Sco1/2: Copper chaperone or Thioredoxin like proteins?

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Cytochrome *c* oxidase (COX) is a multi-subunit enzyme of the mitochondrial respiratory chain. Copper delivery to COX is a long-standing puzzle. In eukaryotes, it has been found that Cox17, shuttles Cu(I) from Ctr, through the cytoplasm, to mitochondria. This Cu(I) is then incorporated into CuA and CuB centers of COX. Other proteins , Sco1/2 and Cox11, mediate the copper insertion in COX subunits. While the precise role of each of these proteins in copper incorporation remains unclear, recent studies have revealed that inherited mutations in these proteins can result in severe pathology in human infants in association with cytochrome *c* oxidase deficiency.

In order to better understand the role of Sco1/2 in copper delivery to cythocrome *c* ossidase we performed a genomic-context analysis based on coding gene position, phylogenetic occurrence and gene fusions. This analysis showed that the function of Sco1/2 is complex and not univocal. Sco1/2 show at the same time a strong correlation with copper enzyme and cytC. This protein could play a role in delivering copper to a variety of different enzymes, not only COX , and/or to play a role as a thioreductase, keeping the copper coordinating residues in a reduced state ready for copper binding. Since in eukaryotes two Sco paraloghs are present, one of them may preferentially interact with subunit II of COX thus favoring COX assembly, while the second one may assist the metallochaperone Cox17 which is responsible for copper recruitment in the inter membrane space of mitochondria.

In order to confirm the above presented hypothesis we cloned the soluble domain of Human Sco1 (H_sco1) and Sco2 (H_sco2) and the respective pathogenic mutants inducing cythocrome *c* deficiency. H_sco1WT and H_sco1 P174L mutant were expressed and purified. Far UV-CD and 1H_NMR experiments showed that the two proteins have similar folding and thermal stability. Both proteins bind Cu(I) in 1:1 ratio. Further analyses and comparisons with H_sco2WT and its pathogenic mutants will be pursued to better understand the functional role of H_sco1/2 proteins in copper assembly to COX.