Protonation dynamics in Cytochrome c Oxidase

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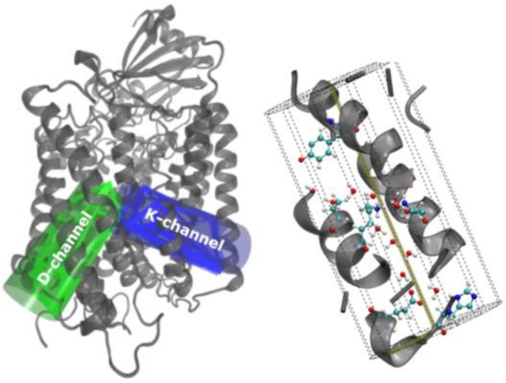

Cytochrome c oxidase, also called complex IV, is a membrane protein in the respiratory chain. It uses the energy gained from the reduction of molecular oxygen with protons to water to pump extra protons through the membrane. The transport of the protons to the reaction centre takes place through two so-called channels, the D- and K-channel, named after an important aspartate (D132) and lysine (K362) residue, respectively. Whereas in the D-channel crystal structures reveal a number of water molecules along which a proton transport via a Grotthuss mechanism appears to be feasible [1], the situation is more complicated in the K-channel. MD simulations reveal that the presence of a proton in the middle of the K-channel, either located at the naming residue K362 or at a water molecule in its vicinity, result in a significantly more hydrated K-channel than in cases where such an excess proton is located at the channel entrance or not present. In addition, the conformational dynamics of important residues in the K-channel also depend on the protonation state, not only of the respective residues themselves but also on the other residues in the channel. Protein residue conformation, hydration level, and width of the channel show a correlation that suggests a higher conformational flexibility of the K362 side chain in its protonated form, i.e. in the presence of more water molecules [2]. Both factors facilitate the transport of a proton through the channel, either carried by a water molecule as a hydronium ion or via the K362 residue. Simulations evaluating the probabilities of proton positions at various heights in the channel suggest an “upward” movement, that is towards the redox centre, to be more probable than a “downwards” movement in which the region around K362 can be understood as a watershed, leading to “up” or “down” movement to which K362 itself contributes in a gating manner, however, further regulated by the protonation state and thus conformation state of the other residues and consequently also the hydration level in the channel.

[1] Ghane, T., Gorriz, R. F., Wrzalek, S., Volkenandt, S., Dalatieh, F., Reidelbach, M., & Imhof, P. Hydrogen-bonded network and water dynamics in the D-channel of cytochrome c oxidase, *The Journal of membrane biology*, **2018**, *251(3)*, 299-314.
[2] Helabad, M. B., Ghane, T., Reidelbach, M., Woelke, A. L., Knapp, E. W., & Imhof, P. Protonation-state-dependent communication in cytochrome c oxidase. *Biophysical journal*, **2017**, *113(4)*, 817-828.