

Multidrug resistance proteins 1/4 (ABCC1 /4) confer resistance to arsenic compounds in human myeloid leukemic HL-60 cells

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Arsenic trioxide (As_2O_3) is established as one of most effective drugs for treatment of patients with acute promyelocytic leukemia (APL), as well as other types of malignant tumors. However, the non-APL HL-60 cells is resistant to As_2O_3 , and little is known about the underlying resistance mechanism for As_2O_3 and its biomethylation products, namely, monomethylarsonous acid (MMA^{III}) on the treatment of tumors. In the present study, we investigated the molecular mechanisms underlying iAs^{III} and its intermediate metabolite MMA^{III} -induced anticancer effects in the non-APL HL-60 cells. Here, we show that the HL-60 cells exhibit resistance to inorganic iAs^{III} ($\text{IC}_{50}=10 \mu\text{M}$), but are relatively sensitive to its intermediate MMA^{III} ($\text{IC}_{50}=3.5 \mu\text{M}$). Moreover, we found that the multidrug resistance protein 1/4 (MRP1/4), but not MRP2, are expressed in HL-60 cells, which reduced the intracellular arsenic accumulation, and conferred resistance to inorganic iAs^{III} and MMA^{III} . Pretreatment of HL-60 with MK571, an inhibitor of MRP1 and 4, significantly increased iAs^{III} and MMA^{III} -induced cytotoxicity and arsenic accumulations, suggesting that the expression of MRP1/4 may lead to HL-60 cells resistance to trivalent arsenic compounds.

Biography

Narenmandula Hua is associate professor in the Department of Pharmacology, Toxicology, and Biochemical Pharmaceutics, College of Pharmaceutical Sciences at Zhejiang University, China. He received a PhD degree in pharmacology and toxicology in 2008 from Chiba University (Japan). Then he completed postdoctoral work at the University of Alberta (Canada) He is currently focused on several topics including arsenic speciation, exposure, metabolism, and health effects; the molecular mechanisms of the carcinogenic effects of thioarsenicals and its metabolism pathway; the role of AS3MT expression in arsenic treatment of patients with acute promyelocytic leukemia (APL), etc.

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