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REVIEW

Activating and inhibitory FcγRs in autoimmune disorders

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Abstract Autoimmune disorders are characterized by the destruction of self-tissues by the immune system. Multiple checkpoints are in place to prevent autoreactivity under normal circumstances. Coexpression of activating and inhibitory Fc receptors (FcR) represents such a checkpoint by establishing a threshold for immune cell activation. In many human autoimmune diseases, however, balanced FcR expression is disturbed. Analysis of murine model systems provides strong evidence that aberrant FcR expression can result in uncontrolled immune responses and the initiation of autoimmune disease. This review will summarize this data and explain how this information might be used to better understand human autoimmune diseases and to develop novel therapeutic strategies.

Keywords Fc receptor · Antibody · Immune complex · Cell activation · Autoimmune disease

Introduction

Arthritis, multiple sclerosis (MS), autoimmune diabetes, and systemic lupus erythematosus (SLE) are autoimmune diseases that affect millions of people worldwide and require continuous medical attention. Linkage and association studies have established that several genetic and non-genetic factors contribute to the development of disease [1]. The importance of the adaptive and innate arms of the immune system in these processes is highlighted by the fact that immunosuppression is an effective treatment for these diseases [2]. Systemic immune suppression, however, renders the patient more susceptible to infections, and treatment has to be stopped during an acute infection, leading to the reoccurrence of autoimmune symptoms. Thus, more specific approaches to eliminate self-reactive cells might have fewer side effects. Indeed, depletion of B cells has shown promising results for autoimmune diseases such as SLE [2, 3]. Research in mouse models that recapitulate the human disease phenotypes has lead to important insights into the mechanisms that cause an uncontrolled immune response and destruction of self-tissues. A normal immune response is characterized by a delicate balance of activating and inhibitory signals, which will determine the strength of the following response [4]. It must be strong and long lasting enough to eliminate foreign pathogens or malignant cells but controlled and specific enough to avoid damage to non-infected or healthy tissues. Several control mechanisms prevent autoreactive or overwhelming immune responses, and potentially harmful cells can be deleted or inactivated at central or peripheral checkpoints. During early B cell development in the bone marrow, for example, cells expressing self-reactive receptors are eliminated by mechanisms such as receptor editing, deletion, or anergy [5–7]. It is widely accepted, however, that this process is incomplete, and self reactive cells can escape into the periphery; in addition, autoreactive B cells can be generated de novo in the periphery during the germinal center reaction [8, 9]. Therefore, other checkpoints must be in place continuously to prevent the accumulation and activation of autoreactive cells. In particular, B cells that secrete class-switched self-reactive antibodies, which can trigger inflammatory effector functions, have to be tightly regulated [10, 11].

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Gene deletion studies in mice have identified the important role of negative regulatory proteins, such as CD5, CD22, CD72, PD-1, CTLA-4, and the inhibitory FcγRIIB (CD32B), which control signals triggered by activating receptors, thus, setting a threshold for immune cell activation. Lack of these proteins results in autoimmune phenotypes and uncontrolled immune responses [12–17]. The hallmark of this protein family is the presence of an immunoreceptor tyrosine-based inhibitory motif (ITIM) [18]. The Fc receptor (FcR) system has become a paradigm for such simultaneous triggering of activating and inhibitory signals, and several proteins of this family have been suggested to be associated with the incidence or severity of human autoimmune disorders, which will be the focus of this review. Besides the FcR family, other players of the innate and adaptive immune system have been associated with autoimmune disorders in mice and humans, which is reviewed elsewhere [19, 20].

Research over the recent years has established that FcRs are central players in several processes that, if not regulated, can lead to the appearance of autoreactive antibodies or autoimmune phenotypes [21, 22]. These range from a failure to delete or prevent the expansion of self-reactive B cells to maintaining dendritic cells (DCs) in an immature and tolerizing state; in addition, the rapid clearance of potential autoantigens such as apoptotic cells by macrophages is important to prevent the initiation of autoimmune processes [23].

A question of balance—coexpression of activating and inhibitory Fc receptors

The family of FcRs is well conserved among different species [11], although the human family is most numerous due to gene duplication and diversification processes [24]. To date, FcRs for all antibody isotypes have been identified. As IgA and IgE FcRs will be discussed elsewhere in this issue, this chapter concentrates on the FcRs for IgG, the FcγRs. Generally, FcRs can be divided into two classes: the activating and the inhibitory FcRs. Most activating receptors cannot signal autonomously and have to associate with additional adaptor molecules to be functional. A notable exception to this rule is the human FcγRIIA, which can transmit activating signals by itself. Therefore, a functional FcR consists of a ligand binding α-domain associated with signaling adaptor molecules containing immunoreceptor tyrosine-based activation motifs (ITAM). Depending on the cell type, the associated signaling adaptor molecules vary. Whereas in the majority of cells, such as monocytes, macrophages, neutrophils, and DCs, FcRs are associated with the common gamma chain (γ-chain); in human natural killer (NK) cells, FcRs are found in combination with the zeta chain (ζ-chain). In addition to the signaling function, these molecules are important for cell-surface expression of the respective α-chains. Animals deficient in the γ-chain lack cell surface expression of all activating FcγRs and several other non-FcR-related proteins such as PIR-A and NK cell cytotoxicity receptors [22, 25]. As expected, these animals demonstrated significant defects in antibody-dependent effector cell responses [26–30]. The inhibitory receptor is a single chain molecule that contains an ITIM in its cytosolic tail [18].

