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Complex structure of mammalian cytochrome c–cytochrome c oxidase reveals a novel protein-protein interaction mode

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Mitochondrial cytochrome c oxidase (CcO) transfers electrons from cytochrome c (Cyt.c) to O2 to generate H2O, a process coupled to proton pumping. To elucidate the mechanism of electron transfer, a crystal structure of the complex of CcO and Cyt.c would be invaluable for mechanistic studies. Two-dimensional (2D) crystals of the mammalian Cyt.c–CcO complex were prepared at higher pH (7.4–9.0) with both proteins in the oxidized state (Osuda et al, 2016), but these 2D crystals could not provide us with a structure of sufficient resolution. We optimized 3D crystallization conditions for ferri-Cyt.c and oxidized CcO at high pH and solved the X-ray structure of the complex at 2.0 Å resolution. The specific interaction between Cyt.c and CcO is stabilized by only six electrostatic interactions between side chains within a small contact surface. From a theoretical calculation based on the complex structure, we identified an electron transfer pathway from the heme c of Cyt.c to CuA of CcO *via* Lys-13 of Cyt.c. Between the two proteins are three water layers, one of which lies between the other two layers without significant direct interaction with either protein. The inter-molecular span between Cyt.c and CcO is longer than those of other complexes by more than 3.0 Å, and the contact surface area of Cyt.c and CcO is smaller than one-third the size of those of other complexes. Cyt.c undergoes large structural fluctuations, using the interacting regions with CcO as a fulcrum. These features of the protein–protein interaction at the docking interface represent the first known example of a new class of inter-protein interaction, which we term "soft and specific". This interaction is predicted to contribute to the rapid association/dissociation of the Cyt.c–CcO complex, which facilitates the sequential supply of four electrons for the O2 reduction reaction.

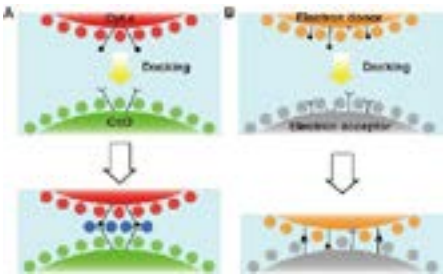

Figure1: *A In the Cyt.c–CcO complex system, water molecules on the surfaces of each protein are preserved to form three layers upon docking, but each protein specifically interacts via the long arms of side chains. B In other ET complex systems, electron donor and acceptor proteins form an ET complex by excluding water molecules on the surface of each protein.*

Biography

Kyoko Shinzawa-Itoh, Associate Professor of University of Hyogo, grew up in Hiroshima Japan. She received her MS degree from Hiroshima University of Graduate School of Integrated Arts and Sciences and her Ph D. in Pharmaceutical Sciences from Hiroshima University of Graduate School of Biomedical & Health Sciences. She worked as assistant professor at the Department of Life Science, Himeji Institute of Technology 1988-2004 and at the Hyogo University of Graduate School of Life Science 2004-2013. She is associate Professor of Picobiology Institute, Graduate School of Life Science University of Hyogo from 2013. She has studied about mitochondrial respiratory complexes.

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