Special Article

The Estrogen Receptor: A Model for Molecular Medicine

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Abstract

The identification of the estrogen receptor (ER) in the laboratory provided a mechanism to describe the target site specificity of estrogen action in uterus, vagina, pituitary gland, and breast cancer. Most importantly, a test was established to predict the outcome of antihormonal therapy in breast cancer, and a target was identified to develop new drugs for the treatment and prevention of breast cancer. The development of tamoxifen for the treatment of all stages of ER-positive breast cancers has resulted in the improved survival of breast cancer patients. However, the recognition of selective ER modulation, i.e., estrogen-like action in bones and lowering circulating cholesterol but antiestrogenic actions in breast and uterus, has resulted in the development of multifunctional medicines with the goal of preventing not only breast and uterine cancer but also osteoporosis and coronary heart disease.

Introduction

The link between hormones and breast cancer growth and development has been recognized for more than a century. In 1896, George Beatson (1) reported that removal of the ovaries from premenopausal women with advanced breast cancer produced a dramatic decrease in tumor size and improved the patient’s prognosis. Beatson had not performed the oophorectomy on a whim but had used the modern principles of translational research. He applied not only the knowledge that removal of the ovaries could, mysteriously, affect the mammary glands in farm animals but also the earlier observations by Ashley Cooper that, in premenopausal women with advanced breast cancer, the size of the tumor increased and decreased during the menstrual cycle. Unfortunately, oophorectomy did not benefit all patients. In 1900, Stanley Boyd (2) at the Charing Cross Hospital accumulated the national case reports of oophorectomy and noted that only one-third of the patients responded to ovarian ablation and responses lasted, on average, for 1–2 years. Although these data were disappointing, endocrine therapy became a standard of care in the treatment of breast cancer. Oophorectomy was subsequently replaced by ovarian irradiation for premenopausal patients, whereas during the 1950s and 1960s, adrenalectomy (3), hypophysectomy (4), and paradoxically, high-dose diethylstilbestrol (5) became treatment options for postmenopausal patients. However, still only one-third of patients responded, so the question to be answered by translational research was, “can the patient who will respond be predicted thereby avoiding noneffective ablative surgery for the majority of the cases?”

In the laboratory, ovariectomy of young mice from strains that developed mammary cancer dramatically reduced the incidence of tumors (6). However, the discovery of estrogenic hormones produced in the ovary by Allen and Doisy (7) prompted the search for a therapeutic antagonist to reduce the incidence of breast cancer in individuals predisposed to the disease by their sensitivity to estrogenic hormones (8). The laboratory question then became, “how do estrogens exert their tissue specificity, and is there a target that can be identified to block estrogen action?”

The prevailing theory to explain estrogen action throughout the 1950s was that estrogens exert their actions by participating in enzymatic processes of metabolism. However, advances in radioisotope chemistry and detection techniques for tritium, facilitated the identification of a receptor protein that mediates the diverse actions of estrogen without metabolic alteration of the hormone itself. These discoveries provided the necessary insight to understand the complexities of steroid endocrinology and opened the door to molecular targeting in the treatment and prevention of breast cancer.

Synthesis and Evaluation of [3H]Estradiol in the Laboratory

High specific activity 6–7 [3H]estradiol (117–195 mCi/mg) was prepared by catalytic tritiation of 6-dehydroestradiol (9). The sc administration of [3H]estradiol to groups of immature rats showed (Fig. 1) that the estrogen target tissues (e.g., uterus and vagina) bound and retained the [3H] label, but traditional nontarget tissues (e.g., muscle, kidney, liver) did not retain the radioactivity. The radioactivity in the uterus was identified as estradiol itself. That this had not undergone reversible oxidation/reduction to estrone, as assumed in the then prevailing concept, was established by the synthesis of 17-tritiated estradiol and demonstration that this does not lose its tritium as it stimulates growth of the rat uterus (10).

