genetic lesions such as p53 ablation, is expected to reveal gastric cancer predisposition and could provide more detailed insight into the roles of Runx3 in tumor initiation and progression and its possible interactions with cofactors. Alternatively, a conditional *Runx3* knockout mouse may serve this purpose. In addition, such mouse models will allow investigation of the extent to which loss of RUNX3 complements or substitutes for other lesions known from gastric cancers, such as E-cadherin loss, RAS mutations, and loss of DCC. It can be expected that this mouse model for gastric cancer will greatly assist unraveling of the underlying molecular causes for this important widespread disease in the coming years.

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The secrets of selective estrogen receptor modulation: Cell-specific coregulation

A specific increase in the level of a single coactivator appears to enhance estrogen action with tamoxifen at some gene targets in uterine cells but not breast cells.

The discovery and development of antiestrogens as treatments for estrogen receptor (ER) positive breast cancer (Lerner and Jordan, 1990) introduced a new approach for targeted therapy with few side effects compared to traditional cytotoxic chemotherapy. The novel so-called nonsteroidal antiestrogens, initially investigated during the 1960s, were all classified as partial estrogen agonists in the rat uterus but with a predominantly antiestrogen action. This pharmacologic activity in the laboratory extrapolated to antitumor action by blocking estrogen-stimulated breast tumor growth at the ER. Tamoxifen was introduced clinically during the 1970s, and the drug has had a profound effect on patient survival. It is estimated that 400,000 women are alive today because of the success of tamoxifen treatment. However, tamoxifen is a pioneering medicine over and above its ability to save lives.

The recognition of selective estrogen receptor modulation in the laboratory during the 1980s (Jordan, 2001) has had important implications not only for the evaluation of the side effects associated with tamoxifen, but also has established the rationale for a new class of drugs, the selective estrogen receptor modulators (SERMs). It is now clear that SERMs have potential as multifunctional medicines. The SERMs express estrogen-like actions in bone, lower circulating cholesterol, but produce an antiestrogenic action in the breast. The actions of tamoxifen in the endometrium are important because they illustrate the concept of selective ER modulation. When both breast and endometrial tumors are implanted into immune deficient mice (Gottardis et al., 1988), tamoxifen enhances the growth of endometrial cancer but prevents the growth of breast cancer. The tamoxifen ER complex is perceived as an estrogen in endometrial cancer cells but as an antiestrogen in breast cancer. This concept translated to the clinic with a predicted modest rise in the incidence of endometrial cancer in postmenopausal women during tamoxifen therapy. The question is, how is the pharmacology of tamoxifen reversed in

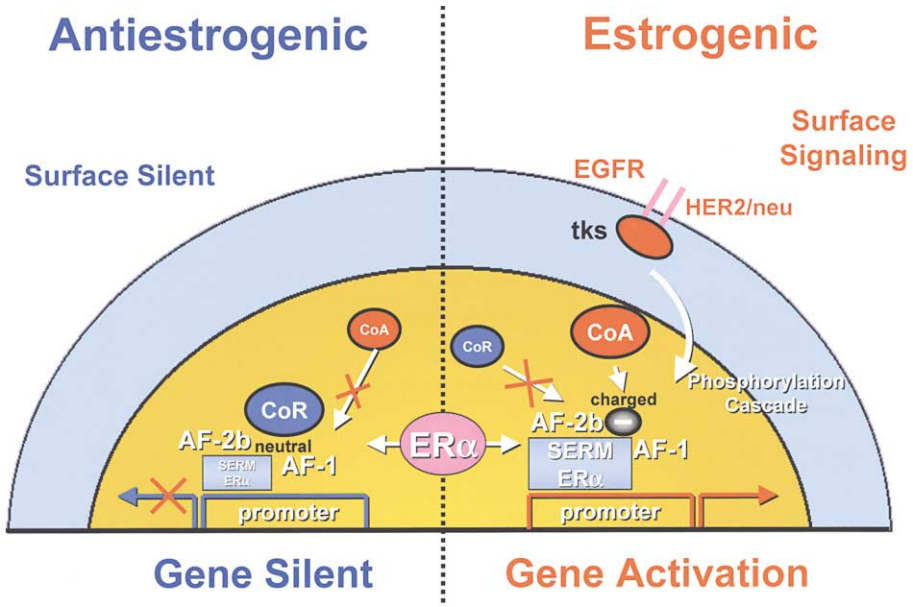

Figure 1. Integrated mechanism for the target site specific action of SERMs in breast or uterine cancer

The two extremes of antiestrogenic or full estrogenic actions are shown. Estrogen-like actions could occur in cells expressing an excess of coactivators (CoAs) and/or a decrease in corepressors (CoRs). The charged surface of a tamoxifen ER complex at AF2b prevents CoR binding. The estrogenic action would be amplified by surface signaling with dimers of epidermal growth factor receptor (EGFR) and HER2/neu activating tyrosine kinases (tks). The phosphorylation cascade can activate AF-1 on ERα directly or activate the excess of CoAs in a high ER environment. Reduced levels of ER prevent the signal transduction pathway and promote antiestrogenic actions in a surface silent cell.

select target tissues?

