Selective Estrogen Receptor Modulation: A Personal Perspective

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Introduction

Professor Paul Ehrlich is the father of experimental chemotherapy. During the first decade of the 20th Century, he reasoned that compounds could be synthesized to exhibit selective toxicity on a parasite without affecting the host. The synthesis, laboratory evaluation, and clinical development of Salvarsan, the 606th compound tested, revolutionized the treatment of syphilis, which was at the time a massive and certain killer (1, 2). The key to success was the notion that a receptor, present only in the parasite, was the target. More importantly, the development of the first successful synthetic therapy for an infectious disease also established a logical approach to the design of all subsequent chemotherapies.

Ehrlich also turned his attention to cancer. His fame was such that this alone evoked statements in the media such as, “The beginning of the end of the cancer problem is in sight,” and by 1912, the Scientific American stated “unquestionably their investigations justify the hopes of a cure of human cancer” (3). However, in 1915, Ehrlich declared, “I have wasted 15 years of my life in experimental cancer” (3). The Nobel Laureate, Paul Ehrlich, died on August 20, 1915, at the age of sixty-one.

A cure for cancer remained elusive throughout the 20th Century, but Ehrlich’s legacy is the demonstration of a logical approach to a complex problem: identify a selective target, identify a drug in the laboratory, test the drug on experimental disease, and conduct clinical studies. On the basis of this process and of a change in the philosophy of treating not just late disease but early disease with adjuvant therapy, progress has been made in the past 30 years that can now be quantitated. In addition, there has been a conceptual shift to use chemotherapy (used in the context of Ehrlich’s definition) as a chemopreventive (4, 5). This has resulted in a paradigm shift to consider SERMs3 as multifunctional medicines (6, 7).

Breast Cancer

Some breast cancers are known to be responsive to estrogen for growth. However, the identification of the ER as the mediator for estrogen action in estrogen-targeted tissues in laboratory animals (8, 9) and the development of the ER assay by Jensen to identify breast cancer patients whose tumor would be responsive to endocrine therapy (10) also provide a suitable target for chemotherapy (used in Ehrlich’s context). The first nonsteroidal antiestrogen, MER 25 (11), was too toxic and of low potency, but ICI 46,474, described by Harper and Walpole (12), was a potent estrogen antagonist with antifertility properties in animals. Fortunately, Walpole was interested in the experimental chemotherapy of cancer (13) and patented one of the potential applications of ICI 46,474 as a treatment of hormone-dependent cancers (14).

Subsequently, preliminary clinical studies in advanced breast cancer showed some activity (15, 16), but ICI 46,474, or tamoxifen as it became known, was only as effective as the standard endocrine therapy at the time diethylstilbestrol (17). The key to additional advances was the findings that (a) there were few side effects (15–17), and (b) the ER was a suitable target for patient selection (18–20).

Clinical Evaluation of Tamoxifen

Progress in the strategic use of endocrine therapy for breast cancer has occurred through the close cooperation between the laboratory and the clinic. The laboratory principles that tamoxifen would benefit ER-positive patients (18–20), long-term adjuvant therapy would be more effective than short-term therapy (21, 22), and tamoxifen could increase the incidence of endometrial cancer (23, 24) have all translated effectively to the clinic (25). It is estimated that there are 400,000 women alive today because of long-term adjuvant tamoxifen treatment (14). This fact is partially responsible for the decreasing death rates from breast cancer observed during the past decade in the United States and United Kingdom (26).

However, tamoxifen is more than a treatment for breast cancer. On the basis of laboratory studies that showed tamoxifen could prevent rat mammary carcinogenesis (27, 28) and the of clinical finding that tamoxifen prevented contralateral breast cancer (29), the worth of tamoxifen was tested successfully to reduce the incidence of breast cancer in high-risk women (30). Tamoxifen is the first chemopreventive to be available to reduce the incidence of breast cancer in pre- and postmenopausal high-risk women.

