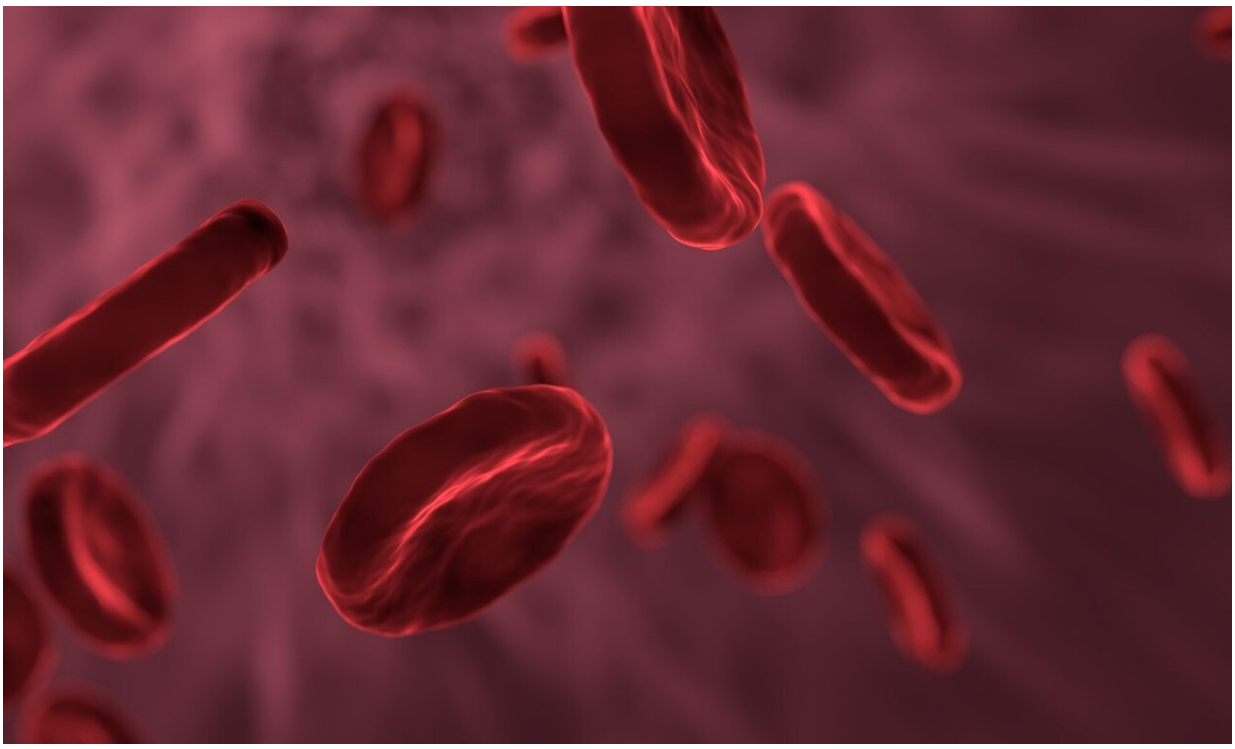
Atherosclerosis can accelerate the development of clonal hematopoiesis, study finds

February 26 2021



Credit: CC0 Public Domain

Billions of peripheral white blood cells are produced every day by the regular divisions of hematopoietic stem cells and their descendants in the bone marrow. Under normal circumstances, thousands of stem cells

contribute progeny to the blood at any given time, making white blood cells a group with diverse ancestry.

Clonal hematopoiesis is a common age-related condition in which the descendants of one of these hematopoietic stem cells begin to dominate substantial portions of the blood. Genome-wide analyses have determined that clonal hematopoiesis is frequently driven by recurrent genetic alterations that confer a competitive advantage to specific hematopoietic stem cells, thus giving them the ability to expand disproportionately.

Multiple independent studies have shown that clonal hematopoiesis often goes hand in hand with atherosclerosis and cardiovascular disease. Since its discovery, this surprising association has been the subject of intense interest from clinicians and researchers alike.

Cardiovascular disease is the main cause of morbidity and mortality in Western countries and represents a massive public health burden. Do clonal expansions in the blood contribute to the progression of atherosclerosis, and if so, how?

Subsequent work showed that indeed, atherosclerotic plaque formation can be exacerbated by immune cells with clonal hematopoiesis-related mutations, thus raising the question whether clonal expansions in the blood should be targeted therapeutically for the prevention of cardiovascular disease.

In a new study published in *Cell*, researchers at Massachusetts General Hospital and Harvard Medical School now suggest a different, additional possibility: Atherosclerosis causes clonal hematopoiesis. Patients with atherosclerosis suffer from hyperlipidemia and inflammation, two conditions that are known to chronically boost hematopoietic stem cell division rates. In the new study, the researchers now demonstrate that

this increased division accelerates the development of clonal hematopoiesis.

Kamila Naxerova, Ph.D., a principal investigator in MGH's Center for Systems Biology and senior author of the study, says: "Patients with atherosclerosis essentially experience 'accelerated time.' This is because the speed with which genetic alterations arise and spread through the hematopoietic system is determined by the underlying rate of stem cell division. From a genetic point of view, you could say that atherosclerosis accelerates aging of the blood. Since clonal hematopoiesis is an age-related condition, atherosclerosis patients are prone to developing it earlier than healthy individuals," says Naxerova, who is also an assistant professor of Radiology at Harvard Medical School.

Naxerova says that her team's findings may potentially be good news for patients with clonal hematopoiesis: "There is no doubt that more research is needed to carefully dissect the connection between clonal hematopoiesis and cardiovascular disease. But our results indicate that clonal hematopoiesis might in some cases only be a relatively harmless sign of an overactive hematopoietic system, and not a danger in itself."

"What makes this study unique is that the interdisciplinary team incorporated mathematical modeling to discover a new paradigm in the atherosclerosis field and further elucidated the interplay between cardiovascular disease and clonal hematopoiesis," says Michelle Olive, Ph.D., Program Officer in the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, part of the National Institutes of Health.

More information: Alexander Heyde et al, Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis, *Cell* (2021). DOI: 10.1016/j.cell.2021.01.049

Provided by Massachusetts General Hospital