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Hypoxia promotes chemoresistance in acute lymphoblastic leukemia cell lines by modulating death signalling pathways

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Abstract

Background:
Several studies show that bone marrow (BM) microenvironment and hypoxia condition can promote the survival of leukemic cells and induce resistance to anti-leukemic drugs. However, the molecular mechanism for chemoresistance by hypoxia is not fully understood.
Methods:
In the present study, we investigated the effect of hypoxia on resistance to two therapies, methotrexate (MTX) and prednisolone (PRD), in two cell models for acute lymphoblastic leukemia (ALL). To look for an implication of hypoxia in chemoresistance, cell viability, total cell density and cell proliferation were analyzed. Survival and death signaling pathways were also screened by “reverse phase protein array” (RPPA) and western blotting experiments conducted on selected proteins to confirm the results.
Results:
We found that hypoxia promotes chemoresistance in both ALL cell lines. The induction of drug-resistance by hypoxia was not associated with an increase in total cell density nor an increase in cell proliferation. Using RPPA, we show that chemoresistance induced by hypoxia was mediated through an alteration of cell death signaling pathways. This protective effect of hypoxia seems to occur via a decrease in pro-apoptotic proteins and an increase in anti-apoptotic proteins. The results were confirmed by immunoblotting. Indeed, hypoxia is able to modulate the expression of anti-apoptotic proteins independently of chemotherapy while a pro-apoptotic signal induced by a chemotherapy is not modulated by hypoxia.
Conclusions:
Hypoxia is a factor in leukemia cell resistance and for two conventional chemotherapies modulates cell death signaling pathways without affecting total cell density or cell proliferation.
Keywords:
ALL, Chemoresistance, Hypoxia, Methotrexate, Prednisolone, RPPA

Full text:

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