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Igg-Reactivity of Intravenous Immunoglobulin Preparations

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We read with interest the study by Néron and Roy [1] in which, they analysed the characterization of a commercial İntravenous İmmunoglobulin (IVIg) preparation by screening its interaction with 9484 proteins of human origin. They used the technology of protein array analysis and identified that 67 proteins are strongly recognized by the immunoglobulin G (IgG) present in IVIg. Néron and Roy [1] obtained acceptable reactivity for heat shock proteins, HLA-DR, thyroglobulin, CD16a (FcγRIIIa receptor), CD64, interleukin-1β, lamin A/C and ferritin, which are all related to immune-modulatory properties of IVIg. To our knowledge very few studies have analyzed the repertoire of IgG reactivities contained in IVIg preparations. In a study by Bussone et al. [2] in which they used a different methodology from Néron and Roy [1], they made a proteomics approach combining 2-DE and immunoblotting with a HUVEC protein extract and an HEp-2 cell protein extract enriched in nuclear proteins was used to reveal a core set of self-antigens recognized by IgG autoantibodies in IVIg preparations. Additionally they used MALDI-TOF-TOF MS analysis for the identification of proteins recognized by IgG. As a result of their study, among the total of 96 different proteins recognized in the HUVEC and HEp-2 cell protein extracts, 14 of these were recognized in both extracts, including 3 glycolysis proteins (alpha enolase, glyceraldehyde-3-phosphate dehydrogenase and triosephosphate isomerase), 4 RNA processing proteins (far upstream element binding protein 2 and heterogeneous nuclear ribonucleoproteins H, K and L) and 2 cytoskeletal proteins (actin cytoplasmic 2 and lamin-A/C) that might be exposed to the immune system through cell proliferation, apoptosis and/or necrosis.

IVIg preparations consist of pooled IgG from a minimum of 1,000 to over 60,000 blood donors, and were conceived as a replacement therapy for patients suffering from primary and secondary immunodeficiencies [3]. However, over the past 20 years, IVIg preparations have been increasingly observed to show therapeutic efficacy in the context of chronic inflammatory and autoimmune diseases, such as immune thrombocytopenic purpura, autoimmune neuropathies, systemic lupus erythematosus, myasthenia gravis, Guillain-Barre syndrome, and Kawasaki disease and additionally in chronic lymphocytic leukemia with frequent infections, bone marrow transplantation and in antibody mediated rejection of solid organ transplantations [4-6]. Delineating the mechanisms of action of IVIg will lead to a better understanding of the disease pathogenesis of autoimmune and inflammatory disorders.

One proposed mechanism of the effect of IVIg therapy is a blockade of FcγRs on phagocytes. In this scenario, the bound IgG prevents immune complexes from being phagocytosed and from delivering an activating signal to the target cells. In a mouse model of ITP, another mechanism has been proposed that involves induction of inhibitory FcγRIIb by IVIg [7]. Additionally, Abe et al. [8] showed that down-modulation of FcγRIIIa receptor has been linked to IVIg treatment of patients with Kawasaki disease. Study of Néron and Roy [1] supports this mechanism by showing that two independent peptides of FcγRIIIa receptor were recognized by IVIg antibodies. Additional mechanisms for the immune-modulation and anti-inflammatory actions of IVIg have been described, inhibition of complement deposition, enhancement of regulatory T cells, inhibition or neutralization of cytokines and growth factors, accelerated clearance of autoantibodies, modulation of adhesion molecules and cell receptors [9]. Despite the large number of publications, the immune-modulatory components of IVIg are still not conclusively established. Previous studies showed that IVIg binds to a diverse panel of self-antigens, especially to functional molecules of the immune system (i.e., CD4, CD5, cytokines, or MHC class I molecules), and thus they could modulate immune responses [10-14]. In a recent study, Mac-Millan et al. [15] reported that both IVIg and F(ab')2 fragments could inhibit the proliferation of T cells to CD3 and CD28 stimulation. Another mechanism by which IVIg could modulate the immune system is by expanding and enhancing the function of forkhead box protein 3 (FOXP3)–positive regulatory T (Treg) cells [16]. Although many recent mechanisms for the effects of IVIg on immune-modulation have been reported, these mechanisms are not mutually exclusive. It especially depends on both the dose of IVIg and the inflammatory process occurring in the disease.

IVIg treatment is generally considered as a safe procedure but has been associated with some serious adverse events such as hemolysis, thrombosis and allergic reactions that are seen especially in immunodeficient patients who receive monthly prophylactic infusions [17]. If the autoreactive IgG is present in IVIg, this could contribute to some of these adverse effects. And, if this is the case, it would be of interest to prepare IVIg with reduced autoreactivity using alternative industrial fractionation processes. Such studies like Néron and Roys' [1] shed light to understand which component or components of the IgG molecule mediate the immune-modulating effects might help investigators design more specific immune-modulating molecules. As Ballow [9] has mentioned, in the future, we can expect new processes to bioengineer the IgG molecule using the tools of molecular biology to incorporate the necessary factors into the IgG molecule that enhance its regulatory properties. The studies by Ravetch and colleagues suggest that this is possible for a sialylated Fc domain fragment [18,19]. It has been well known that IgG molecules have a unique feature of initiating pro and anti-inflammatory reactions. Minor variations in the IgG-attached sugar part could switch an antibody from a pro-inflammatory to an anti-inflammatory state. Function of the complex array of glycovariants present in serum IgG could be an important area for future studies.

The mechanisms of IVIg treatment have been investigated over the past three decades. However, additional experiments are needed to determine the influence of auto-reactive IgG repertoire on the therapeutic effect of IVIg preparations. The elucidation of the mechanisms of IVIg treatment is crucial for a more rationalized clinical use of IVIg.

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