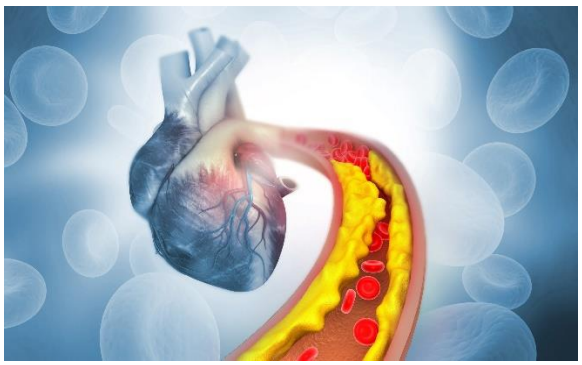
In Middle-Aged Adults Clonal Hematopoiesis Drives Femoral Atherosclerosis

A group of researchers investigated the complex and debated relationship between clonal hematopoiesis (CH) (Expansion of blood cells from a single mutated stem cell) and the development of atherosclerosis (Build-up of plaques in the arteries, leading to narrowed or blocked blood vessels) in healthy middle-aged individuals.



Study

The present study population consisted of 3,692 participants from the Progression of Early Subclinical Atherosclerosis (PESA) study, a longitudinal cohort examining factors related to early subclinical atherosclerosis in healthy middle-aged individuals. At enrollment, participants aged 40 to 55 provided blood Deoxyribonucleic Acid (DNA) samples and underwent multimodal vascular imaging over multiple study visits. Exclusion criteria included existing CVD, immunological disorders, cancer, and other conditions affecting life expectancy or study adherence. The study protocol was approved by the Ethics Committee of Instituto de Salud Carlos III, and all participants provided written informed consent.

Atherosclerosis burden was assessed using noninvasive vascular imaging techniques, including Three-Dimensional Vascular Ultrasound (3DVUS) for femoral and carotid arteries and non-contrast Computed Tomography (CT) for coronary artery calcium scoring (CACS). Atherosclerosis was analyzed based on plaque volume and categorized by severity. The study also evaluated modifiable risk factors such as diabetes, dyslipidemia (Abnormal levels of lipids (fats) in the blood), hypertension, obesity, and hematological traits.

High-sensitivity targeted DNA sequencing was conducted on blood samples to identify CH-related somatic mutations. A custom gene panel was used to detect mutations in 54 CH-related genes. Statistical analysis was performed using RStudio, with adjustments for relevant covariates.

Findings

Previous analyses of whole-exome sequencing (WES) and whole-genome sequencing (WGS) suggested that CH is relatively uncommon among middle-aged individuals, with a frequency of approximately 2-3% in those aged 40 to 55, compared to over 10% in individuals older than 65. However, these findings were limited by the low sensitivity of detecting small mutant clones, especially those with a variant allele fraction (VAF) of less than 5%.

To address this limitation, high-sensitivity targeted sequencing was performed on 3,692 participants from the PESA study, aged 40 to 55 years, using a custom panel targeting 54 CH-

related genes. This approach allowed the identification of CH mutations with a VAF as low as 0.2%, revealing that approximately 25% of the study participants carried at least one detectable CH mutation.

The most frequently observed mutations were in the DNA (Cytosine-5)-Methyltransferase 3 Alpha (DNMT3A) gene, present in 14.8% of individuals, followed by Ten-Eleven Translocation Methylcytosine Dioxygenase 2.

(TET2) mutations in 3.9% of participants. The prevalence of CH increased with age, with each additional year associated with a 9% higher risk of carrying detectable CH mutations. Most mutation carriers had only one detectable mutation, although the likelihood of carrying multiple mutations increased with age. The mutant hematopoietic clones identified in this study were generally smaller than those reported in previous WES or WGS analyses, with 78.8% of mutations having a VAF below 2%.

Interestingly, the study found that the prevalence of DNMT3A-mutant CH was higher in women than in men, with women having a 64% higher risk of carrying detectable DNMT3A mutations. This sex difference was consistent across all age quartiles. Despite the higher prevalence of CH in women, no significant sex-related differences were observed in the prevalence of CH driven by mutations in other genes.

When examining the pathophysiological effects of CH, mutation carriers showed higher absolute blood cell counts across all hematopoietic lineages, though the effect was mild. There was also a trend toward higher blood pressure and glycated hemoglobin (HbA1C) levels among CH carriers, but these associations were not statistically significant after adjusting for age and sex. However, the study's longitudinal analysis revealed a more nuanced relationship between CH and atherosclerosis.

While CH mutation carriers exhibited a greater burden of subclinical atherosclerosis, no significant cross-sectional association was observed after adjusting for traditional cardiovascular risk factors. Nonetheless, CH was independently associated with a 1.5-fold higher risk of developing de novo femoral atherosclerosis, particularly among participants with larger mutant clones.

The study also found that the presence or extent of subclinical atherosclerosis at baseline did not influence the expansion rates of CH mutations over time.

Conclusion

To summarize, recent research has highlighted CH as a potential driver of both blood cancer and nonhematological conditions, particularly atherosclerotic CVD. However, debates persist about whether CH is a causal factor or merely a marker of shared pathophysiological traits.

This study's findings contribute to this debate by suggesting that CH mutations unidirectionally increase the risk of developing femoral atherosclerosis, independent of other cardiovascular risk factors. The relationship between CH and atherosclerosis, in particular, remains uncertain, complicating the development of targeted prevention strategies for CVD in CH carriers.

Further research, particularly into the role of specific mutations like DNMT3A and TET2 and how traditional cardiovascular risk factors may interact with CH, is needed to clarify these dynamics and inform future clinical interventions.

Source:

https://www.news-medical.net/news/20240902/Clonal-hematopoiesis-drives-femoral-atherosclerosis-in-middle-aged-adults.aspx