Unlocking the mysteries of a heart disease trigger

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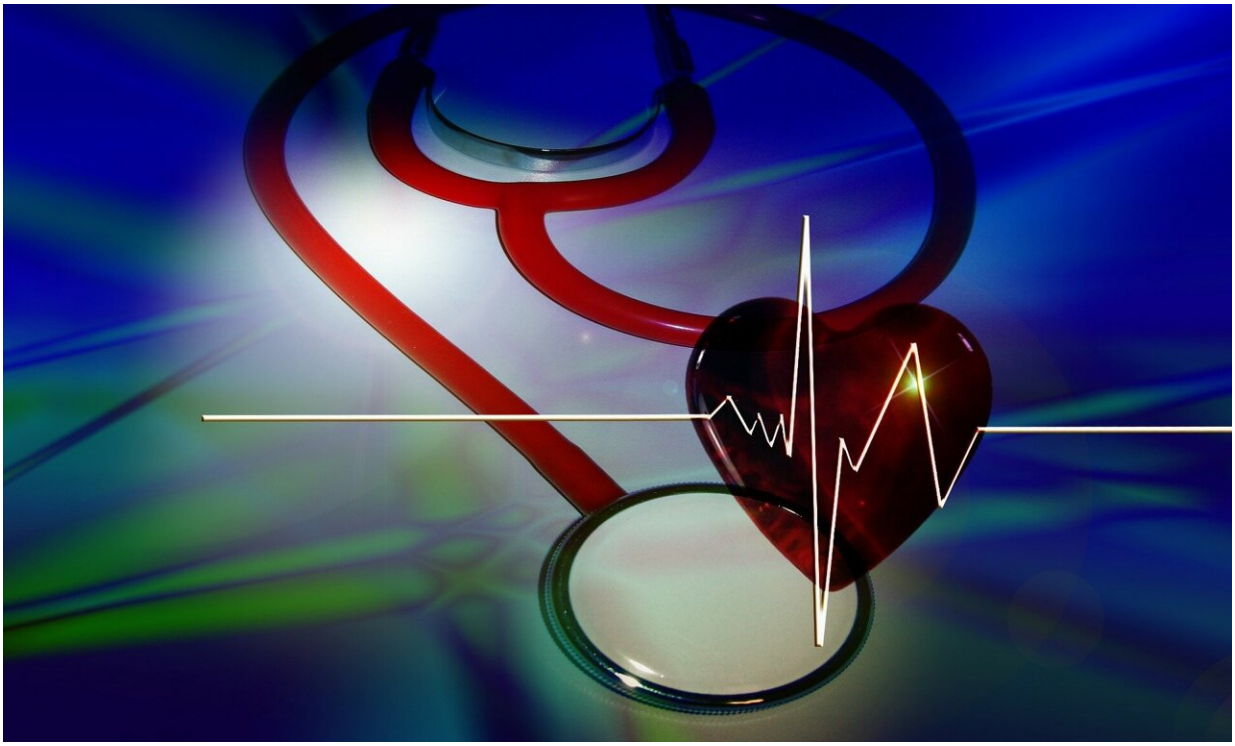

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As the body ages, it is normal for changes in cells to occur.

"Cells divide every day and mutations happen," said Emma M. Groarke, M.D., an attending hematologist and researcher in NHLBI's Hematopoiesis and Bone Marrow Failure Laboratory. "Most of the time

they don't have any effect."

Yet, for some people, mutations in blood-forming cells can multiply and lead to something called clonal hematopoiesis. For a small subgroup of those who have it, this can significantly increase risks for developing heart disease, blood cancer, and other conditions.

Clonal hematopoiesis mostly affects the elderly—about 10–20% of adults ages 70 and older have it while younger adults rarely do. These mutations are often not detected through traditional physical exams, and many people who have them do not experience complications.

"Many of these mutations are low-risk," said Groarke. "A lot of times they just happen naturally with age, and most people remain healthy."

So how do doctors identify the people with high-risk mutations? And how do they create personalized therapies to modify those risks and track conditions associated with clonal hematopoiesis? These are questions NIH-supported researchers have been studying and seek to answer.

Here is what they know so far:

Few people have high-risk mutations, but for those who do the risks are especially high

People can have different types of clonal hematopoiesis. When leukemia-like mutations occur in at least 2% of blood-forming cells and without underlying blood conditions, it's called clonal hematopoiesis of indeterminate potential (CHIP). When unexplained blood conditions or abnormal blood cell counts are present, it is called clonal cytopenia of unknown significance (CCUS).

