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Targeting the Fc receptor in autoimmune disease

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Abstract

Introduction—The Fc receptors and their interaction with immunoglobulin and innate immune opsonins such as CRP are key players in humoral and cellular immune responses. As the effector mechanism for some therapeutic monoclonal antibodies and often a contributor to the pathogenesis and progression of autoimmunity, FcRs are promising targets for treating autoimmune diseases.

Areas covered—This review discusses the nature of different Fc receptors and the various mechanisms of their involvement in initiating and modulating immunocyte functions and their biological consequences. It describes a range of current strategies in targeting Fc receptors and manipulating their interaction with specific ligands while presenting the pros and cons of these approaches. This review also discusses potential new strategies including regulation of FcR expression and receptor cross-talk.

Expert opinion—Fc receptors are appealing targets in the treatment of inflammatory autoimmune diseases. However, there are still knowledge limitations and technical challenges, the most important being a better understanding of the individual roles of each of the Fc receptors and enhancement of the specificity in targeting particular cell types and specific Fc receptors.

1. Introduction

Autoimmune diseases are categorized by the failure of the immune system to limit its target reactivity to harmful foreign antigens. More than 80 different types of local or systemic disorders have been considered to have an autoimmune nature [1]. Instead of producing antibodies only against harmful substances, the immune system loses normal tolerance and produces autoantibodies, leading to tissue inflammation and structural/ functional damage. Both initiation and progression of autoimmune diseases are related to altered functionality of various innate and adaptive immune cells, of which the activation threshold is tuned by cell surface receptors.

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The receptors for the Fc portion of immunoglobulin, Fc receptors (FcRs), are important initiators of antibody mediated defense against harmful pathogens and are also key players in both the pathogenesis and severity of immune complex (IC) mediated autoimmune diseases. FcRs are widely distributed on all types of immunocytes. They function in a variety of humoral and cellular immune responses, including antibody-dependent cellular cytotoxicity (ADCC), phagocytosis, degranulation, cytokine and chemokine expression and immune complex clearance. FcRs are classified by the Ig isotype of their ligands, such as IgG, IgA, IgE and IgM.

2. Different types of Fc receptors

2.1 FcγRs

IgG is the most abundant class of antibody in circulation, constituting 75% of immunoglobulin in serum. The FcγR is a group of surface glycoproteins encoded by eight genes located in chromosome 1q21-23 that bind to the Fc portion of IgG. Besides interacting with IgG, FcγRs also function as receptors for innate immune opsonins (CRP and SAP) and provide a link between innate and acquired immunity. Based on structural homology and differences in affinity this family is further divided into three subfamilies: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) (Figure 1A). FcγR functions either as activating receptors (FcγRI, FcγRIIa/c, FcγRIII) or inhibitory receptors (FcγRIIb), as they signal through immune tyrosine activating or inhibitory motifs (ITAM or ITIM) to elicit or inhibit immune functions. These signaling motifs are either on the ligand binding α-chain, as for FcγRII, or on associated accessory γ-chains (as for FcγRI and FcγRIII) [2]. The ligand binding α-chain of most FcγRs consists of two or three immunoglobulin (Ig)-like domains in extracellular region, a transmembrane domain and an intracellular tail.

2.11 FcγRI—With three extracellular Ig-like domains, FcγRI is the only FcγR with high affinity ($K_d \sim 10^9 \text{ M}^{-1}$), enabling it to bind monomeric IgG strongly. FcγRI family has three genes (*FCGR1A*, *FCGR1B* and *FCGR1C*) but only FcγRIa, product of *FCGR1A*, has been identified as a full length mature receptor [3]. FcγRI has been found on surface of monocytes, dendritic cells (DC), macrophages and neutrophils when they are primed with interferon-γ (IFN-γ) or granulocyte colony stimulating factor (G-CSF) [4].

2.12 FcγRII—*FCGR2* and *FCGR3* gene variants are located in the classical low affinity Fc receptor cluster on human chromosome 1q23. FcγRII subclass is composed by three genes (*FCGR2A*, *FCGR2B* and *FCGR2C*) which encode FcγRIIa, FcγRIIb and FcγRIIc. Being expressed on monocytes, neutrophils, B cells and NK cells, FcγRII (CD32) is the most widely distributed FcγR with low binding affinity to IgG [5]. With two extracellular Ig-like domains, FcγRII has low binding affinity for monomeric IgG, but readily binds IgG aggregates and IC. Unlike other FcγRs, FcγRIIs bear signaling motifs on their own intracellular tails of α-chain and don't require γ-chain for stable expression or function. While FcγRIIa and FcγRIIc contain an ITAM, FcγRIIb distinguishes itself as the only inhibitory Fcγ receptor by comprising an ITIM on its intracellular domain. *FCGR2B* generates three transcripts from alternative splicing: b1 and b2 differ by an insert of 19 amino acids on FcγRIIb1's cytoplasmic tail; b3 lacks part of the signal sequence. FcγRIIb1

is expressed on B cells as the only Fc γ receptor for B cell, while Fc γ RIIb2 is found on myeloid cells as well as Fc γ RIIa. Fc γ RIIc is expressed on NK cells [6, 7]. It has an extracellular domain highly homologous to Fc γ RIIb and an Fc γ RIIa- like cytoplasmic tail as a result of unequal crossover between *FCGR2A* and *FCGR2B*.

2.13 Fc γ RIII—Two genes, *FCGR3A* and *FCGR3B* encode two receptors for Fc γ RIII subclass: Fc γ RIIIa and Fc γ RIIIb. Fc γ RIII is also considered low affinity: Fc γ RIIIa binds monomeric IgG with an intermediate affinity; both Fc γ RIIIa and Fc γ RIIIb bind multimeric IgG and IC efficiently. Fc γ RIIIa is expressed as a transmembrane protein on monocytes, tissue specific macrophages, dendritic cells, δ/γ T cells and most importantly, natural killer (NK) cells [2]. On these cells the γ -chain homodimer is necessary for both stable expression and signal transduction of Fc γ RIIIa. However, in mast cells, Fc γ RIIIa receptor complex is comprised by its α -chain, two γ -chains, as well as a β -chain from IgE receptor. In NK cells, Fc γ RIIIa is also found to be associated with T cell receptor ζ -chain. Fc γ RIIIb is only expressed on neutrophil surface as a GPI anchored protein [8]. Fc γ RIIIb can be cleaved from neutrophil surface upon cell activation.

All Fc γ Rs have preference in terms of binding IgG subclasses. In general, IgG3 and IgG1 are preferred to IgG2 and IgG4. Cellular distribution and binding preference of FcRs are summarized in Table 1.

2.2 Fc ϵ R

The high affinity Fc receptor for IgE, Fc ϵ RI, is a multimeric complex with the receptor α -chain for IgE binding, and the β - and γ -chains for signal transduction (Figure 1B) [9]. Fc ϵ RI expression has been reported on human mast cells, basophils, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, Langerhans cells and platelets. In allergy effector cells like mast cells, Fc ϵ RI signals through $\alpha\beta\gamma$ 2 tetramer for an activating signaling cascade [10].

When the Fc ϵ RI receptor is associated with the γ 2 dimer on antigen presenting cells, it participates in antigen presentation [10]. While traditionally considered an FcR unrelated to autoimmunity, it is currently recognized that 30–40% chronic urticaria has an autoimmune basis, caused by IgG autoantibodies against Fc ϵ RI and IgE, which leads to mast cell activation and release of histamine [11–13]. A second receptor for IgE, Fc ϵ RII (CD23) has also been identified as a low affinity receptor with no structure similarities to other FcRs. Fc ϵ RII is expressed on B cells and is involved in the regulation of IgE production [14].

2.3 Fc α R

The low affinity IgA Fc receptor, Fc α RI (CD89), has an IgA binding α -chain and signals through the ITAM bearing FcR γ -chain, similar to Fc γ RIa and Fc γ RIIIa. However the Fc α RI α -chain does not require the γ -chain for stable expression on neutrophils, eosinophils, monocytes, macrophages and dendritic cells. Fc α RI can trigger inflammatory effects such as respiratory burst and degranulation. However, in some experimental paradigms it also plays anti-inflammatory roles [15, 16].

2.4 FcμR

Unlike IgG, IgE and IgA receptors, the genetic and proteomic identity of the classical Fc receptor for IgM has only recently been elucidated. Kubagawa, Ohno and colleagues have discovered that a molecule initially designated as TOSO, or Fas apoptotic inhibitory molecule 3 (FAIM3), is the long-sought Fc receptor for IgM [17, 18]. FcμR/TOSO carries a single Ig domain in its extracellular region that specifically binds IgM, and a relatively long cytoplasmic tail with no traditional ITAM or ITIM. Of particular interest, FcμR/TOSO is expressed on B cells and NK cells and is the only Fc receptor on T cells [17]. The current uncertainty of FcμR expression in granulocytes could be caused by different activation status of cells in various studies and different affinity of various FcμR detecting antibodies [19–21].

2.5 FcRn

Encoded by gene *FCGRT*, the neonatal Fc receptor (FcRn) is a major histocompatibility complex class I related molecule. It was originally recognized as mediating IgG transportation from mother to offspring for passive immunity [22]. In adults, FcRn functions as a chaperone for IgG, protecting it from catabolism and transferring it across a diverse array of different cells [23]. The FcRn-IgG interaction is strictly pH dependent, favoring acidic environment with a maximum at pH6. FcRn does not conduct signaling through either an ITAM or an ITIM to modulate effector cell functions.

3. FcR signaling properties

Antibody mediated cell activation threshold is tuned by activating and inhibitory FcRs. Upon crosslinking of the activating receptors, the tyrosines in ITAM are phosphorylated by Src family kinases such as Lyn and Fyn, which then leads to the recruitment of the cytosolic protein kinase Syk [24, 25]. Consequences of the activating signaling include oxidative burst, degranulation, phagocytosis, cytokine production, and antibody-dependent cell-mediated cytotoxicity, or in general, the initiation of inflammation and tissue damage in the development of autoimmunity, as well as immune complex elimination. When the inhibitory FcγRIIb is co-engaged with activating Fc receptors or the BCR, the tyrosine-phosphorylated ITIM recruits the SH2 domain- containing phosphatases SHIP or SHP-1 [26]. In B cells, the cascade extends to dissociate Btk and PLC-γ from the BCR signalosome and reduce calcium influx [27]. Through its ITIM, FcγRIIb serves as a negative regulator of immune complex-triggered inflammatory cascades.

4. Strategies for targeting FcRs in autoimmune diseases

Given that hypersensitivity and hyperactivation of immune cells is the root of autoimmune diseases, re-balancing the yin and the yang in immune regulation is the key to restoring more normal immune system functions. This balance could be achieved by modulating the coordination between the activating and the inhibitory signals, raising the threshold for immune complex-triggered activation of immunocytes, and eventually attenuating inflammation and autoimmunity.

