

An autoregulation of DNA binding model of ZNF410 revealed by biophysical study of small-angle X-ray scattering

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ZNF410 is a unique and remarkable transcription factor in that it recognizes a 15-base pair DNA element but has only one single target gene in the mammalian genome in erythroid cells. ZNF410 is composed of uncharacterized N- and C-terminal domains with a tandem array of ordered five zinc fingers (ZFs). Unexpectedly, full-length ZNF410 has reduced DNA binding affinity, compared to that of isolated DNA binding ZF array. AlphaFold predicts a partially folded N-terminal subdomain including a 30-residue long helix and its preceding hairpin loop, which is rich in acidic (aspartate/glutamate) and serine/threonine residues. The hairpin loop is placed into the DNA binding interface of the ZF array. In solution, ZNF410 is a monomer and binds to DNA in 1:1 stoichiometry. Surprisingly, the single best-fit model from the experimental small-angle X-ray scattering profile, in the absence of DNA, is the original AlphaFold model with the N-terminal long-helix and the hairpin loop occupying the ZF DNA binding interface. Upon the DNA binding, the hairpin loop must be displaced. By using a combination of biophysical, biochemical, bioinformatics, and artificial intelligence-based AlphaFold approaches, we suggest that the hairpin loop might mimic the structure and electrostatics of DNA, and provides an additional mechanism, in supplementary to the sequence specificity, to regulate the DNA binding of ZNF410.