Received: 21 January 2022 | Accepted: 26 January 2022

DOI: 10.1111/jth.15659

COMMENTARY

Platelet size as a mirror for the immune response after SARS-CoV-2 vaccination

Thomas Thiele | **Silas L. Schwarz** | **Stefan Handtke**

Institut für Immunologie und Transfusionsmedizin, Universitätsmedizin Greifswald, Greifswald, Germany

Correspondence
Thomas Thiele, Institut für Immunologie und Transfusionsmedizin, Abteilung Transfusionsmedizin, Sauerbruchstrasse, 17487 Greifswald, Germany.
Email: thomas.thiele@med.uni-greifswald.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: 374031971 – TRR 240; Gerhard Domagk Stiftung

Platelets provide cellular hemostasis[1] but also adopt several immune functions. They directly interact with viruses[2] and bacteria,[3] cross-talk with other immune cells,[4] and participate in inflammation and wound repair.[5]

Platelets are known effector cells in adverse immune response to vaccines.[6] A prominent example is the adverse reaction of vaccine-induced immune thrombotic thrombocytopenia (VITT).[7–9] VITT is a rare side effect occurring 4–30 days after application of adenoviral vector based COVID-19 vaccines and caused by immunoglobulin G class platelet-activating antibodies directed against the platelet chemokine platelet factor 4.[7–10] These antibodies form immune complexes with platelet factor 4 that are recognized by platelet Fc gamma IIa receptors,[11] inducing strong activation of platelets and procoagulant platelet formation.[12] Although VITT is a dramatic pathologic process, platelets likely contribute to the intended immunization process after vaccination against SARS-CoV-2. In this context, it is an interesting question how platelets physiologically respond to vaccination against SARS-CoV-2.

In this issue of *Journal of Thrombosis and Haemostasis*, Flego and Cesaroni et al. investigated features of the platelet-immune cross-talk in healthy recipients of two doses of the mRNA-based SARS-CoV-2 vaccine BNT162b2. They found a rapid cytokine response including increased levels of several interleukins, interferons, and tumor necrosis factor-α. They further detected signs of an elevated platelet turnover after vaccination. Platelet counts were only slightly altered but the mean platelet volume (MPV), platelet large cell ratio, and platelet distribution width showed a progressive increase during 20 days after the first vaccination. This increase correlated well with the antibody response against the SARS-CoV-2 spike protein.

The increase of the platelet size indices is indicative of an inflammatory process in response to vaccination following the sequence: I. vaccination → II. cytokine release → III. altered platelet generation → IV. change of platelet size and function (Figure 1). Normal platelet turnover is characterized by an equilibrium between platelet generation and clearance and a reciprocal relationship between platelet size and platelet counts in the circulation.[13,14] This is tightly controlled by thrombopoietin levels.[15] Platelet size *decreases* when healthy subjects receive thrombopoietin.[16] In systemic inflammation, several cytokines influence megakaryopoiesis and platelet generation.[17] For example, interleukin-1α (IL-1α) levels increase upon inflammation and promote platelet release by the rupture of megakaryocytes in the absence of elevated thrombopoietin, which is accompanied by an *increased* platelet size. This was shown in mice, where IL-1α mediated platelet release led to the generation of larger platelets than thrombopoietin-stimulated megakaryocytes.[18] Likewise, Flego, Cesaroni, and colleagues found a strong positive association between elevated MPV and IL-1β levels after vaccination in their study.

