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Molecular Dynamics Simulation of Proton-Conducting Half-Channels in Bacterial F_OF_1-ATP Synthase

Leonid A. Ivontsin[1*], Elena V. Mashkovtseva[1,2], Yaroslav R. Nartsissov[1,3]

[1] Institute of Cytochemistry and Molecular Pharmacology, Moscow, Russia

[2] Pirogov Russian National Research Medical University, Moscow, Russia

[3] Biomedical Research Group, BiDiPharma GmbH, Siek, Germany

ABSTRACT

Adenosine triphosphate (ATP) serves as a universal energy source for numerous biochemical processes. In the cell, ATP synthesis is primarily driven by the protein complex F_OF_1-ATP synthase, which utilizes the electrochemical gradient of hydrogen ions. Despite recent advances in structural biology that have improved our understanding of the spatial organization of proton half-channels, many aspects of this system remain unclear. A key unresolved issue is the mechanism by which proton translocation is coupled to ATP synthesis. This study focuses on the structural characterization of the half-channels and the analysis of potential proton translocation pathways. Molecular dynamics simulations were performed on the membrane-bound F_O factor of ATP synthase from *E. coli* (PDB ID: 6VWK), embedded into three types of lipid bilayers representing different physiological states of the cell. The simulations yielded structural and functional insights into the inlet and outlet proton half-channels. Specific spatial arrangements of polar amino acid residues and water molecules were identified as critical determinants of proton conductivity. Furthermore, the localization of three conserved structural water clusters (W1-W3) was detected. Stable spatial positions (SP) of key amino acid side chains in the a-subunit were determined. The presence of cardiolipin in the membrane was shown to enhance the hydration of the half-channels. To elucidate the role of functionally important protein elements in proton translocation, a mutational analysis was conducted. Simulations of mutant proteins revealed that substitution of certain polar residues significantly alters hydration dynamics, leading to disruption or complete loss of water clusters W1-W3 and, consequently, interruption of the proton conduction pathway.

Keywords: membrane proteins, F_OF_1-ATP synthase, mutations, proton transport, molecular dynamics

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[*]Corresponding Author:

Leonid A. Ivontsin, Department of Mathematical Modeling and Statistical Data Analysis, Institute of Cytochemistry and Molecular Pharmacology, 24/14 6th Radialnaya str., Moscow, 115404, Russia.
Email: ivontsin@icmph.org