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Arsenic Trioxide Induces Erythroid Differentiation and Apoptosis of ATRA Resistant K562 Human Leukemia Cells Through Down-Regulation of Bcl-2

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Background: Arsenic trioxide(As2O3), used to treat human diseases for centuries in traditional Chinese medicine, has been identified as an effective drug for the treatment of acute promyelocytic leukemia(APL). Recent studies showed that As2O3 could induce apoptosis and partial differentiation of APL cells. However, the role of the As2O3 during erythroid differentiation of human leukemic cells remains unknown. In this study, we have investigated in vitro effect of As2O3 on the erythroid differentiation of K562 cell line and expression and regulation of the apoptotic modulators in this process. **Methods and Results**: The viability of K562 cells was not decreased after treatment with low dose (0.1 mM and 0.5 mM) of As2O3 but significantly decreased in high dose (1 mM) The viability of K562 cells was not changed with 1 mM and 10 mM of all trans retinoic acid(ATRA). Expression of glycophorin Aincreased in dose dependent manner after treated with As2O3 but was not changed in ATRA treated K562 cells. Caspase 3 activation was not observed in low dose of As2O3 until 12 days after incubation butcaspase 3 was activated in high dose of As2O3 from day 3. To investigate whether abnormal expression of the apoptotic modulators are involved during erythroid differentiation and apoptosis, we also examined expression of Bcl-2, Bcl-XL, and Baxin K562 cells after treated with As2O3 or ATRA. Expression of Bcl-2 and Bcl-XL was increased in low dose of As2O3 but Bcl-2 was abruptly decreased in high dose of As2O3. Bax was decreased in dose dependent manner.
Conclusions: These results suggest that low dose of As2O3 induces erythroid differentiation of K562 human leukemic cells and high dose of As2O3 induce apoptosis through down-regulation of Bcl-2.

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Antileukemic drugs enhance Apo-2L-induced apoptosis in human lymphoid malignancies.

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Tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL, also known as Apo-2 ligand [Apo-2L]) can induce apoptosis in a wide variety of transformed human cells *in vitro*. In this study, the anticancer activities of Apo-2L with or without chemotherapeutic agents were analyzed in human hematologic malignancies. Here we show treatment with Apo-2L induce apoptosis of the human acute leukemia HL-60, U937, and Jurkat cells in a dose-independent manner, but not in K562 and Raji. Susceptibility of these acute leukemia cell types did not appear to correlate with the levels of the apoptosis-signaling death receptors (DRs) of Apo-2L, ie, DR4 and DR5; decoy receptors (DcR1 and 2). Treatment of human leukemic cells with etoposide or Ara-C induce apoptosis in HL-60, U937, and Jurkat cells, but not in K562 and Raji. Sequential treatment of U937 and Jurkat cells with etoposide or Ara-C, followed by Apo-2L induced significantly more apoptosis than treatment with Apo-2L, etoposide, or Ara-C alone, or cotreatment with Apo-2L and the antileukemic drugs. In HL-60, antileukmic drug followed by APO-2L inhibit apoptosis, cotreatment with Ara-C or etoposide and Apo-2L did not enhance or inhibit apoptosis. In K562 and Raji, sequential or cotreatment with APO-2L and antileukemic drugs did not enhance apoptosis. These findings indicate that treatment with etoposide, Ara-C sensitizes human lymphoid leukemic cells (U937 and Jurkat cells) to Apo-2L-induced apoptosis, but not in HL-60, K562 or Raji.