Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Received: 18 September 2020 | Accepted: 26 October 2020

DOI: 10.1111/jth.15156

FORUM

Is there a role for the ACE2 receptor in SARS-CoV-2 interactions with platelets?

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Funding information
This work was supported by grants from the NIH (K01AG059892 to RAC, and R01HL142804, R01AG048022, R56AG059877, and R01HL130541 to MTR). This work was also supported in part by Merit Review Award Number I01 CX001696 to MTR from the United States (US) Department of Veterans Affairs Clinical Sciences R&D (CSRD). This material is the result of work supported with resources and the use of facilities at the George E. Wahlen VA Medical Center, Salt Lake City, Utah. The contents do not represent the views of the US Department of Veterans Affairs or the United States government. This study was also supported by the Canadian Institutes of Health Research awarded to EB. EB is recipient of senior award from the Fonds de Recherche du Québec en Santé (FRQS).

Abstract

There is an urgent need to understand the underlying mechanisms contributing to thrombotic and inflammatory complications during COVID-19. Data from independent groups have identified that platelets are hyperreactive during COVID-19. Platelet hyperreactivity is accompanied by changes in platelet gene expression, and enhanced interactions between platelets and leukocytes. In some patients, SARS-CoV-2 mRNA has been detected in platelets. Together, this suggests that SARS-CoV-2 may interact with platelets. However, controversy remains on which receptors mediate SARS-CoV-2 platelet interactions. Most, but not all, transcriptomic and proteomic analyses fail to observe the putative SARS-CoV-2 receptor, angiotensin converting enzyme-2, or the cellular serine protease necessary for viral entry, TMPRSS2, on platelets and megakaryocytes. Interestingly, platelets express other known SARS-CoV-2 receptors, which induce similar patterns of activation to those observed when platelets are incubated with SARS-CoV-2. This article explores these findings and discusses ongoing areas of controversy and uncertainty with regard to SARS-CoV-2 platelet interactions.

KEYWORDS
ACE2, COVID-19, platelets, SARS-CoV-2, thrombosis

Manuscript handled by: Katsue Suzuki-Inoue

Final decision: Katsue Suzuki-Inoue, 26 October 2020

1 | INTRODUCTION

SARS-CoV-2 coronavirus emerged in Wuhan, China, in December 2019, and has infected more than 35 million people worldwide.[1] The associated disease, COVID-19, has claimed 1 million lives as of October 2020.[1] While notable manifestations in COVID-19 include acute respiratory distress syndrome, it is now well recognized that thrombosis and cardiovascular manifestations also contribute greatly to morbidity and mortality from COVID-19.[2,3] Thrombotic complications have been observed in hospitalized patients with COVID-19, which are manifested by elevated levels of D-dimer and fibrin degradation products as well as macrothrombi and small vessel thrombosis in multiple organs.[2-5] However, the pathophysiologic cellular drivers of these thrombotic complications are poorly understood.

Platelets are small, cellular fragments derived from their parent cells, megakaryocytes. As platelets are anucleate, megakaryocytes are generally thought to package the molecular factors necessary for platelets to function before they are released into the circulation. In addition to their traditional roles in hemostasis, platelets play critical roles during infectious diseases, which are often associated with a heightened risk of thrombosis. Autopsies from COVID-19 patients have revealed platelet-rich thrombi in microcapillaries in the lungs, heart, kidneys, and skin and abnormally elevated numbers of megakaryocytes in heart and lungs further pointing to dysregulated hemostasis in patients infected with SARS-CoV-2.[6-8]

2 | PLATELET ACTIVATION AND HYPERACTIVTY IN COVID-19

Recently, several independent studies have demonstrated that platelets are activated in COVID-19 patients.[9-14] Platelets from COVID-19 patients are hyperreactive in comparison to healthy donors when activated with traditional platelet agonists such as adenosine diphospate, collagen, and thrombin. This increase in platelet reactivity appears to be, in part, dependent on increased protein kinase C delta, extracellular signal-regulated kinases, and p38 signaling, resulting in increased degranulation and thromboxane B_2 generation.[9,13] Furthermore, platelets from COVID-19 patients release extracellular vesicles as well as dense and alpha granule cargo into the blood, including serotonin, soluble P-selectin, soluble CD40L, platelet-derived growth factor, and platelet factor 4.[10-13] In addition, COVID-19 induces significant changes to the platelet transcriptome, which are distinct in many ways from transcriptional changes observed in influenza and sepsis.[9]