The fact that the uterus and vagina (estrogen target tissues) bound and retained [3H]estradiol implied that a receptor molecule was necessary to initiate the cellular responses associated with estrogen action. We used one of the early nonsteroidal antiestrogens (U-11,100A or nafloxine as it was later known) to demonstrate that the estrogen-binding substance in the rat uterus is a true receptor, involved in hormonal action, in that the progressive inhibition of growth by increasing doses of antiestrogen parallels its inhibition of [3H]estradiol binding (Ref. 10; Fig. 2).
Jack Gorski (11, 12) first used SDGA to identify the rat ER as an extractable protein that sedimentated at around 8S. We adapted the technique of SDGA to identify subtle differences in the size of ERs and proposed a two-step mechanism for the activation of the ER to a reactive complex that initiates cell growth (13). The 8S receptor can be dissociated with 0.4M KCl into a 4S subunit, releasing what we now know to be heat-shock proteins and other molecular chaperones. The 4S ER-estradiol complex is then transformed to a 5S complex that is the active form of the receptor. These data explained the observation that receptor complexes isolated from uteri after tissue binding of [3 H]estradiol in vivo were 5S, but studies with cytoplasmic extracts (cytosols) in vitro at 4°C invariably produces a 4S complex. We found that the 4S complex could be converted to a 5S nuclear ER complex in vitro by warming to physiological temperature (14). The two-step model of estrogen action, i.e., E2 binding to ERs with subsequent activation of the complex, is supported by observations that estradiol binds to the ER to produce a conformational change that permits dimerization and coactivator binding. These molecular events, identified by X-ray crystallography (15, 16), provide the basis for receptor initiated target gene transcription as a prelude to cell replication in estrogen target tissues.

The ER Assay for Breast Cancer

The finding that estrogen target tissues contained ERs but nontarget tissues did not raised the question of whether these concepts translated to the clinic to predict the endocrine responsiveness of breast cancer. The fact that only one in three women respond to any form of endocrine ablative therapy meant that two women were undergoing surgery and intensive medical care without any hope of a favorable outcome. We (E. V. J.) reasoned that if the ER was necessary for estrogen-stimulated growth, then determination of ER in a tumor specimen may be informative. We used SDGA to determine the ER content of tumor cytosols by the size of the 8S ER-estradiol peak and correlated the results with the outcome of adrenalectomy and other ablative therapy (Ref. 17, 18; Fig. 3).

We first reported in 1971 that ER-rich breast cancers were more likely to respond to endocrine ablation than ER-poor breast cancers (17). In general, these data were consistent with all of the clinical correlations presented at a workshop in Bethesda, Maryland, in 1974 sponsored by the Breast Cancer Task Force (18). Of the patients evaluated by extramural review, only 8% of ER-negative tumors responded to additive or ablative therapy, whereas ~60% of patients who were ER positive had an objective response to endocrine therapy (Table 1). Interestingly, the early studies with nonsteroidal antiestrogens used as treatments were not so encouraging.

The results of the 1974 workshop established the ER assay as a valuable predictive test for the endocrine treatment of advanced breast cancer, but the clinical focus on the early detection of breast cancer mandated more sensitive assays for the determination of ER status for small primary tumors. We (E. V. J.) addressed these issues by purifying both calf and...
human ER proteins and raising polyclonal (20, 21) antibodies to them, the first antibodies to any steroid hormone receptor. Because these antibodies form nonprecipitating immune complexes, we detected them by their ability to shift the sedimentation peak of the radioactive estradiol-receptor complex on SDGA. For different monoclonal antibodies to human ERs, we could demonstrate binding to different epitopes by their additive effect on the sedimentation rate of the immune complex. These antibodies provided immunocytochemical (ER enzyme immunoassay; Ref. 22) and immunocytochemical (ER immunocytochemical assay; Refs. 23, 24) assays for detection and measurement of ERs in tissue specimens, with many advantages over the earlier hormone-binding techniques. Most importantly, the immunocytochemical detection of ERs in pathology specimens indicated the heterogeneous nature of breast cancer. Although it was possible that tumors could have different levels of ER based on high or low concentrations in the individual cells, the immunocytochemical assay provided direct evidence that some cells contain ERs, whereas others do not (Fig. 4). Clearly, the genetic instability of breast cancer results in clonal selection so that endocrine therapy in advanced breast cancer (i.e., late stages) would be less likely to cure the disease.

