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Press Release

Why Immune Stem Cells Disappear As We Age

German scientists illuminate underlying mechanism

Adult stem cells are found in almost all of the adult body's tissues. Throughout a person's life, these cells, which, by definition, have not yet fully specialized, contribute to tissue renewal while retaining their ability to continuously replenish their own population. For example, throughout the lifespan, hematopoietic stem cells in a person's red bone marrow continuously produce the cellular components of the blood. These include red blood cells but also white blood cells like the lymphocytes of the immune system. It has been well established that, as we age, our hematopoietic stem cells lose their ability to give rise to the cells and cellular fragments of the blood - especially to those cells that make up our immune system, which helps defend our bodies against disease-bearing pathogens.

Now, the Max-Planck-Research Group on Stem Cell Aging at the University of Ulm, headed by Professor Lenhard Rudolph, has identified the mechanism underlying age-related immune stem cell loss. Stem cells are among those cells in the human body with the greatest longevity record. However, as the body ages mistakes accumulate in its stem cells' genetic material - their DNA. "Our work shows that this age-related DNA damage promotes stem cell differentiation," Rudolph explains. "This, then, is how the stem cells lose their capacity for continued self-renewal, and explains why and how their population is ultimately decimated." It seems that those bone marrow stem cells in charge of renewing the immune system's B and T lymphocyte population are particularly susceptible and are rapidly lost as a direct result of age-related DNA damage.

The researchers used a highly specialized form of RNA interference technology (RNAi) available at HZI Braunschweig to study the molecular specifics underlying this process. The technology allows for the targeted and highly effective 'knockdown' of individual genes of interest in a model organism. Genetic screening protocols based on this technology allowed researchers in Professor Lars Zender's lab at HZI to directly examine a gene's effects in the tissues of mice. "As part of this project we targeted and blocked individual genes in murine hematopoietic stem cells and examined how the suppression of gene function affected cell aging," explains Zender, who is also Professor at the Hanover Medical School (MHH). Their results showed that a gene called BATF appears to play a key regulatory role in the stem cell aging process. If BATF's transcription is being suppressed, the hematopoietic stem cells live longer; if, by contrast, BATF becomes expressed, cellular DNA damage results.

The newly identified mechanism is not only important as it helps explain the deteriorating immune system function seen in old age, but, as Rudolph proposes, "it is conceivable that this mechanism's primary function may be to protect the body against the development of certain types of cancer." As such, the successful elimination of damaged stem cells from the body may prevent cancer development in early adulthood, as mutated stem cells are essentially 'filtered out' of the system. On the other hand, an accumulation of DNA damage can lead to other problems later on in life, as insufficient numbers of functional stem cells are available for critical immune system maintenance.

Ulm's Jianwei Wang, who is first author of the study he worked on for his dissertation, is already thinking one step ahead: "If we were able to increase the lifespan of stem cells of the immune system - albeit without completely losing control over DNA damage - then we could potentially improve immune function in older adults - which means better overall protection against life-threatening infections."

Original publication:

A Differentiation Checkpoint Limits Hematopoietic Stem Cell Self-Renewal in Response to DNA Damage. Cell, Vol. 148, Issue 5, 1001–1014, March 2, 2012.

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