An immune cell secretion may protect patients from transfusion-related lung injury

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What is this research about?

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related death. This rare but serious transfusion reaction is characterized by severe respiratory distress within six hours of receiving a transfusion. Currently, there are no treatments available other than supportive care (oxygen and lung ventilation).

The causes of TRALI remain poorly understood; however, researchers believe that human leukocyte antigen (HLA) antibodies from the donor are frequently involved. To explain why this reaction is triggered in some patients, a two-hit model has been proposed. In this model, two events must occur before TRALI can develop: the transfused blood product must contain problematic antibodies and the recipient must have predisposing risk factors. Researchers have identified several TRALI risk factors, including inflammation, chronic alcohol abuse and smoking. However, the detailed mechanisms of TRALI development remain unclear.

In brief…

Depletion of T regulatory cells or dendritic cells triggers TRALI in mice when stimulated by antibodies, and IL10 treatment protects from lung injury.

Recently, researchers funded by Canadian Blood Services at St. Michael's Hospital in Toronto helped clarify how TRALI develops. The researchers used mouse models of TRALI to examine the importance of different immune cell types, particularly dendritic cells and T regulatory cells. T regulatory cells help prevent autoimmune problems by suppressing immune responses to the body's own cells. Dendritic cells guide the immune system to respond appropriately to immune challenges.

What did the researchers do?

To identify which immune cells are most important for TRALI development, the researchers depleted different types of immune cells in mice, then injected antibodies similar to those frequently implicated in human TRALI. They also examined the role of an anti-inflammatory molecule secreted by immune cells, interleukin 10 (IL10). Specifically, the researchers looked at TRALI development in mice after IL10 treatment or deletion of the *IL10* gene.

Body temperature (an indication of systemic shock) was measured every 30 minutes. Ninety minutes after injection of the antibodies, the mice were euthanized to examine the lungs and measure biomarkers of lung function. TRALI signs included decreased body temperature, a greater wet:dry lung-weight ratio (indicating fluid accumulation), visible lung injuries (e.g. collapses or hemorrhaging) and impaired lung function.

What did the researchers find?

- Mice depleted of T regulatory cells or dendritic cells — but not mice depleted of other immune cell types — developed signs of TRALI, including fluid accumulation and visible injuries in the lungs, after injection with TRALI-inducing antibodies.
- Mice with TRALI had reduced levels of IL10, and mice with the *IL10* gene deleted developed TRALI after injection with TRALI-inducing antibodies (without depletion of immune cells).
- IL10 treatment 15 minutes after TRALI onset reversed respiratory symptoms caused by depletion of immune cells and injection of TRALI-inducing antibodies.

How can you use this research?

The researchers showed that TRALI can be induced by either depleting dendritic cells or T regulatory cells in mice, and then injecting antibodies that are specific for mouse major histocompatibility complex (MHC) Class I antigens (equivalent to human HLA antigens). These results support the two-hit model of TRALI development and provide additional information about why the reaction occurs. In response to an immune trigger such as the antibodies used in this study, IL10 is secreted by specific immune cells (T regulatory cells and dendritic cells). This increase in IL10 is needed to prevent harm from problematic donor antibodies in the transfused blood product.

These findings provide insight into the known risk factors for TRALI. For example, patients with alcoholic hepatitis have low levels of T regulatory cells in their blood, which could be related to an increased risk of TRALI. The new knowledge about TRALI mechanisms revealed in this study could also be used to identify patients at risk of developing TRALI.

The mouse models developed in this study closely mimic TRALI reactions in human patients; similarities include rapid onset, fluid in the lungs (pulmonary edema), decreased platelet numbers and a high mortality rate. These improved model systems will be valuable for future studies investigating TRALI causes and testing potential new therapies.

Most importantly, this study identified IL10 as a major protective factor and potential novel therapeutic for TRALI patients. Pre-treatment of mice with IL10 prevented TRALI from occurring, and IL10 injection 15 minutes after TRALI onset resolved the respiratory symptoms. Although others have shown that IL10 protects from other types of lung injury in mice, this study is the first to show the importance of IL10 in mouse models of TRALI. If these findings can be replicated in clinical trials with human patients, new therapeutics based on IL10 could be developed to help reduce suffering and help save the lives of more patients — or, perhaps, prevent TRALI from developing altogether.

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1. Kapur R, Kim M, Aslam R, McVey MJ, Tabuchi A, Luo A, Liu J, Li Y, Shanmugabhavananthan S, Speck ER, Zufferey A, Yousef G, Zhang H, Rondina MT, Weyrich AS, Porcelijn L, Kuebler WM, Slutsky AS, Semple JW. T Regulatory Cells and Dendritic Cells Protect against Transfusion-Related Acute Lung Injury Via IL-10. *Blood* 2017; 129: 2557-69.

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