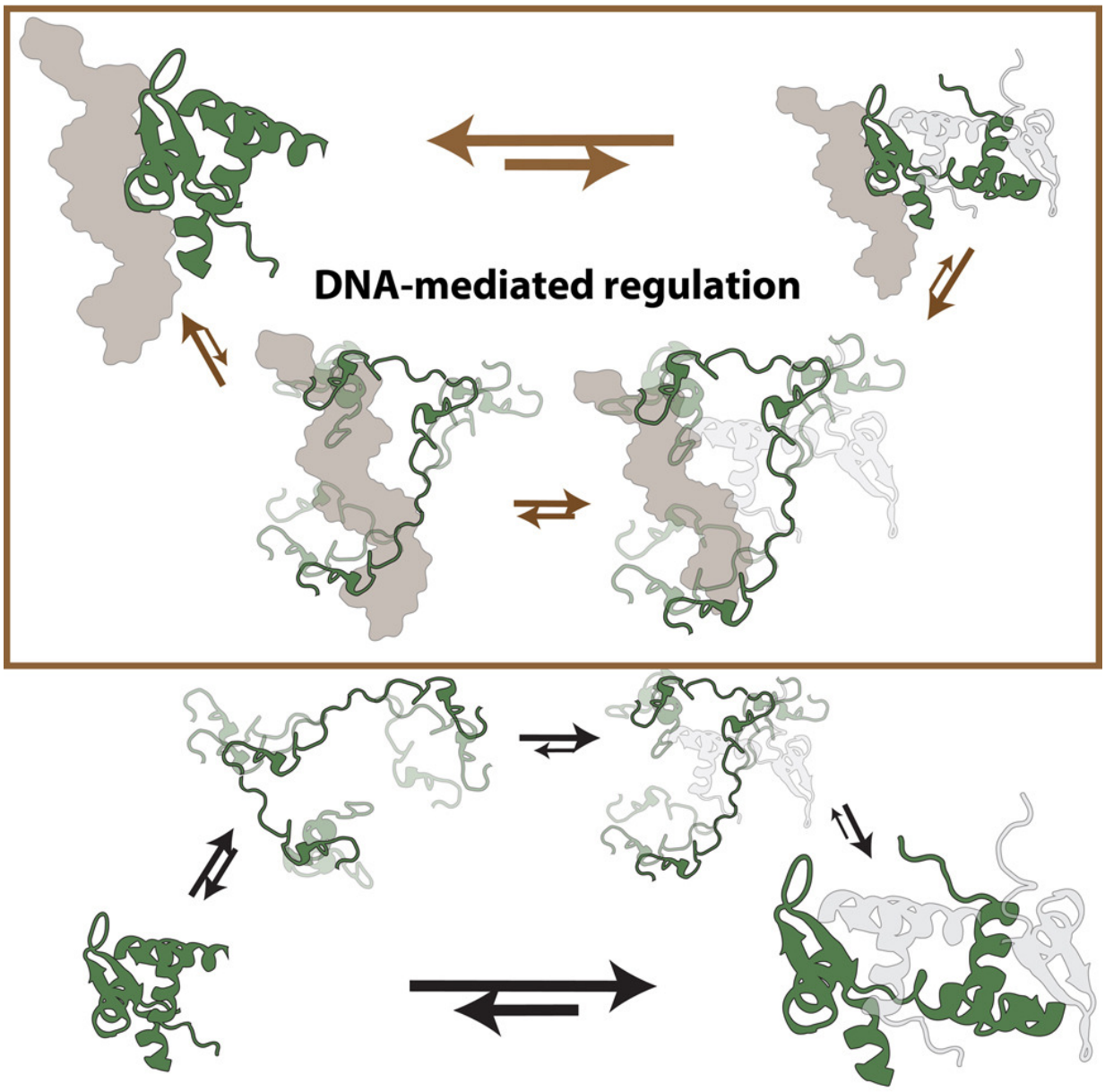

Highlights

•The FKH domain of FoxP1 is structurally dynamic in monomer and dimeric conditions
•The dimerization of the FKH domain stabilizes the intramolecular dynamics
•The presence of DNA destabilizes the dimeric FKH domain and promotes a disordered state
•The presence of DNA favors the monomeric state of the FKH domain

Summary

Transcription factors (TFs) regulate gene expression by binding to specific DNA sequences and gating access to genes. Even when the binding of TFs and their cofactors to DNA is reversible, indicating a reversible control of gene expression, there is little knowledge about the molecular effect DNA has on TFs. Using single-molecule multiparameter fluorescence spectroscopy, molecular dynamics simulations, and biochemical assays, we find that the monomeric form of the forkhead (FKH) domain of the human FoxP1 behaves as a disordered protein and increases its folded population when it dimerizes. Notably, DNA binding promotes a disordered FKH dimer bound to DNA, negatively controlling the stability of the dimeric FoxP1:DNA complex. The DNA-mediated reversible regulation on FKH dimers suggests that FoxP1-dependent gene suppression is unstable, and it must require the presence of other dimerization domains or cofactors to revert the negative impact exerted by the DNA.