Lee CC, Lin YY, Huang MJ, Lin CP, Liu CR, Chow JM, Liu HE. Increased cellular glutathione and protection by bone marrow stromal cells account for the resistance of non-acute promylocytic leukemia acute myeloid leukemia cells to arsenic trioxide in vivo. L

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摘要

Abstract

Arsenic trioxide (ATO) is a novel agent for acute promylocytic leukemia (APL). Studies performed in vitro have demonstrated that ATO also induces cell-cycle arrest and apoptosis in multiple cancers, including non-APL acute myeloid leukemia (AML). To explore the potential use of ATO on non-APL AML, we treated the leukemic cells in vivo using a NOD/SCID animal model. Mice harboring HL-60 or NB-4 leukemia or primary AML-M2 cells were treated daily with 5 mug/g ATO intraperitoneally for a maximum of 6 weeks. Although ATO initially appeared to be effective on HL-60 cells, it failed to decrease the leukemic cells in bone marrow (BM) after the extended treatment (52.2 +/- 10.7% vs. 62.2 +/- 2.6% in the controls; P = 0.51); whereas the same treatment to NB-4 leukemic mice significantly decreased the percentage of leukemic cells in BM. ATO also failed to eradicate the primary AML cells in vivo. The reason for the treatment failure was that HL-60 cells quickly developed resistance in vivo. The drug resistance could be partly attributable to the increase of cellular glutathione as a result of compensatory response to ATO treatment because depletion of glutathione with buthionine sulfoximine reversed the drug resistance in vitro. Meanwhile, BM stromal cells also contributed to the drug resistance. Leukemic cells grown on an adherent layer of MS-5 stromal cells in the presence of ATO were more proliferative and less apoptotic and had increased expression cyclin D1, Bcl-xL and Bcl-2 and decreased expression of p21, likely protecting the leukemic cells from ATO cytotoxicity. Therefore, our study suggests that strategies to

inhibit the compensatory increase of glutathione and block the interaction between leukemic cells and BM stromal cells should be employed before applying ATO to non-APL hematologic malignancies.