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Estrogen and antiestrogen regulation of cell cycle progression in breast cancer cells

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Abstract

The central involvement of estrogen in the development of the mammary gland and in the genesis of breast cancer has lent impetus to studies of the links between estrogen action and the cell cycle machinery. Recent studies of the estrogenic regulation of molecules with known roles in the control of G1/S phase progression have resulted in significant advances in understanding these links. Estrogens independently regulate the expression and function of c-Myc and cyclin D1 and the induction of either c-Myc or cyclin D1 is sufficient to recapitulate the effects of estrogen on cell cycle progression. These pathways converge at the activation of cyclin E–Cdk2 complexes. The active cyclin E–Cdk2 complexes are depleted of the cyclin dependent kinase (CDK) inhibitor p21WAF1/CIP1 because of estrogen-mediated inhibition of nascent p21WAF1/CIP1. Insulin and estrogen synergistically stimulate cell cycle progression, and the ability of estrogen to antagonize an insulin-induced increase in p21WAF1/CIP1 gene expression appears to underlie this effect. Antiestrogen treatment of MCF-7 cells leads to an acute decrease of c-Myc expression, a subsequent decline in cyclin D1, and ultimately arrest of cells in a state with features characteristic of quiescence. An antisense-mediated decrease in c-Myc expression results in decreased cyclin D1 expression and inhibition of DNA synthesis, mimicking the effects of antiestrogen treatment and emphasizing the importance of c-Myc as an estrogen/antiestrogen target. These data identify c-Myc, cyclin D1, p21WAF1/CIP1 and cyclin E-Cdk2 as central components of estrogen regulation of cell cycle progression and hence as potential downstream targets that contribute to the role of estrogen in oncogenesis.

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Introduction

Sex steroid hormones have a major role in the growth and development of target tissues including the mammary gland where they interact with other hormones, growth factors and cytokines in the precise regulation of proliferation and differentiation. The classical model of 17β-estradiol (E2) action involves ligand-mediated activation of the nuclear estrogen receptors ERα and ERβ, which interact directly with estrogen response elements (ERE) in the promoters of target genes and recruit various coactivators to mediate transcriptional regulation (McDonnell & Norris 2002). ERs also regulate transcription through ‘non-classical’ response sites that bind heterologous transcription factors including Sp1, c-Jun/ATF-2 and AP-1, probably via protein–protein interactions since ERs do not bind these sites directly (McDonnell & Norris 2002). Increasing evidence indicates that E2 induces nongenomic effects (often immediate and transient) via signaling pathways more commonly associated with growth factor activation of cell surface receptors (Cato et al. 2002). For example, a nuclear receptor-interacting protein that modulates ERα interaction with the Src family and consequently affects ER transcriptional activity has recently been identified (Wong et al. 2002).
The cell cycle phase-specificity of the effects of estrogens on proliferation and differentiation have focused attention on the role of estrogens and their receptors in regulating processes controlling the entry into, progression through, and exit from the G1 phase of the cell cycle. Central to these cell cycle control mechanisms are cyclin D1-Cdk4 and cyclin E-Cdk2, which phosphorylate substrates including the product of the retinoblastoma susceptibility gene pRB, thereby allowing initiation of DNA synthesis (Weinberg 1995). They are controlled by several mechanisms including: transcriptional activation of cyclin expression, regulatory phosphorylation of the cyclin dependent kinase (CDK) subunit by kinases including the CDK-activating kinase (CAK) and the Cdk2 family of phosphatases, and interactions with members of two distinct families of CDK inhibitors of which p16INK4A and p21WAF1/CIP1 are prototypic (Sherr & Roberts 1997). Members of two distinct families of CDK inhibitors of which Cdc25 family of phosphatases, and interactions with members of two distinct families of CDK inhibitors of which p16INK4A and p21WAF1/CIP1 are prototypic (Sherr & Roberts 1999). Essentially all of these modes of regulation have been documented following estrogen treatment. Another well-studied target of estrogen action with a role in the control of cell cycle progression is c-Myc, a nuclear phosphoprotein of the basic helix-loop-helix family of transcription factors. The recent expansion of knowledge on the molecular mechanisms regulating rates of cell cycle progression has provided a framework within which to develop deeper insight into the mechanistic basis of estrogen-induced mitogenesis and anti-estrogen action in breast cancer cells. This brief review summarizes recent developments in this area.

