ABSTRACT

Iron is an essential element in many living cells. It must be regulated in the living system because its accumulation is toxic. In bacteria the regulation of gene expression is performed by Ferric Uptake Regulation repressor protein (Fur). Fur has been proposed to bind iron as a co-repressor and to it act as a negative regulator of genes. It binds to DNA at specific sequence in Escherichia Coli (A.T rich region called the iron box **5'GATAATGATAATCATTATC'3)**. In this work the structure and conformational changes of Fur E.coli were studied using computational methods, to uncover its structure-function relationship.

The comparative protein modeling was used to model the structure of Fur. Fur consists of three domains: N-terminal, central and C-terminal domains. The N-terminal contains the helix turn helix motif which binds the DNA. The central domain is responsible for dimerization of Fur. Thed C-terminal contains the metal ion binding enclaves. Fur structure carries some resemblance with DtxR especially their DNA binding domains. Visualization of the Fur-DNA complex showed that the N-terminal domain of Fur interacts directly with the major groove of the iron box (which was built using consense 19bp plaindromic DNA sequence). Extensive computations using molecular dynamics proved that metal-binding and DNA-binding induces conformational changes in the Fur dimer. The N-terminal domain of Fur binds directly to the major groove of the iron box. The calculations of the distances between the two monomer subunits of Fur showed that the domain consisting

of residues 40-65 near the N-terminal is responsible for dimerization of Fur. Iron (II) binding sites of fur are discussed. Two major sites were seen on the C-terminal. A site 1 involves Cys92, Cys95, His71, Ile50, Asn72, Gly97 and Ala109. Site 2 involves His145, His143, Asp137, Asp141, Arg139 and Glu140 and iron II is present in distorted octahedral environment. This study shows that metal ion binding to the C-terminal induces conformational changes in the N-terminal. This enhanced the binding affinity of the Fur protein to the DNA. The Fur binding to DNA resulted in DNA tilting and a change in its conformation, Fe^{+2} was found to associate with DNA at high concentrations and mediate the Fur dimer binding to DNA.