Numerous factors can lead to platelet activation and hyperreactivity in COVID-19 patients. Platelets may activate as a primary result of alterations in gene expression or secondarily to the generation of increased soluble pro-coagulant molecules, such as fibrinogen.[2,15] During the overwhelming inflammation that prevails in COVID-19, the accumulation of cytokines and other factors may also activate platelets—among a number of other potential mechanisms. In addition to these indirect mechanisms, viruses can directly activate platelets or megakaryocytes, including dengue virus, influenza virus, human immunodeficiency virus-1 (HIV-1), and encephalomyocarditis virus, offering another potential mechanism for increased platelet activation and hyperreactivity during SARS-CoV-2 infection.[16-21] Viruses can also activate platelets through indirect interactions with FcγRIIA, a mechanism that may take place uniquely if antibodies directed against SARS-CoV-2, or cross-reacting antibodies against more common coronaviruses that generate minor cold symptoms in humans (229E, NL63, OC43, and HKU1), are present.[22] A mechanism in which SARS-CoV-2 directly activates megakaryocytes and platelets appears possible as two independent studies have reported the presence of SARS-CoV-2 mRNA in platelets of some COVID-19 patients.[9,12] However, how SARS-CoV-2 interacts with megakaryocytes and platelets has not fully been elucidated and remains controversial.

3 | POTENTIAL RECEPTORS FOR SARS-COV-2 BINDING TO MEGAKARYOCYTES AND PLATELETS

A putative receptor for the binding and entry of SARS-CoV-2 virus to cells is angiotensin converting enzyme-2 (ACE2).[23] The receptor is highly expressed by nasopharyngeal airway epithelial cells as well as alveolar epithelial cells, vascular endothelial cells, and lung macrophages,[24] which likely explains the notable acute respiratory distress syndrome in COVID-19 patients. In addition to ACE2, the cellular serine protease TMPRSS2 is necessary for cleaving the S protein on SARS-CoV-2, which allows for fusion of viral and cellular membrane and subsequent viral entry to the cell.[25] The expression of ACE2 and TMPRSS2 in platelets and megakaryocytes has not been specifically examined until now. Published work by Manne et al did not detect ACE2 or TMPRSS2 in CD45-depleted platelets from either healthy donors or COVID-19 patients using a number of complementary transcriptomic and proteomic assays, including RNA-seq analysis, real-time polymerase chain reaction, and western blot analysis.[9] These findings were confirmed and extended by Zaid et al using similar techniques, and also demonstrated that ACE2 protein was not present in human platelets using immunocytochemistry.[13] Consistent with this prospective work, retrospective analyses of previously published deep sequencing and microarray datasets from our groups and others,[12,16,26-31] have not identified any ACE2 or TMPRSS2 expression in $CD34^+$-derived, cultured human megakaryocytes or platelets from healthy donors. Furthermore, ACE2 and TMPRSS2 are not expressed in isolated human platelets during acute infectious diseases, including influenza, dengue, and sepsis.[16,29] Proteomic approaches based on mass spectrometry on isolated human platelets have also failed to identify ACE2 or TMPRSS2 protein in platelets.[32] RNA-seq analyses using platelets and megakaryocytes from mice also reveal a lack of ACE2 and TMPRSS2 expression.[31,33] In contrast, a recent study by Zhang et al observed robust ACE2 and TMPRSS2 mRNA and protein expression on platelets from healthy humans and mice.[12] These investigators also used

in vitro assays and in vivo ACE2 transgenic mice to report that both complete SARS-CoV-2 virus as well as the SARS-CoV-2 spike protein are able to induce platelet activation.