4.1 Direct engagement of FcRs

4.11 Blocking/neutralizing activating receptors (antagonist)—Evidence from both murine models and patients suggests a major role of the activating FcRs in initiating and propelling immune complex-mediated inflammation. For example, mice lacking the common Fc γ -chain, thus deficient in activating FcRs, are protected from a series of tissue specific or systemic immune diseases, including the reverse passive Arthus (RPA) reaction, autoimmune skin damages, arthritis, and systemic lupus erythematosus (SLE) nephritis [28]. Human Fc γ RIIa transgenic mice are hypersensitive to pathogenic antibodies and develop destructive arthritic syndromes [29, 30]. Ex vivo experimentation with circulating monocytes from rheumatoid arthritis patients suggest that Fc γ RIIa is responsible for the production of inflammatory cytokines including tumor necrosis factor α (TNF α) and interleukin-1 β (IL-1 β) [31, 32].

Anti-receptor monoclonal antibodies, intact antibodies and antibody fragments and a variety of small molecules have been designed to interact with the Ig-binding domains in the activating FcRs. Some of these approaches have shown encouraging results when tested *in vitro* or *in vivo* for blocking immune complex-mediated cell effects and inflammation. One early example was the mouse anti-human Fc γ RIII mAb 3G8 which was used to successfully treat immune thrombocytopenia (ITP) in primates [33, 34].

Small molecule approaches have been tested as antagonist for activating FcRs. For example, TG19320, a tetrameric peptide derived from combinatorial chemistry, was shown to interfere with IgG/Fc γ R interaction *in vitro*. In a SLE prone mouse strain MRL/*lpr*, the administration of TG19320 prevented glomerulonephritis *in vivo* and enhanced the survival rate to 80% compared to 10% in the placebo group [35]. In a collagen-induced arthritis model, Fc γ RIIa specific small chemical entities inhibited disease development, showed stronger and longer suppression compared to methotrexate, a traditional treatment for RA in human [36]. However, potential limitations in peptide-based therapeutics include reduced affinity compared to whole antibodies, and multivalent antibody aggregates.

Instead of blocking individual receptor, an alternative strategy for interfering in the Ig/FcR binding is to block the immune complex. Soluble, secreted Fc γ RIIa and Fc γ RIIIa are found in circulation in normal individuals, and the level of soluble Fc γ RIIIa in blood has been explored as a marker for RA [37–39]. In murine models, infusion of recombinant soluble Fc γ RIIa and Fc γ RIIIa can inhibit immune complex triggered inflammation [40]. Synthesized soluble Fc γ RIa and Fc γ RIIb have also been shown to absorb pathogenic immune complexes and to reduce disease severity in murine arthritis models [41–43]. Of note, other than serving as decoy receptors for immune complexes, there may be additional pro- or anti-inflammatory effects caused by circulating Fc γ Rs, such as interacting with non-Ig-ligands and inducing the production of IL-12 [44, 45].

4.12 Engagement of the inhibitory Fc γ RIIb (agonist)—The only inhibitory FcR, Fc γ RIIb, serves as a critical negative regulator in immune complex driven reactions. In mice lacking Fc γ RIIb, autoimmune symptoms are exacerbated, and a partial restoration of Fc γ RIIb expression on B cells was able to rescue mice from developing an SLE-like phenotype [46–48]. The important suppressor role of Fc γ RIIb in the development of

autoimmunity is further supported by multiple observations in human that Fc γ RIIb polymorphisms are associated with SLE by affecting either signaling or expression level [49–52]. Fc γ RIIb on memory B cells is also reported to be dysregulated in SLE [53, 54]. These unique inhibitory features mark Fc γ RIIb as an important candidate for therapeutic targets in autoimmunity. However, for many years antibody therapy against Fc γ RIIb had been dampened by the great difficulty in distinguishing Fc γ RIIb from Fc γ RIIa due to their highly homologous extracellular sequences. Several Fc γ RIIb specific mAbs have now been developed [53, 55, 56], one of which, mAb2B6, has been chimerized and humanized to direct myeloid-cytotoxicity against B cells [57]. These antibodies have the potential to serve as novel immune-suppressors in autoimmunity and may have an advantage over CD20 antibodies for their ability to target plasma cells [58]. On the other hand, unlike CD20, Fc γ RIIb is expressed not only on B cells, but many other types of immune cells. Fc γ RIIb-targeting reagents would also bind to Fc γ RIIc, which is expressed as an activating receptor in individuals with an open reading frame minor allele instead of homozygous stop codon alleles.

Another appealing approach is to design bispecific ligands that could crosslink Fc γ RIIb with the BCR on B cells or with other activating FcRs on myeloid cells. These chimeric molecules would presumably put a break at the initiation of activation cascades. One of these, a dual-affinity diabody with an Fv region against Fc γ RIIb and another Fv region against CD79B, successfully triggered the inhibitory signaling pathway, lowered B cell proliferation and antibody production, and inhibited the development of arthritis induced by collagen in a murine model [59]. Recently, a bispecific antibody (XmAb5871) was designed to bind Fc γ RIIb with its Fc domain and a humanized Fv region against CD19. The Fc region was also engineered to have >400-fold increased affinity for Fc γ RIIb compared to native IgG1 Fc [60]. This antibody showed potent inhibitory effect *ex vivo*, as well as efficacy in suppressing humoral immune responses in humanized mouse models. On mast cells or basophils, bispecific antibodies aiming to crosslink Fc γ RIIb with Fc ϵ RI can inhibit IgE mediated histamine release in mouse and non-human primates [61–64].

4.13 Antigen targeting and ADCC—Given the pathogenic role of autoreactive B cells and the production of autoantibodies, another approach is to deplete B cells through ADCC in autoimmune patients. As mentioned earlier, activating Fc γ Rs on effector cells are the mediators for ADCC. A humanized IgG1 mAb against the B cell specific antigen CD20, rituximab, has been used for B cell depletion in non-Hodgkin lymphoma and RA, as well as in trials of SLE, ITP, and an autoimmune neuromuscular disease, myasthenia gravis [65, 66]. Anti-CD20 B cell depletion therapy even showed success in treating chronic urticaria caused by anti-Fc ϵ RI autoantibodies [67]. There are several mechanisms that could explain the effect of rituximab, including complement based cytotoxicity or apoptosis induced by CD20 homo-crosslinking, but the most important mechanism is through FcR-mediated ADCC by NK cells and macrophages. Anti-CD20 antibodies showed no therapeutic effect in mice deficient for FcRs [68]. In SLE patients, the high/low binding polymorphism in Fc γ RIIIa was reported to be associated with efficiency of rituximab [69, 70]. Interestingly, the inhibitory Fc γ RIIb expressed on target B cells promotes internalization of rituximab thus inhibits B cell depletion [71]. These observations indicate the potential for enhancing B

cell depletion efficacy by modifying the Fc domain of the antibody to enhance activating Fc γ R binding and reduce affinity for the inhibitory Fc γ RIIb.

B cell depletion by rituximab has gained wide acceptance after more than a decade of clinical use. However, accumulated evidence suggests it may over-suppress the immune system and increase the risk of certain infections [72]. Comparing to B cell depletion with rituximab, the B cell/Fc γ RIIb targeting strategies would reduce B cell activation without depletion, thus having the potential to avoid or lower the rate of infectious complications. Furthermore, bispecific antibodies may have the potential to co-ligate Fc γ RIIb with disease specific auto-antigens and to provide a precisely controlled auto-antigen-specific suppression of the humoral immunity.

4.2 Post-translational modification of therapeutic abs

The structure of IgG and its carbohydrate composition has been extensively studied. The carbohydrates covalently linked to Asn297 of the CH2 domain has a major influence on the affinity of the Fc for Fc γ Rs. The oligosaccharide chains are highly complex structures of sugars, with a core of N-acetyl-glucosamine (GlcNAc) and mannose residues, and can extend to contain different numbers of galactose, fucose and sialic acid residues. Although Asn297 is not in direct contact with the Fc γ R, the carbohydrates can influence the conformation of the epitope for Fc γ R/Fc binding [73]. Removal of the N-glycans completely aborted FcR binding for all IgG isotypes [74]. In autoimmune mice, when N-glycans on immune complexes were removed by injection of endoglycosidase S, inflammatory responses were reduced and lupus-like symptoms were improved [75]. Engineered IgG with different amounts of bisected GlcNAc could trigger different levels of ADCC [76], and therefore therapeutic antibodies could be engineered to achieve maximal ADCC through optimizing their glycoforms.

Several studies showed that the presence of fucose residues can lead to severely reduced ADCC efficiency [77, 78]. Current efforts focus on the development of cell lines or non-mammalian expression systems that are capable of producing non-fucosylated antibodies [78–83]. De-fucosylated CD20 antibodies derived from the *FUT8* knockout cells possess much higher affinity for Fc γ RIIIa and more than 100-fold higher ADCC [78]. When de-fucosylation was combined with optimized glocoforms, engineered CD20 antibodies displayed maximum level of binding affinity to Fc γ RIIIa, with 50-fold increase for the high binding V158 allele, and 27-fold improvement for the F158 allele [84, 85]. The binding affinity for the inhibitory Fc γ RIIb was minimally affected by these modifications, further contributing to a favorable, optimized depletion antibody.

Decreased levels of galactosylation and sialylation of IgG have been found to associate with disease onset and severity in inflammatory autoimmune conditions such as RA and vasculitis [86–90]. Consistently, highly galactosylated IgG1 has been shown to promote cooperative signaling of Fc γ RIIb with dectin-1, resulting in anti-inflammatory effects [91]. Sialylated IgG in IVIg may contribute to the anti-inflammatory properties of intravenous immunoglobulin (IVIg) through upregulating Fc γ RIIb expression. Enriched sialylated IVIg showed a 10-fold increase in efficacy in treating murine immune complex-induced arthritis

[92]. These observations indicate the potential to modify the sialylation and galactosylation status of IgG for enhanced anti-inflammatory effect.

4.3 Targeting FcRn

Antibodies, especially IgG, play a predominant role in the pathogenesis and the treatment of many autoimmune diseases. In order to treat IgG-mediated autoimmunity, it would be beneficial to lower levels of endogenous pathogenic autoantibodies or to prolong the circulating time of infused therapeutic antibodies. As mentioned earlier, FcRn is well documented as the major factor in regulating IgG metabolism. In adults, it binds to the Fc domain of IgG in a strictly pH-dependent fashion and prevents IgG from degradation after endocytosis. Targeting the FcRn/IgG interaction would be a rational therapy approach.

4.31 Blocking FcRn-IgG interaction to decrease IgG level—One opportunity to treat autoimmune disease is to lower endogenous IgG autoantibody levels by blocking the IgG-FcRn interaction. In the absence of binding to FcRn, IgG would not be able to enter the salvage pathway and would thus be degraded in lysosomes more quickly instead of recycled back into circulation. One straight forward method would be to use recombinant soluble human FcRn. Indeed, several groups have managed to produce suitable amount of soluble human FcRn in both bacteria and mammalian cells while retaining the ability to bind IgG at acidic but not neutral pH [93, 94]. Further cellular and *in vivo* experiments are needed to test the ability of the recombinant FcRn in transporting IgG into acidic endosomes in cells and its protective effect of IgG.