The Properties of a SERM

Progress in developing tamoxifen for chemoprevention depended on the recognition of the unique properties of nonsteroidal antiestrogens. Clearly, if antiestrogens are to be used in well women, and estrogen is necessary to prevent osteoporosis and CHD, then tamoxifen could prevent breast cancer but increase the risk of death caused by osteoporosis and CHD. However, the recognition that tamoxifen was a SERM in the laboratory i.e., produced estrogen-like or anti-estrogenic effects at different target tissues (24, 31) was pivotal to advance the use of tamoxifen in well women. Tamoxifen maintained bone density in rats (32–34), and this translated to improved bone density (35, 36) and a statistically nonsignificant reduction in fractures in postmenopausal women (30). However, it was clear that tamoxifen could not be used widely in well women without elevated risk factors for breast cancer. A new approach was necessary to exploit the properties of SERMs and reduce the risk of breast cancer in the general postmenopausal population.

The laboratory and preliminary clinical finds in the 1980s lead to a paradigm shift in chemopreventive strategies that was simply stated as follows (6): “We have obtained valuable clinical information about..."
this group of drugs that can be applied in other disease states. Research does not travel straight lines, and observations in one field of science often become major discoveries in another. Important clues have been garnered about the effects of tamoxifen on bone and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis. The ubiquitous application of novel compounds to prevent diseases associated with the progressive changes after menopause may, as a side effect, significantly retard the development of breast cancer. The target population would be post-menopausal women in general, thereby avoiding the requirement to select a high-risk group to prevent breast cancer.

The result is raloxifene. Raloxifene (formerly known as LY156,758 or keoxifene) has only weak estrogen-like properties in the rodent uterus (37) but preserves bones in ovariectomized rats (32), prevents rat mammary carcinogenesis at high doses (38), and appears to have reduced activity as a growth stimulator in an experimental model of endometrial cancer (39). Raloxifene has been shown to reduce fractures in women at risk for osteoporosis (40) and to decrease circulating cholesterol (41). Most importantly, raloxifene decreases the incidence of breast cancer (42) and has no estrogen-like action on the uterus (43, 44). Raloxifene is available for the treatment and prevention of osteoporosis and is being tested as a preventive for CHD and breast cancer in selected populations of high-risk postmenopausal women (45).

There is currently enormous interest in developing new SERMs as multifunctional medicines (7, 46). Progress is being facilitated by the elucidation of the complexity of SERM action at the subcellular level. Although it is fair to say that a complete picture for each target site is not known, advances have been made during the past decade that will provide new targets for future endeavors.

**Decisions for a SERM to Modulate Genes**

There are a number of decision points that ultimately will determine the biological response to a SERM (Fig. 1). There are two structurally related ERs, referred to as ERα and ERβ (47), that have some degree of homology with each other. A SERM, therefore, has a choice of receptor molecules. Both ERs have a ligand binding and a DNA binding domain, and can directly bind to DNA to activate gene transcription. There are, however, differences in the AFs that can alter the SERM-ER complex, resulting in increased or decreased estrogenicity. Tamoxifen appears to be more antiestrogenic when complexed with ERβ, compared with ERα (48). It is now clear that the ligand programs the shape of the ER complex (49) so that coactivators or corepressors can bind to the external surface of a SERM-ER complex (50). Coactivators will aid signal transduction, whereas corepressors will block transduction. At the time that a transcriptional complex is to be formed, the SERM-ERαβ complexes must decide whether to homo- or heterodimerize, before initiating gene transcription. Lastly, there is evidence to suggest that SERMs can modulate gene transcription through two distinct mechanisms, either an activating protein-1 pathway, when a protein-protein interaction occurs with fos and jun, or the SERM-ER complex can activate or silence an estrogen response element directly on DNA (51).

At this point, it is not possible to describe all of the mechanisms of SERMs at a target site because the proportions of ERs, coregulator proteins, and pathways at different sites have not been established. However, it is possible to describe the modulation of ERα by SERMs under precise laboratory conditions.

In the early 1990s, it was believed that drug resistance to tamoxifen occurred through mutation of the ER. This would change the pharmacology of an antiestrogen to an estrogen. Although it is now clear that mutations of the ER are not responsible for the development of tamoxifen resistance, the chance finding of a D351Y ER mutation in a tamoxifen-stimulated breast tumor (52), that enhanced the estrogen-like actions of SERMs (53–55), was an invaluable starting point to decipher how SERMs modulate ER function. The change in biology produced by the mutant ER has subsequently been supported by X-ray crystallography (56–58).

