Molecular Mechanisms of Selective Estrogen Receptor Modulator (SERM) Action

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ABSTRACT
In females, estrogens play a key role in reproduction and have beneficial effects on the skeletal, cardiovascular, and central nervous systems. Most estrogenic responses are mediated by estrogen receptors (ERs), either ERα or ERβ, which are members of the nuclear receptor superfamily of ligand-dependent transcription factors. Selective estrogen receptor modulators (SERMs) are ER ligands that in some tissues act like estrogens, but block estrogen action in others. Thus, SERMs may exhibit an agonistic or antagonistic biocharacter depending on the context in which their activity is examined. For example, the SERMs tamoxifen and raloxifene both exhibit ER antagonist activity in breast and agonist activity in bone, but only tamoxifen manifests agonist activity in the uterus. Numerous studies have examined the molecular basis for SERM selectivity. Collectively they indicate that different ER ligands induce distinct structural changes in the receptor that influence its ability to interact with other proteins (e.g., coactivators or corepressors) critical for the regulation of target gene transcription. The relative expression of coactivators and corepressors, and the nature of the ER and of its target gene promoter affect SERM biocharacter. Taken together, SERM selectivity reflects the diversity of ER forms and coregulators, cell type differences in their expression, and the diversity of ER target genes. This model provides a basis for understanding the molecular mechanisms of SERM action, and should help identify new SERMs with enhanced tissue or target gene selectivity.

Selective Estrogen Receptor Modulators (SERMs): Puzzling Pharmacological Agents
In addition to their key role in female reproductive function, estrogens have beneficial actions on unrelated tissues, as demonstrated by the effects of estrogen replacement therapy in postmenopausal women (Mitlak and Cohen, 1997; Cosman and Lindsay, 1999). Estrogens inhibit bone resorption and can prevent osteoporosis. In addition, many studies suggest that estrogens, in part through effects on hepatic lipid metabolism, have beneficial effects on the cardiovascular system and decrease the incidence of coronary heart disease. Although further investigations are required, estrogen exposure also has been associated with improvements in cognitive function and a delay in the onset of Alzheimer's disease. In contrast, estrogen exposure is associated with an increase in the incidence of breast cancer and of various uterine lesions, including tumors (Cosman and Lindsay, 1999).
Breast cancer is the second most common cancer and cause of cancer mortality among women in the United States. Because estrogens are thought to support breast cancer, many estrogen antagonists have been developed. As anticipated, such antiestrogens can inhibit breast cancer growth (Cosman and Lindsay, 1999) and act through the estrogen receptor (ER). However, some of them have been recently re-classified as SERMs because they manifest variable agonist and antagonist properties (biocharacter) when examined in the context of estrogen-dependent responses occurring in various tissues. Moreover, different SERMs exhibit distinct biocharacter profiles (Mitlak and Cohen, 1997; Cosman and Lindsay,
Although the relative agonist and antagonist properties of SERMs in a given tissue could be due to differences in their activities in distinct cell types, in vitro experiments show that individual SERMs can have distinct activities in the same cell type.

One of the first SERMs to be described was tamoxifen (Fig. 1), and, to date, it is the most widely used antiestrogen for the management of breast cancer. In addition to being used for the prevention and treatment of breast cancer, tamoxifen has beneficial effects on bone after menopause. However, prolonged treatment increases the risk for endometrial cancer (Mitlak and Cohen, 1997; Cosman and Lindsay, 1999). Thus, tamoxifen behaves as an ER antagonist in the mammary gland and as an agonist in the uterus and bone. It should also be noted that in the treatment of metastatic breast cancer, although tamoxifen is initially beneficial, it can eventually stimulate tumor growth (Osborne and Fuqua, 1994). More recently, another SERM, raloxifene, is being used for the prevention of osteoporosis (Fig. 1; Cosman and Lindsay, 1999). Like tamoxifen, raloxifene is an ER antagonist in breast and an agonist in bone. However, it does not exert ER agonist properties in the uterus (Mitlak and Cohen, 1997; Cosman and Lindsay, 1999). Both tamoxifen and raloxifene also have beneficial, estrogen-like effects in the liver with respect to lipid metabolism (Mitlak and Cohen, 1997; Cosman and Lindsay, 1999). Taken together, current SERMs are useful pharmacological agents for the prevention and/or treatment of osteoporosis and breast cancer. However, tamoxifen and raloxifene use is not without drawbacks. For instance, these drugs do not alleviate vasomotor symptoms (hot flushes and night sweats) associated with estrogen loss and often exacerbate their frequency and/or intensity (Cosman and Lindsay, 1999). Thus, there is an ongoing, intensive search for SERMs with improved antagonistic effects in breast and uterus and robust agonistic actions in the skeletal, cardiovascular, and central nervous systems.

