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Structural characterisation of mitochondrial complex IV assembly factors

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Cytochrome c oxidase or mitochondrial respiratory chain complex IV catalyses the transfer of electrons from cytochrome c in the intermembrane space, to molecular oxygen in the matrix and therefore contributes to the proton gradient that drives mitochondrial ATP synthesis. Complex IV dysfunction is a significant cause of human mitochondrial disease. Complex IV requires the incorporation of three copper ions, heme a and heme a3 cofactors for the assembly and activity of the complex. Complex IV assembly factors are required for subunit maturation, co-factor incorporation and stabilization of intermediate assemblies of complex IV in humans. Loss-of-function mutations in several genes encoding complex IV assembly factors have been shown to result in diminished complex IV activity and severe pathologic conditions in affected infants [1].

Our study focuses on two mitochondrial complex IV assembly factors, Coa6 and Coa7, that are located in the intermembrane space of mitochondria and contain intramolecular disulfide bonds. Coa6 binds copper with femtomolar affinity and has been proposed to play a role in the biogenesis of the CuA site of complex IV [2,3]. The W59C pathogenic mutation in Coa6 does not affect copper binding or import of the protein into mitochondria but affects the maturation and stability of the protein [3,4]. The precise role of Coa7 in the biogenesis of complex IV is not completely understood. However, patients with Coa7 pathogenic mutations suffer from mitochondrial diseases owing to complex IV deficiency. This presentation will describe the crystal structures of the Coa7 and Coa6 (wild-type and the W59C mutant) proteins and implications for their roles in complex IV assembly and function. To elucidate the atomic structure of the WTCoa6, W59CCoa6 and WTCoa7 proteins, we crystallised and determined their structures to 1.65, 2.18 and 2.40 Å resolution, respectively by X-ray crystallography. Diffraction data were recorded at the Australian Synchrotron on beamline MX2. The crystal structure of WTCoa6 was determined by sulfur single- wavelength anomalous dispersion and the crystal structure of WTCoa7 and W59CCoa6 were solved by molecular replacement.

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