Секция «Биоинформатика»

Mapping the LDAO binding site in ATP-synthase using molecular docking

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FoF1-H+-ATP synthase is a key enzyme for the interconversion of the main cell energy currencies - the transmembrane electrochemical proton potential difference and ATP. This is a multisubunit protein complex located in the prokaryotic cell membrane, in the inner mitochondrial membrane and in the thylakoid membrane in chloroplasts. Depending on the conditions and needs of the cell, the enzyme functions as ATP synthase or as an ATP-dependent proton pump. The extramembrane catalytic core of the enzyme consists of 3 α-subunits, 3 β-subunits and 1 γ-subunit. Catalytic sites are located on the $\alpha\beta$-interface.

A detergent lauryldimethylamine oxide (LDAO) is known to stimulate the ATPase activity of ATP synthases from chloroplasts, mitochondria, and bacteria. The possible mechanism of this activation is associated with non-competitive inhibition of ATP hydrolysis by MgADP (ADP-inhibition). When MgADP is bound at a catalytic site without phosphate, a conformational transition may occur leading to enzyme inactivation. ADP-inhibition is an important regulatory mechanism which possibly prevents the exceeding ATP hydrolysis by ATP synthase when the proton-motive force is low. LDAO was shown to accelerate the release of the inhibitory ADP from catalytic sites, thus re-activating the enzyme [2].

Despite the fact that LDAO was used to assess the strength of ADP-inhibition in ATP synthases from various organisms for many years, the exact mechanism of its action and even its binding site is unknown [1]. In this work we performed molecular docking of LDAO into 4 ATP-synthase structures (mitochondrial, chloroplast and 2 bacterial) using AutoDock Vina software to find possible LDAO binding positions and to propose a mechanism of activation. As a result, two LDAO binding sites were found. The first is the catalytic site where ATP hydrolysis occurs. In this case, LDAO may destabilize the binding of the inhibitory ADP therefore supporting ADP release. The second probable binding site is at the interface between γ-subunit and $\alpha 3\beta 3$ hexamer. LDAO may facilitate γ-subunit rotation, which, as was previously shown [3], also supports the enzyme reactivation.

Docking results are now being verified with molecular dynamics.

Источники и литература

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