The Transition to Tamoxifen

At the beginning of the 1970s, new strategies using the ER as a target for therapeutics were being considered, but early clinical experience with antiestrogens starting in the 1960s were not promising until ICI 46,474 (to be renamed tamoxifen) was developed as the first antiestrogen to be considered safe enough for the treatment of advanced breast cancer (Refs. 25–27; Table 2). Tamoxifen was an unlikely candidate to be a pioneering medicine. Early studies with nonsteroidal antiestrogens showed that the drugs were effective at regulating the reproductive system (28), but in the main the drugs were considered to be too toxic for long-term administration (29). Tamoxifen was discovered as part of a fertility control program by Harper and Walpole (30–32) and Bedford and Richardson (33). The molecule is the trans-isomer of a substituted triphenylethylened and showed potent action as an antiestrogenic agent in the rat (31). Early studies focused on the application of antiestrogens to regulate the sexual cycle (34–36), but Walpole (27) was also interested in cancer research and therapy. Although he conducted no antitumor studies himself, he encouraged research and testing by others (V. C. J.). These studies resulted in the broader application of tamoxifen as a breast cancer treatment and ultimately as a breast cancer preventive. Tamoxifen was tested extensively for advanced breast cancer throughout the world during the 1970s, but it is fair to say that there was little enthusiasm about developing endocrine therapies to treat cancer. Combination chemotherapy was more likely to be successful in curing not only breast cancer but other solid tumors. Indeed, tamoxifen was found to be only as effective as standard treatments but with a reduced incidence of side effects (25, 26, 37). Nevertheless, a strategy for the broad application of tamoxifen as a treatment and preventive of breast cancer was established in the laboratory during the 1970s, which proved to be successful, in patients, some 25 years later. The success of the scientific strategy of translational research was based on the proven activity of tamoxifen as an antiestrogen, a reduced incidence of side effects, and the targeting of specific patient populations.

### Scientific Principles for the Broader Application of Tamoxifen

In the 1970s, investigations of antihormonal therapy for breast cancer used the DMBA-induced rat mammary carcinoma model originally developed by Charles Huggins in Chicago 10 years before (38). The DMBA model was a tremendous breakthrough because a single oral dose of DMBA (20 mg) fed to 50-day-old Sprague Dawley rats results in all animals developing multiple mammary cancers ~150 days later. Tumorigenesis and tumor growth is hormone dependent (39), and most of the tumors have ERs (40, 41). In 1972, I (V. C. J.) had completed a Ph.D. entitled “The estrogenic and antiestrogenic activities of some substituted triphenylethylenes” (my external examiner was Arthur Walpole), and as a pharmacologist, I volunteered to facilitate the development of tamoxifen as a useful breast cancer drug. I first met Elwood Jensen (1972) when he visited the Worcester Foundation in Massachusetts as a member of their Scientific Advisory Board. He generously offered to aid in the evaluation of tamoxifen and supported my training in ER assays and the DMBA-induced rat mammary carcinoma model at the Ben May Laboratories in Chicago, Illinois.

Armed with new knowledge, a systematic evaluation of tamoxifen was initiated at the Worcester Foundation and subsequently at Leeds University sponsored by AstraZeneca (through the good offices of Lois Trench, Arthur Walpole, Roy Cotton, Barry Furr, and Brian Newbould). Unlike today, the goal was not publications, but the discovery of the most appropriate clinical application for a potentially useful breast cancer drug. In fact, there was no general enthusiasm for the concept of endocrine therapy, so the urgency to publish was unnecessary. There was absolutely no sense of a breakthrough for the general scientific and clinical community with tamoxifen in the early 1970s. Clinical research was not able to demonstrate increased response rates compared with standard therapy (25, 37), and the strategies of chemoprevention and long-term adjuvant therapy were not yet even considered by clinical trialists. Nevertheless, a strategic breakthrough was being planned in the laboratory.

