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ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

In-Depth Characterization of the High Risk-Associated Tumor Immune Landscape in Multiple Myeloma

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Introduction

Newly-diagnosed multiple myeloma (MM) patients often share tumor genetic abnormalities associated with a high risk of progression and poor survival. We hypothesized that single-cell transcriptomic characterization of the tumor immune microenvironment (TIME) may be combined with tumor-based risk stratification to uncover novel disease biology mechanisms associated with clinical outcomes and improve risk stratification.

Methods

We performed single-cell RNA sequencing of 361 CD138 negative sorted bone marrow mononuclear cells (BMMCs) samples from 263 MM patients enrolled at time of diagnosis in the Multiple Myeloma Research Foundation CoMMpass study (NCT01454297). Specimens were analyzed at baseline (n=263) across a network of five collaborating academic research centers following assay harmonization. Genetic factors that determine risk were defined as one or more of the following gain- or loss-of-function events derived from baseline genomic sequencing data: del17p14, translocations of the Ig locus with the

MAF/A/B or WHSC1/MMSET/NSD2 loci, and gain of chromosome 1q21. Statistical modeling strategies were used to assess single-cell populations or RNA signatures associations with known risk factors or disease progression (FDR<0.05).

Results

The study generated high-quality single-cell profiles of 731,643 cells from 123 high-risk and 107 standard-risk MM patients based on genetics. Based on distinct transcriptome profiles, BMMCs formed 106 clusters corresponding to 5 major compartments: NK and T cells, B cells, erythrocytes, myeloid cells, and plasma cells. Our preliminary differential abundance analysis comparing high- vs standard-risk patients at baseline uncovered significant differences in the TIME associated with genetic risk. The high-risk group was identified as enriched in effector CD8+, and CD4+ T cells. In contrast, the high-risk group exhibited depletion of naive CD8+ and interferon-associated CD4+ and CD8+ T as compared to the standard-risk group. Within subclusters in the T and NK cells compartment, a higher cytotoxicity signature was observed in high-risk patients, characterized by the expression of granzymes and perforin. Finally, our preliminary survival and progression analysis associated a higher frequency of IDO1-expressing macrophages in worst progression patients, while better outcomes were associated with CD8+ T and B cells expressing androgen response and IL6/STAT3/EMT programs, respectively.

Conclusions

Current approaches for risk stratification are based on bulk measurements of tumor's genetic or epigenetics features, which do not capture the diversity and dynamics of the TIME. Through single-cell transcriptomics, we were able to capture, in high granularity, the TIME and correlate specific immune cell populations and phenotypes with relapse risk and poor prognostic outcomes. These results suggest that immune subpopulations may be an essential novel aspect for improving current risk stratification models.