JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 5, 2022

EDITORIAL COMMENT

Jam-A Unleashed Incites Thromboinflammatory Coronary Artery Disease*

Rory R. Koenen, PhD,[a] Christian Weber, MD[a,b,c,d]

Junctional adhesion molecule A (JAM-A, JAM-1, F11 receptor) is a single transmembrane member of the immunoglobulin superfamily, expressed on the surface of many cell types, including vascular cells, leukocytes, and platelets.[1,2] Through homophilic interactions mediated by its extracellular domain 1, JAM-A is enriched in intercellular junctions and maintains barrier function in epithelial and endothelial cell layers. Under inflammatory conditions, this barrier is lost as JAM-A moves out of the endothelial junctions toward the apical side of the cells where it undergoes adhesive interactions with platelets and leukocytes through homophilic and heterophilic binding to JAM-A and lymphocyte function-associated antigen 1, respectively.[1,2] Inflammation also causes proteolytic release of JAM-A from the surface of endothelial cells and platelets through the action of a disintegrin and metalloproteases-10 and -17.[3] Accordingly, increased circulating levels of soluble JAM-A (sJAM-A) were found to be associated with (vascular) pathologic conditions such as atherosclerosis, hypertension, end-stage kidney disease, and particular forms of cancer. However, it has been unclear whether the release of JAM-A is an epiphenomenon of cell surface protease activation or whether sJAM-A plays rather an active role in regulating cellular actions during disease.

Another open question concerns the function of JAM-A on platelets. It was initially identified as the molecular target for a platelet-activating monoclonal antibody (F11) and termed F11 receptor in 1990.[4] However, its exact function in platelets long remained obscure and JAM-A was later rediscovered as JAM-1, and henceforth mainly known as an endothelial and epithelial junction molecule.[5] Although JAM-A does not appear to transduce signals by itself, later studies showed that JAM-A down-regulates platelet activation by association with integrin $\alpha_{IIb}\beta_3$ and that genetic deletion of JAM-A led to platelet hyperreactivity. Studies in mice demonstrated that JAM-A-deficient platelets had a lower activation threshold, increased aggregation, more robust adhesion to fibrinogen and collagen, and increased thrombosis. In addition, the development of atherosclerosis was accelerated in mice carrying a platelet-specific deletion of JAM-A, which may be attributed to increased platelet reactivity. Although a functional role of JAM-A in vascular inflammation and thrombosis has been clearly demonstrated in mice, evidence in humans is still sparse.

This knowledge gap has been addressed in the study by Rath et al[6] in this issue of *JACC: Basic to Translational Science*. Here, a possible proinflammatory and prothrombotic role of JAM-A was investigated in patients with acute and chronic coronary syndromes. Rath et al have performed a single nucleotide variation (SNV, formerly SNP) analysis and measured sJAM-A levels in cohorts of patients with acute and chronic coronary syndromes and found

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Department of Biochemistry, Cardiovascular Research Institute Maastricht School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands; [b]Institute for Cardiovascular Prevention, Ludwig-Maximilians-Universität, Munich, Germany; [c]German Center for Cardiovascular Research, Partner Site Munich Heart Alliance, Munich, Germany; and the [d]Munich Cluster for Systems Neurology, Munich, Germany.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.03.014

that homozygosity of 2 previously identified minor alleles of the SNVs rs2774276 and rs790056 was associated with a worse event-free survival during long-term follow-up. Consistent with previous findings, homozygous carriers of the rs2774276 and rs790056 minor alleles had elevated plasma levels of sJAM-A. When the patients were stratified in 2 groups of below- and above-median sJAM-A concentrations, elevated sJAM-A levels by themselves were found to be an independent predictor of recurrent myocardial infarction. Given the pivotal role of platelets in acute coronary syndrome, the researchers focused on JAM-A on platelets. On activation, platelets were found to up-regulate surface expression of JAM-A and to shed JAM-A, partly associated with extracellular vesicles, into solution. In patients with coronary artery disease, surface JAM-A expression correlated with that of platelet activation markers. These findings in patients suggest that both plasma levels of sJAM-A and surface expression of JAM-A on platelets can provide information on the presence and future outcome of coronary syndromes.