Three scientific principles were established during the

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**Table 1** Objective breast tumor regressions according to ER assay

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ER+ (%)</th>
<th>ER- (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenalectomy</td>
<td>32/66</td>
<td>4/33</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>25/33</td>
<td>4/53</td>
</tr>
<tr>
<td>Hypophysectomy</td>
<td>2/6</td>
<td>0/8</td>
</tr>
<tr>
<td>Total</td>
<td>59/107</td>
<td>8/94</td>
</tr>
<tr>
<td>Androgen</td>
<td>12/26</td>
<td>2/24</td>
</tr>
<tr>
<td>Estrogen</td>
<td>37/57</td>
<td>5/58</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>51/85</td>
<td>7/82</td>
</tr>
<tr>
<td>Antiestrogen</td>
<td>8/20</td>
<td>5/27</td>
</tr>
<tr>
<td>(not tamoxifen)</td>
<td>(40%)</td>
<td>(18%)</td>
</tr>
</tbody>
</table>
The immunocytochemical identification of ER in a breast tumor. The staining is heterogeneous, thus indicating a mixture of ER-positive and -negative cancer cells.

Table 2  Comparison of early clinical experience with antiestrogens as a treatment for advanced breast cancer

<table>
<thead>
<tr>
<th>Antiestrogen</th>
<th>Daily dose</th>
<th>Year</th>
<th>Response rate</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethamoxtriphetol</td>
<td>500–4500 mg</td>
<td>1960</td>
<td>25%</td>
<td>Acute psychotic episodes</td>
</tr>
<tr>
<td>Clomiphene</td>
<td>100–300 mg</td>
<td>1964–1974</td>
<td>34%</td>
<td>Fear of cataracts</td>
</tr>
<tr>
<td>Nafoxidine</td>
<td>180–240 mg</td>
<td>1976</td>
<td>31%</td>
<td>Cataracts, ichthyosis, photophobia</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>20–40 mg</td>
<td>1971–1973</td>
<td>31%</td>
<td>Transient thrombocytopenia</td>
</tr>
</tbody>
</table>

"The particular advantage of this drug is the low incidence of troublesome side effects (25)." "Side effects were usually trivial (26)."

1970s that have successfully translated to lives saved during the following decades. First, tamoxifen inhibits the binding of [3H]estradiol to rat and mouse target tissues (42, 43), DMBA-induced rat mammary tumors (44), and human tumors (45). In the DMBA rat mammary carcinoma model, tamoxifen was more likely to prevent the growth of ER-positive tumors (46). Thus, the strategy of only using tamoxifen to treat patients with ER-positive breast tumors seemed appropriate. Second, short courses of 1 month of tamoxifen (equivalent to 1 year in patients) administered 1 month after DMBA to destroy microfoci of malignant cells in rat mammary gland were generally unsuccessful in completely controlling tumorigenesis (47). In contrast, continuous treatment with low doses of tamoxifen was completely effective in maintaining 90% of animals tumor free (Ref. 48; Fig. 5). Long adjuvant treatment schedules of tamoxifen were predicted to be more effective than short-term treatment. These first two principles translated to the clinic. The Oxford Overview analysis (49) of randomized clinical trials demonstrated that adjuvant tamoxifen is unable to provide any benefit for the patient with an ER-negative tumor, but 5 years of adjuvant tamoxifen are superior to 1 or 2 years of adjuvant tamoxifen for pre- or postmenopausal women with ER-positive tumors. Four hundred thousand women are alive today because of long-term adjuvant tamoxifen therapy.

The final principle was the demonstration that tamoxifen inhibits the initiation (50, 51) and promotion (47, 48) of DMBA-induced rat mammary carcinogenesis. These data provided the scientific foundation for subsequent studies to evaluate the worth of tamoxifen as a chemopreventive in high-risk women (52, 53).

The National Surgical Breast and Bowel Project chemoprevention trial recruited >13,000 high-risk pre- and postmenopausal women that were randomized to receive 20 mg of tamoxifen daily or placebo for up to 5 years (53). Overall, the result was predictable based upon the substantial clinical database with 20 years of experience with tamoxifen. Tamoxifen produced a 50% decrease in the incidence of breast cancer irrespective of the level of risk. Additionally, tamoxifen caused a 50% reduction in the incidence of ductal carcinoma in situ. These antiestrogenic end points in the breast were complimented by predicted estrogen-like end points in other target tissues. Tamoxifen produced a nonsignificant decrease in the number of hip fractures but a significant 4-fold increase in the incidence of endometrial cancer in postmenopausal volunteers.

