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Regulation of hormonal therapy resistance by cell cycle machinery

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Summary

Estrogen Receptor (ER) plays a central role in the development and progression of breast cancer. Hormonal therapy substantially improves disease-free survival of ER+ve breast tumors, however acquired resistance to endocrine therapies frequently occur. Emerging data implicate growth factor signaling pathways and their cross talk with ER as major cause of resistance. Both these pathways have been recently shown to use cell cycle machinery as downstream effectors in mediating therapy resistance. Several studies have demonstrated deregulation of cell cycle regulators and their cross talk with ER in therapy resistant tumors. The objective of this article is to review the underlying mechanisms by which tumor cells use cell cycle machinery to override hormonal therapy and to explore cell cycle machinery components as novel therapy targets for overcoming hormonal therapy resistance.

Keywords

Cell Cycle; CDKs; Estrogen; Estrogen Receptor; Co-regulators; Breast cancer; Therapy resistance; Antiestroge ns

I. Introduction

Steroidal hormone estradiol (E2) and Estrogen Receptor (ER) plays a central role in the development and progression of breast cancer and 70−80% of breast tumors are ER positive at the time of presentation (McGuire and Clark, 1992). ER positive tumors respond well with therapeutic agents targeting ER functions (Ariazi et al, 2006). Endocrine therapy using Tamoxifen, a selective estrogen receptor modulator (SERM), has been shown to improve relapse-free and overall survival (Lewis-Wambi and Jordan, 2005). More recently, aromatase inhibitors, which deplete peripheral estrogen (E2) synthesis, are shown to substantially improve disease-free survival in postmenopausal women (Leary and Dowsett, 2006). Despite the success of antiestrogens, de novo and/or acquired resistance to endocrine therapies frequently occur. Approximately 30% of these patients acquire resistance to endocrine therapy in later stages and is a significant problem in the treatment regime (Riggins et al, 2007). Although mechanisms for hormonal therapy resistance remain elusive, emerging data implicate growth factor signaling pathways and its cross talk with ER as a major cause of resistance (Shou et al, 2004). Both these pathways have been recently shown to use cell cycle machinery as downstream effectors in mediating therapy resistance (Shou et al, 2004; Perez-Tenorio et al, 2006; Ru et al, 2006). The prime focus of this review is to recapitulate the literature elucidating

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the role of cell cycle machinery as downstream effectors of various pathways leading to hormone therapy resistance.

II. Estrogen receptors and coregulators

The human estrogen receptor (ER) is a key transcriptional regulator in breast cancer biology (Green and Carroll, 2007; Heldring et al, 2007). The biological effects of estrogen is mediated by its binding to the structurally and functionally distinct ERs (ERα and ERβ) (Warner et al, 1999). ER α is the major ER in the mammary epithelium and this has been further shown by ERα (Esr1) knockout mice, which display grossly impaired ductal epithelial cell proliferation and branching (Lubahn et al, 1993; Bocchinfuso and Korach, 1997). ERs comprises an N-terminal activation function 1 (AF1) domain, a DNA-binding domain, and a C-terminal ligand binding region that contains an activation function 2 (AF2) domain (Kumar et al, 1987). The AF-2 of the ER is located in the ligand binding domain, while the N-terminal AF-1 functions in a ligand-independent manner. AF-1 and AF-2 exhibit cell type and promoter context specificity (Berry et al, 1990). Upon binding of E2 to ER, the ligand-activated ER translocates to the nucleus, binds to the responsive element in the target gene promoters, and stimulates gene transcription (genomic/nuclear signaling) (McKenna et al, 1999; McDonnell and Norris, 2002). In addition to its well-studied nuclear functions, ER also participates in non-genomic signaling events in the cytoplasm and membrane. Such signaling has been linked to rapid responses to E2 which generally involves the stimulation of the Src kinase, MAPK, and AKT (Pedram et al, 2002).

Transcriptional activity of ERs is regulated not only by hormones but also by several coregulatory proteins called coactivators and corepressors (McKenna et al, 1999). The transcription functions of ER are shown to be influenced by several coactivators, including SRC1, GRIP1, AIB1, PELP1 and corepressors including nuclear receptor corepressor (NCoR), silencing mediator for retinoic and thyroid receptor (SMRT) and MTA1 (Tsai and O'Malley, 1994; Barnes et al, 2004). Coactivators preferentially associate with ligand bound ER while corepressors have been shown to preferentially associate with antagonist occupied ERs (Jepsen and Rosenfeld, 2002). Evidence suggests that multi-protein complexes containing coactivators, ERs, and transcriptional regulators assemble in response to hormone binding and activate transcription (McKenna et al, 1999). Accumulating evidence suggests that ER-coregulators play an essential role in hormonal responsiveness and cancer progression (Bocchinfuso and Korach, 1997; McKenna et al, 1999).

