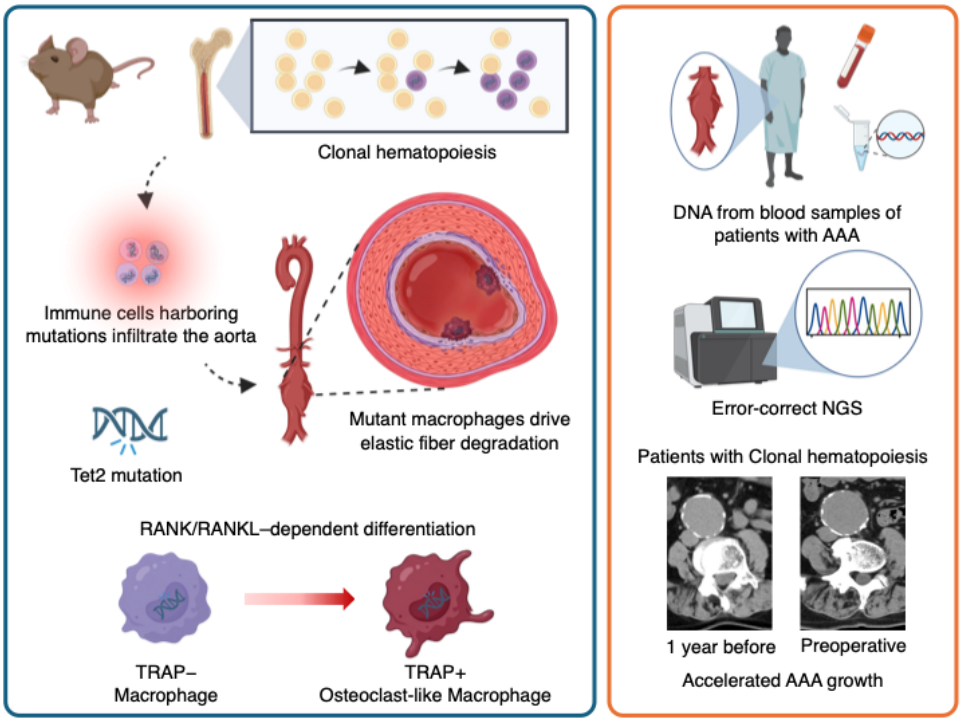
News Release

Tet2-driven Clonal hematopoiesis drives aortic aneurysm via macrophage-to-osteoclast-like differentiation



Key Points

•Age-related clonal hematopoiesis accelerates the progression of abdominal aortic aneurysm.

•Animal studies revealed that macrophages carrying Tet2 mutations differentiate into osteoclast-like cells, which degrade elastin in the aortic wall and promote aneurysm progression.

•Genetic and pharmacological inhibition of the RANK–RANKL signaling pathway suppressed aneurysm development, suggesting a potential medical treatment strategy for abdominal aortic aneurysm.

Summary

A collaborative research team consisting of Jun Yonekawa, a graduate student (first author) in the Department of Cardiology, Nagoya University Graduate School of Medicine; Yoshimitsu Yura, a Clinical Assistant Professor in the Department of Cardiology, Nagoya University Hospital (also affiliated with the Institute for Advanced Research) (corresponding author); Mikito Takefuji, Lecturer; Toyoaki Murohara, Professor in the Department of Cardiology, Nagoya University Graduate School of Medicine; and Hiroshi Banno, Professor of

Vascular Surgery, conducted a study focusing on clonal hematopoiesis—an age-related change in blood that has recently attracted attention—with the aim of developing medical therapies for abdominal aortic aneurysm (AAA).

AAA is a serious condition in which the aorta becomes abnormally dilated, and rupture can result in sudden death. Currently, there are no effective drug treatments to halt aneurysm progression, and surgical repair remains the only definitive therapy once the aneurysm reaches a certain size. Therefore, there is a strong need for the development of medical treatments that can suppress aneurysm growth.

In recent years, clonal hematopoiesis—caused by the accumulation of genetic mutations in blood-forming stem cells with aging, leading to the expansion of mutated blood cell clones—has emerged as a novel risk factor for cardiovascular diseases. In this study, researchers investigated how clonal hematopoiesis contributes to the progression of AAA.

Genetic analysis of blood-derived DNA from patients scheduled for AAA surgery revealed that individuals with clonal hematopoiesis exhibited significantly faster aneurysm growth. Furthermore, animal experiments demonstrated that macrophages carrying mutations in the Tet2 gene acquired osteoclast-like properties and degraded elastin, a key component responsible for maintaining vascular elasticity, thereby accelerating aneurysm progression. This study thus uncovered a previously unrecognized pathological mechanism linking clonal hematopoiesis to vascular destruction.

The researchers also showed that genetic or pharmacological inhibition of the RANK–RANKL signaling pathway, which regulates this differentiation process, effectively suppressed aneurysm progression.

