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Induction of the mitochondrial permeability transition by selenium compounds mediated by oxidation of the protein thiol groups and generation of the superoxide

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Abstract

The cancer chemopreventive effect of selenium compounds cannot be fully explained by the role of selenium as a component of antioxidant enzymes, suggesting that other mechanisms, such as thiol oxidation or free radical generation, also underlie this effect. The toxicities of six different selenium compounds (selenite, selenate, selenocystine, selenocystamine, selenodioxide, and selenomethionine) have now been compared in HepG2 human hepatoma cells and isolated rat liver mitochondria. Selenite, selenocystine, and selenodioxide induced apoptosis in HepG2 cells and mediated oxidation of protein thiol groups in both HepG2 cells and isolated mitochondria. Selenocystamine oxidized protein thiol groups in isolated mitochondria and crude extracts of HepG2 cells but not in intact HepG2 cells, suggesting that this compound is not able to cross the cell membrane. The selenium compounds capable of oxidizing thiol groups also induced the mitochondrial permeability transition (MPT) in isolated mitochondria. Furthermore, they generated the superoxide ($O_2^{\bullet -}$) on reaction with glutathione in the presence of mitochondria, and an $O_2^{\bullet -}$ scavenger inhibited their induction of the MPT. These results suggest that the pro-apoptotic action of selenium compounds is mediated by both thiol oxidation and the generation of $O_2^{\bullet -}$, both of which contribute to opening of the MPT pore.

Keywords: Selenium compounds; Apoptosis; Superoxide anion; Mitochondria; Mitochondria permeability transition

1. Introduction

Mitochondria play an important role in the regulation of apoptosis [1–5]. The intermembrane space of these organelles contains several pro-apoptotic proteins, including cytochrome *c*, procaspases 2, 3, and 9, and apoptosis-inducing factor, all of which are released into the cytosol as a result either of disruption of the outer mitochondrial membrane or of the opening of specific pores [6–8]. The opening of the MPT pore induced by apoptotic stimuli is thus thought to result in swelling of the mitochondrial matrix and consequent rupture of the outer membrane and release of pro-apoptotic proteins. The opening of the MPT pore is regulated by Ca^{2+}, thiol oxidants, ROS, and members of the Bcl-2 family of proteins [9–15].

The production of ROS by mitochondria contributes to a variety of conditions associated with cell death, including ischemia, aging, neurodegeneration, and cancer [3,16–18]. During mitochondrial respiration, electrons are released from their normal transport pathway to molecular oxygen at complexes I and III [19], resulting in formation of the superoxide ($O_2^{\bullet -}$). Mitochondria thus represent the main source of ROS in mammalian cells and accumulate oxidative damage more rapidly than do other cellular components [20]. Although the superoxide is itself damaging to cellular components, it also generates additional reactive oxidants both by dismutation to hydrogen peroxide, which is reduced, usually by a redox active metal ion, such as ferrous ion, to hydroxy radical and hydroxide. Oxidative

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Abbreviations: MPT, mitochondrial permeability transition; ROS, reactive oxygen species; $\Delta\Psi_m$, mitochondrial membrane potential; DTT, dithiothreitol; DTNB, 5,5′-dithiobis-(2-nitrobenzoic acid); PAGE, polyacrylamide gel electrophoresis; NBT, nitroblue tetrazolium; Mn-TBAP, manganese(III) tetrakis(4-benzoic acid)porphyrin; TTFA, 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione.

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