To design rational methods for the discovery and efficient profiling of new SERMs, a need has arisen for a better understanding of the mechanisms underlying their effects, particularly their selectivity. Differences in the uptake and/or the metabolism of SERMs have been suggested to contribute to their tissue-selective actions. Although such mechanisms potentially contribute to SERM selectivity, there is little evidence to support this possibility as a primary mechanism. Furthermore, as will be discussed below, the fact that a given SERM can exhibit ER agonist or antagonist activity on different genes in a given cell type in vitro experiments suggests that it is the mechanism of ligand binding to the ER and of the actions that follow this interaction that determine SERM biocharacter. In other words, the diversity of SERM biological activity reflects the complexity of the mechanisms underlying ER action.

**Mechanisms of Estrogen Receptor Action**

**Estrogen Receptors.** Most estrogen effects are mediated by specific receptors, of which two subtypes have been identified, ERα and ERβ (Gustafsson, 1999). These are encoded...
by two distinct genes that belong to the superfamily of nuclear hormone receptors, which includes receptors for various steroid and thyroid hormones, retinoids, and other small, hydrophobic molecules (Tsai and O'Malley, 1994). ERα and ERβ are similar in size (~600 and 530 amino acids, respectively) and structure (Fig. 2; Gustafsson, 1999). In particular, they share ~53% amino acid identity in the ligand binding domain (LBD), which is located within the carboxyl-terminal half of the molecule and enables it to bind physiological estrogens and synthetic SERMs. Although ERα and ERβ exhibit similar binding properties to most hormones and antiestrogens studied to date (Kuiper et al., 1998), several new compounds have been shown to bind preferentially to specific ER subtypes (Sun et al., 1999).

Estradiol and tamoxifen have been shown to induce very rapid (within 5 min) nongenomic effects. Although some of them appear to be mediated by the ER (Collins and Webb, 1999), the molecular mechanisms involved are poorly understood. Furthermore, ER-independent effects also have been reported. In contrast, ER-dependent genomic effects, which are readily observed after 15 to 30 min of drug treatment, mediate estrogen and SERM responses in various tissues and rely on receptor binding to ligand and subsequent alterations in target gene transcription, events which provide a common framework to understand the actions of SERMs. Moreover, when analyzed for their ability to regulate ER actions on target promoters in in vitro systems, SERMs display two features of selectivity. First, different SERMs can exhibit a distinct biocharacter in a given cell and promoter context, and second, a given SERM can manifest a different biocharacter depending on both the cell and promoter context. To address the mechanisms underlying SERM selectivity, we shall consider first the mechanisms by which the ER regulates the transcription of target genes.

“Classic” Pathway. In the best understood, classic pathway, estradiol binding to the LBD enhances ER interaction with specific DNA sequences, called estrogen response elements (EREs), which may be present at different positions and in varying numbers within the target gene (Tsai and O'Malley, 1994). The DNA binding domain (DBD) of the ER, through which receptors interact with EREs, consists of ~70 amino acids which are centrally located in the protein (Fig. 2). ERα and ERβ share ~96% amino acid identity in their DBDs and exhibit similar DNA binding characteristics on a consensus ERE. However, binding (and subsequent activation) of the osteopontin gene promoter through a variant ERE is achieved by ERα, but not by ERβ (Vanacker et al., 1999).

