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Monoclonal Gammopathies & Multiple Myeloma

FROM PRECURSOR DISEASES TO MULTIPLE MYELOMA: REMODELING OF THE OSTEOBLASTIC NICHE AT SINGLE CELL RESOLUTION

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Introduction: Disrupted osteoblastogenesis and impaired osteoblast (OB) functionality, driven by malignant plasma cells within the bone marrow, characterize multiple myeloma (MM) and its precursor diseases as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). In this context OB niche exhibit transcriptional and functional changes that may promote tumor progression. We aimed to characterize the OB population dynamics at single-cell resolution to identify alterations involved in MGUS to MM progression.

Methods: Rare non-hematopoietic bone microenvironment (BME) cells from 16 patient biopsies from MGUS, SMM, and MM were analyzed by scRNAseq depleting CD235a$^+$, CD45$^+$, CD31$^+$, and CD138$^+$ cells using Chromium 10X Genomics platform. Scanpy version 1.10.4 package was used to identify differentially expressed genes. Pathway and biological process (BPs) enrichment were inferred via ORA and GSVA, while cell trajectories and interactions were assessed using STREAM and CellPhoneDB.

Results: A total of 9,565 osteoblastic cells were profiled revealing three clusters: two representing pre-OB states with distinct functional features that segregate along bifurcating branches of the pseudotime-inferred trajectory. The first pre-OB cluster(Wisp2$^+$) exhibited elevated expression of osteoblastogenesis-associated genes and hematopoietic supportive factors, together with a increased expression of BPs related to extracellular matrix mineralization. The second, *pre OBs*, showed a more immunosuppressive profile, attenuated modulation of bone growth and osteoblastic differentiation, and the expression of dysfunctional genes. The *OBs* represented phenotypically mature cells, enriched for BPs involved in the regulation of osteoclastogenesis and immune responses. We also observed perturbed OB dynamic across disease stages with a significant stepwise depletion of *pre-OBs WISP2+* and a concomitant expansion of dysfunctional *pre-OBs*, together with a strong inverse correlation between *pre-OBs WISP2+* and tumor burden (r:-0.74; p:0.0041). This pattern was consistent between SMM progressors and non-progressors. In MM, *pre-OBs WISP2+* exhibited an upregulated senescence-associated secretory phenotype and a compromised osteogenic differentiation potential, whereas *pre-OBs* upregulated osteoblast-inhibitory genes and showed enrichment of glutamine and glutamate metabolic processes. Finally, preliminary interactome analyses (12,129 paired immune and tumor cells) revealed distinct cross-talk signatures within the bone niche.

Conclusions: Single-cell profiling highlights profound remodeling of the osteoblastic lineage across precursors disease and MM, marked by depletion of pro-osteogenic *pre-OBs WISP2+* and expansion of dysfunctional subsets. This work provides a detailed map of OB dynamics in monoclonal gammopathies showing that transcriptional shifts mirror skeletal niche disruption and may serve as early indicators of tumoral progression toward MM.