Ablation of systemic estrogen production in a breast cancer patient is considered to be one of the first targeted therapies employed for the treatment of a human malignancy. Since Beatson’s (1) initial clinical description of a breast tumor response to oophorectomy in 1896, many approaches that disrupt the estrogen–estrogen receptor (ER) signaling pathway have been developed and used widely in clinical practice. These range from surgical approaches such as oophorectomy, adrenalectomy, and hypophysectomy to the use of highly refined antagonists of the ER and agents that directly target estrogen production, such as aromatase inhibitors. The routine measurement of ER in breast cancers and the relative restriction of hormonally directed therapies to patients with ER-positive tumors has led to a more rational and appropriate use of these modalities.

These antihormone interventions have had a clinically significant benefit for many patients with advanced disease. Moreover, these approaches have made a substantial impact on clinical outcomes when used in the adjuvant setting, and some agents (like tamoxifen) have also shown efficacy when used as part of prevention strategies. Unfortunately, for many patients, the initial clinical benefits are followed by the development of recurrent disease that either does not respond or responds minimally to further manipulation of the estrogen signaling pathway. Other patients display de novo rather than acquired resistance, despite having ER-positive tumors. This antihormone resistance or hormone-independent phenotype has been the subject of intense study for more than 40 years, and many hypotheses have been put forward to address its molecular basis. Proposed resistance mechanisms range from alterations (i.e., mutation, overexpression, or gene amplification) in the ER target to mechanisms that inactivate the therapeutic drug itself. Although these studies have provided some interesting insights, none of these hypotheses has explained the molecular basis of resistance in most nonresponsive human breast cancers.

Since the identification of the progesterone receptor (PR) as a downstream target of the liganded ER and the subsequent development of techniques to routinely measure PR levels in breast cancer specimens, data have accumulated indicating that ER-positive/PR-negative (ER+/PR−) tumors are less responsive than ER+/PR+ tumors to therapies directed at the ER. This finding led many to postulate that a major mechanism of resistance to estrogen/ER-directed treatments was an altered or “nonfunctioning” ER signaling pathway and that a lack of PR expression was a “nonresponsive” human breast cancers. ER+/PR− breast cancers are clinically and biologically distinct tumor subgroups. This study has the advantage of long-term clinical follow-up/outcome data for most of the patients. For a subset of the tumors, the authors have also obtained data on HER-1 and HER-2 levels, allowing them to perform a comprehensive analysis of the potential interplay between ER, PR, HER-1, and HER-2, as well as the respective impact of these various markers on clinical outcome. This is the largest study of its kind published to date, and what shortcomings it has in lack of prospective design and balanced randomization, as well as the vagaries introduced by unplanned subset analysis, are compensated for, in large part, by sheer numbers. This is a valuable correlative study that has provided important insight into the potential mechanisms for resistance to hormonal therapy that has been observed in some human breast cancers. Specifically, the authors hypothesize that PR negativity in ER-positive breast cancer is a surrogate marker of aberrant growth factor receptor signaling that may contribute to tamoxifen resistance. Furthermore, they propose that PR negativity reflects a direct interaction between PR expression and elevated growth factor signaling rather than a loss of functional ER activity.

The definitive finding in the Arpino et al. (3) study is the identification of distinct characteristics of the ER+/PR− and the ER+/PR+ tumors. Using a very large number of tumors in which steroid receptor levels were measured in a highly controlled manner at two central laboratories, this study convincingly shows that ER+/PR− tumors display a more aggressive clinical phenotype than the ER+/PR+ tumors. This conclusion is based on the occurrence of larger tumors, higher frequencies of lymph node positivity, lower median levels of ER, and higher proliferation and aneuploidy rates in the ER+/PR− subgroup than in the ER+/PR+ subgroup. Importantly, this study represents the largest published dataset in which the ER and PR proteins can be analyzed as continuous variables.

The second notable finding presented in this report is that ER+/PR− tumors were more likely to express measurable HER-1 (epidermal growth factor receptor) and/or overexpress HER-2 than ER+/PR+ tumors. Although the growth factor receptor measurements (HER-1 and HER-2) were performed on only a subset (∼4%) of the study samples, the number of tumors for which HER-1 and/or HER-2 was obtained is impressive and appears to be sufficient to identify statistically significant differences associated with PR expression.

