Aged hematopoietic stem cells rejuvenated to be functionally younger

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Researchers have rejuvenated aged hematopoietic stem cells to be functionally younger, offering intriguing clues into how medicine might one day fend off some of the ailments of old age.

Scientists at Cincinnati Children's Hospital Medical Center and the Ulm University Medicine in Germany report their findings online May 3 in the journal *Cell Stem Cell*. The paper brings new perspective to what has been a life science controversy – countering what used to be broad consensus that the aging of hematopoietic stem cells (HSCs) was locked in by nature and not reversible by therapeutic intervention.

HSCs are stem cells that originate in the bone marrow and generate all of the body's red and white blood cells and platelets. They are an essential support mechanism of blood cells and the immune system. As humans and other species age, HSCs become more numerous but less effective at regenerating blood cells and immune cells. This makes older people more susceptible to infections and disease, including leukemia.

Researchers in the current study determined a protein that regulates cell signaling – Cdc42 – also controls a molecular process that causes HSCs from mice to age. Pharmacologic inhibition of Cdc42 reversed HSC aging and restored function similar to that of younger stem cells, explained Hartmut Geiger, PhD, the study's principal investigator and a researcher in the Division of Experimental Hematology/Cancer Biology at Cincinnati Children's, and the Department of Dermatology and Allergic Diseases, Ulm University Medicine.

"Aging is interesting, in part because we still don't understand how we age," Geiger said. "Our findings suggest a novel and important role for Cdc42 and identify its activity as a target for ameliorating natural HSC aging. We know the aging of HSCs reduces in part the response of the immune system response in older people, which contributes to diseases such as anemia, and may be the cause of tissue attrition in certain systems of the body."

The findings are early and involve laboratory manipulation of mouse cells, so it remains to be seen what direct application they may have for humans. Still, the study expands what is known about the basic molecular and cellular mechanisms of aging – a necessary step to one day designing rational approaches to aiding a healthy aging process.

One reason the research team focused on Cdc42 is that previous studies have reported elevated activity of the protein in various tissue types of older mice – which have a natural life span of around two years. Also, elevated expression of Cdc42 has been found in immune system white blood cells in older humans.

In the current study, researchers found elevated activity of Cdc42 in the HSCs of older mice. They also were able to induce premature aging of HSCs in mice by genetically increasing Cdc42 activity in the cells. The aged cells lost structural organization and polarity, resulting in improper placement and spacing of components inside the cells. This disorganization contributed to the cells' decreased functional efficiency.

The researchers then analyzed HSCs from older mice to see if inhibition of Cdc42 would reverse the aging process. They used a specific dose (5uM) of a pharmacologic inhibitor of Cdc42, CASIN, to reduce the protein's activity in the cells – processing them for 16 hours ex vivo in laboratory cultures. This improved structural organization, increased polarity and restored functionality in the older cells to levels found in

young cells.

To test the rejuvenated cells, the researchers used a process known as serial competitive transplantation. This included extracting HSCs from young (2-4 months) and aged (20-26 months) mice and processing them in laboratory cultures. Young and rejuvenated cells were then engrafted into recipient mice. This allowed scientists to compare how well young and rejuvenated aged HSCs started to repopulate and transform into different types of blood cells. It also confirmed that HSCs rejuvenated by targeting Cdc42 do function similarly to young stem cells.

Researchers next plan to test the Cdc42 inhibitor, CASIN, in mice to see how HSCs and various tissues in the laboratory models respond. In particular, they are testing red blood cell production, endurance and immune response in the mice. The research team is also acquiring samples of human HSCs to see how those cells respond in laboratory tests to Cdc42 expression.

Provided by Cincinnati Children's Hospital Medical Center

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