第3回 老化・健康長寿学セミナー

The hematopoietic landscape of naked mole rats uncovers stem cell properties of longevity

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Naked mole rats (NMRs) are recognized as a resilient rodent model in aging research, but very little is known about their stem cells.
Bone marrow (BM) histology revealed less megakaryocytes in NMRs compared to mice, consistently NMR blood features less platelets, and while in humans and mice thrombocytes strongly increase with age, across an NMR cohort between 1-9 years of age platelet levels rather declined. I found monoclonal antibodies cross-reactive with live NMR cells, from which I designed a sorting panel to purify NMR hematopoietic stem and progenitor cells (HSPCs). RNA-Seq with *de novo* Transcriptome assembly from NMR BM to perform gene set enrichment analysis (GSEA) inferred cell type identity of a hematopoietic hierarchy for 4 candidate populations (CP). Cytochemistry and colony assays confirmed CP4 as early erythroid precursor and CP3 as erythromyeloid progenitor and outlined splenic erythropoiesis in healthy NMRs. We further detected in CP1 the highest enrichment for HSC gene sets, although those cells are lineage-marker positive (LIN+), whereas HSPCs in human and mouse are strictly LIN–. While both CP1 and CP2 yield comparable multilineage potential and self-renewal capacity *in vitro* and *in vivo*, CP2 has a higher frequency of quiescent cells, rendering CP2 the most enriched hematopoietic stem cell (HSC) compartment in NMRs. Single-cell RNA-Sequencing further increased the resolution in the NMR HSPC compartment, identified early steps of lymphopoiesis and gave evidence for a bipotent MEP, which recently has been challenged for humans and mice.
Next I performed cross-species transcriptomics between Mouse, Human and NMR HSPCs to reveal strong upregulation of the oxidative phosphorylation pathway in NMR cells. Notably, intracellular ROS levels of NMR HSCs are drastically reduced compared to Mouse HSCs. Interestingly, while NMR HSCs have less mitochondria than young but more than aged murine HSCs, their mitochondrial membrane potential is significantly higher. Conclusively, on the cellular and molecular level NMR hematopoietic stem cells are less mitotically active, more resistant to oxidative stress and feature elevated mitochondrial function. Here I delineate the hematopoietic hierarchy along with exceptional features of the blood system of naked mole rats collectively contributing to their longevity.