Mapping of the Bone Marrow Microenvironment at Single Cell Resolution

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The molecular complexity of the bone marrow (BM) microenvironment and its response to stress are incompletely understood, despite its key role in the regulation of hematopoiesis. Here we map the transcriptional landscape of BM vascular, perivascular, and osteoblast niche populations at single-cell resolution at both homeostasis and under stress hematopoiesis. This analysis revealed a previously unappreciated level of cellular heterogeneity within the BM niche, identified novel cellular subsets, and resolved cellular sources of pro-hematopoietic growth factors, chemokines, and membrane-bound ligands. Under conditions of stress, our studies revealed a significant transcriptional remodeling of these niche elements accompanying the myeloid skewing that characterizes emergency hematopoiesis. Among the stress-induced changes, vascular Notch ligand delta-like 4 (*Dll4*) was significantly downregulated and its vascular-specific deletion was sufficient to recapitulate the shift from lymphoid to myeloid output. In the absence of vascular *Dll4*, the myeloid transcriptional program was prematurely induced at the hematopoietic stem cell (HSC) stage. These findings refine our understanding of the cellular architecture of the BM niche, reveal a dynamic and heterogeneous molecular landscape that is highly sensitive to stress, and illustrate the utility of single cell transcriptomic data in systematically evaluating the regulation of hematopoiesis by discrete niche populations. Finally, we extend these studies in the “leukemic niche” studying the bone marrow microenvironment (and specifically the immune microenvironment) during acute leukemia progression.