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The Science of Selective Estrogen Receptor Modulators:
Concept to Clinical Practice

Commentary on Lippman et al., p. 5242

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Lippman et al. (1) assess the effect of raloxifene on the incidence of breast cancer in women with defined risk factors. However, raloxifene is used in clinical practice for the treatment and prevention of osteoporosis in postmenopausal women. To the casual observer, the application of a medicine to treat and prevent osteoporosis would seem to be counterintuitive as estrogen is known to build bones. It therefore follows that if estrogens build bones in postmenopausal women and estrogens support breast cancer growth (2), then why is there a reported decrease in breast cancer in women taking raloxifene to treat osteoporosis (3, 4)?

The reason is that the class of drugs originally known as “nonsteroidal antiestrogens” are in fact selective estrogen receptor (ER) modulators (SERM), which turn on or turn off target sites around a woman’s body. The recognition of targeted estrogenic and antiestrogenic actions for the two principal players tamoxifen and raloxifene was defined in the latter half of the 1980s (Fig. 1; ref. 5). The concept being tested by Lippman et al. (1) is the roadmap described at the end of the 1980s (2, 6) and used by the pharmaceutical industry to develop numerous new SERMs as potential multifunctional medicines (7).

The Concept

A plan to prevent breast cancer as a public health initiative was initially described at the First International Chemo-prevention meeting in New York in 1987. It is reasonable to simply state the proposal, published from the 1987 meeting and subsequently refined and presented at the annual meeting of the AACR in San Francisco in 1989.

“The majority of breast cancer occurs unexpectedly and from unknown origin. Great efforts are being focused on the identification of a population of high-risk women to test ‘chemopreventive’ agents. But, are resources being used less than optimally? An alternative would be to seize on the developing clues provided by an extensive clinical investigation of available antiestrogens. Could analogues be developed to treat osteoporosis or even retard the development of atherosclerosis? If this proved to be true, then a majority of women in general would be treated for these conditions as soon as menopause occurred. Should the agent also retain antibrast tumor actions, then it might be expected to act as a chemosuppressive on all developing breast cancers if these have an evolution from hormone-dependent disease to hormone-independent disease. A bold commitment to drug discovery and clinical pharmacology will potentially place us in a key position to prevent the development of breast cancer by the end of this century (6).” The concept was refined by 1990 (2). “We have obtained valuable clinical information about this group of drugs that can be applied in other disease states. Research does not travel in 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 apparently, 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 postmenopausal women in general, thereby avoiding the requirement to select a high-risk group to prevent breast cancer.” This concept is exactly what has been translated to clinical practice (3, 4): use a SERM (raloxifene) to treat osteoporosis and reduce the incidence of breast cancer as a beneficial side effect.

Laboratory Evidence for SERM Action

During the 1980s, tamoxifen became the first antiestrogenic therapy targeted to the ER for adjuvant therapy (8). The principle was simple. Those patients with ER-positive breast cancer were most likely to have estrogen-stimulated tumors and tamoxifen could be used to block estrogen action. Current analysis of worldwide clinical trials shows that tamoxifen increases not only disease-free survival but also overall survival (9). In the 1980s, few side effects were noted with tamoxifen compared with cytotoxic chemotherapy so the antiestrogen tamoxifen became the standard of care for ER-positive breast cancer whether the patients were node positive or node negative. The widespread use of tamoxifen in node-negative (low risk) breast cancer patients increased interest in testing the worth of tamoxifen as a potential chemopreventive in high-risk women. The reasons were simple: tamoxifen, an antiestrogen, prevented mammary carcinogenesis in animals (10), reduced the occurrence of contralateral breast cancer (9), and at that time, had no major side effects. Unfortunately, the received wisdom in the 1980s was that estrogen was essential to build bones and prevent osteoporosis. In addition, estrogen lowers circulating cholesterol so there was every reason to believe at that time that...
there would be reductions in coronary heart disease with estrogen replacement. If tamoxifen was used in well women only at risk for breast cancer, then there might be a significant decrease in breast cancer but unacceptable increases in osteoporosis and coronary heart disease. However, progress in translational research was to establish the targeted estrogenic and antiestrogenic actions of the first SERMs (11).

Unexpectedly, both tamoxifen and raloxifene (a failed breast cancer drug known as keoxifene) both maintained bone density in ovariectomized rats (12) at doses that would prevent the development of carcinogen-induced rat mammary tumors (13). These data (i.e., the maintenance of bone density and the prevention of breast cancer) were translated to the clinic first with tamoxifen (14) and subsequently with raloxifene (3). A difference in the target site–specific actions of tamoxifen in the mouse uterus or human breast tumor transplanted into immunodeficient mice (15) resulted in the observation that tamoxifen enhanced the growth of human ER-positive endometrial carcinomas but blocked the growth of breast tumors transplanted into the same immunodeficient animal (16). Again, these data translated to the clinic with a reported small but significant increase in the incidence of endometrial cancer in postmenopausal women (14). Thus, the ER complex was being interpreted differently as separate target sites to either stimulate or block growth (15, 16).

