Changes in Peripheral Blood Cells Linked to Increased CHD

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Genetic mutations in peripheral blood cells might be a contributing cause of coronary heart disease (CHD) and atherosclerosis, especially in older people, new research suggests.

In the study, the presence of clonal hematopoiesis of indeterminate potential (CHIP) — defined as an expanded somatic blood-cell clone in persons without other hematologic abnormalities — was associated with nearly a doubling in the risk for CHD in humans and with accelerated atherosclerosis in mice.

CHIP is common in older people and is known to be associated with an increased risk for hematologic malignancies, the authors, led by Siddhartha Jaiswal, MD, PhD, Brigham and Women's Hospital, Boston, Massachusetts, write.

The authors conclude their new data "support the hypothesis that somatic mutations in hematopoietic cells contribute to the development of human atherosclerosis. We propose that clonal hematopoiesis may be a modifiable risk factor, perhaps through the use of cholesterol-lowering medications or targeting of specific inflammatory pathways."

The findings were published June 21 in *The New England Journal of Medicine*.

CHIP is rare in people younger than 40 years of age but becomes more common over time, with more than 10% of those older than age 70 years carrying the mutation. These carriers have 10 times the risk for a hematologic cancer compared with noncarriers.

In earlier work, Dr Jaiswal and colleagues found that people with CHIP were at increased risk for death from any cause and also, to their surprise, for CHD.

In the current study, they tested the hypothesis that CHIP contributes causally to atherosclerotic cardiovascular disease. They used whole-exome sequencing to detect CHIP in peripheral blood cells and then linked that presence with CHD among participants of four case-control studies, for a total of 4726 patients with CHD and 3529 controls.

In two nested case-control studies, they found that the CHIP carriers had a risk for incident CHD that was 1.9 times as great as that in noncarriers (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.4 - 2.7; $P < .001$).

In two retrospective case-control studies, they found that CHIP carriers had a risk for early-onset myocardial infarction (MI) that was 4 times as great as that in noncarriers (OR, 4.0; 95% CI, 2.4 - 6.7; $P < .001$).

Once the researchers established a correlation between CHIP and CHD, they then assessed causality experimentally in atherosclerosis-prone mice.

They irradiated the mice to remove their blood cells and then gave them mutated blood cells that contained the *Tet2* mutation via a bone marrow transplant.

The *Tet2*-mutated gene was selected because it is the second most commonly mutated gene in CHIP and has been linked to heart disease risk, regardless of age.

The experiment showed that the mice that received the *Tet2* mutation had larger atherosclerotic lesions in the aortic root and aorta than the control mice. In addition, analyses of macrophages from the *Te2* mice showed elevated expression of several chemokine and cytokine genes that contribute to atherosclerosis.

Interestingly, publication of the paper coincided last week with release of positive topline results of the CANTOS trial, showing that a monoclonal antibody, canakinumab (*Ilaris*, Novartis), given on top of standard care, significantly reduced the risk for a composite of cardiovascular death, nonfatal MI, and nonfatal stroke in patients with prior MI and elevated C-reactive protein.

Canakinumab, which is already approved for subcutaneous use in rare autoimmune diseases, works by targeting interleukin-1β (IL-1β), a key cytokine in the inflammatory pathway.

"It really is a complete coincidence that this paper came out last night and this morning the IL-1β drug has worked in a clinical trial and that raises the hypothesis that this subset of patients who might have this blood cell

mutation might preferentially benefit from the IL-1β therapy," said Sekar Kathiresan, MD, also at Massachusetts General Hospital, Boston, and a coauthor on the current paper, in an interview on June 22.

Canakinumab was tested in CANTOS at three different doses in combination with standard care in 10,061 patients with a prior MI and a high-sensitivity C-reactive protein level of 2 mg/L or greater. The primary endpoint was time to first occurrence of MACE, a composite of cardiovascular death, nonfatal MI, and nonfatal stroke.

The full results are expected to be presented later this summer at the European Society of Cardiology Congress, and plans are for the company to begin talks with regulatory agencies, a Novartis spokesperson said.

"We need to look at the final results, but if they hold up to further scrutiny, it would be a major advance," Dr Kathiresan said.

No Longer "Indeterminate"

This work and that of others support the hypothesis that "CHIP is linked to the clinical events of atherosclerosis and that certain CHIP driver genes are involved in regulating inflammation," writes John F. Keaney Jr, MD, chief of cardiovascular medicine, University of Massachusetts Medical School, Worcester, in an accompanying editorial.

"The strongest risk factor for atherosclerosis is age. It's much stronger than anything else," Dr Keaney told *Medscape Medical News*.

"In the past, people have explained it's because when you are older, you've had a longer time of high blood pressure, high cholesterol, and so on," he said. "But when we test for that and see if all of those things explain the effect of age, we find that age itself has something about it that contributes to atherosclerosis."

It's been difficult, then, to explain why aging appears to have its own effect, he added. "This is one of two recent papers that suggest that things that might give you cancer can also give you heart disease."

However, Dr Keaney cautioned that the study is very preliminary.

"There are 74 genes that are linked to this process called CHIP. They only tested one of them in this study. We don't know if all of the others work the same way. As you get older, any one of your genes can get mutated," Dr Keaney said.

"But the main take-home from the study is that the genetic mutations that are going on in cancer might be contributing to the age effect for heart disease," he said.

"CHIP stands for clonal hematopoiesis of indeterminate potential, meaning that we don't know what it causes," he pointed out. "But now, we have several pieces of evidence that it promotes atherosclerosis and heart disease, so it no longer has indeterminate potential, at least as far as cardiovascular disease is concerned. 'Indeterminate' may not be such a good name anymore."

The study was funded by the National Institutes of Health, the Edward P. Evans Foundation, the Leukemia and Lymphoma Society, and others. Dr Jaiswal reports a patent related to a method of identifying and treating a person with a predisposition to or having a cardiometabolic disease. Dr Keaney has disclosed no relevant financial relationships.

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