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Mechanisms of resistance in estrogen receptor positive breast cancer: overcoming resistance to tamoxifen/aromatase inhibitors

Jamie N Mills[1], Alex C Rutkovsky[2] and Antonio Giordano[1]

Several mechanisms of resistance have been identified, underscoring the complex nature of estrogen receptor (ER) signaling and the many connections between this pathway and other essential signaling pathways in breast cancer cells. Many therapeutic targets of cell signaling and cell cycle pathways have met success with endocrine therapy and remain an ongoing area of investigation. This review focuses on two major pathways that have recently emerged as important opportunities for therapeutic intervention in endocrine resistant breast tumors: PI3K/AKT/mTOR cell signaling and cyclinD1/cyclin-dependent kinase 4/6 cell cycle pathways. Additionally, we highlight individual and combination strategies in current clinical trials that target these pathways and others under investigation for the treatment of ER positive breast cancer.

Addresses
[1] Medical University of South Carolina, Department of Medicine, Division of Hematology and Oncology, 39 Sabin St. MSC 635, Charleston, SC 29425, USA
[2] Medical University of South Carolina, Department of Pathology and Laboratory Medicine, 39 Sabin St, Charleston, SC 29425, USA

Corresponding author: Giordano, Antonio (giordana@musc.edu)

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Introduction

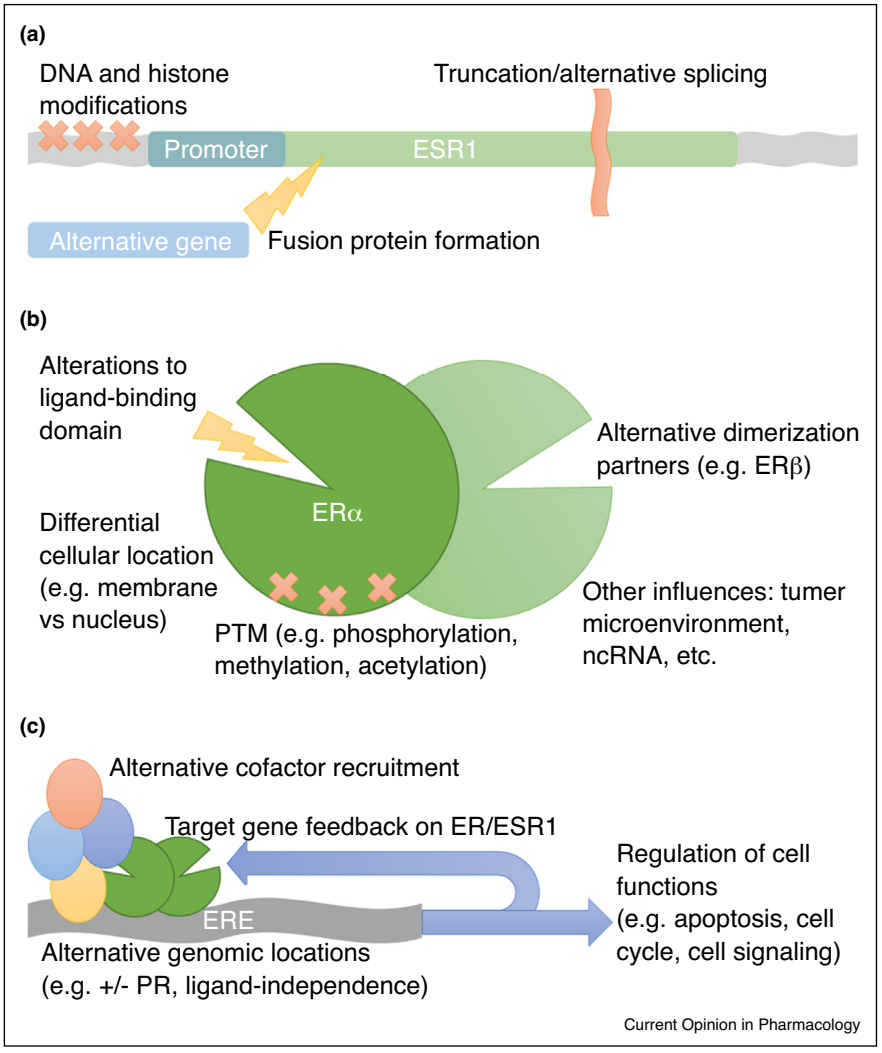
Endocrine therapy has dramatically improved survival in breast cancer patients over the past several decades, however resistance to these therapies remains one of the major causes of breast cancer mortality today [1]. Late recurrence and death from estrogen receptor positive (ER+) breast cancer can occur for at least 20 years after the original diagnosis even after 5 years of adjuvant endocrine therapy [2••]. Identifying mechanisms of resistance and strategies by which to combat these mechanisms is paramount to patient survival.