Humans have eight genes that encode Fcγ-receptors (FcγRIA/IB/IC, FcγRIIA/B/C and FcγRIIIA/B) located on chromosome 1. The majority of other species, including the mouse, have four different classes of IgG FcRs that correspond to their human counterparts: FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcγRIV. FcγRIV is a recently identified receptor with intermediate affinity (10^7 M^{-1}) and restricted subclass specificity. Based on its sequence similarity, it could be considered the mouse homologue to human FcγRIIIA [31–33]. Whereas FcγRI displays high affinity for the antibody constant region (10^8–10^9 M^{-1}), FcγRIIB and FcγRIII have a much lower affinity (~10^6 M^{-1}) [34, 35]. The low-affinity Fc-receptor genes are clustered in close proximity to each other in syntenic regions on chromosome 1 in humans, chimpanzees, and mice. In contrast, the high-affinity FcγRI is located on chromosome 3 in mice and chromosome 1 in humans and chimpanzees [11]. This Fcγ-receptor complexity is mirrored by the existence of several IgG isotypes that show differential binding to FcγRs. In the mouse, the high-affinity FcγRI exclusively binds IgG2a, the medium-affinity FcγRIV binds IgG2a and IgG2b, and the low-affinity receptors FcγRIIB and III bind IgG1, IgG2a, and IgG2b [11]. In humans, IgG1 and IgG3 bind better to FcRs than IgG2 or IgG4. However, due to the presence of multiple FcR alleles that influence the antibody–FcR interaction, the situation is more complex [10]. As will be discussed later, some of these alleles show a significant association with autoimmune diseases, which allows to draw some conclusions about the role of antibody–FcR interactions in these disorders.

Establishing the threshold for cell activation: activating and inhibitory Fc-receptor signaling

As indicated, activating and inhibitory FcRs are coexpressed on the same cell. Thus, immune complex (IC) binding will result in simultaneous triggering of activating and inhibitory signaling pathways (Fig. 1). Factors that determine whether this coengagement results in cell activation or inhibition are the relative affinities of the

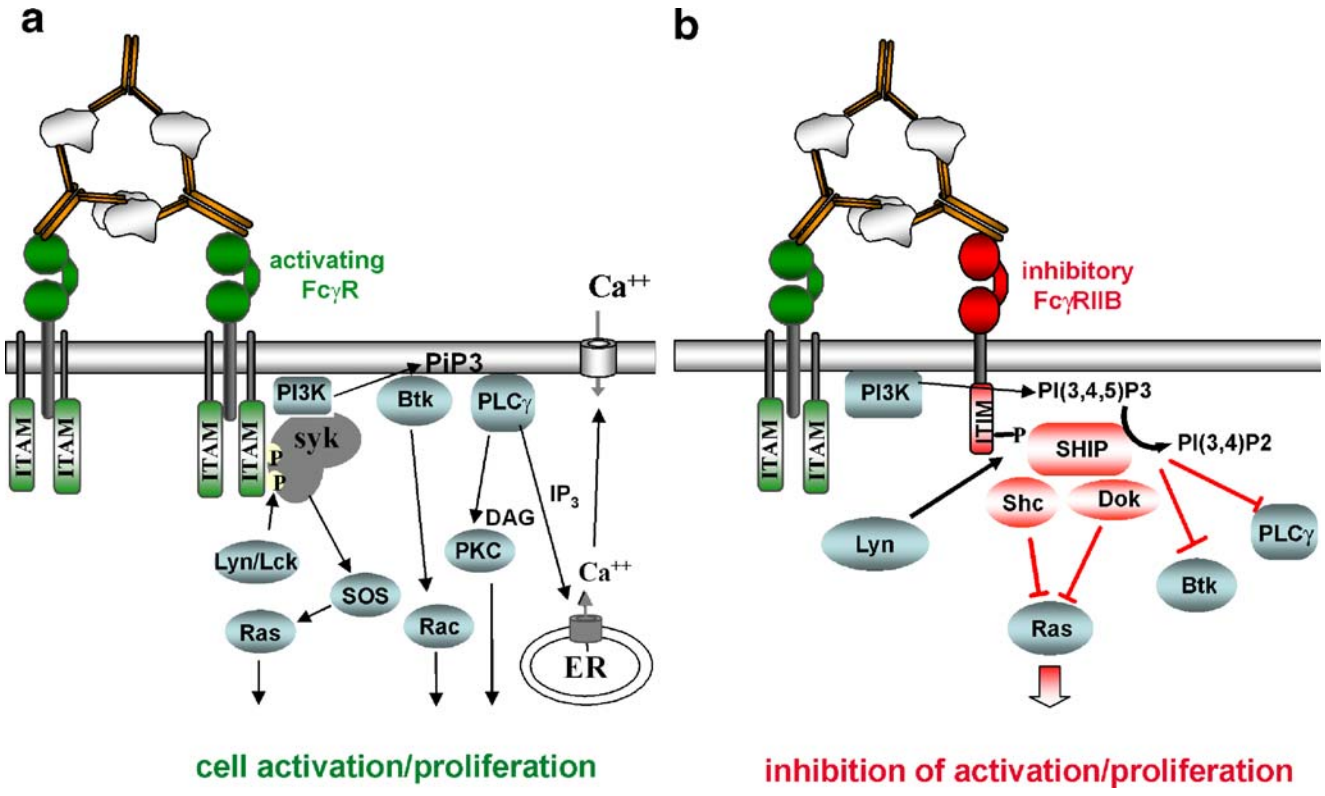

Fig. 1 Signaling pathways of activating and inhibitory FcRs. **a** Immune complex triggered crosslinking of activating FcRs induces phosphorylation of the ITAM motif by members of the SRC-kinase family, resulting in activation of downstream signaling events and cell activation. **b** Simultaneous triggering of the inhibitory FcR interferes with cell activation by recruitment of the phosphatase SHIP and inhibition of activating signaling pathways. The strength of activating versus inhibitory signals triggered by immune complexes is determined by the affinity of individual antibody isotypes to activating and inhibitory FcRs and other factors such as the cytokine environment (see text for details)

antibody isotype to specific FcRs, the expression level of activating and inhibitory Fc-receptors, and the cytokine environment, which can influence their relative expression levels [11]. Moreover, differential antibody glycosylation during an inflammatory response can influence the antibody–FcR interaction and thus regulate antibody activity in mice and humans [36]. Effector responses controlled by these opposing signals most prominently include degranulation of mast cells and neutrophils, release of cytotoxic mediators and inflammatory cytokines by macrophages, antibody dependent cellular cytotoxicity (ADCC), DC activation, phagocytosis, and antigen presentation [22].

