ónNucleic acid recognition from prokaryotes to eukaryotes:

Case studies of a redox-sensing repressor and a pre-mRNA splicing factorô

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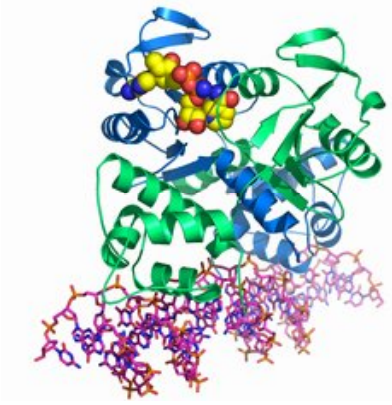
Proteins regulate gene expression at multiple stages ranging from transcription through RNA processing and translation. At each stage, regulatory proteins overcome diverse problems of molecular recognition to associate with the target nucleic acid and respond to cellular signals. This seminar describes and contrasts the structural basis for molecular regulation during two distinct cases of gene expression:

Structure of T-Rex/NAD+/DNA.



Part (1) ***NADH/NAD$^+$ redox-sensing by a Rex-family repressor.*** Among Gram-positive bacteria, the Rex repressor is a key sensor of oxygen availability that regulates gene expression in response to the intracellular NADH/NAD$^+$ ratio. Here, we present the structure of activated *Thermus aquaticus* Rex (T-Rex) as a ternary complex with NAD$^+$ and operator DNA at 2.3 Å resolution. Comparison with the previous structure of T-Rex in the NADH-bound state reveals a dramatic conformational rearrangement releases the protein subunits from the DNA in response to NADH.

Part (2) ***Recognition of the 3' pre-mRNA splice site.*** Almost all human genes contain intervening noncoding introns that must be removed by pre-mRNA splicing. The 3' splice site is marked by consensus sequences, yet variations of these sequences allow specific splice site regulation. Structures of the essential splicing factor U2AF^{65} bound to a series of splice site variants reveals subtle rearrangements that adapt the protein to different RNA sites. Combined with surface plasmon resonance RNA affinities and small angle X-ray scattering data, we propose a model of adjustable binding registers as a means for universal recognition of diverse 3' splice sites by U2AF^{65}.

Altogether, these two examples demonstrate the diversity of conformational changes used by proteins to accomplish gene regulation, from the global rearrangements that dissociate the Rex family repressor from DNA to the subtle rearrangements that adapt U2AF^{65} to different RNA splice sites.