Experimental models

Estrogens and antiestrogens would be expected to exert opposite effects on the same targets given that antiestrogens are competitive inhibitors of the ER-mediated actions of estrogens; thus a greater depth of understanding of the molecular mechanisms that mediate the antiproliferative action of antiestrogens also yields insights into estrogen action. The growth inhibitory effects of antiestrogens in ERα-positive breast cancer cells are profound, and this allowed early demonstration of a G1 phase site of action for antiestrogens (Osborne et al. 1983, Sutherland et al. 1983). Studies using synchronized cells demonstrated that cells were most sensitive to estrogens and antiestrogens in the early G1 phase, immediately following mitosis (Taylor et al. 1983, Leung & Potter 1987, Musgrove et al. 1989), compatible with a model whereby estrogens and antiestrogens acting via the ER regulate the rate of progression through the early G1 phase of the cell cycle.

The growth stimulatory effects of estrogens in cell culture have often been subtle and heavily dependent on the experimental system employed, and thus several methods of cell synchronization have been employed to increase the proportion of cells in the estrogen-sensitive G1 phase of the cell cycle (Osborne et al. 1984, Leung & Potter 1987, Altucci et al. 1996, Foster & Wimalasena 1996, Planas-Silva & Weinberg 1997, Prall et al. 1997). A particularly powerful model system has been breast cancer cells growth-arrested in the G0/G1 phase by pretreatment with antiestrogens and then stimulated by estrogen treatment to progress semisynchronously through the remainder of the G1 phase and into S phase (Osborne et al. 1984, Planas-Silva & Weinberg 1997, Prall et al. 1997). The use of specific estrogen antagonists to achieve cell synchrony in this experimental design permits selective magnification of ER-mediated effects relative to more generalized responses to cell cycle progression, and we have used this model system to dissect the molecular events involved in estrogen stimulation of cell proliferation.

Regulation of c-Myc expression

The mitogenic, apoptotic and oncogenic functions of c-Myc depend upon dimerization with the heterologous protein Max, DNA binding and transcriptional regulation, suggesting that c-Myc acts by regulating genes involved in cell proliferation and/or apoptosis (reviewed in Oster et al. 2002). These functions require the C-terminal dimerization domain, but it has now become evident that the N-terminal region of c-Myc also plays an essential role, particularly in the regulation of cell cycle progression and transformation. The N-terminal region contains a transcription regulation domain, spanning about 150 amino acids, with two evolutionarily conserved motifs named Myc box I and Myc box II (Oster et al. 2002).

In rat uteri (Murphy et al. 1987) and breast cancer cell lines (Dubik et al. 1987), the rapid and direct regulation of c-myc by estrogen, apparently via an atypical ERE (Dubik & Shiu 1992), places c-myc induction amongst the earliest detectable transcriptional responses to E2. Strong evidence that c-Myc is likely to play a key role in estrogen action is provided by the demonstration that c-Myc antisense oligonucleotides inhibit estrogen-stimulated breast cancer cell proliferation (Watson et al. 1991) and that induction of c-Myc in antiestrogen-arrested cells can mimic the effects of estrogen by re-initiating cell cycle progression (Prall et al. 1998). Further experiments with c-Myc mutants lacking Myc box I, Myc box II or the entire N-terminal domain indicate that the N-terminal region of c-Myc including Myc box II is essential for c-Myc-induced cell cycle progression in this model (CM Sergio, EA Musgrove & RL Sutherland, unpublished data).

Regulation of cyclin D1 expression and function

targets of estrogen action. In particular, cyclin D1, which binds to and activates both Cdk4 and Cdk6, has been implicated in estrogen/antiestrogen regulation of cell cycle progression. Cyclin D1 expression declines rapidly following exposure to growth-inhibitory antiestrogens (Musgrove et al. 1993, Watts et al. 1995), while E2 treatment of MCF-7 breast cancer cells that have been growth arrested by a variety of strategies is followed by pronounced increases in cyclin D1 protein expression, cyclin D1–Cdk4 association and Cdk4 activity (Altucci et al. 1996, Foster & Wimalasena 1996, Planas-Silva & Weinberg 1997, Prall et al. 1997). The increase in cyclin D1 expression occurs after the earliest changes in c-Myc expression, but coincides with increased phosphorylation of pRB and precedes S phase entry by some 9 h (see Fig. 1).