Hormone-bound ER interacts with EREs as homo- or heterodimers of ERα and ERβ (Tsai and O'Malley, 1994; Hall and McDonnell, 1999, and references therein). Following DNA binding, the activation of transcription per se involves two domains of the ER, called activation function (AF)-1 and AF-2. The AF-2 domain is located in the relatively well conserved, carboxyl-terminal half of ERα and ERβ, and overlaps with the LBD (Fig. 2). Its activity is induced by estradiol binding. On the other hand, the AF-1 domain is located in the amino-terminal region of the ER, which is poorly conserved between ERα and ERβ both structurally (~30% amino acid identity; Fig. 2) and functionally (Hall and McDonnell, 1999). The AF-1 domain exhibits ligand-independent activity when isolated from the LBD, which can be enhanced by the ras/mitogen-activated protein kinase signaling pathway (Smith, 1998).

Both AFs act, at least in part, by recruiting coactivators, which are molecules that enhance the transcription of target genes without themselves binding DNA (McKenna et al., 1999; Glass and Rosenfeld, 2000). The best characterized ER coactivators include the p160 SRC (Steroid Receptor Coactivator) family members and p300/CBP. Although most studies have focused on the induction of AF-2/coactivator interactions by estradiol and their inhibition by antiestrogens (Hannstein et al., 1996; Vögel et al., 1996; Kalkhoven et al., 1998), several studies have shown that the AF-1 can physically and functionally interact with coactivators in a hormone-independent manner (Lavinsky et al., 1998; Webb et al., 1998; Endoh et al., 1999). Coactivators may function by remodeling the chromatin structure of the target gene promoter, as well as by facilitating the initiation of transcription by general transcription factors and RNA polymerase II through protein-protein interactions (McKenna et al., 1999; Glass and Rosenfeld, 2000).

![Fig. 2. Domain organization and sequence homology of human ERα and ERβ. The bars represent human ERα and ERβ molecules divided into their structural domains (A to F). Amino acid positions are indicated at region boundaries. Functional regions are depicted at the bottom. The percentage of amino acid identity between human ERα and ERβ is indicated for each region.](https://example.com/fig2.png)
Other Pathways and Target Promoters. Estradiol also has been shown to regulate the transcription of some genes that do not contain EREs through functional interactions with other transcription factors that bind to their cognate DNA elements within the promoter region of these genes (McDonnell, 1999). For example, estradiol stimulation of several genes requires the binding of the transcription factors AP-1 or Sp1 to their cognate DNA binding sites, as well as the presence of the ER, but does not involve the direct binding of the ER to DNA (Webb et al., 1995; Saville et al., 2000). In other cases, estradiol induction is mediated by a combination of EREs and Sp1 binding sites located in the same promoter (Saville et al., 2000). Estradiol has also been shown to inhibit the expression of other target genes through interactions with and subsequent negative regulation of transcription factors, such as nuclear factor-κB (NF-κB), CCAAT/enhancer-binding protein β (C/EBPβ), and GATA-1 (McDonnell, 1999). Finally, because some coactivators interact with the ER as well as with other transcription factors (McKenna et al., 1999), the ER may modulate the activity of other transcription factors by competing for binding to common coregulatory proteins.

Molecular Basis for Distinct SERM Biocharacter

General Model. The first model for the regulation of ER activity by estrogens and antiestrogens (for review, see Katzenellenbogen et al., 1996) relied on two assumptions. First, the ER exists in one of two discrete states, either "off" or "on", in every responsive cell. The off state is found in the absence of ligand or in the presence of antagonists, and the on state is specifically induced by agonists. Second, the biocharacter of a ligand is determined entirely by its own structure, which determines its affinity for the receptor and its ability to induce a switch from the off to the on state (or vice versa), regardless of cell type. Thus, any given ligand was predicted to have the same biocharacter in every cell.

To account for the ability of SERMs to activate the ER in some tissues while inhibiting it in others, the current model proposes that the biocharacter of the ligand depends not only on its structure, but also on the particular set of molecules that interact with the ER after it binds to ligand (Katzenellenbogen et al., 1996). We will essentially update that model by taking into account more recent data. It can be summarized as follows: 1) different ER ligands (e.g., SERMs) may bind ERα and ERβ selectively; 2) the nature of the ligand and of the ER subtype determine the conformation of the ER-ligand complex; 3) the structure of the ER-ligand complex determines its ability to interact with other molecules; 4) some of these molecules, as well as the ER subtypes themselves, may be differentially expressed or accessible to the SERM-ER complex in a cell type-specific fashion; and 5) the molecular interactions involving the ER determine its activity on a target promoter.

