

## 97. STEROID REGULATION OF BREAST CANCER CELL PROLIFERATION

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Estrogens are potent mitogens in a number of target tissues including the mammary gland where they play a pivotal role in the development and progression of mammary carcinoma. The demonstration that estrogen-induced mitogenesis is associated with an increased rate of progression through G<sub>1</sub> phase of the cell cycle has focussed attention on the estrogen regulation of molecules in the cyclin/CDK/pRb pathway that controls G<sub>1</sub> to S phase progression. Steroid-responsive breast cancer cells pretreated with a pure estrogen antagonist arrest in quiescence, i.e. G<sub>0</sub>, and respond to estrogen treatment with synchronous progression into S phase. Entry into S phase is preceded by increased expression of c-Myc and cyclin D1, activation of cyclin D1–Cdk4 and cyclin E–Cdk2 complexes and phosphorylation of the retinoblastoma gene product, pRb. Activation of cyclin D–Cdk4 is due predominantly to estrogen-induced transcriptional activation of cyclin D1. In contrast, cyclin E–Cdk2 activation does not involve major changes in cyclin E expression but rather redistribution of the p21 CDK inhibitor away from cyclin E–Cdk2 complexes. This is mediated by two distinct mechanisms: sequestration into newly formed cyclin D1–Cdk4–p21 complexes and transcriptional inhibition of p21 gene expression. In the same model, progestins are growth inhibitory and arrest cells in G<sub>1</sub> phase. Growth arrest is accompanied by decreased expression of both cyclin D1 and cyclin E and induction of the CDK inhibitor p18<sup>INK4C</sup>. These changes lead to reassortment of cyclin–CDK–CDK inhibitor complexes and increasing availability of p27 to form inhibitory cyclin E–Cdk2–p27 complexes. Thus, both cyclin D–Cdk4 and cyclin E–Cdk2 activities are inhibited, resulting in decreased pRb phosphorylation and arrest in G<sub>1</sub> phase. These data indicate that steroid hormones stimulate or inhibit cell cycle progression through effects on multiple targets in the pRb pathway. The aberrant expression of several of these targets in breast cancer, i.e. overexpression of c-Myc, cyclin D1 and cyclin E and loss of expression of p27, potentially contributes to the loss of steroid sensitivity and endocrine resistance associated with the progression of breast cancer.