LIGAND DISSOCIATION PATHWAYS FROM NUCLEAR ESTROGEN RECEPTOR LIGAND BINDING DOMAIN THROUGH MOLECULAR DYNAMICS SIMULATION

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Estrogen Receptor (ER) is an important target for pharmaceutical design. Like other ligand-dependent transcription factors, hormone-binding regulates ER transcriptional activity. Nevertheless, since ligand is well embedded in the Ligand Binding Domain (LBD) the mechanisms by which ligands enter and leave ERs and other nuclear receptors (NRs) remain poorly understood. In these presentation we report results of locally enhanced sampling (LES) Molecular Dynamics (MD) simulations to identify dissociation pathways of two ER ligands (the natural hormone 17ß-estradiol, E_2, and the selective estrogen receptor modulator (SERM) Raloxifene, RAL) from the hERa ligand binding domain (LBD) in monomeric and dimeric forms. As observed in previous simulations for Thyroid Receptor multiple dissociation pathways is observed. E_2 dissociation occurs via two different pathways in ER monomers. One resembles the “mouse-trap” mechanism (Path I), involving repositioning of the cofactor recognition related H12. The other involves separation of H8 and H11 (Path II). RAL leaves the receptor through Path I and through a variation of this pathway in which the ligand leaves the receptor through the loop region between H11 and H12 (Path I’). Remarkably, ER dimerization strongly suppresses Path II for E_2 dissociation and modifies RAL escape routes. We discuss our results in terms of experimental investigations of the effects of ER quaternary state on ligand dissociation rates and suggest that dimerization may play an important, and hitherto unexpected, role in regulation of ligand dissociation rates throughout the NR family.

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