Another approach to blocking IgG-FcRn binding is through engineered “bait” IgG, which occupies endogenous FcRn and prevent binding with endogenous IgG. Such “bait” antibodies have been generated with a much higher affinity for FcRn at both acidic and neutral pHs, thereby providing effectively occupancy of FcRn, leading to degradation of endogenous IgG. These antibodies are also called “Abdegs”: antibodies that enhance IgG degradation [95]. In mouse models, an “Abdeg” engineered by Ward and colleagues significantly increased the clearance of endogenous IgG immune complexes, and induced a rapid decrease of circulating IgG levels [95]. Another engineered IgG1 Abdeg successfully competed with endogeneous IgG in a humanized mouse model and reduced severity of arthritis induced by passive transfer with human pathogenic plasma [96]. It is of great interest to test whether the blocking molecules behave in a similar way in non-human primates or *ex vivo* human systems, as murine FcRn is very different from human FcRn in binding specificity and may perform differently from human FcRn with the same antibody [97].

An FcRn-specific blocking mAb would also provide interference to FcRn-IgG interaction. One such mAb, 1G3, was examined in rat passive and active models of myasthenia gravis, a prototypical antibody mediated autoimmune disease [98]. Administration of 1G3 resulted in amelioration of disease symptoms in a dose-dependent manner. Levels of pathogenic antibody in the serum were also greatly reduced.

Similarly, FcRn-binding synthetic peptides have also been developed. When tested in cynomolgus monkeys, one of these peptides, Syntonix (SYN1436), effectively lowered

levels of endogenous IgG by 80% [99]. In comparison to FcRn blocking antibodies or Abdegs, blocking peptides might have the advantage of being more specific for FcRn but not other IgG receptors, and less likely to induce other Fc γ R-mediated effects.

4.32 Increasing half-life of therapeutic antibodies—Extending serum half-life of therapeutic antibodies or Fc-fusion proteins would improve their efficacy. Longer half-life of therapeutic antibodies may allow lower dose and longer interval between administrations at lowered costs. Through several different approaches including random mutagenesis to computational design algorithms, a series of Fc variants with optimized FcRn affinity have been established and studied in *in vitro* effector functions or *in vivo* activities [100–102]. *In vivo* pharmacokinetic analysis indicated that half-life of engineered antibodies could be prolonged up to five fold [101]. The increased serum persistence of therapeutic antibodies has been shown to enhance cytotoxicity, especially to cells expressing lower levels of target antigen [102]. Of note, the IgG3 isotype does not interact with FcRn with comparable efficiency as other IgG isotypes and consequently, its half-life in serum is naturally much shorter (1 week instead of 3 weeks for IgG1). This property makes IgG3 backbone as a less suitable candidate for IgG therapy.

4.4 FcR genetic variations and potential for personalized medicine

Fc receptors have both highly homologous sequences as well as extensive genetic variations. Nearly every known human Fc receptor contains regulatory and coding polymorphisms that change expression, affinity or signaling. In recent years, emerging data have also demonstrated that Fc receptors have copy number variation [103]. Many of these single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) are associated with a wide range of autoimmune conditions. Known SNPs and CNVs, their functions, and linkage with disease are summarized in Table 2.

One of the most extensively studied genetic variants is the R131H (519G>A) SNP in the second Ig-like domain of Fc γ RIIa [104]. This SNP locates in the receptor-Fc interacting interface and determines the affinity of Fc γ RIIa for human IgG. H131, the high binder, is capable of binding and internalizing IgG2 while R131, the low binder, lacks the ability to interact with IgG2 [105]. Similarly, co-dominantly expressed SNP V158F in Fc γ RIIIa affects binding affinity as well [106]. Only the V158 allele binds IgG4, and it also binds IgG1 and IgG3 with a much stronger affinity compared to the F158 allele. NK cells from homozygous 158V/V donor displayed increased activity compared to the 158F/F NK cells [107]. The difference in receptor affinity for IgG may affect the ability to clear immune complex and the efficacy of IgG-based therapies. Indeed, multiple studies have accessed the relationship between the R131H SNP in Fc γ RIIa and the V158F SNP in Fc γ RIIIa and the response to antibody therapies. Patients with the higher affinity alleles of Fc γ RIIIa responded better to rituximab [108–110]. Also, both of these affinity-affecting SNPs have been shown to influence clinical outcome in RA treatment with infliximab, the anti-tumour necrosis factor (TNF α) therapy [111, 112].

4.5 IVIg

Intravenous immunoglobulin (IVIg) is harvested from the pooled plasma of 3,000 to 100,000 healthy donors. It consists of over 95% IgG with a subclass distribution corresponding to that in normal human serum [113]. Initially used over 60 years ago to treat antibody deficiencies, IVIg was later recognized for its immune-modulating function and has been increasingly used in treating autoimmune conditions [114]. The underlying mechanism of the anti-inflammatory effect of IVIg is controversial and has been attributed to many factors, including complement blockage, inhibition of Fas-induced apoptosis, and various interactions between the IgG Fc domain and FcRs. Here we will discuss three major FcR-related theories.

4.51 Involvement of activating FcγRs—In ITP patients, administration of IVIg can efficiently attenuate platelet clearance from the circulation. The first proposed mechanism is the competitive blockage of the activating FcγRs on myeloid cells by IVIg, which in turn decreases anti-platelet autoantibody mediated phagocytosis or ADCC of platelets [115]. Indeed, in human ITP patients, a blocking antibody for the high affinity FcγRIIIa efficiently interfered with autoantibody mediated platelet depletion [33]. Furthermore, in pediatric ITP patients, intravenous administration of only the Fcγ fragments prepared from IVIg resulted in a rapid recovery in platelet counts [116]. However, given the predominance of monomeric IgG molecules in IVIg which would bind to the high affinity FcγRI but lack the capability to bind to low affinity FcγRs, one would hypothesize that the transfused IVIg might contain small aggregates or would form a small amount of immune complex with endogenous self-antigens, thus enabling competitive blockage of all activating FcγRs, without inducing severe activating effects.

Another proposed mechanism involves the activating FcγRs on dendritic cells, when adoptive transfer of ex vivo IVIg-primed dendritic cells prevented platelet depletion in a murine ITP model [117, 118]. This protective effect was lost if dendritic cells were deficient of FcγRIII, suggesting the importance of ITAM-bearing FcγRs in mediating IVIg signaling, but the exact pathway still remains unclear.

4.52 Involvement of inhibitory FcγRIIb—Samuelsson and colleagues proposed that the anti-inflammatory effect IVIg could also involve FcγRIIb [119]. IVIg failed to protect mice from ITP when expression of FcγRIIb was genetically deleted or blocked with a mAb against mouse FcγRII/III. In other wild type mouse models of nephrotoxic nephritis and arthritis, IVIg also seemed to up-regulate expression of FcγRIIb on macrophages [120, 121]. Kaneko and Ravetch have proposed that a small portion of IVIg, the sialylated IgG, binds to DC-SIGN (a lectin on dendritic cells) and indirectly up-regulates FcγRIIb expression on macrophages [92]. However, mice deficient in ITIM-signaling components SHIP, SHP-1 or Btk responded well to IVIg [122] and the up-regulation of FcγRIIb is not observed in human ITP cases [123]. Further studies will be needed to clarify the involvement of FcγRIIb in IVIg effects.

4.53 Saturation of FcRn—Another explanation for the immune modulating role of IVIg is through competitive binding of FcRn, which then leads to reduced half-life of

autoantibodies. The high dose of infused IgG was shown to increase the rate of anti-platelet antibody clearance in ITP models in wild-type mice but not FcRn-deficient mice [124]. The essential role of FcRn is also supported by observations in autoimmune skin blistering disease and arthritis models [125, 126]. Similar to other proposed mechanisms, variable observations have been reported regarding the involvement of FcRn. In a study conducted by Crow and colleagues, high-dose IVIg in an acute ITP model achieved equivalent extent of efficiency in FcRn-deficient mice compared to wild-type mice [127]. The involvement of FcRn might contribute more to the longer-term effects of IVIg, but not to the immediate suppression seen with IVIg in patients and in acute, induced autoimmune models.

4.6 Inhibiting ITAM signaling elements

In addition to obstructing Ig/FcR engagement, an alternative strategy to interfere with the receptor-driven ITAM signaling pathway is to target downstream signaling components of the activating receptors. In various cell types, Syk is known to be a key kinase in the ITAM signaling cascades initiated by activating receptors, including FcRs and the BCR. Inhibitors of Syk are expected to block syk-dependent FcR-mediated activation of myeloid cells, neutrophils and B cells [128–130]. Indeed, an orally available Syk inhibitor, small chemical entity R406 (tamatinib), efficiently reduced immune complex-mediated inflammation in a reverse-passive Arthus reaction and two arthritis models in mouse [130]. Recently, a prodrug of R406, R788 (fostamatinib), was evaluated in a phase II study for treating rheumatoid arthritis. In 457 RA patients with poor response to methotrexate, oral administration of R788 caused a significant dose-dependent improvement in disease severity, and a clinically significant effect was noted as early as after one week post-treatment [131]. Mild adverse effects have been observed, including diarrhea, hypertension and neutropenia. Of note, as an ATP-competitive kinase inhibitor, R406 and R788 might have limited specificity to Syk. Other kinases and non-kinase targets, such as FMS-related tyrosine kinase 3, Lck, and JAK1/3, might have been involved in the clinical outcomes of R788 in treating autoimmunity [132]. Further studies are in need to optimize doses and to test long term safety for Syk inhibitors.

Another critical kinase in the BCR “signalosome” is Btk, of which phosphorylation is inhibited by Fc γ RIIb crosslinking with BCR. Therefore, an alternative approach to down regulate B cell activation would be the inhibition of Btk. A selective and irreversible Btk inhibitor, PCI-32765, is currently under clinical development. Orally administered PCI-32765 in mice reduced the level of autoantibodies and completely suppressed development of collagen-induced arthritis [133]. In further studies of murine arthritis models induced by either collagen or collagen antibodies, the complete inhibition of disease by PCI-32765 has been confirmed, as the bone and cartilage integrity of the joints were preserved [134]. Of note, the effect of PCI-32765 was not limited to B cells. It also inhibited inflammatory signaling in other Btk-expressing effector cells in arthritis, including monocytes, macrophages and mast cells [134].

