Transmembrane electron transfer in NADPH Oxidase

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ABSTRACT

NADPH oxidase (NOX) form a family of transmembrane proteins involved in the production of reactive oxygen species (superoxide anion or hydrogen peroxide) called ROS that are necessary for the organisms to defend themselves against pathogens. ROS production requires the transfer of electrons across the cell membrane to lead to the reduction of the dioxygen molecule (1). The mechanisms governing the kinetics and thermodynamics of those electron transfer, and especially the role of the environment (protein, membrane, solvent) remains poorly understood nowadays. The recent determination of the structure of some proteins from the NOX family (2,3) allows for their study using molecular simulation. We have undergone the study if the electron transfer between the two heme cofactors inserted in the protein NOX5 using hundreds of nanoseconds-long classical molecular dynamics simulations coupled with QM+M calculations. We have particularly computed the electron transfer reaction free energy and reorganization energy, deciphering the respective contributions of the various parts of the system. The results showed an opposite role of the membrane and solvent/counter-ions. The study of electron tranfer pathways also revealed the presence of aromatic residues between the two hemes that could play an important role in the kinetics of the reaction (4). This work opens the way to a better understanding of the factors that control electron transfer in biological medium.

REFERENCES

(1) Lambeth, J.D. & Neish, A.S. (2014) *Annu. Rev. Pathol. Mech. Dis.* **9**, 119–145 https://doi.org/10.1146/annurev-pathol-012513-104651

(2) Magnani, F. *et al.* (2017) *PNAS* **114**, 6764–6769 https://doi.org/10.1073/pnas.1702293114

(3) Sun, J. (2020) *Nat Struct Mol Biol* **27**, 1086–1093 https://doi.org/10.1038/s41594-020-0501-x

(4) Wu, X. *et al.* (2021) *Frontiers in Chemistry* **9**: 650651 https://doi.org/10.3389/fchem.2021.650651