Reactive oxygen species-dependent HSP90 protein cleavage participates in arsenical As+3- and MMA+3-induced apoptosis through inhibition of telomerase activity via JNK activation

楊良友

Shen SC;Yang LY;Lin HY;Wu CY;Su TH;Chen YC

摘要

Abstract

The effects of six arsenic compounds including As(+3), MMA(+3), DMA(+3), As(+5), MMA(+5), and DMA(+5) on the viability of NIH3T3 cells were examined. As(+3) and MMA(+3), but not the others, exhibited significant cytotoxic effects in NIH3T3 cells through apoptosis induction. The apoptotic events such as DNA fragmentation and chromosome condensation induced by As(+3) and MMA(+3) were prevented by the addition of NAC and CAT, and induction of HO-1 gene expression in accordance with cleavage of the HSP90 protein, and suppression of telomerase activity were observed in NIH3T3 cells under As(+3) and MMA(+3) treatments. An increase in the intracellular peroxide level was examined in As(+3)- and MMA(+3)-treated NIH3T3 cells, and As(+3)- and MMA(+3)-induced apoptotic events were blocked by NAC, CAT, and DPI addition. HSP90 inhibitors, GA and RD, significantly attenuated the telomerase activity in NIH3T3 cells with an enhancement of As(+3)- and MMA(+3)-induced cytotoxicity. Suppression of JNKs significantly inhibited As(+3)- and MMA(+3)-induced apoptosis by blocking HSP90 protein cleavage and telomerase reduction in NIH3T3 cells. Furthermore, Hb, SnPP, and dexferosamine showed no effect against As(+3)- and MMA(+3)-induced apoptosis, and overexpression of HO-1 protein or inhibition of HO-1 protein expression did not affect the apoptosis induced by As(+3) or MMA(+3). These data provide the first evidence to indicate that apoptosis induced by As(+3) and MMA(+3) is mediated by an ROS-dependent degradation of HSP90 protein and reduction of telomerase via JNK activation, and HO-1 induction might not be involved.