Estrogen Receptor Mutations in Breast Cancer—New Focus on an Old Target

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Recent studies have provided strong evidence for the emergence of substantial numbers of constitutively active ESR1 mutations in estrogen receptor–positive metastatic breast cancer that are undetected in primary disease. Some of these mutants remain partially sensitive to current anti-estrogen therapies but effective therapeutics targeted at them may require new approaches. Clin Cancer Res; 20(7); 1724–6. ©2014 AACR.

In this issue of Clinical Cancer Research, Jeselsohn and colleagues (1) report an overall 12% frequency of mutations in the coding sequence of ESR1 in metastatic estrogen receptor–positive (ER+) breast cancers but the lack of their detection in primary disease.

About 80% of primary breast cancers express estrogen receptor α (ERα), the product of the ESR1 gene, and are described as ER+. Estrogen is the primary stimulant of the development and continued growth of ER+ tumors: withdrawal of estrogen from primary ER+ breast tumors decreases proliferation in >90%, although this reduction may be modest in some (2). The mainstay of treatment of ER+ breast cancer is endocrine therapy, in the form of drugs that antagonize the ER (e.g., tamoxifen), therapies that result in estrogen deprivation (e.g., aromatase inhibitors), or fulvestrant, a drug that destabilizes and antagonizes the receptor. Most patients receive endocrine therapy for 5 years starting shortly after surgery (adjuvant therapy).

Endocrine therapy for breast cancer has resulted in markedly reduced recurrence and mortality rates; however, a significant proportion of patients relapse with metastatic disease. If the recurrence has not arisen within a few months of starting adjuvant therapy, these patients will be treated with an alternative endocrine treatment (first-line metastatic treatment). Resultant shrinkage or stasis of metastatic lesions is achieved in many patients and those showing a response have a good chance of responding to subsequent lines of endocrine treatments: patients whose cancer has progressed on tamoxifen often respond to fulvestrant or an aromatase inhibitor and vice versa (3). The lack of cross-resistance suggests that the mechanisms by which this occurs may vary depending upon the prior treatment. Eventually, pan-endocrine resistance develops.

Many mechanisms have been elucidated in model systems of resistance to tamoxifen, and more recently to estrogen deprivation and fulvestrant. These include altered expression of growth factor receptors, such as HER2, or aberrant expression of ER coregulators leading to either ER-independent growth or ER-dependent/ligand-independent growth (4). However, there has been limited confirmation of these findings in the clinic. Although some patients with acquired resistance to tamoxifen show loss of ER in metastases, an obvious route to loss of sensitivity, the majority continue to express ER and there is less evidence for ER loss with resistance to aromatase inhibitors (4, 5). Thus, resistance mechanisms remain incompletely explained and there is little biomarker-related guidance of therapy for metastatic disease.

Despite the central role of estrogens in the development of breast cancer, ERα mutations in primary disease have thus far proved rare (Fig. 1). For example, no ESR1 mutations were identified in a study of 390 ERα primary tumors (6). In metastatic disease, the presence of an ESR1 mutation unique to the metastases was first noted 20 years ago (7), but until very recently, surprisingly few further data accumulated. However, three groups have recently reported substantial numbers of ESR1 mutations in metastatic breast cancer (8–10). The current work of Jeselsohn and colleagues (1) is consistent with and extends these reports. They sequenced the coding region of ESR1, and 182 additional cancer-related genes, in 58 treatment-naïve primary and 76 metastatic ERα HER2− breast tumors and set out to describe better the functional relevance of the observed ESR1 mutations. None of the primaries contained detectable ESR1 mutations but 11 (14.5%) of the metastatic samples contained previously reported mutations (8, 9), clustered in the ligand-binding domain (LBD), predominantly at amino acids 537 or 538, as well as a novel 344insC mutation. Notably, a direct correlation was apparent between the number of endocrine treatments and mutation frequency, which was 5/25 (25%) in tumors from patients receiving an average of seven lines of treatment. All of the other 182 cancer-related genes...
sequenced exhibited similar mutation frequencies between the primary and metastasis.

In the largest of the other recent reports, Toy and colleagues (8) found nine LBD mutations in 36 cases enrolled in a metastatic collection program. In the two cases in which they could also test the primary tumor, the mutation was absent. They also found that 5 of 44 cases from the BOLERO-2 clinical trial of letrozole \( / \) everolimus harbored \( \text{ESR1} \) mutations with the frequency enriched in cases with a long duration of endocrine therapy (8). Similarly, Robinson and colleagues (9) and Merenbakh-Lamin and colleagues (10) reported that 6 of 11 and 5 of 13 cases, respectively, of breast cancer metastases contained LBD-localized \( \text{ESR1} \) mutations. In each of these reports, mutations at 537 and 538 were the most frequent, but others at 534 or 536 were also noted. Given the consistent finding of mutations in the LBD of \( \text{ER} \alpha \), elucidation of their functional significance and susceptibility to therapeutic targeting is of paramount importance.

Functional studies by Jeselsohn and colleagues (1) and others (8–12) provide evidence that many of the mutants are strong promoters of ER signaling and, importantly, are constitutively active in the absence of estradiol and therefore likely to elicit resistance to estrogen deprivation strategies. They stimulate increased expression of ER-regulated genes, and increase proliferation and migration \( \text{in vitro} \) compared with wild-type \( \text{ESR1} \). The \( \text{ESR1} \) mutants have also generally been found to confer reduced sensitivity to anti-estrogens compared with wild-type \( \text{ESR1} \). Although signaling is reduced by 4-hydroxytamoxifen and fulvestrant, much higher doses are required to reach a similar level of inhibition observed in the wild type (1, 8–12). These \( \text{in vitro} \) findings are supported by molecular modeling that indicate
that the mutants favor the agonist conformation and mediate their effects through influence of coactivator or corepressor binding (8). It is also notable that in ER-Y537N-mutant cells, fulvestrant much more modest ER degradation compared with wild type (1) and therefore reduced ability to inhibit ligand-independent activity of ER. This relative resistance to degradation seems less apparent with ER-Y537S (11).

Interestingly, while it has been difficult to sustain patient-derived xenografts (PDX) from ER+ breast cancer tissues, aberrations in the ESR1 gene were found in 4 of 5 luminal breast cancer metastases. This included one case with ER-Y537S that was found in a further PDX in which the ER status was not available. A fusion gene (ESR1/YAP1) was also discovered in an ER+ PDX that, like the point mutations, induced estradiol-independent growth. It is plausible that the drive provided by certain constitutively active ESR1 alterations is a major advantage in promoting survival and growth in the low-estrogen environment of the PDX system. These PDXs are likely to be particularly valuable in elucidation of the best therapeutic approaches for tumors with specific ESR1 alterations.

In summary, there is now substantial evidence for the emergence of functionally aberrant ESR1 mutations, particularly in the LBD, in metastatic ER+ breast cancer, which are undetectable in primary tumors. Correlative evidence is consistent with this emergence being due to selective pressure of multiple endocrine therapies. The genomic instability associated with advanced disease may contribute to the prevalence of the mutations, for example through self-perpetuating defects in DNA-repair mechanisms. ESR1 mutations might also promote the success of the metastatic process and be apparently enriched as a result, although this hypothesis requires their presence below the detection limits of the high-depth sequencing conducted to date. To confirm the role of the mutations as resistance mechanisms and their potential as targets for new therapies requires careful prospective study of metastatic disease aligned with comprehensive genomic and functional analyses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: C.V. Segal, M. Dowsett
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