Interactions of Molecular Chaperones HscA and HscB with the Iron-Sulfur Cluster Assembly Protein IscU

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Genes encoding a specialized molecular chaperone system (*hscA* and *hscB*) are associated with iron-sulfur cluster assembly genes (*iscS*, *iscU*, *iscA*, and *fdx*) in prokaryotes, and genetic studies of both bacteria and eukaryotes suggest that these chaperones play an essential role in iron-sulfur protein biogenesis. HscA is an hsp70-class chaperone (66-kDa) which displays low intrinsic ATPase activity and specific, nucleotide-dependent polypeptide binding activity. HscB is a novel J-type co-chaperone (20-kDa) that serves to regulate the ATPase activity and peptide affinity of HscA. Biochemical and kinetic studies have shown that HscB binds the [FeS]-scaffold protein IscU and targets IscU to the substrate-binding domain of HscA. Peptide array mapping and site-specific mutagenesis studies indicate that HscA binds to a specific recognition sequence of IscU that includes a conserved amino acid sequence, -LPPVK- positioned close to an invariant cysteine residue presumed to be involved in [FeS] cluster formation. Recent spectroscopic and crystallographic studies have revealed the structure of complexes of IscU-derived peptides bound to HscA and suggest that chaperone binding is likely to affect the structure and stability of IscU-[FeS] complexes. The implications of the structure of the HscA-IscU peptide complex for formation and transfer of [FeS] clusters will be discussed.