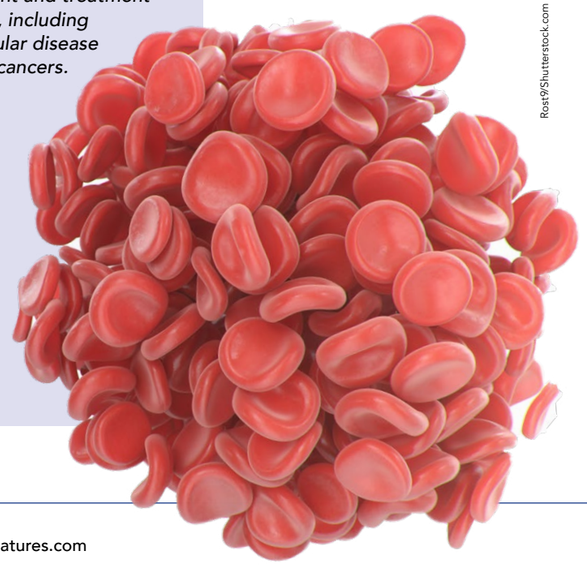
Clonal haematopoiesis

A newly-recognised driver of age-associated disease

Throughout life, blood stem cells produce all blood cells via haematopoiesis. However, sometimes mutations occur in the dividing blood stem cell, causing a substantial proportion of mature blood cells to be derived from a single dominant clone. This 'clonal haematopoiesis' is associated with an increased risk of developing blood disease and cardiovascular disease. Clonal haematopoiesis research often combines multiple disciplines, including cancer biology, cardiovascular disease, and haematology. Professor Kenneth Walsh, School of Medicine at the University of Virginia, USA, and Dr Yoshimitsu Yura, School of Medicine at Nagoya University, Japan, explain that although this area of research is in its infancy, it offers important knowledge about the development and treatment of illnesses, including cardiovascular disease and blood cancers.

Haematopoietic stem cells are found in the bone marrow, where they divide to produce 100 billion new blood cells each day. Multiple rounds of division can sometimes lead to random mutations in the stem cells. Some of these mutations have no effect on the cell, while others will kill the cell. Some mutations may cause preferential production of a specific kind of cell, leading to a large genetically identical population of cells (known as clonal expansion). These cells are also disproportionally increased in the blood, with a single clone often accounting for 2% or more of the blood cells. Clonal expansions in blood cells have been found to occur in relatively healthy individuals who lack overt signs of blood cancer. This pre-cancerous condition has historically been referred to as clonal haematopoiesis. It is sometimes referred to as 'clonal haematopoiesis of indeterminate potential' or 'age-related clonal haematopoiesis' to distinguish it from the clonal expansion of cells that are seen in blood cancers. The pre-cancerous effects of the condition can occur when the clonal population of cells contains mutations in genes that are associated with blood cancers, such as *TET2*, *DNMT3A*, and *ASXL1*. Clonal haematopoiesis is related to ageing, with around half of people over 85 years being affected.



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CLONAL HAEMATOPOIESIS AND HEART DISEASE

People with clonal haematopoiesis are more likely to have atherosclerosis, a build-up of fats, cholesterol, or other substances on the walls of blood vessels (arteries) in the body. This is similar to the effects of high blood pressure or diabetes. In many cases, clonal haematopoiesis is silent, causing no health concerns. However, the condition has been shown to roughly double the risk of developing heart disease or experiencing a stroke, as well as increasing the chance of blood cancers such as leukaemia.

Professor Kenneth Walsh at the School of Medicine, University of Virginia, revealed that mice with clonal haematopoiesis accumulated more plaque in their vessels compared to mice without, suggesting that this could be the reason people are more likely to experience heart-related illness with the condition. His study revealed a potential mechanism through which clonal haematopoiesis may block arteries in the body, causing obstructions that are the underlying cause of heart attacks and strokes. Interestingly, this may be the missing link researchers have been looking for; some people who have heart attacks or strokes do not present with any typical risk factors. Clonal haematopoiesis acts independently from these risk factors to drive the development and progression of cardiovascular disease. Cardiovascular disease is the most common cause of death worldwide, accounting for around a third of all deaths. Therefore, identifying hidden risk factors of the disease may help reduce the burden of the disease.

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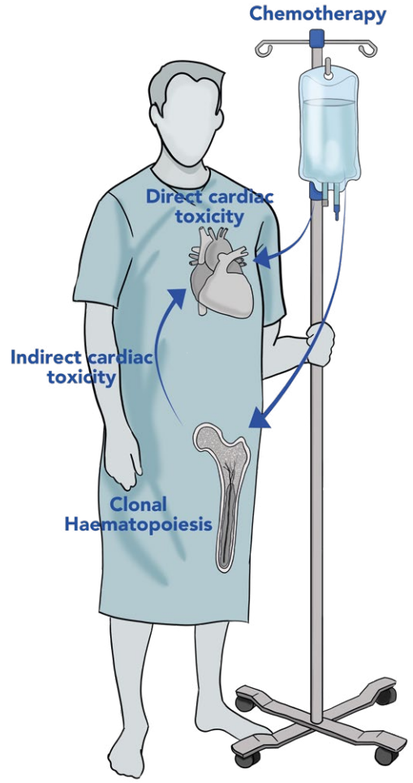
Individuals with clonal haematopoiesis are more likely to have atherosclerosis.



