Exploiting the Resistance to Oxidative Stress in Chronic Myeloid Leukemia Cells Overexpressing P-glycoprotein

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Introduction and objectives. Chronic myeloid leukemia (CML) is characterized by the presence of Philadelphia chromosome. BCR-ABL gene codifies a protein with tyrosine kinase activity that has been the main target to chemotherapy. However, chemoresistance to these inhibitors has already described. Other mechanisms contribute for tumor resistance, including the overexpression of P-gp. Considering that some drugs kill tumor cells by inducing intracellular oxidative stress, we studied the susceptibility of a MDR positive CML cells (Lucena 1) to oxidative stress compared to its generating cell line (K562). Materials and methods. K562 and Lucena 1 cells (1x10⁵/mL) were cultivated in RPMI 1640 containing 10% BFS and penicillin/streptomycin. Cell viability was evaluated by the MTT reduction, trypan blue exclusion, and annexin V-FITC/PI double-staining. Mitochondrial superoxide and cellular ROS generation were evaluated fluorometrically using MitoSOX-Red and CM-H₂DCFDA. GSH levels were estimated using o-phtalaldehyde. Results. The exposure of both cell lines to increasing concentrations of H₂O₂ revealed that Lucena 1 was more resistant than K562 to death. H₂O₂-induced cell death exhibited PI or annexin V/PI positive cells in both cell lines, which was higher in K562 cells. Studies are underway to determine the cell death pathways in this condition. Besides to produce fewer amounts of mitochondrial superoxide than K562, such production was not increased by antimycin A in Lucena 1. Furthermore, when challenged by H₂O₂, general ROS production in K562 was at least twice higher than Lucena 1 cells and it was accompanied by GSH oxidation, what was not observed in Lucena 1. Conclusions. The MDR positive CML Lucena 1 cells exhibited resistance to H₂O₂ when compared to K562. This was already reported for these cells and attributed to catalase overexpression. However, the lack of response to the mitochondrial respiratory chain inhibition suggests that additional mechanisms contribute to such resistance, which are under investigation.

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