JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 3, NO. 1, 2018

EDITORIAL COMMENT

Transcriptional Profiling Identifies Mechanisms Associated With Platelet Activation in HIV Infection*

Nicholas Funderburg, PhD

Platelets are key mediators of hemostasis, but there is a growing appreciation for the roles platelets may play in modulating inflammation and activation of multiple cell types. With this increased recognition of the immunomodulatory function of platelets, studies are focusing on the mechanisms that regulate platelet activation to identify critical intermediates that may be exploited in intervention strategies. In this issue of *JACC: Basic to Translational Science*, Marcantoni et al. (1) describe alterations in the transcriptomes of platelets from

SEE PAGE 9

persons infected with the human immunodeficiency virus (HIV) compared with platelet transcriptomes from uninfected subjects. These changes in mRNA transcript levels have functional consequences on platelet activation. Long-term HIV infection, even in the setting of controlled viral replication during antiretroviral therapy, is often associated with increased immune activation, inflammation, and coagulation (2), and as a consequence, persons living with HIV (PLWH) are at risk for venous (3) and arterial thrombosis (4). Elucidation of the mechanisms behind platelet activation in PLWH may provide novel targets for reduction of thrombotic risk among this population.

Platelets are derived from megakaryocytes, and while these cells lack a nucleus, mRNA and the translational machinery required for protein expression are contained within their cytoplasm. Platelets express a number of surface receptors, including Toll-like receptors and a variety of G-protein coupled receptors; recognition of their ligands by these receptors can result in engagement of intracellular signaling cascades and platelet activation (5). Activated platelets express increased levels of adhesion molecules, including CD62P, and the procoagulant molecule tissue factor. Platelets can also release cytokines and granules that may influence the function and phenotype of surrounding cells. Increased platelet activation has been reported in several disease settings, including cardiovascular disease, sepsis (5), and HIV infection (6). Chronic HIV infection is associated with increased risk for thrombotic cardiovascular events, including myocardial infarction (7), stroke, and deep vein thrombosis, compared with these risks in demographically similar HIV-uninfected populations. The mechanistic details associated with platelet activation and coagulopathy in PLWH have not been adequately explored.

Measuring the translational potential of platelets using unbiased RNA sequencing approaches has shed light onto the functional capabilities of platelets. In previous work, the authors have shown that platelet transcriptome profiling can identify hyper- versus hyporeactive platelets, and that platelet expression of WD-40 repeat domain 1 (WDR1) may be associated with cardiovascular disease progression (8). Here, Marcantoni et al. (1) report that the transcriptomes in platelets from PLWH are altered compared to those of platelets from HIV-uninfected individuals. The authors show that transcript and protein expression of ABCC4 are increased in platelets from PLWH compared with levels in platelets from uninfected

*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 Division of Medical Laboratory Science, School of Health and Rehabilitation Sciences, Ohio State University, Columbus, Ohio. Dr. Funderburg has received consulting fees from Gilead; and funding from the NIH/NHLBI.

The author attests he is 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 *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2018.01.001

subjects and that ABCC4 expression was related to markers of platelet activation (i.e., CD62P and PAC-1). Through a series of in vitro experiments, the authors show that ABCC4 plays a mechanistic role in platelet activation, including intraplatelet signaling and release of S1P and dense granules. Furthermore, platelets from PLWH, compared with platelets from uninfected controls, induced increased pro-inflammatory cytokine expression from monocyte and endothelial cell lines. This platelet effector function was reduced when ABCC4 activity was inhibited. These results implicate ABCC4 as a critical mediator of platelet activation in PLWH, and of subsequent activation of other cell types that may contribute to progression of venous and arterial thrombosis.