The increase of platelet size was associated with phenotypical changes of platelets, including increased levels of the integrins αIIb and Ibα, the inhibitory receptor PECAM-1 and glycoprotein (GP) VI. Larger platelets carry more platelet surface receptors under steady-state platelet turnover and are more responsive to platelet agonists.[19,20] In the study of Flego and Cesaroni et al., however, platelets respond significantly stronger to convulxin (an agonist of GPVI) especially after

Manuscript handled by: James Morrissey

Final decision: James Morrissey, 26 January 2022

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *Journal of Thrombosis and Haemostasis* published by Wiley Periodicals LLC on behalf of International Society on Thrombosis and Haemostasis

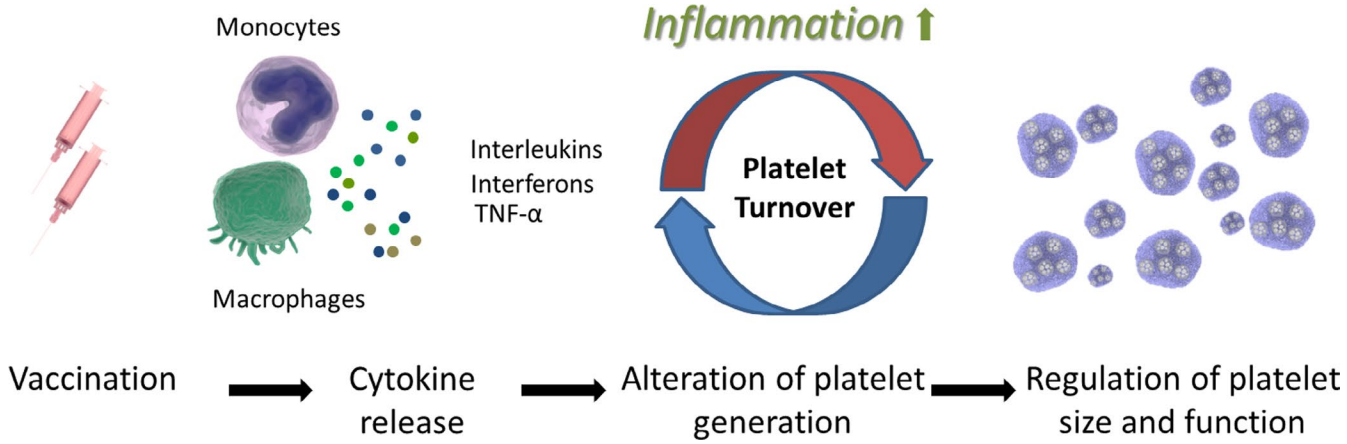

FIGURE 1 Hypothesis how SARS-CoV-2 vaccination affects platelet turnover and function (drawings: https://www.somersault1824.com)

the second vaccination at day 21. At that time point, the MPV and platelet receptor levels were already decreased compared with earlier time points. This could mean that an increased responsiveness is also adopted by smaller platelets on the long run, when platelet turnover has been temporarily increased after vaccination. Consequently, platelet size indices such as the MPV may not be good surrogates for platelet function, when platelet turnover changes. However, the authors reasonably argue, that changes of the MPV, platelet large cell ratio, and platelet distribution width may serve as parameters to judge on the immune response after vaccination. These items are easy to measure by routine cell counters. The authors show that individuals with a fast immune response with regard to anti-spike antibody production experienced a cytokine response shortly after vaccination, which was paralleled by an early increase of the MPV. In contrast, slow responders had a delayed cytokine response accompanied by a delayed increase of platelet size after vaccination.

The observations made by Flego, Cesaroni, and colleagues are useful to generate new hypotheses and highlight that vaccination results in a physiologic inflammatory response involving platelets and their size by affecting platelet turnover. It would be interesting to target these responses also after application of other vaccines and to dissect physiologic from pathologic immune reactions. This will increase our understanding of platelets as contributor and effector cell in rare adverse vaccination reactions. In this regard, the ongoing worldwide vaccination campaign is not only the most sufficient strategy to fight the SARS-CoV-2 pandemic, it may also provide an extraordinary opportunity to study immune functions of platelets.

ACKNOWLEDGMENT

S.H. is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 374031971 – TRR 240. S.L.S. is funded by a Gerhard Domagk Scholarship. Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

Dr. Thiele reports personal fees from Bristol Myers Squibb, Bayer, Daichii Sankyo, Pfizer, Novo Nordisk, Chugai Pharma, and Novartis, all of which are outside of the submitted manuscript. The other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Thomas Thiele, Silas L. Schwarz, and Stefan Handtke wrote the manuscript. Stefan Handtke and Thomas Thiele prepared the figure. All authors approved the final version.

