Platelet transcriptomics sense disease states

John W. Semple

Department of Laboratory Medicine, Division of Transfusion Medicine, Lund University, BMC C14, Sölvegatan 19, 221 84, Lund, Sweden

eBioMedicine 2026;125: 106194

Published Online xxx https://doi.org/10.1016/j.ebiom.2026.106194

Platelets are circulating cellular fragments derived from megakaryocytes in the bone marrow and continually sense the vessel endothelium for damage and initiate primary hemostasis.[1] What has become clear over the many years is that in addition to their primary role in hemostasis, platelets are also multifunctional and are key players in many other physiological and pathological processes e.g. wound repair, inflammatory processes and the immune response.[2–4] In this issue of *eBioMedicine*, Zhang and colleagues[5] advance a provocative idea that platelets are not merely effectors of hemostasis or even passive participants in immunity, but active, information-rich sensors of systemic immune states. By using platelet transcriptomics across hematopoietic stem cell transplantation (HSCT), its complications, and autoimmune/inflammatory diseases, the authors argue that platelets function as accessible, non-invasive reporters of immune dynamics and disease states.

A central strength of the paper is its choice of HSCT as a model system. Immune reconstitution after HSCT is one of the few clinical contexts where the trajectory from innate to adaptive immunity is relatively well characterized and temporally staged.[6,7] By sampling platelets at short-term (20–60 days) and long-term (>180 days) reconstitution, the authors show that platelet transcriptomes mirror this transition: early platelets are enriched for neutrophil and monocyte gene signatures, while later platelets display T- and B-cell–related transcripts. This alignment between known immune recovery kinetics and platelet RNA profiles provides a proof-of-principle that platelet transcriptomes track immune system composition and activity. The correlation analyses linking platelet immune genes to immune cell counts strengthen the argument that platelets are sampling, directly or indirectly, the circulating immune milieu rather than reflecting random noise.

The study also benefits from careful platelet isolation and quality control. Demonstrating <0.1% leukocyte contamination is critical because of the skepticism in platelet transcriptomics that signals simply derive from residual nucleated cells. While no purification is perfect, the authors' approach and transparency about thresholds improve confidence that the observed signals are genuinely platelet-associated.

The extension from "immune monitoring" to "disease sensing" is where the paper becomes particularly interesting. In acute graft-versus-host disease (aGVHD), platelet transcriptomes showed upregulation of neutrophil activation pathways and downregulation of antigen presentation signatures, consistent with known aspects of aGVHD pathobiology.[8] Importantly, these changes were detected even when platelet counts and reconstitution times were similar to complication-free patients, suggesting that platelet RNA profiles may capture qualitative immune states not visible in routine labs. The small longitudinal analysis showing that these signatures track treatment response (decreasing in complete response, persisting in unstable partial response) hints at the possibility of real clinical utility as a monitoring tool. Similarly, in CMV DNAemia, platelets exhibited strong interferon and antiviral gene signatures. The fact that aGVHD-associated signatures did not appear in CMV and vice versa supports some degree of disease specificity rather than a generic "inflammation signal." This disease discrimination is a key requirement if platelet transcriptomics are to become diagnostically useful.

The authors further broaden their claim by analyzing public datasets in systemic lupus erythematosus (SLE) and ulcerative colitis (UC). In both, platelet transcriptomes reflected known immune features: simultaneous innate and adaptive activation in SLE, and T-cell and cytokine-driven inflammation in UC.[9,10] These cross-disease validations are a strength, suggesting generalizability beyond the transplant setting.

The machine learning component is another highlight. Models built on immune gene subsets outperformed those using whole transcriptomes in distinguishing SLE or UC from healthy donors. This is conceptually appealing because focusing on biologically grounded features may reduce noise and improve interpretability. The identification of genes like DNMT1 and TOP1 as diagnostic contributors also illustrates how such models might generate hypotheses about disease biology, not just classifiers (Fig. 1).

Despite these strengths, several limitations need mentioning. First, the mechanistic basis of platelet "sensing" remains inferential. The authors cite RNA transfer from leukocytes and altered megakaryocyte programming as possible sources, which are plausible and supported by prior literature, but this study does not directly dissect these mechanisms. Without

DOI of original article: https://doi.org/10.1016/j.ebiom.2026.106174

E-mail address: john_w.semple@med.lu.se.

