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How our blood vessels age from within

To uncover how endothelial cells, the inner linings of blood vessels. change over the course of a lifespan, an international research team led by Laura de Rooij at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences has created the Human Aging Endothelial Cell Atlas, the first comprehensive atlas of vascular aging. By analyzing gene activity data from more than 375,000 human cells across 290 samples and 12 tissues, the scientists reveal that aging affects different parts of the vascular system in distinct ways. The study, published in *Nature Aging* (DOI 10.1038/s43587-026-01247-3), provides new insights into the biological processes underlying vascular aging and a valuable resource for future research into age-related diseases and vascular repair.

With every heartbeat, blood is pumped through a vast network of vessels throughout our body, delivering vital oxygen, nutrients, and other essential substances to even its most remote corners. But these vessels are far more than passive tubes: Their inner walls are covered by a thin layer of specialized cells called endothelial cells, which regulate blood flow, control what passes into surrounding tissues and help coordinate responses to injury. They even contribute to the specific functions of the organs they serve, such as forming a protective barrier in the brain or supporting filtration in the kidneys. Yet, as we grow older, this finely tuned system can become dysfunctional, increasing the susceptibility to cardiovascular disease and its associated mortality.

Although endothelial cells are essential for vascular and organ function, they are often overlooked in studies of aging. As such, what happens inside endothelial cells as we age, and why their function may deteriorate over time, remains poorly understood. This is the question CeMM Principal Investigator Laura de Rooij and her team set out to answer. Rather than studying blood vessels as a whole, they examined the activity of genes in individual endothelial cells. This approach, known as single-cell analysis, makes it possible to see which genes are active in each cell, and how their activity changes with age. By bringing together data from previously published single-cell studies, the team saw an opportunity to take a closer look at these cells and uncover patterns of vascular aging that might otherwise have remained hidden.

Looking for the fingerprints of aging

In their latest study, published in *Nature Aging* (DOI 10.1038/s43587-026-01247-3) and led by first author Sarah Dobner, a PhD student in de Rooij's group, the team brought together data from 34 existing studies, covering more than 375,000 cells from 290 samples across 12 human tissues. By focusing on tissues classified as healthy or non-diseased, they aimed to identify molecular changes associated with aging rather than changes primarily linked to diagnosed disease. The result is the Human Aging Endothelial Cell Atlas, a resource that

allows scientists to examine how different populations of vascular cells change across the human body.

A particularly intriguing observation concerned the cells lining veins. These cells can give rise to sprouts that develop into new blood vessels, an important part of vascular renewal. Yet in older individuals, they showed reduced activity of several genes involved in vessel formation. This could help explain why blood vessels may become less capable of renewing themselves with age, although the study did not directly measure repair capacity. Across multiple tissues, the researchers also observed increased activity of genes associated with inflammation and cellular senescence, a state in which cells stop dividing and can influence their surroundings. “One of the most striking findings was that endothelial aging does not look the same across the vascular system. By bringing together data from different tissues, we could identify patterns that might have been missed by studying individual organs or endothelial cell types in isolation”, Sarah Dobner, first author and PhD Student in Laura De Rooij’s group, explains.

How cells feel the passage of time

Another discovery concerned how endothelial cells respond to their physical environment. These cells constantly sense the forces of flowing blood and the material surrounding them, translating mechanical signals into biological responses. The atlas revealed age-related changes in genes involved in this process. Experiments in human skin provided further evidence: a protein called YAP, which helps cells respond to mechanical forces, was more frequently found inside the nuclei of endothelial cells from older donors. These observations raise an intriguing question: does increased YAP activity help endothelial cells cope with age-related changes, or does it contribute to the deterioration of blood vessel function?

The researchers also identified a group of genes associated with p21, a protein that can slow or stop cell division. Comparisons with laboratory-grown endothelial cells and mouse models of accelerated aging supported a connection to cellular senescence. However, because these genes also participate in stress responses and vessel growth, they cannot reliably distinguish permanently senescent cells from cells responding to other age-associated challenges. Understanding these differences will be essential before scientists can determine which cellular processes should be targeted in future efforts to maintain vascular health.

A map for the future

The Human Aging Endothelial Cell Atlas provides scientists with a new resource for exploring how blood vessels age across different tissues. An accompanying interactive portal described in the study will help researchers investigate these molecular changes and identify promising directions for future experiments. But the findings also come with limitations: the study compared people of different ages rather than following individuals over time, and incomplete information about donors' lifestyles and medical histories limits the conclusions.

Nevertheless, the atlas reveals that vascular aging is neither uniform nor simple. Some changes may contribute to declining function, while others could represent the body's attempts to protect itself. Understanding the difference

will be essential to discovering how we might one day help our blood vessels stay healthy for longer.

“What excites me about this atlas is that it gives us a way to explore vascular aging across the human body, rather than treating all blood vessels as if they age in the same way. We now have a resource to help investigate which changes accompany endothelial aging, which may contribute to declining vascular function, and which could reflect how endothelial cells adapt to their changing environment”, Laura de Rooij concludes, highlighting the broader implications of the study.

Pictures attached
Photo: First author Sarah Dobner (left) and corresponding author Laura De Rooij (right) (© Wolfgang Däuble/CeMM)
Image: New blood vessels sprouting from an artificial vein lined with human endothelial cells. (© Sarah Dobner)

The Study “Uncovering the transcriptional hallmarks of endothelial cell aging via integrated single-cell analysis” was published in Nature Aging on 23 October. DOI: 10.1038/s43587-026-01247-3

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