The molecules that interact with the ER and affect SERM biocharacter are primarily coregulators (coactivators and corepressors, see below), but may also include specific and general transcription factors and the DNA that provides the organizational context for these interactions. The chromatin structure at the target gene promoter may also vary between cell types and affect ER activity. Post-translational modifications, such as phosphorylation and possibly acetylation of ER and coregulators, may also regulate their interactions and activities (Smith, 1998; Chen et al., 1999; McKenna et al., 1999; Glass and Rosenfeld, 2000). It should also be noted that these interactions may take place in multiple steps. Current studies are assessing the individual roles of the nature of the SERM, ER subtype, target gene promoter, and particular ER-interacting factors, as well as the role of differences between cell types, in SERM selectivity. In general, these issues have been addressed using in vitro cell models in which a specific ER subtype and target promoter are introduced into a given cell type.

Different SERMs Induce Different Conformations of the ER. In many circumstances, different SERMs exert distinct effects on the activity of a given ER subtype in a fixed cell and promoter context. For example, the SERMs tamoxifen, raloxifene, and GW5638 exhibit different biological activities on the complement 3 promoter (which contains imperfect EREs) in a hepatoma cell line expressing exogenous ERα (Willson et al., 1997). Various approaches, using either proteolytic peptide mapping, antibody epitope mapping, crystallography, or affinity selection of peptides, have shown that different ligands induce distinct receptor conformations in the LBD of both ERα and ERβ, and that antiestrogens such as tamoxifen and raloxifene induce structures that are different from that of the unliganded receptor (Martin et al., 1988; McDonnell et al., 1995; Brzozowski et al., 1997; Shiau et al., 1998; Paige et al., 1999; Pike et al., 1999). Furthermore, the structures of ERα and ERβ are similar, but not identical. These observations dispel the notion that the ER exists in only two discrete states as assumed in early models of ER action and suggests that many ligand-receptor complex structures are possible.

SERMs Affect the Ability of the ER to Interact with Coregulators. As discussed above, estradiol enhances ER transcriptional activity by promoting functional and physical interactions with coactivators. Several coactivators have also been shown to interact functionally with tamoxifen-bound ER. Namely, the SRCs, p300/CBP, p68 RNA helicase, and L7/SPA increase the partial agonist activity of tamoxifen on ERE-based promoters (Jackson et al., 1997; Smith et al., 1997; Lavinsky et al., 1998; Webb et al., 1998; Endoh et al., 1999). Furthermore, in a cell line in which tamoxifen stimulates ER activity on such promoters, SRCs are required for this agonistic response (Lavinsky et al., 1998). Interestingly, in the case of L7/SPA, functional and physical interactions with the ER are increased selectively by tamoxifen, but not by estradiol (Jackson et al., 1997). Because different SERMs confer on a given ER the ability to interact with overlapping yet distinct complements of synthetic peptides that resemble receptor-interacting motifs found in coactivators (Paige et al., 1999), it is likely that different SERMs differentially regulate ER-coregulator physical interactions. In the case of those SERMs that do not inhibit the AF-1 activity of the ER, such as tamoxifen (Tzukerman et al., 1994; McDonnell et al., 1995; Willson et al., 1997), the AF-1 may recruit coactivators such as SRCs and p68, which have been shown to interact with this region (Lavinsky et al., 1998; Webb et al., 1998; Endoh et al., 1999). By analogy with the progesterone receptor, the interaction with L7/SPA probably maps to the hinge region of the ER, which is located between the DBD and the LBD (Jackson et al., 1997). Physical interactions of the ER LBD...
with the coactivators studied in this respect were not enhanced by tamoxifen in vitro (Hanstein et al., 1996; Voegel et al., 1996; Kalkhoven et al., 1998), and crystallographic studies indicate that upon either tamoxifen or raloxifene binding, the position of a portion of the LBD (helix 12) prevents coactivator binding to its recognition groove on the surface of the LBD (Shiau et al., 1998). Taken together, these data suggest that the identity of the coactivators and/or the ER regions with which they interact may be different, depending on whether estrogen or a SERM is bound to the ER.

