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Single-cell dissection of immune system aging and acute myeloid leukemia

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Summary

The continuous production of blood cells, known as hematopoiesis, sustains our immune system throughout life. This process relies on rare hematopoietic stem cells (HSCs), which generate all mature blood lineages. However, as individuals age, these stem cells accumulate somatic mutations that confer selective growth advantages, skew differentiation toward the myeloid lineage, and increase the risk of developing myeloid malignancies such as acute myeloid leukemia (AML). Although many of the individual genetic drivers involved in this process are known, how they interact with aging to create therapeutic vulnerabilities remains poorly understood.

This thesis investigates how aging and genetic lesions reshape the transcriptional and epigenetic landscape of blood cell development, with the goal of translating these insights into precision medicine strategies for myeloid cancers. By integrating bulk and single-cell omics technologies with functional assays and computational modeling, this work characterizes key molecular changes in hematopoiesis during aging and malignant transformation. The findings show that aging consistently alters immune cell composition, diminishes the naïve T-cell pool, and activates pro-inflammatory transcriptional programs, particularly through upregulation of the AP-1 complex in monocytes. At the same time, the research demonstrates that epigenetic interventions can expand the HSC pool, providing potential avenues to improve stem cell transplantation and gene therapy.

In the context of AML, the thesis reveals that transcriptional profiling recapitulates known dynamics such as FAB and offers even a more granular view of disease heterogeneity than genetic classifications alone. Patients with identical genetic lesions exhibited distinct transcriptional states that correlated with treatment responses and differentiation trajectories, uncovering substructures within established diagnostic categories. These results suggest that current classification systems may underrepresent the molecular diversity of AML.

Overall, this work bridges the gap between normal aging processes and cancer development, highlighting how age-associated changes in hematopoiesis generate vulnerabilities that could be therapeutically targeted. The research proposes a framework for refining leukemia classification through integrative molecular profiling and lays the foundation for interventions that may prevent or delay the onset of age-related hematological malignancies, moving the field closer to truly personalized treatment strategies.

