dammed lakes, many of which spilled catastrophically.

Long geologic records from river basins bear witness of repeated superflooding. The Columbia basin was affected by superfloods numerous times over the past 1.5 to 2.5 million years (*6*). Its flood sediments were introduced into the Pacific Ocean, where they were transported as turbidity currents along a 1000-km path across the sea floor (*7*). Hydraulic reconstructions of the flood discharges show that their magnitude can be substantial: The Missoula and Altai superfloods achieved peak discharges of about 20 million m^3/s (*5*), comparable to the volume of water moved by many ocean currents.

Ocean currents rarely move faster than a few m/s, whereas superflood flows may move several tens of meters per second. High-discharge floods in narrow, deep bedrock channels also generate immense magnitudes of power per unit area and of bed shear stress (*8*). Paleohydraulic calculations have shown that high-energy floods may lead to large-scale turbulence, cavitation, boulder transport (see the figure), suspension of very coarse particles, and abrupt changes in flow dynamics (*8*). The bedrock is scoured to form longitudinal grooves, giant potholes, inner channels, and cataracts. Deposited material forms giant current ripples composed of gravel and boulders and immense bars of gravel and boulders. Slackwater sedimentation occurs at the margins of the flood discharge channels.

These well-documented features associated with superflooding have been used to infer even more spectacular flooding scenarios during the last ice age. In a recent interpretation of the central Asian evidence, Grosswald (*9*) infers that immense volumes of water were conveyed from the margins of the great ice sheets that occupied what are now the shallow continental shelves of northern Asia. The floodwater moved southwestward, not only cutting spillways between the major north-flowing river systems but also inundating hundreds of kilometers of intervening upland to produce an east-west flow pattern in the topography that is apparent on satellite images of central Asia. Another much-disputed theory ascribes subglacial landforms associated with the late-glacial ice sheets to meltwater flooding beneath the ice, leading to outburst flooding at the ice margins (*10*).

These highly controversial studies of superfloods show that flood science has not achieved the universally accepted valid scientific methodology envisioned by Lyell. Instead, it is my view that superflood studies are motivated by a notion introduced by Whewell, who proposed in 1840 that productive scientific hypotheses work toward achieving "consilience," a kind of confirmation through the unexpected connections and explanatory surprises they engender.

The most unexpected superflood connection has been the discovery of immense flood channels on Mars, which have morphologies that are best explained by direct comparison to flood-eroded landscapes on Earth (*11*). Less spectacular, but highly relevant to human adaptation to flood hazards, is paleoflood hydrology (*12*) in which the generally smaller floods of the last several thousand years are reconstructed with techniques previously applied to the study of the superfloods of the last ice age.

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PERSPECTIVES: BIOMEDICINE

Defining the "S" in SERMs

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Successful treatment of hormone-responsive breast cancer with the drug tamoxifen represents a major accomplishment for cancer chemotherapy. Tamoxifen, which opposes the action of estrogen in certain tissues and mimics the action of this hormone in others, has been an important contributor to the decline in breast cancer mortality rates during the past decade. In the first significant demonstration of cancer chemoprevention, women at high risk of breast cancer who take tamoxifen or a related drug, raloxifene, halve their risk of developing the disease (*1, 2*). But despite its effectiveness in blocking estrogen action in the breast, tamoxifen has an Achilles heel—it stimulates proliferation of endometrial cells in the uterus, putting women who take it at a somewhat increased risk of developing endometrial cancer. Shang and Brown, reporting on page 2465 of this issue (*3*), bring new insight to this conundrum. They reveal that the contradictory action of tamoxifen in the breast and uterus depends on a combinatorial collaboration between its binding partner, the estrogen receptor, and a specific cellular coregulatory protein, which acts on target genes in uterine cells.

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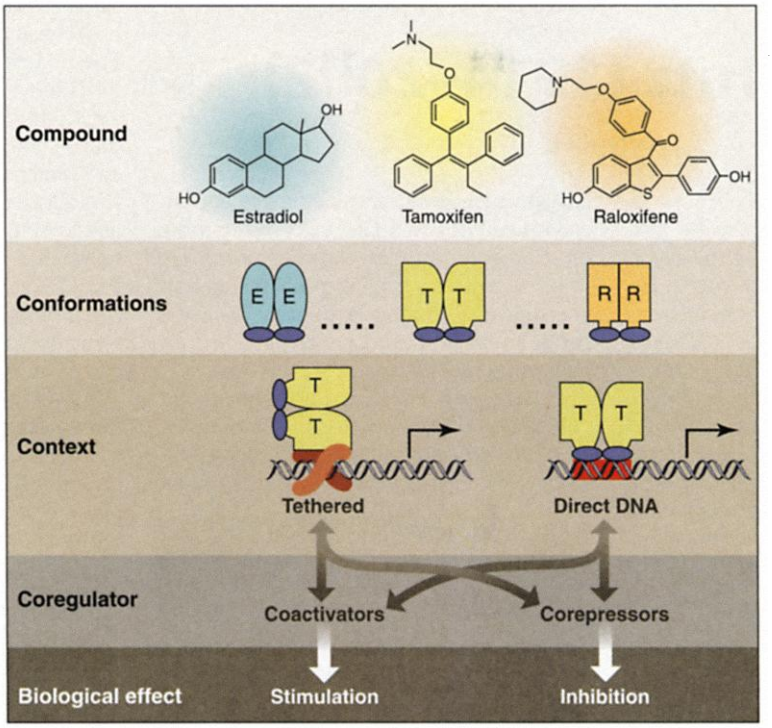
Originally called antiestrogens, tamoxifen and raloxifene are better termed selective estrogen receptor modulators (SERMs). This term appropriately indicates that these compounds are not uniformly estrogen antagonists. Rather, they display an unusual tissue-selective pharmacology: They are agonists in some tissues (bone, liver, and the cardiovascular system), antagonists in other tissues (brain and breast), and mixed agonists/antagonists in the uterus. Tamoxifen has greater uterine-stimulatory activity than raloxifene (*4–6*). Great efforts are under way to improve the tissue selectivity of SERMs so that they are optimized for preventing and treating breast cancer and for alleviating the symptoms of menopause.

