Consequences of the Convergence of Multiple Alternate Pathways on the Estrogen Receptor in the Treatment of Metastatic Breast Cancer

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Abstract

Endocrine therapy is the usual first-line therapy for patients with hormone receptor-positive metastatic breast cancer. However, resistance to hormone therapies frequently occurs during the course of treatment. Growing understanding of the signal cascade of estrogen receptors and the signaling pathways that interact with estrogen receptors has revealed the complex role of these receptors in cell growth and proliferation, and on the mechanism in development of resistance. These insights have led to the development of targeted therapies that may prove to be effective options for the treatment of breast cancer and may overcome hormone therapy resistance. This article reviews current understanding of the cellular receptor signaling pathways that interact with estrogen receptors. It also reviews data from recent ongoing clinical trials that examine the effects of targeted therapies, which might interfere with estrogen receptor pathways and might reduce or reverse resistance to traditional, sequential, single-agent endocrine therapy.

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Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer-related death among women in the United States according to 2016 estimates.[1] Approximately 6% of cases are advanced or metastatic breast cancer (MBC) at diagnosis, and, for those diagnosed at early stages, recurrence to distant sites occurs in 20% to 30%.[2-4] Of patients with breast cancer, approximately 75% have hormone receptor-positive (HR^+) tumors.[5]

Therapies for MBC are aimed at palliation of symptoms with improvement or conservation of quality of life and, potentially, prolongation of survival; unfortunately, prolonged survival is observed in only a small percentage of patients.[6,7] Both hormone receptor status (eg, estrogen receptor [ER] and progesterone receptor [PgR]) and human epidermal growth factor 2 (HER2) status are important predictive markers for treatment efficacy.[7,8] Patients with HR^+ MBC are candidates for initial endocrine therapy (ET).[9] In premenopausal women with MBC, various endocrine treatments are employed, including ovarian suppression or oophorectomy, selective ER modulators such as tamoxifen, aromatase inhibitors (AIs) in conjunction with ovarian suppression, and the selective ER downregulator, fulvestrant, all of which have different mechanisms of action. These mechanisms have been reviewed extensively, demonstrating the diversity of approaches that ultimately antagonize the growth-promoting effects of estrogen on breast cancer cells. These mechanistic differences are also linked to dissimilarities in resistance mechanisms and thus influence treatment selection, particularly in the context of sequencing and the use of combination regimens.[10-17] In the setting of postmenopausal HR^+ MBC, ET has a better tolerability profile and longer time to progression (TTP) than chemotherapy.[18,19] In clinical trials of AIs employed for first- or second-line treatment of postmenopausal patients with MBC, AIs have greater efficacy than either tamoxifen or megestrol acetate.[20]

Resistance to ET in HR^+ MBC is common, and given sufficient time, most patients are faced with disease progression.[21,22] The mechanisms underlying disease progression and the development of resistance to endocrine treatment are complex and not fully understood. Nevertheless, over the past several years, insights into several pathways of resistance have grown and have led to increased understanding of the clinical value of sequential lines of therapy and

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co-targeting strategies. While receiving ET, up to 20% of patients experience a loss of ERs with concomitant loss of response to estrogen.[23] Amplified expression of HER2 may reduce ER levels and serve as an alternative pathway for tumor cell survival.[23,24] Cellular signaling of growth-factor receptors interacts with ER nuclear and nonnuclear pathways and may contribute to resistance through posttranslational modifications of ER and/or coregulators.[25-27] Mutations and/or aberrant forms of ER and their coregulators may also be a primary cause or contribute to the development of resistance to ET.[21,22,25]

The aim of this review is to describe emerging information on cellular pathways that interact with ER and impact cell proliferation and development of resistance to ET. We will discuss the biologic rationale for combining ET with agents that target these pathways and review the current status of clinical trials that are investigating the effects of combination treatments (Table 1). We also illustrate the cellular receptors and intracellular signaling pathways that interact with ER (Figure 1).

