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INVITED REVIEW

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Immunomodulatory and anti-inflammatory properties of immunoglobulin G antibodies

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Summary

Antibodies provide an essential layer of protection from infection and reinfection with microbial pathogens. An impaired ability to produce antibodies results in immunodeficiency and necessitates the constant substitution with pooled serum antibodies from healthy donors. Among the five antibody isotypes in humans and mice, immunoglobulin G (IgG) antibodies are the most potent anti-microbial antibody isotype due to their long half-life, their ability to penetrate almost all tissues and due to their ability to trigger a wide variety of effector functions. Of note, individuals suffering from IgG deficiency frequently produce self-reactive antibodies, suggesting that a normal serum IgG level also may contribute to maintaining self-tolerance. Indeed, the substitution of immunodeficient patients with pooled serum IgG fractions from healthy donors, also referred to as intravenous immunoglobulin G (IVIg) therapy, not only protects the patient from infection but also diminishes autoantibody induced pathology, providing more direct evidence that IgG antibodies play an active role in maintaining tolerance during the steady state and during resolution of inflammation. The aim of this review is to discuss different conceptual models that may explain how serum IgG or IVIg can contribute to maintaining a balanced immune response. We will focus on pathways depending on the IgG fragment crystallizable (Fc) as pre-clinical data in various mouse model systems as well as human clinical data have demonstrated that the IgG Fc-domain recapitulates the ability of intact IVIg with respect to its ability to trigger resolution of inflammation. We will further discuss how the findings already have or are in the process of being translated to novel therapeutic approaches to substitute IVIg in treating autoimmune inflammation.

KEYWORDS
autoimmunity, fc-receptors, immunoglobulin G, intravenous immunoglobulin, resolution of inflammation

1 | INTRODUCTION

Inflammation is a critical aspect of the physiological response to microbial infections. Inflammatory processes are characterized by a synchronized activation of immune cells, by the secretion of a complex network of molecular mediators, and by structural alterations in tissues, such as the opening of blood vessels and an increase in tissue permeability. Once the initiator stimulus of acute

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inflammation is cleared, highly regulated pathways are involved in initiating resolution of inflammation and in promoting tissue regeneration. While acute inflammation is essential to protecting the host against invading pathogens or injury, prolonged chronic inflammation caused by failure to resolve inflammation can cause severe damage to host tissues. A prototype example for diseases, where resolution of inflammation fails or is impaired are autoimmune diseases, where autoreactive immune cells continuously drive inflammatory processes and tissue damage.[1] Autoimmunity develops following breakdown of self-tolerance mechanisms leading to the expansion of autoreactive T cells and/or the production of immunoglobulin G (IgG) autoantibodies, which results in chronic inflammatory responses and tissue destruction. IgG autoantibodies are widely recognized as key mediators of tissue inflammation in many autoimmune diseases including systemic lupus erythematosus (SLE), immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AHA), rheumatoid arthritis (RA), forms of multiple sclerosis, and pemphigoid diseases.[2] Understanding both, the pathways underlying autoimmune/chronic inflammation as well as those responsible for resolution of inflammation thus is critical to develop therapeutic approaches effectively breaking the vicious cycle of autoimmune inflammation.

Of note, IgG antibodies may play an active role in both, the initiation as well as in the resolution phase of autoimmune inflammation.[3,4] On the one hand, they are well established drivers of inflammation by activating innate immune cells including neutrophils, eosinophils, mast cells, monocytes and macrophages via binding to Fcγ-receptors (FcγR) abundantly expressed on the surface of these cells or via activating the complement system[5]; On the other hand, however, they may be involved in limiting self-reactive immune responses and may play a central role in actively preventing excessive inflammatory processes. A notion supporting this concept comes from immunodeficient patients producing insufficient amounts of IgG resulting in recurring microbial infections. Interestingly, these patients are also characterized by a loss of humoral tolerance leading to the production of self-reactive antibodies, suggesting that either normal serum levels of IgG or subspecies of IgG antibodies present in serum are involved in maintaining humoral tolerance.[6,7] More direct evidence for an immunomodulatory activity of IgG comes from the use of pooled serum IgG to inhibit autoantibody dependent autoimmune diseases as well as chronic inflammatory responses. In this therapy serum IgG pooled from thousands of healthy donors (referred to as intravenous immunoglobulin (IVIg) therapy) is administered repeatedly at doses of 1–3 g/kg body weight, which initiates resolution of inflammation and impairs autoantibody activity.[8] The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved IVIG therapy for a variety of autoimmune diseases including Kawasaki disease (KD), multifocal motor neuropathy, immune thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).[9] Moreover, the efficacy of IVIg in dampening excessive inflammation has been shown in a variety of neuropathy syndromes, the recent coronavirus disease-19 (COVID-19) pandemics, and also in women with reproductive failure.[10–13] Finally, autoantibody driven skin blistering diseases including bullous pemphigoid have been demonstrated to respond well to IVIg infusion.[14,15] In summary, there is a broad set of clinical data demonstrating that normal serum IgG (IVIg) levels are critical for maintaining the immune system in a well-balanced state and that serum IgG or as we will discuss in this manuscript at least certain fractions within the pool of serum IgG antibodies can have an active immunomodulatory activity in mice and humans.

2 | MODULATION OF IgG DEPENDENT PRO-INFLAMMATORY PROCESSES BY FC-RECEPTORS

In order to understand the immunomodulatory pathways triggered by pooled serum IgG it is essential to briefly discuss the effector pathways responsible for IgG dependent innate immune effector cell activation and inflammation. For the purpose of the review we will focus on the role of cellular Fcγ-receptors (FcγRs) and the neonatal Fc-receptor (FcRn) in modulating (auto)antibody activity and half-life, respectively. The interaction of the IgG fragment crystallizable (Fc) with the family of FcγRs is centrally involved in triggering autoantibody dependent tissue inflammation.[16–18] This protein family consists of several activating and one inhibitory FcγR, FcγRIIb (Figure 1A).[19] The activating human FcγRs (FcγRIa, FcγRIIa, FcγRIIIa) and their murine counterparts (FcγRI, FcγRIII, FcγRIV) are broadly expressed by most subsets of innate immune cells including monocytes, macrophages, mast cells, eosinophils, NK cells and neutrophils and transmit activating signals through immunoreceptor tyrosine-based activating motifs (ITAM) upon higher order cross-linking by IgG immune complexes (IC) (Figure 1A,B). In contrast FcγRIIb signals through immunoreceptor tyrosine-based inhibitory motifs (ITIM) and limits immune cell activation.[20,21] Of note, due to the low affinity of most activating and the inhibitory FcγRIIb monomeric IgG cannot productively interact with FcγRs, thereby preventing constant activation of immune cells by serum IgG (Figure 1C). Furthermore, isolated co-crosslinking of FcγRIIb does not lead to initiation of inhibitory signaling pathways, but always requires the concomitant triggering of activating signals via ITAM containing immunoreceptors, such as activating FcγRs (Figure 1C). Thus, co-expression and co-crosslinking of activating and inhibitory FcγRs on innate immune effector cells represents an important checkpoint of IgG dependent immune cell activation and the induction of pro-inflammatory effector responses.[19] Consistent with this model, mice deficient in the inhibitory FcγRIIb show enhanced IgG dependent inflammatory responses, while mice lacking all or specific activating FcγRs show impaired IgG dependent pro-inflammatory responses.[22–26]

The strength of negative regulation of IgG responses via FcγRIIb depends on the differential affinity of different IgG subclasses for specific activating and the inhibitory FcγR. For

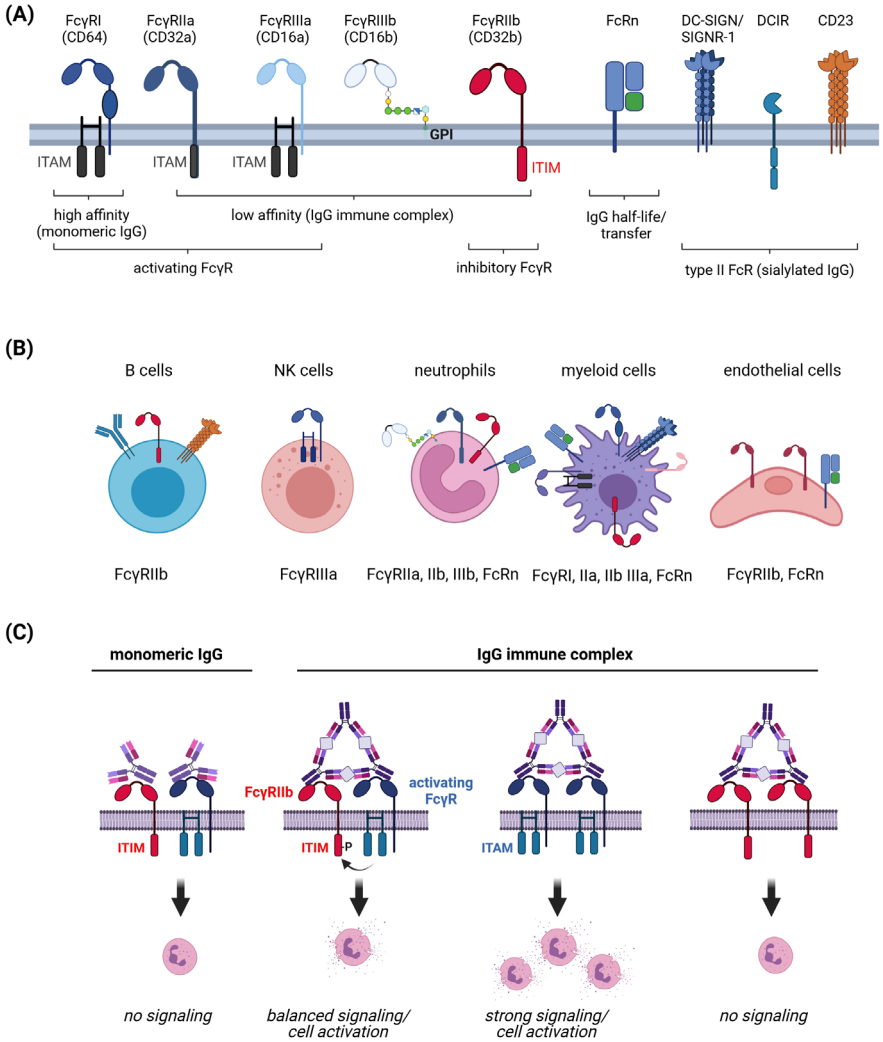

FIGURE 1 Fcγ-receptors as modulatory of autoantibody and immunomodulatory IgG activity. (A) Overview of the family of human Fcγ-receptors, consisting of high and low affinity as well as activating and inhibitory FcγR members. The neonatal FcRn binds IgG at low pH and is critical for maintaining the long half-life of serum IgG. Type II FcRs, including SIGNR1, DC-SIGN, CD23 or DCIR were suggested to ineract with highly sialylated IgG glycoforms. (B) Expression of type I and type II FcRs and FcRn on immune cells. Note that not all immune cells and subsets of immune cells are represented. (C) Shown is the activating of FcγR-dependent signaling pathways through monomeric or multimeric forms of IgG (IgG immune complexes). Whereas monomeric binding of IgG does not lead to productive signaling, the interaction of IgG ICs triggers activating and inhibitory signaling pathways. See text for further details.