To investigate possible functional consequences of the release of sJAM-A into circulation, Rath et al[6] performed studies with isolated platelets and recombinant isolated sJAM-A extracellular domains. When sJAM-A was added alone to platelets, this did not lead to a response. However, when platelets were stimulated with a soluble agonist in combination with sJAM-A, this resulted in a notable up-regulation of platelet aggregation, spreading, and degranulation. On a structural level, the platelet costimulating function of JAM-A could be attributed to extracellular domain 1, suggesting that the level of JAM-A multimerization at the cell surface governs its functions. These findings in model experiments were supported by studies in mice, because injection of sJAM-A resulted in quicker carotid artery occlusion and enhanced thrombus formation in an arterial injury model. An antibody against JAM-A blocked the observed prothrombotic effects by sJAM-A. sJAM-A also enhanced thrombus formation in an ex vivo perfusion model, and this effect was not observed when isolated platelets from mice lacking JAM-A were used. On the level of intracellular signal transduction, addition of sJAM resulted in the phosphorylation of several key kinases involved in platelet signaling (eg, proto-oncogene c-Src, protein kinase B and C, and phosphatidylinositol 3-kinase). In addition, the integrin β_3 chain was phosphorylated on addition of sJAM-A, further highlighting the putative role of JAM-A in platelet spreading and clot retraction.

To investigate a role for sJAM-A in inflammation associated with acute thrombotic events, the effects of sJAM-A on platelet–monocyte interactions were studied. The addition of sJAM-A was found to enhance platelet-monocyte aggregate formation and platelet internalization by monocytes, and this might explain the enhanced foam cell formation induced by sJAM-A–treated platelets and the subsequently enhanced release of proinflammatory cytokines by the monocytes that have taken up sJAM-A–treated platelets. The overall conclusion of the study is that soluble JAM-A acts as a thromboinflammatory factor, and that it can serve as a biomarker for the risk assessment of patients with coronary artery disease.

The study by Rath et al[6] links clinical findings with observations from experimental model systems both in vitro and in vivo. Beyond revealing a role of sJAM-A as a disease biomarker, it also links the proteolytically released protein to key platelet-driven processes in the pathophysiology of coronary artery disease. This work thereby provides compelling evidence of a functional role of (s)JAM-A in human disease and provides a perspective for future clinical use of JAM-A–related biomarkers.

Nevertheless, some questions remain to be addressed. First, because the release of JAM-A may occur from cell-types other than platelets, notably endothelial cells, information on the origin of sJAM-A would provide further knowledge on the processes both preceding and accompanying acute coronary disease. Perhaps such information can be obtained by having a closer look at the JAM-A associated with extracellular vesicles, because these also contain several remnant molecules derived from the parent cell. In addition, it would be interesting to elaborate on possible functions of extracellular vesicle-bound JAM-A in the future. Another open question concerns the proteases involved in the release of JAM-A, which might be others than the already known a disintegrin and metalloproteases, and their activation might be specific for the (patho)physiologic context. Although platelets, leukocytes, and endothelial cells are numerous, whether the sJAM-A (locally) released by these cells is sufficient to achieve effective concentrations to induce the effects seen in the in vitro experiments might be a subject for debate. Taken together, surface-bound JAM-A is proteolytically

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 5, 2022
MAY 2022:462–464

unleashed to propagate thromboinflammatory events during acute coronary artery disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Weber is a van der Laar Professor of Atherosclerosis. Dr Koenen has reported that he has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Christian Weber, Institute for Cardiovascular Prevention, Ludwig-Maximilians-Universität Munich, Pettenkoferstrasse 9, 80336 München, Germany. E-mail: ipek.office@med.uni-muenchen.de OR r.koenen@maastrichtuniversity.nl.

REFERENCES

1. Luissint AC, Nusrat A, Parkos CA. JAM-related proteins in mucosal homeostasis and inflammation. *Semin Immunopathol*. 2014;36(2):211–226.

2. Weber C, Fraemohs L, Dejana E. The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol*. 2007;7(6):467–477.

3. Koenen RR, Pruessmeyer J, Soehnlein O, et al. Regulated release and functional modulation of junctional adhesion molecule A by disintegrin metalloproteinases. *Blood*. 2009;113(19):4799–4809.

4. Kornecki E, Walkowiak B, Naik UP, Ehrlich YH. Activation of human platelets by a stimulatory monoclonal antibody. *J Biol Chem*. 1990;265(17):10042–10048.

5. Martin-Padura I, Lostaglio S, Schneemann M, et al. Junctional adhesion molecule, a novel member of the immunoglobulin superfamily that distributes at intercellular junctions and modulates monocyte transmigration. *J Cell Biol*. 1998;142(1):117–127.

6. Rath D, Rapp V, Schwartz J, et al. Homophilic interaction between transmembrane-JAM-A and soluble JAM-A regulates thromboinflammation: implications for coronary artery disease. *J Am Coll Cardiol Basic Trans Science*. 2022;7(5):445–461.

KEY WORDS acute coronary syndrome, adhesion molecule, inflammation, platelet, thrombosis