Cadmium toxicity toward caspase-independent apoptosis through the mitochondria-calcium pathway in mtDNA-depleted cells

施純明

Shih YL;Hsu SW;Wang SH;Chen WL;Lee MT;Wei YH;Shih CM

摘要.

Abstract

Mitochondria are believed to be integrators and coordinators of programmed cell death in addition to their respiratory function. Using mitochondrial DNA (mtDNA)-depleted osteosarcoma cells (p° cells) as a cell model, we investigated the apoptogenic signaling pathway of cadmium (Cd) under a condition of mitochondrial dysfunction. The apoptotic percentage was determined to be around 58.0% after a 24-h exposure to 25 μM Cd using flow cytometry staining with propidium iodine (PI). Pretreatment with Z-VAD-fmk, a broad-spectrum caspase inhibitor, failed to prevent apoptosis following Cd exposure. Moreover, Cd was unable to activate caspase 3 using DEVD-AFC as a substrate, indicating that Cd induced a caspase-independent apoptotic pathway in ρ υ cells. JC-1 staining demonstrated that mitochondrial membrane depolarization was a prelude to apoptosis. On the other hand, the intracellular calcium concentration increased 12.5.fold after a 2-h exposure to Cd. More importantly, the apoptogenic activity of Cd was almost abolished by ruthenium red, a mitochondrial calcium uniporter blocker. This led us to conclude that mtDNA-depleted cells provide an alternative pathway for Cd to conduct caspase-independent apoptosis through a mitochondria-calcium mechanism.