Estrogen Receptor: A Paradigm for Targeted Therapy

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Nearly two-thirds of breast cancers overexpress estrogen receptors, and endocrine therapy is considered the backbone of systemic therapy both in early and advanced settings. While this is now widely recognized in clinical practice, this is the culmination of outstanding contribution of many investigators and patients. Indubitably, estrogen receptor targeting has had the most impact among targeted therapies and has significantly affected patient survival. In this commentary, we revisit a landmark article published in *Cancer Research* in 1977 by Knight and colleagues, which laid the groundwork for the use of estrogen receptors in prognostication and adjuvant treatment selection, as well as some of the key breakthroughs in estrogen receptor biology that span more than a century.

See related article by Knight and colleagues, Cancer Res 1977;37:4669–71

Estrogen receptors (ER) exist in two forms, ERα and ERβ, encoded by *ESR1* and *ESR2*, respectively. While the ligand-activated transcription factor ERα is considered a key driver of tumorigenesis in ER-positive breast cancers and has served as a basis for the use of ER antagonists, ERβ is typically expressed in patients with ER-negative tumors and its role has not been clearly elucidated. Although ≥ 1% has been used as the threshold for ER positivity based on IHC, studies have shown that patients with tumors that are 1% to 9% ER-positive have clinical and pathologic characteristics similar to ER-negative tumors, and do not appear to benefit significantly from endocrine therapy (1). While testing for ER is now routinely accepted as the clinical standard for breast cancers, this is a result of ground-breaking and painstaking efforts of many researchers over the last century.

Estrogen deprivation, long before the discovery of ER, was shown to be effective in the treatment of breast cancer. The association between estrogen and breast cancer was recognized more than 125 years ago by George Beatson, who detailed his pioneering treatment of advanced breast cancer through bilateral oophorectomy in an article entitled "On Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases." While subsequent studies showed that oophorectomy did not benefit all patients, it provided a biological basis for interrogating the role of estrogen signaling in breast cancer. Jensen and colleagues first described the ER (initially termed estrophilin) in 1958, a pivotal discovery, which toppled the then prevailing notion that estradiol acted as a cofactor. They demonstrated that estradiol was not metabolized but instead was retained in estrogen target tissues such as the uterus (2). They subsequently uncovered that estrogen binds to ER and the complex translocates to the nucleus. They also surmised that ER-enriched breast cancers were more likely to respond to endocrine ablation than ER-poor breast cancers. Jensen and colleagues later purified the ER and constructed a specific mAb to the receptor. This innovative work allowed quantification of ER in tissues, leading to the understanding that the presence of ER is prognostic and predictive for response to antiestrogen therapy. Subsequently, O'Malley and colleagues described the progesterone receptor (PR; ref. 3). These discoveries provided the necessary insight to understand the complexities of steroid receptor endocrinology and opened the door to molecular targeting in the treatment of breast cancers. Later, Jordan and colleagues showed that tamoxifen, then called ICI 46,474 and initially envisioned as a contraceptive pill, inhibited mammary tumor growth in rat models, suggesting that it could have antitumoral activity in patients with ER-enriched tumors, paving the way for clinical trials in breast cancer (4). While the initial attempts of adjuvant endocrine therapy yielded mixed results owing to underpowered clinical studies, subsequent studies with improved design upheld their clinical benefit. The Early Breast Cancer Trialists Collaborative Group analyzed patient data across multiple clinical trials and was instrumental in providing definitive conclusions regarding the use of adjuvant endocrine therapy. The FDA initially approved tamoxifen, a selective estrogen receptor modular (SERM), for treatment of ER-positive advanced breast cancers in 1978. The validation of tamoxifen as an antiestrogen served as a prelude to the use of aromatase inhibitors as well as the selective estrogen receptor downregulator (SERD), fulvestrant, in the treatment of breast cancers.

Dr. William L. McGuire started as a faculty member at the University of Texas Health Science Center (UTHSC) at San Antonio (San Antonio, TX) in 1969. While an endocrinologist by training, he headed the Division of Medical Oncology and spearheaded the research efforts on understanding the biology of hormone receptors in breast cancer. He focused on discerning the role of steroid hormone receptors in predicting endocrine responsiveness and was instrumental in uncovering that the ER status was prognostic and correlated with survival in patients with early-stage breast cancer. Under the leadership of Dr. McGuire, Knight and colleagues examined a series of 145 patients who underwent modified or radical mastectomy between 1973 and 1976 at the UTHSC at San Antonio (5). ER was assessed by the dextran-coated charcoal assay and tumors with levels ≤ 10 femtomoles/mg cytosol protein were deemed ER-negative. They showed that ER-negative tumors were associated with early recurrence despite adjustment for age, tumor size, and nodal status. However, this association was statistically significant only in patients with involvement of ≥ 4 axillary nodes. Of note, a significantly higher percentage of ER-negative tumors was observed in patients ≤ 50 years of age, suggesting a biologically aggressive tumor phenotype in premenopausal women. Although this was a small retrospective study with limited follow up, it provided early evidence on the prognostic utility of ER and was a seminal link in the long chain of events that has led up to our current understanding of breast cancers. Validating this work, Lippman and

