

Molecular Dynamics Simulation of the Human Estrogen Receptor Alpha: Contribution to the Pharmacophore of the Agonists

Dessislava Jereva, Filip Fratev, Ivanka Tsakovska, Petko Alov, Tania Pencheva, Ilza Pajeva

Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria

dessi@biomed.bas.bg, fratev@biomed.bas.bg, itsakovska@biomed.bas.bg, petko@biophys.bas.bg, tania@biomed.bas.bg, pajeva@biomed.bas.bg

Keywords: Molecular dynamics, Estrogen receptor, Pharmacophore.

Human estrogen receptor alpha (ER α) is one of the most studied targets for *in silico* screening of bioactive compounds. The estrogenic activity of a vast number of chemicals has been studied for their potentially adverse effects on the hormone regulation of the endocrine system. The commonly accepted presentation of the ER α agonist pharmacophore includes terminal phenolic groups and a hydrophobic core with a rigid framework [1]. In this study we report on molecular dynamic (MD) simulations of ER α to get a deeper structural insight into the agonist-receptor interactions and the pharmacophore pattern of compounds with agonistic activity. We rely on a crystallographic structure of a complex of ER α with an agonist of picomolar affinity (PDB ID 2P15, <http://www.rcsb.org/pdb/explore/explore.do?structureId=2P15>). As the X-ray structure has mutation in the key structural element for ER α agonistic activity (helix 12, Y537S), a series of MD simulations have been performed on the wild type receptor to prove the stability of the agonist-receptor interactions. The results suggest that the pharmacophore of compounds with ER α agonistic activity can be extended by a feature that occupies a free hydrophobic region of the binding pocket. The results imply also that MD simulations are a powerful *in silico* tool for both protein dynamics and structure investigation, especially when mutations are available that can potentially disturb the protein structure and functions. The work is supported by the National Science Fund of Bulgaria (grant DTK 02-58).

References

- [1] A. C. Pike, *Lessons learnt from structural studies of the oestrogen receptor*. Best Pract Res Clin Endocrinol Metab 2006 **20** 1-14.