

The role of metabolism on the chemoresistance of leukemia cells

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Chronic myeloid leukemia (CML) affects millions of people in the whole world. CML treatment depends on drugs that may have durable responses. However, some patients develop resistance to certain drugs frequently used in treatment. The exposure of these cells to different drugs for a certain time, select cells more or less resistant to the drugs. The biochemical study of chemoresistance is important to understand this big complex that selects these resistant cells, which further exacerbates the disease. In this work we propose to investigate the metabolism of CML cell lines, sensitive and resistant to certain drugs, in order to characterize the biochemical profile of resistant cells. We used three different cell lines: the first is a cell line derived from patients with CML in blast crisis, called K562. The other are sublineages derived from the first, and were generated by selecting resistant cells after treatment with vincristine and daunorubicin, these being Lucena-1 and FEPS, respectively. The metabolic profile of these cells was carried out by respirometric assays, mtDNA quantification, real-time PCR, and the activity of two key enzymes in cellular metabolism: Hexokinase-2 (HK2) and G6PDH (glucose 6-phosphate dehydrogenase). The resistant cells displayed a flow of oxygen and a relative amount of mtDNA lower than K562. Furthermore, the activity of hexokinase-2 didn't have significant differences in FEPS. The activity of G6PDH was significantly increased in FEPS compared to other two cell lines. Finally, there was a significant increase in the relative expression of hexokinase-2, Mitofusin-1 and UCP2 in the resistant cell lines. The UCP2 protein was shown to be an important target related to cell chemoresistance, in addition to its possible role in the Warburg Effect. New experiments are currently under way aiming at expanding the list of enzymes involved in metabolism of the three cell lines as well as elucidating the mechanism of chemoresistance.

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