example, mouse IgG1 binds better to FcγRIIb than to its activating FcγR, FcγRIII.[27] Accordingly, IgG1 activity is greatly enhanced in mice deficient in FcγRIIb. In contrast, mouse IgG2a/c or IgG2b bind better to the activating FcγRI and FcγRIV, resulting in a smaller level of negative regulation by FcγRIIb. Furthermore, the level of expression of activating versus the inhibitory Fc RIIb on a given effector cell is another decisive factor modulating the activation of innate immune effector cells. For example, in certain tissues such as the skin or brain, FcγRIIb is the predominant FcγR expressed on tissue resident macrophages.[28,29] Moreover, FcγRIV is expressed either at very low levels or even absent during the steady state, which may lead to a very strong inhibition of IgG2a/c and IgG2b responses in these specific organ environments. In contrast, in the kidney and subsets of lung macrophages FcγRIV is highly expressed and much smaller levels of the inhibitory FcγRIIb are present.[28] Of note, many pro-inflammatory cytokines (e.g. IFNγ, TNFα) are known to upregulate activating and downregulate the inhibitory FcγRIIb on innate immune cells, thereby limiting FcγRIIb dependent inhibitory effects and fueling IgG dependent innate immune cell activation.[30,31] Finally, factors modulating the binding strength of IgG subclasses to activating versus inhibitory FcγRs impact effector cell activation. This includes the size (multimeric state) of an IgG immune complex (IC) as well as IgG glycosylation.[32,33] For example, a lack of penultimate fucose residues in the IgG Fc-associated sugar moiety will enhance IgG binding to FcγRIIIa but not affect binding to the inhibitory FcγRIIb, thereby resulting in enhanced activation of effector cells expressing FcγRIIIa.[5,34] In contrast, a high level of galactose residues may increase the ability of IgG molecules to bind C1q, leading to the enhanced activation of the classical complement pathway.[35] Interestingly, however, pre-clinical data from mice suggests that not the classical (C1q-dependnet) but rather the alternative pathway of complement activation contributes to autoantibody dependent inflammatory processes at least in specific disease model systems.[36] In contrast, high levels of terminal sialic acid residues result in a reduced affinity for both, activating FcγRs and the inhibitory FcγRIIb.[37] The absence of IgG Fc glycosylation results in a loss of IgG binding to both, cellular FcγRs and C1q. Of note, small IgG IC, such as IgG trimers or hexamers may even act as inhibitors of innate immune effector cell activation as they bind to activating Fc Rs, but do not trigger signaling pathways leading to cell activation.[38–43]

3 | REGULATION OF IgG HALF-LIFE VIA THE NEONATAL FcRn

Apart from FcγRs, the neonatal FcRn is essential for IgG activity as it regulates IgG half-life by protecting IgG from intracellular degradation. FcRn is broadly expressed in endothelial cells and in many immune cells including monocytes and macrophages.[44,45] Upon endocytosis of IgG by FcRn expressing cells, FcRn binds IgG at a low pH in endosomal vesicles and transports it back to the cell surface, where FcRn affinity for IgG is strongly reduced due to a shift to a neutral pH, thereby releasing IgG back into the circulation or-if recycled locally-into tissues.[46] Consistent with this notion the induction of IgG dependent autoimmune pathology is largely impaired in FcRn deficient mice due to degradation of endocytosed IgG in lysosomal vesicles. Additionally, FcRn is involved in modulating the activity of IgG IC (IgG-IC).[47] For instance, it was shown that the ternary complex composed of FcRn and FcγRIIa in endosomal compartments of dendritic cells (DC) is needed to induce optimal antigen-specific T cell responses to IgG-IC.[48] Moreover, a reduction in pro-inflammatory cytokines (TNF-α, IL-12, and IL-6) and inflammation was noted in patients with RA upon blockade of FcRn even without a strong reduction in serum autoantibody levels, suggesting that the interaction of FcRn with FcγRs not only promotes antigen presentation but also modulates other innate immune effector responses.[48,49] In summary, the pro-inflammatory activity of IgG is critically dependent on the IgG Fc-domain and its interaction with cellular FcγRs, the complement system and the neonatal FcRn.

4 | PATHWAYS OF IVIg ACTIVITY

Numerous mechanisms of action of high-dose IVIg therapy have been proposed to operate in different disease contexts, including mechanisms dependent on the IgG F(ab) or Fc-domain.[3] Due to limitations in space we will focus on IVIg Fc-dependent mechanisms of action in this manuscript as pre-clinical data obtained in various mouse models of autoantibody-dependent and-independent inflammatory diseases as well as data from human clinical trials demonstrate that the isolated IVIg Fc-domain can inhibit autoantibody dependent inflammation in ITP and Kawasakis disease, strongly supporting the notion that an IgG Fc-domain dependent pathway is a major contributor to IVIg activity in vivo in mice and humans.[50–55] We will further separate the IgG Fc-domain dependent anti-inflammatory pathways of IVIg activity into two sections, covering (1) IVIg dependent competition with natural IgG effector pathways and (2) IVIg mediated immunomodulation (Figure 2).

5 | IVIg-DEPENDENT COMPETITION WITH IgG EFFECTOR FUNCTIONS

As mentioned before, for IVIg to have a therapeutic activity a very high dose of IgG in the range of 1-3 g/kg has to be administered. Such a high dose requirement may suggest that IVIg can directly interfere/compete with endogenous IgG autoantibody-triggered effector pathways important for inflammation. As discussed, effector pathways critical for the pro-inflammatory activity of autoantibodies include the activation of innate immune effector cells via cross-linking activating FcγRs, triggering of complement pathway activation, and FcRn-dependent regulation of autoantibody half-life.[19,35,46] Based on the protection of mice lacking individual or all activating FcγRs and based on previous studies with FcγRIIIa-blocking antibodies in ITP patients it was clear that blocking access of IgG-IC to activating FcγRs by IVIg is an efficient way of attenuating IC-mediated autoimmune pathology.[54,56] Based on the rapid activity of IVIg in normalizing platelet counts in pediatric and adult ITP patients it was discussed early on that a blockade of the reticuloendothelial system (RES), or in other words a blockade of an FcγR-dependent phagocytosis of IgG-platelet ICs, would be a plausible mechanism of IVIg activity.[53,57,58] Indeed, two studies demonstrated that in IVIg treated patients the clearance of IC was slowed down.[58,59] For this mechanism to operate, IVIg would need to be able to bind to activating FcγRs strong enough to block access of circulating or local ICs without activating down-stream activating signaling pathways. Indeed, small levels of IgG dimers can be detected in IVIg preparations and enriching for those dimeric IgG fractions was shown to attenuate the autoantibody induced reduction of platelet numbers in a mouse ITP model system.[60] Furthermore, certain IgG Fc trimers or even hexamers as well as higher order multimers have been shown to efficiently interfere with IC binding to activating FcγRs (Figure 4A).[42,43,61,62] One has to keep in mind, however, that an important quality control step in producing IVIg is to minimize the content of even small IgG aggregates, suggesting that the varying IVIg dimer content present across different IVIg preparations/batches may not be sufficient to fully block autoantibody dependent tissue pathology via blocking FcγRs. Moreover, only specific structures of recombinantly generated ICs were able to bind FcγRs without down-stream activation of effector cells, which is critical to prevent fueling instead of blocking inflammation especially during ongoing inflammation.[42,62]

The second pathway relevant for autoantibody activity is that the autoantibody has a half-life long enough to reach its target structures/tissues and to accumulate in sufficient amounts to cross-link activating FcγRs on tissue resident or recruited innate immune effector cells. With respect to IVIg therapy, a high dose infusion of IgG (as present in IVIg) could indeed behave as a competitor for IgG (auto)antibody binding/recycling to FcRn and thus induce autoantibody degradation. Indeed, autoantibody levels were shown to be reduced upon IVIg infusion in some studies and autoantibody induced skin blistering disease was diminished in a neonatal mouse model system.[63–66] On the other hand, deglycosylated IVIg, which loses binding to type I and type II FcRs but maintains binding to FcRn lost its activity in mouse model systems of inflammatory arthritis, arguing at least against a general role of FcRn for IVIg activity.[37,67–69] Another point to consider is that a certain reduction of autoantibody half-life may not always be sufficient to reduce autoimmune pathology. For example, very low