It is now appreciated that the pharmacology of estrogens is tripartite, relying not just on the ligand and estrogen receptor but also on third parties, such as gene promoter elements and coregulatory proteins (*7*). Crystal structures of the estrogen receptor bound to different ligands (estrogen, tamoxifen, or raloxifene) reveal that ligands of different sizes and shapes induce a spectrum of receptor conformational states (*8, 9*). These states are then "interpreted" by the cellular complexion of coregulators and the environment of the local promoter of the target gene.

The estrogen receptor is a versatile transcriptional regulator and can interact with target genes, either by binding directly to DNA response elements or through indirect

tethering to other DNA binding transcription factors. Coregulator proteins, which may be general or receptor specific (*10, 11*), are recruited to the receptor in a ligand-dependent manner. Such coregulator proteins include coactivators, which enhance transcription, and corepressors, which reduce transcription (see the figure) (*12, 13*). With all of these partners, there would appear to be numerous combinatorial possibilities for achieving tissue-specific and gene-specific regulation by SERMs. Yet the specific molecular partners responsible for the differential stimulatory activity of tamoxifen and raloxifene in the uterus compared with their antagonism in the breast have not been identified.



SERMs in the spotlight. The selective actions of SERMs (selective estrogen receptor modulators) in different tissues result from a combinatorial collaboration among several factors. Estradiol, an estrogen, or specific SERMs, such as tamoxifen or raloxifene, all bind to the estrogen receptor, inducing distinctly different receptor conformations. These different receptor conformations then interact with the regulatory sequences of target genes in different ways (for example, direct DNA interaction versus tethering to other transcription factors). The type of interaction and the cellular levels of coregulator proteins (coactivators or corepressors) determine the distinct patterns of coregulator recruitment to the ligand-receptor-gene assembly. In this way, either stimulation or inhibition of specific biological effects is elicited.

Shang and Brown identify the coactivators and corepressors that are recruited by the estrogen receptor to several target genes in breast and uterine cancer cells, in the presence of either the estrogen estradiol or the SERMs tamoxifen and raloxifene. In both uterine and breast cancer cells, at genes where the estrogen receptor interacts directly with DNA, estradiol recruited coactivators, and both SERMs recruited corepressors. In addition, estradiol and raloxifene dictated the same pattern of coregulator recruitment at genes where the estrogen receptor becomes tethered to other transcription factors. Remarkably, however, in uterine cells where tamoxifen is an estrogen agonist, this SERM recruited coactivators rather than corepressors to gene sites where the estrogen receptor works by tethering. In contrast, tamoxifen recruited corepressors to the same gene sites in breast cancer cells, where it acts as an estrogen antagonist. The authors further show that the agonism of tamoxifen could be attributed specifically to the coactivator SRC1, which is present at a higher level in uterine cells than in mammary gland cells. Thus, the stimulatory (agonistic) activity of tamoxifen in the uterus depends on three critical features: the conformation of the tamoxifen-receptor complex, the promoter context (tethered interaction versus direct DNA binding of the estrogen receptor), and the availability of a specific coactivator (SRC1) (see the figure).

Although the Shang and Brown study greatly advances our understanding of the molecular basis for the differential tissue- and gene-selective activities of SERMs, it also raises important mechanistic and medical issues. Despite the existence of numerous cellular coregulators, there is already considerable evidence for their tissue-selective and functionally distinct activities (*14–16*). This is consistent with the finding that tamoxifen agonism in uterine cells is specifically dependent on higher amounts of SRC1 in this tissue. Will differential recruitment of coactivators to the estrogen receptor-tamoxifen complex in uterine cells, at gene sites where the estrogen receptor is tethered rather than bound directly, prove to be a general phenomenon, applicable to cells in other tissues where tamoxifen is an estrogen agonist? Will these observations made in cancer cells also hold true for normal cells? What is the part played in SERM selectivity by estrogen receptor β, the other receptor subtype found in many breast cancers and estrogen target tissues? Tamoxifen is effective in the treatment of breast cancer, yet tamoxifen resistance—which is in fact a manifestation of increased tamoxifen agonism—often develops and compromises treatment (*17, 18*). Is this resistance attributable to changes in the level or activity of coregulators, such that the receptor-tamoxifen complex more effectively recruits certain coactivators or fails to recruit corepressors?

Our understanding of the molecular partners involved in the cell- and gene-selective activity of tamoxifen and raloxifene, advanced by the Shang and Brown study, provides a foundation for the development of SERMs that are optimized for breast cancer prevention and treatment and menopausal hormone replacement. In addition, similar approaches based on an appreciation of the combinatorial collaboration of compound, conformation, context, and coregulators should be of value in developing selective analogs of hormone ligands that bind to other nuclear receptors, such as SPRMs (progestins), SARMs (androgens), SGRMs (glucocorticoids), and SPARMs (peroxisome proliferator-activated receptor ligands) (*19*).

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