Signaling pathways of activating FcRs

The affinity of the majority of activating FcRs for monomeric antibodies is not sufficient for stable binding and induction of signaling. High-affinity receptors, like FcγRI and FcεRI, can associate with monomeric IgG or IgE antibodies, but activating signals are only triggered upon replacement of bound IgG by ICs (in the case of FcγRI) or upon allergen binding and concomitant crosslinking of cell-surface-bound IgE [37, 38]. Ligands that bind with low affinity cannot trigger sustained receptor aggregation and might even behave as antagonists [39]. FcR aggregation by ICs induces a relocation into cell membrane subdomains called lipid rafts that are enriched in signaling molecules such as SRC-protein kinases (Fig. 1a) [40]. Tyrosine residues in the ITAM motif of the γ-chain then become phosphorylated by SRC kinases, creating SH2 docking sites for the subsequent recruitment of SYK kinases. Depending on cell type and the receptor in question, different members of the SRC-kinase family, such as LYN, HCK, or LCK, are involved in phosphorylation of the γ-chain (Fig. 1a). This enables members of the SYK-kinase family to bind and to recruit and phosphorylate a number of downstream targets including the linker for activation of T cells, multi-molecular adaptor complexes, and members of the BTK and TEC-kinase family [41–43]. Important downstream events triggered by SYK-mediated activation of phosphatidylinositol 3-kinase and phospholipase-Cγ (PLCγ) are sustained calcium release and protein kinase C activation. Moreover, the Ras–Raf–MAPK

pathway becomes activated through Sos present in the multimolecular adaptor complex [22, 44].

Inhibitory signaling pathways

Depending on the cell type, alternatively spliced forms of the inhibitory FcR, FcγRIIB, have been described, which have a differential capacity to endocytose bound ICs (termed FcγRIIB-1 and FcγRIIB-2). FcγRIIB-1 is expressed on B cells, whereas the endocytic FcγRIIB-2 shows a myeloid expression pattern [44]. All of these splice forms, however, contain the ITIM motif and trigger inhibitory signaling pathways. On B cells, FcγRIIB regulates activating signals transmitted by the B cell receptor (BCR), whereas on mast cells, neutrophils, or macrophages, it balances activating signals triggered by Fcε- or Fcγ-receptors [22, 44]. Upon co-aggregation with its activating counterpart, LYN phosphorylates the ITIM motif, which leads to the recruitment of SHIP (SH2-domain containing inositol 5′ phosphatase). SHIP activation leads to enhanced hydrolysis of phosphatidyl inositol intermediates and thereby interferes with the membrane recruitment of BTK and PLCγ, resulting in inhibition of ITAM-signaling mediated calcium release and downstream effector functions (Fig. 1b) [45, 46]. Moreover, tyrosine-phosphorylated SHIP can bind to Shc and Dok, thereby inhibiting activation of the Ras pathway and ultimately cell proliferation. A third ITIM- and SHIP-independent signaling pathway has been described for crosslinking of FcγRIIB on B cells without concomitant activating signals by the BCR. This leads to B cell apoptosis via Abl-family kinase-dependent pathways [47, 48]. Although the in vivo relevance of this pathway remains to be established, this situation may arise during the germinal center reaction when somatic hypermutation generates BCRs that lose specificity for their cognate antigen retained in the form of ICs on follicular DCs. Thus, FcγRIIB has been suggested to be important for keeping tolerance.

Disturbing the threshold—horror autotoxicus

There are several ways how balanced signaling through activating and inhibitory FcR pairs might be perturbed, ranging from aberrant expression of FcRs to allelic variants of activating receptors that have a differential affinity for certain antibody isotypes [10, 11, 49]. Most of our current knowledge stems from gene deletion studies and autoimmune models in mice and indirect data from human autoimmune patients. Loss or inactivation of FcRs in humans has only been described for the high-affinity FcγRI and FcγRIIIB. Whereas FcγRI deficiency had no apparent impact on health, a significant amount of individuals that lost FcγRIIIB expression had autoimmune disorders [50–53]. As activating and inhibitory FcR pairs are expressed on a variety of cell types, the resulting phenotypes are a complex mixture of impaired responses at several stages throughout the adaptive and innate immune response. The following paragraphs will summarize these phenotypes with respect to the affected cell types and the molecular changes resulting in impaired FcR-dependent responses.

Changing the expression level of the inhibitory receptor on B cells

FcγRIIB, together with other negative regulatory proteins such as CD22 or CD72, regulates activating signals triggered by the BCR, thus setting a threshold for B cell activation [45, 54, 55]. Loss of FcγRIIB was therefore predicted to result in uncontrolled B cell activation. This was confirmed by the generation of FcγRIIB-deficient mice that spontaneously develop a lupus like disease characterized by the production of autoantibodies and premature death due to severe glomerulonephritis [12, 16]. This autoimmune phenotype is strain dependent; mice on the C57BL/6, but not the Balb/c, background develop autoimmune disease, suggesting that other epistatic modifiers are involved in disease susceptibility and severity [56]. Supporting this notion, Balb/c mice, double deficient in programmed death 1 (PD-1) and FcγRIIB, developed autoimmune hydronephrosis, whereas mice that were only deficient in one of these inhibitory proteins did not [57]. Moreover, Balb/c FcγRIIB-knockout mice showed enhanced disease phenotypes in a model of pristane-induced lupus [58]. In addition, Balb/c mice have been suggested to be more efficient in silencing autoreactive heavy chains by receptor editing than C57Bl/6 mice, making the latter strain more permissive for the development of autoimmunity [59, 60].

