

Biophysical Characterization of Proton Gating in Dissected Modules of Complex I

Sofia Badolato¹, Jobst Liebau¹, Patricia Saura¹, Adel Beghiah¹, Sarah Rossmann¹, Hyunho Kim¹, Ana P. Gamiz-Hernandez¹, Ville R.i. Kaila¹

¹ Stockholm University, Stockholm, Sweden

Complex I is a fundamental enzyme in cellular respiration and energy metabolism of the cell. It couples the electron transport from NADH to quinone with the pumping of protons across the inner mitochondrial membrane, powering the synthesis of ATP. However, the remarkable long-range proton pumping mechanism of Complex I is still unsolved and highly debated. To elucidate the role of key residues in proton pumping process, we dissect here the bacterial Complex I into its individual antiporter modules and study its proton conduction properties by optical and NMR spectroscopic studies, site-directed mutagenesis, and multiscale molecular simulations. We identify how unique conformational changes in key gating residues, together with electrostatic tuning principles, modulate the proton conduction in proteoliposomes, and how disease-related mutations perturb the process. Taken together, our study provides new insights in the long-range energy transduction mechanism of Complex I.