How might we reconcile these apparently discordant findings on whether platelets and megakaryocytes express ACE2 and TMPRSS2? Differences in ethnicities may explain the discrepant observations of ACE2 and TMPRSS2 RNA expression as Manne et al[9] and Zaid et al[13] included individuals from North America and North Africa while Zhang et al[12] studied individuals from Asia. Interestingly, ACE2 and TMPRSS2 RNA were below the limit of detection in a publicly available microarray-based platelet transcriptomics dataset which includes a relatively large proportion of healthy Black individuals.[30] Alternatively, reported differences may be due to differences in methods to isolate platelets for RNA0based assays. Both Manne et al[9] and Zaid et al[13] used CD45+ beads to bind and thereby deplete any residual leukocytes from washed platelet preparations. In contrast, Zhang et al[12] used gel-purified platelets. While a monocyte-specific marker (eg, CD14) was used to confirm the absence of white blood cells, perhaps lymphocytes, natural killer cells, and other white blood cells lacking CD14 expression were inadvertently present in platelet preparations used for RNA studies. For protein-based assays, differences in antibody binding epitopes and/or non-specific binding may have played a role. The work by Zhang et al[12] also provided intriguing mechanistic evidence of platelet hyperactivation following the injection of SARS-CoV-2 spike protein in K18 human ACE2 transgenic mice. As human ACE2 expression is driven by the epithelial cell cytokeratin-18 promoter,[34] it remains uncertain as to whether human ACE2 was expressed by megakaryocytes and platelets in these transgenic mice and how these observations can be reconciled with those made in humans. Future studies are needed to confirm whether the transgenic expression of the receptor in mice reflects the expression profile in humans.

While the definitive answer of whether platelets express ACE2 and TMPRSS2 remains to be solved, it is very important to not lose sight of consistencies between these reports, and how concordant findings advance our understanding and are foundational for further studies. Not only did all studies demonstrate platelet activation in SARS-CoV-2 infection, they also confirmed that the SARS-CoV-2 virus can be found within platelets. This suggests that there may be ACE2-independent mechanisms whereby SARS-CoV-2 directly interacts with, and possibly enters, platelets. What could this receptor be? In contrast to ACE2 and TMPRSS2, CD147 (basigin) is a highly glycosylated transmembrane protein robustly expressed in blood cells.[35,36] CD147 is believed to also be an alternative receptor for SARS-CoV[37] and SARS-CoV-2[38] as well as for HIV-1 and measles.[39,40] The expression of CD147 in blood cellular lineages is suggested to be more elevated in male than female individuals, and is upregulated in conditions of asthma, chronic obstructive pulmonary disease, and obesity,[35] which is consistent with the reported risks factors underlying complications in COVID-19. However, the role of CD147 in SARS-CoV-2 infection remains controversial as additional studies have been unable to observe binding of the SARS-CoV-2 spike protein to CD147.[41] While the role of CD147 remains unclear in SARS-CoV-2 infection, RNA-seq[16,26,29-31] and proteomic analysis indicate robust expression of CD147 on platelets with an estimated 2000 copies per platelet.[32] Interestingly, previous studies from our group and others suggest engagement of CD147 through homotypic or heterotypic interactions induces P-selectin expression, CD40L release, and platelet adherence similar to findings observed when SARS-CoV-2 interacts directly with platelets.[36,42] The studies by Zhang et al[12] would also support a direct CD147 interaction with SARS-Cov-2 and the spike protein as they used competitive inhibition through the use of recombinant ACE2 and antibodies against the spike protein on SARS-CoV-2 to probe regulators of SARS-CoV-2–dependent platelet activation rather than only blocking platelet ACE2 specifically. Thus, there remains the possibility other receptors such as CD147 are responsible for mediating SARS-CoV-2 platelet interactions. Of note, red blood cells, which are more numerous than platelets in circulating blood, also express CD147[43] and may compete against platelet CD147 for SARS-CoV-2 virus binding.

