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ORAL ABSTRACTS

101.RED CELLS AND ERYTHROPOIESIS, EXCLUDING IRON

Spatial Mapping Reveals Distinct Erythroid Niches in Mice and Humans during Development and Stress

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Like hematopoiesis, erythropoiesis requires erythroid niche nurturing and support. While extensive studies have revealed various components and functions of the HSC niches, the erythroid niche is less characterized. The most studied erythroid niche is the bone marrow erythroblastic island (EBI), which comprises a central macrophage surrounded by developing erythroblasts. However, most of the reported studies of EBI involve in vitro reconstitution of mixed cell populations that do not recapitulate in vivo niches. Here, we utilized multiple spatial mapping technologies, including spatial transcriptomics and whole-mount imaging studies, to characterize erythropoiesis in mouse and human hematopoietic tissues during development and under stress.

We first utilized the Visium platform from 10x Genomics to study the spatial transcriptomic profiles of the E14.5 mouse fetal liver, which is the major organ for murine fetal definitive erythropoiesis. The Visium platform contains barcoded spots with a diameter of 55 μm, which is suboptimal for single-cell analyses but ideal for the investigation of cell-cell interactions within their microenvironment. We found that each hepatic lobe exhibited different cluster distributions, indicating distinct cell compositions among different anatomic loci. Further deconvolution of the clusters and co-analysis with corresponding single-cell RNA sequencing data revealed that there was a higher positive correlation between erythroid cells and C1q+ macrophages compared to other macrophages, suggesting that C1q+ macrophages are more likely to be EBI macrophages in mouse. C1q+ macrophages exhibited high expression of known genes involved in EBI macrophage function and erythropoiesis. Cyclic immunofluorescence (CyCIF) and whole-mount immunofluorescence analyses further demonstrated the co-localization of C1q+ macrophages with erythroid cells in the E14.5 fetal liver. This strong positive correlation between C1q+ macrophages and erythroid cells was also observed across different stages of fetal liver development, newborn bone marrow, and adult spleen under physiologic and stress conditions. These findings demonstrate that C1q+ macrophages as EBI macrophages are conserved across different hematopoietic organs in mice.

We next applied the same technologies to human hematopoietic tissues during development and stress. In contrast to the mouse, we did not observe a strong positive correlation between erythroid cells and C1q+ macrophages or other macrophages in the human fetal liver. Instead, there is a strong association between erythroid progenitor and maturing erythroid cells. This strong association is also found in different developmental stages of the human fetal liver as well as the bone marrow, which becomes even stronger in regenerating human bone marrow after chemotherapy. We also recapitulated these findings in a human bone marrow organoid model. These results demonstrate the erythroid cell self-sustaining capacities in human erythropoiesis.

Taken together, our findings reveal the distinct erythroid niches in mice and humans during development and stress, which provides a comprehensive understanding of erythropoiesis during evolution.

Disclosures No relevant conflicts of interest to declare.

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