Unraveling the Structure Function and Dynamics of ArsR/SmtB Trascriptional Repressors

The ubiquitously present ArsR/SmtB family of metal ion sensing transcriptional repressor proteins function *via* a mechanism of allosteric inhibition in which metal ion binding triggers a quaternary structural change that drives off DNA. The zinc sensor protein Staphylococcus *aureus* CzrA is an extensively studied ArsR/SmtB protein whose DNA binding affinity is reduced by ~6 kcal/mol on binding zinc. Using computational methodologies, we investigated the mechanism of transcriptional repression in CzrA and successfully provided a rationale for experimental mutagenesis results. We find that DNA binding weakens the inter-subunit interactions in CzrA while zinc binding strengthens them. The related protein, *Mycobacterium tuberculosis* NmtR binds to zinc in a CzrA-like binding site but prefers binding to nickel. In the absence of experimental structures, we successfully determined the protein's allosteric response on binding to DNA, nickel and zinc. The structural dynamics of the apo forms of these proteins indicate that they adopt a conformation that is not conducive for DNA. A specific hydrogen-bonding pathway connecting the metal binding sites to the DNA-binding interface observed in the zinc bound forms of these proteins plays a critical role in their regulatory mechanism. Quantum-mechanical calculations show that zinc binding has a localized effect on this pathway, and strengthens the first hydrogen bond interaction by ~10 kcal/mol. Our studies provide an insight into the development of metal-ion specificity and allosteric response pathways in proteins that evolved from a common ancestry.