More importantly, keoxifene (raloxifene) was noted to have less estrogenic-like actions in the rodent uterus (17) and human endometrial cancer (18) and again this translated to the clinic (3).

Thus, at the end of the 1980s, the foundation for SERM action had been established with a path for progress in prevention described clearly. The SERM ER complex was switching on or switching off target sites around a woman’s body (Fig. 1).
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Modulating Molecular Mechanisms

During the past decade, there has been an enhanced understanding of the complex decision network in tumors and estrogen target tissues that modulate the actions of the SERM receptor complex (Fig. 2). Although there was originally believed to be only one ER, it is now clear that at least two ERs (ER-α and ER-β; ref. 19) can modify estrogen or SERM action. A SERM can choose an ER based on receptor affinity and pharmacokinetics. The two receptors are distributed differently around the human body and may modify ligand interactions by homodimerization or heterodimerization as well as possible interaction with other proteins to modulate signal transduction. Indeed, the idea that the ER is a genomic signaling mechanism must now be modified because ERs are present at the cell membrane to be part of the rapid phosphorylation signal transduction mechanism and are part of the mitochondrial mechanisms for cell survival (20). However, the ligand structure is also important to cause distinct ER folding that will in turn affect the subsequent interactions with other proteins, such as coactivators or corepressors.Raloxifene and tamoxifen are a case in point with minor differences in ligand interaction with specific amino acids producing different intrinsic estrogen actions (5). The tamoxifen ER complex is more estrogen-like in vitro and this may extrapolate to more estrogen-like action in uterus. In contrast, the raloxifene ER complex is much less estrogen-like and has fewer estrogen-like properties in uterus.

The SERM ER complex is modified subsequently by interaction with coactivators that can enhance gene transcription and corepressors that can reduce gene expression (21). The phosphorylation cascade from cell surface growth factor receptors can also enhance ER action further at specific phosphorylation sites on the activating functions of ER (22) or indeed by the phosphorylation of coactivator molecules (23). The interaction of a specific SERM with ER can also determine whether the SERM ER complex will accumulate or be degraded through the proteosome system at a specific tissue site (24). Clearly, accumulation of SERM ER complexes at a target site creates unanticipated opportunities for the SERM ER complex to activate genes through traditional (genomic) or tethered (nongenomic) activation (activator protein sites) of promoter regions of a specific genome (Fig. 2).

Overall, the coordination of the decision network within the separate cell types of a target tissue will result in switching on or switching off tissues around a patient’s body.

A Future for Pharmacology

Raloxifene seems to offer distinct advantages as a SERM for postmenopausal women’s health. The fashion of using indefinite hormone replacement therapy (synthetic estrogen and progesterin) is now past in the wake of the Women’s Health Initiative (25). In contrast to hormone replacement therapy, raloxifene clearly does not increase the incidence of breast cancer when used long-term to treat osteoporosis. Women have a 65% to 70% decrease in breast cancer incidence (3, 4) and this is superior to the 50% noted with tamoxifen in the prevention trials (14). But, will raloxifene do as well in the general population of women at risk for breast cancer rather than those who already have low estrogen levels and a very low risk for breast cancer (1)? Tamoxifen and raloxifene are competitive inhibitors of estrogen binding to the ER. To act as an antiestrogen in aberrant breast epithelium, the receptor must be blocked all the time. It is known that raloxifene has poor bioavailability (2%) in women (26) and the group of SERMs related to raloxifene have very rapid excretion. In contrast, tamoxifen has an extremely long half-life with drug levels that can be measured up to 6 weeks after stopping treatment. Tamoxifen is metabolized to high-affinity antiestrogens (27), whereas raloxifene is not. It may be that compliance becomes an issue in healthy postmenopausal women with a high body mass index and, as a consequence, higher circulating levels of estrogen. The appropriate dose of raloxifene that is good for building bones may not be optimal for completely blocking the growth of occult breast cancer over the first 5 years of treatment. Only the continuous blockade of occult tumor ER may be optimally effective at reducing both invasive and noninvasive breast cancer when the drug is applied outside the setting of the Lippman study (1). Analysis of the results of the
Study of Tamoxifen And Raloxifene (STAR) will be important for future studies. Clearly, the next generation of SERMs may need to be long acting if they are to become optimal multifunctional agents to prevent breast cancer and osteoporosis.

There is value in deciphering the target site–specific actions of ligands at ER-α and ER-β (28). Numerous diseases may be treated with receptor-specific ligands. However, because the promise of SERMs has become a clinical reality, this has caused a re-examination of other members of the steroid receptor superfamily. In the decades to come, perhaps there will be selective androgen receptor modulators, selective glucocorticoid receptor modulators, etc. that create a new dimension for multifunctional medicines in medical practice.

References
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