Membrane Bioenergetics: Based On The International Workshop Held At Cranbrook Schools, Bloomfield Hi

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Elevated zinc induces endothelial apoptosis via disruption of glutathione metabolism: role of the ADP translocator

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Abstract

Zinc is the second-most abundant transition metal within cells and an essential micronutrient. Although adequate zinc is essential for cellular function, intracellular free zinc (Zn^{2+}) is tightly controlled, as sustained increases in free Zn^{2+} levels can directly contribute to apoptotic endothelial cell death. Moreover, exposure of endothelial cells to acute nitrosative and/or oxidative stress induces a rapid rise of Zn^{2+} with mitochondrial dysfunction and the initiation of apoptosis. This apoptotic induction can be mimicked through addition of exogenous $ZnCl_2$ and mitigated by zinc-chelation strategies, indicating Zn^{2+}-dependent mechanisms in this process. However, the molecular mechanisms of Zn^{2+}-mediated mitochondrial dysfunction are unknown. Here we report that free Zn^{2+} disrupts cellular redox status through inhibition of glutathione reductase, and induces apoptosis by redox-mediated inhibition of the mitochondrial adenine nucleotide transporter (ANT). Inhibition of ANT causes increased mitochondrial oxidation, loss of ADP uptake, mitochondrial translocation of bax, and apoptosis. Interestingly, pre-incubation with glutathione ethyl ester protects endothelial cells from these observed effects. We conclude that key mechanisms of Zn^{2+}-mediated apoptotic induction include disruption of cellular glutathione homeostasis leading to ANT inhibition and decreases in mitochondrial ATP synthesis. These pathways could represent novel therapeutic targets during acute oxidative or nitrosative stress in cells and tissues.

Keywords

Mitochondrial dysfunction; Apoptosis; Redox status

Introduction

Understanding the nature of how cells transduce, interpret, and respond to stress signals, both in terms of extracellular perception as well as signals from within, is fundamental for discovering and developing new therapies and interventions for situations where cells, tissues, and organs lose the ability to maintain homeostatic balance. It is now apparent reactive oxygen and nitrogen species (ROS, RNS, respectively) serve as signal transduction molecules in biological systems. ROS such as hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\cdot-}$) are also increasingly understood to have complex and highly nuanced signal transduction roles in cells and tissues (Forman and Torres 2001). However, these same chemical species can also initiate signaling pathways that result in apoptosis (Bauer 2000). We, and others, have previously reported that exposure of pulmonary artery endothelial cells to elevated levels of ROS and/or

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