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Postranslational modifications significantly alter the binding-folding pathways of proteins associating with DNA

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Many important regulators of gene activity are natively disordered, but fully or partially order when they bind to their targets on DNA. Interestingly, the ensembles of disordered states for such free proteins are not structurally featureless, but can qualitatively differ from protein to protein. In particular, in random coil like states the chains are swollen, making relatively few contacts, while in molten globule like states a significant collapse occurs, with ensuing high density of intra-protein interactions. Furthermore, since many DNA binding proteins are positively charged polyelectrolytes, the electrostatic self-repulsion also influences the degree of collapse of the chain and its conformational preferences in the free state and upon binding to DNA. In our work, we have found that the nature of the natively disordered ensemble significantly affects the way the protein folds upon binding to DNA. In particular, we showed that posttranslational modifications of amino acid residues, such as lysine acetylation, can alter the degree of collapse and conformational preferences for a free protein, and also profoundly impact the binding affinity and pathways for the protein DNA association. These trends will be discussed in the context of DNA interacting with various histone tails and the p53 protein.