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Elucidating the role of adenine nucleotide transporter in mitochondrial swelling: an experimental and computational approaches

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Abstract

Mitochondria produce over 90% of cellular ATP and actively participate in maintaining ion homeostasis, redox status, lipid metabolism, and cell growth. Changes in the matrix volume of mitochondria affect their functional and structural integrity. Modest volume increases associated with modulation of the inner mitochondrial membrane can activate electron transfer chain and oxidative phosphorylation, whereas excessive swelling impairs structural organization of the membrane and initiate mitochondria-mediated cell death mechanisms. Therefore, clarifying the precise mechanisms of excessive mitochondrial swelling is important for regulation of mitochondria-mediated cell death pathways in response to energy and oxidative stresses. Opening of non-selective mitochondrial permeability transition pores (mPTP) is the primary cause of excessive matrix swelling. The molecular identity remains unknown and recent studies suggest the existence of two or more types of mPTP that can be composed of different protein(s). The adenine nucleotide translocator (ANT) and F_OF_1-ATP synthase were proposed to be potential mPTP core components that can act together or independently each other. Here, we elucidated the role of ANT in mPTP opening by applying both experimental and computational approaches. mPTP opening was evaluated in cardiac mitochondria that were exposed to moderate and high Ca^{2+} concentrations in the absence and presence of respiratory substrates and ADP. We developed a detailed model of the ANT transport mechanism including the matrix (ANT_M), cytosolic (ANT_C), and pore (ANT_P) states of the transporter that was able to simulate our experimental data. In addition, we corroborated and simulated our ANT model based on previous ANT kinetics data. The model was successful not only in simulating ANT pore state transition, but also explained the potential role of ANT in mPTP opening in cardiac mitochondria.

This is the full abstract presented at the Experimental Biology meeting and is only available in HTML format. There are no additional versions or additional content available for this abstract.