SOURCE

University Children's Hospital, Ulm, Germany.

ABSTRACT

Malignant brain tumors are the most common solid tumors in children. The overall prognosis for this group of patients is still poor, emphasizing the importance of more effective therapies. Betulinic acid (Bet A) has been described as a novel cytotoxic compound active against melanoma and neuroblastoma cells. Here we report that Bet A was active against medulloblastoma and glioblastoma cell lines. In addition, Bet A exerted cytotoxic activity against primary tumor cells cultured from patients in 4 of 4 medulloblastoma-tumor samples tested and in 20 of 24 glioblastoma-tumor samples. Since a small percentage of primary-glioblastoma-tumor cells (4/24) did not respond to Bet-A treatment, resistance to Bet A might occur. Induction of apoptosis by Bet A involved mitochondrial perturbations, since inhibition of the mitochondrial permeability transition by the mitochondrion-specific inhibitor bongkrekic acid (BA) reduced Bet-A-induced apoptosis. In addition, mitochondria undergoing Bet-A-induced permeability transition triggered DNA fragmentation in isolated nuclei. Cytochrome c was released from mitochondria of Bet-A-treated cells, and might be involved in activation of caspases. Following treatment with Bet A, caspase-8, caspase-3 and PARP were proteolytically processed. Inhibition of caspase cleavage by the broad-range caspase inhibitor zVAD.fmk strongly reduced Bet-A-induced apoptosis, indicating that apoptosis was mediated by activation of caspases. Since Bet A did not exhibit cytotoxicity against murine neuronal cells in vitro, these findings suggest that Bet A may be a promising new agent for the treatment of medulloblastoma and glioblastoma cells that clearly warrants further pre-clinical and clinical evaluation.

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