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<sup>D1</sup>/cdk4 holoenzyme to promoter *via* a constitutively bound E2F/pRb complex. This kinetic transcription factors interplay, which reflects the early cell cycle changes resulting from timed gene expression induced by E in hBC cells, 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 G<sub>1</sub> phase by different classes of NRs.

Genome-scale gene expression profiling analyses of hBC cells response to estrogens identifies discrete patterns of hormone-dependent gene activation and inhibition and uncovers multiple hormone specific gene regulation events. Interestingly, E target genes are not randomly distributed in the genome as, for example, chromosome 17 is particularly rich in hormone-activated gene clusters. These results suggest a higher level of regulation of genome activity by female sex steroids.

Research supported by grants RBNE0157H\_001 and 2002067514\_002 from MIUR and by a research grant from AIRC.