

甾体激素受体功能特异性的结构基础

张馨、叶玉珍、丁达夫

中国科学院上海生命科学研究院生物化学与细胞生物学研究所

甾体激素受体家族包括雌激素受体、雄激素受体等五个亚家族,在机体组织细胞的生长分化、发育生殖、内环境稳定等几乎所有生理过程中都起着重要的作用。研究甾体激素受体亚家族的特异性可以加深对该家族功能的理解,并且具有潜在的临床应用价值。采用进化踪迹方法对该家族的配体结合域(LBD)进行分析,探讨了决定亚家族功能特异性的结构基础。结果表明,甾体激素受体的各亚家族可能同相应的内源性配体存在着共进化关系;配体结合处的踪迹残基决定了受体-配体间的氢键作用和疏水相互作用模式并导致了亚家族的配体结合特异性。上述结论可用于甾体激素受体的配体结合特异性的改造以及新型组织选择性配体(如选择性雌激素受体调节剂, SERM)的设计。

STRUCTURAL BASIS OF FUNCTIONAL SPECIFICITY OF STEROID RECEPTORS

The steroid receptors include the estrogen receptor, androgen receptor, progesterone receptor, glucocorticoid receptor and mineralocorticoid receptor. They are involved in almost all physiological activities, including reproduction, homeostasis, cell proliferation, differentiation and death. Elucidating the specificity of steroid receptors' subfamily will deepen our understanding of their functions and has potential pharmaceutical applications. We used the evolutionary trace method to analyze structural basis of functional specificity of steroid receptors. Results indicated that steroid receptors and its endogenous ligands may experience some coevolutionary process; trace residues in ligand-binding sites display different hydrogen-bond interactions and van der Waals contacts between receptors and its ligands, which decide subfamilies' ligand binding specificity. These informations can be used to modify ligand specificity of steroid receptors and design tissue-selective ligands (e.g. selective estrogen receptor modulator).

关键词

甾体激素受体 (Steroid receptor); 配体结合域 (Ligand-binding domain); 加权进化踪迹分析 (Weighted evolutionary tracing); 踪迹残基 (Specific residue)