5. Future strategies

5.1 Regulation of FcR expression

The ratio of activating versus inhibitory receptor determines the activation threshold and controls the function of immunocytes. A panel of cytokines can regulate Fc receptor expression. For example, through altering the transcriptional activity of promoter regions, tumor necrosis factor α (TNF α) increases Fc γ RIIa, reduces Fc γ RIIb expression, while IL-10 up-regulates all ITAM-bearing Fc γ Rs [135]. However, when TNF α is combined with IL-4 and IL-13, the expression of activating Fc γ Rs is greatly reduced, skewing monocytes towards an inhibitory phenotype [135]. Treatment with infliximab, the TNF inhibitor, led to increased Fc γ RIIb expression on neutrophils in RA [136]. In murine B cells, IL-4 could enhance B cell immune functions by reducing inhibitory Fc γ RIIb and a few other negative co-receptors in the BCR signalosome [137]. *In vitro* experiments also showed that expression of Fc γ RIIIa is up-regulated by TGF- β , IFN- γ and M-CSF [138]; expression of Fc γ RI is up-regulated by G-CSF and IFN- γ [139–141]. Also, rheumatoid arthritis patients treated with IFN- γ have increase in neutrophil Fc γ RI expression [142]. Dysregulation and dysfunction of Fc γ Rs are often observed at sites of inflammation in autoimmune diseases. A better understanding of changes in Fc γ R profile in different cytokine milieu would help dissect the mechanisms involved in Fc γ R regulation and would lead to potential therapeutic use.

Besides cytokines, many other factors are known to affect Fc γ R expression and function. For example, C5a, the soluble complement fragment released at sites of inflammation, up-regulates Fc γ RIIIa and down-regulates Fc γ RIIb simultaneously [143, 144]. In recent years, microRNAs (miRs) have gained attention as critical regulators of gene expression. Xie and colleagues identified mir-127 as an anti-inflammatory factor in lung inflammation by suppressing Fc γ RI expression on macrophages [145]. Genetic diversity is related to levels of receptor expression as well. The 2B.4 haplotype of *FCGR2B* promoter (Table X) alters transcription factor binding, increases Fc γ RIIb expression, and is a risk factor for SLE [52].

The potential for therapeutically exploiting these observations relies on the development of new targeting/delivery strategies and techniques. One of the promising revenues is utilizing our advancing knowledge in epigenetic manipulation, such as designing antisense oligonucleotides or modulators of transcription factors to selectively up- or down-regulate targeted genes [146]. Novel gene-silencing compounds, such as pyrrole-imidazole (PI) polyamides, showed favorable specificity for targeted double strand DNA [147]. DNA methylation is another essential epigenetic modification that plays critical roles in regulation of genes, development and disease. In humans, both DNA and protein methylation is controlled by a group of 344 enzymes and effector proteins that “read, write and erase” methylation [148]. Development of small molecule modulators of elements of this “methylome” machinery would pave the way to developing novel therapeutic approaches to modulate FcRs.

5.2 Receptor cross-talk

Toll-like receptors (TLRs) and integrins are capable of independent signaling and function, and they also work in cross-talking networks with Fc receptors through several mechanisms, including physical co-association, shared binding of multi-valent ligands and inter-related signaling cascades. Therefore, a potential FcR targeting strategy would be to disrupt receptor-driven crosstalk.

Cooperation between TLRs and Fc γ R may be driven by shared complex ligands. TLR7 and TLR9, the pattern recognizing receptors for ssRNA and DNA CpG motifs respectively, might interact with nucleic acid- containing immune complexes, which are abundant in serum from patients with autoimmune disease, such as SLE. DNA/RNA ICs stimulate autoreactive B cells through co-engagement of BCR and TLR7/TLR9. The signal strength required for this activation is modulated by Fc γ RIIb [149]. TLRs and Fc γ R are also co-expressed in macrophages, plasmacytoid dendritic cells (pDCs) and neutrophils. DNA-containing ICs purified from the serum of patients with active SLE were shown to activate pDCs, monocytes, B cells and neutrophils in a TLR9/Fc γ RII-dependent manner [150]. The crosstalk between the surface receptors and the endosomal TLRs starts with the Fc γ RII-facilitated internalization of DNA-containing ICs, which are delivered into endosomal compartments where they engage TLRs [150].

In addition to Fc γ R-facilitated TLR activation, cross-modulation of receptor expression may occur between TLR9 and the IgE receptor Fc ϵ RI on pDCs. IgE/Fc ϵ RI crosslinking reduced TLR9 expression, which led to decreased IFN α production. Similarly, when pDCs were exposed to TLR9 ligands, Fc ϵ RI expression greatly decreased as well [151]. The mechanism of this counter-regulation is not known yet but may involve type I IFN, upregulated after TLR9 activation, followed by down regulation of Fc ϵ RI.

The level of Fc γ RIIb expression on monocyte-derived dendritic cells (mDCs) sets the threshold for TLR4-mediated cell activation in response to IC stimulation. Fc γ RIIb inhibits TLR4-mediated DC maturation, reduces secretion of pro-inflammatory cytokines, which in turn inhibits T cell proliferation, and primes T cells to produce anti-inflammatory Th2 cytokines [152]. The machinery for this effect may be interacting signaling components. Activation of Fc γ RIIb ITIM recruits phosphorylated SHIP and down-regulates PI3K and Akt, which are key molecules in TLR4 signaling. Consistent with the experimental data, a high level of expression of Fc γ RIIb on DCs is associated with reduced disease activity and quiescence in RA patients without anti-rheumatic drugs [152]. Similarly, expression of Fc γ RIIb or the lack of Fc γ RIIa or FcR γ -chain on macrophages and DCs may exert negative regulatory roles in TLR4 responses [153–155].

In human neutrophils, LPS/TLR4 triggers increased expression of Fc γ RIIa. Fc γ RIIa and immune complexes also can activate TLR4 signaling cascades in LPS-primed neutrophils [156]. The molecular mechanisms for this crosstalk are not fully understood, but it is Btk dependent [156]. This observation might guide us to explore the use of Btk inhibitors (discussed in section 6) in controlling neutrophil-mediated inflammation. Rittirsch and colleagues also reported crosstalk between TLR4 and Fc γ RIIa in neutrophils and macrophages, wherein TLR4 was co-immunoprecipitated with Fc γ RIIa after aggregated

IgG engagement, hinting at a physical association between TLR4 and Fc γ RIIIa. TLR4-deficient cells lost sensitivity to IC stimulation; and TLR4-deficient mice were resistant to acute lung injury after IC deposition [157]. In their model, TLR4 signaling seemed to be an essential part for Fc γ RIIIa ITAM phosphorylation and consequential signaling cascades. Based on this observation and the aforementioned crosstalk between TLR4/7/9 and FcRs, one would envision the potential use of TLR inhibitors in treating many types of FcR-mediated inflammation.

6. Conclusions

Fc receptors are appealing targets in the treatment of inflammatory autoimmune diseases. Targeting approaches include blocking activating Fc receptors, activating inhibitory Fc γ RIIb, utilizing activating receptors for antigen targeting and ADCC-mediated cell depletion, engineering IgG through amino acid changes or sugar modification for optimized affinity and engagement, targeting FcRn to manipulate IgG half-lives, and inhibiting key elements in ITAM signaling. Our growing knowledge about the genetic complexity in Fc receptors also helps to explain individual variations in clinical outcomes. A better understanding of the structure, signaling, function, and genetic diversity of Fc receptors and their interaction with immunoglobulin will lead to safer, more sophisticated and efficient therapies in autoimmune diseases.

7. Expert opinion

The Fc receptors and FcR-mediated signaling pathways are promising targets in the treatment of autoimmune conditions, both in the maintenance of host immune tolerance and in the enhanced efficacy of antibody therapies. How to enhance the specificity for both targeting specific cell types and routing through particular receptors are important development challenges.

The only inhibitory FcR, Fc γ RIIb, is an attractive target, especially with the development of bispecific molecules. The co-engagement of Fc γ RIIb with BCR on B cells/plasma cells, with other activating Fc γ R on pDCs, or with Fc ϵ RI on mast cells could utilize its inhibitory effect to therapeutic advantage. Precise cell-specific modulation of Fc γ RIIb expression might offer a new therapeutic pathway, as demonstrated by reduction in autoimmunity by increased B-cell expression of Fc γ RIIb in mice [48] and reduced monocyte activation with IL4- induced upregulation of Fc γ RIIb expression in RA patients [158].

Most types of immune cells express more than one kind of activating Fc γ Rs. It is incompletely understood whether different activating Fc γ Rs are redundant or have specialized functions which can act synergistically. A better understanding of relative importance of different activating FcRs on the same cell type may identify more specific therapeutic targets. For example, as the primary FcR on NK cells, Fc γ RIIIa controls the efficiency of NK cell mediated ADCC. Modifying Fc γ RIIIa expression on mononuclear phagocytes would alter clearance efficiency of antibody coated cells or autoimmune disease-related immune complexes. Through protein engineering in the Fc domain or modifications in glycosylation, therapeutic antibodies might be able to overcome the different receptor

affinities due to allelic variations in Fc γ RIIIa and Fc γ RIIa in patients, thus enhancing the responsive rate in the whole population.

In summary, a better appreciation for both expression and function of various Fc receptors, as well as modification strategy of their ligands, will enhance the targeting specificity of therapeutic antibodies and chemical entities for both the cell type and the receptor and pave the way towards more effective and refined treatment for autoimmune diseases.

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Bibliography

1. Marmont AM. Defining criteria for autoimmune diseases. *Immunol Today*. 1994; 15(8):388. [PubMed: 7916953]
2. Nimmerjahn F, Ravetch JV. Fc-receptors as regulators of immunity. *Adv Immunol*. 2007; 96:179–204. [PubMed: 17981207] ** A comprehensive review on types of Fc receptors, their signaling and functions.
3. Ernst LK, van de Winkel JG, Chiu IM, et al. Three genes for the human high affinity Fc receptor for IgG (Fc gamma RI) encode four distinct transcription products. *J Biol Chem*. 1992; 267(22):15692–15700. [PubMed: 1379234]
4. Hoffmeyer F, Witte K, Schmidt RE. The high-affinity Fc gamma RI on PMN: regulation of expression and signal transduction. *Immunology*. 1997; 92(4):544–552. [PubMed: 9497497]
5. Capel PJ, van de Winkel JG, van den Herik-Oudijk IE, et al. Heterogeneity of human IgG Fc receptors. *Immunomethods*. 1994; 4(1):25–34. [PubMed: 8069524]
6. Ernst LK, Metes D, Herberman RB, et al. Allelic polymorphisms in the Fc gamma RIIC gene can influence its function on normal human natural killer cells. *J Mol Med*. 2002; 80(4):248–257. [PubMed: 11976734]
7. Breunis WB, van Mirre E, Bruin M, et al. Copy number variation of the activating FCGR2C gene predisposes to idiopathic thrombocytopenic purpura. *Blood*. 2008; 111(3):1029–1038. [PubMed: 17827395]
8. Simmons D, Seed B. The Fc gamma receptor of natural killer cells is a phospholipid-linked membrane protein. *Nature*. 1988; 333(6173):568–570. [PubMed: 2967436]
9. Kinet JP. The high-affinity IgE receptor (Fc epsilon RI): from physiology to pathology. *Annu Rev Immunol*. 1999; 17:931–972. [PubMed: 10358778] ** A comprehensive review on Fc epsilon RI.
10. Turner H, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilon RI. *Nature*. 1999; 402(6760 Suppl):B24–B30. [PubMed: 10586892]
11. Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest*. 1995; 96(6):2606–2612. [PubMed: 8675625]
12. Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med*. 1993; 328(22):1599–1604. [PubMed: 7683772]
13. Tong LJ, Balakrishnan G, Kochan JP, et al. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol*. 1997; 99(4):461–465. [PubMed: 9111489]
14. Yokota A, Kikutani H, Tanaka T, et al. Two species of human Fc epsilon receptor II (Fc epsilon RII/CD23): tissue-specific and IL-4-specific regulation of gene expression. *Cell*. 1988; 55(4):611–618. [PubMed: 2972386]
15. Barrow AD, Trowsdale J. You say ITAM and I say ITIM, let's call the whole thing off: the ambiguity of immunoreceptor signalling. *Eur J Immunol*. 2006; 36(7):1646–1653. [PubMed: 16783855]

