RESEARCH IMPACT CASE STUDY

Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

Intravenous immunoglobulin therapies: Understanding how and why they work

What was achieved?

Scientists at Canadian Blood Services have been studying the underlying biological mechanisms of intravenous immunoglobulin (IVIg) therapies to better understand who IVIg works best for and why. Although IVIg was first used in 1952 to treat patients with immune deficiencies, we still know little about how it works. Results from this research can be used to support the development of effective alternatives to IVIg (Tong et al., 2020).

How was this achieved?

Immunoglobulin therapies use antibodies to boost the immune system in patients with immune deficiencies, fight infections in people with weakened immune responses, and treat patients with autoimmune diseases by regulating the immune system. Immunoglobulin that are administered intravenously are called intravenous immunoglobulin therapies. IVIg is made from plasma collected from thousands of human donors. In Canada, IVIg is provided to hospitals by Canadian Blood Services. Demand for immunoglobulin therapies continues to grow in Canada and around the world.

Varied responses to IVIg among patients suggest something within the patients' immune systems may explain why it works well in some people but not others. To better understand how IVIg works, our research network examined how IVIg interacts with patient immune systems to reduce inflammation in the body.

Researchers from our network discovered that immunoglobulin therapies cause human macrophages (a type of activated white blood cell) to produce large amounts of an anti-inflammatory molecule called interleukin-10 (IL-10). This IL-10 molecule may help explain how immunoglobulin therapies reduce inflammation (Hubbard et al., 2020; Kozicky et al., 2015, 2018; Kozicky & Sly, 2017) and why they can be used to treat a wide range of inflammatory disorders. Researchers also discovered that interleukin-11 (IL-11) may also contribute to the anti-inflammatory effect of immunoglobulin therapies. This suggests that regulating IL-11 may improve the efficacy of IVIg therapies (Figueiredo et al., 2014; Lewis et al., 2018).

One of our recent discoveries is that IVIg may work by regulating a process called trogocytosis. This process boosts the immune system when immune cells exchange molecules or membrane fragments (Cruz-Leal etnal., 2024). Knowing how IVIg acts could lead to the development of more targeted therapies for autoimmune diseases. Our research on trogocytosis was featured on the cover of the February 2024 issue of *Blood*, a high-impact, peer-reviewed medical journal.

Importantly, a study from our research network also uncovered a gene that may explain why people respond differently to immunoglobulin therapies. The gene they found has two forms. In people with one form of the gene, immunoglobulin therapies work well and reduce inflammation. However, in people with a second form of the gene, these therapies do not work well. This is because people with the second form of the gene produce less IL-10. Sequencing this specific gene in people can determine who will respond best to IVIg therapies. Researchers confirmed the predictive model of this gene using mouse testing in 2019 (Kozicky et al., 2019).

In another first, our researchers discovered a way to deliver IVIg to specific areas of the brain. IVIg usually has a difficult time crossing the blood–brain barrier, but this new technique increased the delivery of IVIg into the hippocampus 39-fold. This discovery may inform the development of IVIg as a potential treatment for neurological conditions and diseases such as Alzheimer's disease (Dubey et al., 2020).

What was the impact and outcome?

These insights into how IVIg works have made it possible to develop several potential IVIg replacement drugs (see our other case study, IVIg Use in Immune Thrombocytopenia: Preventing Platelet Destruction and Exploring IVIg Alternatives). The hope is that these alternatives may reduce the burden on the IVIg supply and improve patient outcomes.

These findings bring significant benefits to patients and health-care systems. A personalized approach to treatment can optimize outcomes for people with various

immune-related disorders. Knowing that genetic variation in specific genes has an impact on how patients respond to IVIg therapies helps identify which patients will respond best to these therapies and which patients may benefit more from another treatment option.

There are are also potential economic benefits to IVIg alternatives. IVIg is costly to manufacture and distribute. The development of alternative IVIg replacement drugs could lead to cost savings in health-care systems and make therapies more accessible to more patients.

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