Although genetic deletion of FcγRIIB results in loss of inhibitory signaling on a variety of cell types, there is evidence that the appearance of autoantibodies is a B cell autonomous phenomenon. Autoimmune-prone mouse strains such as NZB, NOD, BXSB, and MRL express reduced levels of FcγRIIB on activated and germinal-center B cells due to a polymorphism in the FcγRIIB promoter [61–64]. Moreover, FcγRIIB bone marrow chimeras expressing normal levels of the inhibitory receptor on radiation-resistant cells but lacking FcγRIIB on B cells develop autoantibodies and disease [12]. Another important issue is to understand at which stage(s) of B cell development FcγRIIB regulates tolerance. As indicated, autoreactive B cells can be generated throughout B cell development [6]. There is accumulating evidence that FcγRIIB mediates its function during late stages of B cell

maturation in mice and humans, thus representing a distal checkpoint [59, 65, 66]. By using a mouse strain in which the endogenous Ig locus has been replaced with an autoreactive heavy chain, it was shown that the absence of FcγRIIB resulted in the accumulation of IgG-positive, autoreactive plasma cells [59]. FcγRIIB deficiency did neither impact early events in the bone marrow such as receptor editing nor did it prevent the development of IgM-positive, autoreactive B cells. After class switching to IgG, however, FcγRIIB was essential in preventing the expansion of autoreactive B cells and their maturation into plasma cells. Taking the considerably higher pathogenic potential of IgG compared to the IgM antibody isotypes into account, this relatively late stage of FcγRIIB-mediated negative regulation might be sufficient to prevent the initiation of severe autoreactive processes. Thus, FcγRIIB might serve as the final barrier to control class-switched, autoreactive B cells that would otherwise induce tissue pathology by secretion of large amounts of pathogenic antibodies.

The most important question is whether these data obtained in murine model systems help to explain the development of human autoimmune disease. Analysis of human autoimmune patient cohorts indicates that this is the case, and that some of the underlying mechanisms of aberrant FcγRIIB expression are quite similar in humans and mice. For instance, polymorphisms in the human FcγRIIB promoter have been linked to the development of SLE [65, 67, 68]. The strongest association was found with a polymorphism that leads to a decreased binding of the transcription factor AP-1, resulting in a reduced surface expression of FcγRIIB on activated B cells of human lupus patients [65]. Another study showed that memory B cells of SLE patients failed to upregulate FcγRIIB expression on memory B cells, and this lower expression level was correlated with a reduced threshold for B cell activation [66] consistent with a previous study describing that B cells from lupus patients showed enhanced triggering of activating signaling pathways after BCR stimulation [69]. Such quantitative assessments of FcγRIIB expression have been complicated until the recent development of a novel antibody specific for the human inhibitory FcγRIIB [70]. It will be of interest to determine what the mechanism of this aberrant expression is and if any of the known FcγRIIB polymorphisms are involved in this phenotype. The results of these studies fit to the data obtained in murine model systems identifying FcγRIIB as a checkpoint during late stages of B cell development. Moreover, an allelic variant of FcγRIIB has been associated with human SLE and arthritis in several Asian populations (Table 1) [71–74]. In this allele, the exchange of a non-polar isoleucine residue in the transmembrane domain (amino acid 232) for a threonine results in an impaired recruitment to lipid rafts and thus exclusion from productive signaling [75–77]. This represents a novel mechanism of impaired FcγRIIB function and is unique to humans. There are, however, great disparities between different human populations and ethnicities highlighting the importance of the genetic background and other susceptibility factors for the development of autoimmune disease (Table 1). Thus, although several studies found clear associations between SLE and the FcγRIIB-I232T allele in Asian patients, Caucasians did not show this association [74]. In the latter group, aberrant transcription due to promoter polymorphisms was found more consistently [65, 74]. Similarly, the decreased expression of FcγRIIB on memory cells of SLE patients was overrepresented in the African–American population [66].

Table 1 Human Fc-receptor alleles associated with SLE

Fc-receptor	Disease association	Population	Mechanism	References
FcγRIIB	SLE incidence	Caucasian	Promoter polymorphism (impaired transcription factor binding)	[65, 67, 68]
		African–American	Decreased expression on memory cells	[66]
		Asian	Allelic variant (FcγRIIB^{232T}) excluded from lipid rafts	[71–77]
FcγRIIA	SLE incidence/ severity	African–American, Brazilian, German, Korean, Hispanic, Thai	Low-affinity 131R allele	[71, 126, 128, 129, 131, 133, 136, 137, 144]
FcγRIIIA	SLE incidence/ severity	Caucasian, Dutch and Korean	Low-affinity 158F allele	[127, 130, 134, 145]
FcγRIIIB	SLE incidence/ severity	Thai, Spanish, Japanese	Low-affinity NA2 allele	[71, 138, 139]

FcγRIIB as a regulator of DC activity

DCs have long been recognized as central mediators that, depending on their activation state, determine whether an adaptive immune response or tolerance is induced [78]. Several groups have shown that crosslinking of FcRs on DCs by ICs results in cell activation and cross-presentation of endocytosed antigen on MHC class I molecules to CD8+ cytotoxic T cells [79–82]. As low levels of ICs are constantly present in the serum, FcγRIIB might be crucial in preventing spontaneous activation of DCs. Indeed, blocking FcγRIIB on human DCs was sufficient to induce DC maturation by serum ICs. Besides up-regulation of costimulatory molecules, these DCs were more potent in generating and activating antigen specific T cells [70, 83], as described before for mouse DCs deficient in FcγRIIB expression [84]. Although beneficial for immunotherapeutic or vaccination approaches, this suggests that a slight deregulation of FcγRIIB expression might result in the initiation of autoreactive processes. It will be of great interest to determine if FcR-mediated uptake of ICs containing autoantigens by DCs plays a role in autoimmune diseases that depend on the priming of autoreactive T cells. In addition, expression of the inhibitory receptor on DCs present in epithelia has been implicated in establishing tolerance to air-borne and food allergens [85].

