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Probing the Long-range Proton-electron Coupling Mechanisms of Respiratory Complex I

Adel Beghiah [1], Patricia Saura [1], Niklas Hoja [1], Franziska Hoeser [2], Terezia Kovalova [1], Thorsten Friedrich [2], Ville R. I. Kaila [1]

[1] Stockholm University, Stockholm, Sweden

[2] Albert-Ludwigs Universität Freiburg, Freiburg, Germany

The NADH:ubiquinol oxidoreductase or Complex I is a crucial enzyme of the respiratory chains that generates the proton motive force (pmf) powering the synthesis of ATP. Complex I catalyses the transfer of electrons from NADH to quinone that induces the translocation of protons across the membrane domain up to 200 Å away from the quinone site. However, the long-range coupling mechanism is poorly understood and highly debated. Moreover, dysfunction of Complex I is responsible for half of the mitochondrial disorders. To elucidate the coupling between quinone catalysis and proton pumping, we combine here site-directed mutagenesis with biochemical and biophysical characterization together with structural determination and multiscale simulations. We show that key conserved carboxylates bridging the Q tunnel with the antiporter subunits in the Escherichia coli Complex I, provide a key coupling element between quinone reduction and proton translocation. On a general level, our combined findings provide new functional insight into the long-range proton coupled electron transfer reactions in biology.