III. Estrogen and cell cycle progression

It is well accepted that estrogen induces mitogenesis by recruiting non-cycling cells into the cell cycle and by increasing the rate of progression from G_1 to S phase. However, the molecular mechanism by which E2-ER signaling controls cell proliferation is not completely understood. Induction of the early-response genes (such as c-myc and c-fos) is proposed as one mechanism of this process (Prall et al, 1998a; Lamb et al, 2000), whereas regulation of Cyclin Dependent Kinase (CDK2 and CDK4) activities was proposed as another (Neuman et al, 1997; Prall et al, 1997; Foster et al, 2001). Each phases of cell cycle (G1, S, G2 and M) is strictly under the control of different Cyclins and CDKs. CDK4 and CDK2 enhance G1-S transition in the cell cycle and for tumorigenesis, indicating that phosphorylation of downstream effector proteins by CDKs is vital for cell proliferation. Previous studies have shown that Cyclin D1-CDK4 and Cyclin ECDK2 are major regulators of G1/S transition, while Cyclin A-CDK2 controls S-phase and Cyclin B1-CDK1 controls transition through M-phase. The kinases are traditionally known to phosphorylate many key downstream substrates, most notably retinoblastoma and exhibit strict and elegant control of cell cycle progression. In addition, Cyclin D1 was identified as a target of E_2 action, and estrogen treatment was shown to up-regulate Cyclin D1 levels (Altucci

et al, 1996). Up-regulation of Cyclin D1 by ER signaling is accompanied by an increased proliferative response in breast cancer cells. E2 is shown to induce Cdc25A, a tyrosine phosphatase that controls G1-S transition in cell cycle by regulating the dephosphorylation of Cyclin-dependent kinase complexes (Ru et al, 2006). Collectively, these findings suggest that Estrogen induces proliferation of ER-positive breast epithelial cells by stimulating G_1/S transition, which is associated with increased cyclin D1 expression and activation of CDKs (Foster et al, 2001). Since CDK4 and CDK2 are key players for G1-S transition in the cell cycle and for tumorigenesis, ER crosstalk with CDKs will have implications in therapy resistance.

IV. ER coregulators and cell cycle progression

Evolving evidence suggests that many of the ER coregulators play a vital role in cell cycle progression. Emerging evidence suggest that oncogenic ER-coregulatory proteins such as AIB1, PELP1 modulate Cyclin D1 expression and function, thus may enhance tumorigenesis and therapy resistance. We have summarized below some of the ER coregulators that are shown to play a role in E2-ER mediated cell cycle progression.

A. AIB1

ER coregulator SRC3/AIB1 is shown to regulate cell cycle machinery in numerous ways. AIB1 is shown to enhance E_2-dependent induction of Cyclin D1, suggesting a role for ER coregulators in modulating Cyclin D1 expression (Planas-Silva et al, 2001). AIB1 is also shown to interact with E2F directly and modulate its transactivation function and is required for E2F1-mediated gene expression (Louie et al, 2004). Recent evidence also suggests that AIB1 has oncogenic potential and the transformation ability of AIB1 has been ascribed to its ability to control the expression of genes important for initiating DNA replication like cdc6, MCM7, Cyclin E, and CDK2 (Louie et al, 2006). E2F regulates AIB1 expression by cooperating with the transcription factor specificity protein 1 (Sp1) without direct interaction with E2F consensus sites, suggesting a positive feedback regulatory loop comprising of E2F and AIB1 (Mussi et al, 2006)

B. Ciz1

Ciz1, a p21(Cip1/Waf1)-interacting zinc finger protein is shown to function as an ER co-regulator and Ciz1 over-expression confers estrogen hypersensitivity and promotes the growth rate, anchorage independency, and tumorigenic properties of breast cancer cells. These effects on cell cycle progression is shown to be ER dependent through upregulation of Cyclin D1 expression (Den et al, 2006). However, a direct role of Ciz1 in DNA replication process in S phase has also been suggested. Ciz1 co-localizes with PCNA during S phase while depletion of Ciz1 restrains cell proliferation by inhibiting entry to S phase (Coverley et al, 2005).