Whereas the essential role of DCs in regulating T cell responses is well accepted, it has only recently become clear that DCs are also important for the B cell response [86–88]. Unlike in macrophages, which rapidly degrade phagocytosed material, antigen taken up by DCs is degraded more slowly and therefore present in an intact form for prolonged times [89]. This might allow antigen transport from the periphery to lymphoid organs where it can be presented to B cells. DC–B cell interactions have been observed in vivo, and it has been suggested that this interaction is important for the generation of an IgG response in vitro and in vivo [88]. The role of FcγRIIB in this process is that ICs taken up via FcγRIIB are inefficiently degraded and recycled for cell surface presentation to B cells. In contrast, uptake via FcγRIII results in a faster degradation of the antigen [86]. The importance of this novel function of FcγRIIB for human or murine autoimmune diseases remains to be established.

The role of FcγRIIB in the efferent response: controlling innate immune effector cell activation

Besides its regulatory role on B cells and DCs in the afferent response, FcγRIIB is an important modulator of inflammatory effector cells, such as mast cells, neutrophils, and macrophages, during the efferent phase of an immune response [22]. On these cell types, FcγRIIB is coexpressed with activating FcRs of varying affinities and isotype specificities and negatively regulates signals delivered by these receptors. Lack of FcγRIIB leads to elevated IC-mediated inflammation and phagocytosis, as demonstrated by an enhanced Arthus reaction, systemic anaphylaxis, anti-GBM glomerulonephritis, immunothrombocytopenia (ITP), hemolytic anemia, collagen-induced arthritis, and IgG-mediated clearance of pathogens and tumor cells [11, 21]. On allergic effector cells such as mast cells and basophils, FcγRIIB regulates activating signals triggered by crosslinking FcεRI, resulting in an enhanced IgE-mediated anaphylaxis and heightened sensitivity to allergic rhinitis [90]. Moreover, FcγRIIB deficiency renders otherwise resistant mouse strains susceptible to development of certain forms of collagen induced arthritis [91]. As described for human autoimmune disease in some of these models both increased autoantibody production due to FcγRIIB deficiency on B cells and heightened effector cell responses are likely to contribute to the observed phenotype.

Another long known observation is that IgG2a and IgG2b antibodies trigger stronger effector responses than IgG1 or IgG3 in passive antibody transfer models [92–100]. Similarly, in highly pathogenic autoimmune models such as the accelerated nephrotoxic nephritis (NTN) model, the pathogenic autoantibodies are of the IgG2b isotype [101]. In human SLE patients, IgG1, IgG3, and to a lesser extent IgG2 anti-DNA antibodies dominate in the serum, whereas all subclasses can be found in kidney biopsies [102–105].

The molecular mechanism of differential antibody isotype activity was addressed recently [97]. It was shown that the differences in affinity of different IgG isotypes for activating and inhibitory FcRs might explain this phenomenon [33, 97]. By measuring the affinities of all antibody isotypes for the various FcRs and dividing the affinities of antibody isotypes for activating FcRs by the affinity for the inhibitory receptor a so-called A/I ratio was established which predicted antibody activity in vivo [11, 97]. Thus, IgG1 (which only binds to the FcγRIII/FcγRIIB pair) has a lower affinity for the activating than for the inhibitory FcR (A/I-ratio $\ll 1$) resulting in lower activity. In contrast, IgG2a and IgG2b have 20- to 40-fold higher affinity for the activating FcγRIV than for FcγRIII/FcγRIIB, which results in preferential triggering of FcγRIV and a lower degree of negative regulation by the inhibitory FcR. As will be discussed below, other factors such as cytokines or differential antibody glycosylation can affect this ratio. In humans, the presence of different activating FcR alleles that have differential affinities for certain human antibody isotypes might result in a similar situation, thus changing the A/I ratio and antibody activity.

The activating FcRs in the efferent response

In contrast to the inhibitory FcγRIIB, expression of activating FcRs is limited to DCs and innate immune effector cells such as mast cells, basophils, monocytes, macrophages, neutrophils, and NK cells. There is considerable heterogeneity in the expression of specific activating FcRs. In the mouse, macrophages express all activating FcRs (I, III, and IV), DCs mainly express FcγRI and III, neutrophils express FcγRIII and IV, and NK cells express FcγRIII. Genetic inactivation of all activating FcRs by deletion of the common γ-chain in mice results in abrogated or heavily impaired IC or allergen-mediated responses, such as ADCC, release of inflammatory mediators, cytokine release, and phagocytosis of ICs [11, 29]. As several activating FcRs are coexpressed on the same cell, subsequent deletion of the individual ligand-binding α-chains was crucial in elucidating the role of the individual FcRs for the activity of different antibody isotypes. Identifying the receptor and cell type responsible for tissue pathology in autoimmune diseases might allow the development of more specific therapeutic interventions. Consistent with its in vitro isotype binding profile, activating FcγRIII was essential for IgG1-mediated effector functions in a variety of models, like arthritis, glomerulonephritis, IgG-dependent anaphylaxis, IgG-mediated hemolytic anemia, and ITP [33, 93, 97, 106–110].

In contrast, IgG2b activity was not impaired in FcγRIII or FcγRI knockout mice but was almost completely abrogated in mice injected with an FcγRIV blocking antibody in passive and active models of antibody-mediated inflammation, including models of ITP and NTN [93, 94, 97, 101]. In the NTN model, mice were injected with a sheep hyperimmune serum specific for murine glomerular basement membranes (GBM). To enhance disease development, mice were pre-immunized with sheep serum, which resulted in an IgG2b-dominated antibody response [101]. After injection of the sheep anti-GBM serum, many animals died within 8–10 days due to severe inflammation and kidney failure. In the presence of an FcγRIV-blocking antibody, however, animals did not develop fatal glomerulonephritis. Despite C3 deposition in the kidneys, the observed pathology was fully dependent on activating FcRs as observed before [26, 28, 111–113]. This suggests that identification and blocking of the responsible activating FcRs in human autoimmune disease might be a promising therapeutic intervention.