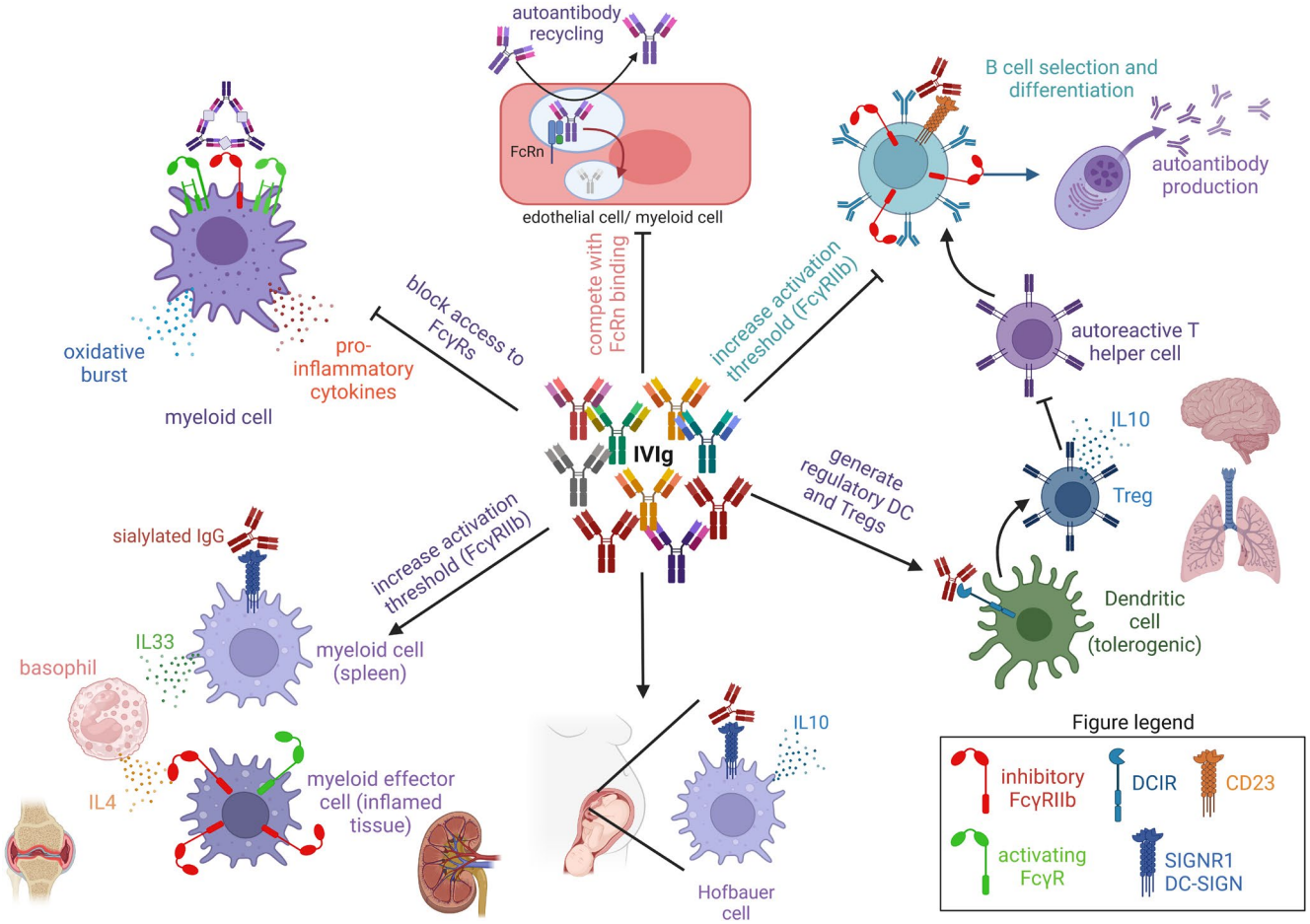

FIGURE 2 IgG Fc-fragment dependent pathways of IVIg activity. Shown is an overview of IVIg-dependent activities, including the competition with immune complex binding to activating FcγRs, the competition with autoantibodies to bind to FcRn, the induction of increased levels of Fc RIIb expression on B cells and myeloid cells to increase the threshold for activation, the induction of regulatory T cell responses via dendritic cell, and the promotion of tolerance at the materno-fetal interface. Some of these pathways are dependent on highly sialylated IgG glycovariants within the IVIg preparation and require type II FcRs such as SINGR1, DC-SIGN, DCIR or CD23. Note that certain immunomodulatory pathways have been described in specific organ/disease contexts. See text for further details.

levels of autoantibodies may suffice to trigger pathology. Thus, if autoantibodies are produced in excessive amounts and have easy access to their target structure a reduction by half may not be sufficient to effectively interfere with autoantibody activity. An example for such a scenario is ITP, where autoantibodies have easy access to their antigen (platelets) in blood and rapidly trigger an uptake of opsonized platelets by phagocytic cells, such as splenic macrophages or Kupffer cells in the liver.[19,70] Indeed, autoantibody induced platelet depletion occurred normally in FcRn deficient mice.[71] For slower acting autoantibodies, such as autoantibodies which have to become deposited in tissues to induce a pro-inflammatory response (e.g. in RA or skin blistering diseases), a reduction of autoantibody half-life to fifty percent may have much stronger effects on autoantibody induced tissue pathology as tissue autoantibody levels may not reach amounts high enough to efficiently trigger downstream activation of effector pathways.[19,72] Based on this potential mode of action of IVIg therapy, many FcRn blocking reagents (either Fc-domains with increased affinity for FcRn or FcRn specific blocking antibodies) have been developed and have been demonstrated to efficiently interfere with autoantibody dependent inflammation in pre-clinical as well as in clinical settings.[73–75] Indeed, FcRn blockade has become an important therapeutic tool to interfere with autoantibody dependent inflammation and tissue destruction (Figure 4B).[76,77] Naturally, the FcRn blocking activity of these recombinant monoclonal antibodies or Fc-fragments is much higher compared to IVIg-dependent FcRn blockade. Interestingly, IVIg levels are frequently lowered in responding patients over time, suggesting that as discussed for IVIg induced block of IC binding to activating FcγRs, IVIg dependent competition for FcRn binding likely only represents a fraction of the therapeutic activity of IVIg. Moreover, it needs to be considered that an FcRn blockade will not only reduce the level of pathogenic autoantibodies but also of protective IgG species. Although IVIg infusion may also have this effect, the polyclonal nature of the IVIg preparation will at the same time—supply protective IgG species into the patient thereby maintaining protective immunity while reducing autoantibodies at the same time. An important further point to consider is that IVIg also suppresses T cell driven

autoimmune diseases where autoantibodies may not play a dominant role as we will discuss in the next chapter. Under these circumstances, FcRn blocking reagents may not be expected to have therapeutic activity and thus may have a more restricted portfolio of clinical applications.

In summary, both IVIg mediated blockade of IC access to activating FcγRs as well as IVIg dependent reduction in autoantibody half-life may contribute to IVIg activity. It is clear, however, that additional pathways must be triggered to explain the full spectrum of IVIg activities in different model systems.[3,78] Most importantly, sometimes a single IVIg infusion triggers long lasting effects (more than 100 days) not compatible with the short lived effects on FcγR or FcRn blockade and the IVIg half-life of two to three weeks.[63]

6 | IVIg-MEDIATED IMMUNOMODULATION

There are two major observations in mice and humans, suggesting that treatment with IVIg triggers additional pathways resulting in broader immunomodulatory effects. Firstly, several studies in mice noted an upregulation of the inhibitory FcγRIIb on myeloid cells (monocytes, macrophages, DC) and B cells upon IVIg infusion (Figure 2).[50,79–81] In humans, IVIg infusion normalized the decreased level of FcγRIIb expression on monocytes and B cells in patients with chronic inflammatory demyelinating polyneuropathy (CIDP), suggesting that at least in specific diseases similar immunomodulatory pathways of IVIg activity operate in mice and humans.[81] As mentioned earlier, the co-expression of activating FcγRs with the inhibitory FcγRIIb sets a critical threshold for activation of innate immune effector cells.[19] Thus, an IVIg induced upregulation of FcγRIIb would limit innate immune effector cell activation and potentially modulate the quality of the induced effector response. Moreover, antigen uptake via FcγRIIb into DCs may result in the priming of regulatory T cell responses or the deletion of antigen specific T cells.[82–85] Direct experimental evidence suggesting that FcγRIIb plays an important role for IVIg activity comes from mice lacking FcγRIIb expression. Indeed, the IVIg-dependent suppression of ITP,[79,86] RA,[87] allergic lung inflammation[51] and nephrotoxic nephritis[50] has been shown to be abrogated or diminished in the absence of FcγRIIb. Of note, an upregulation of FcγRIIb on B cells increases the threshold for B cell activation and thus may directly interfere with autoantibody production or the generation of new self-reactive antibodies.[88] In addition, enhancing FcγRIIb expression on plasma blasts and plasma cells may sensitize them for induction of apoptosis via IgG IC, which may reduce the number of autoantibody producing long lived plasma cells at least to some extent.[89] Of note, a recent study using a systems biology approach emphasized that in humans IVIg mediated modulation of B cell responses, e.g. autoantibody or cytokine production may play a major target for the therapeutic activity of IVIg.[90]

The second consistent observation in mice and humans is an expansion of regulatory T cells (Treg) upon IVIg, IVIg Fc-domain, or sialylated Fc-domain infusion (Figure 2).[63,91–96] Tregs are important modulators of effector T cell responses and can suppress autoreactive CD4+ T cell and consequently also CD8 T cell and B cell responses, which could explain the long term effects IVIg has at least in certain patients (Figure 2).[97] In line with this notion, many studies have shown that IVIg modulates dendritic cell (DC) development or activation state, allowing Treg priming.[98–100] Of note, in mice specific DC subsets play a critical role for induction of antigen specific Treg responses.[101] In addition to DCs, multiple studies noted an effect of IVIg on monocyte and macrophage activation, leading to more anti-inflammatory, immunosuppressive myeloid states which could contribute to a local immune milieu supporting Treg differentiation.[102–105] With respect to T cell driven mouse models especially the experimental autoimmune encephalitis (EAE) model or allergic airway hyperresponsiveness (AHR) models are widely used to study IVIg-mediated suppression of autoreactive T cell driven inflammatory responses. In both model systems, the repetitive infusion of IVIG leads to a pronounced expansion of Tregs and a suppression of T cell driven pro-inflammatory processes.[106,107] In line with the data in mouse model systems, an expansion of Tregs during IVIg therapy has been observed in human ITP and KD patients.[94,107–110] Thus, it is clear that IVIg or serum IgG from healthy individuals plays an active role in keeping the immune system in balance and is able to recalibrate uncontrolled/excessive inflammatory responses via setting increased thresholds for innate immune effector cell activation or more globally via the induction of Treg responses. As mentioned, FcγRIIb expression on DCs is one factor underlying the priming of Treg responses providing a link between both immunomodulatory pathways and putting FcγRIIb on center stage as an immune checkpoint underlying IVIg activity (Figure 2). In parallel to the induction of Treg responses it is important to note that an uptake of antigens into DCs via FcγRIIb, but also via other FcγRs in the absence of co-stimulatory signals or FcγR-crosslinking, results in an activation of antigen specific T cells followed by their rapid deletion, providing an alternative means of deleting potentially autoreactive T cells during the steady state.[83] In summary, the inhibitory FcγRIIb is a key checkpoint for both, the induction of self-reactive immune responses and as a modulator of the effector phase of IgG responses (Figure 2).

7 | ROLE OF IVIg SIALYLATION FOR IVIg DEPENDENT IMMUNOMODULATION

One assumption why the very high dose of 1-3 g/kg of IVIg is required for achieving an anti-inflammatory and immunomodulatory activity is that not the high dose itself is critical for of IVIg activity but rather that smaller IgG fractions within the IVIg preparation are the active components. With respect to the IgG Fc, the major factors contributing to heterogeneity are the four different IgG subclasses (IgG1, IgG2, IgG3, IgG4) and their specific IgG Fc glycosylation pattern.[111–114] As discussed, both, IgG subclass as well as glycosylation are well known to modulate IgG binding to

the family of FcγRs.[35] Early on, several findings pointed towards a role for IgG glycosylation as an important factor underlying IVIg activity. Thus, it was noted that during active inflammation IgG glycosylation changes towards glycoforms with low levels of terminal sialic acid and galactose residues.[52,115] If some of these IgG glycoforms would have an active anti-inflammatory activity, a potential mode of action of IVIg could be to replenish these missing IgG glycoforms.

More direct evidence was provided by experiments demonstrating that IVIg deglycosylation and more importantly also IVIg desialylation resulted in a loss of the anti-inflammatory activity in a wide variety of mouse model systems of autoantibody induced inflammation under preventive (ITP, RA, EAE, Guillain-Barree syndrome, nephrotoxic nephritis, EBA, acute/allergic lung inflammation) as well as therapeutic (ITP, EBA, RA) treatment schemes.[50,51,95,116–119] The finding that IgG glycosylation and sialylation is an important factor for IVIg activity has been confirmed in immunodeficient mice transplanted with a human immune system (human immune system humanized mice), suggesting that IVIg also requires terminal sialic acid residues to diminish autoantibody mediate pathology on the background of an outbred human immune system.[117] Of further relevance for the translation of this finding into clinical application, enriching IVIg or IgG Fc fragments for terminal sialic acid residues resulted in enhanced therapeutic activity[43,120] again under preventive and therapeutic treatment conditions. Interestingly, a small clinical trial in human ITP patients also noted that highly sialylated IVIg resulted in therapeutic activity at a ten-fold reduced dose. In summary, sialylated IgG glycoforms within the IVIg preparation seem to play a critical role for the immunomodulatory activity of IVIg and seem to operate in T cell as well as autoantibody dependent models of autoimmune inflammation (Figure 2).

