New blood: Lab-grown stem cells bode well for transplants, aging research

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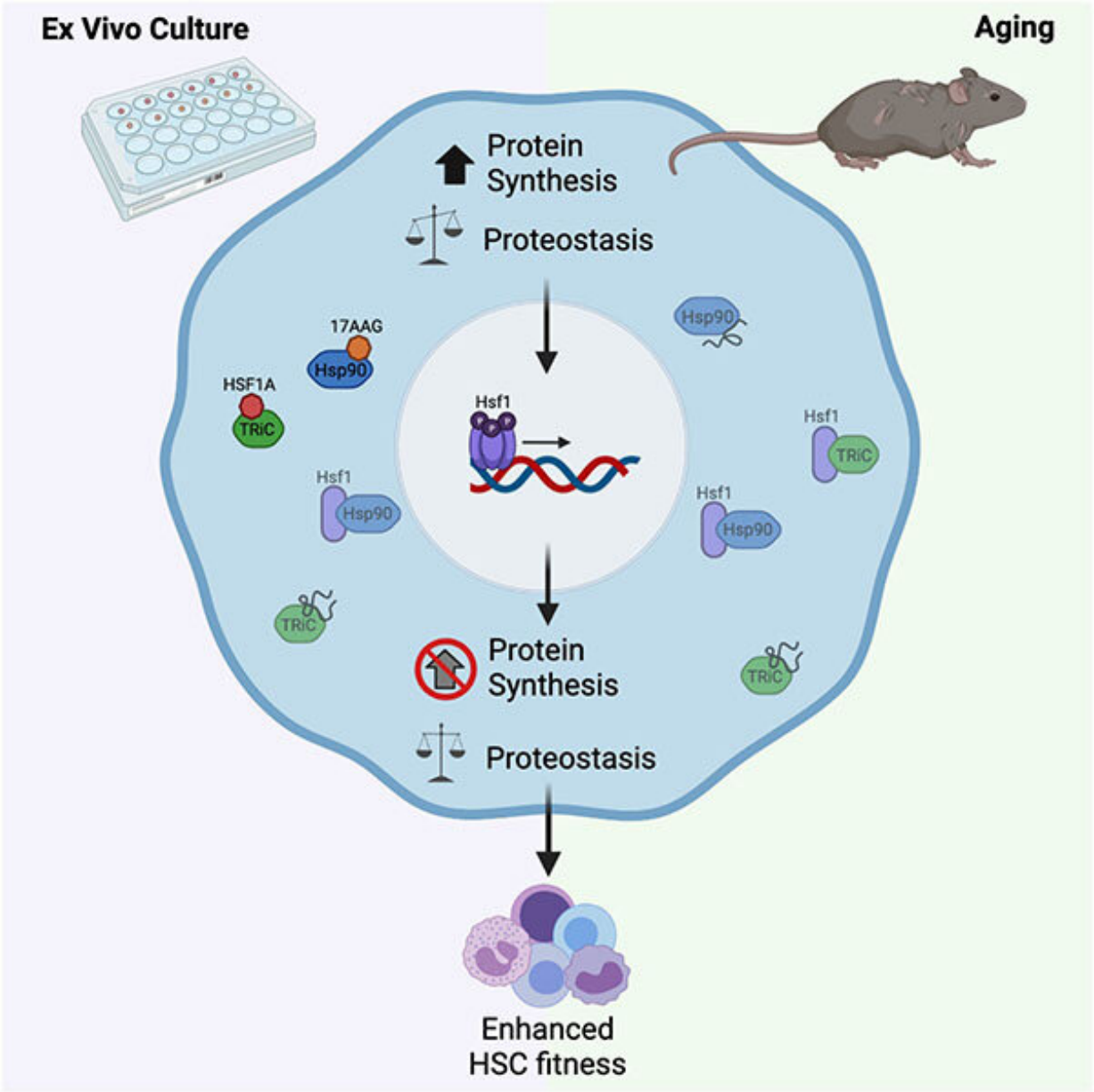

The HSF1-mediated heat shock pathway promotes proteostasis in hematopoietic stem cells in culture and during aging. Credit: Cell Stem Cell

Hematopoietic stem cells—the precursors to blood cells—have been notoriously difficult to grow in a dish, a critical tool in basic research. Scientists at University of California San Diego School of Medicine have identified the underlying issue and developed a method to keep cultured cells healthy. These findings, they say, are positive news for patients seeking stem cell transplants—and may hint at a new way to ward off aging.

The findings will be published in the August 12, 2021 online issue of *Cell Stem Cell*.

In bone marrow transplants, hematopoietic stem cells are infused intravenously to reestablish blood production in patients whose bone marrow or immune system is damaged. The procedure is used to treat diseases such as leukemia, lymphoma, aplastic anemia and immune deficiency disorders. However, donor stem cells are not always available for patients who need them.

"Even for patients who do receive stem cell therapies, transplanting more cells yields fewer complications and increases chances of overarching success," said senior author Robert Signer, Ph.D., assistant professor of medicine at UC San Diego School of Medicine.

While other researchers have tried to culture hematopoietic stem cells by recreating the bone marrow environment in a dish, Signer's team instead asked what internal mechanism makes the cells unhealthy to begin with, and could they remedy that process directly?

Lead author Miriama Kruta, Ph.D., postdoc in Signer's lab at the time of the study, and colleagues found that in the foreign environment of the culture dish, stem cells begin producing excess proteins, causing extreme stress. The state of stress activates the heat shock response, a highly conserved stress reduction pathway regulated by heat shock factor 1 (HSF1). The researchers identified two different small molecules that super-activate the *HSF1* gene. By adding these to the culture, the enhanced activity of the heat shock pathway helped rebalance the cells' state of equilibrium or homeostasis.

"Now, we can preserve high-quality stem cells in culture over a prolonged period of time," said Signer. "We hope the increased quality will lead to improved clinical outcomes."

The recovery of protein homeostasis by enhanced *HSF1* activation was shown in both mouse and human hematopoietic stem cells. The next step, said Signer, is to test how these small molecules affect the outcome of human stem cells in transplantation systems.

The researchers discovered the heat shock pathway isn't just important in a Petri dish, it also keeps stem cells healthy in their native bone marrow during aging. While *HSF1* is inactive in the stem cells of young adults, it is turned on in middle-aged and older adults.

"*HSF1* is activated during aging to keep your stem cells fit," said Signer. "Protein damage impairs stem cells during aging and likely contributes to disrupting blood and immune cell production in older people." Signer said super-activating *HSF1* might eventually be used to improve stem cell and tissue function in aging to prevent blood disorders and boost immunity in older adults.

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