These findings highlight a new perspective on AAA pathophysiology, emphasizing age-related changes in blood cells in addition to vascular structural abnormalities, and suggest promising avenues for the development of medical therapies.

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Research Background

AAA is a major age-related vascular disease in which the aorta gradually

enlarges and may rupture, often resulting in sudden death. Currently, there are no effective drug therapies to prevent aneurysm progression, and surgical intervention remains the only curative treatment once the aneurysm reaches a critical size. This situation contrasts sharply with ischemic heart disease, where advances in pharmacological therapies and catheter-based interventions have dramatically improved patient outcomes.

Although aneurysm diameter and morphological features are used to assess the risk of expansion and rupture, few additional clinical indicators are available, highlighting the need for deeper mechanistic understanding and improved risk stratification. Pathologically, AAA is characterized by degeneration of the extracellular matrix, loss of vascular smooth muscle cells, and infiltration of immune cells in the aortic wall. However, the mechanisms driving these pathological changes remain incompletely understood.

In recent years, clonal hematopoiesis—an age-associated condition in which blood-forming stem cells acquire genetic mutations leading to the expansion of specific blood cell populations—has emerged as a key contributor to multiple age-related diseases. By altering immune cell function and promoting chronic inflammation, clonal hematopoiesis has been linked not only to cardiovascular disease but also to osteoporosis, chronic obstructive pulmonary disease, and chronic liver disease.

Despite these findings, the role of clonal hematopoiesis in the development and progression of AAA has remained unclear. Against this background, the present study aimed to elucidate the pathological significance of clonal hematopoiesis in AAA progression.

Research Results

The researchers first conducted a clinical study to examine the relationship between clonal hematopoiesis and AAA in patients scheduled for aneurysm surgery. Genetic analysis of peripheral blood DNA combined with retrospective clinical data revealed that approximately 60% of patients exhibited clonal hematopoiesis. Importantly, patients with clonal hematopoiesis showed a significantly faster rate of aneurysm expansion.

To establish a causal link, the team next performed animal experiments using a mouse model of clonal hematopoiesis driven by Tet2 mutations. These mice exhibited accelerated aneurysm progression and greater increases in aortic diameter compared with control animals. Histological analysis demonstrated pronounced thinning and fragmentation of elastin in the aortic wall, along with marked infiltration of macrophages and degeneration of surrounding vascular smooth muscle cells.

Further mechanistic studies revealed that, in the clonal hematopoiesis model,

macrophages were more likely to differentiate into osteoclast-like cells that possess tissue-degrading properties. These osteoclast-like cells produced enzymes such as MMP-9, which break down the extracellular matrix and elastin in the aortic wall, thereby promoting aneurysm progression.

Finally, targeting the RANK–RANKL signaling pathway involved in this differentiation process effectively suppressed aneurysm development. Both genetic interventions and pharmacological treatments—including anti-RANKL antibodies and the widely used osteoporosis drug alendronate—significantly reduced clonal hematopoiesis–driven aneurysm progression.

Research Summary and Future Perspective

The findings of this study suggest that, in patients with AAA, risk stratification may be improved by incorporating clonal hematopoiesis as a novel biological marker in addition to conventional indicators such as aneurysm size and morphology.

In the future, patients identified as having clonal hematopoiesis may benefit from more tailored follow-up strategies, including optimized surveillance intervals and intensive lifestyle interventions such as strict smoking cessation guidance. Furthermore, these insights pave the way toward the development of targeted medical therapies aimed at slowing aneurysm progression in high-risk individuals.

Publication

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Authors：Jun Yonekawa[1], Yoshimitsu Yura[1], Junmiao Luo[1], Katsuhiro Kato[1], Shuta Ikeda[2], Yohei Kawai[2,3], Tomoki Hattori[1], Ryotaro Okamoto[1], Mari Kizuki[1], Emiri Miura-Yura[4], Keita Horitani[5], Kyung-Duk Min[6], Takuo Emoto[7], Hiroshi Banno[2], Mikito Takefuji[1], Kenneth Walsh[8], Toyoaki Murohara[1]

1. Department of Cardiology, Nagoya University School of Medicine, Nagoya, Japan
2. Division of Vascular and Endovascular Surgery, Department of Surgery, Nagoya University Hospital, Nagoya, Japan
3. Department of Vascular Surgery, Aichi Medical University, Nagakute, Japan.
4. Division of Diabetes, Department of Internal Medicine, Aichi Medical University School of Medicine, Nagakute, Japan.
5. Department of Medicine II, Kansai Medical University, Osaka, Japan

6. Department of Cardiovascular and Renal Medicine, Hyogo Medical University, Hyogo, Japan.
7. Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
8. Division of Cardiovascular Medicine, Robert M. Berne Cardiovascular Research Center, University of Virginia School of Medicine, Charlottesville, VA, United States

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