Growing blood stem cells in the lab to save lives

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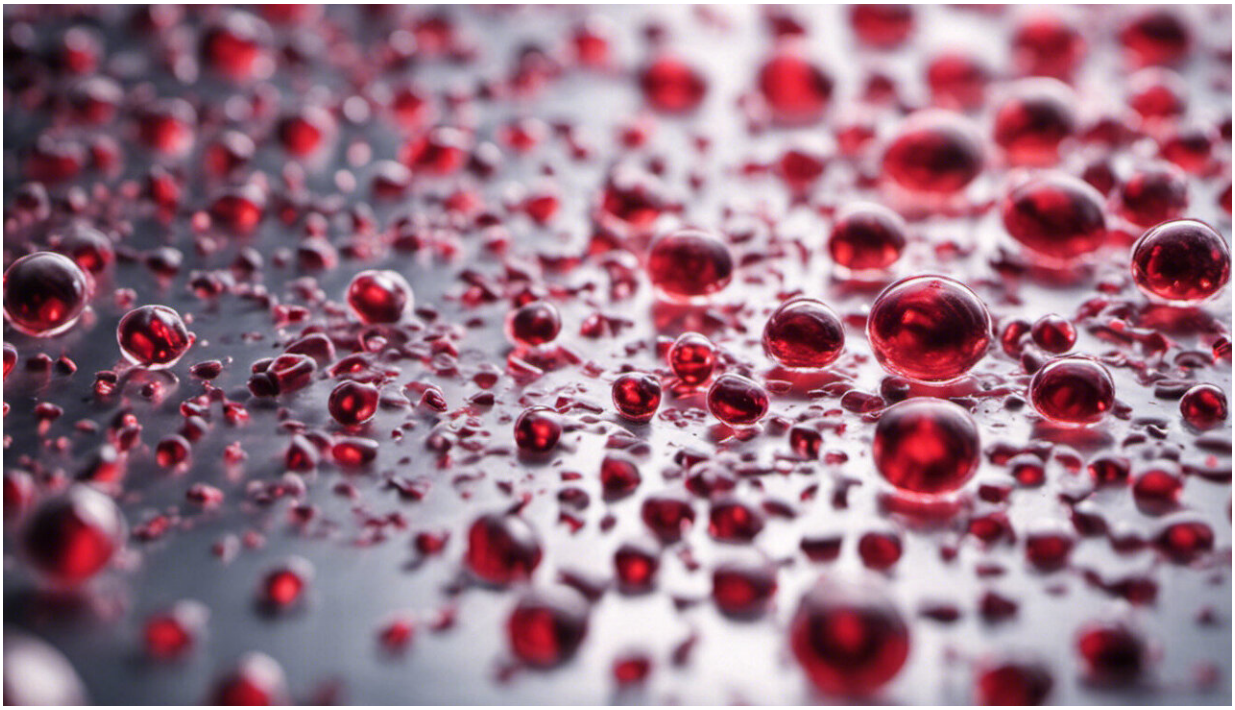

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Hematopoietic stem cells (HSCs) are important immature blood cells in bone marrow that can be triggered to develop into any blood cell type. HSC transplants can be used to treat conditions where bone marrow is damaged and no longer able to produce healthy blood cells, but the widespread and safe use of HSCs is limited by barriers to cell growth

and expansion in the lab (i.e., ex vivo). Now, a team led by researchers at the University of Tsukuba has established a novel culture system that supports long term ex vivo expansion of HSCs.

Human HSCs are frequently and easily obtained from umbilical cord blood, but this yields an insufficient number of HSCs for proper transplantation. Though ex vivo HSC expansion is clearly necessary, this goal has been difficult to achieve. In previous research, cell signaling molecules called cytokines and a protein called albumin have frequently been used to stimulate HSC expansion, but have only short-term success.

"Other teams have shown promising results using novel approaches for HSC ex vivo expansion, including the addition of small molecules, certain hydrogels, various growth factors, or small molecule inhibitors to the cell culture media," explains Professor Satoshi Yamazaki, senior author of the study published in *Nature*.

Though cytokines were once believed to be indispensable for ex vivo HSC growth, the research team hypothesized other new approaches as suitable alternatives. Starting with mouse HSCs, they previously found that albumin could be replaced by a synthetic polymer. This not only overcame the albumin-related problem of variability between batches used in different experiments, but also prevented the negative effects of impurities that commonly arise.

When the research team applied this method to human HSCs, they noted less robust proliferation than in mouse HSCs. After molecular analysis, they observed decreased activity of vital signaling molecules called PI3K and AKT. To address this, they found that adding chemicals for activating PI3K and AKT could significantly improve human HSC growth.

"We also found that adding a receptor agonist chemical known as

butyzamide could stimulate cell proliferation, providing a good alternative to cytokines that were commonly used in the past," says Professor Yamazaki.

Adding a compound called UM171, as well as a specific polymer, improved the results by supporting long-term HSC expansion. Using a technique known as RNA sequencing, the team confirmed the successful effects of this system on gene expression in individual cells. Furthermore, transplanting the HSCs into mice supported engraftment and growth of the cells that were expanded using their new culture system.

Given the importance of ex vivo expansion of human HSCs, the newly established system using an optimal chemically defined cell culture medium provides a suitable alternative to systems using typical cytokine-containing media. This work may help advance various HSC-related therapeutics in clinical development and potentially save lives.

More information: Masatoshi Sakurai et al, Chemically defined cytokine-free expansion of human haematopoietic stem cells, *Nature* (2023). DOI: 10.1038/s41586-023-05739-9

Provided by University of Tsukuba

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