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POSTER ABSTRACTS

703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Epigenetic Scarring Leads to Irreversible NK Cell Dysfunction in Myeloid Malignancies

Bijender Kumar[1], Anand Singh, PhD[1], Rafet Basar, MD[2], Nadima Uprety[2], Ye Li, MDPhD[2], Huihui Fan, PhD[3], Mayra Shanley, PhD[2], Sunil Acharya, PhD[4], Mayela Carolina Mendt, PhD[2], Paul Lin, MD PhD[2], Alexander Biederstädt, MD[2], Hind Rafei, MD[5], Pinaki Banerjee, PhD[2], Vakul Mohanty, PhD[6], Hila Shaim, MD[2], Merve Dede[7], Luciana Melo Garcia, MDMSc[8], Lucila Nassif Kerbauy, MD PhD[2], Ana K. Nunez Cortes, MD[2], Qi Miao[7], Jinzhuang Dou[7], Francia Silva Reyes[1], Xingliang Guo[7], Mecit Kaplan[2], Sonny Ang[2], Xin Ru Jiang[2], Enli Liu, MD[2], Bin Liu, PhD[2], Richard E. Champlin, MD[2], Hagop Kantarjian, MD[9], David Marin, MD[2], Ken Chen, PhD[6], Hussein A Abbas, MDPhD[9], Elizabeth J. Shpall, MD[2], Kunal Rai, PhD[1], Katayoun Rezvani, MD PhD[2], May Daher, MD[2]

[1]The University of Texas MD Anderson Cancer Center, Houston
[2]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX
[3]The University of Texas Health Science Center at Houston, Houston
[4]D, The University of Texas MD Anderson Cancer Center, Houston, TX
[5]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Missouri City, TX
[6]Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX
[7]The University of Texas MD Anderson Cancer Center, Houston, TX
[8]CHU de Québec - Université Laval, Quebec, Canada
[9]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) belong to the same spectrum of myeloid malignancies and have extremely poor outcomes in the relapsed/refractory setting. Despite advances in the understanding of the pathogenesis and molecular mechanisms of these disorders, and incremental improvements in treatment regimens, patients with MDS and AML often relapse and fail to achieve cure. These and other factors underscore the urgent need for new therapeutic alternatives that will improve the clinical outcomes of these patients. Immunotherapy using checkpoint molecule inhibitors and adoptive cell therapy using autologous immune effector cells have been mostly unsuccessful in patients with MDS and AML. This could be due to the immunosuppressive tumor microenvironment in the bone marrow niche or to intrinsic dysfunction in the immune effector cells of these patients.

Natural killer (NK) cells are innate lymphocytes that play an important role in cancer immune surveillance and have distinct advantages over T cells as candidates for immunotherapy. Myeloid blasts are inherently susceptible to NK cell-mediated killing as they express many of the ligands recognized by NK cell activating receptors. However, malignant myeloid blasts are capable of adapting and developing defense mechanisms that allow them to evade NK cell-mediated cytotoxicity. Little is known about the mechanisms of NK cell immune evasion developed by myeloid blasts. Here, we show that NK cells from patients with myeloid malignancies display a global dysfunction with severely impaired secretory function and killing capacity. Single cell RNAseq and mass cytometry experiments revealed that these NK cells from MDS and AML patients display an exhausted phenotype at the transcriptomic and proteomic levels. We also show that these NK cells have an altered metabolism compared with age matched healthy control NK cells. We show that this dysfunction is mediated by a crosstalk between myeloid blasts and NK cells and cell-cell contact dependent release of transforming growth factor beta (TGF-β). This crosstalk leads to a profound epigenetic reprogramming of NK cells driven by transcription factors known to mediate exhaustion and immune suppression. Myeloid blast-induced NK dysfunction and epigenetic state of exhaustion can be prevented by pharmacologically inhibiting the TGF-β pathway or knockout of *TGFBR2* in NK cells. However, our data reveal that once this dysfunction occurs it is irreversible owing to epigenetic scarring driven by the transcription factor BATF. In fact, we show that TGF-β induces the expression of BATF in NK cells, which in turn mediates a gene regulatory program leading to NK cell dysfunction by driving the expression of exhaustion and inhibitory genes (e.g. *HAVCR2, ENTPD1, CTLA4, TGFBR2*).

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Collectively, our findings reveal a novel mechanism of NK cell immune evasion manifested by stable epigenetic rewiring and inactivation of NK cells by myeloid blasts. Our data support the use of allogeneic sources for adoptive NK cell therapy in combination with strategies aiming at preventing immune suppression to treat myeloid malignancies rather than therapies aiming at reversing or rescuing the function of autologous NK cells.

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