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Unraveling The Structural Impact of Dna on Rara/rxr Transcriptional Regulation

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Retinoic acid receptor alpha (RARα) is a nuclear receptor essential for embryogenesis and homeostasis regulation in vertebrates. It forms a heterodimer with RXR and binds to specific elements in the genome (e.g., DR0, DR1, DR5, and IR0). In the absence of the retinoic acid, RARα/RXR recruits corepressors (e.g., NCoR) to silence target genes; upon ligand binding, coactivators are recruited, leading to gene activation. RARα binds to different DNA elements across cell differentiation stages, driving its transcriptional response. We used MD simulations coupled to SAXS to show that DR0 and DR1 dictate binding patterns, inducing high RARα compactness and favoring interdomain contacts, but not on IR0 and DR5. These conformational signatures persist upon NCoR binding, highlighting DNA's role in repressive complex formation dynamics. HDX-MS reveals that DNA allosterically stabilizes RARα-ligand and coregulator interactions while destabilizing RXR, explaining its silenced role. Notably, we identify a novel NCoR interface that contributes to receptor repressiveness. Our work establishes DNA as an active modulator of RARα/RXR transcriptional activity and underscores the power of integrating biophysics, structural, and computational approaches to elucidate nuclear receptor function.