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Upregulation of HLA-E Drives Defective Natural Killer Cell Targeting in Venetoclax-resistant Acute Myeloid Leukemia

Daniel J. Chandra[1,2], Faith Burns[2], Yoko Kosaka[2], Stephen E. Kurtz[2], Jeffrey W. Tyner[2], Evan F. Lind[2], and Jennifer N. Saultz[1,2]

1Division of Hematology/Medical Oncology, Oregon Health & Science University, Portland, OR 97239
2Knight Cancer Institute, Oregon Health & Science University, Portland OR, 97239

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Abstract

Acute myeloid leukemia (AML) is the most common leukemia in adults and is primarily diagnosed in older patients. The combination of the BCL2 inhibitor, venetoclax, with a hypomethylating agent has recently become standard of care front-line therapy for patients who are unfit for high intensity induction chemotherapy and allogeneic stem cell transplantation. However, for patients who experience disease refractoriness/relapse, second line treatment options are limited. Natural killer (NK) cells have been shown to have potent anti-tumor effects in AML may represent a potential therapeutic option for patients with progression after venetoclax-based therapy. Our group recently showed, however, that venetoclax-resistant (VR) AML blasts are less susceptible to NK cell-mediated killing, and the mechanisms underlying this phenomenon are not yet defined.

We investigated the sensitivity of AML blasts to NK cell cytotoxicity through in vitro co-culture assays with human AML cell lines and NK cells derived from a healthy donor. We found that the venetoclax-resistant AML blasts were less susceptible to NK cell killing compared to the wild-type (WT) counterpart. In order to understand why VR AML blasts are resistant to NK cell-mediated killing, we investigated differences in NK cell ligands between WT and VR OCI-AML-2 cells and found that VR cells upregulated HLA-E. Given prior evidence showing that HLA-E upregulation in relapsed AML is mediated by interferon-γ, we stimulated WT AML blasts with interferon-γ and found that not only did this lead to upregulation of HLA-E, but it also led to decreased NK cell mediated lysis. This dysfunctional phenotype was abrogated by treatment with the JAK1/2 inhibitor, ruxolitinib. Overall, our findings suggest that the HLA-E and interferon-γ axis is a potential therapeutic target for enhancing NK cell responses in venetoclax-resistant AML.