Mediating of Caspase-independent apoptosis by cadmium through the metochondria-ROS pathway in MRC-5 fibroblasts

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摘要

Abstract

Cadmium (Cd) is an environmental pollutant of global concern with a 10-30-year biological half-life in humans. Accumulating evidence suggests that the lung is one of the major target organs of inhaled Cd compounds. Our previous report demonstrated that 100 microM Cd induces MRC-5 cells, normal human lung fibroblasts, to undergo caspase-independent apoptosis mediated by mitochondrial membrane depolarization and translocation of apoptosis-inducing factor (AIF) from mitochondria into the nucleus. Here, using benzyloxycarbonyl-Val-Ala-Asp-(ome) fluoromethyl ketone (Z-VAD.fmk) as a tool, we further demonstrated that Cd could induce caspase-independent apoptosis at concentrations varied from 25 to 150 microM, which was modulated by reactive oxygen species (ROS) scavengers, such as N-acetylcysteine (NAC), mannitol, and tiron, indicating that ROS play a crucial role in the apoptogenic activity of Cd. Consistent with this notion, the intracellular hydrogen peroxide (H2O2) was 2.9-fold elevated after 3 h of Cd treatment and diminished rapidly within 1 h as detected by flow cytometry with 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) staining. Using inhibitors of the mitochondrial electron transport chain (ETC) (oligomycin A and rotenone for complex I and V, respectively) and mitochondrial permeability transition pore (MPTP) (cyclosporin A and aristolochic acid), we coincidently found the ROS production, mitochondrial membrane depolarization, and apoptotic content were almost completely or partially abolished. As revealed by confocal microscopy staining with chloromethyl-X-rosamine (CMXRos) and an anti-AIF antibody, the collapse of mitochondrial membrane potential induced by Cd (3 h-treatment) was a prelude to the translocation of caspase-independent

pro-apoptotic factor, AIF, into the nucleus (after 4 h of Cd treatment). In summary, this study demonstrated that, in MRC-5 fibroblasts, Cd induced caspase-independent apoptosis through a mitochondria-ROS pathway. More importantly, we provide several lines of evidence supporting a role of mitochondrial ETC and MPTP in the regulation of caspase-independent cell death triggered by Cd.