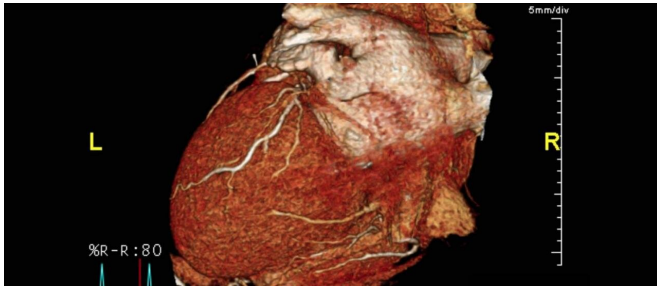


Anti-inflammatory therapies have potential to prevent heart disease in the elderly

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Credit: Columbia University

Therapies that soothe inflammation could be an effective way to prevent heart disease in people with a common age-related blood condition, according to a new study from researchers at Columbia University Vagelos College of Physicians and Surgeons.

The researchers identified how the [blood](#) condition, called clonal hematopoiesis, worsens atherosclerosis, and their findings suggest that an anti-inflammatory drug previously tested in a wider population of people with cardiovascular disease may have potential if used only in those with clonal hematopoiesis.

"The main message from our research is that anti-inflammatory therapies for atherosclerotic [heart disease](#) may be particularly effective in patients with clonal hematopoiesis," says Alan Tall, MD, the Tilden Weger Bieler Professor of Medicine, the study's co-senior author with Nan Wang, MD, associate professor of medical sciences (in medicine).

Their study was published online March 17 in *Nature*.

Aging contributes to heart disease

Although great strides have been made in reducing atherosclerotic heart disease with therapies such as statins that reduce cholesterol, many people still have increased disease despite these current treatments.

"Over the years, researchers have learned that the aging process itself is a major contributor to cardiovascular disease," says Trevor P. Fidler, Ph.D., associate research scientist in medicine, the study's first author. "But how aging itself can lead to heart disease—and how it could be prevented—is not well understood."

Common blood condition increases heart disease

In the new study, the researchers took a close look at a common blood condition, called clonal hematopoiesis, that is associated with aging.

Clonal hematopoiesis is thought to occur in roughly 10% of people over age 70, and most people have no symptoms. But researchers recently realized that the condition—for unknown reasons—raises the risk of heart disease by 40%.

Clonal hematopoiesis occurs when hematopoietic (blood) stem cells acquire mutations. As people age, each [hematopoietic stem cell](#) acquires genetic mutations, though most of these mutations have no impact. But in clonal hematopoiesis, some mutations supercharge the stem cell so that it produces a greater number of blood cells compared with other [stem cells](#).

Study of mice reveals source of extra heart risk

Clonal hematopoiesis usually arises when one of four specific genes is mutated. The Columbia team looked specifically at JAK2, which imparts the strongest risk of premature coronary artery [disease](#).

In atherosclerosis, white blood cells called macrophages accumulate in plaques and proliferate as the plaque grows.

Provided by Columbia University

In studies of mice, the researchers found that the JAK2 mutations led to a number of changes in macrophages that increased macrophage proliferation, increased inflammation in the atherosclerotic plaques, and enhanced the plaque's necrotic core.

"We know in humans that such regions are associated with unstable plaques, which can rupture, causing [heart](#) attacks or strokes," Fidler says.

The researchers also traced the molecular mechanisms that led to these changes, including increased activation of the AIM2 inflammasome, a complex of proteins that induces inflammation.

Targeting inflammasome may reduce cardiovascular risk

Inhibiting various components of the inflammasome improved the stability of the plaques, as did inhibition of IL-1 β , a product of the inflammasome.

Though an IL-1 β inhibitor called canakinumab reduced cardiovascular events in a clinical trial, the drug was associated with a small risk of infection and has not been marketed to reduce [cardiovascular disease](#).

"If instead we take a precision medicine approach and only use canakinumab to treat patients with JAK-driven clonal hematopoiesis," Fidler says, "we may increase the cardiovascular benefit. Even if infection risk remains unchanged, we may provide an overall benefit to this specific population."

The study is titled "The Aim2 inflammasome exacerbates atherosclerosis in clonal hematopoiesis."

More information: Trevor P. Fidler et al. The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis, *Nature* (2021). [DOI: 10.1038/s41586-021-03341-5](#)

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