ResearchUnit #51

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Fighting inflammation with inflammation

What is this research about?

Inflammation is characterized by redness, heat, swelling, pain and loss of function. It is a sign that the immune system is fighting something harmful. While helpful to fight injury or infection, excessive or inappropriate inflammation can cause disease. Inflammatory diseases include autoimmune diseases, which occur when the immune system attacks the body with inappropriate immune and inflammatory responses. Approximately 80 disorders are considered autoimmune, affecting an estimated 4.5 per cent of people. Autoimmune diseases include rheumatoid arthritis, type 1 diabetes and Crohn's disease.

The usual treatment for inflammatory and autoimmune diseases is to suppress the immune system (immunosuppressive therapy). This is usually effective but can have serious side effects, especially when used long term. Alternatives to immunosuppressive treatments include intravenous immunoglobulin (IVIg) which can work for some patients with autoimmune diseases. How IVIg works to treat autoimmune diseases is not clear. IVIg is an expensive plasma-derived drug. Its use in inflammatory and autoimmune disorders is growing rapidly and the supply of IVIg is limited, so finding alternative treatments is desirable.

IN BRIEF: Antibodies against red blood cells are a previously unexplored avenue to treat inflammatory and autoimmune disorders.

Here, researchers show that an inflammatory antibody against red blood cells can treat inflammatory disease. This approach is opposite to the usual immunosuppressive approaches to treat these diseases. The findings suggest that antibodies against red blood cells are a previously unexplored avenue to treat inflammatory and autoimmune disorders.

What did the researchers do?

The researchers began by investigating an autoimmune disease called ITP or immune thrombocytopenia. In ITP the immune system generates antibodies against blood platelets, causing their destruction in the spleen. This destruction involves immune cells called macrophages (a type of white blood cell) and a receptor on these cells called the Fc receptor or FcγR. The destruction of platelets leads to low platelet

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counts and a risk of bleeding. Interestingly, anti-D, an antibody recognizing red blood cells, is an effective treatment in many ITP patients. Why it is effective is unclear, and so far, anti-D's use in inflammatory disorders has been limited to ITP. In this study, the researchers used another red blood cell antibody called Ter119, which has been used as a model to understand how anti-D works in ITP. Ter119 is a mouse antibody, and the researchers conducted their study in mice. They looked at mouse models of ITP and other inflammatory and autoimmune diseases, including arthritis and transfusion-related acute lung injury (TRALI) – a rare but serious adverse effect of transfusion. They tested Ter119 to see if it could prevent the development of or effectively treat these inflammatory diseases. They used laboratory tests to examine immune cells and immune mediators to try to understand the mechanisms of the effects they saw.

What did the researchers find?

The red blood cell antibody Ter119 can treat murine ITP. This occurs through a mechanism not directly linked to anemia (the expected result of red blood cell destruction after treatment with a red blood cell antibody).

Ter119 can prevent and treat arthritis in three different mouse models of arthritis tested. Ter119 could prevent arthritis when given prophylactically (i.e. before the disease develops) and could treat already established arthritis (i.e. reverse established disease and improve inflammation and histology in joints affected by arthritis).

The Ter119 antibody Fc domain appears to be important for its therapeutic effects in inflammatory diseases. When Fc-domain function of Ter119 was impaired, it could no longer treat arthritis but could still cause anemia.

Ter119 induces monocyte (another type of white blood cell) chemokines, causes changes in monocytes in the blood and liver, and blocks the accumulation of chemokines, complement components and inflammatory cells, all of which could modulate inflammation. This suggests Ter119 helps resolve inflammatory and immune disorders by remodeling or redirecting the immune response.

Ter119 prevents TRALI in a mouse immune inflammatory model that mimics human TRALI.

How can you use this research?

Ter119 is considered an inflammatory antibody, as it leads to an increase in body temperature and induces inflammatory cytokines, but this research shows it has a potential role as an anti-inflammatory in mouse models of autoimmune disease. The

results indicate that Fc receptor or complement interactions could be important for the therapeutic actions of Ter119.

This research suggests that antibodies against red blood cells are a potential option to treat inflammatory and autoimmune disorders. Developing these red blood cell antibodies as alternative therapies to IVIg and anti-D in autoimmune or inflammatory disease could help reduce demand for these blood donor-derived plasma products. The research also advances understanding of how IVIg and anti-D work and challenges the idea these treatments work by a similar mechanism in ITP.

This is basic research in mice. While useful to explore potential therapies and shed light on mechanisms of action, as of yet this research cannot be directly translated to humans. To translate this research into humans, researchers would need to find a human-reactive antibody with similar properties and test it in a human system.

This work was conducted with an industry partner – CSL Behring – who performed some of the studies after the initial discovery by the Lazarus group. The approach uncovered may have broad therapeutic potential and could be an alternative to immune suppression which is the cornerstone of current treatment approaches to autoimmune disorders.

About the research team: This research was led by Alan Lazarus, a Canadian Blood Services scientist, a professor of medicine at the University of Toronto, and a member of the Toronto platelet immunology group at the Keenan Research Centre for Biomedical Science at St. Michael's Hospital, Toronto. Colleague Heyu Ni, a Canadian Blood Services scientist and a professor in the departments of medicine, laboratory medicine and pathobiology, and physiology at the University of Toronto, and the platform director for hematology, cancer, and immunologic diseases at St. Michael's Hospital, was also an author. Other authors include academic collaborators in Canada, Sweden, and the Netherlands, and industrial collaborators from CSL Behring AG and CSL Ltd in Switzerland and Australia.

This ResearchUnit is derived from the following publication(s):

[1] Crow AR, Kapur R, Koernig S, *et al*.: Treating inflammatory disease with an anti-erythrocyte antibody. *Sci Transl Med 2019 Vol. 11, Issue 506, eaau8217. DOI:* 10.1126/scitranslmed.aau8217

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