C. CARM1/PRMT4

CARM1 is a methyltransferase that associate with ER coregulators and regulate transcription by histone H3 methylation and is essential for estrogen induced cell cycle progression (Chen et al, 1999). SiRNA mediated depletion of CARM1 in ER positive MCF7 and T47D cells reduced E2 mediated cell cycle progression (Frietze et al, 2008). Recent evidence also suggest that CARM1 regulate not only E2 mediated E2F expression but also expression of E2F target genes. The recruitment of CARM1 to E2F target genes and associated increase in H3R17 dimethylation during transcriptional activation has been shown to be dependent on another ER coactivator AIB1(Frietze et al, 2008). In a recent study, expression of Cyclin E gene has been shown to correlate with recruitment of CARM1 on its promoter and associated increase in H3-R26 and H3-R17 methylation at its promoter (El et al, 2006). Consistent with the role of

CARM1 in regulating cell cycle genes, CARM1 knockout mice show small embryos and perinatal lethality (Yadav et al, 2003).

D. PELP1/MNAR

PELP1 is another ER coregulator that is shown to play a role in E2-mediated G1/S-phase progression (Balasenthil and Vadlamudi, 2003). PELP1 is a pRb-interacting protein and PELP1 deregulation promotes cyclin D1 expression. Breast cancer model cells, which overexpressed PELP1 showed persistent hyperphosphorylation of the pRb protein in an E2 dependent manner accompanied with increase in proliferation rate (Balasenthil and Vadlamudi, 2003). Recent studies suggested that PELP1 is a phospho-protein and its phosphorylation changes during cell cycle progression. PELP1 interacts with G1/S phase CDKs (both CDK4 and CDK2), and is a novel substrate to both of these enzymes (Chandrasekharan Nair et al, 2008a). Furthermore, increased PELP1 expression in a mammary gland during pregnancy, when the rate of cell proliferation is high, supports a physiological role for PELP1 in E2-mediated cell cycle progression in mammary glands (Vadlamudi et al, 2001). PELP1 is also known to interact with key proteins like Src, PI3K, four and a half LIM only protein2 to mediate E2 dependent non-genomic functions of ER. Mitogenic stimulus promotes PELP1 interaction with growth factor signaling component, epidermal growth factor (EGFR), HER2, STAT3, and hepatocyte growth factor regulated tyrosine kinase substrate (HRS) (Vadlamudi and Kumar, 2007). PELP1 has highest tissue expression in brain, testes, ovary and uterus (Khan et al, 2005; Vadlamudi and Kumar, 2007) and studies from rodent biology suggest that PELP1 is developmentally regulated and expressed at classical steroid target sites in brain like hippocampus, cortex, hypothalamus, amygdale and septum (Khan et al, 2005). Collectively, these emerging findings suggest that PELP1 plays a key role in relaying mitogenic signals, both in cytoplasm and nucleus and therefore is an attractive therapeutic target. The fact that siRNA mediated knockdown of PELP1 reduces cell proliferation in MCF-7 breast cancer cells strongly suggest that blocking PELP1 functions will undeniably benefit cancer therapeutic regime (Chandrasekharan Nair et al, 2008).

V. Modulation of cell cycle progression by anti-estrogens

Estrogens and anti-estrogens both are shown to exert their functions in G1 phase, where they regulate Cyclin D1 and Cyclin E expression and hence modulate the kinase function of CDK4 and CDK2, respectively. Inhibition of CDK kinase function leads to accumulation of hypophosphorylated retinoblastoma and resulting in cell cycle arrest. In short, the consensus is that estrogen accelerates the G1 phase passage while antiestrogens inhibit cell cycle progression by affecting these key cell cycle proteins. On the contrary, a recent transcriptional profiling presented a rather intriguing result regarding functioning of tamoxifen at the molecular level. Tamoxifen and estrogen both positively regulated a large set of cell cycle genes like cmyc, myb, fos, cdc25a, Cyclin E, Cyclin A2, and stk15 while the differential effect was on only few cell cycle genes, most notably on Cyclin D1 (Hodges et al, 2003). Interestingly, only Tamoxifen but not Roloxifene induced these key cell cycle regulators (Hodges et al, 2003).

