Study reveals secrets of energy metabolism, promising better blood transfusions

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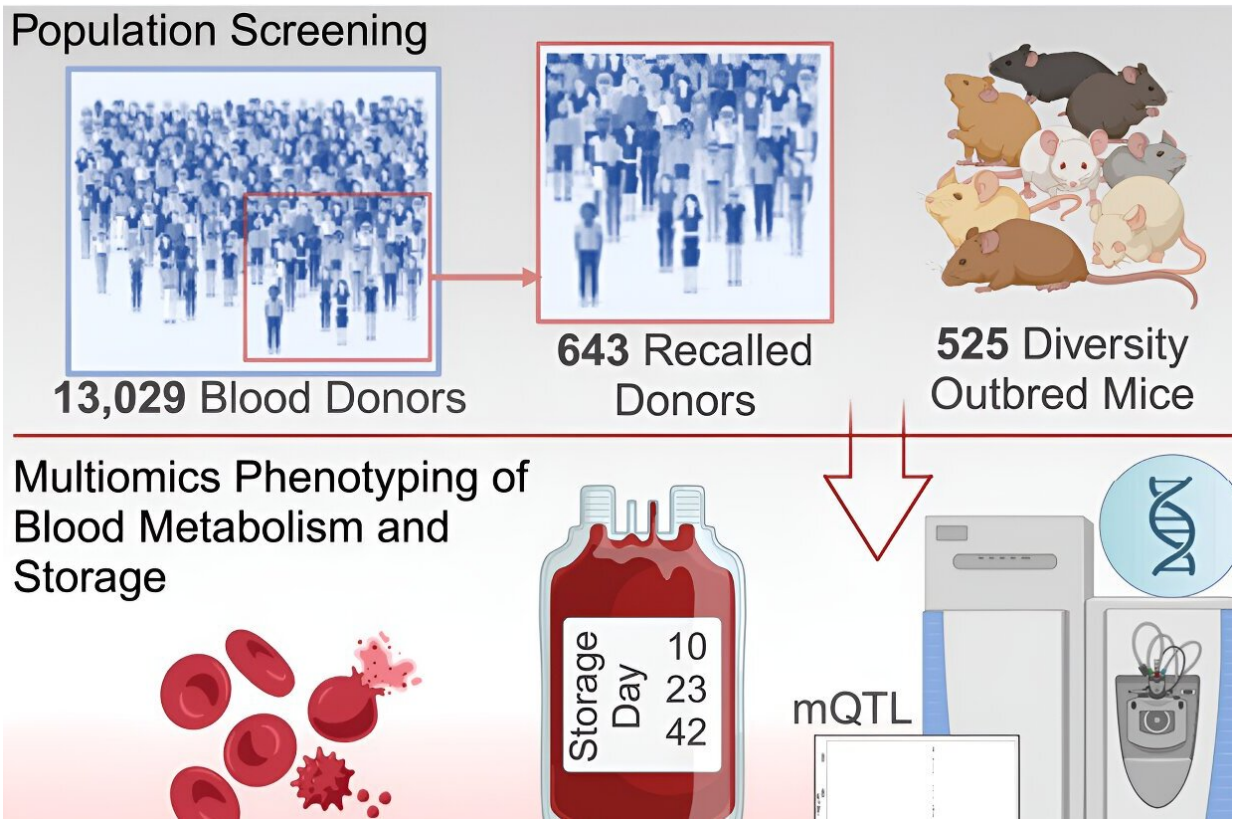

Graphical abstract. Credit: *Cell Metabolism* (2024). DOI: 10.1016/j.cmet.2024.06.007

Researchers at the University of Colorado School of Medicine have uncovered insights into how red blood cells function and survive during

storage—discoveries that could lead to better outcomes for patients receiving blood transfusions.

The study, led by Angelo D'Alessandro, Ph.D., and Travis Nemkov, Ph.D., professor and associate research professor, respectively, in the Department of Biochemistry and Molecular Genetics, and published in *Cell Metabolism*, highlights the biological and genetic factors that impact the energy status of stored red blood cells.

New avenues for personalized medicine

"Blood transfusion saves lives," said D'Alessandro, "but not all blood units are created equal, owing to donor and processing factors, including how long blood is stored in the blood bank before transfusion."

In the largest study of its kind, the team characterized blood from 13,000 donors to identify genetic and biological factors that regulate human glycolysis. Nemkov added, "This metabolic pathway is not only critical to red blood cell biology, but also a key regulator of human responses to exercise, cancer (the Warburg effect), aging and neurodegeneration, linking red blood cell function to overall human health."

"This study opens new avenues for personalized medicine in transfusion science," said D'Alessandro, the study's senior and corresponding author.

"Identifying and utilizing these biomarkers will enable us to tailor blood storage conditions to individual donor profiles, ultimately enhancing patient outcomes. By integrating the genetic and biological markers into blood storage protocols, it may be possible to extend the shelf life of stored blood, optimize blood inventory management and ensure that patients receive higher-quality transfusions."

Red blood cells lack nuclei and mitochondria, which makes glycolysis

their only source of adenosine triphosphate (ATP) generation. ATP is the main energy currency of all cells. In red blood cells, this molecule regulates their capacity to bind and release oxygen and prevents them from hemolyzing, or breaking down. This is particularly important for stored red blood cells, not just as they age in blood banks but also to ensure they survive in circulation and perform their function after transfusion.

Identified genetic markers

Younger donors and those of Hispanic descent were shown to have higher levels of ATP in their stored blood. Importantly, the study identified specific genetic markers that affect red blood cell glycolysis. These genetic polymorphisms, particularly in the PFKP, HK1 and CD38/BST1 genes, were linked to better storage outcomes and reduced cell breakdown.

"Our research highlights the importance of considering donor demographics and genetic background in blood storage practices," said first-author Nemkov. "By understanding these factors, we can develop strategies to improve the quality and efficacy of stored blood."

The study also suggests that ATP and hypoxanthine (HYPX) levels could serve as biomarkers for predicting the quality of stored red blood cells and their performance after transfusion. Higher ATP levels were associated with lower hemolysis, meaning the cells are less likely to break down and provide better outcomes post-transfusion.

The research team involved an international group of experts, including Kirk Hansen, Ph.D., professor in CU's Department of Biochemistry and Molecular Genetics, and investigators at Vitalant Research Institute, University of California in San Diego, Columbia University in New York, the Jackson Laboratory, RTI International and the University of

Virginia.

More information: Travis Nemkov et al, Biological and genetic determinants of glycolysis: Phosphofructokinase isoforms boost energy status of stored red blood cells and transfusion outcomes, *Cell Metabolism* (2024). DOI: 10.1016/j.cmet.2024.06.007

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