Several mechanisms of resistance to endocrine therapies have been identified, many centered around the structure, activation, and complex functions of ER, as well as cross-talk between the estrogen signaling network and other cellular pathways. The major form of ER in breast cancer is ERα, encoded by *ESR1*, and the major function of ER is as a transcription factor controlling genes associated with cell survival and proliferation [3]. ER function is influenced by circulating estrogens and related molecules, giving ER-targeted therapies their success. Post-translational modifications also influence function, localization, and interaction with other regulators. In addition to ERα, there also exists transcription factor ERβ, encoded by *ESR2*, as well as alternatively spliced and truncated variants of *ESR1*/ERα [4]. The biology of ER is complex and how breast tumors can gain ER function then maintain this despite ER inhibition is not well understood. Thus, the mechanism of action of various endocrine therapies is complicated, varies, and remains an active area of investigation.

Known mechanisms of resistance to hormone therapies are complex and include epigenetic regulation of *ESR1* expression [5,6], *ESR1* mutations [7–12], alternative splicing events [3], *ESR1* truncation and fusion events [13], post-translational modifications [14,15], alterations in the hormone binding domain [7,16], alternative recruitment sites within the genome [17], differential recruitment of coregulators [18], feedback loops by ER target genes on expression/activity of ER [19•], downstream actions of ER target genes on growth factor pathways and other signaling networks [20,21••], influences of the tumor microenvironment [22], and many others (Figure 1). The details of these mechanisms are beyond the scope of this review but have been thoroughly described by others [23,24]. The complexity of ER function in tumor cells underscores the heterogeneity of breast cancer biology and demonstrates a necessity for continued basic research and clinical demonstration to effectively target the pathways essential to tumor cell survival.

Much literature exists detailing the mechanisms of resistance. This review highlights two major pathways that have recently emerged as important opportunities for therapeutic intervention in endocrine resistant breast tumors: the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) cell signaling pathway and the cyclin D1/cyclin-dependent kinase

Figure 1



Diagrammatic representation of known mechanisms of resistance to endocrine therapy. Mechanisms of resistance to endocrine therapy are known to occur at several levels. **(a)** At the level of *ESR1*, modifications include epigenetic modification of histone proteins and DNA to alter *ESR1* transcription, truncation, alternative splicing events, and fusion events with alternative DNA sequences to produce variations of the ER protein. **(b)** The events outlined above can result in alterations to the ligand-binding domain and differential cellular localization of the receptor, altering function. Additionally, homo-dimerization or heterodimerization can occur as well as various post-translational modifications (PTM), dependent upon alterations to the proteome of tumor cells and possibly other factors, such as tumor microenvironment and non-coding RNA molecules, resulting in modifications to ER function and target gene selection. **(c)** Activated ER binds estrogen response elements (ERE) to dictate target genes for transcriptional activation, however alternate recruitment sites are well document and largely dependent upon recruitment of specific cofactors and tethering proteins, such as progesterone receptor (PR). Differential recruitment of cofactors can also lead to repression of transcription rather than activation, modifying the downstream outcome of ER activation. Target genes can create feedback loops to modify ESR1/ER expression and behavior, including cross-talk with other signaling pathways in the cell. Finally, all of the events outlined above converge on regulation of essential cellular functions, therefore identifying the many opportunities for development of endocrine therapy resistance has profound effects on clinical control of tumorigenesis.

(CDK)4/6 cell cycle pathway. Inhibitors to these pathways have been developed, assessed in preclinical studies, and investigated in multiple clinical trials, each with marked benefit toward improving survival but also with specific challenges and limitations discussed below.

PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR pathway is essential for cell growth and survival, protein synthesis, and glucose metabolism. It is dysregulated in many tumor types, prompting investigation of inhibition of this pathway in many cancer models, including the triple negative

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