In addition to CD147, emerging evidence suggests CD26 may play a role in SARS-CoV-2 infection. Previous studies have demonstrated Middle East respiratory syndrome (MERS)-CoV utilizes CD26 to infect cells and recent structural studies suggest CD26 might also bind SARS-CoV-2.[44] However, a query of prior platelet RNA-seq and proteomic datasets suggest that platelets and megakaryocytes

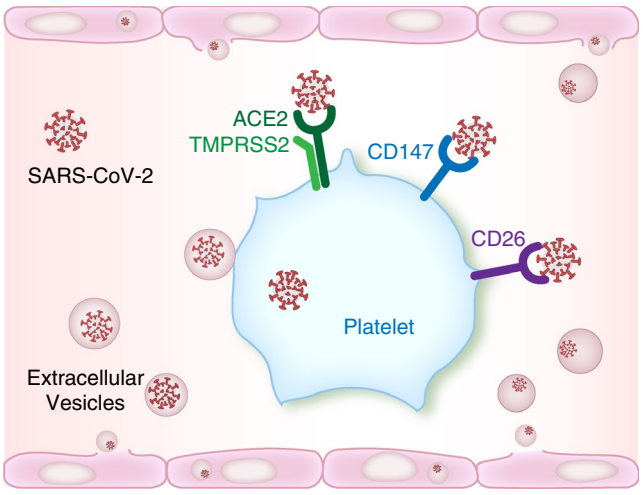

FIGURE 1 Possible mechanism(s) for SARS-CoV-2 interactions with platelets. A subset of platelets from COVID-19 patients contain SARS-CoV-2 mRNA. Angiotensin converting enzyme-2 (ACE2) and TMPRSS2 are the primary mechanism for entry of SARS-CoV-2 into cells, but the expression of these proteins on platelets remains controversial. Manne et al[9]and Zaid et al[13]recently observed the absence of both proteins in platelets based on RNA-seq, real-time polymerase chain reaction analysis, and proteomic approaches.[9,13]In contrast, Zhang et al[12]demonstrated expression of both ACE and TMPRSS2 on platelets.[12]It remains possible that SARS-CoV-2 may use ACE2-independent binding partners to interact with platelets, including CD147 and CD26. Extracellular vesicles containing SARS-CoV-2 released from infected endothelial cells may also interact with platelets, therefore allowing interactions and viral cellular entry independent of direct virus binding

do not express CD26, either under healthy baseline conditions or during acute infectious disease settings, including COVID-19.[9,32] While these findings certainly deserve confirmation in future studies, currently available evidence would indicate that interactions between SARS-CoV-2 and platelets are unlikely to occur only through CD26. In addition to direct virus interaction with megakaryocytes and platelets, it is possible SARS-CoV-2 virus released into extracellular vesicles from infected white blood cells or endothelial cells can be internalized by platelets, resulting in SARS-CoV-2 virus positive platelets through indirect uptake of viral particles contained inside extracellular vesicles.[45-48]

4 | CONCLUSIONS AND FUTURE DIRECTIONS

Independent studies from across the globe have shed light on platelet responses during SARS-CoV-2 infections. These studies have consistently identified that platelets are hyperreactive in COVID-19, and this hyperreactivity may contribute to injurious host thromboinflammatory responses. There also remains the possibility that platelets may serve as a cellular reservoir for SARS-CoV-2 infection, replication, and spread. Further studies elucidating these mechanisms are considered to be a high research priority. Additionally, understanding whether or not there are population-based differences in the expression of putative SARS-CoV-2 entry receptors on platelets is critical. This is particularly important in light of emerging clinical data demonstrating a disproportionate burden of disease among some populations. In addition—or perhaps as an alternative mechanism to—ACE2 and TMPRSS2, other platelet receptors and mechanisms may regulate SARS-CoV-2 engagement of platelets (Figure 1).

CONFLICT OF INTEREST

MTR is a member of the Scientific Advisory Board for Acticor Biotech SAS and holds a relevant patent.

AUTHOR CONTRIBUTIONS

Drafting of the manuscript: RAC, MTR and EB; concept and design: all authors; critical revision and editing of the manuscript: all authors.

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How to cite this article: Campbell RA, Boilard E, Rondina MT. Is there a role for the ACE2 receptor in SARS-CoV-2 interactions with platelets? *J Thromb Haemost*. 2021;19:46–50. https://doi.org/10.1111/jth.15156