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Structure and mechanism of respiratory complex I

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NADH-ubiquinone oxidoreductase (complex I) is the first and largest enzyme in the respiratory chain of mitochondria and many bacteria. It couples electron transfer between NADH and ubiquinone to the translocation of four protons across the membrane. It is a major contributor to the proton flux used for ATP generation in mitochondria, being one of the key enzymes essential for life as we know it. Mutations in complex I lead to the most common human genetic disorders. It is an L-shaped assembly formed by membrane and hydrophilic arms. Mammalian mitochondrial complex I consists of 45 subunits of about 1 Megadalton in total, whilst the prokaryotic enzyme is simpler and generally consists of 14 conserved "core" subunits. Bacterial enzyme can be used as a "minimal" model to understand the mechanism of complex I. We have determined first atomic structures of complex I using bacterial enzyme, starting with the hydrophilic domain, followed by the membrane domain and the structure of the entire Thermus thermophilus complex (536 kDa, 16 subunits, 9 Fe-S clusters, 64 TM helices) [1]. More recently we solved the structure of the entire mammalian complex I by the latest cryo-EM methods [2]. In mitochondria respiratory complexes exist not in isolation, but as larger supercomplexes or "respirasomes". We have determined the architecture of ~ 1.7 Megadalton CICIII2CIV respirasome by cryo-EM [3]. Our structures suggest a unique mechanism of coupling between electron transfer in the hydrophilic domain and proton translocation in the membrane domain of complex I via long-range (up to ~200 Å) conformational changes. I will discuss our current work, which is aimed at elucidating the molecular details of the coupling mechanism through determination of structures of the complex in different redox states with various bound substrates/inhibitors, using both X-ray crystallography and cryo-EM.

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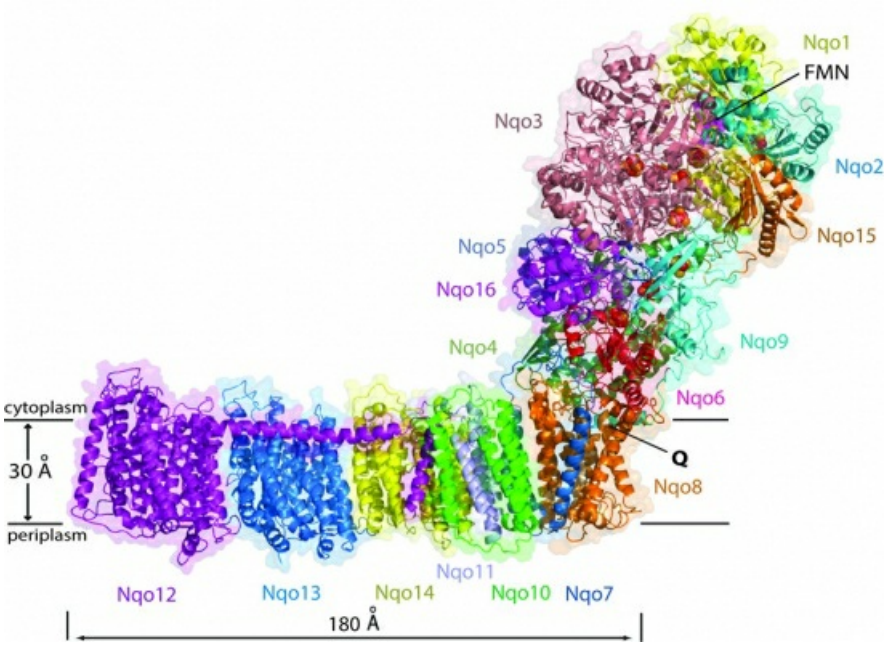
[2] K. Fiedorczuk, J.A. Letts, G. Degliesposti, K. Kaszuba, M. Skehel & L.A. Sazanov (2016) Nature, 538, 406-410.
[3] J.A. Letts, K. Fiedorczuk & L.A. Sazanov (2016) Nature, 537, 644-648.



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