Platelet activation has been shown to be associated with both monocyte and T-cell activation in PLWH (6). This may be due to similar upstream mediators driving activation of these cell types, or these associations may be related to direct and indirect interactions among platelets and leukocytes. Binding of activated platelets to monocytes, T cells, and neutrophils may be mediated by interactions between surface receptors, including P-selectin on the platelet and PSGL-1 on leukocytes, promoting intracellular signaling (5). Activated platelets also release pro-inflammatory cytokines (i.e., interleukin-1β) and the signaling molecule CD40L, each of which may influence the activation state of several cell types. The work by Marcantoni et al. (1) implicates ABCC4 as a potential target for inhibition of platelet cytokine and granule release, and subsequent activation of neighboring cells. While these platelet/cell interactions contribute to cellular activation, a role for platelet-mediated immune suppression has also been identified. Platelets can inhibit the effector function of CD8+ T cells through a mechanism whereby thrombin-activated platelets secrete transforming growth factor-beta (9). Further studies exploring the immunomodulatory consequences of platelet activation and the proteins that regulate platelet activation are necessary.

Appreciation of the mechanistic details that lead to increased platelet activity in PLWH could lead to novel therapeutic interventions. Previous work by this group has reported an effect of aspirin administration on platelet activity in PLWH (10), but this finding was not reproduced in a placebo-controlled clinical trial (11). The authors speculate that increased platelet expression of ABCC4 in PLWH before aspirin treatment may have played a partial role in this null finding, as ABCC4 may mediate export of aspirin from platelets, reducing its effectiveness. Studies using other platelet-inhibiting medications, including clopidogrel, prasugrel, or ticagrelor, may have a beneficial effect on coagulopathy in PLWH, but further research is needed, as some of these medications may have adverse interactions with antiretroviral therapy regimens. Understanding the mechanisms that underpin the increased ABCC4 expression in platelets in PLWH and a greater appreciation for the complex interactions among platelets and other cell types may advance treatment strategies aimed at reducing thrombotic risk in PLWH and in HIV uninfected populations as well.

ADDRESS FOR CORRESPONDENCE: Dr. Nicholas Funderburg, Ohio State University, School of Health and Rehabilitation Sciences, Division of Medical Laboratory Science, 453 West 10th Avenue, 535A Atwell Hall, Columbus, Ohio 43210. E-mail: nicholas.funderburg@osumc.edu.

REFERENCES

1. Marcantoni E, Allen N, Cambria MR, et al. Platelet transcriptome profiling in HIV and ATP-binding cassette subfamily C member 4 (ABCC4) as a mediator of platelet activity. J Am Coll Cardiol Basic Trans Sci 2018;3:9–22.

2. Funderburg NT. Markers of coagulation and inflammation often remain elevated in ART-treated HIV-infected patients. Curr Opin HIV AIDS 2014;9:80–6.

3. Musselwhite LW, Sheikh V, Norton TD, et al. Markers of endothelial dysfunction, coagulation and tissue fibrosis independently predict venous thromboembolism in HIV. AIDS 2011;25:787–95.

4. Ford ES, Greenwald JH, Richterman AG, et al. Traditional risk factors and D-dimer predict incident cardiovascular disease events in chronic HIV infection. AIDS 2010;24:1509–17.

5. Rondina MT, Weyrich AS, Zimmerman GA. Platelets as cellular effectors of inflammation in vascular diseases. Circ Res 2013;112:1506–19.

6. Mayne E, Funderburg NT, Sieg SF, et al. Increased platelet and microparticle activation in HIV infection: upregulation of P-selectin and tissue factor expression. J Acquir Immune Defic Syndr 2012;59:340–6.

7. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab 2007;92:2506–12.

8. Montenont E, Echagarruga C, Allen N, Araldi E, Suarez Y, Berger JS. Platelet WDR1 suppresses platelet activity and is associated with cardiovascular disease. Blood 2016;128:2033–42.

9. Mudd JC, Panigrahi S, Kyi B, et al. Inflammatory function of CX3CR1+ CD8 T cells in treated HIV infection is modulated by platelet interactions. J Infect Dis 2016;214:1808–16.

10. O'Brien M, Montenont E, Hu L, et al. Aspirin attenuates platelet activation and immune activation in HIV-1-infected subjects on antiretroviral therapy: a pilot study. J Acquir Immune Defic Syndr 2013;63:280–8.

11. O'Brien MP, Hunt PW, Kitch DW, et al. A randomized placebo controlled trial of aspirin effects on immune activation in chronically human immunodeficiency virus-infected adults on virologically suppressive antiretroviral therapy. Open Forum Infect Dis 2017;4:ofw278.

KEY WORDS HIV-1, inflammation, platelet activation