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Architecture of mammalian mitochondrial respiratory complex I

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Abstract

Mitochondrial Complex I is a key metabolic enzyme in the respiratory chain of mammalian mitochondria, also called NADH:ubiquinone oxidoreductase. It has an overall molecular weight of ~900 kDa and carries out the initial step in funnelling electrons from the oxidation of NADH into the oxidative phosphorylation system and is a major contributor to the transmembrane proton motive force that drives ATP synthesis and mitochondrial ion and protein transport. Mammalian complex I is composed of more than 40 different proteins, of which 14 core subunits are essential for catalysis and proton translocation. The remaining proteins play a role in assembly, stability and regulation of the complex are collectively termed supernumerary subunits.

Using single-particle electron cryo-microscopy, we have determined the structure of complex I from bovine heart mitochondria at ~5 Å resolution. The map reveals several salient features of Complex I including the eight iron-sulphur (FeS) clusters essential for electron transfer between the sites of NADH oxidation and ubiquinone reduction and the core membrane domain with 60 transmembrane helices that form the proton translocation pathway. The belt of detergent and lipid that surrounds the complex is also clearly visible at a lower contour level and defines the membrane boundary. The map also reveals the arrangement of the supernumerary subunits around the core including 18 additional transmembrane helices. The ability to obtain a high-resolution structure of such a large membrane protein complex without crystals will aid in understanding how the electron transfer is coupled to proton transport.