Thioridazine induced-cell death is accompanied by Akt and p38 activation without the involvement of STAT-1

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INTRODUCTION. Thioridazine (TR) is a well known anti-psychotic drug derived from phenotiazines. Recently it was demonstrated that this drug was able to induce the mitochondrial permeability transition in isolated rat liver mitochondria associated to cytochrome c release. Also, unpublished data from our lab showed the induction of cell death in tumor cells associated to disruption of calcium homeostasis. In this work it was investigated the modulation of three proteins involved with cell death/survival signaling (Akt, p38, and STAT-1) induced by TR in K562 chronic myeloid leukemia cells.

MATERIAL AND METHODS. Cells were cultivated in RPMI 1640 (Sigma) supplemented with 10% BFS (Gibco) and penicillin/streptomycin. Cell viability was evaluated by the MTT reduction assay and Trypan blue exclusion test with TR concentrations ranging from 2.5 to 30 µM incubated for 24 h with 2x10^4 cells. The expression of the three proteins was evaluated after 30 min incubation of 1x10^6 cells with 25 µM TR by flow cytometry analysis using monoclonal antibodies.

RESULTS AND DISCUSSION. TR was able to promote cell death in K562 cells in a concentration dependent manner and the EC50 obtained was approximately 9 µM. In relation to signaling pathways, the pre-incubation of K562 cells with TR resulted in an increased Akt phosphorylation, which in turn may result in the activation of the mTOR pathway. Furthermore, it was also observed the activation of p38 without any changes in the STAT-1. The cross-talk between the Akt and p38 MAPK pathways may regulate the cell death/survival fate. CONCLUSIONS. These preliminar results point to the involvement of Akt and p38 signaling in the TR-induced K562 cell death.

Keywords: cell death signaling, K562 cells, thioridazine.
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