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INSIGHTS ON THE PROTON TRANSLOCATION PATHWAYS IN BACTERIAL F_oF_1-ATP SYNTHASE

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Abstract

Molecular dynamics simulations were used to study the structure of proton half-channels of F_oF_1-ATP synthase. A proton transfer chain consisting of conserved amino acid residues and water molecules clusters was identified. The effect of cardiolipins on protein hydration was evaluated. Mutational analysis was conducted to investigate the role of functional elements of the protein structure in the process of proton transport.

Adenosine triphosphate (ATP) plays a vital role in biochemical processes. In the cell, ATP synthesis is carried out by a universal molecular motor called F_oF_1-ATP synthase, utilizing the energy from a proton electrochemical gradient. Despite recent structural studies leading to the clarification of the proton half-channel's locations, many questions remain unanswered. The key unresolved issue is the coupling of proton transfer with ATP synthesis.

For the investigation of the structure of half-channels and the analysis of potential proton movement areas, molecular dynamics simulations of the membrane F_o factor of ATP synthase from *E. coli* embedded in three types of lipid bilayer corresponding to different biological cell states.

It was found that the inlet half-channel had a composite structure, including an aqueous cavity in the protein *a*-subunit through which protons penetrated into the half-channel, and the narrow tract in the region near the key *c*D61 residue of the *c*-subunit. In this bottleneck, a sequence of conserved amino acid residues (*a*E219, *a*D119, *a*H245, *a*N214, and *a*Q252) forming a proton transfer chain was discovered. Additionally, we detected the localization of three structural water molecule clusters (W1–W3) that were necessary for the proton transport continuity. Existence of stable spatial positions (SP) of the significant amino acid side chain of *a*N214 was a necessary condition for facilitating proton transport [1]. The influence of cardiolipin content on half-channels hydration was examined. The outlet half-channel was a water-filled cavity through which a proton could easily move in bulk [2]. Mutational analysis was conducted to investigate the role of functional elements of the protein structure in the process of proton transport [3]. The results of MD simulations of the mutant enzyme indicate that substitutions of conserved polar residues significantly affected hydration levels, leading to drastic changes in the occupancy and capacity of the structural water molecule clusters (W1–W3), up to their complete disappearance and consequently to the proton transfer chain disruption.

References

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