Molecular response to traumatic injury characterized for first time

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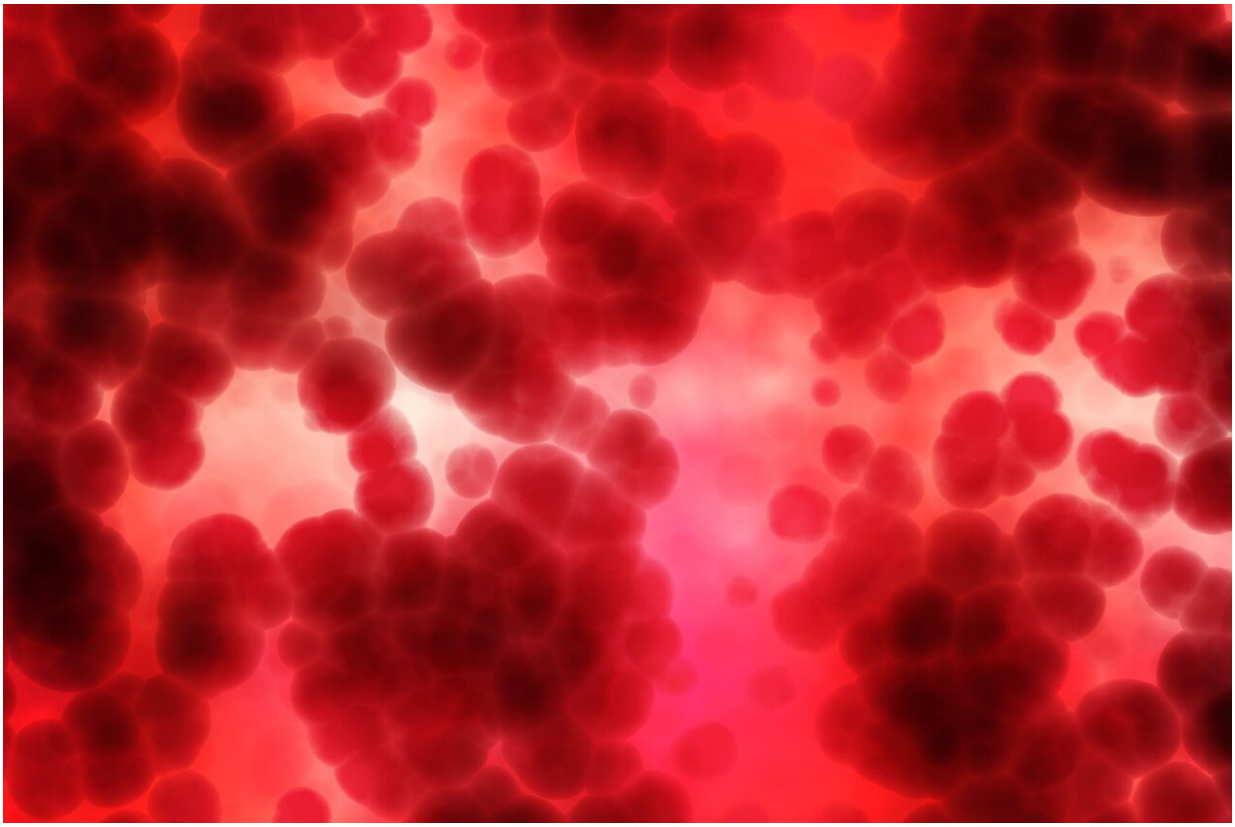

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The first-ever, in-depth characterization of the body's response to traumatic injury was published today in *Cell Reports Medicine* by University of Pittsburgh School of Medicine physician-scientists. The

results of their multiomics analysis—which spanned thousands of circulating molecules—offers an opportunity to refine personalized approaches to trauma management in the most severely injured patients.

"We are finally seeing a comprehensive picture of how the human body responds to systemic injury, when a person is taken from a state of relative health and pushed into an almost lethal state within microseconds," said main corresponding author Timothy Billiar, M.D., distinguished professor of surgery at Pitt and chief scientific officer for UPMC. "We've never quite known how different components of the human injury response fit together, so this is a trauma researcher's dream come true."

When emergency medical response teams get called into action, they know that time is of the essence. The arsenal of therapeutic tools available to trauma responders is limited, and, for patients who suffered massive injury from a car crash or a fall, every lost second can mean the difference between life and death.

Prehospital care therapies, such as thawed blood plasma administered even before the patient makes it to the hospital, can be astonishingly successful in increasing the odds of survival. More than three years ago, a clinical trial led by Pitt School of Medicine clinicians showed that trauma patients at risk of hemorrhagic shock who received two units of blood plasma during air medical transport were 10% more likely to survive than those who did not.

"The 10% reduction in mortality borders on unprecedented," said clinical trial lead and co-senior author Jason Sperry, M.D., M.P.H., professor in the departments of surgery and critical care medicine in Pitt's School of Medicine. "In the decades of research on trauma interventions, we have never seen such a big impact from such a small intervention. The benefits of giving plasma to trauma patients during air

transport are extraordinary and practice-changing."

But not every trauma patient benefits from early plasma administration. To ensure that therapeutic interventions are distributed in a way that maximizes the benefits and minimizes the waste of precious resources—especially during the ongoing plasma shortage further worsened by the pandemic—there is a strong need to identify those most likely to respond favorably to plasma early after injury.

Such an identification—which mirrors personalized approaches frequently used in the field of oncology—has never been achieved for trauma before.

"Despite how ubiquitous the problem is, the current therapies available for trauma patients are blunt instruments," said co-senior author Matthew D. Neal, M.D., the Roberta G. Simmons Associate Professor of Surgery at Pitt. "The complexity of perturbations that happen to a human body within seconds after injury is not something that we've ever understood before."

By analyzing thousands of circulating proteins and lipids, along with byproducts of cell metabolism and biomarkers of vessel injury, the clinicians discovered that human traumatic injury response could be classified into two "endotypes." They also found that only endotype 2 patients who also suffered traumatic brain injury benefitted from the infusion of thawed plasma—nearly 70% of those patients were alive 30 days after the injury, compared to 25% of endotype 1 patients.

The group also identified a single blood biomarker—a nerve cell enzyme called ubiquitin carboxyl-terminal esterase L1, or UCHL1, that is predictive of a favorable response to thawed plasma therapy.

Understanding the universe of interactions between molecules released

into the bloodstream after traumatic injury has been a dream of health scientists for decades. The progress in technologies that allow for high-throughput identification of circulating biomarkers, combined with newly available computational techniques, have finally made it possible to peek behind the curtain and uncover part of the complexity behind the body's response to sudden and severe injury.

Translating these insights into clinical practice is the next great race, doctors say. Point-of-care diagnostics that allow physicians to quickly test for a panel of blood biomarkers already exist and might be available more widely in the next five years, with this recent study guiding clinical action based on the results.

More information: Junru Wu et al, Multi-omic analysis in injured humans: Patterns align with outcomes and treatment responses, *Cell Reports Medicine* (2021). DOI: 10.1016/j.xcrm.2021.100478

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