Emerging evidence suggest that CDK inhibitors are also regulated by antiestrogens in mediating growth arrest. Tamoxifen treated breast cancer cell lines show a reduction in Cyclin D, increase p27 and simultaneous increase in Cyclin E-CDK2 bound p27 (Chu et al, 2005). In the same study, combination treatment of Tamoxifen along with a dual HER1/HER2 inhibitor, lapatinib (GW572016) showed more profound effect on these cell cycle regulators and rapid cell cycle arrest in all the three cell lines tested. Transduction of Tamoxifen treated cells with p-27 peptides (TAT-p27) helped in maintaining quiescence and made the cells resistant to mitogen stimulation (Carroll et al, 2003). These studies evoke the potential of using anti-p27 molecules in future to reverse Tamoxifen resistance. The recent findings that miRNAs also

regulate Tamoxifen response in cancer cells is an exciting advance in understanding therapy resistance. Upregulation of miR-221 and/or miR-222 has been directly shown to promote therapy resistance through downregulation of ER α (Zhao et al, 2008).

Recent studies also implicated role of p53 in Tamoxifen mediated cell cycle arrest. Ichikawa et al. reported a concomitant increase in p53 expression and p21, a known CDK2 inhibitor in Tamoxifen treated MCF7 in time and dose dependent manner, suggesting possible role of p53 in mediating the G1 arrest caused by Tamoxifen (Ichikawa et al, 2008).

Future studies, however, are required to understand whether antiestrogens affect the expression of Cyclins at transcriptional level or whether unidentified intermediary players govern this pathway in a similar fashion as p53. Identifying key G1-S transition regulatory genes that are relieved of pRb mediated repression due to treatment with antiestrogens will be a priority to unravel more downstream players in antiestrogen mediated cell cycle arrest and such studies will further enhance understanding of antiestrogen resistance.

VI. Cell cycle regulators and hormonal therapy resistance

There has been phenomenal advance in our understanding the role of cell cycle regulators in hormonal therapy resistance. Since tamoxifen mediate the cell cycle arrest by deregulating cell cycle regulators, it is perhaps not surprising that aberrant change in cell cycle machinery often contribute to induction of antiestrogen resistance. We have summarized below the evidence that showed potential role of the regulators of cell cycle machinery in promoting therapy resistance (Figure 1).

A. Cyclin D1

Cyclin D1 was originally cloned as an oncogene (Motokura et al, 1991) and over-expression of Cyclin D1 has been noted in over 50% of human breast tumors of all histological types (Gillett et al, 1994; Kenny et al, 1999). There is surmounting evidence to suggest that altered Cyclin D1 expression promotes antiestrogen resistance (Wilcken et al, 1997; Pacilio et al, 1998; Hui et al, 2002).Cyclin D1 binds ER and increases its transcriptional activity (Neuman et al, 1997). This ability of Cyclin D1 to transactivate ER functions was independent of estrogen stimulation and interestingly, on its CDK4 association as well (Neuman et al, 1997). Over-expression of Cyclin D1 indeed was able to overcome the growth arrest mediated by antiestrogens but Cyclin D1 mutant that is unable to activate CDK4 but having intact ER transactivating potential was not able to promote cell proliferation in the presence of antiestrogens (Bindels et al, 2002). Cyclin D1 is shown to be over-expressed among different Tamoxifen resistant breast cancer cells (Kilker et al, 2004) and Cyclin D1 specific siRNAs restored the sensitivity of these cells to Tamoxifen suggesting therapies targeting Cyclin D1 may have therapeutic effect in hormonal therapy resistant cells (Kilker and Planas-Silva, 2006).

Furthermore, an alternative splice variant of Cyclin D1 named Cyclin D1b is reported to be over expressed in a variety of breast cancers (Betticher et al, 1995; Hosokawa et al, 1997; Wang et al, 2008) and appears to function as a nuclear oncogene (Lu et al, 2003). Cyclin D1b is also known to associate with CDK4 with a weaker kinase activity and over-expression of this alternative transcript Cyclin D1b is shown to overcome the antiestrogen mediated cell cycle arrest (Wang et al, 2008). Unlike Cyclin D1, this effect was independent of ER transactivation as Cyclin D1b lacks nuclear receptor interaction LXXLL motif but retains binding site for CDK4 (Wang et al, 2008).

