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How blood stem cells diversify

Different types of bone marrow stem cells give rise to blood and immune cells. A team led by Simon Haas now reports in "Nature Cell Biology" how that diversity develops. The findings could help improve stem cell therapies, including treatments for blood cancers.

Every day, the body produces vast numbers of blood and immune cells –all of them from stem cells located in bone marrow. Scientists have long known that these stem cells have diverse characteristics — for example, they differ in how quickly they divide or in the specific types of cells they become. But exactly how this diversity arises and why it matters has remained unclear.

Now, a team led by three researchers from Heidelberg and Berlin scientist Dr. Simon Haas provides the first coherent explanation for this phenomenon in "Nature Cell Biology." According to the study, there are no fixed subgroups of blood stem cells in the bone marrow.

Instead, all stem cells change along a predefined developmental path: from a slow, highly potent state to a more active state, but with more limited developmental potential. "A better understanding of stem cell behavior could help make therapies based on these cells, such as treatments for leukemia, more effective," says Haas.

Biological experiments and mathematical models

Haas leads a research group in the joint research focus Single-Cell Approaches for Personalized Medicine at the Berlin Institute of Health in the Charité (BIH), the Max Delbrück Center, and Charité – Universitätsmedizin Berlin. He is also Professor of Single-Cell Technologies and Precision Medicine at the Precision Healthcare University Research Institute at Queen Mary University of London. His laboratory is based at the Berlin Institute for Medical Systems Biology of the Max Delbrück Center (MDC-BIMSB).

Haas is one of four senior authors of the current study. Together with Dr. Michael Milsom of the German Cancer Research Center (DKFZ) and the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM), he was primarily responsible for the experimental part of the work. The two other senior authors — Dr. Daniel Hübschmann of the National Center for Tumor Diseases Heidelberg, DKFZ, and Heidelberg University, and Dr. Thomas Höfer of DKFZ — carried out the mathematical modeling that helped the team reach its conclusions.

A shared pathway

"To find out how the diversity of blood stem cells arises, we isolated more than a thousand of these cells individually, labeled each one with a fluorescent protein, and then transplanted them into mice," explains Dr. Florian Grünschläger, a former doctoral student in the Haas lab and one of the study's three first authors. "This allowed us to track their development in the animals and observe which blood and immune cells emerged from them, when they appeared, and in what quantities."

By combining high-resolution single-cell technologies with mathematical modeling, the researchers discovered a surprising pattern: All blood stem cells develop along a shared trajectory. At first, they divide and differentiate only slowly, but over time they become faster and more active. As they progress along this path, not only does the speed of cell production change, but also the types of blood and immune cells they predominantly generate. The stem cells cannot reverse course once they have progressed along this path.

Blood stem cells compete

"One key finding of our study is that stem cells do not act in isolation," says Dr. Esther Rodríguez Correa, another first author and former doctoral researcher in the Milsom lab. "Instead, slow and fast cells compete with one another to produce the

different mature blood and immune cells." Which cells are ultimately produced depends partly on the developmental stage of the stem cell and partly on the body's current needs.

"The competition between stem cells, along with several feedback signals from the body — for example in the form of cytokines — determines the final outcome," explains Haas. "It ensures that the proper balance between different blood and immune cells is maintained while also allowing the body to respond rapidly to stress, such as an infection or major blood loss."

Haas and his colleagues believe that many of the findings in mice can be extrapolated to humans. "At the very least, they explain numerous observations in the human blood and immune system," says Haas. "If we gain a more detailed understanding of how blood-forming stem cells behave in the body, we will also be able to better predict and control their behavior in patients." Stem cell therapies and bone marrow transplants, which have long been used to treat leukemia and other blood disorders, could thus become more refined and more effective.

Literature

Esther Rodríguez Correa, Florian Grünschläger, Tamar Nizharadze, et al. (2026): „A kinetics-based model of haematopoiesis reveals extrinsic regulation of skewed lineage output from stem cells". Nature Cell Biology,
DOI: 10.1038/s41556-026 – 01958-0

Press release

26-May-2026
Source: Max Delbrück Center for Molecular Medicine in the Helmholtz Association

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