Beyond the relevance of sialylated IgG glycoforms for the therapeutic activity of IVIg in these model systems, it is interesting not note that in mice during the steady-state especially IgG2c and IgG2b subclasses contain highly sialylated sugar structures, whereas only a small fraction of sialylated IgG1 is present.[111,113] In contrast to the strong regulation of mouse IgG1 activity via a relatively strong binding to the inhibitory FcγRIIb, IgG2b and IgG2c subclasses bind much better to activating FcγRs.[27] Thus it is tempting to speculate that steady state sialylation of the highly active IgG2 subclasses in mice may regulate their activity via reducing binding to activating Fc Rs and that these IgG subclasses may have immunomodulatory activities. More recent studies elucidated that IgG sialylation may play an important role in tolerance induction at the maternal-fetal interface by stimulating IL10 production by fetal macrophages (Hofbauer cells) in the placenta.[121] Furthermore a lack of IgG sialylation was suggested to contribute to obesity induced insulin resistance via modulating binding of serum IgG to FcγRIIb expressed on endothelial cells.[122] In summary, there is a broad set of data demonstrating that in a wide variety of mouse model systems sialylated IgG glycoforms can have an active immunomodulatory activity (Figure 2).

8 | PATHWAYS UNDERLYING THE SIALIC ACID DEPENDENT IVIg ACTIVITY

Before we proceed with a more detailed description of specific molecular and cellular pathways underlying the activity of highly sialylated IgG glycoforms it has to be noted that this is a very active and rapidly developing field of research. Importantly, it has become clear that especially the generation of highly sialylated IgG glycoforms is not trivial and requires well-established protocols to generate highly tetrasialylated IgG glycoforms with enhanced therapeutic activity.[43] As before we will discuss sialic acid dependent IVIg mediated suppression of autoantibody dependent and independent model systems separately. With respect to autoantibody dependent model systems, the threshold set by co-expression of activating FcγRs and the inhibitory FcγRIIb plays an important role in setting a threshold for innate immune effector cell activation. Early on, studies had suggested that in mice IVIg infusion leads to an upregulation of the inhibitory FcγRIIb on myeloid cells,[80] suggesting that IVIg may increase the threshold for effector cell activation via autoantibodies. Consistent with these findings also highly sialylated IVIg fractions required Fc RIIb for their inhibitory activity.[67,68] However, it also became clear that IgG glycoforms rich in terminal sialic acid residues had a reduced affinity for Fc RIIb, suggesting that no direct binding of IVIg to FcγRIIb occurs.[37,122] Instead studies from several independent laboratories over the last two decades have identified that highly sialylated IVIg fractions gained the ability to interact with a variety of C-type lectin receptors including SIGNR-1, DC-SIGN, CD23 and DCIR, which has led to introducing the term type II FcRs to separate them from the family of canonical FcγRs.[18,68,121,123–125] More recently IVIg binding to DC-SIGN was confirmed on Hofbauer cells.[121] Although several independent laboratories have detected a direct binding of IVIg to type II FcRs it should be noted that other studies could not confirm a direct binding.[126,127]

Regardless of this issue, which requires further investigations, IVIg activity was impaired in different autoimmune mouse model systems in which specific type II FcRs either were lacking or blocked by monoclonal antibodies. Interestingly however, a disease or organ specific impact of these different type II FcRs was noted (Figure 2). Thus, mouse SIGN-R1 or human DC-SIGN were shown to be responsible for IVIg activity in mouse models of ITP[116] and joint inflammation such as inflammatory arthritis.[120] A major difference between both model systems is the effector cell involved in mediating autoantibody activity and the level of inflammation. Whereas in the ITP model system opsonized platelets are cleared by Kupffer cells in the absence of inflammation,[70] the serum transfer arthritis model is characterized by a high level of joint inflammation and immune cell activation.[36] Consistent with this difference in the inflammatory milieu different pathways downstream of type II FcRs were noted. In the model of inflammatory arthritis it was demonstrated that IVIg required an intact splenic architecture and induced an IL33 release in a SIGNR1 dependent fashion, which triggered a secretion of IL4 by basophils.[120]

Indeed, IL4 deficient mice no longer responded to IVIg treatment in a model of serum transfer arthritis.[120] Moreover, the injection of IL33 or IL4 suppressed arthritis development, suggesting that both cytokines are indeed key immunomodulatory factors for suppressing immunopathology at least in murine RA. Interestingly, IL4 is a well-known factor to upregulate FcγRIIb on myeloid cells (but not on B cells), explaining how highly sialylated IVIg preparations trigger the upregulation of FcγRIIb (Figure 2). Increased levels of IL33 and an expansion of basophils were also observed in subsets of RA patients treated with IVIg.[128] In contrast, in the ITP model system, neither the spleen, IL33, nor basophils or IL4 were required for IVIg activity.[116,129] This is consistent with data from human clinical studies, demonstrating that IVIg activity is maintained in splenectomized patients.[57,130]

Concerning the upregulation of FcγRIIB on B cells it has been shown in a different study using highly sialylated hemagglutinin specific antibodies that binding of sialylated IgG to CD23 on B cells results in upregulation of FcγRIIb. Of note IL4 upregulates CD23 on B cells allowing an optimal interaction of sialylated IgG with B cells and a subsequent up-regulation of FcγRIIb (Figure 2).[125] In contrast, CD22 a well-known inhibitory sialic acid specific C-type lectin receptor on B cells was dispensable for IVIg activity.[131] In contrast to the majority of studies investigating IVIg activity under preventive treatment conditions, only very few studies have addressed IVIg dependent immunomodulatory pathways under therapeutic conditions. In line with previous results IVIg activity depended on sialylated IgG glycoforms, but the requirement for specific type II, such as SignR1 was less pronounced once inflammation has been established.[132] Thus, during different phases of autoimmune diseases varying sets of type II FcRs may contribute to the anti-inflammatory activity of IVIg.[87,116]

With respect to the expansion of Tregs by IVIg, which allows an efficient suppression of inflammatory processes in models of EAE, experimental colitis, as well as in acute lung inflammation it was shown that IVIg sialylation is also important for Treg induction.[95,133,134] Of note, depending on the disease context different pathways were noted to be involved in IVIg dependent immunosuppression. In the EAE model for example, highly sialylated IVIg or IgG Fc-fragments carrying mutations, such as the F241A mutation, mimicking highly sialylated IVIg activity mediated the suppression of T cell dependent central nervous system inflammation,[95] which was dependent on SIGNR1 or hDC-SIGN expression on myeloid cells,[95] in line with previous studies in models of RA. Further in line with the arthritis model, IVIg induced IL33 led to an expansion of Tregs and the injection of IL33 alone was able to reduce EAE pathology. In a similar manner the injection of IVIg in a T cell transfer colitis model also induced Treg expansion and suppression of gut inflammation. As mentioned before, a recent study noted that sialylated IgG binding to DC-SIGN on Hofbauer cells may be involved in maintaining tolerance at the materno-fetal interface, demonstrating a natural immunomodulatory activity of the sialylated IgG-type II FcR axis beyond therapeutic interventions.[121] Interestingly, in a model of AHR, sialylated IVIg binding to the dendritic cell immunoreceptor (DCIR) on lung myeloid cells, which lacked SIGNR1 expression, was shown to be critical for suppression of lung inflammation.[133] In addition, IVIg internalization and inhibitory signaling via SHP2 and SHIP1 were required for IVIg activity in this model system.[133] As previous studies using the same model system had suggested that FcγRIIb on DCs was critical for IVIg activity it is tempting to speculate that down-stream of the sialylated IgG interaction with DCIR, FcγRIIb contributed to the initiation of inhibitory signaling pathways. In the latter model IVIg was suggested to drive DC towards a differentiation state allowing efficient priming of Tregs.[133] In addition, it was noted that within the IgG Fc-domain certain peptide stretches exist, which (upon presentation on MHC II molecules) allow a predominant expansion of Tregs, which have also been referred to as Tregitopes.[96,135] Indeed Tregitopes have been suggested to improve asthma by expansion of antigen-specific Tregs in a mouse model of allergic AHR.[136] Whether DCIR or SIGNR1 dependent uptake of sialylated IgG glycovariants enhances presentation of Tregitopes on DCs remains to be studied.

In summary, there is a wealth of data supporting the notion that sialylated IgG species are an IgG glycoform with active immunomodulatory activities and represent an important active component within the IVIg preparation. It is also clear, however, that depending on the inflammatory milieu of the disease (inflammatory versus no inflammation), treatment initiation (preventive versus therapeutic), and affected organ (joint, lung, platelets, central nervous system) different immunomodulatory pathways may be responsible for IVIg activity. Thus, clearly more work is required to identify disease and disease stage specific pathways triggered by sialylated IgG species to fully comprehend and translate these findings to the human clinical situation.

9 | FCγRIIb DEPENDENT IMMUNOMODULATORY PATHWAYS OF IVIg ACTIVITY BEYOND SIALYLATION

As we have discussed in the last chapters, the inhibitory FcγRIIb is a critical checkpoint controlling the activation of a broad spectrum of innate and adaptive immune cells and centrally involved in IVIg dependent immunomodulation. In addition to the modulation of activating signaling pathways triggered by IC dependent co-crosslinking with activating FcγRs, FcγRIIb also acts in concert with other activating immune receptors. One long known example is the modulation of B cell receptor signaling to achieve the selection of high affinity antigen specific B cells during affinity maturation in secondary lymphoid organs.[22,137] Mechanistically, antigens bound by pre-existing IgG antibodies would allow BCR binding and co-crosslinking of FcγRIIb to allow B cell activation only in the case of very strong BCR signaling. Thus, in the setting of activating FcγRs and the BCR, both, the activating receptor as well as FcγRIIb would be bound to a ligand. This indeed is essential, as in the absence of triggering an activating receptor, no inhibitory signaling can occur (Figure 1C). There is accumulating evidence, however,

that inhibitory FcγRIIb signaling may be initiated via activating cell surface receptors in the absence of ligand binding to the respective activating receptor. Indeed, three independent studies over the last ten years indicate that *dendritic cell associated C-type lectin 1* (Dectin-1) may be one such receptor (Figure 3).[138] Dectin-1, also referred to as Clec7a has been identified as a non-TLR pattern recognition receptor on myeloid cells recognizing fungal cell wall components such as zymosan and β-glucans. In addition, self-ligands including Galectin-9, annexins, and N-glycan structures were suggested to be recognized by Dectin-1, indicating functions of Dectin-1 beyond pathogen recognition.[139] Dectin-1 contains a cytoplasmic ITAM-like (hemITAM) motif and was shown to transduce activating signals via unconventional Syk-dependent and –independent signaling pathways. However, Dectin-1 does not bind IgG or specific IgG glycoforms and hence would not be considered a type II FcR.[87] However, a lack of Dectin-1 was demonstrated to diminish FcγRIIb dependent inhibitory signaling suggesting that somehow Dectin-1 can interact with FcγRIIb. Thus, inhibitory signaling pathways triggered by FcγRIIb required for the generation of gut associated tolerogenic DCs via mucin 2 binding to FcγRIIb were abrogated in the absence of Dectin-1 (Figure 3A).[140] Moreover, galactosylated mouse IgG1 ICs were shown to inhibit neutrophil activation via FcγRIIb and this inhibitory effect was abrogated in Dectin-1 deficient mice (Figure 3B).[141] As mentioned, in both studies, no direct ligand binding occurred to Dectin-1. Instead, it was suggested that Dectin-1 may be part of FcγRIIb complexes and was required for phosphorylating the FcγRIIb ITIM motif and initiation of down-stream inhibitory signaling pathways.[141] As discussed before, phosphorylation of the cytosolic ITIM domain of FcγRIIb has to occur via an ITAM containing receptor (usually activating FcγRs or the B cell receptor) and exclusive crosslinking of the inhibitory FcγRIIb does not initiate signaling (Figure 1C).

