From Structure to Function:
UCP1 Cavity Interactions Revealed by Molecular Dynamics Simulations

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Mitochondria, the cell's powerhouses, primarily produce adenosine triphosphate (ATP), but under cold exposure, brown adipose tissue (BAT) uniquely utilizes non-shivering thermogenesis to dissipate energy as heat instead. Central to this process is uncoupling protein 1 (UCP1), which, in the presence of long-chain fatty acids (FAs) or other uncouplers like dinitrophenol and CCCP, facilitates a regulated transport of protons across the inner mitochondrial membrane, thereby generating heat. While nucleotides inhibit this process, FAs function as weak, protein-independent uncouplers, mainly limited by the transport of the FA anion across the membrane. According to the fatty acid cycling hypothesis [1], UCP1 catalyzes this crucial step. Nonetheless, the specific molecular mechanisms underlying both the UCP1-facilitated transport of FA anions and its inhibition remain poorly understood.

In our study, we propose two distinct pathways for FA anion translocation (sliding) at the UCP1 protein-lipid interface, converging at critical arginine residues, R84 and R183, located in the nucleotide-binding region. Our findings indicate that the protonation of the FA anion facilitates its release from the protein-lipid interface [2]. Interestingly, the addition of ATP prior to the introduction of FAs entirely inhibits protein-mediated proton transport, through binding to both R84 and R183. In contrast, when ATP is introduced in the presence of FAs, the inhibition is only partial, suggesting that the competition between ATP and FAs alters the degree of proton transport regulation. Molecular dynamics (MD) simulations are conducted on cryo-EM structures of UCP1 in both nucleotide-free (PDB: 8HBV) and ATP-bound (PDB: 8HBW) states, with results correlating well with conductance measurements of membranes reconstituted with UCP1 [3].

Taken together, our findings enhance the understanding of UCP1's role in regulating the proton gradient. Unraveling the precise molecular mechanisms of proton transport is crucial for comprehending the processes of non-shivering thermogenesis and energy balance in mammals, both of which are fundamental to cellular function.

References:

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