Researchers have discovered that when it comes to heart disease and blood cancers, only a tiny fraction of adults with CHIP and CCUS face increased risks. But for high-risk adults, the risks are strikingly high.

Investigators using data from the Atherosclerosis Risk in Communities (ARIC) study found that most adults ages 70 and older with clonal hematopoiesis—about 60%—had low-risk mutations and no additional risks for cardiovascular disease.

These findings are published in *JAMA Network Open*. Significantly, however, the 6% of adults with high-risk mutations had a nearly three-times increased risk for having a fatal heart attack or stroke.

A tool can help calculate risks

To help identify adults who have increased risks for developing cardiovascular disease or cancer, researchers use a clonal hematopoiesis risk calculator. To determine a person's risk, they can input multiple factors, including the type of mutation someone has, how many mutations they have, the proportion of cells with mutations, and other variables, such as age and blood cell counts.

Adults with high-risk mutations and increased risks for heart disease can then work with a physician to help offset those risks, such as by taking steps to prevent the disease from developing or by considering secondary approaches, such as statin therapy.

However, Pradeep Natarajan, M.D., the director of preventive cardiology at Massachusetts General Hospital and an associate professor of medicine at Harvard Medical School, noted that even with these steps the inflammation driving cardiovascular risks is still there. This is why he and others have been studying how to inhibit or quell inflammatory pathways linked to specific mutations. This approach is similar to

personalizing cancer therapy.

"We are all trying to be oncologists," said Natarajan. "Where there are great examples of drivers of disease, we are trying to target those drivers."

Clinical trials for treatment are launching

As researchers improve their understanding of clonal hematopoiesis, they are supporting clinical trials to identify new treatments.

Two new studies, including a Phase I and Phase II trial, are investigating whether altering inflammatory pathways among adults with heart disease who have TET2 CHIP mutations (which are often linked to heart disease) may improve outcomes. The Phase I study is testing the benefits of inhibiting the NLRP3 pathway, while the Phase II study is assessing the outcomes of altering IL-6 and IL-18 pathways in adults with DNMT3A and TET2 CHIP mutations.

A sub-analysis of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) had previously found that an antibody used to block the inflammatory pathway IL-1β significantly reduced risks for cardiovascular events, including heart attack and stroke, among adults with TET2 CHIP mutations who had heart disease. Yet, more research is needed to validate these findings. Researchers are also studying ways to update therapies to target JAK2 mutations to offset cardiovascular risks.

"We went from not even knowing the condition existed 10 years ago to testing therapies," said Alexander G. Bick, M.D., Ph.D., an assistant professor of medicine at Vanderbilt University Medical Center. "That's an example of how quickly precision medicine is moving."

Clonal hematopoiesis research is advancing new scientific frontiers

As therapeutic research advances, teams of specialists, including geneticists, hematologists, cardiologists, and oncologists, have established clonal hematopoiesis clinics to help adults with high-risk mutations navigate their care.

"We don't want to tell people they have a disease that isn't really a disease," said Groarke. "Rather, we want to select the patients who are at risk and follow them more closely."

Groarke is leading a 10-year natural history study to assess how clonal hematopoiesis may influence other facets of health and disease. This includes studying links to metabolic conditions, infections, vitamin levels, and chronic lung and liver disease. Researchers are also studying instances, such as with telomere disorders, where these mutations may thrive.

Additionally, other investigators have launched trials to study how clonal hematopoiesis may coexist with or enhance risks for conditions like heart failure, pulmonary embolisms, and lupus. Surprisingly, investigators found that CHIP is associated with a reduced incidence of Alzheimer's disease.

"CHIP causes inflammation, which causes coronary artery disease and heart failure and contributes to strokes, but in Alzheimer's it is something completely different," said Bick. He explained that with Alzheimer's disease, the mutated cells seem to clear out instead of fuel the growth of inflammatory plaque. "It's an example of how these somatic mutations are opening up a window to biology that we didn't even know existed."

"Clonal hematopoiesis is just the tip of the iceberg," said Natarajan. Researchers are working to better detect and prevent other diseases through an NIH consortium that's studying additional types of acquired mutations throughout the body.

"It will be a new frontier for understanding not just the genome we're born with, but the genome that each and every cell in our body has (that can occur over time)," added Bick.

More information: Seyedmohammad Saadatagah et al, Clonal Hematopoiesis Risk Score and All-Cause and Cardiovascular Mortality in Older Adults, *JAMA Network Open* (2024). DOI: 10.1001/jamanetworkopen.2023.51927

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