Nature Medicine: CNIC scientists discover a new cardiovascular risk factor and identify a drug able to reduce its effects

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Two studies carried out at the CNIC provide key information about a newly identified cardiovascular risk factor, clonal hematopoiesis, and its treatment with the ancient medication colchicine

To the known **risk factors for cardiovascular disease**—high blood pressure, high cholesterol, diabetes, overweight and obesity, smoking, and physical inactivity—a new one has to be added: **clonal hematopoiesis**. This condition is triggered by acquired mutations in blood stem cells and was already known to be associated with an elevated cardiovascular risk. However, until now it was uncertain if clonal hematopoiesis was a cause or consequence of cardiovascular disease. Now, a new study published in ***Nature Medicine*** and carried out by researchers at the **Centro Nacional de Investigaciones Cardiovasculares (CNIC)** resolves this critical debate by establishing clonal hematopoiesis as a new risk factor for atherosclerosis—the formation of lesions in the arterial wall that underlies most cardiovascular disorders. In a second study, published in the ***European Heart Journal***, the CNIC scientists propose the ancient medication colchicine as the central plank of personalized strategies to alleviate the effects of clonal hematopoiesis associated with acquired mutations in the *TET2* gene. The results of these important studies will be presented today at the **European Society of Cardiology meeting** in London, UK.

Acquired mutations in blood cell lineages: a new cause of atherosclerosis

An adult person produces hundreds of thousands of blood cells every day. This high rate of cell division unavoidably entails the accumulation of DNA mutations in the dividing cells. These mutations are known as somatic mutations, and are acquired, not inherited. “Although most somatic mutations are innocuous, some give the affected cells a competitive advantage that allows them to expand and progressively accumulate, generating clonal populations of mutated blood cells, a phenomenon known as clonal haematopoiesis,” explained **José Javier Fuster**, who led the *Nature Medicine* study, for which it has received support from Fundación “la Caixa”.

These mutations had already been proposed as a possible risk factor for cardiovascular disease; however, the exact nature of the relationship had remained unclear. As Dr. José Javier Fuster, coordinator of the CNIC “Novel Mechanisms of Atherosclerosis” program, explained, “some earlier studies suggested that **somatic mutations linked to clonal hematopoiesis contribute directly to cardiovascular disease** and thereby accelerating the development of atherosclerosis. On the other hand, others proposed that it is atherosclerosis that causes clonal hematopoiesis by increasing the proliferation of blood stem cells and thereby generating a higher proportion of mutated blood cells.”

The *Nature Medicine* study clarifies the relationship between clonal hematopoiesis and atherosclerosis through a longitudinal analysis of data from the **PESA-CNIC-Santander study**. PESA (Progression of Early Subclinical Atherosclerosis) is a prospective study of more than 4000 apparently healthy middle-aged participants who have undergone periodic examinations using advanced imaging technology since 2010 to detect the presence and progression of asymptomatic atherosclerosis. PESA is a collaborative initiative of the CNIC and Santander Bank. “The PESA study has already made very important contributions to our understanding of cardiovascular disease, and its longitudinal nature and unique characteristics provide an ideal framework for carrying out this important study on the relationship between clonal hematopoiesis and atherosclerosis,” said **Dr. Valentín Fuster**, CNIC General Director, principal investigator on the PESA study, and co-lead author on the *Nature Medicine* study.

The researchers used high-sensitivity DNA sequencing technology to detect somatic mutations in blood samples and assessed the presence and progression of atherosclerosis detected with noninvasive imaging techniques in the PESA participants. “The study was a multidisciplinary effort involving specialists in basic science and cardiology, together with the specialized technical expertise of the Bioinformatics, Genomics, and Clinical Trials Units at the CNIC,” said José Javier Fuster.

Participants who had mutations linked to clonal hematopoiesis at the start of the study were more likely to develop atherosclerosis in the following years

The results of the study clearly demonstrate that participants who had mutations linked to clonal hematopoiesis at the start of the study were more likely to develop atherosclerosis in the following years. On the other hand, the presence and extent of atherosclerosis had no influence on the expansion of mutated blood cells. “These results indicate that the mutations contribute to the development of atherosclerosis but are not a consequence of it,” explained co-first author Miriam Díez-Díez. “However, it remains possible that other factors, such as genetic profile or lifestyle, might modulate the effects of clonal hematopoiesis, and future studies are planned to examine this possibility,” added **Beatriz L. Ramos-Neble**, the other co-first author on the study.

The results of the study have clear clinical implications and identify clonal hematopoiesis as a cardiovascular risk factor completely different from the traditional risk factors studied in recent decades. This novelty holds promise for the **development of new strategies for the prevention of cardiovascular disorders**. “By demonstrating that the mutations linked to clonal hematopoiesis precede atherosclerosis and contribute to its development, our research suggests that blocking the effects of these somatic mutations could help to prevent cardiovascular disease,” claimed Dr. José Javier Fuster.

The second CNIC study, published in the *European Heart Journal*, lays the groundwork for this.

An ancient drug to alleviate a new cardiovascular risk factor

The best characterized mutations linked to clonal hematopoiesis are those that affect the *TET2* gene. In a 2017 study published in *Science*, Dr. José Javier Fuster’s team showed that mutations in *TET2* accelerate the development of atherosclerosis in animal models. In the new study published in the *European Heart Journal*, the CNIC group, in partnership with the team led by **Dr. Pradeep Natarajan at the *Broad Institute* in Boston**, show that the adverse effects of *TET2* mutations on cardiovascular health can be alleviated by treatment with the anti-inflammatory drug colchicine.

The CNIC team demonstrated that administration of colchicine to animals with *TET2* mutations slows the development of atherosclerosis to a rate similar to that seen in non-mutated animals. In parallel, the Broad Institute scientists showed that **individuals with *TET2* mutations and who had been treated with colchicine for other conditions had a lower risk of myocardial infarction** than untreated patients with similar mutations.

Plant preparations containing colchicine have been used for thousands of years in traditional medicine, and the drug is used in modern medicine to treat inflammatory conditions such as gout. “Colchicine is a very cheap medicine, available throughout the world, and is approved for the prevention of cardiovascular disease by the European Medicines Agency and by the FDA in the USA. There is therefore no major obstacle to its use for the prevention of cardiovascular disease in people with *TET2* mutations,” emphasized **Dr. María Ángeles Zuriaga**, who conducted the experimental studies at the CNIC and is the first author on the *European Heart Journal* study.

Dr. José Javier Fuster underlined the important implications of the study for personalized medicine. “In clonal hematopoiesis, each mutated gene acts through different mechanisms and will therefore likely require specific interventions to target its effects. This study lays the groundwork for using colchicine for/in the personalized prevention of cardiovascular disease of carriers of mutations in *TET2*, but new clinical trials will be needed to conclusively demonstrate its effectiveness in these individuals.”

The PESA study is cofunded by the CNIC and Santander Bank. The two studies were additionally funded by the Spanish *Ministerio de Ciencia, Innovación e Universidades* (PLEC2021-008194), the Spanish cardiovascular research network (CIBERCV), Fundación “la Caixa” (LCF/PR/HR17/52150007; LCF/PR/HR22/52420011), and Fundación ‘La Marató TV3’ (202314-31).

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