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Stem Cells in Deep Sleep as a Secret Reserve

Researchers at the German Cancer Research Center (DKFZ) and the HI-STEM* Stem Cell Institute have discovered a group of particularly long-lived blood stem cells in mice. These cells remain in a dormant state for an exceptionally long time while retaining their ability to generate new blood cells. This newly discovered cell population may be responsible for sustaining blood regeneration and immune defense throughout a mouse's entire life.

Our bodies produce billions of new blood cells every day. These cells transport oxygen, fight pathogens, and help stop bleeding. Blood stem cells in the bone marrow are responsible for this vital replenishment. They can renew themselves and produce all types of blood cells - for a lifetime.

To prevent this ability from being exhausted prematurely, many blood stem cells spend a large part of their lives in a sort of dormant state. Only when they are needed do they begin to divide. A team led by researchers at DKFZ and HI-STEM has now identified a special population of stem cells that can remain in this dormant state even longer than previously known blood stem cells.

A previously overlooked stem cell reserve

To identify blood stem cells, researchers use specific protein markers on the cell surface. One of the most important is CD150. Cells lacking CD150 were therefore often not classified as blood stem cells. The new study shows, however, that a particularly interesting population of stem cells is hidden among these very cells, characterized by the surface protein EPCR.

While other blood stem cells divide at least occasionally, the newly described cells remain inactive for months in mice. After more than 200 days, only about two percent of conventional blood stem cells still exhibited a "quiescence marker." In contrast, about 10 to 15 percent of the newly characterized stem cells were still positive for this marker. This "deep sleep" could be crucial in enabling the cells to retain their regenerative capacity and ability to produce blood for an exceptionally long time.

Blood stem cells are often awakened from their dormant state by inflammatory signals allowing the body to produce additional immune cells. However, repeated activation depletes stem cell reserves. In the mice studied, the newly described cell population responded to inflammatory stimuli much more cautiously than conventional blood stem cells.

Different Stem Cells for Different Tasks

The Heidelberg team also discovered that the two stem cell groups have different focuses when it comes to forming new blood cells: While the previously known CD150-positive stem cells are more oriented toward the generation of red blood cells and platelets, the newly identified "deep sleepers" show a greater tendency to differentiate into immune cells, particularly lymphocytes.

Nevertheless, both groups can generate all major blood cell types. The researchers confirmed this through transplantation experiments in mice: Even individual cells from the newly characterized population were able to generate all blood cell types and sustain them for life. This ability was maintained even after serial transplantation.

"We show here that blood stem cells do not constitute a uniform cell population but rather comprise different subpopulations with distinct properties and functions," says first author Dawn Lin. Lead author Andreas Trumpp adds, "Blood stem cells form the basis for stem cell transplants, which are used to treat leukemias and other severe blood disorders. A better understanding of how these cells remain functional even in old age could help further improve these therapies in the future and prevent our blood and immune systems from becoming less effective as we age."

However, the stem cell expert emphasizes that it has not yet been proven that a comparable, particularly long-lived stem cell population exists in humans. "We already have initial evidence of this—that's our next project!"

Publication
Dawn S. Lin, Isabell Alexandra Guckes, Ian Ghezzi, Pia Sommerkamp, Esther Rodríguez-Correa, Enrico Frigoli, Santiago Cerrizuela, Lukas PM Kremer, Sina Bergemann, Nesrine Aroua, Frank Y. Huang, Patrick Stelmach, Andreas Narr, Mari Carmen Romero-Mulero, Petra Zeisberger, Markus Sohn, Simon Anders, Marieke A.G. Essers, Nina Cabezas-Wallscheid, Ana Martin-Villalba, Michael D. Milsom, Maria C. Puschhof, Andreas Trumpp: *EPCR Expression Marks CD150neg Deeply Dormant Long-term Hematopoietic Stem Cells,* Cell Stem Cell 2026
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Further information

- German Cancer Research Center (DKFZ)