In line with the previous studies we noted that the Dectin-1/FcγRIIb axis may also be required at least for specific anti-inflammatory effects of IVIg in a model of RA (Figure 3C). Thus, whereas IVIg was efficient in suppressing bone erosions in wildtype mice, the bone protective effect of IVIg was lost in FcγRIIb as well as Dectin-1 deficient mice.[87] Of note, Dectin-1 and FcγRIIb are co-expressed on inflammatory monocytes, which are the precursor cells of osteoclasts during inflammatory processes in the joint tissue.[142] In the absence of Dectin-1, IVIg was no longer able to suppress the differentiation of inflammatory monocytes into osteoclasts, suggesting that IVIg directly acts on inflammatory monocytes in this model system. Computational simulations of the interaction of Dectin-1 and FcγRIIb in the context of a cell membrane and super resolution microscopy studies suggested that Dectin-1 stabilized Fc RIIb clusters, which may allow an interaction with monomeric IgG subclasses as well as with IVIg (Figure 3D,E).[87] Indeed, FcγRIIb variants which could not interact with Dectin-1 lost the ability

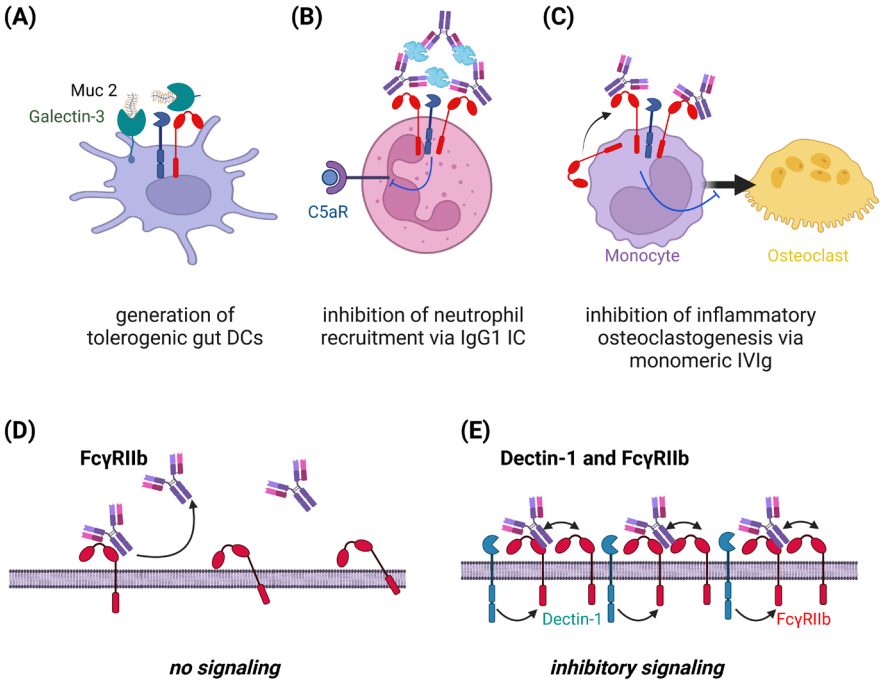

FIGURE 3 Modulation of FcγRIIb activity via Dectin-1. Shown are different pathways of Dectin-1 dependent modulation of FcγRIIb function. In the absence of Dectin-1, FcγRIIb was no longer able to induce the generation of tolerogenic dendritic cells in the gut via galectin-1/mucin 2 binding (A), was no longer able to inhibit neutrophil activation via galactosylated mouse IgG1 immune complexes (B) and lacked the ability to suppress monocyte differentiation to osteoclasts via IVIg (C). Mechanistically, in the absence of Dectin-1, FcγRIIb may be present in membrane conformations/clusters not allowing IgG binding (D), whereas in the presence of Dectin-1 FcγRIIb may be stabilized in conformations/higher order clusters allowing IVIg binding (E). See text for further details.

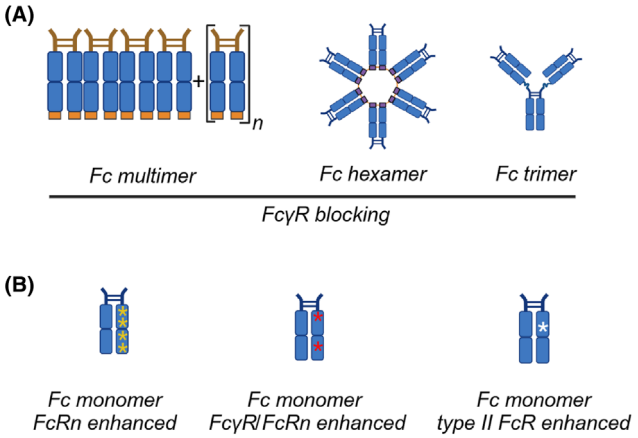

FIGURE 4 Therapeutic replacement strategies for IVIg. (A) Schematic representation of different Fc-multimers (higher order Fc multimers [stradomer], Fc-hexamers, Fc-trimers) to block the interaction of autoantibodies with FcγRs. (B) Shown are monomeric IgG Fc variants with enhanced binding to FcRn to enhance autoantibody degradation, with enhanced binding to FcγRs and FcRn, to simultaneously block access of autoantibodies to FcγRs and FcRn, or with enhanced binding to type II FcRs to mimic the activity of highly sialylated IVIg variants.

to interact with monomeric IgG. Furthermore, IVIg was not able to suppress osteoclastogenesis in mice with a mutated FcγRIIb ITIM domain, suggesting that indeed FcγRIIb signaling is required for IVIg activity. It is important to point out that in contrast to a previous study which noted an important role of Dectin-1 for inhibition of neutrophil activation via FcγRIIb[141] we did not observe an effect of Dectin-1 on the IVIg dependent inhibition of neutrophil recruitment to the joints. This may be due to the different FcγRIIb ligands involved in the different model systems: galactosylated IgG1 ICs versus monomeric IVIg. Thus, although many details about the interaction of Dectin-1 with FcγRIIb remain to be elucidated it seems clear that Dectin-1 supports inhibitory signals transduced via FcγRIIb on DCs, neutrophils and monocytes, albeit via different ligands (galectin-3, IgG IC, monomeric IgG). Although speculative at the moment, Dectin-1 could orchestrate/stabilize larger inhibitory FcγRIIb clusters in the cell membrane that sensitize immune cells for more efficient inhibitory signaling via monomeric ligands.

10 | SUBSTITUTION OF IVIg WITH RECOMBINANT THERAPIES

A major issue with IVIg therapy is that IVIg is a primary blood product and depending on the availability of blood/serum donations and patient demand there can be shortages in supply, warranting efforts to replace IVIg or at least certain activities of IVIg with recombinant products. As mentioned, a more detailed understanding of the molecular and cellular pathways involved in IVIg activity has already translated into novel therapies (Figure 4).[76] Most prominently, blocking the interaction of IgG with FcRn via blocking antibodies or Fc-fragments has shown impressive clinical effects. In addition, the development of IgG mulitmers to block the interaction of autoantibodies with Fc Rs has shown very promising pre-clinical effects. However, compared to FcRn blockade this approach is more complicated for several reasons. Most importantly, IgG multimers (stradomers, hexamers, trimers) in principle mimic ICs and thus can trigger pro-inflammatory cytokine release or activate the complement system.[42,143] Indeed, IgG1 hexamers while efficiently blocking Fc Rs can induce a pro-inflammatory cytokine response in ex vivo assays with human peripheral blood, which to a large extend was dependent on IgG1 hexamer binding to Fc Rs platelets and neutrophils. However, in vivo in non-human primates or mice no major cytokine release was observed upon IgG1 hexamer or multimer administration, which may be explained at least in part due to their short half-life in vivo.[39] In general, IgG trimers were less prone to induce pro-inflammatory cytokine responses.[42,144] Further reducing the size of the therapeutic molecule, a monomeric IgG1 Fc-domain that was engineered for a better binding to FcRn to allow blocking autoantibody binding to FcRn and additionally for a better binding to activating FcγRs to simultaneously block autoantibody binding to activating Fc Rs. Indeed, this approach allowed to interfere with the pathogenic activity of autoantibodies in two murine models of inflammatory arthritis and immunothrombocytopenia.[145] Beyond a direct block of IgG effector functions, IgG1 Fc-domains carrying an F241A mutation, which mimics the activity of highly sialylated IVIg, have proven to be efficient in inhibiting autoantibody as well as T cell dependent inflammatory processes and are being developed for the clinical application.[95,146] Although the presence of terminal sialic acid residues was not required for the anti-inflammatory effect it is interesting to note that the presence of sialic acid improved the half-life of the molecule suggesting that the hepatic asialoreceptor, which modulates protein half-life via detecting the loss of sialylation, has access to the Fc-linked sugar moiety of the Fc-fragment.[147] Finally, Fc-linked enzymes responsible for adding terminal galactose and sialic acid residues were injected into mice to increase the level of IgG sialylation and thus the presence of this immunomodulatory IgG glycoform in vivo. Indeed this approach was efficient in reducing autoantibody driven organ inflammation in different murine model systems.[148] The advantage of this approach compared to the targeted deglycosylation or degradation of IgG (auto)antibodies via administration of enzymes such as EndoS (removing the IgG sugar moiety) or IdeS (degrading the IgG molecule) is that a relatively small increase in sialic acid containing IgG glycovariants may be sufficient to modulate the entire inflammatory cascade, whereas a direct targeting of IgG antibody function may be less efficient also due to the fact that specific IgG subclasses and IgG IC maintain their activity even with a minimal sugar domain.[32,149–153] In summary, therapeutic approaches mimicking the blocking as well as the immunomodulatory activities of IVIg show very promising effects. Ideally, a combination of both mechanisms as present in IVIg preparations may come close to fully recapitulating IVIg activity with a recombinant product.