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Several preclinical studies evaluating the interaction of growth factor signaling and steroid hormone pathways in controlling the growth of breast cancer cells have been previously reported. Compelling evidence began to appear indicating that some peptide growth hormone signaling pathways like HER-1 or HER-2 may play a prominent role in the pathogenesis of certain breast cancers. Subsequent data demonstrated that there was apparent cross-talk between these growth regulatory systems. Evidence emerged that ER stimulation could modulate HER-2 levels in breast cancer cell lines (4). These data were followed by preclinical studies clearly showing the converse, i.e., that HER-2 overexpression was associated with tamoxifen resistance (5) and that HER-2 could directly modulate ER levels (6). This latter association appeared to occur through direct signaling to ER by the HER-2 pathway. These signaling events were associated with the appearance of a tamoxifen-resistant phenotype in cells that were previously responsive to the drug. The preclinical observations were followed by a series of clinical correlative studies that began to show an association between the peptide growth factor receptor pathways (predominantly HER-2) and tamoxifen resistance. All of these findings have led to a new hypothesis that implicates peptide growth factor pathways as possible mediators of the steroid hormone–independent phenotype in some human breast cancers.

The third major finding in the Arpino et al. study extends this new hypothesis by reporting that the association of HER-1 and HER-2 expression with recurrence and survival in tamoxifen-treated patients varied with PR status. In other words, while the HER-1 and HER-2 expression levels were both associated with higher recurrence risk in the tamoxifen treated patients as a whole, the statistical significance of this association appears to be apparent only in the ER+/PR− and not the ER+/PR+ tumors. This finding may in part be due to the fact that an ER+/PR+ phenotype that is also truly HER-1 overexpressing or HER-2 amplified is quite rare (7). Indeed, the authors note that some of the subgroups used in this part of the analysis are small, and the authors caution that this should be considered a hypothesis-generating study only. This finding, however, leads to the provocative speculation that PR levels may reflect the status of growth factor receptor signaling in human breast cancer and that the expression of PR is even more sensitive (decreased more) than ER when HER-1 is present or when HER-2 is overexpressed.

The authors further hypothesize that the decreased PR expression may be occurring directly by growth factors, which is mechanistically quite different from invoking the nonfunctional ER hypothesis to explain tamoxifen resistance. One wonders if a direct, or even ER-independent decrease in PR expression by peptide growth factor signaling could explain the relatively poor correlation between ER and PR message levels in recent microarray profiling expression data. For example, the ER:PR correlation coefficient in the van’t Veer data (8) is lower than that from other experimentally validated ER target genes (9). The association of HER-1 or HER-2 levels with the ER+/PR+ phenotype and the relatively poor clinical response of these tumors to hormonal manipulation provide further evidence for the evolving hypothesis that the peptide hormone pathways are replacing, at least in part, the steroid hormone pathways in regulating growth for these tumors.

It is also clear from the Arpino et al. study that PR status has important clinical relevance not only for predicting response to antiendocrine therapy but also possibly for the presence of altered peptide growth factor receptor signaling. These data could have a profound translational clinical impact on directing therapeutic interventions for patients who have ER-positive tumors but who display a steroid hormone–resistant or –independent phenotype. Currently, there are several ongoing, large randomized clinical studies aimed at evaluating the combined use of hormonally directed therapeutics and targeted peptide receptor–directed drugs, such as trastuzumab, erlotinib, and the dual kinase (HER-1 and HER-2) inhibitor lapatinib. These studies are being performed in defined subsets of breast cancer patients, and the various receptor levels, i.e., ER, PR, HER-1, and HER-2, are being determined prospectively. The results of these studies will undoubtedly shed further insight on our emerging understanding of the interplay of the steroid and peptide hormone signaling pathways and their interrelated roles in the pathogenesis of human breast cancer. This work further demonstrates that this is an area of translational research rich with therapeutic possibilities.

REFERENCES