Similar to IgG2b, IgG2a antibody activity was greatly impaired in mice with blocked FcγRIV activity in models of antibody-mediated clearance of platelets, B cells, or tumor cells, and neither deficiency in members of the complement cascade nor in FcγRI or III had a significant effect on antibody activity [94, 97, 100]. Depending on the model system, the amount of ICs and effector cell type, FcγRI and FcγRIII variably contributed to IgG2a activity [93, 114–116]. For example, in a model of autoimmune hemolytic anemia (AIHA) that—in contrast to the ITP model—requires higher antibody doses and several days for developing a maximal response, FcγRIII was significantly involved in mediating IgG2a activity [93]; in addition, the complement component C3 enhanced IgG2b and IgG3 activity [117]. Regarding the role of FcγRIII in this model, it was recently demonstrated that C5a, a strong inflammatory mediator, induces upregulation of FcγRIII, which is important for the development of AIHA [118, 119]. Further, generation of C5a occurred independently of the classical and alternative complement pathways and was triggered in an FcR-dependent fashion [118]. Moreover, it was suggested that Kupffer cells in the liver are the main effector cell type that mediates red blood cell phagocytosis, and it is not known if FcγRIV is expressed on these cells. Taken together, this demonstrates the influence of the effector cell type and the cytokine milieu on the cellular FcR expression pattern, which will be discussed in greater detail later.

In humans, low-affinity FcγRs bind better to IgG1 and IgG3 than to IgG2 or IgG4. However, certain FcγRIIA and IIIA alleles show increased binding to human antibody isotypes [10]. For instance, the FcγRIIA^{131H} allele binds IgG2 approximately tenfold better than FcγRIIA with arginine at that position (FcγRIIA^{131R}). Similarly, human FcγRIIIA^{158V} has a higher affinity for IgG1 and IgG3 than its 158F counterpart [10]. This selectively higher affinity of the activating FcR increases the A/I ratio and predicts that cytotoxic antibodies show a higher activity in such individuals. Indeed, cancer patients with the FcγRIIIA^{158V} allele responded better to antibody therapy [120–122]. In autoimmune patients, the FcγRIIIA^{158V} allele was linked to more severe arthritis in Caucasians [123, 124]. In the majority of studies, however, the low-affinity alleles have been identified as risk factors for the development or severity of autoimmune disease. Several studies have found an association of the low-affinity FcγRIIIA^{158F} and the FcγRIIA^{131R} alleles with the incidence and severity of lupus nephritis and arthritis [71, 125–137]. In addition, the low-affinity allele of human FcγRIIIB (FcγRIIIB-NA2) has been associated with SLE [71, 138, 139]. Alternatively, a low-copy-number polymorphism of this gene was associated with glomerulonephritis in humans and rats [140]. The results of these various studies suggested a model in which FcRs on macrophages or neutrophils might be involved in clearance of ICs containing potential autoantigens under non-inflammatory conditions, thereby preventing the initiation of autoimmune responses. Data from other model systems indicate that inefficient or delayed clearance of apoptotic cells can lead to the loss of tolerance and is associated with autoimmune diseases such as SLE [23, 141–143].

As described for FcγRIIB, a strong heterogeneity exists between different ethnicities and populations. For example, studies in African–American, Brazilian, German, and Thai populations have found significant associations between the FcγRIIA^{131R} allele and SLE disease susceptibility or severity of nephritis [71, 126, 128, 129, 131, 133, 136, 137, 144]. Moreover, several studies in Caucasian, Dutch, and Korean populations have found associations between the FcγRIIIA^{158F} allele and disease susceptibility and severity [127, 130, 134, 145]. In addition, some studies have found a connection between the FcγRIIIB-NA2 allele and SLE in Thai, Spanish, and Japanese populations [71, 138, 139]. In contrast, the FcγRIIA^{131R} allele was not increased in SLE or nephritis in African–Caribean, British, Dutch, Greek, Hispanic, Korean, and Spanish populations [127, 130, 134, 139, 145–149]. Similarly, studies in Chinese, German, and African–American populations have found no associations between the FcγRIIIA^{158F} and the FcγRIIIB-NA2 allele [71, 127, 131, 138, 144, 150, 151].

Exogenous factors modulating the balance—cytokines and sugar

Several studies have addressed the impact of cytokines on Fc-receptor expression. Frequently, cytokines regulate expression of the associated signaling adaptors (β- and γ-chains), which leads to a concomitant change in α-chain expression, as shown for transforming growth factor β (TGF-β), IL-4, and IL-10 [152, 153]. Moreover, inflammatory cytokines/mediators such as TNF-α, C5a, or LPS tend to upregulate activating receptors such as Fcα-, Fcε-, and Fcγ-receptors, whereas TH-2 cytokines such as TGF-β, IL-4, and IL-10 seem to decrease expression [33, 153, 154]. These effects can be cell-type specific as IL-4 upregulates the inhibitory FcγRIIB on myeloid cells but has the opposite effect on activated B cells [155].

The outcome of cytokine-mediated changes in activating and inhibitory expression might vary depending on the differential regulation of IgG isotypes by the inhibitory FcR. Thus, IgG2a and, to a lesser degree, IgG2b antibodies might be insensitive to elevated FcγRIIB expression relative to the severe impairment of IgG1 activity. During antibody-mediated inflammation, however, the steady state ratios change in favor of the activating FcRs, as the release of inflammatory mediators, such as IFN-γ and C5a, can upregulate activating Fcγ-receptors and at the same time reduces FcγRIIB expression levels [156, 157]. Under these circumstances, autoreactive IgG1 antibodies are capable of triggering severe damage. In fact, the regulation of FcR expression by cytokines is coupled to the regulation of isotypes by these same cytokines: TH-1 cytokines such as IFN-γ induce class switching to IgG2a, TH-2-type cytokines (IL-4) induce class switching to IgG1, and TGF-β induces switching to IgG2b [158, 159]. As these cytokines also influence Fc-receptor expression, the pathogenicity of an autoimmune response will be determined by both cytokine-mediated regulation of class switching and the changes in expression levels of the responsible activating versus inhibitory FcRs. This dual regulation might allow the development of new therapeutic strategies to treat autoimmune disease.

