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The structural biology of mitochondrial respiratory complex assembly

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The mitochondrial oxidative phosphorylation system generates the bulk of cellular ATP, fuelling the energy demands of most eukaryotes. Five multi-subunit protein complexes in the mitochondrial inner membrane, termed complexes I to V, comprise the oxidative phosphorylation system. Many of these complexes require redox active cofactors, such as metal atoms and flavin for activity. The enzyme cytochrome *c* oxidase (CcO; Complex IV), which is the terminal oxidase of the mitochondrial respiratory chain requires three copper ions for assembly and activity of the complex. Succinate:quinone oxidoreductase (SQR; Complex II) functions in energy metabolism, coupling the tricarboxylic acid cycle and electron transport chain in bacteria and mitochondria and requires covalent incorporation of the cofact FAD for activity. The biogenesis of flavinylated SdhA, the catalytic subunit of SQR, is assisted by a highly conserved assembly factor termed SdhE in bacteria.

The protein Coa6 is located in the intermembrane space of mitochondria and is required for CcO assembly, with a suggested a role in the Cu-delivery pathway to CcO [1]. Our recent work has shown that Coa6 binds Cu(I), however the mechanism of how Coa6 mediates Cu-delivery is unknown. Studies on a clinically-relevant mutation of the Coa6 protein, C59W, have proposed that the mutation acts to disrupt protein-protein interactions between Coa6 and its proposed protein partners with identified roles in CcO assembly, leading to dysfunctions in Cu incorporation into CcO [3].

This presentation will describe the crystal structure of the native Coa6 and W59C mutant proteins and implications for the role of this protein in CcO assembly. The structure of *Escherichia coli* SdhE in complex with SdhA will also be described, which provides a structural explanation for the loss-of-function mutation, Gly78Arg, in SDHAF2, which causes hereditary paraganglioma 2 [4].

References:

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