Endocrine resistance in breast cancer: what really matters?

In 1896, George Beatson [1] showed that oophorectomy resulted in tumor remission in a proportion of women with metastatic breast cancer. With over two-thirds of breast cancers demonstrating high expression of estrogen receptor (ER), known to contribute to tumor growth and progression, Beatson’s findings revolutionized the management of this disease, paving the way to the discovery of anti-hormonal agents such as tamoxifen, known to selectively modulate the ER. Most recently, aromatase inhibitors that function by preventing extragonadal peripheral estrogen synthesis have also demonstrated clinical activity in various settings. In fact, both classes of agents have been shown in large randomized clinical trials to improve relapse-free survival and to reduce incidence of contralateral breast cancers in women with early-stage breast cancer and overall survival in patients with advanced disease [2–4].

Despite these tremendous advances in the therapeutic management of women with hormone-sensitive breast cancers, a significant proportion will experience disease progression secondary to either an inherently intrinsic or acquired resistance to endocrine agents. As a result researchers have focused both on clearly defining ER biology and subsequently discerning the mechanisms involved in developing endocrine resistance. Like other steroid hormones, the classic pathway of estrogen receptor signal transduction involves estrogen binding to the intracellular portion of the ER, triggering a series of events that lead to altered gene transcription, which results in the production of proteins that drive cell division and promotes angiogenesis and cell survival, resulting in breast cancer growth and progression [5]. However, further investigations have elucidated other mechanisms of ER activation such as the binding of estrogen ligand to the cell surface portion of the ER [6]. In addition, in the absence of an estrogen ligand the receptor can be activated via growth factor receptor-driven kinase pathways [5] followed by the activation of key downstream signaling kinases such as the p42/44 mitogen-activated protein kinase (MAPK) and Akt, resulting in subsequent cell proliferation and survival. It is this molecular cross-talk between ER and growth factor signaling pathways that is one of the most critical contributors to the development of resistance to endocrine therapy.

In an attempt to overcome endocrine resistance, clinical studies have focused on developing novel agents that can reverse resistance at the ER level or target downstream estrogen signaling elements. Several studies have demonstrated that overactivity of the Akt pathway is involved in endocrine resistance. The principal enzyme involved in this pathway, phosphatidylinositol-3-kinase (PI3K), cannot be directly inhibited, however; studies have focused on inhibiting its key target protein rapamycin (mTOR). In this issue of the journal, Beeram and colleagues [7] report on the use of an mTOR kinase inhibitor in reversing endocrine resistance in a breast cancer model in vivo. The authors generated an MCF-7 subline with constitutively activated Akt (myristolated or myrAkt1MCF-7) that demonstrated resistance both to the aromatase inhibitor letrozole and to fulvestrant. The authors successfully demonstrated that co-treatment with the mTOR inhibitor RAD-001 restored sensitivity of the breast cancer cell lines to both endocrine agents. Similarly, the mTOR inhibitor temsirolimus (CCI-779) has been shown in in-vivo models to restore sensitivity of cancer cells to tamoxifen [8]. This elegant work provides the support for prospectively designed clinical trials that have significant chances to improve the outcome of patients with hormone receptor (HR)-positive disease. Interestingly, data from a recently completed phase II trial showed efficacy when temsirolimus was combined with letrozole [9] and currently a phase II trial is assessing the combination of RAD-001 with letrozole in the neoadjuvant setting. If this combination proves to be effective it will represent one of only a few examples of rationally designed and clinically successful therapy in HR-positive disease. In fact, the complexity of the endocrine-related pathway in cancer cells means that attempts to propose new agents or to develop effective, rationally designed combinations have not always been successful.

The realization that, despite the expression of ER, currently the best predictor of response to endocrine therapy, a proportion of women treated with tamoxifen in either the adjuvant or metastatic setting would eventually progress, led to the development of other endocrine agents with different mechanisms of action. Aromatase inhibitors have gained widespread acceptance, rapidly replacing tamoxifen as first-line treatment in both the adjuvant and metastatic setting. Fulvestrant, an agent that binds, blocks and degrades ER, has been shown in preclinical and clinical studies to retard growth of tamoxifen-resistant breast tumors [10, 11]. Despite these therapeutic advances our ability to take full advantage of ER inhibition is limited by the development of resistance, which ultimately develops to all forms of endocrine therapy.

Continuous activation of growth factor signaling pathways, the major mechanism implicated in the development of endocrine resistance in breast cancer cells, is thought to occur as a result of either upregulation of growth factor receptors or excessive supply of their ligands, which ultimately leads to continuous activation of growth factor receptors and their
The correct combined approaches to affect the more limited estrogen expression but with replicative properties, regarding the existence of a ‘tumorigenic stem cell’ with possible that heterogeneity of the disease, particularly may be a somewhat simplistic approach. Furthermore, it is hypothesize that the problem may lie in the use of single agents without an actual improvement in response rate [18]. Similarly, tipifarnib plus letrozole compared to letrozole alone showed assessing the combination of the farnesyl transferase inhibitor the combination arm [17]. A randomized phase II trial assessing the combination of the farnesyl transferase inhibitor tipifarnib plus letrozole compared to letrozole alone showed a longer duration of an objective response for the combination, without an actual improvement in response rate [18]. Similarly, results of a trial evaluating the combination of anastrozole with the tyrosine kinase inhibitor gefitinib [19] have not been encouraging. Based on those disappointing results, one can hypothesize that the problem may lie in the use of single agents inhibiting individual signal transduction pathways. Therefore, it has been proposed that another, possibly more efficacious approach would be to completely inhibit estrogenic signals and their downstream signaling pathways by using multiple signal transduction inhibitors. Although preclinical models have produced results that have favored this approach [20], in the clinical setting the combination of anastrozole and tamoxifen did not improve results [21]. Additionally, approaches looking at restoring baseline estrogen sensitivity by manipulating the hormonal environment have also been assessed, with encouraging results [22].

When taken together all the preclinical and clinical evidence indicates that the therapeutic management of women with hormone-sensitive breast cancers using single endocrine agents may be a somewhat simplistic approach. Furthermore, it is possible that the heterogeneity of the disease, particularly regarding the existence of a ‘tumorigenic stem cell’ with limited estrogen expression but with replicative properties, can explain a portion of the estrogen-refractory cases [23, 24]. It is possible that the next step forward would be to identify the correct combined approaches to affect the more differentiated and truly ‘endocrine-sensitive’ cells and the other population of otherwise ‘endocrine-refractory’ cells. This approach could consider including various signal transduction inhibitors in combination with the numerous endocrine agents available, but also novel agents capable of targeting those refractory stem cells. In summary, the complexity of endocrine resistance in breast cancer requires the coordinated efforts of tumor biologists and translational clinical investigators to address ‘what really matters’—the improved outcome of patients—taking into consideration the multiple components of this problem.

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