Gating of water and proton transfer in the respiratory enzyme

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The membrane-bound enzyme cytochrome *c* oxidase is responsible for cell respiration in aerobic organisms, and conserves free energy from O_2 reduction into an electrochemical proton gradient by coupling the redox reaction to proton pumping across the membrane[1]. O_2 reduction produces water at a bimetallic heme a_3/Cu_B active site next to a hydrophobic cavity deep within the membrane. Transport of these water molecules out of the enzyme is critical. As in the aquaporins it must be rigidly controlled. Otherwise water-mediated proton transfer may compromise proton-pumping and lower the efficiency of ATP synthesis. Here, we report molecular dynamics simulations that suggest that a conserved arginine-haem propionate ion pair provides a gate to the hydrophobic cavity, which exhibits thermal opening and closure that is remarkably governed by the enzyme's redox state and the number of water molecules in the cavity. Exit of water from the cavity is observed via this gate, which explains the extraordinary spatial specificity of water expulsion from the enzyme observed recently[2]. An important role of this gate also in the proton pumping mechanism is supported by site-directed mutagenesis experiments.

1. Bloch, D., Belevich, I., Jasaitis, A., Ribacka, C., Puustinen, A., Verkhovsky, M.I. & Wikström, M. (2004) *Proc. Natl. Acad. Sci. USA* 101, 529-533.
2. Schmidt, S., McCracken, J. & Ferguson-Miller, S. (2003) *Proc. Natl. Acad. Sci. USA* 100, 15539-15532.