ESTROGEN RECEPTOR CO-PEPTIDE BINDING STUDIES USING THE MM-PBSA METHOD

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Abstract: Estrogen receptors (ER) are known as nuclear receptors. They exist in the cytoplasm of human cells and serves as a DNA binding transcription factor that regulates gene expression. However the estrogen receptor also has additional functions independent of DNA binding. The human estrogen receptor comes in two forms, alpha and beta. This work focuses on the alpha form of the estrogen receptor. The ER is found in breast cancer cells, ovarian stroma cells, endometrium, and the hypothalamus. In a previous work we examined the protein unfolding from the antagonist form found in the 3ERT PDB crystal structure. The 3ERT PDB crystal structure has the estrogen receptor bound to the cancer drug 4-hydroxytamoxifen. The 4-hydroxytamoxifen ligand was extracted before the simulation, resulting in new conformational freedom due to absence of van der Waals contacts between the ligand and the receptor. The conformational changes that result expose the binding clef of the co peptide beside Helix 12 of the receptor forming an apo conformation. Two key conformations in the loops at either end of the H12 are produced resulting in the antagonist to apo conformation transformation. The results were produced over a 42ns Molecular Dynamics simulation using the AMBER FF99SB force field. After continued dynamic simulations we conducted MM-PBSA binding calculations of the co-peptide bound to the estrogen receptor.