Involvement of reactive oxygen species and caspase 3 activation in arsenite-induced apoptosis.

陳彥州

Chen YC;Lin-Shiau SY and Lin JK

Abstract

Recent studies indicate that arsenic may generate reactive oxygen species to exert its toxicity. However, the mechanism is still unclear. In this study, we demonstrate that arsenite is able to induce apoptosis in a concentration- and time-dependent manner; however, arsenate is unable to do so. An increase of intracellular peroxide levels was accompanied with arsenite-induced apoptosis, as demonstrated by flow cytometry using DCFH-DA. N-Acetyl-L-cysteine (a thiol-containing antioxidant), diphenylene iodonium (an inhibitor of NADPH oxidase), 4,5-dihydro-1,3-benzene disulfonic acid (a selective scavenger of O2-), and catalase significantly inhibit arsenite-induced apoptosis and intracellular fluorescence intensity. In contrast, allopurinol (an inhibitor of xanthine oxidase), indomethacin (an inhibitor of cyclooxygenase), superoxide dismutase, or PDTC had no effect on arsenite-induced cell death. Activation of CPP32 activity, PARP (a DNA repair enzyme) degradation, and release of cytochrome c from mitochondria to the cytosol are involved in arsenite-induced apoptosis, and Bcl-2 antagonize arsenite-induced apoptosis by a mechanism that interferes in the activity of CPP32. These results lead to a working hypothesis that arsenite-induced apoptosis is triggered by the generation of hydrogen peroxide through activation of flavoprotein-dependent superoxide-producing enzymes (such as NADPH oxidase), and hydrogen peroxide might play a role as a mediator to induce apoptosis through release of cytochrome c to cytosol, activation of CPP32 protease, and PARP degradation.