Another factor that can influence the interaction of antibodies with cellular FcRs is the sugar moiety attached to the asparagine residue at position 297 in the antibody Fc-fragment. Deletion of this sugar side-chain results in loss of FcR binding [160]. In addition, this core sugar structure contains variable amounts of branching and terminal sugar residues such as *N*-acetylglucosamine, fucose, galactose, and sialic acid. Presence or absence of these terminal or branching sugar residues can significantly influence antibody–FcR interactions. Thus, antibodies without fucose bind approximately tenfold stronger to mouse-activating FcγRIV and human FcγRIIIA [161–163]. In contrast, high levels of terminal sialic acid residues impair antibody binding to FcRs [36], and there is evidence that antibody sialylation levels differ during an immune response. Antibodies from human arthritis patients and autoimmune mouse strains such as MRL/lpr have reduced amounts of terminal sialic acid and galactose and were found to be more pathogenic [164–167]. Similarly, murine serum IgG antibodies have reduced amounts of sialic acid after induction of nephrotoxic nephritis [36]. Taken together, these studies indicate that antibody sialylation represents another mechanism-regulating antibody activity, and manipulating antibody sialylation levels in vivo might be a promising strategy to decrease autoantibody-associated pathogenicity.

Regaining the balance—therapeutic interventions that modulate FcR expression

The most important question is how this information might be used to develop strategies that restore a balanced immune response and stop autoimmune processes. Regarding the lower expression level or functional impairment of the inhibitory receptor on B cells in SLE, one approach would be to restore FcγRIIB expression by gene transfer. This approach was recently tested in autoimmune prone mouse strains like NZM, BXSB, and FcγRIIB-knockout mice [168]. These animals had strongly reduced levels of autoantibodies and did not develop glomerulonephritis. Highlighting the threshold nature of autoimmunity, restoration of FcγRIIB expression on approximately 40% of peripheral B cells was sufficient to prevent the development of autoantibodies and autoimmune disease [22, 168].

Instead of gene transfer, one could manipulate the expression level of activating and inhibitory receptors with anti-inflammatory drugs. The successful use of high-dose intravenous gamma globulin (IVIG) for the treatment of several autoimmune diseases provides an excellent example of the validity of this approach.

Currently, IVIG is used to alleviate autoimmune symptoms in SLE, Kawaski disease, and MS [169]. IVIG consists of the pooled serum IgG fraction of thousands of human donors and has to be given at high doses to obtain its beneficial anti-inflammatory activity. Immunotherapeutic studies in mice and humans have shown that the Fc portion of IVIG antibodies is responsible for its activity [101, 106, 170, 171]. Although several mechanisms of IVIG action have been proposed [169], mounting evidence suggests that the inhibitory FcγRIIB is essential for the anti-inflammatory activity of IVIG. In mouse models of ITP, rheumatoid arthritis, and nephrotoxic nephritis, IVIG administration blocked autoantibody-mediated inflammation; this protective effect was abolished in mice deficient in the inhibitory FcγRIIB [101, 106, 171]. More importantly, IVIG upregulated FcγRIIB expression on effector macrophages, resulting in a heightened threshold for cell activation. In addition, IVIG induced a significant reduction of the triggering activating FcγRIV in the NTN model, thus strongly modulating the balance of activating and inhibitory receptors [101]. As FcγRIIB upregulation was absent in mice lacking CSF-1-dependent macrophages, a two-cell model was suggested in which IVIG binds to CSF-1-dependent macrophages, resulting in upregulation of FcγRIIB on effector macrophages (Fig. 2) [106].

A longstanding question was why such high doses of IVIG were required to achieve its therapeutic effects. One possibility was that the actual active component is only a minor fraction of the total IVIG preparation. Indeed, each of the four IgG isotypes in the IVIG preparation contains

