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ACUTE LYMPHOBLASTIC LEUKEMIA - THERAPY, EXCLUDING TRANSPLANTATION POSTER II | NOVEMBER 20, 2009

Overcoming Chemotherapy Resistance in Childhood Acute Lymphoblastic Leukemia by Targeting Ion Channels.

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Abstract

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Despite improvements in cure rates, chemotherapy resistance remains a major obstacle to successful treatment in a significant proportion of children with acute lymphoblastic leukemia (ALL), particularly in those with relapsed ALL. Bone marrow mesenchymal cells (MSC) can contribute to generate drug resistance in leukemic cells and several mechanisms have been proposed to explain this effect such as molecular interactions between stroma-derived factor 1a (SDF-1a) and its receptor CXCR4 that could trigger integrin engagement and activation of the downstream signaling cascades which would promote survival of leukemia cells. Recent evidence indicates that integrins can form macromolecular complexes with ion channels, and that the resulting integrin/channel complex can regulate cell survival. Among ion channels, those encoded by the *ether-a-gò-gò-related gene 1*, hERG1 channels, have been shown to form protein complexes with integrins in several tumor cell types. In experiments with the ALL

cell lines REH, RS4;11 and 697 we found that ALL cell contact with MSC induced the expression of a plasma membrane signaling complex constituted by hERG1 channels, the b_1 integrin subunit and the chemokine receptor CXCR4 on the surface of ALL cells. This protein complex triggered the activation of pro-survival intracellular signaling pathways. We found that hERG1 channels are central to this protective mechanism. The three cell lines and all cases (n = 63) of primary ALL expressed hERG1; exposure to hERG1 blockers could abrogate the protective effect of MSC and considerably enhanced the cytotoxicity of chemotherapeutic drugs commonly used to treat ALL, such as doxorubicin, prednisone and methothrexate. Indeed, MSC-mediated chemoresistance could be overcome by several hERG1 blockers, including classical class III antiarrhythmics, such as E4031 and Way 123,398, as well as other agents classified as hERG1-blocking drugs, such as sertindole and erythromycin. These results were observed in both ALL cell lines and primary ALL cells and were corroborated by studies in murine models of ALL. In particular, hERG1 blockers could overcome MSC-mediated drug resistance of ALL cells engrafted in immunodeficient mice: mice treated with hERG1 blockers had a marked increase in the rate of apoptosis of ALL cells in the bone marrow, a reduced leukemia burden and ALL infiltration of the liver and spleen. Notably, hERG1 blockers also improved the anti-leukemic effect of corticosteroids in mice injected with corticosteroid-resistant cells (the cell line REH). In fact E4031 reduced bone marrow engraftment, and this effect was related to an increased apoptosis of ALL cells, and was higher than that produced by dexamethasone. Treatment with dexamethasone and E4031 nearly abolished leukaemia development in mice. In sum, hERG1 blockade results impedes ALL cell growth and enhances the effect of anti-ALL chemotherapy. Because some of the hERG1 inhibitors that proved effective in this study are available for clinical use and should not carry the risk of serious cardiac arrhythmia, they should be consider for inclusion in clinical trials for drug-resistance ALL.

Disclosures

No relevant conflicts of interest to declare.

Author notes

* Asterisk with author names denotes non-ASH members.