Spring 2017

Targeting Survival Signaling in T-ALL

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T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive cancer of the blood and bone marrow in which T-cell progenitors undergo developmental arrest and acquire neoplastic capabilities. Approximately 1,500 adult cases of T-ALL are diagnosed each year in the United States. While initial remission rate approaches 80%, relapse is common and the five-year survival rate for relapsed patients is only 7%, highlighting the need for new therapies. CXCR4, a surface receptor for the chemokine CXCL12, is significantly upregulated in many T-ALLs and is essential for T-ALL growth and proliferation. Activation of c-MYC is common in T-ALL and is thought to play a central role in disease pathogenesis. c-MYC induces proliferative stress in cells resulting in cell death in the absence of pro-survival signaling. We hypothesize that CXCR4 signaling promotes T-ALL growth through upregulation of the anti-apoptotic protein MCL-1. It follows that inhibition of CXCR4 signaling, by decreasing MCL-1 expression, may selectively induce apoptosis in T-ALL cells. We further hypothesize that CXCR4 inhibition would synergize with chemical agents disrupting other survival signaling, such as PI3K- and BCL2-mediated pathways. Here we show that the novel CXCR4 inhibitor BL8040, developed for the treatment of hematological malignancies and currently undergoing Phase II clinical trials for mobilization of hematopoietic stem cells, has anti-tumor activity in T-ALL both *in vitro* and *in vivo*. We also show that inhibition of PI3K and BCL2 proteins with BKM-120 and ABT-263, respectively, is toxic to T-ALL cells. Our data add to a growing body of evidence supporting the targeting of CXCR4, as well as the development of rational combination therapies, in patients with relapsed or refractory T-ALL.