Archivum Immunologiae et Therapiae Experimentalis, 2003, **51**, 399–406
PL ISSN 0004-069X

Review

New Insights into the Pathophysiology and *in Vivo* Function of IgG Fc Receptors through Gene Deletion Studies

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Abstract. Fc-receptors for IgG (FcγRs) are critically involved at multiple stages of an immune response, ranging from antigen presentation and regulation of antibody production to the end-stage effector mechanisms of inflammation. IgG autoantibodies that are detectable in the majority of autoimmune diseases are ligands for FcγRs. The three classes, FcγRI, FcγRII, and FcγRIII, vary in their antibody affinity, cellular expression and *in vivo* function. We review the current knowledge on the regulation and diverse functions of the distinct FcγRs and describe the evidence of their important immunoregulatory roles in autoimmunity based on recent work in animal models.

Key words: IgG Fc receptors; gene deletion; autoimmunity.

Introduction

Autoimmunity is considered to evolve from an erroneous action of the immune system directed against various self tissue sites. An increasing number of diseases has been classified as of autoimmune origin and mediated either by T lymphocytes and/or by antibodies. Autoantibody-mediated cellular destruction has been shown to be the causative agent in the development of cytopenias such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP). Another example of a well-understood role of autoantibodies in autoimmunity is the interference with certain receptor structures. In Graves's disease, pathogenic self-reactive antibodies directed against the thyroid-stimulating-hormone (TSH) receptor hyperactivate this receptor, while in myasthenia gravis autoantibodies functionally block the acetylcholine receptor on the neuro-muscular synapse resulting in severe muscular weakness. In the majority of autoimmune diseases, however, the specific role of antibodies remains less clear. Autoantibodies against islet cells of the pancreas appear less important than specific T cells against the same epitopes for the induction of autoimmune diabetes mellitus. Other immune complex (IC)-related disorders are considered autoimmune due to the presence of autoantibodies, while the relevant autoantigen remains unknown, as in rheumatoid arthritis (RA) and systemic lupus erythematodes (SLE). Cross-reactivity between target and self antigens has been proposed to explain the inflammation directed against synovial tissues in RA, renal tissue or clotting factors as in SLE.

During the last years, with the advent of mice genetically ablated in their Fc receptors for IgG (FcγRs) and

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other integral components of the inflammatory cascade (such as complement), and with their use in various experimental disease models, our insight into the critical end-stage effector mechanisms that trigger antibody-induced autoimmune disease pathology could be greatly extended. Starting from the initial knowledge that FcγRs mediate cellular effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis, FcγRs are now considered in a much broader sense as crucial immune regulators linked to the initiation of autoimmune diseases. This view ranges from the maintainance of central and peripheral tolerance to the regulation of antibody clearance and antigen presentation.

FcγRs as a Regulative System

Expressed on the cell surface of many immune effector cells, FcγRs are located both topografically and functionally at the interface of the humoral and cellular immune system. Three distinct classes of FcγRs differing in molecular size, cellular distribution, function and affinity to IgG isotypes are found on leukocytes in both mice and humans: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). FcγRs have been extensively characterized as to their genes, structure, binding pattern, and function[23].

In brief, all FcγRs are members of the immunoglobulin superfamily of proteins and are encoded by a total of 8 genes in humans, 3 for the high-affinity FcγRI (FcγRIA, FcγRIB, and FcγRIC) and 5 for the low-affinity FcγRs, FcγRII (FcγRIIA, FcγRIIB, and FcγRIIC) and FcγRIII (FcγRIIIA and FcγRIIIB), while single genes encode the three main types of murine FcγRs. In mice, FcγRI and FcγRIII are activation receptors that form multimeric complexes together with their signal transduction subunit (the common FcRγ-chain), characterized by the presence of a cytoplasmic immunoreceptor tyrosine-based activatory motif (ITAM). FcγRI (FcγRIA in humans) is constitutively expressed on macrophages and dendritic cells and can be further induced on mesangial cells in response to stimulation by several cytokines. The activation-triggered induction of FcγRI on neutrophils and eosinophils by interferon (IFN)-γ, interleukin (IL)-10 and G-CSF in humans, however, is not observed in mice. FcγRI binds monomeric as well as complexed IgG with a specificity for murine IgG2a and IgG2b, but not IgG1 isotypes (human FcγRIA mainly interacts with human IgG1 and IgG3). High affinity is a unique property for FcγRI, dependent on a third extracellular Ig-like domain not present in FcγRII and FcγRIII receptors. FcγRIII (the murine homologue of human FcγRIIIA) binds IgG in the form of ICs (IgG1, IgG2a and IgG2b, but not IgG3). FcγRIII is thus the principal activatory IgG1 receptor in mice[26]. The other low-affinity FcγRII (the murine homologue of human FcγRIIB), from which two distinct isoforms, b1 and b2, are generated by alternative mRNA splicing, shares with FcγRIII a similar affinity and specificity in the interaction with IgG ICs. In contrast to FcγRIII, however, FcγRIIb1 and FcγRIIb2 are monomeric receptors that contain an immunoreceptor tyrosine-based inhibitory motif (ITIM) responsible for mediating inhibitory rather than activatory functions. In addition, FcγRIIb2, which has a 47-amino-acid deletion in its cytoplasmatic domain, mediates endocytosis and facilitates the clearance of ICs, while FcγRIIb1 lacks endocytosis. FcγRIIb2 and FcγRIII are co-expressed on myeloid cells, including neutrophils, mast cells and macrophages. Among lymphocytes, the b1 isoform of FcγRII is present on B cells, while natural killer cells express FcγRIII. On myeloid cells, FcγRIIb2 receptors are normally expressed at a 1.5- to 2-fold higher level than FcγRIII. This implies that for efficient cellular activation through aggregation of activating FcγRs, a change in the ratio of expression of activating/inhibitory FcγRs is required. Recent data suggest that agonists such as lipopolysacharide and IFN-γ can cause this kind of inverse regulation[38]. In IC-triggered activation, C5a anaphylatoxin acts physiologically as the major regulator of activating versus inhibitory FcγRs and this linkage between complement activation and FcγR regulation has recently been proposed to determine the initiation of inflammation in autoimmune disease[7].