11 | SUMMARY AND OUTLOOK

Since the identification that an infusion of high dose pooled serum IgG preparations ameliorates autoimmune pathology more than 40 years ago, major progress has been made in understanding how IVIg works. This field of research is a prime example of how a clinical finding more or less made by chance has led to in depth mechanistic studies in pre-clinical model systems, which are now translated back into a broad spectrum of novel clinical applications. Nonetheless, research over the last decade has also emphasized that most likely the type of disease, disease state and the organ specific immune environment will determine the precise molecular and cellular pathways involved in the immunomodulatory activity of IVIg. Thus, further research into organ and disease specific pathways of IVIg activity will be necessary to fully understand the immunomodulatory activities of IgG. As before, these studies will identify not only new basic biological principles underlying the regulation of the immune system during steady state and activation, but also identify new therapeutic avenues to treat patients.

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CONFLICT OF INTEREST STATEMENT

F. Nimmerjahn is an advisor to Nuvig therapeutics.

DATA AVAILABILITY STATEMENT

Not applicable.

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REFERENCES

1. Ludwig RJ, Vanhoorelbeke K, Leypoldt F, et al. Mechanisms of autoantibody-induced pathology. *Front Immunol*. 2017;8:603.
2. Nimmerjahn F, Ravetch JV. The antiinflammatory activity of IgG: the intravenous IgG paradox. *J Exp Med*. 2007;204(1):11-15.
3. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol*. 2013;13(3):176-189.
4. Bayry J, Negi VS, Kaveri SV. Intravenous immunoglobulin therapy in rheumatic diseases. *Nat Rev Rheumatol*. 2011;7(6):349-359.
5. Nimmerjahn F, Ravetch JV. Fcγ receptors as regulators of immune responses. *Nat Rev Immunol*. 2008;8(1):34-47.
6. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*. 1981;1(8232):1228-1231.
7. Imbach P, Morell A. Idiopathic thrombocytopenic purpura (ITP): immunomodulation by intravenous immunoglobulin (IVIg). *Int Rev Immunol*. 1989;5(2):181-188.
8. Gelfand EW. Differences between IGIV products: impact on clinical outcome. *Int Immunopharmacol*. 2006;6(4):592-599.
9. Galeotti C, Kaveri SV, Bayry J. IVIG-mediated effector functions in autoimmune and inflammatory diseases. *Int Immunol*. 2017;29(11):491-498.
10. Danieli MG, Piga MA, Paladini A, et al. Intravenous immunoglobulin as an important adjunct in the prevention and therapy of coronavirus 2019 disease. *Scand J Immunol*. 2021;94(5):e13101.
11. Sung N, Han AR, Park CW, et al. Intravenous immunoglobulin G in women with reproductive failure: the Korean Society for Reproductive Immunology practice guidelines. *Clin Exp Reprod Med*. 2017;44(1):1-7.
12. Walgaard C, Jacobs BC, Lingsma HF, et al. Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial. *The Lancet Neurology*. 2021;20(4):275-283.
13. Lehmann HC, Hartung HP. Plasma exchange and intravenous immunoglobulins: mechanism of action in immune-mediated neuropathies. *J Neuroimmunol*. 2011;231(1–2):61-69.
14. Yang A, Uhlenhake E, Murrell DF. Pemphigoid gestationis and intravenous immunoglobulin therapy. *Int J Women's Dermatol*. 2018;4(3):166-169.
15. Maglie R, Hertl M. Pharmacological advances in pemphigoid. *Curr Opin Pharmacol*. 2019;46:34-43.
16. Anania JC, Chenoweth AM, Wines BD, Hogarth PM. The human FcgammaRII (CD32) family of leukocyte FcR in health and disease. *Front Immunol*. 2019;10:464.
17. Daeron M. Fc receptors as adaptive immunoreceptors. *Curr Top Microbiol Immunol*. 2014;382:131-164.
18. Pincetic A, Bournazos S, DiLillo DJ, et al. Type I and type II fc receptors regulate innate and adaptive immunity. *Nat Immunol*. 2014;15(8):707-716.
19. Nimmerjahn F, Ravetch JV. Anti-inflammatory actions of intravenous immunoglobulin. *Annu Rev Immunol*. 2008;26(1):513-533.
20. Hargreaves CE, Rose-Zerilli MJ, Machado LR, et al. Fcγ receptors: genetic variation, function, and disease. *Immunol Rev*. 2015;268(1):6-24.
21. Junker F, Gordon J, Qureshi O. Fc gamma receptors and their role in antigen uptake, presentation, and T cell activation. *Front Immunol*. 2020;11:1393.
22. Takai T, Ono M, Hikida M, Ohmori H, Ravetch JV. Augmented humoral and anaphylactic responses in FcγRII-deficient mice. *Nature*. 1996;379(6563):346-349.
23. Nakamura A, Yuasa T, Ujike A, et al. Fcγ receptor IIB–deficient mice develop Goodpasture's syndrome upon immunization with type IV collagen: a novel murine model for autoimmune glomerular basement membrane disease. *J Exp Med*. 2000;191(5):899-906.
24. Yuasa T, Kubo S, Yoshino T, et al. Deletion of Fcγ receptor IIB renders H-2b mice susceptible to collagen-induced arthritis. *J Exp Med*. 1999;189(1):187-194.
25. Clynes R, Maizes JS, Guinamard R, Ono M, Takai T, Ravetch JV. Modulation of immune complex–induced inflammation in vivo by the coordinate expression of activation and inhibitory fc receptors. *J Exp Med*. 1999;189(1):179-185.
26. Takai T, Li M, Sylvestre D, Clynes R, Ravetch JV. FcR gamma chain deletion results in pleiotrophic effector cell defects. *Cell*. 1994;76(3):519-529.
27. Nimmerjahn F, Ravetch JV. Divergent immunoglobulin G subclass activity through selective fc receptor binding. *Science*. 2005;310(5753):1510-1512.
28. Vorsatz C, Friedrich N, Nimmerjahn F, Biburger M. There is strength in numbers: quantitation of fc gamma receptors on murine tissue-resident macrophages. *Int J Mol Sci*. 2021;22(22):12172.
29. Kerntke C, Nimmerjahn F, Biburger M. There is (scientific) strength in numbers: a comprehensive quantitation of fc gamma receptor numbers on human and murine peripheral blood leukocytes. *Front Immunol*. 2020;11:118.

30. Nimmerjahn F, Bruhns P, Horiuchi K, Ravetch JV. FcγRIV: a novel FcR with distinct IgG subclass specificity. *Immunity*. 2005;23(1):41-51.
31. Nimmerjahn F, Ravetch JV. Fcgamma receptors: old friends and new family members. *Immunity*. 2006;24(1):19-28.
32. Lux A, Yu X, Scanlan CN, Nimmerjahn F. Impact of immune complex size and glycosylation on IgG binding to human FcγRs. *J Immunol*. 2013;190(8):4315-4323.
33. Bruhns P, Iannascoli B, England P, et al. Specificity and affinity of human Fcγ receptors and their polymorphic variants for human IgG subclasses. *Blood, the Journal of the American Society of Hematology*. 2009;113(16):3716-3725.
34. Ferrara C, Grau S, Jäger C, et al. Unique carbohydrate–carbohydrate interactions are required for high affinity binding between FcγRIII and antibodies lacking core fucose. *Proc Natl Acad Sci*. 2011;108(31):12669-12674.
35. Nimmerjahn F, Vidarsson G, Cragg MS. Effect of posttranslational modifications and subclass on IgG activity: from immunity to immunotherapy. *Nat Immunol*. 2023;24(8):1244-1255.
36. Ji H, Ohmura K, Mahmood U, et al. Arthritis critically dependent on innate immune system players. *Immunity*. 2002;16(2):157-168.
37. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from fc sialylation. *Science*. 2006;313(5787):670-673.
38. Lewis BJ, Ville J, Blacquiere M, et al. Using the K/BxN mouse model of endogenous, chronic, rheumatoid arthritis for the evaluation of potential immunoglobulin-based therapeutic agents, including IVIg and fc-μTP-L309C, a recombinant IgG1 fc hexamer. *BMC Immunol*. 2019;20:1-10.
39. Qureshi O, Rowley T, Junker F, et al. Multivalent fc γ-receptor engagement by a hexameric fc-fusion protein triggers fc γ-receptor internalisation and modulation of fc γ-receptor functions. *Sci Rep*. 2017;7(1):17049.
40. Spirig R, Campbell IK, Koernig S, et al. rIgG1 fc hexamer inhibits antibody-mediated autoimmune disease via effects on complement and FcγRs. *J Immunol*. 2018;200(8):2542-2553.
41. Tradtrantip L, Felix CM, Spirig R, Morelli AB, Verkman A. Recombinant IgG1 fc hexamers block cytotoxicity and pathological changes in experimental in vitro and rat models of neuromyelitis optica. *Neuropharmacology*. 2018;133:345-353.
42. Ortiz DF, Lansing JC, Rutitzky L, et al. Elucidating the interplay between IgG-fc valency and FcγR activation for the design of immune complex inhibitors. *Sci Transl Med*. 2016;8(365):365ra158.
43. Washburn N, Schwab I, Ortiz D, et al. Controlled tetra-fc sialylation of IVIg results in a drug candidate with consistent enhanced anti-inflammatory activity. *Proc Natl Acad Sci*. 2015;112(11):E1297-E1306.
44. Roopenian DC, Akilesh S. FcRn: the neonatal fc receptor comes of age. *Nat Rev Immunol*. 2007;7(9):715-725.
45. Pyzik M, Kozicky LK, Gandhi AK, Blumberg RS. The therapeutic age of the neonatal fc receptor. *Nat Rev Immunol*. 2023;23(7):415-432.
46. Ghetie V, Ward ES. Multiple roles for the major histocompatibility complex class I–related receptor FcRn. *Annu Rev Immunol*. 2000;18(1):739-766.
47. Blumberg L, Humphries J, Sa J, et al. Blocking FcRn in humans reduces circulating IgG levels and inhibits IgG immune complex–mediated immune responses. *Sci Adv*. 2019;5(12):eaax9586.
48. Hubbard JJ, Pyzik M, Rath T, et al. FcRn is a CD32a coreceptor that determines susceptibility to IgG immune complex-driven autoimmunity. *J Exp Med*. 2020;217(10):1-14.
49. Baker K, Rath T, Flak MB, et al. Neonatal fc receptor expression in dendritic cells mediates protective immunity against colorectal cancer. *Immunity*. 2013;39(6):1095-1107.
50. Kaneko Y, Nimmerjahn F, Madaio MP, Ravetch JV. Pathology and protection in nephrotoxic nephritis is determined by selective engagement of specific fc receptors. *J Exp Med*. 2006;203(3):789.
51. Yamamoto M, Kobayashi K, Ishikawa Y, et al. The inhibitory effects of intravenous administration of rabbit immunoglobulin G on airway inflammation are dependent upon Fcγ receptor IIb on CD11c+ dendritic cells in a murine model. *Clin Exp Immunol*. 2010;162(2):315-324.
52. Seeling M, Brückner C, Nimmerjahn F. Differential antibody glycosylation in autoimmunity: sweet biomarker or modulator of disease activity? *Nat Rev Rheumatol*. 2017;13(10):621-630.
53. Imbach P, d'Apuzzo V, Hirt A, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*. 1981;317(8232):1228-1231.
54. Debré M, Griscelli C, Bonnet M, et al. Infusion of Fcγ fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet*. 1993;342(8877):945-949.
55. Hsu C-H, Chen M-R, Hwang F-Y, Kao H-A, Hung H-Y, Hsu C-H. Efficacy of plasmin-treated intravenous gamma-globulin for therapy of Kawasaki syndrome. *Pediatr Infect Dis J*. 1993;12(6):509-512.
56. Clarkson SB, Bussel JB, Kimberly RP, Valinsky JE, Nachman RL, Unkeless JC. Treatment of refractory immune thrombocytopenic purpura with an anti-Fcγ-receptor antibody. *N Engl J Med*. 1986;314(19):1236-1239.
57. Bussel JB, Kimberly RP, Inman RD, et al. Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. *Blood*. 1983;62(2):480-486.
58. Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med*. 1982;306(21):1254-1258.
59. Kimberly RP, Salmon JE, Bussel JB, Crow MK, Hilgartner MW. Modulation of mononuclear phagocyte function by intravenous gamma-globulin. *J Immunol*. 1984;132(2):745-750.
60. Machino Y, Suzuki E, Higurashi S, et al. Chemically dimerized intravenous immunoglobulin has potent ameliorating activity in a mouse immune thrombocytopenic purpura model. *Biochem Biophys Res Commun*. 2012;418(4):748-753.
61. Czajkowsky DM, Andersen JT, Fuchs A, et al. Developing the IVIG biomimetic, Hexa-fc, for drug and vaccine applications. *Sci Rep*. 2015;5(1):9526.
62. Zuercher AW, Spirig R, Baz Morelli A, Kasermann F. IVIG in autoimmune disease-potential next generation biologics. *Autoimmun Rev*. 2016;15(8):781-785.
63. Clark AL, Gall SA. Clinical uses of intravenous immunoglobulin in pregnancy. *Am J Obstet Gynecol*. 1997;176(1 Pt 1):241-253.
64. Hansen RJ, Balthasar JP. Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. *Thromb Haemost*. 2002;88(6):898-899.
65. Hansen RJ, Balthasar JP. Effects of intravenous immunoglobulin on platelet count and antiplatelet antibody disposition in a rat model of immune thrombocytopenia. *Blood*. 2002;100(6):2087-2093.
66. Li N, Zhao M, Hilario-Vargas J, et al. Complete FcRn dependence for intravenous Ig therapy in autoimmune skin blistering diseases. *J Clin Invest*. 2005;115(12):3440-3450.
67. Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG fc. *Science*. 2008;320(5874):373-376.
68. Anthony RM, Wermeling F, Karlsson MC, Ravetch JV. Identification of a receptor required for the anti-inflammatory activity of IVIG. *Proc Natl Acad Sci USA*. 2008;105(50):19571-19578.
69. Fiebiger BM, Maamary J, Pincetic A, Ravetch JV. Protection in antibody and T cell-mediated autoimmune diseases by antiinflammatory IgG fcs requires type II FcRs. *Proc Natl Acad Sci USA*. 2015;112(18):E2385-E2394.
70. Wohner M, Brechtelsbauer S, Friedrich N, et al. Tissue niche occupancy determines the contribution of fetal-versus bone-marrow-derived macrophages to IgG effector functions. *Cell Rep*. 2024;43(2):113757.

