

Long-range Energy Conversion in the Respiratory Complex I

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Abstract:

Respiratory Complex I is a redox-driven proton-pump, which drives proton-pumping across the mitochondrial inner membrane and bacterial cytoplasmic membrane by reduction of quinones. The established electrochemical proton gradient provides the driving force for active transport and synthesis of ATP and is thus crucial for biological energy conversion. Complex I comprises a membrane domain with three antiporter-like subunits, catalyzing the proton-pumping process, and a soluble domain, responsible for reduction of quinones by electron transfer from NADH. Remarkably, site-directed mutagenesis experiments show that mutation of titratable residues in the antiporter-like subunit, ~200 Å away from site of quinone reduction, inhibits both proton-pumping as well as quinone reductions. To explain this long-range proton-coupled electron transfer mechanism, both indirect and direct coupling models have been suggested. However, despite the recent elucidation of the complete intact structure of Complex I, the molecular principles of the coupling principles remain elusive. We present here results from large-scale classical and hybrid quantum-classical (QM/MM) molecular dynamics (MD) simulations of Complex I, embedded in biologically realistic environments. Our simulations indicate that water molecules provide important elements in the proton-pumping process. Our findings may form a basis for understanding long-range energy transduction in Complex I, and mechanistic similarities to other redox-driven proton-pumps such as Cytochrome c Oxidase and bacteriorhodopsin.

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