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Research may reveal why people can suddenly become frail in their 70s

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A groundbreaking theory of ageing that explains why people can suddenly become frail after reaching their 70s has raised the prospect of new therapies for the decline and diseases of old age.



Researchers in Cambridge discovered a process that drives a “catastrophic” change in the composition of blood in older age, increasing the risk of blood cancers and anaemia, and impairing the effectiveness of white blood cells to fight infection.

The scientists believe similar changes occur in organs throughout the body, from the skin to the brain, potentially underpinning why people often age healthily for decades before experiencing a more rapid decline in their 70s and 80s.

“What’s exciting about this work is there may be a common set of processes at work,” said Dr Peter Campbell, a senior author on the study and head of the cancer, ageing and somatic mutation programme at the Sanger Institute in Cambridge. “Ultimately the goal would be slowing or intervening in the ageing process, but at the very least we see an option to use this to measure biological age.”

Ageing is a complex process, but many scientists have suspected that the gradual buildup of mutations in cells gradually degrades the body’s ability to function properly. The latest research suggests that thinking is wrong, or at best incomplete, and places the blame instead on “selfish” cells that rise to dominance in old age.

Working with scientists at the Wellcome-MRC Cambridge Stem Cell Institute, Campbell and his colleagues studied blood cells across the age range from newborns to people in their 70s and 80s. They found that adults under 65 had a wide range of red and white blood cells produced by a diverse population of 20,000 to 200,000 different types of stem cells in their bone marrow.

In the over-65s, the picture was radically different. About half of their blood cells came from a measly 10 or 20 distinct stem cells, dramatically reducing the diversity of the per-

son's blood cells, with consequences for their health.

Writing in the journal *Nature*, the researchers explain that while stem cells involved in making blood gather mutations over time, most of these changes are harmless. But problems arise when rare "driver" mutations make stem cells grow faster, often producing lower-quality blood cells as a trade-off. When a person is in their 30s and 40s, the growth advantage of the aberrant stem cells makes little difference, but at 70 and over these fast-growing cells come to dominate blood cell production.

"The exponential growth explains why there is such a sudden change in frailty after the age of 70, why ageing hits at that sort of age," said Campbell. Faster-growing blood stem cells are linked to blood cancers and anaemia, but also make people less resilient to infections and medical treatments such as chemotherapy.

"What we know about other organ systems is that many of the same observations apply," Campbell added. The researchers now intend to look for the same process in skin to understand why ageing leads to wrinkles and slower wound healing.

Dr Elisa Laurenti, an assistant professor at the Wellcome-MRC Cambridge Stem Cell Institute and joint senior researcher on the study, said chronic inflammation, smoking, infection and chemotherapy could all produce stem cells with cancer-causing mutations.

"We predict that these factors also bring forward the decline in blood stem cell diversity associated with ageing," she said. "It is possible that there are factors that might slow this process down, too. We now have the exciting task of figuring out how these newly discovered mutations affect blood function in the elderly, so we can learn how to minimise disease risk and promote healthy ageing."