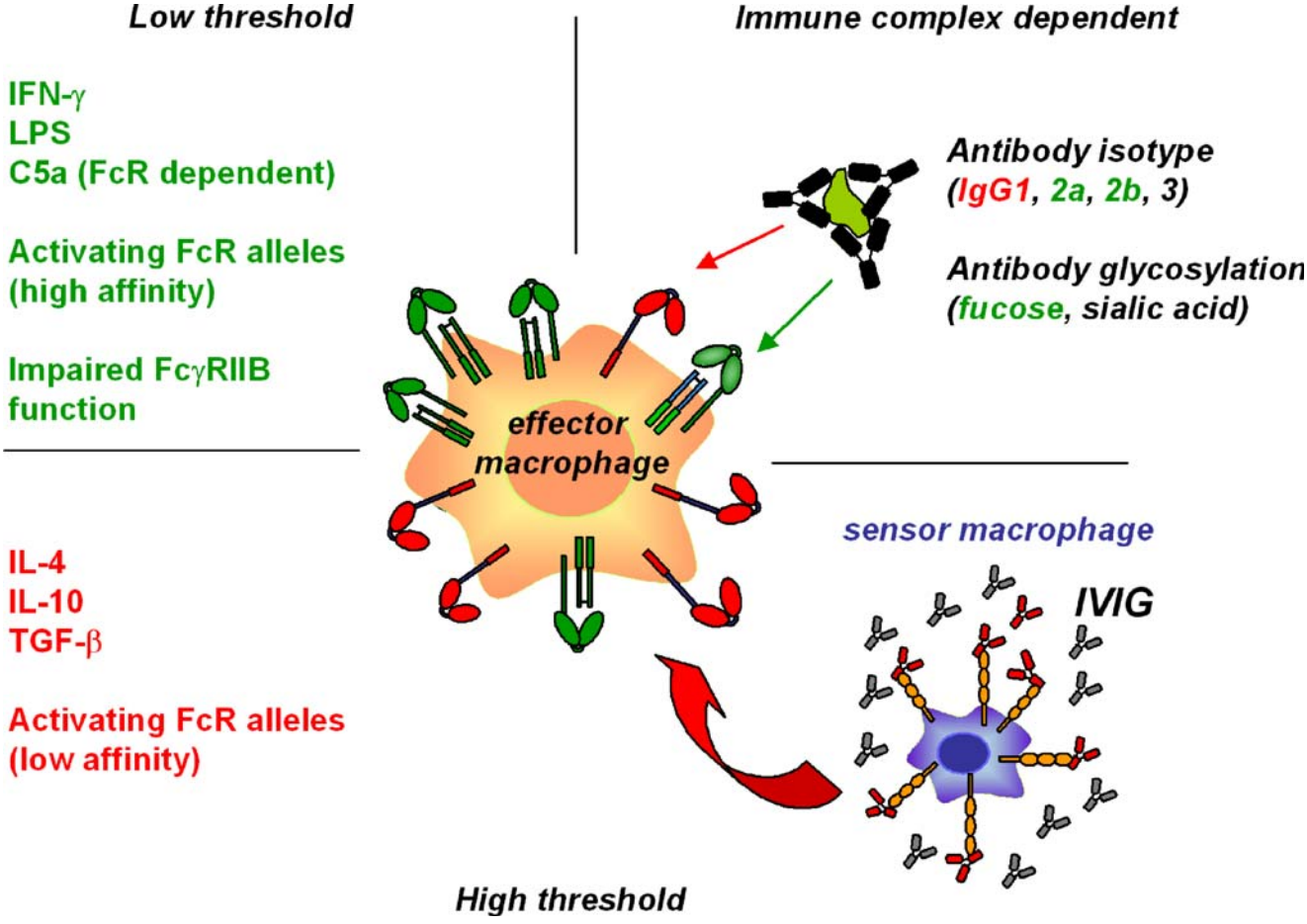

Fig. 2 Factors that influence FcR-dependent effector cell activation. Factors that shift the balance towards cell activation or inhibition are shown in *green* or *red*, respectively. Inflammatory cytokines/mediators such as IFN-γ, LPS or C5a upregulate activating FcRs (shown in *green*) resulting in a lower threshold for cell activation. In addition, allelic variants of activating and inhibitory receptors that influence antibody binding or FcR function might have similar effects. A higher threshold for cell activation is induced by anti-inflammatory cytokines or therapeutics such as IVIG that upregulate the inhibitory FcγRIIB (shown in *red*). In addition, activating FcR alleles with low affinity for antibody isotypes will trigger activating signaling pathways less efficiently. Moreover, the composition of ICs with respect to antibody isotype and antibody glycosylation pattern determines if activating or inhibitory signals will dominate

differentially glycosylated sugar moieties attached to the Fc region resulting in considerable heterogeneity. Recently, it was shown that the sialic-acid-rich IgG fraction in the IVIG preparation might be the active component. By using the sialic-acid-rich IVIG Fc portion, the therapeutic dose of IVIG could be reduced by a factor of 10 [36]. Other proteins like fetuin or transferrin that contain similar sialic-acid-rich sugar side chains did not recapitulate the anti-inflammatory activity, indicating that the amino acid backbone of the antibody Fc portion was required, too. Together with the previous observations, this suggests a model in which sialic-acid-rich IVIG binds to a receptor on CSF-1-dependent macrophages that indirectly induces the modulation of activating and inhibitory FcRs on effector macrophages (Fig. 2). As sialic-acid-rich antibodies bind FcRs with reduced affinity, the cell surface receptor responsible for this anti-inflammatory effect is most likely not a conventional FcR [36]. Thus, the identification and selective triggering of this putative IVIG receptor might enhance the anti-inflammatory activity of IVIG.

In addition, TH-2 cytokines such as IL-4 that induce FcγRIIB upregulation and downregulate activating FcRs might have therapeutic value. Along these lines, adoptive transfer of DCs engineered to produce high levels of IL-4 blocked active arthritis in mice [172, 173]. Besides modifying FcR expression levels, this would also skew the antibody response to IgG1 rather than IgG2a and IgG2b, resulting in a more strict regulation by the inhibitory receptor. Moreover, IL-4 inhibits the TH-1 cytokines, IL-2 and IFN-γ, suppressing inflammatory macrophage activation.

Whereas these previous approaches predominantly interfere with the effector phase of an autoimmune response, an alternative strategy would target DCs and thus block the initiation phase. Elegant work by the groups of Steinman and Nussenzweig [78] suggests that targeting antigens to immature DCs in vivo results in the induction of tolerance. Antigen targeting is achieved by genetic fusion to a DEC-205 specific antibody that selectively recognizes DCs. To prevent activation of DCs by crosslinking activating FcRs, this antibody contains a mutation that abrogates FcR binding. With the current development of antibodies with preferential binding to activating or inhibitory FcRs, one could generate a DEC-205 antibody that specifically engages FcγRIIB to deliver a strong tolerogenic signal and block the priming of autoreactive cells.

Conclusions

Research over the recent years has provided important insights into the regulation of cell activation by cellular FcRs. Disturbing the threshold set by coexpression of activating and inhibitory FcRs results in an uncontrolled immune response ultimately leading to the loss of tolerance and the initiation of autoimmune pathology. The inhibitory FcγRIIB represents a distal checkpoint during B cell development and regulates the expansion of autoreactive memory or plasma cells in mice and humans. In addition, it controls the activation of innate immune effector cells including neutrophils, mast cells, and macrophages. Restoring FcγRIIB expression might be a promising strategy to interfere with self-destructive processes both in the initiation and effector phase of an autoimmune response. Despite disparate results between different human populations, the analysis of autoimmune patients has demonstrated that low-affinity allelic variants of activating FcRs are frequently associated with the severity or incidence of autoimmune diseases, suggesting that impaired removal of ICs by FcRs contributes to disease development. Finally, the antibody–FcR interaction is significantly influenced by the antibody glycosylation pattern. Autoimmune patients and mice with active autoimmune disease have antibodies with a lower level of terminal galactose and sialic acid, which enhances the interaction with cellular FcRs. Thus, influencing antibody glycosylation might be another strategy to interfere with autoimmune pathology.

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