

The cytotoxicity of arsenic trioxide to normal hematopoietic progenitors and leukemic cells is dependent on their cell-cycle status

劉興璟

Liu HJ

摘要

Abstract

Arsenic trioxide (ATO) is a novel agent to treat acute promyelocytic leukemia (APL). ATO can degrade chimeric PML-RAR proteins and induce apoptosis in various cancer cells. However, its effects on primary hematopoietic CD34+ have not been examined. In this study, we compared the effects of ATO on HL60 leukemic cells and primary umbilical cord blood (UCB) CD34+ cells. HL60 cells and UCB CD34+ cells were cultured with different concentrations of ATO for up to three weeks and examined for changes of cell cycle. We found that ATO (< or = 5 microM) caused prolongation of G1/S and G2/M phase in a dose-dependent manner. The percentage of cells in G2/M increased significantly (from 8.6 to 53.8%). High-dose ATO (> or = 25 microM) caused non-specific cell death in HL60 cells without any changes in cell cycle. In contrast to HL60 cells, UCB CD34+ cells were more resistant to high-dose ATO and most ATO-resistant CD34+ cells remained in G0/G1 phase. Primary cells that were resistant to ATO were rich in CD34+ cells. We further show that the ATO resistance was not related to the expression of P-glycoprotein (MDR-1). Our results suggest that the resistance to ATO in primitive UCB CD34+ cells is most likely related to its cell-cycle status. These results could be useful to design treatments for non-APL malignancies and to enrich hematopoietic stem cells in clinically applicable settings.