16. Monteiro RC, Van De Winkel JG. IgA Fc receptors. *Annu Rev Immunol.* 2003; 21:177–204. [PubMed: 12524384] ** A comprehensive review on FcαRI
17. Kubagawa H, Oka S, Kubagawa Y, et al. Identity of the elusive IgM Fc receptor (FcμR) in humans. *J Exp Med.* 2009; 206(12):2779–2793. [PubMed: 19858324]
18. Shima H, Takatsu H, Fukuda S, et al. Identification of TOSO/FAIM3 as an Fc receptor for IgM. *Int Immunol.* 2010; 22(3):149–156. [PubMed: 20042454]
19. Lang KS, Lang PA, Meryk A, et al. Involvement of Toso in activation of monocytes, macrophages, and granulocytes. *Proc Natl Acad Sci U S A.* 2013; 110(7):2593–2598. [PubMed: 23359703]
20. Honjo K, Kubagawa Y, Kubagawa H. Is Toso/IgM Fc receptor (FcμR) expressed by innate immune cells? *Proc Natl Acad Sci U S A.* 2013; 110(28):E2540–E2541. [PubMed: 23671064]
21. Lang KS, Lang PA, Meryk A, et al. Reply to Honjo: Functional relevant expression of Toso on granulocytes. *Proc Natl Acad Sci U S A.* 2013; 110(28):E2542–E2543. [PubMed: 24003457]
22. Story CM, Mikulska JE, Simister NE. A major histocompatibility complex class I-like Fc receptor cloned from human placenta: possible role in transfer of immunoglobulin G from mother to fetus. *J Exp Med.* 1994; 180(6):2377–2381. [PubMed: 7964511]
23. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol.* 2007; 7(9):715–725. [PubMed: 17703228] ** A comprehensive review on FcRn.
24. Wang AV, Scholl PR, Geha RS. Physical and functional association of the high affinity immunoglobulin G receptor (Fc gamma RI) with the kinases Hck and Lyn. *J Exp Med.* 1994; 180(3):1165–1170. [PubMed: 8064233]
25. Ghazizadeh S, Bolen JB, Fleit HB. Physical and functional association of Src-related protein tyrosine kinases with Fc gamma RII in monocytic THP-1 cells. *J Biol Chem.* 1994; 269(12):8878–8884. [PubMed: 8132624]
26. Ono M, Okada H, Bolland S, et al. Deletion of SHIP or SHP-1 reveals two distinct pathways for inhibitory signaling. *Cell.* 1997; 90(2):293–301. [PubMed: 9244303]
27. Bolland S, Pearse RN, Kurosaki T, et al. SHIP modulates immune receptor responses by regulating membrane association of Btk. *Immunity.* 1998; 8(4):509–516. [PubMed: 9586640]
28. Ravetch JV, Bolland S. IgG Fc receptors. *Annu Rev Immunol.* 2001; 19:275–290. [PubMed: 11244038]
29. Tan Sardjono C, Mottram PL, van de Velde NC, et al. Development of spontaneous multisystem autoimmune disease and hypersensitivity to antibody-induced inflammation in Fcγ receptor IIa-transgenic mice. *Arthritis Rheum.* 2005; 52(10):3220–3229. [PubMed: 16200626]
30. Tsuboi N, Asano K, Lauterbach M, et al. Human neutrophil Fcγ receptors initiate and play specialized nonredundant roles in antibody-mediated inflammatory diseases. *Immunity.* 2008; 28(6):833–846. [PubMed: 18538590]
31. Mullazehi M, Mathsson L, Lampa J, et al. Surface-bound anti-type II collagen-containing immune complexes induce production of tumor necrosis factor alpha, interleukin-1beta, and interleukin-8 from peripheral blood monocytes via Fc gamma receptor IIA: a potential pathophysiologic mechanism for humoral anti-type II collagen immunity in arthritis. *Arthritis Rheum.* 2006; 54(6):1759–1771. [PubMed: 16736518]
32. Belostocki K, Park MS, Redecha PB, et al. FcγRIIa is a target for modulation by TNFα in human neutrophils. *Clin Immunol.* 2005; 117(1):78–86. [PubMed: 16084773]
33. Clarkson SB, Kimberly RP, Valinsky JE, et al. Blockade of clearance of immune complexes by an anti-Fc gamma receptor monoclonal antibody. *J Exp Med.* 1986; 164(2):474–489. [PubMed: 2941515]
34. Clarkson SB, Bussell JB, Kimberly RP, et al. Treatment of refractory immune thrombocytopenic purpura with an anti-Fc gamma-receptor antibody. *N Engl J Med.* 1986; 314(19):1236–1239. [PubMed: 2939345]
35. Marino M, Ruvo M, De Falco S, et al. Prevention of systemic lupus erythematosus in MRL/lpr mice by administration of an immunoglobulin-binding peptide. *Nat Biotechnol.* 2000; 18(7):735–739. [PubMed: 10888840] An important paper on targeting activating FcγR with small molecule antagonist in treating SLE.

36. Pietersz GA, Mottram PL, van de Velde NC, et al. Inhibition of destructive autoimmune arthritis in FcgammaRIIa transgenic mice by small chemical entities. *Immunol Cell Biol.* 2009; 87(1):3–12. [PubMed: 19030019]
37. de Haas M, Kleijer M, Minchinton RM, et al. Soluble Fc gamma RIIIa is present in plasma and is derived from natural killer cells. *J Immunol.* 1994; 152(2):900–907. [PubMed: 8283059]
38. Rappaport EF, Cassel DL, Walterhouse DO, et al. A soluble form of the human Fc receptor Fc gamma RIIA: cloning, transcript analysis and detection. *Exp Hematol.* 1993; 21(5):689–696. [PubMed: 8513871]
39. Huizinga TW, Ioan-Facsinay A. Soluble FcgammaRIIIa as a marker for rheumatoid arthritis: the use of genetics in selected populations to study pathogenetic pathways. *J Rheumatol.* 2003; 30(9): 1904–1906. [PubMed: 12966588]
40. Werwitzke S, Trick D, Sondermann P, et al. Treatment of lupus-prone NZB/NZW F1 mice with recombinant soluble Fc gamma receptor II (CD32). *Ann Rheum Dis.* 2008; 67(2):154–161. [PubMed: 17557887]
41. Ellsworth JL, Hamacher N, Harder B, et al. Recombinant soluble human FcgammaRIa (CD64A) reduces inflammation in murine collagen-induced arthritis. *J Immunol.* 2009; 182(11):7272–7279. [PubMed: 19454724]
42. Ellsworth JL, Maurer M, Harder B, et al. Targeting immune complex-mediated hypersensitivity with recombinant soluble human FcgammaRIa (CD64A). *J Immunol.* 2008; 180(1):580–589. [PubMed: 18097060]
43. Magnusson SE, Andren M, Nilsson KE, et al. Amelioration of collagen-induced arthritis by human recombinant soluble FcgammaRIIb. *Clin Immunol.* 2008; 127(2):225–233. [PubMed: 18346938]
44. Galon J, Paulet P, Galinha A, et al. Soluble Fc gamma receptors: interaction with ligands and biological consequences. *Int Rev Immunol.* 1997; 16(1–2):87–111. [PubMed: 9651787]
45. de la Salle H, Galon J, Bausinger H, et al. Soluble CD16/Fc gamma RIII induces maturation of dendritic cells and production of several cytokines including IL-12. *Adv Exp Med Biol.* 1997; 417:345–352. [PubMed: 9286384]
46. Bolland S, Ravetch JV. Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. *Immunity.* 2000; 13(2):277–285. [PubMed: 10981970]
47. Yajima K, Nakamura A, Sugahara A, et al. FcgammaRIIB deficiency with Fas mutation is sufficient for the development of systemic autoimmune disease. *Eur J Immunol.* 2003; 33(4): 1020–1029. [PubMed: 12672068]
48. McGaha TL, Sorrentino B, Ravetch JV. Restoration of tolerance in lupus by targeted inhibitory receptor expression. *Science.* 2005; 307(5709):590–593. [PubMed: 15681388] * An important paper on the inhibitory effect of FcγRIIb.
49. Li X, Wu J, Carter RH, et al. A novel polymorphism in the Fcgamma receptor IIB (CD32B) transmembrane region alters receptor signaling. *Arthritis Rheum.* 2003; 48(11):3242–3252. [PubMed: 14613290]
50. Floto RA, Clatworthy MR, Heilbronn KR, et al. Loss of function of a lupus-associated FcgammaRIIb polymorphism through exclusion from lipid rafts. *Nat Med.* 2005; 11(10):1056–1058. [PubMed: 16170323]
51. Su K, Li X, Edberg JC, et al. A promoter haplotype of the immunoreceptor tyrosine-based inhibitory motif-bearing FcgammaRIIb alters receptor expression and associates with autoimmunity. II. Differential binding of GATA4 and Yin-Yang1 transcription factors and correlated receptor expression and function. *J Immunol.* 2004; 172(11):7192–7199. [PubMed: 15153544]
52. Su K, Wu J, Edberg JC, et al. A promoter haplotype of the immunoreceptor tyrosine-based inhibitory motif-bearing FcgammaRIIb alters receptor expression and associates with autoimmunity. I. Regulatory FCGR2B polymorphisms and their association with systemic lupus erythematosus. *J Immunol.* 2004; 172(11):7186–7191. [PubMed: 15153543]
53. van Mirre E, van Royen A, Hack CE. IVIg-mediated amelioration of murine ITP via FcgammaRIIb is not necessarily independent of SHIP-1 and SHP-1 activity. *Blood.* 2004; 103(5): 1973. author reply 1974. [PubMed: 14976068]

