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Meeting abstract

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Arsenite induces oxidative stress and caspase 3-mediated apoptosis in human neuroblastoma cells involving p53

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Arsenic trioxide (As2O3) induces cell death in human neuroblastoma cells. Clinical trials are currently performed to elucidate the use of arsenic trioxide in cancer therapy. Here, we show that arsenic trioxide treatment activates caspase 3 and triggers an upregulation of p53, c-Jun and ATF3 expression in human neuroblastoma cells. Cell death, caspase 3 activity and enhanced expression of p53, c-Jun, and ATF3 was attenuated in neuroblastoma cells that had been treated with the antioxidant N-acetyl cysteine, indicating that arsenic trioxide cytotoxicity is based on the generation of oxidative stress. Experiments involving lentiviral-mediated expression of either a dominant-negative mutant of p53 or a p53-specific short hairpin RNA showed that p53 is essential for arsenite-induced cell death of neuroblastoma cells. In contrast, down-regulation of c-Jun and ATF3 expression by short hairpin RNA interference or inhibition of the transcriptional activity of c-Jun did not rescue neuroblastoma cells from arsenite-induced cell death. Cells were protected from arsenite-toxicity following expression of Bcl-2 or Bcl-xL or mutants of Bcl-2 and Bcl-xL that had been targeted to the endoplasmic reticulum (ER), suggesting that mitochondria and the ER are involved in the apoptotic signaling cascade initiated by arsenite.