ORCID

Thomas Thiele https://orcid.org/0000-0003-0177-6508
Silas L. Schwarz https://orcid.org/0000-0003-3804-2778
Stefan Handtke https://orcid.org/0000-0002-7331-8998

REFERENCES

1. Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev*. 2011;25(4):155-167.
2. Chabert A, Hamzeh-Cognasse H, Pozzetto B, et al. Human platelets and their capacity of binding viruses: meaning and challenges? *BMC Immunol*. 2015;16:26.
3. Palankar R, Kohler TP, Krauel K, Wesche J, Hammerschmidt S, Greinacher A. Platelets kill bacteria by bridging innate and adaptive immunity via platelet factor 4 and FcgammaRIIA. *J Thromb Haemost*. 2018;16(6):1187-1197.
4. Gaertner F, Massberg S. Patrolling the vascular borders: platelets in immunity to infection and cancer. *Nat Rev Immunol*. 2019;19(12):747-760.
5. Menter DG, Kopetz S, Hawk E, et al. Platelet "first responders" in wound response, cancer, and metastasis. *Cancer Metastasis Rev*. 2017;36(2):199-213.
6. Gunther A, Bramer D, Pletz MW, et al. Complicated long term vaccine induced thrombotic immune thrombocytopenia-a case report. *Vaccines (Basel)*. 2021;9(11):1344.
7. Schultz NH, Sorvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384(22):2124-2130.
8. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. 2021;384(22):2092-2101.
9. Thiele T, Weisser K, Schonborn L, et al. Laboratory confirmed vaccine-induced immune thrombotic thrombocytopenia: retrospective analysis of reported cases after vaccination with ChAdOx-1 nCoV-19 in Germany. *Lancet Reg Health Eur*. 2022;12:100270.

10. Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384(23):2202-2211.
11. Huynh A, Kelton JG, Arnold DM, Daka M, Nazy I. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature*. 2021;596(7873):565-569.
12. Althaus K, Moller P, Uzun G, et al. Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia. *Haematologica*. 2021;106(8):2170-2179.
13. Ittermann T, Feig MA, Petersmann A, et al. Mean platelet volume is more important than age for defining reference intervals of platelet counts. *PLoS One*. 2019;14(3):e0213658.
14. Handtke S, Steil L, Greinacher A, Thiele T. Toward the relevance of platelet subpopulations for transfusion medicine. *Front Med (Lausanne)*. 2018;5:17.
15. Handtke S, Thiele T. Large and small platelets - (when) do they differ? *J Thromb Haemost*. 2020;18(6):1256-1267.
16. Harker LA, Roskos LK, Marzec UM, et al. Effects of megakaryocyte growth and development factor on platelet production, platelet life span, and platelet function in healthy human volunteers. *Blood*. 2000;95(8):2514-2522.
17. Muller-Newen G, Stope MB, Kraus T, Ziegler P. Development of platelets during steady state and inflammation. *J Leukoc Biol*. 2017;101(5):1109-1117.
18. Nishimura S, Nagasaki M, Kunishima S, et al. IL-1alpha induces thrombopoiesis through megakaryocyte rupture in response to acute platelet needs. *J Cell Biol*. 2015;209(3):453-466.
19. Handtke S, Steil L, Palankar R, et al. Role of platelet size revisited-function and protein composition of large and small platelets. *Thromb Haemost*. 2019;119(3):407-420.
20. Handtke S, Wesche J, Palankar R, Greinacher A, Thiele T. Function of large and small platelets differs, depending on extracellular calcium availability and type of inductor. *Thromb Haemost*. 2020;120(7):1075-1086.

How to cite this article: Thiele T, Schwarz SL, Handtke S. Platelet size as a mirror for the immune response after SARS-CoV-2 vaccination. *J Thromb Haemost*. 2022;20:818–820. doi:10.1111/jth.15659