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Elevated gadd153/chop expression during resveratrol-induced apoptosis in human colon cancer cells.

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Resveratrol (3,4′,5 tri-hydroxystilbene), a natural phytoalexin found at high levels in grapes and red wine, has been shown to induce anti-proliferation and apoptosis of human cancer cell lines. Resveratrol induced dose-dependent apoptotic cell death in colon carcinoma cells, as measured by FACS analysis and internucleosomal DNA fragmentation assays. We demonstrate for the first time that resveratrol induce CCAAT/enhancer-binding protein-homologous protein (CHOP). Resveratrol-induced CHOP mRNA (and also protein) expression was inhibited by JNK specific inhibitor, but not ERK, p38 MAPK, PI3K and NF- B inhibitors. Resveratrol-induced expression of CHOP involves the putative Sp1 site within the CHOP promoter region. Using a combination of the Sp1 cDNA transfection, the luciferase reporter assay and Sp1 inhibitor assay, we found that Sp1 site is required for resveratrol-mediated activation of the CHOP promoter. Suppression of CHOP expression by CHOP si RNA and treatment with mithramycin A attenuated resveratrol-induced apoptosis. Taken together, the present studies suggest that induction of CHOP protein may be involved, at least in part, in resveratrol-induced apoptosis.

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Caspase-dependent and caspase-independent apoptosis induced by evodiamine in human leukemic U937 cells

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Evodiamine is one of the major bioactive compounds that have been isolated and purified from the fruit of Evodiae fructus. Evodiamine exhibits antitumor activities against the human tumor cells, including multidrug-resistant tumor cells. However, the molecular mechanism involved in cell death induced by evodiamine treatment remains poorly understood. In the present study, we showed that evodiamine activated the caspase-dependent apoptotic pathway. This apoptosis was only partially inhibited by a pancaspase inhibitor benzyloxycarbonyl-Val-Ala-Aspfluoromethyl ketone, which suggested that evodiamine-induced apoptosis in leukemic U937 cells is partially caspase independent. We observed the nuclear translocation of apoptosis-inducing factor in evodiamine-induced apoptosis of U937 cells, which may be responsible for the caspase-independent apoptotic execution. We next showed that evodiamine induced the substantial amount of apoptosis both in Bcl-2- and Akt-overexpressing U937 cells but not in human peripheral blood mononuclear cells. Although benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone inhibited caspase activity in Bcl-2-overexpressing U937 cells, it completely prevented neither the induction of apoptosis or the nuclear translocation of apoptosis-inducing factor, which suggests that evodiamine is, at least in part, able to bypass the resistance of leukemia cells via caspase-independent apoptotic pathways. Thus, therapeutic strategy using evodiamine may warrant further evaluation.