In addition to activating CDK4, Cyclin D1 is also shown to promote hormonal therapy resistance through other pathways (Ishii et al, 2008). Cyclin D1 is known to mediate STAT3

repression but cells treated with Tamoxifen can potentially reverse this STAT3 repression by the redistribution of Cyclin D1 from STAT3 to ER-complex. This was confirmed by in vivo nude mice assays, where it was shown that growth of Cyclin D1–overexpressing tumors was stimulated by Tamoxifen treatment with concurrent elevation and activation of STAT3 (Ishii et al, 2008). PI3K/AKT or MAPK/ERK1 signaling is also reported to contribute to Cyclin D1 expression and promote to therapy resistance to Tamoxifen underscoring the importance of cross talk between various mitogenic pathways with cell cycle machinery in ultimately achieving antiestrogen resistance (Kilker et al, 2004).

Cyclin D1 negative tumor patients show better relapse free survival upon Tamoxifen-based therapy while Cyclin D1 expression correlated well with poor outcome upon antiestrogen treatment (Rudas et al, 2008). Clinical study with randomized post-menopausal breast cancer patients also show that Cyclin D1 over-expression correlates with poor outcome with Tamoxifen treatment (Stendahl et al, 2004). Similar results were obtained with premenopausal breast cancer patients with Cyclin D1 gene amplification (Jirstrom et al, 2005). Collectively these emerging finding suggest importance of Cyclin D1 as a useful predictive marker in the selection of Tamoxifen-based therapy regime.

B. Cyclin E

Deregulation of Cyclin E in breast cancer model cells has been shown to resist cell cycle arrest mediated by Tamoxifen and this effect in part was attributed to the aberrant activation of E2F-Rb pathway (Dhillon and Mudryj, 2002). Subsequent studies showed that Cyclin E level showed good correlation with poor relapse-free-survival in patients treated with antiestrogens (Span et al, 2003). Interestingly, Cyclin E was not observed to be good prognostic marker for breast cancer as a whole, however, Cyclin E is a good predictor of antiestrogen resistance (Span et al, 2003; Desmedt et al, 2006). Another important feature of Cyclin E is its tumor specific proteolytic cleavage, yielding low molecular weight (LMW) forms of Cyclin E (Porter et al, 2001). Recent reports suggest that these LMW Cyclin E, lacking varying amount of amino terminal region of whole length Cyclin E, plays a vital role in promoting hormone therapy resistance (Akli et al, 2004). The LMW forms of Cyclin E could complex with CDK2 and accounts for increased CDK2 activity as compared to full length Cyclin E (Akli et al, 2004). LMWCyclin E overexpressing MCF-7 cells showed greater resistance toward ICI- 182,780 mediated growth arrest as compared to full length Cyclin E and this resistance was attributed to decreased inhibitory effects of p21 and p27 on these LMW-Cyclin E forms (Akli et al, 2004).

C. Cyclin A

Emerging evidences suggest that Cyclin A also play important role in hormone therapy resistance. Detection of Cyclin A over expression by immuno-histochemical methods correlated well with early breast cancer relapse and can be considered a good marker of Tamoxifen resistance (Michalides et al, 2002). Cyclin A is also known to associate with CDK2 and phosphorylates ER and thereby increase its transactivation potential (Trowbridge et al, 1997). Cyclin A/CDK2 complex phosphorylates Ser-104 and Ser-106 located in the AF-1 domain of ER and increase its transcriptional activity (Rogatsky et al, 1999). The ER transactivation through CDK2-Cyclin A phosphorylation is evident in presence and the absence of estrogen stimulation and also with Tamoxifen treatment (Rogatsky et al, 1999). Large scale randomized trials are however required to understand the potential of CDK2-Cyclin A mediated phosphorylation of ER as a prognostic marker for assessing the efficacy of antiestrogen therapy regime.

D. Cyclin dependent kinases

Most downstream events in antiestrogen resistance signaling pathways, like upregulation of various Cyclins ultimately converge upon modulation of Cyclin Dependent Kinases; the most conspicuous of which is the activation of Cyclin Dependent Kinase 2 (CDK2) (Dhillon and Mudryj, 2002; Akli et al, 2004). Apart from CDK2, CDK10 has been recently implicated in hormone resistance. CDK10 is a newly reported player in mediating antiestrogen therapy resistance, identified by functional genomics approach (siRNA screen) (Iorns et al, 2008; Swanton and Downward, 2008). An unbiased loss of function SiRNA screen performed by Iorns et al, identified modulators of Tamoxifen sensitivity and found that RNAi mediated downregulation of CDK10 increases ETS2-driven transcription of c-RAF, resulting in MAPK pathway activation and independence from ER pathway. Loss of CDK10 in ER positive breast cancer was shown to be associated with relapse of cancer after anti-hormone therapy. CDK10 is cdc2 related kinase found to play important role in G2-M progression. While no Cyclins have been identified to associate with CDK10, it is known that ETS2 is interacting partner of CDK10 (Kasten and Giordano, 2001). This low amount of CDK10 in antiestrogen resistant cells were attributed to the methylation of CDK10 promoter in vivo, underscoring the importance of epigenetic changes accompanying the hormone resistance phenotype (Iorns et al, 2008).