The effect of estrogen on cyclin D1 protein expression appears to be predominantly transcriptionally mediated, since increased expression of cyclin D1 mRNA precedes changes in cyclin D1 protein (Altucci et al. 1996, Prall et al. 1997). Inhibitors of protein synthesis block the estrogen-induced increase in cyclin D1 mRNA (Altucci et al. 1996, Prall et al. 1997), indicating that cyclin D1 is directly regulated by ER. However, the cyclin D1 promoter region does not contain a classical ERE. Instead, induction by ERα has been mapped to a cAMP response element (CRE) close to the transcription start site (Sabbah et al. 1999, Castro-Rivera et al. 2001) and a more distal Sp1 site bound by both ERα and Sp1 in chromatin immunoprecipitation assays (Castro-Rivera et al. 2001). An AP-1 site has partly overlapping functions with the CRE although it mediates a relatively weak response on its own (Liu et al. 2002). Interestingly, ERα and ERβ have opposing actions on the cyclin D1 promoter although both are transcriptional activators at ERE-containing promoters (Liu et al. 2002).

Compelling evidence that cyclin D1 plays an essential role in estrogen-induced cell cycle progression comes from studies in which cyclin D1 is either functionally inhibited, or its expression is enforced ectopically. Thus, when either antibodies against cyclin D1, or the Cdk4-specific inhibitor p16INK4A are introduced into MCF-7 cells by microinjection,

Figure 1 A model of estrogen effects on molecules regulating G1 phase progression in MCF-7 cells. See text for details. D1, cyclin D1; E, cyclin E; p21, p21RAS/CP1. Shaded cyclin–CDK complexes are inactive.
Estrogen fails to stimulate G1/S phase progression (Lukas et al. 1996), indicating that cyclin D1 is necessary for estrogen action. Conversely, induced expression of cyclin D1 in MCF-7 or T-47D breast cancer cells that have been growth-arrested in G1 phase by pretreatment with antiestrogens is followed by Cdk4 activation, increased phosphorylation of pRB and subsequent S phase entry, thereby mimicking the actions of estrogen (Wilcken et al. 1997, Prall et al. 1998).

**Estrogen activation of cyclin E–Cdk2 holoenzyme complexes and CDK inhibitor involvement**

In addition to activation of cyclin D1–Cdk4 complexes, estrogen also activates cyclin E–Cdk2 complexes within ~3 h, substantially preceding entry into S phase (Foster & Wimalasena 1996, Planas-Silva & Weinberg 1997, Prall et al. 1997). This is in contrast to cell cycle progression stimulated by other mitogens in which cyclin E–Cdk2 activation is associated with G1/S phase transition (Ho & Dowdy 2002), suggesting that cyclin E–Cdk2 has a particularly important role in estrogen-induced cell cycle progression. However, following estrogen treatment there is little or no change in the levels of cyclin E, Cdk2, or the CDK inhibitors, p21WAF1/CIP1 and p27KIP1 in either total cell lysates or the cyclin E–Cdk2 complexes prior to entry into S phase (Prall et al. 1997). The mechanistic basis for this effect is thus not readily apparent and has subsequently been explored in detail (Planas-Silva & Weinberg 1997, Prall et al. 1997, 2001).

Some mechanistic insights into the activation of cyclin E–Cdk2 by estrogen are provided by studies utilizing MCF-7 cells that contain either inducible c-Myc or cyclin D1. Similar to the situation following estrogen treatment, expression of c-Myc or cyclin D1 is sufficient to activate cyclin E–Cdk2 by promoting the formation of high molecular weight complexes lacking the CDK inhibitor p21WAF1/CIP1 (Prall et al. 1998, see Fig. 1). c-Myc expression was not accompanied by increased cyclin D1 expression or Cdk4 activation, nor was cyclin D1 induction accompanied by increases in c-Myc. Similarly, others have demonstrated that activation of conditionally c-Myc alleles (MycER) does not activate cyclin D1 transcription (Solomon et al. 1995) despite some conflicting earlier reports (Jansen-Durr et al. 1993, Daksis et al. 1994). The ability of cyclin D1 induction to activate cyclin E–Cdk2 is compatible with the suggestion that synthesis of cyclin D1 is an important component of this response (Planas-Silva & Weinberg 1997). However, an increase in cyclin D1 alone is not sufficient to restore full activation of cyclin E–Cdk2 following growth arrest, unless cyclin D1 levels are elevated to approximately twofold the level induced by maximally stimulatory concentrations of estrogen (Prall et al. 1998). In contrast, c-Myc induction to the level reached after estrogen treatment is sufficient to quantitatively mimic estrogen activation of cyclin E–Cdk2 and cell cycle progression.

