Poster #31

Homology Modeling of the Estrogen Receptor Subtype β (ERβ), the Androgen Receptor (AR), and the Glucocorticoid Receptor (GR): Investigation of Mutational Effects on Ligand Binding.

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Multiple sequence analysis reveals a remarkable degree of conservation across members of the steroid hormone receptor superfamily. Furthermore, the ligand binding domains (LDBs) of those receptors for which crystal structures are known bear a high degree of structural conservation despite their wide differences in ligand-binding specificities and target genomic effects. Capitalizing on this significant degree of sequence and structural conservation, we have applied computational homology modeling techniques to derive three-dimensional structures of the LBDs of ERβ, AR, and GR. Using the crystal structure of ERα and the homology model of ERβ, we demonstrate a strong correlation between computed binding energies and published values of the observed relative binding affinity (RBA) for a variety of compounds for both receptors. The classical male hormone, testosterone, elicits its genomic effects through the AR. We are currently employing the AR homology model to assess the influence of specific mutations within the LDB as they relate to androgen insensitivity syndrome (AIS). The GR, a ligand-inducible transcription factor that controls the transcriptional status of numerous genes through its natural ligand cortisol, plays a key role in numerous physiological functions including inflammation and asthma, the immune system, fetal lung development, brain development, bone mineral homeostasis, and hepatic nutrient metabolism. The GR homology model is being employed to guide the discovery of novel, and much needed, therapeutic agents to modulate these processes.

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