E. CDK inhibitors

Down regulation of p21 has been implicated with Tamoxifen resistant phenotype. Somatic deletion of p21 gene in human breast cancer cells demonstrated that these cells were resistant to Tamoxifen mediated growth arrest (Abukhdeir et al, 2008). The mechanism behind this effect was attributed to increased ER phosphorylation at serine 118 by CDK complex upon p21 decrease. Role of ER phosphorylation as an effector of Tamoxifen resistance was elucidated by transfecting p21 null-MCF10A cells with ER cDNA constructs with Serine118 mutated to alanine. These transfected cells became responsive to Tamoxifen, proving that ER activation is the downstream element in p21 mediated Tamoxifen growth resistant phenotype (Abukhdeir et al, 2008). Antiestrogen resistance could be abolished by treating cells with antisense p21 or p27 oligonucleotides, leading to activation of Cyclin Dependent Kinase 2 (Cariou et al, 2000).

Among various molecular pathways implicated in down regulating CDK inhibitors, MAPK/MEK activation is notable (Donovan et al, 2001). MEK inhibitor, U0126 was used to inhibit MEK pathway and re-sensitized to growth arrest by antiestrogen in LY-2 model cells of antiestrogen resistance. Different phospho-isoforms of p27 were detected in these antiestrogen resistant model cells that may contribute toward generating resistance phenotype (Donovan et al, 2001). Detailed studies are however warranted to delineate and correlate specific sites of phosphorylation on p27 with clinical outcome with antiestrogen therapy.

Localization of CDK inhibitors has also been implicated in the development of antiestrogen resistance. Studies have shown that heregulin β1 over-expression that activates PI3K and MAPK pathway, also promotes p21 localization into cytoplasm (Perez-Tenorio et al, 2006). Tumors with increased cytoplasmic localization of p21 respond poorly with Tamoxifen treatment (Perez-Tenorio et al, 2006). In premenopausal women with early breast cancer, an increase in p27/KIP1 expression was able to predict better relapse free survival upon Tamoxifen combination treatment (Pohl et al, 2003). This trial included 512 randomized patients wherein multivariate analysis revealed decreased p27 expression to be correlated with poor outcome upon combination endocrine therapy. A recent study indicated that p27kip1 is another important target of miR-221 that promotes mediate resistance to hormonal therapy (Miller et al, 2008).

F. Retinoblastoma and E2Fs

Rb-E2F pathway plays a fundamental role in cell proliferation and deregulation is frequently observed in breast cancer. siRNA mediated Rb ablation is able to overcome the growth arrest by antiestrogen treatment and using in vivo xenograft model, Rb deficient tumors were shown to retain the ability to grow in spite of Tamoxifen treatment (Bosco et al, 2007). Furthermore, the same study included analysis of 60 human breast cancer patients treated with Tamoxifen to generate a Rb gene expression signature (Bosco et al, 2007). Another study found that expression of viral T-antigens in breast cancer cells (MCF7) that promote inactivation of endogenous Rb, elicited antiestrogen resistance (Varma and Conrad, 2000). P53 binding ability of T-antigen was however shown not required for this phenotype. In continuation of this work, Conrad and colleagues elucidate the molecular mechanism behind Rb's role in promoting antiestrogen resistance (Varma et al, 2007). Inducible pyLT cell lines were utilized to demonstrate that functional inactivation of pRb can lead to CDK2/Cyclin A activation and reversal of antiestrogen mediated cell cycle arrest. The new hypothesis put forward was that ER^+ Rb^- tumors showing increased CDK2 activity and resulting hormone therapy resistance can be targeted by agents blocking CDK2. Currently many such CDK2 targeting drugs (although not very specific ones) are available in clinical trials and need to be evaluated in the context.