It is now known that the antiestrogenic side chain of a SERM interacts differently with the surface amino acid D351. The structure-function relationships of ERα can be examined by stable transfection of mutant ERs into ER-negative breast cancer cells using TGFα as a target gene in situ to evaluate the estrogenicity of SERMs (53, 54, 59). The aspartate at amino acid 351 of ERα is important for the interaction of the antiestrogenic side chains of SERMs and is critical to regulate SERM programming (56, 57, 60). The surface charge of D351 is not neutralized or shielded by the side chain of 4-hydroxy-tamoxifen; therefore, in a coactivator-rich environment, these proteins may bind to the SERM-ER complex to initiate TGFα gene transcription. In contrast, the side chain of raloxifene shields the surface amino acid D351 and produces only an antiestrogenic complex at the TGFα gene target. The hypothesis to explain the enhanced estrogen-like action of 4-hydroxytamoxifen has been tested by interrogating the SERM-ER complex. The substitution of a noncharged amino acid at position 351 (e.g., glycine) silences the estrogen-like action of the 4-hydroxytamoxifen-ER complex (61). This observation is consistent with the idea that the 4-hydroxytamoxifen-ER complex must bind coactivators at a novel site other than the traditional AF-2 site, which...
is blocked by helix 12 in the 4-hydroxytamoxifen-ER complex (57). The new activating site for coactivator binding on the SERM-ER complex is called AF-2b (61), which is distinct from the coactivator binding site AF-2 used by estrogens in the ligand binding domain (57). Additionally, changing the side chain of 4-hydroxytamoxifen to that of GW 7604 with a carboxylic acid has been found to repel the aspartate at 351 and silence estrogen action in the complex (62). The compound GW 7604 is the active metabolite of the tamoxifen analogue GW 5638 (63), which apparently has potential for the treatment of breast cancer (64). Lastly, the raloxifene-ER complex can be made more estrogen-like by substituting a bigger negatively charged amino acid, such as tyrosine-351 (65). Thus, the estrogen-like action of SERMs is controlled through an interaction with a surface amino acid at 351. Fig. 2 summarizes the recent literature on the SERM-ER complex.

Remarkably, the crystallization of the pure antiestrogen ICI 164,384 with ERβ (66) shows that the antiestrogenic side chain follows the same path in the ER complex as the side chain of raloxifene (58). To do this, the steroid must flip over 180° in the ligand binding domain. This maneuver had been predicted previously (67). The difference between a SERM and a pure antiestrogen is that the AF-2b region on the surface of the ER is now disrupted by the antiestrogenic side chain and programmed for early destruction (68, 69) via an intact helix 12 (65).

Opportunities in “Chemotherapy”

The essence of Professor Paul Erhlich’s therapeutic strategy was to develop chemotherapy that would kill the target cell and not affect the host. The development of tamoxifen followed Erhlich’s method of translating laboratory findings in model systems to aid patients. But, tamoxifen provided a greater insight into drug action and has opened the door to new opportunities. The recognition that the tamoxifen-ER complex can have either antiestrogenic or estrogenic actions at different targets (31) and the clinical proof of principle of the SERM concept (36) encouraged the development of raloxifene for the prevention of osteoporosis. Now, numerous new SERMs (63, 64, 70–73) are being evaluated as multifunctional medicines.

The concept that selective compounds (such as SERMs) can enhance or repress signal transduction through the ER is now being advanced further with an evaluation of the selective androgen receptor modulators for the androgen receptor (74, 75), selective aryl hydrocarbon receptor modulators for the aryl hydrocarbon receptor (76), selective peroxisome proliferator-activated receptor modulators for the peroxisome proliferator-activated receptor γ (77), and selective thyroid receptor modulators for the thyroid receptor (78). The general applicability of modulating multiple receptors, or indeed orphan receptors, holds the promise of treating and preventing diseases that were beyond intervention a decade ago.

Acknowledgments

Dr. Jordan is the Diana, Princess of Wales Professor of Cancer Research. This article is dedicated to the staff, students, and fellows in my laboratory, whose persistent efforts for more than 30 years have turned ideas into improved health care.

References


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