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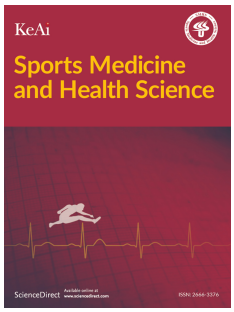

Red blood cells as delivery vessels for exerkines: A novel transfusion-based Strategy

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PII: S2666-3376(26)00076-4

DOI: https://doi.org/10.1016/j.smhs.2026.06.002

Reference: SMHS 363

To appear in: *Sports Medicine and Health Science*

Received Date: 8 June 2026

Revised Date: 29 June 2026

Accepted Date: 29 June 2026

Please cite this article as: Misiti F, Red blood cells as delivery vessels for exerkines: A novel transfusion-based Strategy, *Sports Medicine and Health Science*, https://doi.org/10.1016/j.smhs.2026.06.002 .

Letter to Editor

Red blood cells as delivery vessels for exerkines: A novel transfusion-based Strategy

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Dear Editor,

Recent translational perspectives highlight the therapeutic potential of exercise-conditioned plasma, which is now considered ready for early-phase clinical trials across various non-communicable diseases, including cancer and Alzheimer's disease, given the well-established benefits of exercise (1,2). Despite these promising advances in plasma transfusion, we propose a more refined approach using washed and filtered red blood cells (RBC) from regularly exercising donors as the primary therapeutic vehicle to deliver the health-promoting effects of exercise in patients. This hypothesis is grounded in the unique biology of the RBC. The RBC is not merely an inert carrier of oxygen. During its 120-day lifespan, RBCs continuously interact with the plasma milieu, actively sampling and accumulating circulating molecules. It has recently been highlighted that receptors, including toll-like receptor 9 (TLR9) (3) and multispecific chemokine receptors (DARC) (4,5), allow RBC and RBC-derived extracellular vesicles (RBC-EV) to interact with myokines, exercise-responsive miRNAs, and even metabolites, collectively known as exerkines (6), released during skeletal muscle contraction. While the direct binding mechanisms between RBCs and exerkines are still being fully mapped, RBCs and RBC-EVs may both function as a homeostatic 'sink' for these circulating factors (7).

Why focus on RBC instead of whole plasma? First, RBC transfusion is the most common, safest, and most standardized medical procedure, with well-established protocols for storage, cross-matching, and infusion that help avoid adverse reactions. Second, RBCs act as a slow-release delivery system. Following transfusion, senescent or hemolyzed RBC are cleared by the recipient's macrophages, potentially leading to a gradual and sustained release of accumulated exerkines into the recipient's circulation. Third, RBC-derived extracellular vesicles (RBC-EV) have been suggested to be generated during a 30 min period of cycling exercise (8). From a mechanistic perspective, this model aligns perfectly with the multiomic characterization of EVs. As noted by Silvestri et al. (1), exercise-derived EVs deliver complex cargo, including miRNAs, proteins, metabolites, and myokines, which are shaped by exercise intensity and duration and modulate tumor microenvironments, enhance immune surveillance, and protect against chemotherapy-induced cardiotoxicity.

Several critical steps are required to validate this hypothesis. First, preclinical studies using, among others, animal models of Alzheimer's disease and cancer should be conducted where RBCs from exercise-trained donors are transfused into sedentary, diseased recipients. Second, comprehensive omics profiling of RBCs and RBC-EV from human athletes, compared with sedentary controls, is required to identify and quantify the exercise-specific RBC markers as a function of exercise duration, type, and frequency. Third, the safety and feasibility of using "exercise-conditioned RBC" must be established, including consideration of potential storage lesions and immunomodulatory effects. In conclusion, while transfusion research rightly focuses on plasma and isolated EVs, we argue that RBCs enriched with RBC-EV from regularly exercising donors offer a clinically attractive, scalable, and biologically plausible alternative for delivering the systemic benefits of exercise to patients across different pathologies.

References

1. Silvestri, M., Fantini, C., Duranti, G., et al. (2026). Exercise-derived extracellular vesicles in oncology: a new frontier for translational nanomedicine. Journal of Translational Medicine, 24, 283.

2. Tari AR, Berg HH, Videm V, Brathen G, White LR, Rosbjorgen RN, et al. Safety and efficacy of plasma transfusion from exercise-trained donors in patients with early Alzheimer's disease: protocol for the ExPlas study. BMJ Open. 2022; 12: e056964.

3. Hotz, M.J.; Qing, D.; Shashaty, M.G.S.; Zhang, P.; Faust, H.; Sondheimer, N.; Rivella, S.; Worthen, G.S.; Mangalmurti, N.S. Red Blood Cells Homeostatically Bind Mitochondrial DNA through TLR9 to Maintain Quiescence and to Prevent Lung Injury. Am. J. Respir. Crit. Care Med. 2018, 197, 470–480.

4. Neote, K.; Darbonne,W.; Ogez, J.; Horuk, R.; Schall, T.J. Identification of a Promiscuous Inflammatory Peptide Receptor on the Surface of Red Blood Cells. J. Biol. Chem. 1993, 268, 12247–12249.

5. Xiong, Z.; Cavaretta, J.; Qu, L.; Stolz, D.B.; Triulzi, D.; Lee, J.S. Red Blood Cell Microparticles Show Altered Inflammatory Chemokine Binding and Release Ligand upon Interaction with Platelets. Transfusion 2011, 51, 610–621.

6. Novelli G., Calcaterra G., Casciani F., Pecorelli S., Mehta J.L. 'Exerkines': A Comprehensive Term for the Factors Produced in Response to Exercise. Biomedicines. 2024; 12:1975. doi: 10.3390/biomedicines12091975.

7. Misiti F, Falese L, Iannaccone A, Diotaiuti P. Erythrocytes as a Source of Exerkines. Int J Mol Sci. 2025 Oct 3;26(19):9665.

8. Nemkov, T.; Skinner, S.C.; Nader, E.; Stefanoni, D.; Robert, M.; Cendali, F.; Stauffer, E.; Cibiel, A.; Boisson, C.; Connes, P.; et al. Acute Cycling Exercise Induces Changes in Red Blood Cell Deformability and Membrane Lipid Remodeling. *Int. J. Mol. Sci.* 2021, *22*, 896.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Francesco Misiti reports was provided by University of Cassino and Southern Lazio. Francesco Misiti reports a relationship with University of Cassino and Southern Lazio that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.