As a result of the clinical evaluation of tamoxifen, the medicine was the first to be Food and Drug Administration approved for reducing the incidence of breast cancer in high-risk premenopausal and postmenopausal women. However, the targeted use of tamoxifen in discrete populations of high-risk women was not seen as making a significant future impact in...
reasoned that if tamoxifen was an effective breast cancer drug of antiestrogens or SERMs as they became known. It was proposed to exploit the pharmacology of nonsteroidal estrogens (52). The drug was, therefore, not appropriate for use in the general population because of the known increased risk of mammary carcinogenesis (58), demonstrated a new principle of target site-specific action. In other words, the antiestrogenic isomer in the mixture was responsible for the target site-specific effects. In other words, the antiestrogenic isomer could combine with novel receptors to produce estrogen-like effects in bone. The finding that tamoxifen (the pure antiestrogenic isomer) and raloxifene (then known as keoxifene), a drug that failed to be developed as a breast cancer treatment, both maintained bone density in ovariectomized rats (55), raised the question whether the estrogenic or the antiestrogenic isomer in the mixture was responsible for the target site-specific effects. Overall, these data suggested that the tamoxifen ER complex has differential actions at estrogen target tissues throughout the body. Tamoxifen ER complexes were selectively antiestrogenic in breast but estrogen-like in the bones and the uterus/endometrial cancer (61). At the end of the 1980s, tamoxifen was advanced as a chemopreventive for women with a high risk of breast cancer (52). The drug was, therefore, not appropriate for use in the general population because of the known increased risk of endometrial cancer (62). As a result, a new prevention strategy was proposed to exploit the pharmacology of nonsteroidal antiestrogens or SERMs as they became known. It was reasoned that if tamoxifen was an effective breast cancer drug but maintained bone density and reduced circulating cholesterol, why not develop other members of the drug class to prevent osteoporosis or atherosclerosis and reduce breast cancer as a beneficial side effect? The target population would be postmenopausal women in general, and the need to select women at risk for breast cancer would be unnecessary (54). Raloxifene was the obvious choice because the molecule was less estrogen-like in the rodent uterus (60, 63). Raloxifene had already been tested in patients with breast cancer (64), and there was every reason to believe that raloxifene would mimic tamoxifen and preserve bone density in postmenopausal women (65, 66). Most importantly, tamoxifen was found to produce rat liver carcinogenesis (67, 68) in the early 1990s, but raloxifene was not carcinogenic in liver.

Raloxifene has completed testing for the treatment and prevention of osteoporosis in high-risk women, and the SERM reduces the incidence of spinal fractures (69). Evaluation of breast cancer incidence in the same population confirms the original hypothesis (54) that the application of a SERM for the treatment and prevention of osteoporosis will reduce the incidence of breast cancer (70, 71).

As a result of these conceptual advances, it is clear that raloxifene could be the first of a series of new multifunctional medicines (72). Raloxifene is currently being tested in the study of tamoxifen and raloxifene to determine the efficacy of raloxifene to reduce the incidence of breast cancer in high-risk women. Additionally, raloxifene is being evaluated as an agent to reduce the incidence of coronary heart disease in high-risk postmenopausal women. The trial is referred to as raloxifene use for the heart, and data should be available in 2005. The trial results will be extremely important in light of the recent reports that standard hormone replacement therapy, in fact, does not decrease the risk of coronary heart disease and has significant life-threatening side effects (73).

The successful development of tamoxifen and raloxifene for use as SERMs to prevent breast cancer and osteoporosis, respectively, has encouraged the investigation of the structure function relationships of SERMs and to understand why one SERM may be more estrogen-like than another at a target site.

