Atherosclerosis 288 (2019) 156–157

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Editorial

Calcification associates with transcriptomic signatures related to plaque stability in carotid arteries

ARTICLE INFO

Keywords:
Calcification
Peripheral arteries
CT scan
Transcriptomic analysis
Atherosclerosis

Cardiovascular disease (CVD) remains the leading global cause of death, with atherosclerosis as the prominent cause of fatal events in coronaries and peripheral arteries.

In this issue of *Atherosclerosis*, the paper by Karlöf et al. presented novel data that may provide an insight into the way we could identify stable lesions in carotid arteries.

For decades, numerous research groups have worked to identify patients at risk, and more importantly, lesions susceptible to induce infarcts, strokes or acute ischemia in limbs. Circulating biomarkers (proteins, miRNAs, microvesicles, lipids, cells …) can be potent diagnostic tools for a reliable indication for global disease progression [1–4], but still fail to identify and locate high risk lesions for preventive surgical interventions. Anatomical and molecular imaging is the most promising approach for surgically preventing acute cardiovascular events. Molecular imaging strategies combining anatomical and functional imaging modalities (MRI, CT, PET/SPECT, ultrasound, fluorescence) are emerging from preclinical studies to target high risk lesions with critical features like heavy inflammation burden, high metabolic rate, or marked protease activity [5–9].

Vascular calcification is a strong and independent predictive factor for cardiovascular complications and mortality [10]. It derives from passive and active processes that are at least partly comparable to cartilage and bone mineralization. In coronary arteries, noninvasive imaging of vascular macrocalcification has been used to detect patients at risk for further events (calcium score) [11]. While calcifications can affect plaque stability depending on their size, nature, extend and location within the lesion, clinical data establishing their direct contribution to plaque symptomatology are still scarce.

In their latest study, published in this issue of *Atherosclerosis*, Karlöf et al. used conventional CT scan to identify patients with light and heavy calcification in carotid arteries. They correlated heavily calcified lesions with molecular features classically associated with stable lesion, supporting the notion that macro-calcification could indeed stabilize the plaque [12].

The authors selected patients undergoing carotid endarterectomy with different degrees of calcification in carotid lesions, detected by preoperative angiography, and investigated if global gene expression profiles discriminated patients based on their sole calcification burden and symptomatology. Transcriptomic analysis first compared patients with the most calcified lesions to the least calcified plaques (n = 10 each), then between symptomatic and asymptomatic patients (n = 7 each). High calcification score significantly correlated with increased expression of smooth muscle cell (SMC) markers, extracellular matrix (ECM) related genes, and osteogenic factors, and with downregulation of molecules typically associated with macrophage, ECM degradation, chemokines, and osteoclasts. This finding further illustrates that extended calcification in carotid lesions are found in so-called 'stable' phenotype plaques, with relative repressed or low inflammation burden, high SMC/ECM content (fibrotic lesions), and active osteogenic processes. The authors even revealed a panel of 20 genes explaining up to 65% of the variance between groups with proteoglycan 4 (PRG4) as the top regulated gene in heavily calcified plaques. Authors extended most of their transcriptomic findings to patients with intimal and medial calcification using tissue microarrays (TMA).

This work adds new data regarding molecular signatures of atherosclerotic calcification and explore new angles for identifying stable or unstable lesions. However, among the main limitations of this pilot study, authors failed to reach any significant correlation between calcification burden and patient symptomatology, though this link was already established in previous studies [13–15].

PRG4 emerged as the most significantly upregulated gene in heavily calcified lesions, but was downregulated in asymptomatic *vs*. symptomatic patients with high calcification burden.

Its functional role in plaque calcification was not investigated in the present paper, but these preliminary data further suggest the critical role of cartilage and bone-related extracellular matrix (ECM) proteins as potential scaffold for macrocalcification in so-called "*stable*", fibrotic

DOI of original article: https://doi.org/10.1016/j.atherosclerosis.2019.05.005

https://doi.org/10.1016/j.atherosclerosis.2019.06.906
Received 4 June 2019; Received in revised form 13 June 2019; Accepted 19 June 2019
Available online 21 June 2019

lesions [16–19], in contrast to microcalcifications likely originating from collagen I degradation in inflamed lesions [20]. Additional work remains necessary to further explore this question. As regard to clinical practice and preoperative diagnosis, much larger patient cohorts need to ascertain the impact of macrocalcification on plaque's stability in peripheral arteries, based on plaque imaging (CT) and patients' symptoms.

