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Key regulators in bee venom-induced apoptosis are Bcl-2 and caspase-3 in human leukemic U937 cells through downregulation of ERK and Akt

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Bee venom (BV) has been known to inhibit proliferation and induce apoptosis in cancer cells. However, the molecular mechanisms involved in BV-induced apoptosis are still uncharacterized in human leukemic cells. In the present study, we report that BV induces apoptosis in leukemic U937 cells through downregulation of ERK and AKT signal pathway. Furthermore, BV-induced apoptosis was accompanied by downregulation of Bcl-2, activation of caspase-3 and a subsequent poly(ADP-ribose)polymerase (PARP) cleavages. The induction of apoptosis also was accompanied by the downregulation of the inhibitor of apoptosis protein (IAP) family proteins. Caspase-3 inhibitor, z-DEVD-fmk, was significantly capable of restoring cell viabilityand BV-induced apoptosis through caspase-3 activation was significantly attenuated in Bcl-2-overexpressing cells. These results indicate that downregulation of Bcl-2 plays a major role in the initiation as an activator of a caspase-3 involved with BV-induced apoptosis. BV also triggered the activation of p38 MAPK and JNK, and downregulation of ERK and Akt. PD98059 (an inhibitor of ERK) or LY294002 (an inhibitor of Akt), but not an inhibitor of p38 MAPK and JNK, significantly decreased cell viability and increased lactate dehydrogenase (LDH)release. The results indicated that key regulators in BV-induced apoptosis are Bcl-2 and caspase-3 in human leukemic U937 cells through downregulation of the ERK and Akt signal pathway.

Keywords : Bee venom; MEK/ERK; Akt; Bcl-2; Caspase-3; Apoptosis

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PD98059 triggers G1 arrest and apoptosis in human leukemic U937 cells through downregulation of Akt signal pathway

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MEK/ERK pathways are frequently activated in acute myelogenous leukemia, and this signal pathway's inhibitor has made it an interesting candidate for cancer chemotherapy. Little is known, however, about the effects of cellular and molecular mechanisms on human leukemic U937 cells. In the present study, we found that treatment with PD98059 significantly arrests the G1 phase through up-regulation of cyclin-dependent kinase (Cdk) inhibitor, and produces morphological features of apoptosis in U937 cells, which were associated with poly(ADP-ribose)polymerase (PARP) cleavage and PLC-γ1 degradation. PD98059 also decreased the Cdk-2, Cdk-4, cyclin D1, and cyclin E expression, and increased high levels of the mitotic inhibitors $p16^{INIa}$, $p21^{Waf1/Cip1}$, and $p27^{Kip1}$. Also, Bcl-2's overexpression and a caspase-3 inhibitor z-DEVD-fmk significantly attenuated PD98059-induced apoptosis through the down-regulation of caspase-3 activity, but did not attenuate G1 phase arrest. Moreover, PD98059 down-regulated Akt phosphorylation and produced a synergy effect of apoptosis with LY294002 co-treatment. Thus, our results imply that PD98059-induced apoptosis is significantly involved in down-regulation of Bcl-2, caspase-3 activity, the Akt pathway, and some of the biological functions in U937 cells.

Keywords : PD98059, MEK/ERK, Akt, Bcl-2, Caspase-3, Apoptosis