Estrogen Receptor Structures Reveal the Basis of SERM Action and Ligand Discrimination

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Estrogens regulate the expression of diverse regulatory proteins and growth factors via one or both of two estrogen receptor subtypes (ER? & ER?). The structural events underlying ligand-specific coactivator and/or corepressor recruitment and transcriptional activation remain poorly understood for the nuclear receptor superfamily. Subtype and ligand-specific recruitment of coregulators and modulation of target genes have important implications for understanding the specificity of nuclear receptor signaling, and for treatment of a variety of diseases, including cancer. The development of ER subtype-selective ligands provides a molecular tool to study unresolved issues in the structural linkage between ligand and transcription. In order to understand the relationship between nuclear receptor ligand positioning and the formation of the coactivator-binding pocket, we have solved multiple ER?? LBD structures and investigated the determinants of ligand selectivity between the two estrogen receptor subtypes. Structurally guided amino acid substitutions demonstrate that ligands have distinct "hot-spot" amino acids required for selectivity. Residues within the ligand-binding pocket as well as distal secondary structural interactions contribute to subtype specific positioning of the ligand and transcriptional output. These data demonstrate the importance of long-range interactions in the transmission of information through the nuclear receptor ligand-binding domain, and in determining the specificity of closely related receptor subtypes, such as ER? and ER?. This information should prove useful in the design of SERMs with tissue- and pathway-selective behaviors.