Biochemical reconstitution of the FeS cluster transfer process using purified chaperone proteins

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Iron-sulfur clusters (FeS) are prosthetic groups of many proteins that are critical for key metabolic processes such as: electron transfer chains, cofactors biosynthesis, RNA /DNA transactions and regulation of gene expression. In eukaryotic cells, mitochondria play a central role in FeS biogenesis for both: their own proteins and proteins functioning in other cellular compartments. In humans, disruption in mitochondrial FeS biogenesis leads to numerous, often fatal, diseases. The FeS biogenesis process can be divided into two steps: (i) FeS synthesis on a specialized scaffold protein and (ii) FeS transfer from the scaffold protein onto recipient proteins. Each of these steps engages dedicated proteins that form multi-protein complexes. The activity of these complexes depends on specific protein-protein interactions among their components. Although most of the proteins involved in FeS cluster biogenesis have been identified, the molecular mechanism of this process is not well understood. In particular, little is known about the importance of individual protein-protein interactions for the efficiency of both the synthesis and the transfer of FeS clusters. We are going to analyze these requirements using circular dichroism (CD) spectroscopy which is the only reliable method that allows kinetic measurements of the FeS synthesis and transfer.

Main aim of my study is to investigate FeS transfer, mediated by chaperone system, from the scaffold protein onto recipient proteins. By using both native proteins and their variants defective in individual protein-protein interactions, we aim to dissect the significance of these interactions for the rate and the yield of FeS transfer. Our studies will elucidate the molecular mechanisms behind FeS biogenesis. Moreover, due to the evolutionary conservation of the FeS biogenesis process, our results obtained for yeast proteins will be easily adapted to human proteins. Thus, they will help us to understand the molecular basis of human pathologies related to mutations in genes encoding proteins functioning in FeS biogenesis. In the long run, our results may also allow development of knowledge-based therapies.