[P19] Computational study of Nuclear Receptor PPARγ: implications of pathological mutations on the structural dynamics

Djamila Boughenaya, Annick Dejaegere, Roland H. Stote

Integrative Structural Biology Dept., IGBMC - CNRS UMR 7104 - Inserm U 964, rue Laurent Fries, BP 10142, 67404 Illkirch CEDEX France

Peroxisome proliferators activated receptor, PPARγ, is member of the nuclear hormone receptor (NR) super family that functions as a ligand-induced gene transcription factor. PPARγ shares the canonical modular structure of NRs, which consists of well-conserved DNA- and ligand-binding domains. Acting as heterodimer with retinoic acid receptor, RXR, PPARγ plays a crucial role in the regulation of fatty acid storage and glucose metabolism. It is also a major target of anti-diabetic drugs due to it potential to regulate insulin sensitivity in human body. In addition to its important physiological functions, recent experimental studies have shown the implication of this protein in cancers; PPARγ mutants were found to highly expressed in bladder cancer tumors. These mutant PPARγs were shown to be more transcriptionally active than the wild-type protein[1], but experimental X-ray structures[2] did not shed any light on significant structural differences between them and the wild type. Here we used molecular dynamics simulations to investigate the effect of these mutations on the structural dynamics of PPARγ ligand-binding domain (LBD). From our results, we found that the point mutations stabilized the LBD in a way that created favorable conditions for the binding of coactivator protein. A stable LBD/coactivator complex is essential for the subsequent recruitment of the transcription machinery and expression of target genes. This mutation-induced increase in stability of the LBD-coactivator complexes suggests a mechanism for their increased transcriptional activity.

Bibliography :

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2. N. Rochel, IGBMC, personal communication