CLONAL HAEMATOPOIESIS IN CANCER PATIENTS

Walsh explains that there is another condition that is distinct from age-related clonal haematopoiesis. Therapy-associated clonal haematopoiesis occurs in some individuals who have undergone cancer treatment – treatments such as chemotherapy target rapidly dividing cells by inducing DNA damage causing cell death. However, cells with mutations in some of the DNA damage-response genes may have a growth advantage by gaining resistance to this treatment. This form of clonal haematopoiesis may also contribute to the high prevalence of cardiovascular disease in patients who have undergone cancer therapies.

Patients with cancer display increased medium- to long-term risk for cardiovascular disease. Notably, the mortality due to cardiovascular disease in this population is typically greater than that of cancer itself after a ten-year follow-up. Therefore, given the recent proliferation of new cancer therapies and the longer survival of cancer patients, there is an increasing need to identify the molecular mechanisms that contribute to the cardiovascular disease observed in these patients.

Walsh and his colleague Dr Yoshimitsu Yura, School of Medicine at Nagoya University, carried out bone marrow transplants in mice to assess the hypothesis that therapy-associated

Clonal haematopoiesis is related to ageing, with around half of people over 85 years being affected.

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Walsh has found a potential mechanism through which clonal haematopoiesis may block arteries in the body, causing obstructions that are the underlying cause of heart attacks and strokes.

clonal haematopoiesis might have a causal role in cardiovascular disease development. They replaced some of the mouse's normal blood stem cells with cells that carry faulty versions of the genes involved in DNA damage response. The mice were then treated with a hypertensive drug to mimic one of the risk factors associated with cardiovascular disease.

The mice with experimental clonal haematopoiesis showed worse cardiac function than the mice without, suggesting that this could be the reason people are more likely to experience heart-related illness with therapy-associated clonal haematopoiesis.

more pro-inflammatory cytokine than normal. In particular, they produced higher levels of a cell-signalling molecule called interleukin-1ß. This means that targeting interleukin-1ß could be a possible therapeutic target for preventing heart disease in cancer survivors who exhibit clonal haematopoiesis. These findings provide precedence for the concept that therapy-associated clonal haematopoiesis can contribute to the development of cardiovascular disease in cancer patients and cancer survivors who have undergone therapy with genotoxic agents.

Clonal haematopoiesis mutations are generally acquired rather than inherited.

The condition has been shown to roughly double the risk of developing heart disease or experience a stroke.

Macrophages are cells that are best known for their role in surrounding and engulfing dead or infected cells. However, they can also drive the development of cardiovascular disease by becoming attached to arteries and promoting inflammation. The researchers found that the cells with a mutation in DNA damage-response genes produce

There is little patients can do to prevent the occurrence of clonal haematopoiesis. However, blood tests are available that can measure the level of clonal haematopoiesis a person has if they wish to understand more about their increased risk of developing health issues later in life. This may encourage individuals to reduce their risk in other ways, such as stopping smoking and adhering to a healthy lifestyle.

Understanding more about the accumulation of mutated blood cells can lead to more effective treatments to protect the cardiovascular system, especially age-related illness or cancer-therapy related cardiovascular disease. Understanding these mechanistic pathways will provide the opportunity to develop precision or personalised approaches to medicine that could be tailored to a specific blood-cell clone in an individual. Walsh and Yura are also involved in studies with human subjects to understand more about clonal haematopoiesis in elderly individuals who have lived long and healthy lives without the increased risk of cardiovascular disease or cancer, to understand what has allowed their bodies to cope with this process.

Behind the Research

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Research Objectives

Kenneth Walsh's research focuses on the field of clonal haematopoiesis – the mechanisms that give rise to clonal expansions in haematopoietic cells – and the health consequences of these events.

Detail

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Bio

Kenneth Walsh received his PhD in biochemistry from the University of California at Berkeley and post-doctoral training at the Massachusetts Institute of Technology. He is the Lockhart B McGuire Professor in the Department of Medicine, University of Virginia. His current work focuses on the roles of clonal haematopoiesis in cardio-metabolic disease and other age-related disorders.

Yoshimitsu Yura received his MD and PhD in medicine from Nagoya University and post-doctoral training at the University of Virginia. Currently, he is assistant professor at Nagoya University Hospital. He investigates the role of clonal haematopoiesis on development of cardiovascular disease and the underlying molecular mechanisms.

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References

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Personal Response

Do you think we can prevent or treat clonal haematopoiesis, or should we be focusing on ways to manage the risks associated with the condition?

"Currently, there is no known way to prevent or treat clonal haematopoiesis. Defining the molecular mechanisms underlying clonal haematopoiesis will thus provide a framework to develop interventions for healthy ageing and disease treatment."

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