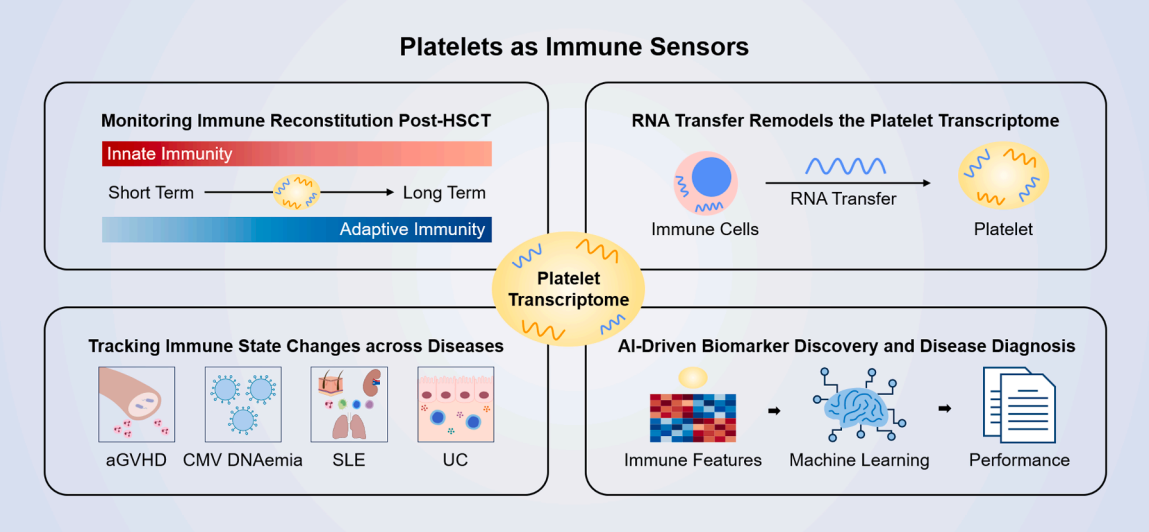

Fig. 1: Schematic showing the complexity of platelet transcriptomics in sensing disease progression. Analyzing the platelet transcriptome may be able to monitor innate and adaptive immune reconstitution post-HSCT (Upper left panel). It appears that RNA transfer from immune cells may remodel the platelet transcriptome (Upper right panel). This may allow for the tracking of immune state changes across various disease states including diseases such as GVHD, CMV DNAemia, SLE, and UC (Lower left panel). Importantly, machine learning may allow for AI-driven biomarker discovery and disease diagnosis.

distinguishing inherited megakaryocyte RNA from acquired RNA, it is difficult to know whether platelets are active sensors, passive collectors, or a mixture of both. Functional experiments e.g., tracing RNA transfer or profiling megakaryocytes post-HSCT would strengthen causal claims. Second, sample sizes in several subgroups, particularly complications like CMV DNAemia (n = 6) and longitudinal aGVHD analyses, were small. While understandable in a clinical setting, this raises concerns about overfitting and stability of gene signatures. External validation cohorts will be essential before clinical translation. Third, transcriptomic changes do not necessarily equate to functional consequences. Platelets are anucleate, and while they can translate RNA, the extent to which these immune transcripts alter platelet behavior is not addressed. It remains possible that platelet RNA profiles are excellent biomarkers but limited effectors. Finally, confounding factors such as medications, conditioning regimens, infections, or endothelial injury may influence platelet RNA content. The authors mitigate some of this through inclusion criteria, but in real-world practice, disentangling these variables will be challenging.

Conceptually, the paper contributes to a broader shift in how we view circulating blood components, as dynamic biosensors rather than static cell types. Platelets are especially attractive because they are abundant, easy to obtain, and already central to clinical workflows. If validated, platelet transcriptomics could complement or, in some settings, substitute for more invasive immune monitoring strategies. This work positions platelets as integrators of immune information, capable of reflecting immune reconstitution, detecting transplant complications, and sensing autoimmune and inflammatory disease states. While mechanistic depth and large-scale validation are still needed, the study is forward-looking and opens a fertile area for research at the interface of hematology, immunology, and precision medicine. Even if platelets ultimately serve more as biomarkers than "sensors" in an active sense, their transcriptomes may become a valuable window into systemic immunity.

Contributors

JWS wrote the first draft and edited the manuscript. The author approves the final manuscript.

Declaration of interests

The author declares no conflicts of interest.

Acknowledgements

Funding for this study was received from The Swedish Research Council (JWS # 2021-01310), The Swedish Government Funds for Clinical Research (ALF; JWS, #20220073), and The Alfred Österlund Foundation (JWS).

References

1 Jurk K, Kehrel BE. Platelets: physiology and biochemistry. *Semin Thromb Hemost*. 2024;50(5):794–803.
2 Maouia A, Rebetz J, Kapur R, Semple JW. The immune nature of platelets revisited. *Transfus Med Rev*. 2020;34(4):209–220.
3 Kapur R, Semple JW. The nonhemostatic immune functions of platelets. *Semi Hematol*. 2016;53(Suppl 1):S2–S6.
4 Kapur R, Zufferey A, Boilard E, Semple JW. Nouvelle cuisine: platelets served with inflammation. *J Immunol*. 2015;194(12):5579–5587.

5 Zheng L, Feng D, Wu Y, et al. Platelets as immune sensors: monitoring immune dynamics and diagnosing disease States across multiple disorders. *eBioMedicine*. 2026. https://doi.org/10.1016/j.ebiom.2026.106174.

6 Ogonek J, Kralj Juric M, Ghimire S, et al. Immune reconstitution after allogeneic hematopoietic stem cell transplantation. *Front Immunol*. 2016;7:507.

7 Hammoudi T, Nucera S, Troullioud Lucas AG, et al. Harmonized immune recovery monitoring after HCT: evidence and practical guidance from the Westhafen Intercontinental Group. *Blood Adv*. 2025;9(23):6141–6157.

8 Leveque-El Mouttie L, Koyama M, Le Texier L, et al. Corruption of dendritic cell antigen presentation during acute GVHD leads to regulatory T-cell failure and chronic GVHD. *Blood*. 2016;128(6):794–804.

9 Ahmed A, Li S, Yu JJ, Shao WH. Immunopathogenesis of systemic lupus erythematosus: interplay of innate and adaptive immunity, microbiome dysbiosis, and emerging therapeutic targets. *Pathophysiology*. 2025;32(4):61.

10 Shimomori Y, Yokoyama Y, Kurumi H, et al. Unraveling the complexity of ulcerative colitis: insights into cytokine dysregulation and targeted therapies. *EXCLI J*. 2025;24:638–658.