JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 72, NO. 13, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

A Role for Extracellular Matrix in Atherosclerotic Plaque Erosion*

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In 2002, working with Frank Kolodgie and Renu Virmani, we set out to identify whether there were unique extracellular matrices (ECMs) associated with different types of culprit human atherosclerotic lesions, including stable plaques, eroded plaques, and plaque ruptures (1,2). Such experiments are important because specific components of the ECM can regulate different key events in the pathogenesis of atherosclerosis (3). One of the most consistent findings of the 49 culprit lesions that we examined was an increase in hyaluronan and versican in a layer that formed at the border of the plaque/thrombus interface in eroded plaques. Both hyaluronan and versican are known to accumulate in different forms of vascular disease (3-7). This result was a bit surprising because previous studies had implicated the collagens and other ECM components as forming this interface, which was then proposed to promote coagulation and thrombosis. Furthermore, we found that the major hyaluronan receptor, CD44, was highly localized to a subset of smooth muscle cells at the plaque/thrombus interface along with platelets and fibrin. Hyaluronan is an ECM polysaccharide that is synthesized by multiple cell types in the vascular wall by endogenous cells as well as by cells that gain access to the vascular wall, such as a variety of different leukocyte populations including platelets (8). Hyaluronan interacts with a number of molecules involved in the coagulation cascade, such as fibrin, fibrinogen, and fibronectin, forming a provisional matrix potentially influencing events associated with thrombosis (3,8).

These observations raised the possibility that hyaluronan is critical for early events leading to coagulation and initiation of thrombosis. Although these studies implicated hyaluronan as a potential player in thrombosis, several questions remained: Was there any evidence of altered hyaluronan metabolism in eroded plaques? What was the source of hyaluronan? Was hyaluronan intact or degraded? What factors regulated hyaluronan accumulation?

Additional support for the involvement of hyaluronan in eroded plaques comes from studies done by Peter Libby's group at Harvard (9). These investigators were interested in developing a mouse model for eroded plaques and found that a prerequisite for plaque erosion in the mouse was an accumulation of hyaluronan in the hyperplastic intima and the recruitment of neutrophils impacting endothelial cell loss and thrombosis in a TLR2-dependent manner. Evidence was presented in their study that enzymes involved in the synthesis and turnover of hyaluronan in this mouse model were altered. Hyaluronan, as an ECM molecule, may be present either intact where it tends to be anti-inflammatory or degraded into proinflammatory fragments capable of interacting with TLR agonists such as TLR2. Such changes in hyaluronan turnover are thought to control, in part, events associated with cell death and other inflammatory responses (1,9-11).

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The findings reported by Pedicino et al. (12) in this issue of the *Journal* represent a landmark study that addresses these questions and significantly adds to our understanding of the factors that lead to plaque erosion and thrombosis. The authors examined whether gene expression involving hyaluronan metabolism was altered in patients with acute coronary syndromes compared with patients that had stable angina or no coronary disease (control

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.07.031

patients). The exciting aspect of this work builds on previous observations implicating hyaluronan in plaque erosion, but goes further to identify specific cell types involved as well as candidate genes important in promoting hyaluronan changes that take place in plaque erosion. This study reports that compared with stable angina or control patients, peripheral blood mononuclear cells (PBMCs) isolated from patients with eroded plaques had elevated levels of both hyaluronidase 2 (an enzyme that degrades hyaluronan) and CD44v6 (a variant of the hyaluronan binding protein, CD44). Interestingly, these differences were more prominent in patients who were smokers compared with those that did not smoke. Evaluation of the PBMCs from patients with eroded plaques also revealed colocalization of Hyal2 and CD44 on the surface of the PBMCs and a tendency for these PBMCs to bind platelets.

Collectively, these results support a central role for hyaluronan in plaque erosion. A proposed schema for the events outlined in the preceding text is shown in Figure 1 of the paper by Pedicino et al. (12), which nicely summarizes the data generated in the study. Clearly, a mechanistic role for hyaluronan and molecules that associate with hyaluronan in plaque erosion needs to be considered as therapeutic strategies are developed for treating or inhibiting the thrombotic events that take place in plaque erosion.

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REFERENCES

1. Kolodgie FD, Burke AP, Farb A, et al. Differential accumulation of proteoglycans and hyaluronan in culprit lesions: insights into plaque erosion. Arterioscler Thromb Vasc Biol 2002;22:1642–8.

2. Kolodgie FD, Burke AP, Wight TN, Virmani R. The accumulation of specific types of proteoglycans in eroded plaques: a role in coronary thrombosis in the absence of rupture. Curr Opin Lipidol 2004;15:575–82.

3. Wight TN. A role for proteoglycans in vascular disease. Matrix Biol 2018 Feb 27 [E-pub ahead of print].

4. Toole BP, Wight TN, Tammi MI. Hyaluronan-cell interactions in cancer and vascular disease. J Biol Chem 2002;277:4593–6.

5. Fischer JW. Role of hyaluronan in atherosclerosis: current knowledge and open questions. Matrix Biol 2018 Mar 3 [E-pub ahead of print].

6. Viola M, Karousou E, D'Angelo ML, et al. Extracellular matrix in atherosclerosis: hyaluronan and proteoglycans insights. Curr Med Chem 2016;23:2958–71.

7. Grandoch M, Bollyky PL, Fischer JW. Hyaluronan: a master switch between vascular homeostasis and inflammation. Circ Res 2018;122:1341–3.

8. Wight TN. Provisional matrix: a role for versican and hyaluronan. Matrix Biol 2017;60-61:38–56.

9. Franck G, Mawson T, Sausen G, et al. Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in mice: Implications for superficial erosion. Circ Res 2017;121:31–42.

10. Kolodgie FD, Burke AP, Farb A, et al. Plaque erosion. In: Virmani R, Narula J, Leon MB, Willerson JT, editors. The Vulnerable Atherosclerotic Plaque: Strategies for Diagnosis and Management. Malden, MA: Blackwell Publishing, 2007.

11. Quillard T, Franck G, Mawson T, Folco E, Libby P. Mechanisms of erosion of atherosclerotic plaques. Curr Opin Lipidol 2017;28:434–41.

12. Pedicino D, Vinci R, Giglio AF, et al. Alterations of hyaluronan metabolism in acute coronary syndrome: implications for plaque erosion. J Am Coll Cardiol 2018;72:1490–503.

KEY WORDS hyaluronan, thrombosis, vascular disease, versican