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Monoclonal Gammopathies & Multiple Myeloma

INTEGRATED MULTIOMIC IMMUNE PROFILING DEFINES THE BIOLOGICAL BASIS OF MRD PERSISTENCE IN MULTIPLE MYELOMA

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Minimal residual disease (MRD) status is a strong predictor of outcome in multiple myeloma (MM), yet the immune mechanisms underlying MRD persistence or clearance remain unclear. To elucidate these mechanisms, we investigated the immunological correlates of MRD using an integrated multi-omic approach to dissect the cellular and functional remodeling of the bone marrow (BM) microenvironment after therapy.

Flow cytometry was performed on BM aspirates from 23 ASCT-eligible MM patients (14 with undetectable MRD [uMRD] and 9 with persistent MRD [pMRD]) at baseline and day +100 post-ASCT. In eight patients (4 uMRD, 4 pMRD) with available baseline samples, additional 10-color panels were applied to achieve in-depth immune profiling of BM and peripheral blood. For seven patients (4 uMRD, 3 pMRD), baseline single-cell RNAseq integrated with TCR/BCR and 30-antibody CITE-seq was used to characterize the BM immune landscape.

At baseline, pMRD patients exhibited lower frequencies of $CD27^{-}/CD28^{-}/CD38^{-}$ T/NK cells compared with uMRD. At day +100, pMRD patients showed increased granulocytes, decreased lymphocytes, and higher granulocyte-to-lymphocyte ratio. A concomitant expansion of $CD27^{+}/CD28^{-}/CD38^{-}$ T/NK cells was also noted. Extended immune profiling revealed that pMRD patients had reduced total T cells but an altered effector-to-naïve balance, with enrichment of $CD8^{+}$ effector memory cells and depletion of $CD8^{+}$ naïve cells in BM—mirrored in peripheral blood. Since no further differences were detected in terms of immune subset abundance, we next investigated qualitative transcriptional differences using a single-cell RNA sequencing approach. Baseline transcriptomic profiling revealed distinct immune programs associated with MRD status. In uMRD patients, $CD8^{+}$ effector T cells showed enrichment in genes involved in adaptive immunity and memory maintenance pathways—including T-cell activation and differentiation, antigen processing and presentation, and memory formation—indicating a bone marrow milieu that supports sustained immune surveillance and coordinated B–T cell interactions. Similarly, $CD14^{+}$ monocytes from uMRD patients displayed enrichment in activation and chemotaxis pathways (e.g., XYZ, SIAIHD, AISDSND), suggestive of enhanced support for T-cell–mediated immunity. Conversely, $CD14^{+}$ monocytes from pMRD patients upregulated genes (e.g., *XTW, ESD, FHAUIS*) linked to humoral and innate immune responses, including antibacterial and antimicrobial peptide activity, B-cell activation and isotype switching, and toll-like receptor signaling. Finally, T-cell receptor (TCR) repertoire analysis demonstrated greater clonal variability and absence of dominant effector clones in pMRD patients at baseline, suggesting impaired immune coordination and reduced anti-myeloma activity. In conclusion, uMRD patients show a coordinated, therapy-enhanced immune microenvironment, whereas MRD persistence reflects immune dysfunction, suggesting targets to restore immune competence.