Separation of the cyclin E–Cdk2 complexes by gel filtration chromatography indicated that estrogen treatment was associated with the formation of high molecular weight complexes (Prall et al. 1997), and that induction of c-Myc or cyclin D1 likewise led to the formation of active high molecular weight cyclin E–Cdk2 complexes (Prall et al. 1998). These complexes constituted a minority of the cyclin E–Cdk2 protein but were of high specific activity, accounting for the majority of cyclin E–Cdk2 activity, and relatively deficient in p21WAF1/CIP1 and p27KIP1. Estrogen treatment relieves the inhibitory activity of p21WAF1/CIP1 towards cyclin E–Cdk2 (Planas-Silva & Weinberg 1997, Prall et al. 1997), the result of a decrease in newly synthesized p21WAF1/CIP1, which has a greater inhibitory activity than pre-existing p21WAF1/CIP1 (Prall et al. 2001). The repression of p21WAF1/CIP1 during estrogen-induced proliferation may involve transcriptional repression by c-Myc since p21WAF1/CIP1 is a c-Myc target (Gartel et al. 2001, van de Wetering et al. 2002) and is down-regulated after c-Myc induction in this system (CM S S, EA Musgrove & RL Sutherland, unpublished results). The pRB-related protein p130, which can compete with p21WAF1/CIP1 for cyclin-CDK binding (Zhu et al. 1995, Shiyanov et al. 1996) is recruited to the cyclin E–Cdk2 complex following estrogen treatment and c-Myc or cyclin D1 induction, contributing to the increased size of the complex and the decreased association with p21WAF1/CIP1 (Prall et al. 1998, see Fig. 1).

Supporting a role for Cdc25A in estrogen action, antisense Cdc25A oligonucleotides inhibited estrogen-induced Cdk2 activation and DNA synthesis while inactive cyclin E–Cdk2 complexes from p16INK4A-expressing, estrogen-treated cells were activated in vitro by treatment with recombinant Cdc25A and in vivo in cells overexpressing Cdc25A (Foster et al. 2001). These studies establish Cdc25A as another growth-promoting target of estrogen action and further indicate that estrogens independently regulate multiple components of the cell cycle machinery.

There is compelling evidence that several mitogenic growth factors, particularly those of the epidermal growth factor and insulin-like growth factor (IGF) families, interact with ER-mediated signaling to regulate cell proliferation. Estrogens and insulin/IGF-I are potent mitogens for breast epithelial cells and, when co-administered, induce synergistic stimulation of cell proliferation (van der Burg et al. 1988).

In an MCF-7 breast cancer cell model where serum deprivation and concurrent treatment with the antiestrogen ICI 182,780 inhibited both growth factor and estrogen action, co-administration of insulin/IGF-I and estrogen induced synergistic stimulation of S-phase entry (Lai et al. 2001). This was accompanied by synergistic activation of high molecular mass cyclin E–Cdk2 complexes lacking p21WAF1/CIP1. A central component of this synergistic effect was the ability of estrogen to antagonize an insulin-induced increase in p21WAF1/CIP1 gene expression, with consequent activation of
Figure 2 A model of antiestrogen effects on molecules regulating G_1 phase progression in MCF-7 cells. See text for details. ICI, steroidal antiestrogen; D1, cyclin D1; E, cyclin E. Shaded cyclin – CDK complexes are inactive.

cyclin E-Cdk2, again emphasising the importance of p21^{WAF1/CIP1} as an estrogen target.

