A Molecular Dynamics Investigation of Ligand-Mediated PPARγ Transrepression

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Background and Hypothesis: PPARγ is a nuclear receptor expressed in most cells of the body and exerts metabolic function, including adipocyte differentiation and insulin sensitization. This mechanism is termed transactivation, where ligand binding leads to transcription of target genes. However, PPARγ also has a transrepression activity, where ligand binding inhibits other transcriptional pathways, leading to regulation of the immune system. While the molecular mechanisms of transactivation are well understood, there is little research on the mechanisms of transrepression. Previous studies have implied that these activity states act independently and can be selected for in small molecule design campaigns, but this has yet to be accomplished. Therefore, the aim of this project was to investigate if distinct molecular interactions exist between PPARγ transactivation versus transrepression using a combined computational and structural biology approach.

Methods: Molecular dynamics (MD) simulations were performed using the CHARMM molecular modeling software to produce 300 ns simulations of PPARγ-ligand complexes. Simulations were analyzed to identify potential protein-ligand interactions, and distances were measured between atoms of interest and compared.

Results: Although PPARγ's binding site is large, structural analyses showed that most ligands remained near their initial starting position within the binding pocket throughout an MD simulation. Starting coordinates were taken from previously solved crystal structures or via manual docking based on molecular similarities. Four residues were identified to consistently interact with most of the ligands: Arg280, Ser342, Glu259, and Cys285. These residues differ from previously reported interactions associated with PPARγ transactivation.

Conclusion: Our results suggest that these residues may play a role in PPARγ transrepression, but these conclusions are preliminary and should be confirmed through further investigation. Future research would include performing replicate simulations and mutational analyses to further explore the involvement of these residues in PPARγ transrepression. Additional PPARγ ligands should also be explored.