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Blood 142 (2023) 1584–1585

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Single-Cell Polyfunctional Proteomic Profiling Reveals Temporal and Niche Differences in CD4 and CD8 T Cells in Acute Myeloid Leukemia Following PD-1 Blockade Therapy

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Immune checkpoint blockade (ICB) has revolutionized solid tumor treatment by unleashing T cell cytotoxic potential, however, its effectiveness in leukemias such acute myeloid leukemia (AML) has been limited. Understanding the functional states of T cells in AML within the context of ICB is crucial to understanding its limited therapeutic potential. Here, we leveraged the IsoPlexis single cell secretome platform to assess T cell polyfunctional activity in relapsed/refractory (RelRef) AML patients treated on the phase 2 clinical trial with combination azacitidine and nivolumab (Aza/Nivo) (NCT02397720). We isolated CD4 and CD8 T cells by magnetic bead sorting from the peripheral blood (PB) and bone marrows (BMs) of 21 AML patients before (pretreatment) and after ICB (post-ICB). Isolated CD4 and CD8 cells were stimulated with CD3/CD28 agonism and functionally characterized by IsoPlexis, which measures T cell secreted cytokines, chemokines, and effector molecules at the single-cell level. In total, we characterized 52 patient samples (30 from PB and 22 from BMs). Functional CD4 and CD8 profiles were correlated with clinical and demographic characteristics of the patients. This enabled us to explore the temporal and niche differences in T cell functional states, specifically in the context of PD-1 blockade therapy, in a unique cohort of AML patients at both a pseudobulk and single-cell level.

At the pseudobulk level, we observed baseline activity in the chemoattractive, effector, and regulatory functional groups was higher in both PB and BM CD8 cells compared to CD4 cells (Fig 1A), suggesting increased polyfunctionality in CD8 T cells prior to treatment. Analysis comparing pretreatment and post-ICB polyfunctionality revealed similar response patterns in CD4 and CD8 T cells in both the PB and BM spaces. Interestingly, CD4 T cells exhibited increased polyfunctional activity post-ICB in both PB and BM as compared to CD8 T cells. These findings point to an unexpected contribution of CD4 T cells with ICB therapy in AML.

We employed an unbiased, unsupervised neighborhood analysis which leveraged the nearest cellular neighbor based on the log fold-change in secreted proteins between samples from distinct timepoints to reveal post-ICB CD4 and CD8 T cells aggregated into distinct cellular neighborhoods (Fig 1B). Both CD4 and CD8 analysis revealed distinct groups highlighting one group containing pre-ICB cells, and another group containing pre- and post-ICB cells. This suggests that T cell functionality is predetermined prior to ICB therapy. Comparative analysis at the single-cell level further identified higher expression of chemoattractive, inflammatory, regulatory, and stimulatory polyfunctional groups in non-responders (NR) in the BM for both CD4 and CD8 T cells, and higher expression of the chemoattractive group in NRs in the PB for CD4 cells. This suggests that BM polyfunctionality may be more critical in terms of ICB response.

This study provides a novel single-cell functional analysis of T cells from both PB and BM compartments in RelRef AML patients treated with ICB. Our findings suggest the functional state of T cells in the circulating state and residence within the leukemia microenvironment are not equivalent and that there are dynamic changes of T cell functionality with ICB which has broad implications for correlative sample analysis in the ICB setting.

Disclosures Alfayez: *Amgen:* Honoraria; *Johnson & Johnson:* Consultancy, Honoraria, Research Funding; *Pfizer:* Honoraria; *Novartis:* Honoraria; *Biologics:* Consultancy, Honoraria; *Abbvie:* Research Funding; *Astellas:* Honoraria; *AstraZeneca:* Honoraria. **Daver:** *AROG:* Consultancy; *Daiichi Sankyo:* Consultancy, Research Funding; *FATE:* Research Funding; *Trovagene:* Research Funding; *Hanmi:* Research Funding; *Novimmune:* Research Funding; *Glycomimetics:* Research Funding; *Genentech:* Consultancy, Research Funding; *Jazz:* Consultancy; *Pfizer:* Consultancy, Research Funding; *Syndax:* Consultancy; *Novartis:* Consultancy; *Shattuck Labs:* Consultancy; *Celgene:* Consultancy; *ImmunoGen:* Consultancy, Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Gilead:* Consultancy, Research Funding; *Astellas:* Consultancy, Research Funding; *AbbVie:* Consultancy, Research Funding; *Trillium:* Consultancy, Research Funding; *Amgen:* Consultancy, Research Funding; *Agios:* Consultancy; *Servier:* Consultancy, Research Funding; *Kite, a Gilead company:* Consultancy, Research Funding; *Kronos Bio:* Research Funding.

Figure 1

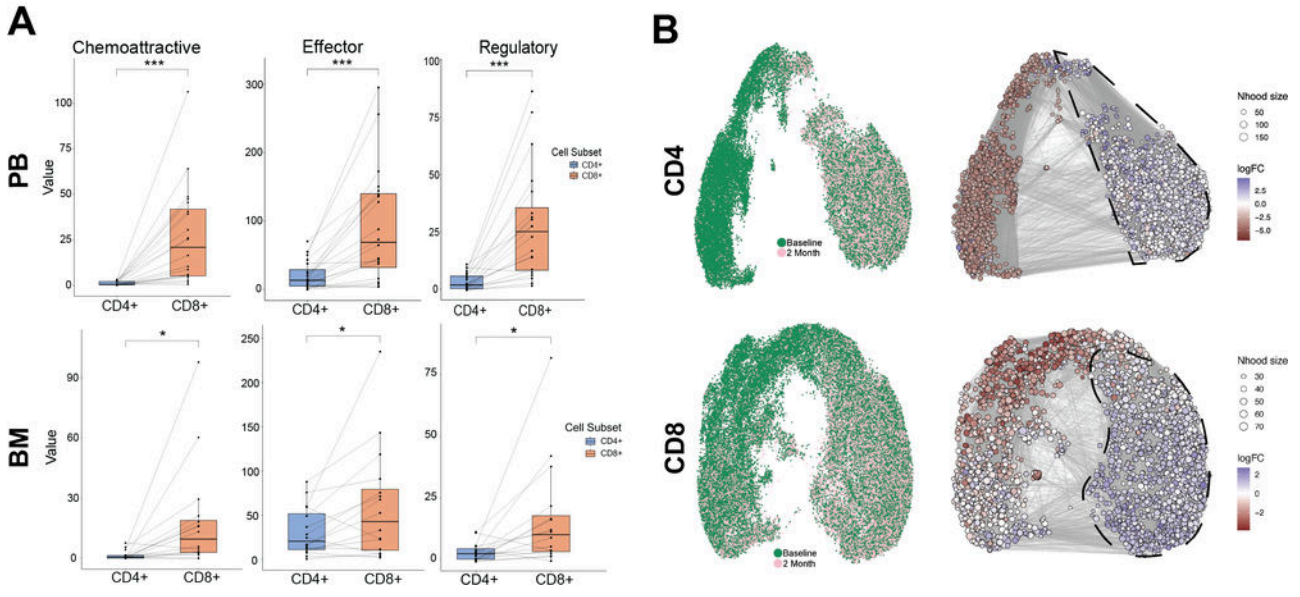

Figure 1

https://doi.org/10.1182/blood-2023-188268