71. Crow AR, Suppa SJ, Chen X, Mott PJ, Lazarus AH. The neonatal fc receptor (FcRn) is not required for IVIg or anti-CD44 monoclonal antibody-mediated amelioration of murine immune thrombocytopenia. *Blood*. 2011;118(24):6403-6406.
72. Akilesh S, Petkova S, Sproule TJ, Shaffer DJ, Christianson GJ, Roopenian D. The MHC class I-like fc receptor promotes humorally mediated autoimmune disease. *J Clin Invest*. 2004;113(9):1328-1333.
73. Kasprick A, Hofrichter M, Smith B, et al. Treatment with anti-neonatal fc receptor (FcRn) antibody ameliorates experimental epidermolysis bullosa acquisita in mice. *Br J Pharmacol*. 2020;177(10):2381-2392.
74. Vaccaro C, Zhou J, Ober RJ, Ward ES. Engineering the fc region of immunoglobulin G to modulate in vivo antibody levels. *Nat Biotechnol*. 2005;23(10):1283-1288.
75. Pigors M, Patzelt S, Reichhelm N, et al. Bullous pemphigoid induced by IgG targeting type XVII collagen non-NC16A/NC15A extracellular domains is driven by fc gamma receptor-and complement-mediated effector mechanisms and is ameliorated by neonatal fc receptor blockade. *J Pathol*. 2024;262(2):161-174.
76. Shock A, Humphreys D, Nimmerjahn F. Dissecting the mechanism of action of intravenous immunoglobulin in human autoimmune disease: lessons from therapeutic modalities targeting Fcγ receptors. *J Allergy Clin Immunol*. 2020;146(3):492-500.
77. Ward ES, Gelinas D, Dreesen E, et al. Clinical significance of serum albumin and implications of FcRn inhibitor treatment in IgG-mediated autoimmune disorders. *Front Immunol*. 2022;13:892534.
78. Murthy S, Patzelt S, Kunstner A, Busch H, Schmidt E, Sadik CD. Intravenous Ig ameliorates disease in a murine model of anti-Laminin 332 mucous membrane pemphigoid. *J Invest Dermatol*. 2024;144(12):2671-2681.e1.
79. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory fc receptor. *Science*. 2001;291(5503):484-486.
80. Bruhns P, Samuelsson A, Pollard JW, Ravetch JV. Colony-stimulating factor-1-dependent macrophages are responsible for IVIG protection in antibody-induced autoimmune disease. *Immunity*. 2003;18(4):573-581.
81. Tackenberg B, Jelcic I, Baerenwaldt A, et al. Impaired inhibitory Fcgamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. *Proc Natl Acad Sci USA*. 2009;106(12):4788-4792.
82. Yamazaki S, Iyoda T, Tarbell K, et al. Direct expansion of functional CD25+ CD4+ regulatory T cells by antigen-processing dendritic cells. *J Exp Med*. 2003;198(2):235-247.
83. Lehmann CH, Baranska A, Heidkamp GF, et al. DC subset–specific induction of T cell responses upon antigen uptake via Fcγ receptors in vivo. *J Exp Med*. 2017;214(5):1509-1528.
84. Boruchov AM, Heller G, Veri M-C, Bonvini E, Ravetch JV, Young JW. Activating and inhibitory IgG fc receptors on human DCs mediate opposing functions. *J Clin Invest*. 2005;115(10):2914-2923.
85. Dhodapkar KM, Krasovsky J, Williamson B, Dhodapkar MV. Antitumor monoclonal antibodies enhance cross-presentation of cellular antigens and the generation of myeloma-specific killer T cells by dendritic cells. *J Exp Med*. 2002;195(1):125-133.
86. Siragam V, Brinc D, Crow AR, Song S, Freedman J, Lazarus AH. Can antibodies with specificity for soluble antigens mimic the therapeutic effects of intravenous IgG in the treatment of autoimmune disease? *J Clin Invest*. 2005;115(1):155-160.
87. Seeling M, Pöhnl M, Kara S, et al. Immunoglobulin G-dependent inhibition of inflammatory bone remodeling requires pattern recognition receptor Dectin-1. *Immunity*. 2023;56(5):1046-1063. e1047.
88. Pisitkun P, Deane JA, Difilippantonio MJ, Tarasenko T, Satterthwaite AB, Bolland S. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. *Science*. 2006;312(5780):1669-1672.
89. Espéli M, Bashford-Rogers R, Sowerby JM, et al. FcγRIIb differentially regulates pre-immune and germinal center B cell tolerance in mouse and human. *Nat Commun*. 2019;10(1):1970.
90. Segú-Vergés C, Caño S, Calderón-Gómez E, et al. Systems biology and artificial intelligence analysis highlights the pleiotropic effect of IVIg therapy in autoimmune diseases with a predominant role on B cells and complement system. *Front Immunol*. 2022;13:901872.
91. Bayry J, Lacroix-Desmazes S, Carbonneil C, et al. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. *Blood, the Journal of the American Society of Hematology*. 2003;101(2):758-765.
92. Bayry J, Mouthon L, Kaveri SV. Intravenous immunoglobulin expands regulatory T cells in autoimmune rheumatic disease. *J Rheumatol*. 2012;39(2):450-451.
93. Ephrem A, Chamat S, Miquel C, et al. Expansion of CD4+ CD25+ regulatory T cells by intravenous immunoglobulin: a critical factor in controlling experimental autoimmune encephalomyelitis. *Blood, the Journal of the American Society of Hematology*. 2008;111(2):715-722.
94. Delfraissy JF, Tchernia G, Laurian Y, Wallon C, Galanaud P, Dormont J. Suppressor cell function after intravenous gammaglobulin treatment in adult chronic idiopathic thrombocytopenic purpura. *Br J Haematol*. 1985;60(2):315-322.
95. Fiebiger BM, Maamary J, Pincetic A, Ravetch JV. Protection in antibody-and T cell-mediated autoimmune diseases by antiinflammatory IgG fcs requires type II FcRs. *Proc Natl Acad Sci*. 2015;112(18):E2385-E2394.
96. Hsieh L-E, Song J, Tremoulet AH, Burns JC, Franco A. Intravenous immunoglobulin induces IgG internalization by tolerogenic myeloid dendritic cells that secrete IL-10 and expand fc-specific regulatory T cells. *Clin Exp Immunol*. 2022;208(3):361-371.
97. Miyara M, Sakaguchi S. Natural regulatory T cells: mechanisms of suppression. *Trends Mol Med*. 2007;13(3):108-116.
98. Aubin É, Lemieux R, Bazin R. Indirect inhibition of in vivo and in vitro T-cell responses by intravenous immunoglobulins due to impaired antigen presentation. *Blood, the Journal of the American Society of Hematology*. 2010;115(9):1727-1734.
99. Bayry J, Lacroix-Desmazes S, Delignat S, et al. Intravenous immunoglobulin abrogates dendritic cell differentiation induced by interferon-α present in serum from patients with systemic lupus erythematosus. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 2003;48(12):3497-3502.
100. Ohkuma K, Sasaki T, Kamei S, et al. Modulation of dendritic cell development by immunoglobulin G in control subjects and multiple sclerosis patients. *Clin Exp Immunol*. 2007;150(3):397-406.
101. Yamazaki S, Dudziak D, Heidkamp GF, et al. CD8+ CD205+ splenic dendritic cells are specialized to induce Foxp3+ regulatory T cells. *J Immunol*. 2008;181(10):6923-6933.
102. Das M, Karnam A, Stephen-Victor E, et al. Intravenous immunoglobulin mediates anti-inflammatory effects in peripheral blood mononuclear cells by inducing autophagy. *Cell Death Dis*. 2020;11(1):50.
103. Kozicky LK, Menzies SC, Hotte N, Madsen KL, Sly LM. Intravenous immunoglobulin (IVIg) or IVIg-treated macrophages reduce DSS-induced colitis by inducing macrophage IL-10 production. *Eur J Immunol*. 2019;49(8):1251-1268.
104. Kozicky LK, Zhao ZY, Menzies SC, et al. Intravenous immunoglobulin skews macrophages to an anti-inflammatory, IL-10-producing activation state. *Journal of Leucocyte Biology*. 2015;98(6):983-994.
105. Saha C, Kothapalli P, Patil V, ManjunathaReddy GB, Kaveri SV, Bayry J. Intravenous immunoglobulin suppresses the polarization of both classically and alternatively activated macrophages. *Hum Vaccin Immunother*. 2020;16(2):233-239.
106. Durandy A, Kaveri S, Kuijpers T, et al. Intravenous immunoglobulins–understanding properties and mechanisms. *Clin Exp Immunol*. 2009;158(Supplement_1):2-13.