Structure Function Relationships

Once tamoxifen was established as a valuable drug for the adjuvant treatment of breast cancer in the early 1980s (74, 75), we (V. C. J.) focused on laboratory studies to describe the molecular mechanisms of action of estrogens and antiestrogens (76, 77). One successful approach used the regulation of the prolactin gene in primary cultures of cells from the anterior pituitary gland. It was reasoned that the assay would not only provide insight into the direct actions of ligands at a gene target without concerns about pharmacokinetics and metabolism (78) but also provide insight into rat mammary carcinogenesis that was prolactin dependent (79). Overall, extensive structure function relationship studies were used to propose a molecular model of estrogen and antiestrogen action (crocodile model). The proposal required the sealing of a planar estrogen within the ligand binding domain to transform the ER complex into its active state so...
that gene transcription could be initiated. In contrast, the three-dimensional shape of the triphenylethylene wedges into the ligand binding domain and prevents full ER activation by keeping the jaws open. This was achieved by the bulky alkylaminoethoxy side chain of antiestrogens that was proposed to interact with an antiestrogenic region of the receptor protein to modulate estrogen and antiestrogen action (Fig. 6). The task of identifying the critical antiestrogenic region was advanced with the cloning and sequencing of the ER gene (80–82). However, the mechanics of antiestrogen action at the ER were advanced by the discovery of a natural mutation of the ERs (D351Y) in a tamoxifen-stimulated human tumor (83–86). The mutant ER modulates the conversion of raloxifene from an antiestrogen to an estrogen. The pivotal observation opened the door to a broader understanding of ER modulation by SERMs.

The reason for the molecular modulation of SERMs D35Y ER remained obscure until the resolution of the X-ray crystallography of the ligand binding domain of the estrogen or antiestrogenic receptor complex (Refs. 15, 16; Fig. 6). The crocodile model was essentially correct, with the planar estrogen sealed within the ligand binding pocket, but the three-dimensional SERM blocked the closure process by relocating helix 12 away from the ligand binding pocket. The bulky side chain for the SERM relocated helix 12, thereby preventing coactivator molecules from binding to the appropriate site on the external surface of a SERM ER complex (AF-2; Ref. 16).

However, the question could be asked, “why is tamoxifen more promiscuous than raloxifene in target sites like the uterus?” The reason is the relationship between D351 in the ER and the antiestrogenic side chain of the SERM. Raloxifene’s side chain is one angstrom closer to D351, and it shields and neutralizes the change (Fig. 7). In contrast, the side chain for tamoxifen cannot neutralize D351 so the site allosterically influences activating function 1 at the proximal end of the ER. On the basis of the structure function relationships of the side chain and the amino acid at 351, it is possible to predictably modulate the SERM ER complex (87–90). The conversation between the bulky antiestrogenic side chain on SERMs and aa351 is the critical first step to change the charge and shape of external surface of a SERM ER complex (Fig. 8). These studies complement the important studies with coregulatory (corepressor and coactivator) molecules that are currently providing an important insight into the target site-specific effects of SERMs. These data provide the foundation for a new generation of
targeted molecules that can be developed for multiple diseases (91, 92).

**Conclusions and Future Prospects**

The identification of the ER has not only proved to be a successful therapeutic target for the treatment and prevention of breast cancer but also has proved to be a selective molecular model for all subsequent efforts to design targeted therapeutics in cancer. The success of tamoxifen as a pioneering medicine has opened the door to the development of other novel approaches to the treatment of breast cancer using pure antiestrogens (93, 94) or aromatase inhibitors (95) and the broad application of SERMs in women’s health (91, 92). Most importantly, the novel idea of modulating the ER with specific ligands has been essential for the current expansion of the principle to develop medicines targeted toward other members of the steroid receptor superfamily.

**Fig. 7** A comparison of the external surface of the ER liganded with either 4-hydroxytamoxifen (A) or raloxifene (B). The antiestrogenic side chain of raloxifene is 1 angstrom closer to D351 (aspartate) when compared with the situation with tamoxifen.

**Fig. 8** The structure function relationships of the tamoxifen or raloxifene complex. Alteration in the antiestrogenic side chains of either tamoxifen (A) or raloxifene (B) modulates the estrogenic and antiestrogenic actions of the SERM ER complex. Similarly, the alteration in the charge and size of the aa at 351 alters the interaction with the antiestrogenic side chain to modulate estrogen-like properties. These data summarize refs. 87–90.

**References**


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