ESC European Society of Cardiology

European Heart Journal (2024) **45**, 313
https://doi.org/10.1093/eurheartj/ehad701

INVITED DISCUSSION FORUM

Inflammation contributes to the pathogenic effects of subclinical atherosclerosis

Fátima Sánchez-Cabo [1,2], Valentín Fuster [1,3]*, and Enrique Lara-Pezzi [1,2]*

[1]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernandez Almagro, 3, 28029 Madrid, Spain; [2]Centro de Investigacion Biomedica en Red en Enfermedades Cardiovasculares (CIBERCV), Spain; and [3]The Zena and Michael A. Wiener Cardiovascular Institute/Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, One Gustave L. Levy. Place, New York, NY 10029, USA

Online publish-ahead-of-print 4 November 2023

This commentary refers to 'Subclinical atherosclerosis and accelerated epigenetic age mediated by inflammation: a multi-omics study', by F. Sánchez-Cabo *et al.*, https://doi.org/10.1093/eurheartj/ehad361 and the discussion piece 'Immunology and atherosclerosis: is there an individual ID which defines our susceptibility?', by I. Lozano *et al.*, https://doi.org/10.1093/eurheartj/ehad700.

We thank Lozano and colleagues for their insightful comments about our manuscript describing the association between subclinical atherosclerosis (SA) and epigenetic age acceleration (EAA) mediated by inflammation.[1] The association between inflammation and atherosclerosis has been known for decades and has proven key at different stages of atherosclerotic plaque formation, including its genesis.[2] However, inflammation is a very broad term involving different types of immune cells, their subpopulations, and cytokines, which might be found in circulation or in the local milieu.[3] In our study, we identified a number of pathways and genes suggestive of a pro-inflammatory phenotype that might mediate the association between atherosclerosis at a subclinical level and EAA, which is an accurate predictor of all-cause and cardiovascular-related deaths. These results are very relevant since they reinforce the role of inflammation in the long-term pathogenic consequences of atherosclerosis at a subclinical level. However, further studies using single-cell RNA-seq are needed in order to identify the specific immune cell subpopulations responsible for this association, so that these findings can be translated into new therapeutic targets. Our bulk transcriptomics and methylomics data suggest that CD4 cells and their subtypes are highly relevant in the pathogenic consequences of SA. Moreover, we found that NR4A1 was downregulated in individuals with SA (logFC = −0.27, $P < .001$) and in those with EAA (logFC = −0.39, $P < .001$), suggesting an imbalance between the pro-inflammatory subset of T effector cells Th17 and the regulatory T cells, which has been previously associated with the development of atherosclerosis.[4] More generally, an imbalance between pathogenic Th17 and Treg cells has been observed in autoimmune diseases such as rheumatoid arthritis, one of the contexts reported by Lozano and colleagues, who also suggest a role of senescence in the association between SA and accelerated epigenetic aging. Cellular senescence is defined as an irreversible cell cycle arrest and it is frequently accompanied by a pro-inflammatory phenotype[5] referred to as senescence-associated secretory phenotype (SASP), which is characterized by the production of pro-inflammatory cytokines and metalloproteases. Our data identified several genes involved in the SASP, such as *MMP9*, *IL1B*, *NAIP*, and *NLRC4*. While these genes are also general markers of inflammation and cardiovascular diseases, it is worth exploring the role of different senescent cellular types in the pathogenic effect of SA.

Finally, Lozano *et al.* conclude that there are 'intrinsic immune characteristics of each individual which would conform an ID of each subject which could make us more resistant or susceptible against external assaults and in the case of atherosclerosis would modulate the response to the traditional coronary risk factors'. While we agree with this notion, we believe that more molecular information at the single-cell level, together with genetic data, needs to be analysed in large longitudinal cohorts to examine this possibility in a conclusive manner.

Declarations

Disclosure of Interest

All authors declare no conflict of interests.

References

1. Sánchez-Cabo F, Fuster V, Silla-Castro JC, González G, Lorenzo-Vivas E, Alvarez R, *et al.* Subclinical atherosclerosis and accelerated epigenetic age mediated by inflammation: a multi-omics study. *Eur Heart J* 2023;**44**:2698–709. https://doi.org/10.1093/eurheartj/ehad361
2. Devesa A, Lobo-González M, Martínez-Milla J, Oliva B, García-Lunar I, Mastrangelo A, *et al.* Bone marrow activation in response to metabolic syndrome and early atherosclerosis. *Eur Heart J* 2022;**43**:1809–28. https://doi.org/10.1093/eurheartj/ehac102
3. Matsuura Y, Kanter JE, Bornfeldt KE. Highlighting residual atherosclerotic cardiovascular disease risk. *Arterioscler Thromb Vasc Biol* 2019;**39**:e1–9. https://doi.org/10.1161/ATVBAHA.118.311999
4. Tsilingiri K, de la Fuente H, Relaño M, Sánchez-Díaz R, Rodríguez C, Crespo J, *et al.* Oxidized low-density lipoprotein receptor in lymphocytes prevents atherosclerosis and predicts subclinical disease. *Circulation* 2019;**139**:243–55. https://doi.org/10.1161/CIRCULATIONAHA.118.034326
5. Stojanovic SD, Fiedler J, Bauersachs J, Thum T, Sedding DG. Senescence induced inflammation: an important player and key therapeutic target in atherosclerosis. *Eur Heart J* 2020;**41**:2983–96. https://doi.org/10.1093/eurheartj/ehz919

* Corresponding author. Tel: +34 91 453 12 00, Email: vfuster@cnic.es, Tel: +34 91 453 12 00, Email: elara@cnic.es