SIMULTANEOS INHIBITION OF GSH AND SURVIVIN OVERCOME RESISTANCE TO ARSENIC IN CANCER CELLS

Ferreira, A.C.S., Vasconcelos F.C., Silva, K.L., Maia, R.C., Kwee, J.K.

Laboratório de Hematologia Celular e Molecular, Serviço de Hematologia, Hospital do Câncer, HC1, Instituto Nacional de Câncer, Rio de Janeiro, Brazil.

Arsenic trioxide (ATO) has recently been shown to be clinically active in cancer. Reactive oxygen species (ROS) production is one of the main mechanisms of ATO apoptosis induction. ATO-resistance involves overproduction of intracellular antioxidant Glutathione (GSH), extrusion from the cell mediated by drug pumps such as multidrug resistance protein (MRP1) which is frequently amplified in cancer cells. Since is known that ROS inhibit survivin, a member of the inhibitor of apoptosis (IAP) protein family, we evaluated and compared the role of GSH in ATO-resistance mechanism using two cell lines of human small cell lung cancer: GLC4 and GLC4/ADR (overexpressing MRP1). GLC4/ADR exibited 2,4 times more intracellular GSH and was 14-fold more resistant to ATO than GLC4. ROS production by ATO was observed using flow cytometry. We compared the apoptosis index ATO induction and survivin expression in both cell lines, with and without buthionine sulfoximine (BSO), an inhibitor of GSH synthesis. Western blotting and Annexin V assays showed reduced expression of survivin and increased sensitivity to ATO in both cell lines when previously treated with BSO. These results suggest that enhancement of ATO-ROS apoptosis induction in ATO-resistant cells, is modulated by GSH.

Key words: Arsenic Trioxide, Glutathione, Survivin and Reactive Oxygen Species
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