G. c-Myc

c-Myc is a well known cell cycle regulator and oncogene frequently up regulated in breast cancer. It is also one of the earliest estrogen responsive gene, showing a noticeable increase in protein level within 15 min of estrogen treatment (Dubik et al, 1987). C-myc expression when induced in MCF-7 using Tet-on expression system could potentially abrogate antiestrogen mediated growth arrest (Venditti et al, 2002). Similar results were obtained in a different study, wherein over expression of c-myc down regulated p21 expression and mediated antiestrogen resistance(Mukherjee and Conrad, 2005). C-myc expression can rescue the G1 arrest mediated by Tamoxifen by activating CDK2/Cyclin E complex and further phosphorylation of p130 (Prall et al, 1998a). Involvement of c-myc in regulating p21 expression levels and contributing to emergence of antiestrogen resistance is also reported (Mukherjee and Conrad, 2005). p21 levels in antiestrogen resistant cells increased when treated with cmyc siRNAs, suggesting important role of c-myc in downregulating p21 levels and promoting hormonal therapy resistance (Mukherjee and Conrad, 2005).

From the above mentioned studies, we present an interesting case that cell cycle regulators play a vital role in the emergence of hormone therapy resistance. However, the studies performed so far do not provide clear distinction of using cell cycle regulators as prognostic markers of therapy resistance or therapeutic targets against resistant cells. The key challenge in this area is to unequivocally show that targeting cell cycle regulators can potentially reverse the hormone therapy resistance but the side effects may limit their use as evidenced by recent studies. Targeting kinase functions of CDK2 is a feasible option and currently there are some ongoing clinical studies employing pan CDK inhibitors against non-small cell lung cancer like r-roscovitine (Seliciclib or CYC202). Our lab has recently tested the efficacy of combinatorial usage of r-roscovitine with Tamoxifen against various hormone resistant cell lines like MCF-tam (resistant to Tamoxifen), MCF-7-Her2 (overexpressing Her2), and MCF7-PELP1 (overexpressing PELP1) and found encouraging results in sensitizing these cells to Tamoxifen treatment (Chandrasekharan Nair et al, 2008b). Another possibility to overcome toxic side effects would be to explore nanotechnology methods that allow cancer cell specific delivery of the cell cycle inhibitors reducing toxic side effects. Such combinatorial use of cell cycle inhibitors along with classical hormone therapy represents a novel therapeutic modality to circumvent the problem of toxicity and to enhance therapeutic success.

VII. Conclusions and Future Direction

The estrogen receptor (ER) plays a central role in the progression of breast cancer and endocrine therapy is widely used to target ER+ve breast cancer. Despite the positive effects, de novo and/or acquired resistance to endocrine therapies frequently occur. Most downstream events in the resistance signaling pathways appear to converge upon modulation of cell cycle regulatory proteins. Evolving evidence suggests that cell cycle machinery cross talk with estrogen receptors, ER-coregulators and growth factor receptors and such interaction play a role in the development of therapy resistance. It is therefore of great interest to understand how cell cycle machinery promotes therapy resistance. Since cell cycle dependent kinases cross talk with nuclear receptors and coregulators to regulate various downstream genes, we believe that associated nucleosomal histone modification via methylation and acetylation could play a vital role in therapy resistance. There is scarcity of studies toward understanding cell cycle dependent histone/DNA modifications and epigenetic changes that contribute toward acquiring hormone therapy resistance. Similarly, identifying newer substrates of CDKs and investigating their potential role in therapy resistance will provide novel insights into the mechanistic basis of Tamoxifen resistance. Combinatorial therapy using CDK inhibitors along with conventional hormone therapy is a feasible option to resensitize the cells against hormone therapy resistance. Future microRNA profiling studies is expected to identify new miRNAs that regulate cell cycle machinery, thus increase the repertoire of novel targets for interfering hormone therapy resistance. Future studies are also warranted in safe delivery of cell cycle inhibitors utilizing new technologies (such as targeted nano particles) to enable to use these new drugs with less side effects. We strongly believe that further understanding of the molecular mechanisms by which tumor cells use cell cycle machinery to acquire therapy resistance will provide novel therapeutic targets, which in conjunction with conventional hormone therapy will be useful in targeting therapy resistant tumors.

