The Effect of Mutations in the Ligand Binding Pocket on the Function of Ftz F1

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Purpose: Nuclear receptors are a family of transcription factors that regulate a range of biological processes. While most are regulated by ligands, orphan receptors have been found to have no known ligands and instead function by the active conformation of their ligand binding pockets. By examining the effects of mutations in the ligand binding pocket of orphan receptor Ftz F1, this project aims to understand how orphan receptors may be synthetically mutated and targeted in drug development. Procedure: PCR mutagenesis was used to introduce mutations in Ftz F1's ligand binding pocket. These mutations were sequenced and then transformed into bacteria. Afterwards, the bacteria was lysed and purified for protein samples. A thermal shift assay was conducted to determine the melting point of each protein sample as well as the melting points of each protein while being bound to Ftz's LxxLL peptide. Results: The melting points of the GK plus peptide and the GY plus peptide samples were significantly greater than the wild type plus peptide samples, thus exhibiting a higher stability. The LF plus peptide and LV plus peptide samples displayed the opposite. Conclusions: The findings of this study suggest that mutations speeding up the dynamic behavior in Ftz F1's ligand binding pocket may result in less stability and thus help down regulate the correlated gene. Specifically, this study may be applied to the LRH1 human receptor.

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