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651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Single-Cell RNA Sequencing Identifies Distinct Immune Microenvironment in Patients with Primary Plasma Cell Leukemia

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Background: Primary plasma cell leukemia (PCL) is a highly aggressive form of multiple myeloma (MM). While recent advances in cellular immunotherapy have significantly improved the outcome of patients with MM, these benefits have been limited for PCL patients, and their survival remains poor. This is in partly attributable to our limited understanding of the dysregulated immune microenvironment in PCL. Furthermore, distinct biological features of PCL compared with MM have not been clearly defined. In this regard, we performed single-cell RNA sequencing of bone marrow (BM) immune cells and tumor cells from patients with MM and PCL at diagnosis and compared them with BM immune cells from healthy donors.
Methods: Single-cell analysis was performed using 10X Genomics with BM mononuclear cells (BMMCs) isolated from healthy donors (n=3), MM patients (n=2), PCL patients with lower circulating plasma cells (5-20%) (PCL-1) (n=2), and PCL patients with higher circulating plasma cells (>20%) (PCL-2) (n=2) at diagnosis. Sequencing files were processed with CellRanger (10x Genomics) and the data were analyzed with the Seurat toolkit. Cell types were annotated with SingleR based on the Human Primary Cell Atlas built-in references. Pre-B cells, B cells, plasmablasts, plasma cells, granulocyte/macrophage progenitors (GMPs), hematopoietic stem and progenitor cells (HSPCs), myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs), classical monocytes, non-classical monocytes, T cells, natural killer (NK) cells, and stromal cells between healthy donors, MM, PCL-1, and PCL-2 were annotated.
Results: We sequenced a total of 85,268 BMMCs to analyze the heterogeneity and transcriptomic features of BMMCs from healthy, MM, and PCL patients. We characterized changes in the transcriptomic features of T cells, NK cells, monocytes, and DCs between healthy, MM, PCL-1, and PCL-2. We examined CD8 $^{+}$ and CD4 $^{+}$ T cell subsets based on differentiation status, including *CCR7* $^{+}$ *CD45RA* $^{+}$ naïve (TN), *CCR7* $^{+}$ *CD45RA* $^{-}$ central memory T (TCM), *CCR7* $^{-}$ *CD45RA* $^{-}$ effector memory (TEM), and *CCR7* $^{-}$ *CD45RA* $^{+}$ terminally differentiated effector memory T (TEMRA) cells. The proportion of CD8 $^{+}$ TN was decreased in MM, PCL-1, and PCL-2 compared with healthy, while the proportion of TEM was increased in MM and PCL-2 compared with healthy. Of note, the proportion of *CD8* $^{+}$ *NKG7* $^{+}$ cells was highest in PCL-2, followed by PCL-1 and MM, which were minimally detected in healthy. Among CD4 $^{+}$ T cells, the proportion of regulatory T cells did not differ between the groups. However, cytotoxic CD4 $^{+}$ T cells was increased in MM, PCL-1, and PCL-2 compared with healthy. Analysis of NK cells revealed that the proportion of immature NK cells was decreased, while the proportion of mature NK cells was increased in patients with MM, PCL-1, and PCL-2 compared with healthy. We also examined the plasma cells and observed that diversity in plasma cell types is increased in PCL-1 and PCL-2 compared with MM, indicating that the PCL clone is heterogeneous.
Conclusion: We demonstrate the characteristics of BM immune cells in PCL by single-cell RNA sequencing. Additional analyses are ongoing to uncover the association between PCL burden and BM immune cell composition and to gain insight into PCL heterogeneity and define high-risk PCL. Our work should improve our understanding to decipher therapeutic options for PCL.

Disclosures No relevant conflicts of interest to declare.

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