54. Mackay M, Stanevsky A, Wang T, et al. Selective dysregulation of the FcgammaRIIB receptor on memory B cells in SLE. *J Exp Med*. 2006; 203(9):2157–2164. [PubMed: 16923849]
55. Veri MC, Gorlatov H, Li S, et al. Monoclonal antibodies capable of discriminating the human inhibitory Fcgamma-receptor IIB (CD32B) from the activating Fcgamma-receptor IIA (CD32A): biochemical, biological and functional characterization. *Immunology*. 2007; 121(3):392–404. [PubMed: 17386079]
56. Su K, Yang X, Li H, et al. Expression profile of FcgammaRIIb on leukocytes and its dysregulation in systemic lupus erythematosus. *J Immunol*. 2007; 178(5):3272–3280. [PubMed: 17312177]
57. Rankin CT, Veri MC, Gorlatov S, et al. CD32B, the human inhibitory Fc-gamma receptor IIB, as a target for monoclonal antibody therapy of B-cell lymphoma. *Blood*. 2006; 108(7):2384–2391. [PubMed: 16757681]
58. Xiang Z, Cutler AJ, Brownlie RJ, et al. FcgammaRIIb controls bone marrow plasma cell persistence and apoptosis. *Nat Immunol*. 2007; 8(4):419–429. [PubMed: 17322888]
59. Veri MC, Burke S, Huang L, et al. Therapeutic control of B cell activation via recruitment of Fcgamma receptor IIB (CD32B) inhibitory function with a novel bispecific antibody scaffold. *Arthritis Rheum*. 2010; 62(7):1933–1943. [PubMed: 20506263]
60. Horton HM, Chu SY, Ortiz EC, et al. Antibody-mediated coengagement of FcgammaRIIb and B cell receptor complex suppresses humoral immunity in systemic lupus erythematosus. *J Immunol*. 2011; 186(7):4223–4233. [PubMed: 21357255] * An important paper on targeting FcγRIIb with engineered bi-specific antibodies.
61. Zhu D, Kepley CL, Zhang M, et al. A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation. *Nat Med*. 2002; 8(5): 518–521. [PubMed: 11984598]
62. Tam SW, Demissie S, Thomas D, et al. A bispecific antibody against human IgE and human FcgammaRII that inhibits antigen-induced histamine release by human mast cells and basophils. *Allergy*. 2004; 59(7):772–780. [PubMed: 15180766]
63. Mertsching E, Bafetti L, Hess H, et al. A mouse Fcgamma-Fcepsilon protein that inhibits mast cells through activation of FcgammaRIIB, SH2 domain-containing inositol phosphatase 1, and SH2 domain-containing protein tyrosine phosphatases. *J Allergy Clin Immunol*. 2008; 121(2): 441–447 e5. [PubMed: 17949802]
64. Van Scott MR, Mertsching E, Negrou E, et al. Systemic administration of an Fcgamma-Fc(epsilon)-fusion protein in house dust mite sensitive nonhuman primates. *Clin Immunol*. 2008; 128(3):340–348. [PubMed: 18583194]
65. Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant*. 2006; 6(5 Pt 1):859–866. [PubMed: 16611321]
66. Gurcan HM, Keskin DB, Stern JN, et al. A review of the current use of rituximab in autoimmune diseases. *Int Immunopharmacol*. 2009; 9(1):10–25. [PubMed: 19000786] ** A comprehensive review on anti-CD20 monoclonal antibody therapy in autoimmune diseases.
67. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. *J Allergy Clin Immunol*. 2011; 128(6):1354–1355. [PubMed: 21958584]
68. de Haij S, Jansen JH, Boross P, et al. In vivo cytotoxicity of type I CD20 antibodies critically depends on Fc receptor ITAM signaling. *Cancer Res*. 2010; 70(8):3209–3217. [PubMed: 20354182]
69. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol*. 2003; 21(21): 3940–3947. [PubMed: 12975461]
70. Anolik JH, Campbell D, Felgar RE, et al. The relationship of FcgammaRIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus. *Arthritis Rheum*. 2003; 48(2):455–459. [PubMed: 12571855]
71. Lim SH, Vaughan AT, Ashton-Key M, et al. Fc gamma receptor IIB on target B cells promotes rituximab internalization and reduces clinical efficacy. *Blood*. 2011; 118(9):2530–2540. [PubMed: 21768293]

72. Gea-Banacloche JC. Rituximab-associated infections. *Semin Hematol.* 2010; 47(2):187–198. [PubMed: 20350666]
73. Radaev S, Motyka S, Fridman WH, et al. The structure of a human type III Fcγ receptor in complex with Fc. *J Biol Chem.* 2001; 276(19):16469–16477. [PubMed: 11297532]
74. Jefferis R, Lefranc MP. Human immunoglobulin allotypes: possible implications for immunogenicity. *MAbs.* 2009; 1(4):332–338. [PubMed: 20073133]
75. Albert H, Collin M, Dudziak D, et al. In vivo enzymatic modulation of IgG glycosylation inhibits autoimmune disease in an IgG subclass-dependent manner. *Proc Natl Acad Sci U S A.* 2008; 105(39):15005–15009. [PubMed: 18815375]
76. Umana P, Jean-Mairet J, Moudry R, et al. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. *Nat Biotechnol.* 1999; 17(2):176–180. [PubMed: 10052355] * An important paper on manipulating antibody affinity for FcγR through modifying glycosylation.
77. Shields RL, Lai J, Keck R, et al. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human FcγRIII and antibody-dependent cellular toxicity. *J Biol Chem.* 2002; 277(30):26733–26740. [PubMed: 11986321]
78. Yamane-Ohnuki N, Kinoshita S, Inoue-Urakubo M, et al. Establishment of FUT8 knockout Chinese hamster ovary cells: an ideal host cell line for producing completely defucosylated antibodies with enhanced antibody-dependent cellular cytotoxicity. *Biotechnol Bioeng.* 2004; 87(5):614–622. [PubMed: 15352059]
79. Mori K, Kuni-Kamochi R, Yamane-Ohnuki N, et al. Engineering Chinese hamster ovary cells to maximize effector function of produced antibodies using FUT8 siRNA. *Biotechnol Bioeng.* 2004; 88(7):901–908. [PubMed: 15515168]
80. Kanda Y, Yamane-Ohnuki N, Sakai N, et al. Comparison of cell lines for stable production of fucose-negative antibodies with enhanced ADCC. *Biotechnol Bioeng.* 2006; 94(4):680–688. [PubMed: 16609957]
81. Kanda Y, Imai-Nishiya H, Kuni-Kamochi R, et al. Establishment of a GDP-mannose 4,6-dehydratase (GMD) knockout host cell line: a new strategy for generating completely non-fucosylated recombinant therapeutics. *J Biotechnol.* 2007; 130(3):300–310. [PubMed: 17559959]
82. Imai-Nishiya H, Mori K, Inoue M, et al. Double knockdown of α1,6-fucosyltransferase (FUT8) and GDP-mannose 4,6-dehydratase (GMD) in antibody-producing cells: a new strategy for generating fully non-fucosylated therapeutic antibodies with enhanced ADCC. *BMC Biotechnol.* 2007; 7:84. [PubMed: 18047682]
83. Cox KM, Sterling JD, Regan JT, et al. Glycan optimization of a human monoclonal antibody in the aquatic plant *Lemna minor*. *Nat Biotechnol.* 2006; 24(12):1591–1597. [PubMed: 17128273]
84. Ferrara C, Brunner P, Suter T, et al. Modulation of therapeutic antibody effector functions by glycosylation engineering: influence of Golgi enzyme localization domain and co-expression of heterologous β1,4-N-acetylglucosaminyltransferase III and Golgi α-mannosidase II. *Biotechnol Bioeng.* 2006; 93(5):851–861. [PubMed: 16435400]
85. Ferrara C, Stuart F, Sondermann P, et al. The carbohydrate at FcγRIIIa Asn-162. An element required for high affinity binding to non-fucosylated IgG glycoforms. *J Biol Chem.* 2006; 281(8):5032–5036. [PubMed: 16330541]
86. Ercan A, Cui J, Chatterton DE, et al. Aberrant IgG galactosylation precedes disease onset, correlates with disease activity, and is prevalent in autoantibodies in rheumatoid arthritis. *Arthritis Rheum.* 2010; 62(8):2239–2248. [PubMed: 20506563]
87. Pasek M, Duk M, Podbielska M, et al. Galactosylation of IgG from rheumatoid arthritis (RA) patients--changes during therapy. *Glycoconj J.* 2006; 23(7–8):463–471. [PubMed: 17006638]
88. van de Geijn FE, Wuhler M, Selman MH, et al. Immunoglobulin G galactosylation and sialylation are associated with pregnancy-induced improvement of rheumatoid arthritis and the postpartum flare: results from a large prospective cohort study. *Arthritis Res Ther.* 2009; 11(6):R193. [PubMed: 20015375]
89. Jefferis R. Recombinant antibody therapeutics: the impact of glycosylation on mechanisms of action. *Trends Pharmacol Sci.* 2009; 30(7):356–362. [PubMed: 19552968]

