Mapping the Dynamic Conformational Landscapes of PPARγ

Meilin AN[1], Ana Ligia Scott[2], Ana Milinsk[1], Annick Dejaegere[1], Roland H. Stote[1]

1. Institute of Genetics and Molecular and Cellular Biology (IGBMC), CNRS UMR 7104 - Inserm U 1258, 67404 Illkirch, France

2. UFABC - Universidade Federal do ABC, Center for Mathematics, Computation and Cognition, São Paulo, Brazil

meilin.an@igbmc.fr

Abstract

Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-regulated nuclear receptor crucial to metabolic regulation and inflammation, making it a key therapeutic target. Its activity is tightly linked to the conformational state of its ligand-binding domain (LBD), particularly the dynamic behavior of helix 12 (H12), which modulates coactivator recruitment. While static structures have provided snapshots of active or repressive conformations, the full spectrum of PPARγ dynamics remains incompletely characterized.

In this study, we systematically investigated the conformational landscape of the PPARγ LBD using a combination of molecular dynamics (MD) and enhanced sampling strategies. Explicit-solvent MD simulations revealed limited structural flexibility, with conformations largely trapped in a narrow basin. In contrast, implicit-solvent simulations and excitation-based methods — including Molecular Dynamics with excited Normal Modes (MDeNM) and Variational Mode Sampling (V-MOD) — significantly broadened the sampled conformational space, capturing large-scale motions relevant to functional transitions.

Despite their diverse sampling characteristics, these methods consistently revealed that H12 undergoes continuous, rather than discrete, rearrangements. This dynamic continuum challenges the classical notion of well-defined functional states and motivates the development of contact-based metrics and tailored clustering strategies for future analyses.

Keywords

Nuclear receptors; PPARγ; molecular dynamics; conformational landscape; MDeNM; enhanced sampling; helix 12 dynamics

References

1. Weikum, E. R., Liu, X., Ortlund, E. A. (2018). The nuclear receptor superfamily: A structural perspective. *Protein Science*, 27(11), 1876–1892.

2. Lehrke, M., Lazar, M. A. (2005). The many faces of PPARγ. *Cell*, 123(6), 993–999.

3. Frenkel, D., Smit, B., Ratner, M. A. (1997). Understanding molecular simulation: From algorithms to applications. *Physics Today*, 50(7), 66.