A recent article in *Science* by Shang and Brown (2002) describes two novel differences between genes activated by the tamoxifen ER complex in uterine or breast cancer cells: (1) gene transcription depends on nontraditional promoter docking for activation, and (2) gene activation depends upon an elevated level of a specific coregulatory protein SRC-1. The advance is intriguing because an understanding of the complex issue of SERM action has such important implications in therapeutics. However, the report by Shang and Brown is part of an evolving story that will continue to take many twists and turns before the secrets of SERMs are fully deciphered.

Berry and coworkers (Berry et al., 1990) were the first to show that the estrogen-like effects of tamoxifen complexes were dependent both on the promoter and the cell context. The AF-1 region at the N-terminal end of the ER was identified as the site for the superinduction of the tamoxifen ER complex signal pathways in the correct context.

Current thinking about SERM action has focused attention on specific coregulators of signal transduction. SERMs can produce specific conformational changes in the external shape of the ER complex that in turn influence the binding of corepressors to prevent transcription or coactivators to enhance transcription (Katzenellenbogen et al., 1996) (Figure 1). Shang and Brown (2002) provide compelling evidence that the up- or downregulation of the coactivator SRC-1 can increase or decrease the estrogen-like action of the tamoxifen ER complex in either breast or endometrial cancer cells. The coactivator model is based on the law of mass action; i.e., more coactivator at a site activates, and less coactivator deactivates, the SERM receptor complex. However, the SERM raloxifene is not influenced by these molecular maneuvers. Raloxifene, a chemical cousin of tamoxifen, selectively enhances estrogen-like actions in bones, breast, and liver (to lower circulating cholesterol levels), but most importantly has less estrogen-like activity in the uterus. This fact supports the author's model, but what is the difference between tamoxifen and raloxifene?

The key appears to be the surface amino acid aspartate at position 351 in ERα. This aspartate has only a weak interaction with the antiestrogenic side chain of tamoxifen. In contrast, the antiestrogenic sidechain of raloxifene completely shields and neutralizes the charge. The exposure of a surface charge could therefore be connected with the promiscuous estrogen-like properties of the tamoxifen ER complex. Indeed, molecular manipulation of the raloxifene ER complex by changing the charge at 351 and the side chain of raloxifene results in the modulation of the antiestrogenic complex to an estrogen (Liu et al., 2002). It is argued that an increased charge at 351 prevents the binding of corepressor modules (Yamamoto et al., 2001) (Figure 1). Thus, the give and take of coregulators by the SERM receptor complex can explain some, but not all, of the target site specific actions of SERMs.

A study of cancer can provide an insight into the physiology of SERM action, because the malignant cell has such a profound ability to adapt its biochemistry to survive. Tamoxifen has a unique form of acquired drug resistance in breast and uterine cancer expressed as tamoxifen-stimulated growth. Raloxifene is crossresistant with tamoxifen in breast and endometrial cancer, so a simple increase of coactivators or loss of corepressors may not be the whole story.

Cell surface signaling through the epidermal growth factor receptor family is associated with increased phosphorylation pathways that promote growth. The estrogen-like action of the tamoxifen ER complex can be modulated by phosphorylation cascades that either converge on AF-1 or the coactivators (Feng et al., 2001). Indeed, the fact that estrogen can downregulate HER-2/neu (a member of the EGFR family) synthesis by sequestering SRC-1, but tamoxifen can enhance the transcription of HER-2/neu by releasing excess SRC-1 from the SERM ERα complex, creates an intriguing model to facilitate the development of drug resistance and the self-sustaining activation of the tamoxifen ER complex (Newman et al., 2000). The central role for SRC-1 in the expression of the estrogen-like effects of tamoxifen identified by Shang and Brown (2002) creates a starting point to examine the possibility of a cell surface phosphorylation cascade for the modulation of the SERM ER complex in endometrial cancer. It is therefore appropriate to take an integrated view of the target site activa-

tion of genes by SERMs in cancer (Figure 1). A decrease in coactivators (CoA) in a corepressors (CoR) dominant environment predestines antiestrogen action in the cell with a silent surface. In contrast, a cell where the SERM ER complex is charged and cannot bind CoRs will be predestined to have estrogen-like effects. If CoAs were increased and the cell surface was activated to produce a phosphorylation cascade, this would be predicted to enhance the estrogen-like of an appropriate SERM.

The successful clinical application of tamoxifen has driven research to seek clinical improvements and understand the molecular mechanisms of SERMs. Tamoxifen has been referred to as the Rosetta Stone with which to decipher molecular mechanisms at the ER that have importance in health care. Now the expectation is to develop a series of multifunctional medicines to treat and, most importantly, prevent a spectrum of diseases ranging from breast cancer and osteoporosis to coronary heart disease. The Shang and Brown article is yet another step toward that goal.

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