Molecular Modeling of NOX5 protein: Impact of the Initial Structure and Membrane composition

Etcheverry Baptiste[1], de la Lande Aurélien[1], Baaden Marc[2], Cailliez Fabien[1]

[1] Institut de Chimie Physique, Université Paris-Saclay, CNRS (UMR 8000), 15 avenue Jean Perrin 91405, Orsay, France. ; [2] ACNRS, Université de Paris, UPR 9080, Laboratoire de Biochimie Théorique, 13 rue Pierre et Marie Curie, F-75005, Paris, France.
baptiste.etcheverry@universite-paris-saclay.fr

Electron Transfer within proteins is an essential process for cellular activity. NADPH oxidases are transmembrane proteins whose main function in many organisms is the production of reactive oxygen species. In the NOX5 isoform, the reduction of dioxygen to superoxide ions occurs after several steps of electron transfer between redox cofactors (two hemes and a flavin) across the cell membrane. In a previous work of our group[1], the electron transfer between the hemes in the NOX5 protein was studied using molecular dynamics simulations based on the first experimental structure of a NOX protein.[2] Our aim is now to investigate the behavior of the NOX5 protein and the successive steps of electron transfer responsible for its activity using theoretical chemistry methods.

Recently, new experimental structures of NOX proteins[3][4] have been determined using cryo-electron microscopy showing rather large deviation from the previous model, which might have an impact on the electron transfer process. In this work we present molecular dynamics studies of the NOX5 protein, modeled with a classical force field representation in a biological environment (membrane, counter-ions, water). The construction of the models of the NOX5 protein will be described in detail, as well as the analysis of trajectories of several hundred nanoseconds in each redox state involved in the steps of transmembrane electron transfer. We will explore the role of the initial atomic positions (based on the two types of experimental data) and membrane composition.

The structural analysis of these trajectories will be described, as well as the first calculations of the electron transfer parameters in the framework of Marcus theory[5]. Our goal is the free energy ΔG of electron transfer. The comparison of the different simulations will provide information about the influence of the different simulation conditions on the structural and dynamic properties of the protein and on the electron transfer.

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