90. Jefferis R. Glycosylation as a strategy to improve antibody-based therapeutics. *Nat Rev Drug Discov.* 2009; 8(3):226–234. [PubMed: 19247305]
91. 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. [PubMed: 22922409]
92. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science.* 2006; 313(5787):670–673. [PubMed: 16888140]
93. Andersen JT, Justesen S, Berntzen G, et al. A strategy for bacterial production of a soluble functional human neonatal Fc receptor. *J Immunol Methods.* 2008; 331(1–2):39–49. [PubMed: 18155020]
94. Feng Y, Gong R, Dimitrov DS. Design, expression and characterization of a soluble single-chain functional human neonatal Fc receptor. *Protein Expr Purif.* 2011; 79(1):66–71. [PubMed: 21453773]
95. Vaccaro C, Zhou J, Ober RJ, et al. Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels. *Nat Biotechnol.* 2005; 23(10):1283–1288. [PubMed: 16186811]
96. Petkova SB, Akilesh S, Sproule TJ, et al. Enhanced half-life of genetically engineered human IgG1 antibodies in a humanized FcRn mouse model: potential application in humorally mediated autoimmune disease. *Int Immunol.* 2006; 18(12):1759–1769. [PubMed: 17077181]
97. Vaccaro C, Bawdon R, Wanjie S, et al. Divergent activities of an engineered antibody in murine and human systems have implications for therapeutic antibodies. *Proc Natl Acad Sci U S A.* 2006; 103(49):18709–18714. [PubMed: 17116867]
98. Liu L, Garcia AM, Santoro H, et al. Amelioration of experimental autoimmune myasthenia gravis in rats by neonatal FcR blockade. *J Immunol.* 2007; 178(8):5390–5398. [PubMed: 17404325]
99. Mezo AR, McDonnell KA, Hehir CA, et al. Reduction of IgG in nonhuman primates by a peptide antagonist of the neonatal Fc receptor FcRn. *Proc Natl Acad Sci U S A.* 2008; 105(7):2337–2342. [PubMed: 18272495]
100. Ghetie V, Popov S, Borvak J, et al. Increasing the serum persistence of an IgG fragment by random mutagenesis. *Nat Biotechnol.* 1997; 15(7):637–640. [PubMed: 9219265]
101. Zalevsky J, Chamberlain AK, Horton HM, et al. Enhanced antibody half-life improves in vivo activity. *Nat Biotechnol.* 2010; 28(2):157–159. [PubMed: 20081867]
102. Lazar GA, Dang W, Karki S, et al. Engineered antibody Fc variants with enhanced effector function. *Proc Natl Acad Sci U S A.* 2006; 103(11):4005–4010. [PubMed: 16537476]
103. Niederer HA, Willcocks LC, Rayner TF, et al. Copy number, linkage disequilibrium and disease association in the FCGR locus. *Hum Mol Genet.* 2010; 19(16):3282–3294. [PubMed: 20508037]
104. Clark MR, Clarkson SB, Ory PA, et al. Molecular basis for a polymorphism involving Fc receptor II on human monocytes. *J Immunol.* 1989; 143(5):1731–1734. [PubMed: 2527271]
105. Warmerdam PA, van de Winkel JG, Gosselin EJ, et al. Molecular basis for a polymorphism of human Fc gamma receptor II (CD32). *J Exp Med.* 1990; 172(1):19–25. [PubMed: 2141627]
106. Wu J, Edberg JC, Redecha PB, et al. A novel polymorphism of FcγRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. *J Clin Invest.* 1997; 100(5):1059–1070. [PubMed: 9276722]
107. Koene HR, Kleijer M, Algra J, et al. Fc γRIIIa-158V/F polymorphism influences the binding of IgG by natural killer cell Fc γRIIIa, independently of the Fc γRIIIa-48L/R/H phenotype. *Blood.* 1997; 90(3):1109–1114. [PubMed: 9242542]
108. Cartron G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood.* 2002; 99(3):754–758. [PubMed: 11806974]
109. Hatjiharissi E, Xu L, Santos DD, et al. Increased natural killer cell expression of CD16, augmented binding and ADCC activity to rituximab among individuals expressing the Fc{γ}RIIIa-158 V/V and V/F polymorphism. *Blood.* 2007; 110(7):2561–2564. [PubMed: 17475906]
110. Ruysen-Witrand A, Rouanet S, Combe B, et al. Fcγ receptor type IIIa polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab. *Ann Rheum Dis.* 2012; 71(6):875–877. [PubMed: 22368231]

111. Canete JD, Suarez B, Hernandez MV, et al. Influence of variants of Fc gamma receptors IIA and IIIA on the American College of Rheumatology and European League Against Rheumatism responses to anti-tumour necrosis factor alpha therapy in rheumatoid arthritis. *Ann Rheum Dis*. 2009; 68(10):1547–1552. [PubMed: 18930989]
112. Tutuncu Z, Kavanaugh A, Zvaifler N, et al. Fc gamma receptor type IIIA polymorphisms influence treatment outcomes in patients with inflammatory arthritis treated with tumor necrosis factor alpha-blocking agents. *Arthritis Rheum*. 2005; 52(9):2693–2696. [PubMed: 16142749]
113. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*. 2001; 345(10):747–755. [PubMed: 11547745]
114. Novaretti MC, Dinardo CL. Clinical applications of immunoglobulin: update. *Rev Bras Hematol Hemoter*. 2011; 33(3):221–230. [PubMed: 23049300]
115. Jin F, Balthasar JP. Mechanisms of intravenous immunoglobulin action in immune thrombocytopenic purpura. *Hum Immunol*. 2005; 66(4):403–410. [PubMed: 15866704]
116. Debre M, Bonnet MC, Fridman WH, et al. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet*. 1993; 342(8877):945–949. [PubMed: 8105212]
117. Crow AR, Song S, Siragam V, et al. Mechanisms of action of intravenous immunoglobulin in the treatment of immune thrombocytopenia. *Pediatr Blood Cancer*. 2006; 47(5 Suppl):710–713. [PubMed: 16933274]
118. Siragam V, Crow AR, Brinc D, et al. Intravenous immunoglobulin ameliorates ITP via activating Fc gamma receptors on dendritic cells. *Nat Med*. 2006; 12(6):688–692. [PubMed: 16715090]
119. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science*. 2001; 291(5503):484–486. [PubMed: 11161202]
120. Kaneko Y, Nimmerjahn F, Madaio MP, et al. Pathology and protection in nephrotoxic nephritis is determined by selective engagement of specific Fc receptors. *J Exp Med*. 2006; 203(3):789–797. [PubMed: 16520389]
121. Bruhns P, Samuelsson A, Pollard JW, et al. Colony-stimulating factor-1-dependent macrophages are responsible for IVIG protection in antibody-induced autoimmune disease. *Immunity*. 2003; 18(4):573–581. [PubMed: 12705859]
122. Crow AR, Song S, Freedman J, et al. IVIg-mediated amelioration of murine ITP via Fc gammaRIIB is independent of SHIP1, SHP-1, and Btk activity. *Blood*. 2003; 102(2):558–560. [PubMed: 12649142]
123. Shimomura M, Hasegawa S, Seki Y, et al. Intravenous immunoglobulin does not increase Fc gammaRIIB expression levels on monocytes in children with immune thrombocytopenia. *Clin Exp Immunol*. 2012; 169(1):33–37. [PubMed: 22670776]
124. 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. [PubMed: 12529736]
125. 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. [PubMed: 16284651]
126. Akilesh S, Petkova S, Sproule TJ, et al. The MHC class I-like Fc receptor promotes humorally mediated autoimmune disease. *J Clin Invest*. 2004; 113(9):1328–1333. [PubMed: 15124024]
127. Crow AR, Suppa SJ, Chen X, et al. 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. [PubMed: 22001393]
128. Seow CJ, Chue SC, Wong WS. Piceatannol, a Syk-selective tyrosine kinase inhibitor, attenuated antigen challenge of guinea pig airways in vitro. *Eur J Pharmacol*. 2002; 443(1–3):189–196. [PubMed: 12044809]
129. Yamamoto N, Takeshita K, Shichijo M, et al. The orally available spleen tyrosine kinase inhibitor 2-[7-(3,4-dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino]nicotinamide dihydrochloride (BAY 61-3606) blocks antigen-induced airway inflammation in rodents. *J Pharmacol Exp Ther*. 2003; 306(3):1174–1181. [PubMed: 12766258]

130. Braselmann S, Taylor V, Zhao H, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. *J Pharmacol Exp Ther.* 2006; 319(3):998–1008. [PubMed: 16946104]
131. Weinblatt ME, Kavanaugh A, Genovese MC, et al. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N Engl J Med.* 2010; 363(14):1303–1312. [PubMed: 20879879]
132. Mocsai A, Ruland J, Tybulewicz VL. The SYK tyrosine kinase: a crucial player in diverse biological functions. *Nat Rev Immunol.* 2010; 10(6):387–402. [PubMed: 20467426]
133. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A.* 2010; 107(29):13075–13080. [PubMed: 20615965]
134. Chang BY, Huang MM, Francesco M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. *Arthritis Res Ther.* 2011; 13(4):R115. [PubMed: 21752263]
135. Liu Y, Masuda E, Blank MC, et al. Cytokine-mediated regulation of activating and inhibitory Fc gamma receptors in human monocytes. *J Leukoc Biol.* 2005; 77(5):767–776. [PubMed: 15703199]
136. Belostocki K, Pricop L, Redecha PB, et al. Infliximab treatment shifts the balance between stimulatory and inhibitory Fc gamma receptor type II isoforms on neutrophils in patients with rheumatoid arthritis. *Arthritis Rheum.* 2008; 58(2):384–388. [PubMed: 18240208]
137. Rudge EU, Cutler AJ, Pritchard NR, et al. Interleukin 4 reduces expression of inhibitory receptors on B cells and abolishes CD22 and Fc gamma RII-mediated B cell suppression. *J Exp Med.* 2002; 195(8):1079–1085. [PubMed: 11956299]
138. Allen JB, Wong HL, Guyre PM, et al. Association of circulating receptor Fc gamma RIII-positive monocytes in AIDS patients with elevated levels of transforming growth factor-beta. *J Clin Invest.* 1991; 87(5):1773–1779. [PubMed: 1708784]
139. Kerst JM, van de Winkel JG, Evans AH, et al. Granulocyte colony-stimulating factor induces hFc gamma RI (CD64 antigen)-positive neutrophils via an effect on myeloid precursor cells. *Blood.* 1993; 81(6):1457–1464. [PubMed: 7680917]
140. Guyre PM, Morganelli PM, Miller R. Recombinant immune interferon increases immunoglobulin G Fc receptors on cultured human mononuclear phagocytes. *J Clin Invest.* 1983; 72(1):393–397. [PubMed: 6192145]
141. Valerius T, Repp R, de Wit TP, et al. Involvement of the high-affinity receptor for IgG (Fc gamma RI; CD64) in enhanced tumor cell cytotoxicity of neutrophils during granulocyte colony-stimulating factor therapy. *Blood.* 1993; 82(3):931–939. [PubMed: 7687898]
142. Goulding NJ, Knight SM, Godolphin JL, et al. Increase in neutrophil Fc gamma receptor I expression following interferon gamma treatment in rheumatoid arthritis. *Ann Rheum Dis.* 1992; 51(4):465–468. [PubMed: 1534001]
143. Shushakova N, Skokowa J, Schulman J, et al. C5a anaphylatoxin is a major regulator of activating versus inhibitory Fc gammaRs in immune complex-induced lung disease. *J Clin Invest.* 2002; 110(12):1823–1830. [PubMed: 12488432]
144. Tsuboi N, Hernandez X, Li T, et al. Regulation of human neutrophil Fc gamma receptor IIa by C5a receptor promotes inflammatory arthritis in mice. *Arthritis Rheum.* 2011; 63(2):467–478. [PubMed: 21280001]
145. Xie T, Liang N, Liu J, et al. MicroRNA-127 inhibits lung inflammation by targeting IgG Fc gamma receptor I. *J Immunol.* 2012; 188(5):2437–2444. [PubMed: 22287715]
146. Juliano RL, Dixit VR, Kang H, et al. Epigenetic manipulation of gene expression: a toolkit for cell biologists. *J Cell Biol.* 2005; 169(6):847–857. [PubMed: 15967809]
147. Iguchi A, Fukuda N, Takahashi T, et al. RNA binding properties of novel gene silencing pyrrole-imidazole polyamides. *Biol Pharm Bull.* 2013; 36(7):1152–1158. [PubMed: 23628892]
148. Wigle TJ, Copeland RA. Drugging the human methylome: an emerging modality for reversible control of aberrant gene transcription. *Curr Opin Chem Biol.* 2013; 17(3):369–378. [PubMed: 23619004]
149. Avalos AM, Uccellini MB, Lenert P, et al. Fc gammaRIIB regulation of BCR/TLR-dependent autoreactive B-cell responses. *Eur J Immunol.* 2010; 40(10):2692–2698. [PubMed: 20809520]

