How aging changes the blood system in humans and mice

The reservoir of blood stem cells shrinks with age. It becomes increasingly dominated by stem cells that produce immune cells associated with chronic inflammation. Almost all of the 60-year-olds studied show this change. Researchers from the Centre for Genomic Regulation and the Institute for Research in Biomedicine, both in Barcelona, and the German Cancer Research Center (DKFZ) published their findings in the journal Nature. The discovery could help explain the chronic inflammation that occurs with age and makes us more susceptible to disease. It could also help identify early warning signs of unhealthy aging processes long before symptoms appear or blood cancer develops.

A new study in the journal Nature explains how age reshapes the blood system. In both humans and mice, a few stem cells, or "clones", outcompete their neighbours and gradually take over blood production. The blood stem cell reservoir shrinks and becomes dominated by clones which show a preference for producing myeloid cells, immune cells linked to chronic inflammation.

The changes were detectable by age 50 and almost universal by age 60. The authors of the study suspect the loss of clone diversity could help explain 'inflammaging', the persistent chronic inflammation that emerges during ageing and which can make us more vulnerable to disease. The team observed the pattern in both mice and humans, suggesting the findings are a fundamental feature of blood ageing across species.

The work can lead to new strategies which spot early warning signs of unhealthy ageing long before symptoms appear, helping prevent diseases like cancer or immune disorders. It also opens the door to studying the viability of rejuvenation therapies in humans, efforts which have traditionally been the focus of animal research.

"Our blood stem cells compete for survival. In youth, this competition produces a rich, diverse ecosystem while in old age, some drop out entirely. A few stem cells take over, and these work extra hard to compensate. This reduces diversity, which is bad for the blood system's resilience. Diverse stem cells can respond to different stresses, so the dominance of a handful of clones makes the whole system more fragile," says Lars Velten, Centre for Genomic Regulation (CRG) in Barcelona and co-corresponding author of the study.

The scientists had to solve a long-standing technical challenge to make their discovery. In youth, humans have between 50,000 to 200,000 active blood stem cells which create between 100 to 200 billion new blood cells every day.

To solve this problem, the team focused on epimutations. These are epigenetic changes in the chemical tags, also known as methylation marks, attached to DNA. The tags help cells know which genes to switch on or off. When a stem cell divides, methylation marks are copied to its daughter cells, leaving behind a permanent, natural 'barcode' that researchers can 'scan' or read to chart each cell's position in the family tree.

"Our cells carry genetic alterations which collectively make us unique individuals. But we're also a mosaic of epigenetic alterations. Groups of cells, even if they end up doing different jobs, carry shared methylation marks which tie them back to a common ancestor stem cell. We've been finally able to construct the epigenetic family tree by reading information written directly into the DNA of each cell," says Alejo Rodriguez-Fraticelli from IRB Barcelona, co-corresponding author.

The researchers developed a new technique called EPI-Clone which reads methylation barcodes from individual cells They used it to reconstruct the history of blood production in both mice and humans, helping trace which stem cells contributed to making blood, and which had dropped out of the race over time.

"DNA methylation works like a kind of binary code. At each position in the genome, a site is either methylated or not, like a 1 or a 0," explains Michael Scherer, bioinformatician and co-first author of the study who led the work at the CRG and is now at the German Cancer Research Center (DKFZ).

"This simple on-off information can be transformed into a natural barcode, one that each stem cell passes on to its descendants. Five years ago, I wouldn't have thought this possible at single-cell resolution, across tens of thousands of cells. It's been a huge leap forward in technology," Scherer adds.

In young blood, thousands of different stem cells contributed to a rich and diverse pool of red blood cells, white blood cells and platelets. But EPI-Clone revealed that in older mice, up to 70 percent of blood stem cells belonged to just a few dozen large clones, compared with around 50 percent in younger mice.

The picture is similar in humans, though the exact percentage varied between the dozen healthy donors between 35 and 70 years old which formed part of the study. The study found that by age 50, many blood stems cells begin to drop out and larger clones begin to take over, while by age 60 and beyond, the shift becomes even more pronounced. “The change from diversity to dominance isn’t random but clock-like,” says Indranil Singh, co-first author of the study at IRB Barcelona. “By age 50, you can already see it starting, and after 60 it becomes almost inevitable.”

The study also found that some large clones harboured mutations linked to clonal haematopoiesis (CH), a process where some blood stem cells acquire mutations that allow them to grow and multiply faster than others. The phenomenon becomes more common with age and has been shown to increase the risk of heart disease, stroke, and leukaemia. However, many of the dominant clones identified by EPI-Clone had no known mutations at all, suggesting that clonal expansion is a general feature of ageing blood, not just a sign of cancer risk.

The findings mean clinicians could one day assess clonal behaviour itself for early detection, offering doctors a way to monitor how a person’s blood stem cell pool is ageing years before disease develops. People with faster loss of diversity, or rapid expansion of risky clones, could be flagged for preventive care.

The study also observed that in both older humans and mice, many of the dominant clones show a preference for producing myeloid cells. These are immune cells linked to chronic inflammation. Previous studies in mice have shown that selectively removing myeloid-biased stem cells can restore a younger profile of blood stem cells, boosting the production of infection-fighting lymphocytes and improving immune responses.

Such rejuvenation therapies in humans are still a long way off. To achieve this, researchers would first have to identify which clones are problematic – something that has not been possible until now. EPI-Clone is suitable for clinical research because it works with naturally occurring barcodes.

“If we want to go beyond generic anti-aging treatments and achieve true precision medicine against aging, this is exactly the tool we need,” says Lars Velten. ”We can only repair what we can see, and EPI-Clone makes this possible for humans for the first time.” “We have shown what is possible,” summarizes Rodriguez-Fraticelli. ”Now it's about refining EPI-Clone to test appropriate strategies in clinical research."

Publication:

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Further information

- German Cancer Research Center (DKFZ)