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IV Ig immune inhibitory activity: APC is key

Beng H. Chong and James J. H. Chong  UNIVERSITY OF NEW SOUTH WALES

In this issue of Blood, Aubin and colleagues show that IV Ig interacted with FcγRs on APCs, resulting in reduced antigen presentation and inhibition of antigen-specific T-cell response. This finding suggests a key role for APCs in IV Ig action.

Recent evidence suggests that an essential step in the immunopathology of autoimmune disease (AD) involves antigen-presenting cells (APCs) presenting antigen to antigen-specific CD4+ T helper cells, which, in turn, induce antigen-specific B cells to produce autoantibodies (see figure). Costimulatory molecules including CD40 and CD154 play an important role in these cellular interactions, which perpetuate the disease. Autoantibodies bind autoantigens to form immune complexes (ICs) that are taken up by APCs via FcγRs for antigen processing and presentation, thus maintaining the pathogenic loop.

Intravenous immunoglobulin (IV Ig) has been used to treat AD for more than 2 decades. The precise mechanism(s) of action is still unclear. In this issue of Blood, Aubin and colleagues provide evidence suggesting that IV Ig acts at the level of APC even though they found that IV Ig inhibited antigen-specific T-cell and B-cell response. Mice immunized with ovalbumin (OVA) in the presence of IV Ig generated reduced numbers of antigen-specific T cells compared with mice immunized with OVA in the absence of IV Ig. IV Ig treatment during OVA immunization significantly reduced OVA-specific antibody production. These suppressive activities of IV Ig were not the result of decreased APC surface expression of MHCII and CD80/CD86 costimulatory molecules, as previously postulated, but were the consequence of IV Ig interfering with IC binding to activating FcγRs expressed on APC.

Three mechanisms have been proposed for the immune suppressive action of IV Ig in which pathogenic IgG/IC and FcγRs on APC are believed to have a role.

Mechanism 1: IV Ig competes with IC for activating FcγRs. In this mechanism, high-dose IV Ig competes with IC for activating FcγRs on APC surface. Data of Aubin et al would favor this mechanism. First, these investigators showed that 2.4G2, FcγRIII-specific monoclonal antibody blocked OVA-IC binding to bone marrow dendritic cells (BM-DCs), used as APC in this study. Second, they found that intact IV IgG inhibited antigen-specific T-cell response but its F(ab')2 fragments did not. Third, BM-DCs from γ chain-deficient mice (lacking FcγRs) failed to activate CD4+ T cells in the presence of IC. Altogether, their results suggest that IV Ig via its Fc domain competes with IC for binding to activating FcγRs expressed on APCs, consequently reduces APC antigen presentation, and inhibits CD4+ T-cell activation and other downstream immune responses. One reservation in interpreting these data is that monomeric IgG in
IVIg binds activating FcγRs (FcγRIII and VI) with low affinity, and it would seem surprising that IVIg would be able to compete with IC for binding to these Fc receptors.

**Mechanism 2:** IVIg induces expression of inhibitory FcγRs. Kaneko and colleagues showed recently that 1% to 2% of IgG in IVIg has sialic acid at the Asn297-linked glycan, and IVIg enriched in Fc-sialylated IgGs has increased immune inhibitory activity. These investigators proposed a mechanism of action for IVIg in which Fc–sialylated IgGs bind to a unique receptor (still to be identified) on macrophages/APCs and up-regulate expression of inhibitory FcγRs such as FcyRIIB. Up-regulation of inhibitory FcγRs delutes out the effects of activating FcγRs. They also argued that as Fc–sialylated IgGs are present only in small quantities in IVIg, this explains the high dose of IVIg required for immune inhibitory effect. In contrast, Aubin et al observe that IVIg inhibited antigen presentation to the same degree with BM-DC (APC) from FcyRIIB−/− and FcyRIIB+/+ (wild-type) mice, suggesting that the immune inhibitory effect of IVIg is FcyRIIB-independent.

**Mechanism 3:** IVIg saturates FcRn binding; FcRn binds pathogenic or non-pathogenic IgGs and protects them from catabolism. The third mechanism postulates that high doses of IVIg saturate the available FcRn binding sites and expose pathogenic autoantibodies, not bound to FcRn, to catabolic removal, thus reducing the amount of circulating autoantibodies. Consistent with this mechanism, Li et al showed that IVIg-treated wild-type mice, but not neonate FcRn-deficient mice, were protected from developing bullous skin disease when the animals were infused with antibodies from patients with pemphigus vulgaris. Mechanism 3, however, is not yet widely accepted because there is some evidence against FcRn having a role in IVIg action.

An important drawback in the study of Aubin et al is that they did not use an autoimmune disorder animal model and their findings may not necessarily represent the effects of IVIg in AD. Further studies are required, particularly studies using an autoimmune experimental system. Nevertheless, the findings in this study are helpful in providing insights into the mechanism(s) of IVIg action. If subsequently confirmed by further studies, the knowledge gained may inform development of effective novel therapies for AD, such as developing antibodies, peptides, or small molecules that block IC binding to activating FcγRs on APCs.

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**REFERENCES**


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**HIT: more than just heparin**

Theodore E. Warkentin  
McMaster University

In this issue of *Blood*, Lubenow and colleagues provide the first strong evidence that there is much more besides heparin in triggering the adverse drug reaction, HIT.  

As with any drug reaction, however, only a minority of patients who receive the offending drug are affected. Usually, this is attributed to poorly defined “idiosyncratic” (patient-specific) factors. But in the case of HIT, the perception has grown that there must be additional nondrug, but also nonsynodisyncretic, factors that influence immunization risk. The evidence behind this concept has been mostly indirect. For example, surgical patients appear to be more likely to develop HIT than medical patients. This is very different from an “idiosyncratic” reason where Mr X has an inherently higher risk of HIT than Mr Y. Rather, both Mr X and Mr Y would have a higher risk of HIT if they received heparin in the context of surgery, rather than if they received heparin as medical patients.

Now, Lubenow et al provide direct evidence that nondrug factors do indeed strongly influence anti-PF4/heparin immunization and HIT risk. They performed a randomized controlled trial comparing 2 types of heparin—unfractionated heparin (UFH) and a low–molecular-weight heparin (LMWH) preparation (certoparin)—administered for thromboprophylaxis after trauma. Patients were classified as “major” and “minor” trauma and were systematically evaluated for immunization (various tests for anti-PF4/heparin antibodies) and for HIT (thrombocytopenia and/or thrombosis bearing a temporal relationship to formation of platelet-activating antibodies). In their study, major trauma referred primarily to fractures of the pelvic, femur, tibia, fibula, or humerus; minor trauma to almost everything else (usually, distal upper-extremity, shoulder, and distal lower-extremity fractures).

The table summarizes the frequency of anti-PF4/heparin antibody immunization, as per a combination of immunoassays, categorized by severity of trauma (major, minor) and for type of heparin (UFH, LMWH). The corresponding data for clinical HIT are also shown.

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