MASTER'S THESIS

Computational studies of nuclear receptors: estrogen receptors, glucocorticoid receptors, and farnesoid X receptor

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Computational Studies of Nuclear Receptors: Estrogen Receptors, Glucocorticoid Receptors, and Farnesoid X Receptor

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Abstract

The nuclear receptors (NRs) constitute a superfamily of numerous transcription factors that regulate the expression of genes involved in critical biological functions. Dysfunction of NR signaling leads to various common diseases. Understanding of the exact activation processes of these receptors has great potential in curing NR-related diseases and is currently a hot research topic. There are, however, limitations using experimental methods on the studies of molecular structures and protein dynamics. The rapid development of theoretical and computational methodologies have allowed for more realistic and microscopic scale studies on such aspects. In this thesis, computational methods including bioinformatics, coarse-grained simulation, ligand-docking study, molecular dynamics simulation and free-energy calculation will be employed in studying three selected NRs (estrogen receptor, glucocorticoid receptor and farnesoid X receptor) in relation to their biological properties. We first give a general bioinformatic study on the steroid hormone receptor subfamily of NR, revealing some unique structural characteristics of estrogen receptor critical of its biological properties. The partial folding process of helix-12 (putatively the critical AF2 of NRs) and some estrogen receptor mutants are then described. Ligand-binding configuration studies of glucocorticoid receptor and farnesoid X receptor are finally investigated for their drug design aspects.

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