The role of endoplasmic reticulum in cadmium-induced mesangial cell apoptosis

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摘要

Abstract

Cd is an industrial and environmental pollutant that affects many organs in humans and other mammals. However, the molecular mechanisms of Cd-induced nephrotoxicity are unclear. In this study, we show that endoplasmic reticula (ER) played a pivotal role in Cd-induced apoptosis in mesangial cells. Using Fluo-3 AM, the intracellular concentration of calcium ([Ca(2+)](i)) was detected as being elevated as time elapsed after Cd treatment. Co-treatment with BAPTA-AM, a calcium chelator, was able to significantly suppress Cd-induced apoptosis. Calcineurin is a cytosolic phosphatase, which was able to dephosphorylate the inositol-1,4,5-triphosphate receptor (IP(3)R) calcium channel to prevent the release of calcium from ER. Cyclosporine A, a calcineurin inhibitor, increased both [Ca(2+)](i) and the percentage of Cd-induced apoptosis. However, EGTA and the IP(3)R inhibitor, 2-APB, were able to partially modulate Cd cytotoxicity. These results led us to suggest that the extracellular and ER-released calcium plays a crucial role in Cd-induced apoptosis in mesangial cells. Following this line, we further detected the ER stress after Cd treatment since ER is one of the major calcium storage organelles. After Cd exposure, GADD153, a hallmark of ER stress, was upregulated (at 4h of exposure), followed by activation of ER-specific caspase-12 and its downstream molecule caspase-3 (at 16h of exposure). The pan caspase inhibitor, Z-VAD, and BAPTA-AM were able to reverse the Cd-induced cell death and ER stress, respectively. Furthermore, the mitochondrial membrane potential (DeltaPsi(m)) was depolarized significantly and cytochrome c was released after 24h of exposure to Cd and followed by mild activation of caspase-9 at the 36-h time point, indicating that mitochondria stress is a late event. Therefore, we concluded that ER is the major killer organelle in Cd-induced mesangial cell apoptosis and that calcium oscillation plays a pivotal role