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Biography

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Abbreviations

CDK	cyclin-dependent kinase
EGF	epidermal growth factor
ER	estrogen receptor
MAPK	mitogen-activat ed protein kinase
MNAR	modulator of nongenomic actions of the ER
NR	nuclear receptor
PI3K	phosphatidylinositol-3 kinase
PELP	proline-, glutamic acid-, and leucine-rich protein
PKA	protein kinase A
pRb	retinoblastoma protein

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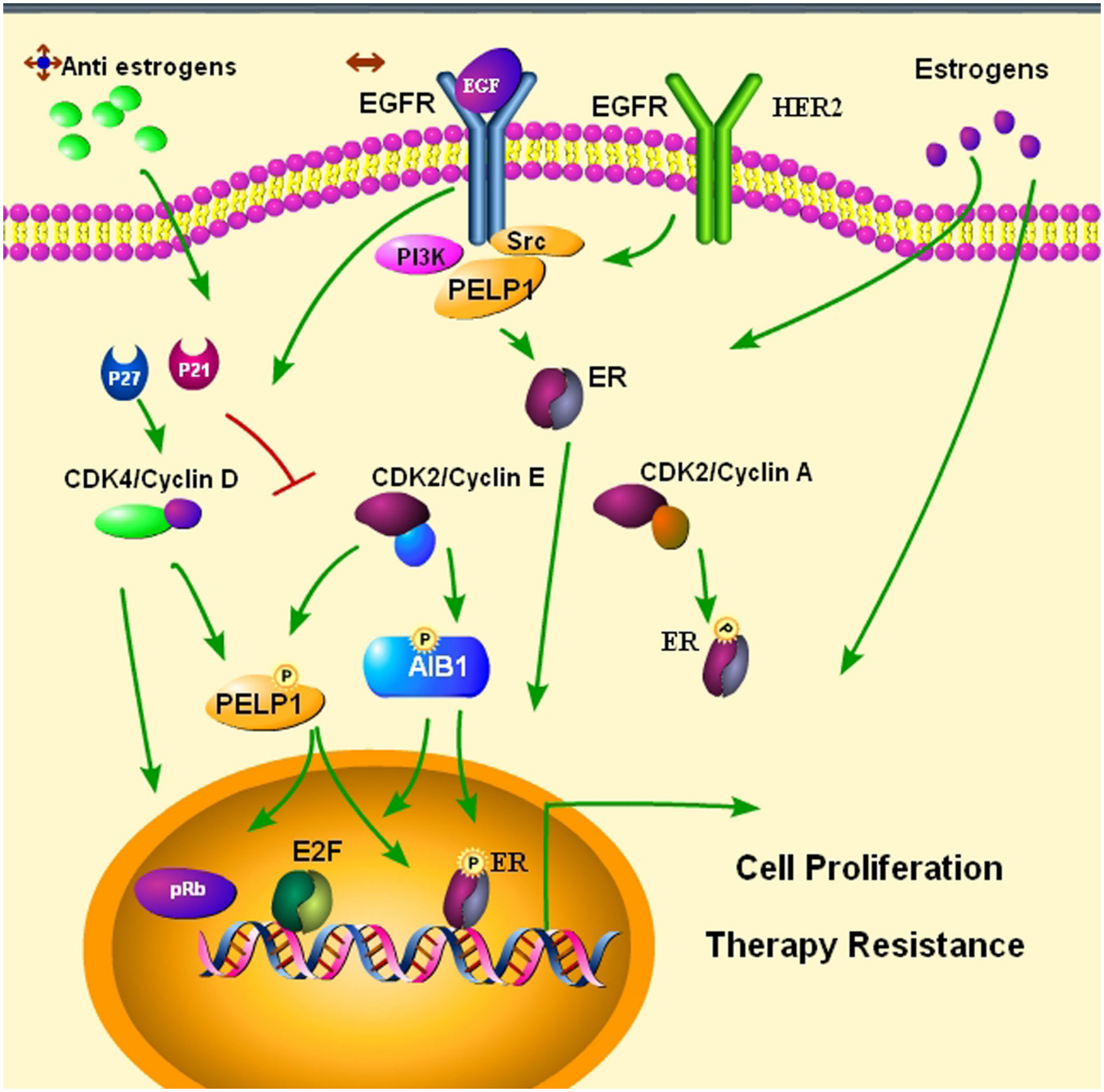

Figure 1.
Schematic representation of the current understanding of regulation of hormonal therapy resistance by cell cycle machinery. Convergence of growth factors and estrogen receptor signaling pathways in therapy resistant cells suggest that deregulation cell cycle regulators are likely to contribute to the development of therapy resistance in breast cancer cells.