Molecular mechanisms of growth regulation by antiestrogens

The pure antiestrogen ICI 182,780 arrests MCF-7 cells in a state with characteristics of quiescence (G_0), as indicated by the formation of p130/E2F4 complexes and the accumulation of hyperphosphorylated E2F4 (Carroll et al. 2000, Fig. 2). In this state they are relatively resistant to the mitogenic effects of growth factors (Lai et al. 2001). Antiestrogen-mediated G_0/G_1 arrest is associated with decreased cyclin D1 gene expression, inactivation of cyclin D1-Cdk4 complexes, and decreased phosphorylation of pRB (Musgrove et al. 1993, Watts et al. 1995). Inhibition of cyclin E-Cdk2 activity also occurs prior to a decrease in the S phase fraction, and is dependent on p21^{WAF1/CIP1} since treatment with antisense oligonucleotides to p21^{WAF1/CIP1} attenuates the effect (Carroll et al. 2000). Recruitment of p21^{WAF1/CIP1} to cyclin E-Cdk2 complexes is, in turn, dependent on decreased cyclin D1 expression (Carroll et al. 2000, Fig. 2).

The importance of cyclin D1 in antiestrogen action is indicated by the observation that overexpression of cyclin D1 decreased sensitivity to antiestrogen inhibition at 24 and 48 h while overexpression of cyclin E produced a less pronounced early cell-cycle effect, indicating only partial resistance to antiestrogen inhibition in the short term (Hui et al. 2002). Neither overexpression of cyclin D1 or cyclin E conferred antiestrogen resistance in longer-term assays (Pacilio et al. 1998, Hui et al. 2002). p27^{Kip1} is another essential mediator of cell cycle arrest by antiestrogens since antisense-mediated down-regulation of p27^{Kip1} abrogates antiestrogen-induced cell cycle arrest in MCF-7 human breast cancer cells (Cariou et al. 2000). Furthermore, MAP kinase (MAPK) activation contributes to antiestrogen resistance through down-regulation of p27^{Kip1} (Donovan et al. 2001). However, p21^{WAF1/CIP1} antisense treatment resulted in a decrease in p27^{Kip1} protein levels, while changes in p21^{WAF1/CIP1} protein levels were not observed following treatment with p27^{Kip1} antisense (JS Carroll, A Swarbrick, EA Musgrove, & RL Sutherland, unpublished data). These data suggest that p21^{WAF1/CIP1} initiates inhibition of cyclin E/Cdk2 and consequent accumulation of p27^{Kip1}. 
Given the importance of c-Myc in estrogen-induced mitogenesis, it is perhaps not surprising that constitutive c-Myc expression confers resistance to antiestrogen treatment (Venditti et al. 2002). Oligonucleotide antisense inhibition of c-Myc leads to inhibition of cyclin D1 expression, subsequent redistribution of p21<sup>WAF1/CIP1</sup> from cyclin D1–Cdk4 to cyclin E–Cdk2 complexes, and a decline in cyclin E–Cdk2 enzymatic activity (Carroll et al. 2002), thereby recapitulating the initial downstream events that culminate in growth arrest after ICI 182,780 treatment (Fig. 2). Simultaneous repression of p21<sup>WAF1/CIP1</sup> attenuated the growth-inhibitory effects of reduced c-Myc expression, emphasizing the importance of this CDK inhibitor in c-Myc action in these cells (Carroll et al. 2002). While the effects of estrogens on cell cycle regulatory molecules largely mirror the effects of antiestrogens, one difference is the relationship between c-Myc and cyclin D1. Induction of c-Myc does not increase cyclin D1 expression, but antisense-mediated reduction in c-Myc leads to decreased cyclin D1 expression. Thus, although cyclin D1 expression is dependent on c-Myc, c-Myc is not limiting for cyclin D1 expression.

