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Monoclonal Gammopathies & Multiple Myeloma

CHARTING RESIDUAL DISEASE TRAJECTORIES IN MULTIPLE MYELOMA USING SINGLE-CELL RNA AND IMMUNE REPERTOIRE PROFILING

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Multiple myeloma (MM) is a multistep plasma cell malignancy marked by profound clonal heterogeneity. Despite therapeutic advances, MM remains incurable, with relapse driven by therapy-resistant clonal plasma cells (cPCs) and a remodeled microenvironment.

In this scenario, Measurable Residual Disease (MRD) has emerged as a key biomarker of treatment response, with MRD negativity being associated with improved progression-free and overall survival. However, current MRD detection strategies focus exclusively on cell enumeration, neglecting the functional state and resistance potential of residual clones. To address this unmet need, we established a longitudinal single-cell approach integrating transcriptomic and immune repertoire profiling to trace cPC evolution from diagnosis to MRD and identify adaptive resistance mechanisms.

Fourteen MM patients were analyzed. Most received D-VTD induction followed by ASCT and lenalidomide maintenance (64.3%); others underwent tandem ASCT, Elranatamab-based maintenance or DRD therapy. In total, 46,476 bone marrow cells underwent scRNA-seq and paired BCR genotyping. BCR repertoire and clonotype reconstruction were performed with dedicated pipelines, and transcriptomic and inferred CNV profiling compared diagnostic and MRD stages.

We detected 16,988 CD138$^+$ plasma cells, including 16,337 clonal and 651 polyclonal cells. At the MRD timepoint, 12 clonal and 138 polyclonal cells were identified across five patients. BCR repertoire and Dandelion network analysis highlighted a reshaped clonal architecture from diagnosis to MRD within the same individuals toghether with a polyclonal BM reconstitution.

MRD-associated cPCs displayed altered transcriptional states with upregulation of pro-inflammatory and survival programs (TGF-β, IL6–JAK/STAT3, TNF-α/NF-κB). Of note, at diagnosis, cPCs showed enrichment in ribosomal and biosynthetic pathways, while MRD-associated cells favored kinase activity and phosphorylation-related gene sets, hallmarks of signaling adaptation and drug resistance. Diagnostic cPCs were enriched in biosynthetic pathways, whereas MRD cells favored kinase and phosphorylation signatures, suggesting signaling adaptation and drug resistance. CNV analysis showed canonical aberrations at diagnosis and retained or unique subclonal features at MRD, indicating selection of therapy-resistant subclones.

This single-cell strategy revealed molecular mechanisms of MRD persistence. Integrating scRNA- and scVDJ-seq enabled precise detection of residual resistant clones and uncovered inflammatory and survival pathways driving their persistence. CNV data support subclonal selection under treatment pressure. Although less sensitive than NGF or ClonoSEQ, single-cell profiling provides unique functional insight, highlighting actionable pathways for MRD-directed therapy. Expansion of sample size and resolution will further define molecular drivers of resistance and support personalized strategies for durable remission.