Cells regulating blood stem cell maintenance are diverse and conserved between species

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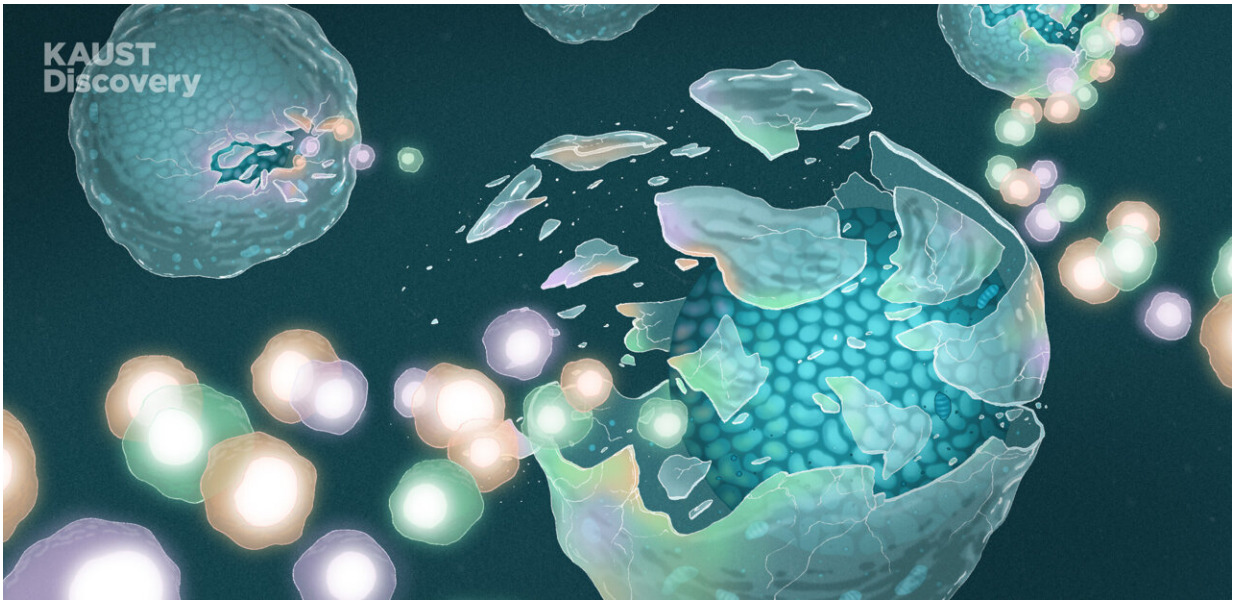

KAUST bioscientists are developing new methods to combine single-cell sequencing datasets, which will help to improve understanding of cellular identity and function. The team has used the method to study the bone marrow microenvironment in greater detail. Credit: KAUST; Joana C. Carvalho

Deep molecular analysis of the bone marrow microenvironment reveals that the cells regulating blood stem cell maintenance are more diverse than expected and have features likely to be conserved between species.

Tissues contain many different cell types, and it remains challenging to

understand how they interact and contribute to tissue function. Now, state-of-the-art bioinformatics has enabled an international research team to uncover the complexity and high degree of conservation of the bone marrow (BM) microenvironment that regulates blood stem cells.

Blood stem cells can self-renew—thereby retaining their stemness—as well as differentiate, giving rise to all cell types in the blood, including white blood cells, red blood cells and platelets. The BM microenvironment or "niche," where blood stem cells reside, is essential for regulating blood stem cell self-renewal and differentiation. Yet, little is known about the cellular composition of the niche and the diverse functions of its constituents.

"We don't yet understand the composition of the BM niche and how it integrates local and systemic inputs to regulate hematopoiesis," says David Gomez-Cabrero, a bioinformatician and computational biologist at KAUST. Gomez-Cabrero has been developing new methods to combine single-cell sequencing datasets to improve understanding of cellular identity and function. Single-cell technologies enable researchers to accurately profile the genes, proteins and metabolites in individual cells.

Gomez-Cabrero, working with Spanish researchers at Clinica Universitaria de Navarra and the Center for Applied Medical Research, has carried out an integrative analysis of three distinct mouse BM niche datasets, focusing on two cell types that are involved in blood stem cell maintenance: endothelial and mesenchymal stromal cells.

The *iScience* study describes how, by integrating single-cell gene expression data (single-cell RNA sequencing) for each of these cell types, the authors were able to unravel the heterogeneity of these niche cells, identifying multiple cellular subtypes and molecular states. Each subtype is defined by the expression of a particular set of genes, which

provides clues about the cells' function and stage of differentiation. In total, they characterized 14 endothelial subclusters and 11 mesenchymal subclusters. "We have uncovered a previously unrecognized level of heterogeneity and specialization of endothelial and mesenchymal cells in the bone marrow," says Jesper Tegner, computational biologist and co-author.

When the results in mice were compared with those from human BM samples, some of the subcluster gene signatures and known niche factors regulating hematopoiesis were conserved. This suggests that the biological mechanisms defining the BM microenvironment are likely to be shared between species, explains Gomez-Cabrero.

To further understand the composition and regulation of cells in the BM microenvironment and their interactions, Gomez-Cabrero and researchers Borja Saez and Felipe Prosper will continue to integrate other data modalities, such as epigenetics, proteomics and imaging data, into their analyses. "Once all the cell types have been characterized, cell-cell interactions can be better defined," he says.

More information: Jin Ye et al, Deconvolution of the hematopoietic stem cell microenvironment reveals a high degree of specialization and conservation, *iScience* (2022). DOI: 10.1016/j.isci.2022.104225

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