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Peptide profiling: Correlating estrogen receptor conformation with biological response

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Chemicals found in the environment have been found to behave like the body's natural estrogen, estradiol. These exogenous estrogen-mimicking compounds have been termed xenoestrogens. Both estradiol and xenoestrogens can bind two estrogen receptors (ERs), ER alpha and ER beta, to elicit biological responses. The receptors are ligand inducible transcription factors that exhibit unique biological actions. While estradiol binds both receptors equally, some xenoestrogens have been shown to bind ER beta preferentially. When the ER is bound, the ligand induces a unique ER shape and in turn causes an array of tissue-specific biological responses. For example, the ligand tamoxifen, a commonly used breast cancer pharmaceutical, exhibits an ER antagonist response in the breast and an ER agonist response in the bone. This dual ligand quality characterizes what is now known as a selective estrogen receptor modulator (SERM). Peptide profiling, a novel ER ligand screening assay, is a method that can potentially identify SERMS by correlating *in vitro* ER conformation with *in vivo* biological response. Each ligand is screened using a two-hybrid fusion protein reporter gene assay. Upon ligand binding, the ER assumes a conformation; with this induced shape, some ER-interacting peptides will be able to bind while others will not. After screening a ligand against a library of fifteen different peptides, a unique peptide profile will figuratively illustrate the induced ER conformation. Eight xenoestrogens were screened in this experiment: estradiol, a natural physiological estrogen; resveratrol and genistein, two phytoestrogens; MPP, bisphenol A, and 4-hydroxytamoxifen, all synthetic estrogens; α-endosulfan and methoxychlor, both insecticides used on crops. Each ligand was found to have a unique peptide profile and, implicitly, a distinct ER conformation. The next step will be to determine each ligand's tissue specific activity and identify the unique peptide fingerprint that predicts its *in vivo* biological response. By correlating a ligand's tissue specific estrogenic activity with its unique ER conformation, peptide profiling will not only further elucidate tissue-specific ER activity differences but could also be used as a high-throughput screening tool for other potential environmental xenoestrogens and identify novel therapeutic SERMs.