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MITOCHONDRIAL ION CHANNELS AS KEY GATEKEEPERS OF CELL LIFE AND DEATH

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Mitochondria are involved in oxidative phosphorylation, thermogenesis, reactive oxygen species production, and intracellular Ca^{2+} homeostasis. Mitochondrial dysfunction during metabolic inhibition causes energy depletion and loss of cellular function and integrity, leading to cell death. Mitochondria possess a highly permeable outer membrane and an inner membrane that was originally thought to be relatively impermeable to ions to preventdissipation of the electrochemical gradient for protons. Ion channels on the mitochondrial inner membrane influence membrane potential ($\Delta\Psi_m$) and cell function in specific ways that can be detrimental to cell survival. Mitochondrial K^+channels (mitoK_{Ca} and mitoK_{ATP}) are important determinants of resistance to ischemic damage and apoptosis, and may be clinically recruitable to prevent cardiac ischemic injury. In contrast, inner membrane anion channel (IMAC) initiates oscillations of mitochondrial redox and membrane potential, and thus might influence the overall function of the cell. In this study we recorded IMAC in cardiac mitochondrial inner membrane using nano patch-clamp techniques, and we tested whether IMAC confersprotection against ischemic-reperfusion injury or not. We demonstratedthat metabolic inhibition can trigger synchronized oscillations in $_m$, ROS production, and mitochondrial redox potential. In the open-channel current-voltage curve, single channel currents with a full unitary conductance of 107 pS were often observed. DIDS, 4'-chlorodiazepham and PK11195 decreased the channel activity and prevented metabolic inhibition-induced $_m$ loss. They also protected cardiac myocytes against ischemic-reperfusion injury. We are now trying to confirm the nature and molecular identity of the channel components. Our results suggest that IMAC is present in cardiac mitochondria and plays a role as key arbiters of cell life and death. Our studies may contribute to understanding the close relationship between mitochondrial ion channels, membrane potential, and the overall function of the cell. The ion channels should be present in all cell types containing mitochondria and the implications for normal as well as for pathophysiological cell function are universal.

Key Words: Mitochondria, Mitochondrial ion channels, Membrane potential ($\Delta\Psi_m$)