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Antiestrogens and the Cell Cycle

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1. INTRODUCTION

Recognition of the involvement of estrogen in the growth of breast cancer stemmed from observations made a century ago, when it was shown that ovariectomy in cases of pre-menopausal breast cancer could lead to tumor regression (1). Subsequent research in experimental models of carcinogen-induced mammary cancer revealed that estrogen was essential for both the initiation and progression of the disease. These observations, together with the demonstration that some breast tumors had a specific binding protein for estrogen, the estrogen receptor (ER), and that ER status was correlated with response to endocrine therapy, provided the rationale for the introduction of the antiestrogen tamoxifen in the treatment of breast cancer (2). Tamoxifen is currently the...
treatment of choice for hormone-dependent breast cancer both in advanced disease and as an adjuvant to surgery in early breast cancer. Recent overviews of the outcome of randomized clinical trials of adjuvant tamoxifen therapy demonstrate significant reductions in risk of recurrence, increased overall survival, and reduced incidence of contralateral breast cancer (3,4). In addition to tamoxifen and other nonsteroidal antiestrogens, steroidal antiestrogens have been described (5,6) that generally exhibit pure antagonist activity, in contrast to the partial antagonist properties of tamoxifen. Such compounds are potentially more potent therapeutically than tamoxifen and early experience in the clinic shows efficacy in cases where tumors are resistant to tamoxifen. Thus antiestrogens of various structural classes with differing tissue-specific estrogen agonist/antagonist properties have an established and expanding role in the treatment of breast cancer. The accepted basis of their clinical efficacy in breast cancer is inhibition of estrogen-induced mitogenesis but the molecular basis of this action has not been fully elucidated. This chapter summarizes research from this laboratory aimed at understanding the mechanistic basis for estrogen/antiestrogen control of breast cancer cell-cycle progression.

2. EFFECTS OF ANTIESTROGENS ON CELL-CYCLE PROGRESSION

2.1 Cell-Cycle Effects In Vitro

Initial insights into mechanisms of antiestrogen action as growth inhibitory agents came from studies on the effects of antiestrogens on breast cancer cell proliferation in vitro. Early experiments showed that the relative cell number and rate of thymidine incorporation into DNA of ER-positive (but not ER-negative) breast cancer cells were markedly reduced by antiestrogen treatment (7,8). These compounds are predominantly cytostatic rather than cytotoxic in vitro and this is associated with arrest of cells in the G1 phase of the cell cycle, with a resulting decrease in the relative proportion of cells synthesising DNA (S phase, Fig. 1A) (9–13). A typical response to antiestrogens of all structural classes is shown in Fig. 1B where MCF-7 breast-cancer cells growing exponentially in 5% fetal calf serum (FCS) with a doubling time of 28 h are treated with the steroidal pure antiestrogen ICI 182780. Little change is apparent over the first 8 h of exposure, but the proportion of cells in S phase then falls continuously to reach a minimum by 24 h. These decreases are mirrored by increases in the proportion of cells in G1 phase. Experiments with cells synchronized by mitotic selection demonstrate that only those cells in early-to-mid G1 phase are susceptible to growth arrest (9,11). Cells in plateau phase, where the proportion of proliferating cells is reduced, are relatively insensitive, suggesting that only actively cycling cells are sensitive to antiestrogen (13,14). Compatible with an antiestrogen-mediated, reversible inhibition of cell-cycle progression