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ARSENITE INDUCES APOPTOSIS IN HUMAN MELANOMAS VIA TNF α OR TRAIL-MEDIATED PATHWAYS

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Arsenic is a well established human carcinogen and is associated with a variety of cancers including those of skin. Paradoxically, arsenic has also been used, amid at low doses, in the treatment of leukemia for over a century. Here we demonstrate that low concentrations of arsenite (2-10 μ M) that has little or no effects on either normal melanocytes or fibroblasts may induce apoptosis of human melanomas, including highly metastatic ones, in spite of low surface Fas levels. A decrease in surface expression of Fas receptor, which is required to initiate apoptotic signaling following its interaction with Fas ligand (FasL), is common in metastatic melanomas. The two pre-requisites that dictate apoptotic response of melanomas upon arsenite treatment are low nuclear NF- κ B activity and an endogenous expression of TNF α . Under these conditions, melanoma cells acquired sensitivity to TNF α -mediated killing. On the other hand, signaling pathways including those of ERK, JNK and c-Jun play protective role against arsenite-induced oxidative stress and apoptosis via positive control of heme oxygenase-1 (HO-1) expression, which possess strong anti-apoptotic activities. Simultaneous inhibition of PI3K-AKT and MEK-ERK pathways induces TRAIL-mediated apoptosis of LU1205 human melanoma cells. The presence of low-dose of arsenite substantially accelerates TRAIL-mediated cell death of melanoma. Taken together, these data suggest that arsenite may be a powerful therapeutic agent in the treatment of melanoma.