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Peptides As A New Family Of Compounds With Estrogen-like Activity

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Currently used anti-estrogenic drugs against hormone dependent-breast cancer, and estrogenic drugs used in treatment of osteoporosis, are associated with risk factors (Pradhan et al., 2002). Therefore, there is a strong need to develop selective estrogen receptor modulators with better tissue selectivity (Jordan, 2003). In a recent study (Venkatesh et al, 2002) we used a monoclonal antibody to estradiol (mAb-E2) to screen a phage-display peptide library, and identified a 15-mer peptide (peptide H5) that recognizes mAb-E2 (IC_{50} 1 μM) and estrogen receptor (ER)α (IC_{50}500 μM) but not ERβ, and displays estrogen-like activity in vitro and in vivo. In this study we designed and prepared peptides that are based on peptide H5, that possess improved estrogenic activity, by evaluating their binding to mAb-E2 and to ERs. Initially, we determined the minimal binding sequence of peptide H5 capable of binding mAb-E2 and ER. Subsequently, a systematic single-residue replacements of the minimal sequence, followed by multiple residue replacements, yielded hexa- and hepta-peptides with increased affinities to mAb-E2 and to ER. The most promising peptides, VSWFFE (EMP-1; see Fig. 1) and VSWFFED (EMP-2), bind mAb-E2 with high affinity (IC_{50} of 6 and 30 nM, respectively), recognize ERs with increased affinity (IC_{50} of 100 μM for ERα, and 100 - 250 μM for ERβ), and possess estrogenic activity in-vivo. The short peptides described in this study may be used as potential lead-compounds for developing new ER ligands.

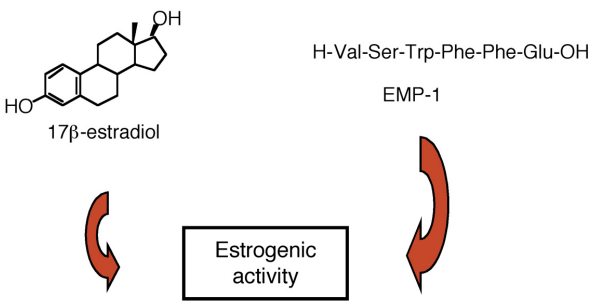

Fig. 1 *Chemical structures of the steroid hormone estradiol (E2) and amino acid sequence of the synthetic peptide EMP-1, which possess estrogen-like activity.*

Selected Publications

Pradhan, A.D., Manson, J.E., Rossouw, J.E., Siscovick, D.S., Mouton, C.P., Rifai, N., Wallace, R.B., Jackson, R.D., Pettinger, M.B. and Ridker, P.M. (2002) Inflammatory Biomarkers, Hormone Replacement Therapy, and Incident Coronary Heart Disease: Prospective Analysis From the Women's Health Initiative Observational Study. JAMA, 288, 980-987

Venkatesh, N., Zaltsman, Y., Somjen, D., Gayer, B., Boopathi, E., Kasher, R., Kulik, T., Katchalski-Katzir, E. and Kohen, F. (2002) A synthetic peptide with estrogen-like activity derived from a phage-display peptide library. Peptides, 23, 573-580

Jordan, V.C. (2003) Antiestrogens and selective estrogen receptor modulators as multifunctional medicines. 1. Receptor interactions. J. Med. Chem., 46, 883-908

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