Compartmentalization of copper used in assembly of cytochrome *c* oxidase within the mitochondrion

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Assembly of cytochrome *c* oxidase in the inner mitochondrial membrane requires a number of accessory proteins. The delivery and insertion of copper ions in the CuA and CuB sites of yeast cytochrome *c* oxidase (CcO) requires at least five proteins- Cox11, Cox17, Cox19, Cox23 and Sco1. Cox17 and Cox19 are Cu(I) binding proteins localized with the mitochondrial inner membrane space (IMS) and appear to provide copper ions for the inner membrane accessory proteins Sco1 and Cox11 required for formation of the CuA and CuB sites, respectively. The source of copper ions for the CcO assembly appears to originate within the mitochondrial matrix. The matrix copper pool exists within a low Mr complex with novel spectroscopic properties. Over expression of matrix-targeted Cu binding proteins including human Sod1 or the Crs5 metallothionein yields a diminution in the matrix Cu pool and a respiratory-deficient phenotype that can be suppressed by supplemental copper in the growth medium. The use of the matrix copper pool as a copper source for IMS assembly of the Cu centers in CcO suggests the existence of an inner membrane transporter for delivery of the matrix copper to the IMS. Copper transported into the IMS is associates with Cox17 which is a specific Cu(I) donor to both Sco1 and Cox11. Two cysteinyl residues present as a CxxxC motif in Sco1 and a distant His form a Cu(I) binding site, but this complex can convert to a Cu(II) complex that may be important in the assembly of the mixed valent, binuclear CuA site.