On the other hand, corepressor proteins mediate transcriptional repression by several nuclear receptors, such as the thyroid hormone and retinoic acid receptors, in the absence of their cognate agonists (McKenna et al., 1999; Glass and Rosenfeld, 2000). Two coreshapers, SMRT and N-CoR, reduce the agonist activity of tamoxifen, but not estradiol (Jackson et al., 1997; Smith et al., 1997; Lavinsky et al., 1998). Furthermore, blocking N-CoR and SMRT function promotes the agonist activity of tamoxifen in cells in which it normally is an antagonist (Lavinsky et al., 1998). Tamoxifen-bound ER can physically interact with N-CoR and SMRT (Jackson et al., 1997; Smith et al., 1997; Lavinsky et al., 1998). Moreover, in cells in which tamoxifen is an antagonist, tamoxifen, but not estradiol, enhances ER interactions with N-CoR (Lavinsky et al., 1998). Recently, two other proteins, called REA (Montano et al., 1999) and HET/SAF-B (a nuclear matrix protein; Oesterreich et al., 2000), have been shown to bind to the ER and repress its activity in the presence of tamoxifen and estradiol. Importantly, REA increases the inhibitory potency of tamoxifen.

Cumulatively, these data suggest that different ligands confer on the ER the ability to interact with distinct subsets of coactivators and corepressors that regulate receptor function. Moreover, the relative expression of SMRT and SRC-1 in a given cell type has been shown to affect the ability of tamoxifen to activate the ER (Smith et al., 1997). Together, these data suggest that SERM biocharacter is determined, at least in part, by the specific set and/or the ratio of coactivators and corepressors expressed in a given cell with which the ER interacts as a consequence of its binding to ligand. Furthermore, the cell type-dependence of SERM biocharacter could be due in part to differences between cell types in the relative expression levels of coregulators, especially those that differentially interact with the ER, depending on whether it is bound to estradiol or a SERM. Indeed, the expression of some coregulators has been found to vary in different cell lines and tissues (Voegel et al., 1996; Kalkhoven et al., 1998), and in intraductal carcinoma in comparison to normal mammary gland (Kurebayashi et al., 2000).

**SERM Biocharacter Depends on the Nature of the ER Subtype.** In cell lines transfected with an ERE-based reporter, tamoxifen is a partial agonist of ERα and a pure antagonist of ERβ (Hall and McDonnell, 1999). Similarly, on an AP-1-based target gene transfected into uterine cell lines, both tamoxifen and raloxifene exhibit a different activity depending on whether ERα or ERβ is expressed (Paech et al., 1997; Jones et al., 1999); interestingly, in this cell and promoter context, estradiol effects also depend on the nature of the ER subtype (Paech et al., 1997). Furthermore, when both ER subtypes are coexpressed in the same cell, their combined response to a ligand can be distinct from the responses of either subtype alone and likely depends on the ratio between ERα and ERβ (Hall and McDonnell, 1999; Jones et al., 1999). The fact that ERα and ERβ are differentially expressed in various tissues (Gustafsson, 1999) and can respond differentially to a given SERM may partially account for the tissue-selectivity of SERMs. Whereas raloxifene has a 4-fold higher affinity (relative to 17β-estradiol) for ERα than ERβ, the relative affinity of tamoxifen for both receptors is similar (Kuiper et al., 1998). Thus, receptor-ligand affinity considerations are not likely to make a major contribution to the selective activity of these SERMs, and the molecular mechanisms underlying differences between ER subtypes with respect to SERM activity remain to be defined. Because in vitro studies have shown that SERM-bound ERα and ERβ interact with different complements of synthetic peptides that resemble the receptor-interacting motifs found in coactivators (Paige et al., 1999), it seems likely that the two receptors possess different abilities to interact with coregulatory molecules.

**SERM Biocharacter Depends on the Nature of the Target Promoter.** This has been illustrated for both ERα and ERβ. For example, in a uterine cell line transfected with ERs, tamoxifen increases the activity of an AP-1-based promoter at least as well as estradiol, is a full antagonist on an ERE-containing promoter, and is a partial agonist on the TGFβ promoter, in which both ERE and Sp1 sites play a role in mediating ER effects (Webb et al., 1995; Jones et al., 1999). The exact sequence of the ERE may also affect SERM activity. Indeed, a synthetic, variant ERE promotes higher agonist activity of tamoxifen compared with the consensus ERE in transient transfection experiments (McDonnell, 1999). The influence of local chromatin structure on SERM biocharacter and the possibility of a differential use of coregulators on specific promoters remain to be investigated.

