Intrinsically disordered regions can enhance protein binding and differentiation among DNA target sites toward optimization of protein drugs

Intrinsically disordered regions (IDRs) provide structural flexibility useful for mediating diverse functions, such as cellular signaling, transcription, and regulation. Intrinsically disordered proteins exist in 40-50% of the human proteome. The structural plasticity of IDRs presents an opportunity to exploit dynamic protein-DNA binding. We used the basic region/helix-loop-helix/ leucine zipper (bHLHZ) family of transcription factors as scaffolds to construct structural analogues to the Myc/Max protein, which is associated with >70% of cancers. Our latest version, MEF, competitively binds to the E-box (enhancer box, 5'CACGTG) DNA motif, thereby inhibiting the activity of proto-oncogenic Myc/Max. To further optimize MEF, we replaced the loop in the HLH region with the longer loop of the bHLHZ transcription factor USF1. The USF1 loop can improve affinity and specificity by providing more flexibility and electrostatic contacts with DNA bases flanking the E-box. We are studying how mutations in both the length and identity of residues affect MEFU's affinity and specificity to the DNA sequences flanking the E-box. This work can illuminate how IDRs contribute to finetuning DNA binding to optimize protein drugs against undruggable diseases.