Farnesyltransferase inhibitors (FTIs) are a new class of anticancer drugs that are presently in phase III clinical evaluation (Johnston & Kelland 2001). The demonstration that FTIs prevent estrogen-stimulated cell cycle progression implicates prenylated proteins in estrogen action. Since major components of cytoplasmic signaling pathways include low molecular weight GTPases such as Ras that require prenylation for function, one mechanism for this effect is inhibition of the non-genomic effects of estrogen, i.e. activation of the Src/MAPK/ERK pathway. Consistent with this idea, FTIs interfere with estrogen regulation of progesterone receptor, cyclin D1 and c-Myc, but no genes containing a classical ERE (Doisneau-Sixou et al. 2003a). In MCF-7 cells, FTI L744,832 induces a two- to threefold increase in cyclin D1 and markedly increases p21<sup>WAF1/CIP1</sup> transcription (Sepp-Lorenzino & Rosen 1998). This increase in p21<sup>WAF1/CIP1</sup> is p53-dependent and mediates the inhibition of cyclin E–Cdk2 activity, reduced pRB phosphorylation and G<sub>0</sub> arrest. FTI-277 and tamoxifen induce an additive effect on inhibition of breast cancer cell proliferation and the additive effect is probably predominantly due to the recruitment of p27<sup>Kip1</sup> and, to a less extent, p21<sup>WAF1/CIP1</sup> into cyclin E–Cdk2 complexes (Doisneau-Sixou et al., 2003b). By altering the non-genomic effects of ER, the FTIs may be a new class of ‘antiestrogens’ to combine with tamoxifen or ICI 182,780.

Summary and conclusions

The development of powerful in vitro model systems, wherein breast cancer cells are growth-arrested with a pure antiestrogen and cell cycle progression reinitiated with estrogen and/or overexpressed proteins, has facilitated dissection of some early molecular events in estrogen and antiestrogen action, illustrated in Figs 1 and 2. This indicates that the mitogenic effects of estrogen appear to be mediated by at least two apparently distinct pathways, of which c-Myc and cyclin D1, respectively, are the key regulators. The net result of estrogen-induced c-Myc or cyclin D1 expression is early activation of cyclin E–Cdk2 by the formation of high molecular weight cyclin E–Cdk2 complexes associated with the pocket protein p130 and deficient in the CDK inhibitor p21<sup>WAF1/CIP1</sup>. Phosphorylation of pRB is a primary target of cyclin E–Cdk2 activity, resulting in the well-documented release of E2F transcription factors necessary for DNA synthesis and progression from G<sub>1</sub> to S phase of the cell cycle.

‘Pure’ nonsteroidal antiestrogens, e.g. ICI 182,780, elicit a sequence of events that includes an acute decrease in c-Myc, a subsequent decline in cyclin D1 and a consequent loss of cyclin D1–Cdk4 complexes. This results in redistribution of p21<sup>WAF1/CIP1</sup> from cyclin D1–Cdk4/6 complexes to cyclin E–Cdk2 complexes, inhibition of cyclin E–Cdk2, hypophosphorylation of the pocket proteins and ultimately growth arrest in a state with characteristics of quiescence (Fig. 2). Although the initial events in inhibition of cyclin E–Cdk2 are predominantly mediated by p21<sup>WAF1/CIP1</sup>, p27<sup>Kip1</sup> plays a major role in maintaining growth arrest. Some minor differences in response are apparent in different cell lines (Watts et al. 1995, Carroll et al. 2000, Hui et al. 2002) but the key features of this model, i.e. the central importance of c-Myc, cyclin D1 and redistribution of the CDK inhibitors p21<sup>WAF1/CIP1</sup> and p27<sup>Kip1</sup>, are conserved. One important but underexplored issue is the degree to which the cell cycle events following treatment with the ‘pure’ steroidal antiestrogens are also elicited by selective estrogen modulators (SERMs) including nonsteroidal antiestrogens like tamoxifen. There appears to be significant overlap, but recent data from this laboratory indicate differences in the growth arrest states induced by the two classes of antiestrogen (unpublished data).

Emerging evidence indicates that the non-genomic effects of estrogen play an important role in mediating its mitogenic effects. The relative roles of the transcriptional activity of ERα and these non-genomic effects in mediating specific critical responses to estrogen, e.g. c-Myc and cyclin D1 induction, are as yet unclear, although recently developed model systems offer new insights. For example, inhibition of membrane ER signaling impairs estrogen activation of cyclin D1 and cell cycle progression (Razandi et al. 2003). Further experimentation to explore such questions will offer important new insights into estrogen/antiestrogen action, with the possibility of identifying potential new therapeutic targets and prognostic indicators in breast cancer.

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