**Influence of Intracellular Signaling Pathways on SERM Activity.** SERM biocharacter may vary depending on the activity of intracellular signaling pathways that are induced by extracellular factors (e.g., growth factors) and can cross talk to ERs (Smith, 1998). Indeed, in the ERα-positive human breast cancer cell line MCF-7, activation of the cAMP/protein kinase A pathway increases the partial agonist activity of tamoxifen and decreases its antagonist activity (Fujimoto and Katzenellenbogen, 1994). Similarly, in HeLa (uterine cervical adenocarcinoma) cells, both cAMP and dopamine, a neuromodulator that acts in part through the cAMP/protein kinase A pathway, increase the partial agonist activity of tamoxifen (Smith et al., 1997). Effects such as these could contribute to the resistance of ER-positive breast cancer to tamoxifen therapy (Fujimoto and Katzenellenbogen, 1994). Cyclic AMP apparently increases the agonist activity of tamoxifen by altering the recruitment of coregulators. Indeed, CAMP (as well as epidermal growth factor) inhibits the tamoxifen-induced recruitment of the corepressor SMRT to ERα (Lavinsky et al., 1998). Also, SRC-1 enhances ER activity induced by cAMP and tamoxifen (Smith et al., 1997). More generally, extracellular signals may modulate SERM activity by regulating the expression, activity, and interactions of ERs and their coregulators.

**Conclusions and Perspectives**

Major advances in our understanding of ER action provide a framework for studying the mechanistic basis of SERM
effects. In this model, the biocharacter of a given SERM, which can range from full agonist to inverse agonist, is determined by its structure, the ER it binds to, and the set of molecules that interact with the ER-SERM complex in a particular cell and promoter context. Because SERM selectivity appears to reflect the diversity of ER subtypes and coregulators, differences in their expression, and the complexity of ER target gene promoters, it is crucial to explore these aspects of ER action in more detail. In particular, there is a need to identify physiologically and clinically relevant ER target genes, as well as the DNA elements and transcription factors that mediate ER effects on these genes.

Coregulators play a key role in this model, so a major goal is to understand how their recruitment to ERα and ERβ is controlled by the nature of the SERM, target promoter, and cell type, and how their activity is regulated. In this regard, there is a need to fully characterize existing and yet-to-be-identified coregulators that physically and functionally interact with the ER bound to estrogens and SERMs. These studies should include the mapping of coregulator-interacting regions in the ER and defining the structural constraints of ER-coregulator interactions. Another crucial issue is to examine the expression patterns of coregulators in various cell types and in normal versus abnormal tissues, and to assess the effects of SERMs on their expression. There is also a need to analyze the effects of intracellular signaling pathways on the recruitment of coregulators to the ER and on their intrinsic activity, and to understand how coregulators cooperate with each other to integrate the actions of the ER and other transcription factors at specific promoters. Other aspects that need to be further investigated are the potential role of nongenomic actions of estrogens and SERMs, and of tissue-specific differences in the uptake and metabolism of SERMs. Finally, future studies should also assess the potential role of physiological ER ligands other than 17β-estradiol (e.g., estrone and sulfated estrogens) in mediating or modulating estrogenic responses in a tissue-specific manner (Baracat et al., 1999).

Combined with the further identification of clinically relevant target genes, these studies should improve the efficiency of designing and profiling new SERMs to meet clinical needs. Critical tools now in hand include structural modeling based on crystallographic data of ER-SERM-coactivator interactions (Shiau et al., 1998), affinity selection of peptides that mimic specific ER-interacting surfaces found in coregulators (Norris et al., 1999), ER transcriptional activity assays in cellular systems in vitro, and SERM profiling in animals. By taking advantage of the molecular diversity of ERs and of their targets, and defining their selective involvement in various estrogenic responses, it should be possible to design new SERMs with biological activity profiles that meet specific medical needs.

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