Structural Basis of TRA16-Mediated Inhibition of TR4 Transcriptional Activation in Diabetes

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Abstract

Diabetes mellitus is a prevalent metabolic disorder worldwide, in which the nuclear receptor TR4 promotes disease progression by transcriptionally activating key genes such as *PEPCK* and *SCD1*. The associated protein TRA16 has been shown to specifically inhibit TR4; however, its precise molecular mechanism remains unclear. In this study, we successfully expressed and purified full-length TR4, TRA16, and their complex through optimization of fusion tags, host strains, and induction conditions. Crystallization of the TRA16–TR4 complex was achieved using the hanging-drop vapor diffusion method, yielding diffraction data at approximately 3.8 Å resolution, from which the three-dimensional structure was determined. In parallel, the structure of TRA16 was predicted using AlphaFold3 and further analyzed through molecular docking and molecular dynamics simulations. The results suggest that TRA16 inhibits TR4 by directly interacting with either the DNA-binding domain (DBD) or the ligand-binding domain (LBD) of TR4, with high model fitting scores supporting the reliability of the interaction modes. This study elucidates the structural basis and molecular mechanism by which TRA16 suppresses TR4-mediated transcriptional activation, providing new insights into TR4 regulation in diabetes. The resolved complex structure and identified key interaction sites offer a critical framework for the rational design of small-molecule or peptide-based TR4 inhibitors, with significant potential for precise therapeutic intervention and reduced side effects.

Keywords

Diabetes Mellitus, Nuclear Receptor TR4, TRA16, Transcriptional Regulation, Complex Structure, Molecular Docking and Dynamics Simulation

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