

## Inflammation accelerates aging of the hematopoietic system

**In mice, inflammation in early to mid-life leads to a permanent decline in functional blood stem cells, according to a recent publication by scientists from the German Cancer Research Center (DKFZ) and the Stem Cell Institute HI-STEM\*. The ability of the blood stem cells to regenerate was suppressed for at least one year after challenge with inflammation, suggesting that infection and inflammation may act as a prominent driver of age-associated functional decline in tissues. In line with this, mice exposed to such challenges in early life developed clinically relevant features of aging that are often observed in elderly humans.**

Blood stem cells in the bone marrow provide a lifelong replenishment of the different cell types making up the blood system. In addition, they are also capable of making new stem cells, in a process called "self-renewal". In older people, diseases of the hematopoietic system often occur, such as anemia or certain forms of blood cancer. Such diseases are thought to be caused by an age-associated decline in stem cell self-renewal. However, mouse models housed under highly controlled, pathogen-free conditions, rarely spontaneously develop such age-related diseases.

According to experts, the cause of this age-related loss of function of the hematopoietic system is a chronic low-grade inflammatory condition called inflammaging, that only develops in later life and impairs the function blood stem cells. "However, the question that we wanted to answer was whether inflammation and infections in early life can permanently damage blood stem cells and thus promote aging of the blood system," says Mick Milsom of the German Cancer Research Center and the Stem Cell Institute HI-STEM. "We have therefore carried out time-consuming experiments to determine for how we observe an inhibitory effect on stem cell function following infection and inflammation, and came to the surprising conclusion that we never see any evidence of stem cell recovery, suggesting that this process is long-lasting or perhaps even irreversible."

Mice were challenged several times with a pro-inflammatory substance or bacteria, with four-week intervals between injections. The lack of stem cell recovery between each round of challenge meant that these treatments resulted in an additive inhibitory effect, supporting a model that explains age-associated tissue dysfunction and disease: where separate instances of infection or inflammation can have a cumulative inhibitory effect on stem cell function, even if separated by months or years.

The researchers subsequently identified the cause of the dysfunctional hematopoiesis: Blood stem cells failed to self-renew as they were forced to divide in response to the inflammatory stimuli. The long-term consequence of a lack of self-renewal is that the hematopoietic system becomes exhausted. "This observation in mice contradicts common doctrine: we had previously believed that, after inflammatory challenge, blood stem cells revert into a so-called dormant state that preserves their capacity for self-renewal," says Milsom, explaining this surprising aspect of his work.

Importantly, the inflammation in young mice led to persistent changes in the hematopoietic system resembling age-related changes often found in elderly people. These include anemia and decreased number of cells in the bone marrow. "Inflammation and infection at a young age appear to accelerate the aging of the hematopoietic system," Milsom said, summarizing the findings. "Our next challenge is to explore whether prophylactic anti-inflammatory treatment could delay the development of age-related diseases of the blood system, while still preserving the immune response against pathogens."

\* The Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM) gGmbH was founded in 2008 as a public-private partnership by the DKFZ and the Dietmar Hopp Foundation.

### Publication

Ruzhica Bogeska, et al.: Inflammatory exposure drives long-lived impairment of hematopoietic stem cell self-renewal activity and accelerated aging. CELL Stem Cell 2022, DOI: 10.1016/j.stem.2022.06.012

## Press release

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## Further information

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