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Cooperativity in Transcriptional Regulation: A Molecular Dynamics Approach

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Objectives

Transcription factors (TFs) are the primary drivers of gene regulation by binding to specific DNA sites with adequate affinity and stability [1]. TFs often cooperate as homodimers or heterodimers for a more delicate regulation [2]. Granyhead-like 3 (GRHL3) and Hepatocyte nuclear factor 4 alpha (HNF4α) are TFs that form heterodimers to initiate mesenchymal to epithelial transition (MET), a cell-fate alteration important in development and cancer progression [3]. In this work, we investigate the role of DNA sequence in modulating the cooperativity of transcription factors.

Methods

We developed atomistic structural models of free or nucleosomal DNA bound to human GRHL3, as well as models also including HNF4α, and performed molecular dynamics simulations.

Results

Our molecular dynamics simulations show that the two TFs cooperate when GRHL3 is bound to its native DNA sequence, but the cooperativity is disrupted by mutations in the specific DNA sequence, potentially halting MET progression.

We also investigated NF-κB p50, a TF involved in inflammation, immune response, cell division, cellular differentiation, and survival. Simulations of DNA-bound NF-κB p50 revealed homodimeric cooperativity and progressive DNA bending—suggestive of transcription-associated DNA melting. We find that the TF specificity can be established by not only the cognate DNA sequence but also by the flanking sequences upstream and downstream.

Conclusions

Our findings demonstrate that the DNA sequence is crucial for the heterodimer or homodimer cooperativity between TFs, consequently for the DNA dynamics and conformation, and gene regulation.

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