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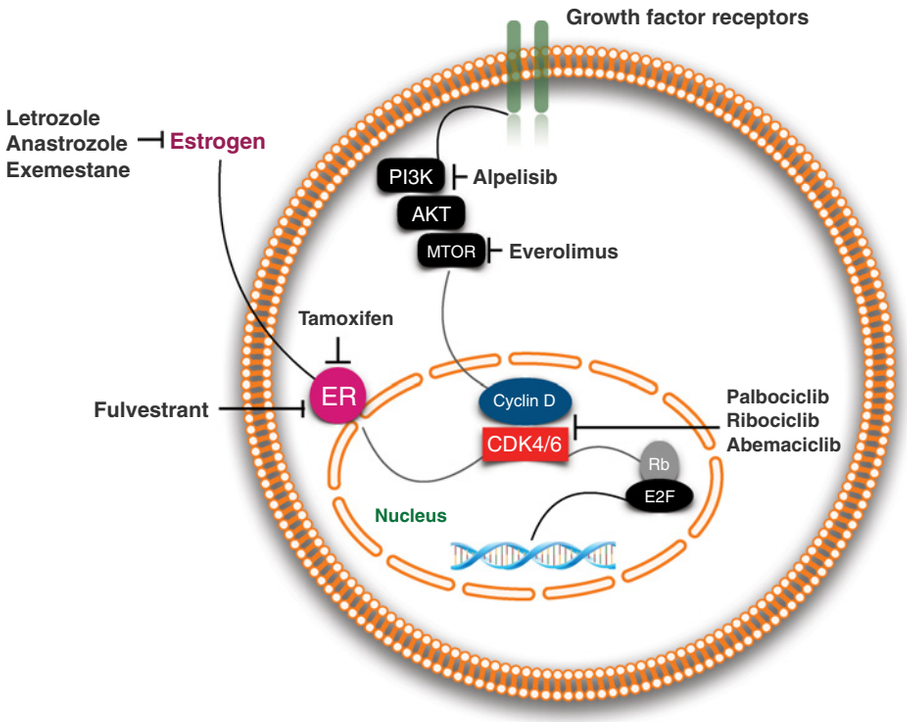

Figure 1.
Overview of ER signaling and approved therapeutic agents that have been developed to target multiple aspects of this pathway.

colleagues studied the relationship between response to chemotherapy and hormone receptor status in patients with metastatic breast cancer (MBC). In a retrospective analysis of 70 patients with MBC, they showed that objective responses to chemotherapy were primarily observed in patients with ER- and PR-low or -negative tumors, suggesting that ER status was an important predictor of response to chemotherapy (6). Remarkably, they also posited that premenopausal women may show greater sensitivity to chemotherapy and meaningful clinical benefit in the adjuvant setting, a hypothesis that still holds true even in some patients with ER-positive tumors. These, and extensive subsequent research, provided credence to the current routine assessment of ER for treatment decision making in clinical practice.

Since then, breast cancers have been further categorized into distinct molecular subtypes based on mRNA expression profiling (7). These include basal-like, HER2-enriched, luminal A, and luminal B subtypes that closely correlate with the traditional classification based on clinical behavior and histopathologic features, with basal-like representing ER-negative/HER2-negative tumors, HER2-enriched representing ER-negative/HER2-positive, and luminal A and B subtypes representing ER-positive breast cancers. The luminal subtype, characterized by the expression of ER-related genes and genes characteristic of epithelial lining of the duct lumen such as cytokeratins 8 and 18, shows great heterogeneity molecularly, as well as in response to therapy and prognosis. Luminal B tumors show lower ER and PR expression as well as higher expression of proliferation-related genes and are associated with worse clinical outcomes compared with luminal A. Notably, a subset of luminal B tumors also show HER2 overexpression. We now realize that breast cancer is a unifying diagnosis of an amalgam comprised of multiple different molecular subtypes with varying clinical patterns.

Although endocrine agents have yielded significant improvements in the survival of ER-positive tumors, therapeutic resistance is inevitable, limiting overall clinical benefit. Acquired mutations in the ligand-binding domain of *ESR1* have been described to develop over time in metastatic patients who have been exposed to antiendocrine therapy, particularly in those treated with aromatase inhibitors, leading to inferior clinical outcomes (8). However, these mutations are infrequent in primary breast cancers, suggesting clonal selection with exposure to estrogen deprivation. Currently, there is no approved agent targeting *ESR1* mutations. Multiple studies evaluating novel SERDs and SERMs targeting *ESR1* are ongoing.

While single-agent endocrine therapy was initially considered the mainstay of therapy of ER-positive early-stage and advanced breast cancers, recent studies have established that combination therapies targeting canonical pathways that interplay with ER signaling lead to better clinical responses and survival (**Fig. 1**). Cell-cycle and PI3K pathway inhibitors have demonstrated significant improvement in clinical outcomes in combination with antiestrogen therapy and are currently approved for use in advanced breast cancers (9, 10). The former have also shown promise in high-risk ER-positive early breast cancers, potentially altering their natural history and clinical course.

Knowledge of the past provides us with a crucial perspective of current treatment and a greater appreciation of incremental advances made over time. The pioneering work of Knight and colleagues, as well as many others, laid the foundation for use of biomarkers in prognostication and therapeutic selection and has changed the landscape of breast cancers. Identification of the ER has not only proved to be a successful therapeutic target for breast cancers, but also has proved to be an archetype for subsequent efforts to design targeted therapies in other tumor types.

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