Estrogen-Receptor Signaling

ER functions through 2 separate but interrelated pathways: nuclear (genomic) and nonnuclear (nongenomic) pathways. The nuclear pathway mediates the effects of ER on genomic activity, thereby altering expression of many genes involved in physiologic cell function and in abnormal cell proliferation, resulting in tumorigenesis.[28] The ER nuclear pathway is activated by estrogen binding, receptor dimerization and translocation to the nucleus, interaction with coregulator proteins (both coactivators and corepressors), and through estrogen response elements modulation of gene transcription.[29] ER coregulators have been implicated in the pathogenesis of breast cancer. Most notable is amplified in breast cancer 1, which, as its name implies, is overexpressed in breast cancers. Moreover, amplified in breast cancer 1 overexpression may play a role in resistance to ET.[30] The nonnuclear pathway of ER function (originating in cellular cytoplasm) is mediated by estrogen-bound ER acting outside the cell nucleus through interaction with multiple cellular signaling pathways, tyrosine kinases, and membrane-bound growth factor-receptor pathways, including HER2, insulin-like growth factor-1 receptor (IGF1R), and fibroblast growth factor receptor (FGFR).[31,32] Multiple levels of interaction or crosstalk between ER and growth factor and tyrosine kinase pathways may contribute to ER actions. These interactions include modulation of ER activity, upregulation of competing pathways and development of resistance to ET, and alternative or escape pathways for cellular proliferation and tumorigenesis.

Estrogen can modify the activity of growth factor pathways by increasing levels of growth factors such as transforming growth factor-α and IGF1R and, alternatively, by altering the expression of epidermal growth factor receptors (EGFR).[27,32,33] Conversely, activation of growth factor-receptor signaling pathways may downregulate expression of ER, resulting in decreased estrogen effects.[34,35] This crosstalk, which can up- or downregulate competing pathways between ER and growth factor-receptor signaling, is recognized as a major mechanism of ET resistance, and implies that ER-positive (ER^+)/HER2-positive ($HER2^+$) breast cancer should be treated with a combination of ET and HER2 inhibitors or antagonists.[36]

In addition to ER and HER2 status, assessment of PgR status is also typically used to characterize MBC and shape treatment decisions. In normal breast tissue, ER and PgR appear to be expressed in different epithelial populations and regulate distinct pathways; estrogen is involved in extracellular signaling and progesterone is associated with cell growth.[8] This independent activity is altered in breast cancer cells where ER and PgR expression become correlated and converge on pathways that promote tumor growth and metastasis, and both PgR and ER become regulated by estrogen.[8] Although PgR in ER^+ patients with MBC has been used as a predictor of response to ET, it is controversial and not as well-accepted as the role of ER.[37]

Data indicate that ER^+/PgR-negative (PgR^-) breast tumors are not as responsive to selective ER modulator therapy as ER^+/PgR-positive (PgR^+) tumors. One proposed mechanism for this antiestrogen resistance involves aberrant growth factor signaling (a marker for loss of PgR), but other unknown contributory mechanisms are also likely to play a role. Further research is needed to identify such mechanisms and thereby refine therapeutic strategies.[38]

In a recent study of MBC, PgR was found to associate with ER in the presence of agonist ligands, and the ER-PgR ligand-activated complex acted to modify chromatin-binding events and gene transcription, leading to an antitumorigenic effect.[39] Stimulation with progesterone in an estrogen-rich context induced interactions between known ER cofactors and PgR, but did not alter the association of those cofactors with ER, yielding an ER-PgR binding complex that promoted cell death, apoptosis, and differentiation pathways.[39] This finding, coupled with the association between PgR gene (*PgR*) copy number loss and poorer clinical outcome possibly owing to a reduction in ER-PgR binding complex formation, suggests a more intricate relationship beyond PgR as a simple marker for ER pathway function in the MBC setting.[39] Although this contrasts with hormone replacement studies in which synthetic progesterone (medroxyprogesterone) was associated with an increased breast cancer risk, it was found that natural progesterone did not have the same effect, which suggests different mechanisms of action for synthetic agonists.[40,41] Interestingly, semi-synthetic progestin, megestrol acetate, provided clinical benefit to ER^+ patients with MBC who experienced disease progression after estrogen suppression with a nonsteroidal AI.[42] Molecular subtyping of tumors may offer additional insight into treatment of early-stage and locally advanced breast cancer. In a study that evaluated molecular subtype and diagnostic classification of the 154 patients classified as Luminal type B (high risk), a group that is typically sensitive to chemotherapy, 145 were ER^+ and 99 were PgR^+ tumors.[43] Among the Luminal B patients, pathologic complete response was 85%, suggesting a possible association between ER/PgR status and the benefit of chemotherapy.[43] Clearly the complex relationship between ER and PgR depends on many factors, including genomic alteration, interaction of cofactors at a transcriptional level, relative levels of estrogen and progesterone in the tumor cell environment, and possibly variations in conformational changes related to the form of the agonist.

Growth-Factor Receptors

Growth-factor receptors, particularly receptor tyrosine kinases, play an integral role in growth promotion, cellular proliferation, and tumorigenesis. Growth-factor pathways may act as ER-independent drivers of tumor growth and survival, contributing to resistance to