Molecular Dynamics of Complex II within a Lipid Membrane: structural insights on protein regulation of electron and proton transfer

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Complex II:SQR is a large transmembrane complex that has a dual role in metabolic reactions: participates in the Krebs cycle and in the electron transport chain. This complex has been pointed recently to be an ideal target to combat oxidative stress, since there is increasing evidence that it is an important source of ROS, if not the major one under specific conditions related to disease scenarios [1,2].

In order to characterize this complex with atomic level detail, we have carried QM calculations (to parameterize the cofactors) and molecular dynamics simulations with the complex within a lipid membrane in different oxidation states.

The molecular dynamics simulations gave us insight regarding: i) the role of the protein covalent linkage to the flavin adenine cofactor; ii) how the protein environment modulates the iron-sulfur clusters in the different redox states; iii) how the redox state of the [Fe_3S_4] cluster modulates substrate (ubiquinone) binding [3].

The final objective of these studies is the development of improved pharmaceutical agents to amend the consequences of oxidative stress, improving wellbeing and providing more effective means of attacking cancer cells.

References:

[1]Quinlan, C. L. et al. Journal of Biological Chemistry 2012, 287, 27255.
[2]Ralph, S. J. et al. Pharm Res 2011, 28, 2695.
[3]Carvalho, ATP; Swart, M. Structural insights on the Biding modes of UQ to complex II (in preparation)