

EDITORIAL COMMENT

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



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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

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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

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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-1 β) 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.

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