107. Kaufman GN, Massoud AH, Dembele M, Yona M, Piccirillo CA, Mazer BD. Induction of regulatory T cells by intravenous immunoglobulin: a bridge between adaptive and innate immunity. *Front Immunol*. 2015;6:469:1-10.
108. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet*. 2004;364(9433):533-544.
109. Burns J, Song Y, Bujold M, et al. Immune-monitoring in Kawasaki disease patients treated with infliximab and intravenous immunoglobulin. *Clin Exp Immunol*. 2013;174(3):337-344.
110. Franco A, Touma R, Song Y, et al. Specificity of regulatory T cells that modulate vascular inflammation. *Autoimmunity*. 2014;47(2):95-104.
111. Kao D, Lux A, Schaffert A, Lang R, Altmann F, Nimmerjahn F. IgG subclass and vaccination stimulus determine changes in antigen specific antibody glycosylation in mice. *Eur J Immunol*. 2017;47(12):2070-2079.
112. Wuhrer M, Stam JC, van de Geijn FE, et al. Glycosylation profiling of immunoglobulin G (IgG) subclasses from human serum. *Proteomics*. 2007;7(22):4070-4081.
113. Zaytseva OO, Seeling M, Kristic J, Lauc G, Pezer M, Nimmerjahn F. Fc-linked IgG N-glycosylation in FcgammaR Knock-out mice. *Front Cell Dev Biol*. 2020;8:67.
114. Zhao Y, Raidas S, Mao Y, Li N. High-throughput glycan profiling of human serum IgG subclasses using parallel reaction monitoring peptide bond fragmentation of Glycopeptides and microflow LC-MS. *J Proteome Res*. 2024;23(2):585-595.
115. Arnold JN, Wormald MR, Sim RB, Rudd PM, Dwek RA. The impact of glycosylation on the biological function and structure of human immunoglobulins. *Annu Rev Immunol*. 2007;25(1):21-50.
116. Schwab I, Biburger M, Krönke G, Schett G, Nimmerjahn F. IVI g-mediated amelioration of ITP in mice is dependent on sialic acid and SIGNR 1. *Eur J Immunol*. 2012;42(4):826-830.
117. Schwab I, Mihai S, Seeling M, Kasperkiewicz M, Ludwig RJ, Nimmerjahn F. Broad requirement for terminal sialic acid residues and FcγRIIB for the preventive and therapeutic activity of intravenous immunoglobulins in vivo. *Eur J Immunol*. 2014;44(5):1444-1453.
118. Bayry J, Ahmed EA, Toscano-Rivero D, et al. Intravenous immunoglobulin: mechanism of action in autoimmune and inflammatory conditions. *The Journal of Allergy and Clinical Immunology: In Pract*. 2023;11(6):1688-1697.
119. Zhang G, Massaad CA, Gao T, et al. Sialylated intravenous immunoglobulin suppress anti-ganglioside antibody mediated nerve injury. *Exp Neurol*. 2016;282:49-55.
120. Anthony RM, Kobayashi T, Wermeling F, Ravetch JV. Intravenous gammaglobulin suppresses inflammation through a novel TH2 pathway. *Nature*. 2011;475(7354):110-113.
121. Choi H, Yang S-W, Joo J-S, et al. Sialylated IVIg binding to DC-SIGN+ Hofbauer cells induces immune tolerance through the caveolin-1/NF-kB pathway and IL-10 secretion. *Clin Immunol*. 2023;246:109215.
122. Tanigaki K, Sacharidou A, Peng J, et al. Hyposialylated IgG activates endothelial IgG receptor FcγRIIB to promote obesity-induced insulin resistance. *J Clin Invest*. 2018;128(1):309-322.
123. Ahmed AA, Giddens J, Pincetic A, et al. Structural characterization of anti-inflammatory immunoglobulin G fc proteins. *J Mol Biol*. 2014;426(18):3166-3179.
124. Sondermann P, Pincetic A, Maamary J, Lammens K, Ravetch JV. General mechanism for modulating immunoglobulin effector function. *Proc Natl Acad Sci*. 2013;110(24):9868-9872.
125. Wang TT, Maamary J, Tan GS, et al. Anti-HA glycoforms drive B cell affinity selection and determine influenza vaccine efficacy. *Cell*. 2015;162(1):160-169.
126. Crispin M, Yu X, Bowden TA. Crystal structure of sialylated IgG fc: implications for the mechanism of intravenous immunoglobulin therapy. *Proc Natl Acad Sci USA*. 2013;110(38):E3544-E3546.
127. Yu X, Vasiljevic S, Mitchell DA, Crispin M, Scanlan CN. Dissecting the molecular mechanism of IVIg therapy: the interaction between serum IgG and DC-SIGN is independent of antibody glycoform or fc domain. *J Mol Biol*. 2013;425(8):1253-1258.
128. Sharma M, Schoindre Y, Hegde P, et al. Intravenous immunoglobulin-induced IL-33 is insufficient to mediate basophil expansion in autoimmune patients. *Sci Rep*. 2014;4(1):5672.
129. Lewis BJB, Leontyev D, Neschadim A, Blacquiere M, Branch DR. GM-CSF and IL-4 are not involved in IVIG-mediated amelioration of ITP in mice: a role for IL-11 cannot be ruled out. *Clin Exp Immunol*. 2018;193(3):293-301.
130. Newland AC, Treleaven JG, Minchinton RM, Waters AH. High-dose intravenous IgG in adults with autoimmune thrombocytopenia. *Lancet*. 1983;1(8316):84-87.
131. Schwab I, Seeling M, Biburger M, Aschermann S, Nitschke L, Nimmerjahn F. B cells and CD 22 are dispensable for the immediate antiinflammatory activity of intravenous immunoglobulins in vivo. *Eur J Immunol*. 2012;42(12):3302-3309.
132. Schwab I, Mihai S, Seeling M, Kasperkiewicz M, Ludwig R, Nimmerjahn F. Broad requirement for terminal sialic acid residues and FcgRIIB for the preventive and therapeutic activity of intravenous immunoglobulins in vivo. *Eur J Immunol*. 2014;44(5):1444-1453.
133. Massoud AH, Yona M, Xue D, et al. Dendritic cell immunoreceptor: a novel receptor for intravenous immunoglobulin mediates induction of regulatory T cells. *J Allergy Clin Immunol*. 2014;133(3):853-863. e855.
134. Trinath J, Hegde P, Sharma M, et al. Intravenous immunoglobulin expands regulatory T cells via induction of cyclooxygenase-2–dependent prostaglandin E2 in human dendritic cells. *Blood, the Journal of the American Society of Hematology*. 2013;122(8):1419-1427.
135. Cousens L, Najafian N, Martin WD, De Groot AS. Tregitope: immunomodulation powerhouse. *Hum Immunol*. 2014;75(12):1139-1146.
136. Dembele M, Tao S, Massoud AH, et al. Tregitopes improve asthma by promoting highly suppressive and antigen-specific tregs. *Front Immunol*. 2021;12:634509.
137. Bolland S, Ravetch JV. Spontaneous autoimmune disease in FcγRIIB-deficient mice results from strain-specific epistasis. *Immunity*. 2000;13(2):277-285.
138. Brown GD. Dectin-1: a signalling non-TLR pattern-recognition receptor. *Nat Rev Immunol*. 2006;6(1):33-43.
139. Mata-Martínez P, Bergón-Gutiérrez M, Del Fresno C. Dectin-1 signaling update: new perspectives for trained immunity. *Front Immunol*. 2022;13:812148.
140. Shan M, Gentile M, Yeiser JR, et al. Mucus enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals. *Science*. 2013;342(6157):447-453.
141. Karsten CM, Pandey MK, Figge J, et al. Anti-inflammatory activity of IgG1 mediated by fc galactosylation and association of FcγRIIB and dectin-1. *Nat Med*. 2012;18(9):1401-1406.
142. Seeling M, Hillenhoff U, David JP, et al. Inflammatory monocytes and Fcγ receptor IV on osteoclasts are critical for bone destruction during inflammatory arthritis in mice. *Proc Natl Acad Sci*. 2013;110(26):10729-10734.
143. Rowley TF, Peters SJ, Aylott M, et al. Engineered hexavalent fc proteins with enhanced fc-gamma receptor avidity provide insights into immune-complex interactions. *Communications Biology*. 2018;1(1):146.
144. Zhang X, Owens J, Olsen HS, et al. A recombinant human IgG1 fc multimer designed to mimic the active fraction of IVIG in autoimmunity. *JCI Insight*. 2019;4(2):1-19.
145. Monnet C, Jacque E, de Romeuf C, et al. The dual targeting of FcRn and FcγRs via monomeric fc fragments results in strong inhibition of IgG-dependent autoimmune pathologies. *Front Immunol*. 2021;12:728322.

146. Sneed SL, Reese BB, Laureano AF, et al. An engineered immunomodulatory IgG1 fc suppresses autoimmune inflammation through pathways shared with iv immunoglobulin. *J Clin Invest*. 2024;134(4):e172980.
147. Park EI, Manzella SM, Baenziger JU. Rapid clearance of sialylated glycoproteins by the asialoglycoprotein receptor. *J Biol Chem*. 2003;278(7):4597-4602.
148. Pagan JD, Kitaoka M, Anthony RM. Engineered sialylation of pathogenic antibodies in vivo attenuates autoimmune disease. *Cell*. 2018;172(3):564-577 e513.
149. Albert H, Collin M, Dudziak D, Ravetch JV, Nimmerjahn F. In vivo enzymatic modulation of IgG glycosylation inhibits autoimmune disease in an IgG subclass-dependent manner. *Proc Natl Acad Sci USA*. 2008;105(39):15005-15009.
150. Kao D, Danzer H, Collin M, et al. A monosaccharide residue is sufficient to maintain mouse and human IgG subclass activity and directs IgG effector functions to cellular fc receptors. *Cell Rep*. 2015;13(11):2376-2385.
151. Mihai S, Albert H, Ludwig RJ, et al. In vivo enzymatic modulation of IgG antibodies prevents immune complex-dependent skin injury. *Exp Dermatol*. 2017;26(8):691-696.
152. Nandakumar KS, Collin M, Olsen A, et al. Endoglycosidase treatment abrogates IgG arthritogenicity: importance of IgG glycosylation in arthritis. *Eur J Immunol*. 2007;37(10):2973-2982.
153. Segelmark M, Bjorck L. Streptococcal enzymes as precision tools against pathogenic IgG autoantibodies in small vessel Vasculitis. *Front Immunol*. 2019;10:2165.

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