150. Means TK, Latz E, Hayashi F, et al. Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. *J Clin Invest*. 2005; 115(2):407–417. [PubMed: 15668740]
151. Schroeder JT, Bieneman AP, Xiao H, et al. TLR9- and FcεRI-mediated responses oppose one another in plasmacytoid dendritic cells by down-regulating receptor expression. *J Immunol*. 2005; 175(9):5724–5731. [PubMed: 16237063]
152. Wenink MH, Santegoets KC, Roelofs MF, et al. The inhibitory Fc gamma IIB receptor dampens TLR4-mediated immune responses and is selectively up-regulated on dendritic cells from rheumatoid arthritis patients with quiescent disease. *J Immunol*. 2009; 183(7):4509–4520. [PubMed: 19734236]
153. Zhang Y, Liu S, Liu J, et al. Immune complex/Ig negatively regulate TLR4-triggered inflammatory response in macrophages through Fc gamma RIIB-dependent PGE2 production. *J Immunol*. 2009; 182(1):554–562. [PubMed: 19109188]
154. Chu CL, Yu YL, Shen KY, et al. Increased TLR responses in dendritic cells lacking the ITAM-containing adapters DAP12 and FcRgamma. *Eur J Immunol*. 2008; 38(1):166–173. [PubMed: 18081038]
155. Dunn-Siegrist I, Leger O, Daubeuf B, et al. Pivotal involvement of Fc gamma receptor IIA in the neutralization of lipopolysaccharide signaling via a potent novel anti-TLR4 monoclonal antibody 15C1. *J Biol Chem*. 2007; 282(48):34817–34827. [PubMed: 17921137]
156. Krupa A, Fudala R, Florence JM, et al. Bruton's tyrosine kinase mediates Fc gamma RIIA/Toll-like receptor-4 receptor crosstalk in human neutrophils. *Am J Respir Cell Mol Biol*. 2013; 48(2):240–249. [PubMed: 23239500]
157. Rittirsch D, Flierl MA, Day DE, et al. Cross-talk between TLR4 and Fc gamma Receptor III (CD16) pathways. *PLoS Pathog*. 2009; 5(6):e1000464. [PubMed: 19503602]
158. Wijngaarden S, van de Winkel JG, Jacobs KM, et al. A shift in the balance of inhibitory and activating Fc gamma receptors on monocytes toward the inhibitory Fc gamma receptor IIB is associated with prevention of monocyte activation in rheumatoid arthritis. *Arthritis Rheum*. 2004; 50(12):3878–3887. [PubMed: 15593228]
159. van der Pol WL, van den Berg LH, Scheepers RH, et al. IgG receptor IIA alleles determine susceptibility and severity of Guillain-Barre syndrome. *Neurology*. 2000; 54(8):1661–1665. [PubMed: 10762510]
160. Li X, Ptacek TS, Brown EE, et al. Fc gamma receptors: structure, function and role as genetic risk factors in SLE. *Genes Immun*. 2009; 10(5):380–389. [PubMed: 19421223]
161. Brun JG, Madland TM, Vedeler CA. Immunoglobulin G fc-receptor (Fc gamma R) IIA, IIIA, and IIIB polymorphisms related to disease severity in rheumatoid arthritis. *J Rheumatol*. 2002; 29(6):1135–1140. [PubMed: 12064825]
162. Dijkstra HM, Scheepers RH, Oost WW, et al. Fc gamma receptor polymorphisms in Wegener's granulomatosis: risk factors for disease relapse. *Arthritis Rheum*. 1999; 42(9):1823–1827. [PubMed: 10513795]
163. Karassa FB, Trikalinos TA, Ioannidis JP, et al. Role of the Fc gamma receptor IIA polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Arthritis Rheum*. 2002; 46(6):1563–1571. [PubMed: 12115187]
164. Shrestha S, Wiener H, Shendre A, et al. Role of activating Fc gamma R gene polymorphisms in Kawasaki disease susceptibility and intravenous immunoglobulin response. *Circ Cardiovasc Genet*. 2012; 5(3):309–316. [PubMed: 22565545]
165. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. *Nat Genet*. 2011; 43(12):1241–1246. [PubMed: 22081228]
166. Onouchi Y, Ozaki K, Burns JC, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. *Nat Genet*. 2012; 44(5):517–521. [PubMed: 22446962]
167. Saruhan-Direskeneli G, Hughes T, Aksu K, et al. Identification of multiple genetic susceptibility Loci in takayasu arteritis. *Am J Hum Genet*. 2013; 93(2):298–305. [PubMed: 23830517]

168. Edberg JC, Langefeld J, Wu CD, et al. Genetic linkage and association of Fcgamma receptor IIIA (CD16A) on chromosome 1q23 with human systemic lupus erythematosus. *Arthritis Rheum.* 2002; 46(8):2132–2140. [PubMed: 12209518]
169. Morgan AW, Barrett JH, Griffiths B, et al. Analysis of Fcgamma receptor haplotypes in rheumatoid arthritis: FCGR3A remains a major susceptibility gene at this locus, with an additional contribution from FCGR3B. *Arthritis Res Ther.* 2006; 8(1):R5. [PubMed: 16356189]
170. Jonsen A, Gunnarsson I, Gullstrand B, et al. Association between SLE nephritis and polymorphic variants of the CRP and FcgammaRIIIa genes. *Rheumatology (Oxford).* 2007; 46(9):1417–1421. [PubMed: 17596285]
171. Hatta Y, Tsuchiya N, Ohashi J, et al. Association of Fc gamma receptor IIIB, but not of Fc gamma receptor IIA and IIIA polymorphisms with systemic lupus erythematosus in Japanese. *Genes Immun.* 1999; 1(1):53–60. [PubMed: 11197306]
172. Foster CB, Zhu S, Erichsen HC, et al. Polymorphisms in inflammatory cytokines and Fcgamma receptors in childhood chronic immune thrombocytopenic purpura: a pilot study. *Br J Haematol.* 2001; 113(3):596–599. [PubMed: 11380443]
173. Willcocks LC, Lyons PA, Clatworthy MR, et al. Copy number of FCGR3B, which is associated with systemic lupus erythematosus, correlates with protein expression and immune complex uptake. *J Exp Med.* 2008; 205(7):1573–1582. [PubMed: 18559452]
174. Tse WY, Abadeh S, Jefferis R, et al. Neutrophil FcgammaRIIIb allelic polymorphism in anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. *Clin Exp Immunol.* 2000; 119(3):574–577. [PubMed: 10691933]
175. Wu J, Ji C, Xie F, et al. FcalphaRI (CD89) alleles determine the proinflammatory potential of serum IgA. *J Immunol.* 2007; 178(6):3973–3982. [PubMed: 17339498]

Highlights

- Fc receptors, through engagement of ligands, bridge the innate and adaptive immune systems.
- Because of their frequent contribution to immune mediated diseases, FcRs are promising targets for clinical intervention.
- Strategies for FcR targeting vary according to disease pathogenesis and rationale of treatment.
 - Interruption of activating FcR/immune complex interactions attenuate immune complex mediated inflammation and autoimmunity, which is achieved by blocking the FcRs with specific antibody (fragments) and small molecules, or by neutralizing immune complex with soluble recombinant FcRs.
 - Engagement of the Fc γ RIIb suppresses immune cell signaling. Current strategies for targeting Fc γ RIIb include specific monoclonal antibody and bispecific ligands.
 - Targeting activating FcRs is an important strategy for efficient depletion of immunocytes through FcR-mediated ADCC.
 - Modification in the glycosylation, fucosylation, galactosylation, or sialylation status of IgG may be useful in manipulate binding affinity of therapeutic antibodies.
 - The primary factor in regulating IgG metabolism, FcRn, can be targeted to decrease endogenous IgG level or to increase the half-life of therapeutic antibodies.
- Future research should be based on a better understanding of the individual roles of different FcRs, and focus on enhancing the targeting specificity for both the receptor and the cell type.

Figure 1.
Structure of human classical Fc Receptors

Table 1

General features of human Fc Receptors.

Receptor	FcγRI	FcγRIIa	FcγRIIb	FcγRIIc	FcγRIIIa	FcγRIIIb	FcεRI	FcαRI	FcμR	FcRn
Ligand specificity	IgG1=IgG3>IgG4>>IgG2	IgG3 IgG1>IgG2>>IgG4	IgG3 IgG1=IgG4>>IgG2	IgG1=IgG4>>IgG2	IgG3 IgG1>>>IgG4	IgG2	IgE	IgA	IgM	IgG4>IgG1>IgG3>IgG2
Distribution	Monocyte	✓	✓		✓		✓	✓		✓
	Macrophage	✓	✓		✓		✓	✓		✓
	DC	✓	✓		✓		✓	✓		✓
	Mast cell		✓				✓			
	Neutrophil	✓	✓				✓	✓		
	Basophil		✓				✓			
	Eosinophil	✓					✓	✓		
	NK cell			✓	✓				✓	
	B cell		✓						✓	✓
	T cell								✓	
	Platelet		✓				✓			

Table 2

Functional impact of genetic variations of FCGRs and association with autoimmune diseases.

Receptor	Genetic variation	Effect	SNP associations with autoimmunity
FcγRIIa	R131H	H131: higher affinity, can bind IgG2	ITP[159], SLE[160], RA[161], GPA[162], Lupus nephritis[163], KD[164–166]
	rs10919543	increasing mRNA expression	TA[167]
FcγRIIb	I232T	T232: altered partitioning to lipid rafts; altered signaling capability	SLE[160]
	2B.1/2B.4*	2B.4: higher promoter activity/expression	SLE[160]
FcγRIIc	STP/Q13	STP: pseudogene; Q13:expression	ITP[7]
	CNV	altered protein expression level	ITP[7]
FcγRIIIa	V158F	V158: higher affinity for IgG1, IgG3	SLE[168], RA[169], GPA [162], Lupus nephritis[170]
	CNV	Altered protein expression level	
FcγRIIIb	NA1/NA2**	NA1: higher affinity	SLE[171], ITP[172]
	CNV	Altered protein expression level	SLE[173], ANCA vasculitis [103, 174]
FceRI	–66T/C	–66T:higher promoter activity/expression	
	–315C/T	–315T:higher promoter activity/expression	
FcαRI	S248G	G248: higher IgA-mediated activation	SLE[175]
FcRn	VNTR***	altered promoter activity/expression	

* Promoter haplotype. 2B.1: –120G-386T; 2B.4: –120C-386A.

** Coding haplotype. NA1: 141G 147C 227A 349G; NA2: 141C 147T 227G 349A.

*** VNTR: variable number of tandem repeats

ITP: idiopathic thrombocytopenia purpura; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; GPA: Granulomatosis with polyangitis (Wegener's granulomatosis); KD: Kawasaki disease; TA: Takayasu's arteritis; ANCA:anti neutrophil cytoplasmic antibodies.