Conflicts of interest

The author declared he does not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

[1] C. Lopez-Pedrera, et al., New biomarkers for atherothrombosis in antiphospholipid syndrome: genomics and epigenetics approaches, Front. Immunol. 10 (2019) 764.
[2] A. Dickhout, R.R. Koenen, Extracellular vesicles as biomarkers in cardiovascular disease; chances and risks, Front. Cardiovasc. Med. 5 (2018) 113.
[3] M.S. Conte, et al., Pro-resolving lipid mediators in vascular disease, J. Clin. Investig. 128 (9) (2018) 3727–3735.
[4] S. Jaiswal, et al., Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease, N. Engl. J. Med. 377 (2) (2017) 111–121.
[5] Y. Li, T.M. Liu, Discovering macrophage functions using in vivo optical imaging techniques, Front. Immunol. 9 (2018) 502.
[6] C. Celeng, et al., PET molecular targets and near-infrared fluorescence imaging of atherosclerosis, Curr. Cardiol. Rep. 20 (2) (2018) 11.
[7] M.R. Dweck, et al., Noninvasive molecular imaging of disease activity in atherosclerosis, Circ. Res. 119 (2) (2016) 330–340.
[8] A. Vrachimis, et al., New molecular probes of vascular inflammation, Q. J. Nucl. Med. Mol. Imaging 60 (3) (2016) 194–204.
[9] T. Quillard, et al., Molecular imaging of macrophage protease activity in cardiovascular inflammation in vivo, Thromb. Haemostasis 105 (5) (2011) 828–836.
[10] P.W. Wilson, et al., Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality, Circulation 103 (11) (2001) 1529–1534.
[11] N. Alexopoulos, P. Raggi, Calcification in atherosclerosis, Nat. Rev. Cardiol. 6 (11) (2009) 681–688.
[12] E. Karlof, et al., Correlation of computed tomography with carotid plaque transcriptomes associates calcification with lesion-stabilization, Atherosclerosis 288 (2019) 175–185.
[13] C.M. Wahlgren, et al., Human carotid plaque calcification and vulnerability. Relationship between degree of plaque calcification, fibrous cap inflammatory gene expression and symptomatology, Cerebrovasc. Dis. 27 (2) (2009) 193–200.
[14] K.R. Nandalur, et al., Composition of the stable carotid plaque: insights from a multidetector computed tomography study of plaque volume, Stroke 38 (3) (2007) 935–940.
[15] J.M. Davaine, et al., Osteoprotegerin, pericytes and bone-like vascular calcification are associated with carotid plaque stability, PLoS One 9 (9) (2014) e107642.
[16] D. Ngai, M. Lino, M.P. Bendeck, Cell-matrix interactions and matricrine signaling in the pathogenesis of vascular calcification, Front. Cardiovasc. Med. 5 (2018) 174.
[17] O. Okamoto, S. Fujiwara, Dermatopontin, a novel player in the biology of the extracellular matrix, Connect. Tissue Res. 47 (4) (2006) 177–189.
[18] Y. Fu, W. Kong, Cartilage oligomeric matrix protein: matricellular and matricrine signaling in cardiovascular homeostasis and disease, Curr. Vasc. Pharmacol. 15 (3) (2017) 186–196.
[19] Y. Fu, et al., Shift of macrophage phenotype due to cartilage oligomeric matrix protein deficiency drives atherosclerotic calcification, Circ. Res. 119 (2) (2016) 261–276.
[20] J.D. Hutcheson, et al., Genesis and growth of extracellular-vesicle-derived microcalcification in atherosclerotic plaques, Nat. Mater. 15 (3) (2016) 335–343.

Thibaut Quillard
UMR1238 INSERM, Université de Nantes, CHU de Nantes, Nantes, France
E-mail address: thibaut.quillard@univ-nantes.fr.