Many aspects of the regulation of distinct cell signaling by FcγRs have been elucidated during the last years, demonstrating that FcγRs form a tightly regulated system of activation and inhibition which itself is part of a broader system that regulates the immune system. Aggregation of the FcRγ chain-containing FcγRs, FcγRI and FcγRIII, by IgG ICs triggers the ITAM-dependent cell activation that is initiated by SRC-family protein kinase-mediated phosphorylation of tyrosine residues in the FcRγ-ITAM motif. This is then followed by the recruitment of Syk kinase, which interacts with the phosphorylated ITAM via its SRC-homology 2 (SH2) domain. Downstream effects of Syk activation include the activation of phospholipase Cγ and PI-3 kinase, which are involved in Ca^{2+} mobilization, stimulation of mitogen-activated protein kinase (MAPK), and reorganization of the cytoskeleton. As a result of FcRγ-activation signaling, mast cells and macrophages subsequently release various cytokines, degranulate,

and mediate phagocytosis. The FcRγ-mediated effector functions are controlled by the inhibitory signaling of the co-expressed ITIM-containing FcγRIIb2 *in vitro* and *in vivo*[9]. In addition, the B cell-specific FcγRIIb1 isoform also serves as a negative regulator of B cell function, and this might counteract the development of autoimmune diseases. The simultaneous aggregation of the B cell receptor (BCR) with FcγRIIb1 inhibits BCR activation and the downstream response of the B cell, including antigen presentation, proliferation and antibody production. Hereby, the inhibitory FcγRIIb1 signaling is initiated by the phosphorylation of the ITIM tyrosine, leading to the recruitment of several SH2-domain phosphatases, of which the inositol polyphosphate 5' phosphatase (SHIP) is one of the primary effectors of FcγRIIb1 inhibition. Importantly, FcγRIIb1 not only inhibits BCR-induced signaling but also delivers an apoptotic signal independent of BCR activation. These findings might suggest that FcγRIIb1 can contribute to the negative selection of B cells that express low-affinity BCRs as discussed recently[2, 45].

In vivo Function of FcγRs

FcγRs are involved at multiple stages of an immune response, beginning with antigen presentation to regulation of antibody production, and, finally, the effector mechanisms of inflammation.

Antigen recognition and presentation

Activating FcγRs mediate the enhanced internalization of complexed antigens by presenting cells (APCs). This FcγR-dependent process is of primary importance in the regulation of antibody production. The critical contribution of the FcRγ chain has been shown in triggering DC maturation, antigen presentation by the MHC class I[40], and the selection of epitopes presented by the MHC class II[1]. FcRγ-deficient mice have an abrogated antibody response in the BSA-TNP immunization model. Since B cells do not contain the FcRγ chain nor do they express activating FcγRI or FcγRIII, this *in vivo* effect is likely to be attributable to APC-T cell interaction[51]. However, whether the regulation of antigen selection and presentation is crucially involved in the development of autoimmune disease awaits further investigation.

Antibody production

As outlined before, the antibody synthesis of B cells is regulated by the FcγRIIb1 inhibition of BCR activation. Apoptotic signals of FcγRIIb1 may further contribute to the preservation of peripheral tolerance with elimination of self reactive B cells during maturation. A first indication that B cell regulation by FcγRIIb1 can be relevant for the induction of autoimmunity was given in a model of autoimmune glomerulonephritis (GN). Previously healthy mouse strains were rendered susceptible to the development of spontaneous GN by transfer of FcγRII-deficient B cells[8]. Since in this model FcγRIIb2 is preserved on myeloid cells, the increased antibody production of FcγRIIb$^{-/-}$ mice in the BSA-TNP immunization model seems to depend on the lack of FcγRIIb1 regulation on B cells.

Regulation of inflammation

In the efferent part of the immune system, autoantibodies may exert their pathologic effects after binding either to cell surfaces or to soluble antigens, referred to as a type II and type III hypersensitivity reaction, respectively. The crucial role of FcγR in the initiation of these reactions was studied in various mouse models of disease.

Type II hypersensitivity. If bound to a given cell surface, autoantibodies may induce a cytotoxic immune response by activation of phagocytosis, ADCC, or activation of complement. In a passive model of AIHA, for example, the injection of IgG antibodies directed against red blood cell (RBC) epitopes resulted in FcγR--dependent erythrophagocytosis by spleen macrophages and liver Kupffer cells. The pathogenic effects of the autoantibodies in the immune clearance of RBCs varied between different IgG isotypes due to the involvement of FcγRIII in case of IgG1 versus FcγRI and FcγRIII in case of IgG2a[22, 34]. More variable findings were made in models of ITP, as deficiency in activating FcγRs prevented platelet destruction induced only by some, but not by the majority of anti-platelet antibodies[15, 36, 37]. For example, antibodies against a clinically relevant antigen, the $\alpha_{IIb}\beta_3$ integrin (GPIIbIIIa, fibrinogen receptor), induce thrombocytopenia in a FcγRI/III-independent manner, while the accompanying systemic inflammatory response and severe hemorrhage and bleeding remain regulated by activating FcγRs and the inhibitory FcγRII[37]. The ADCC effector function is shown to depend on FcγR regulation in various tumor disease models using specific anti-tumor antibodies. These antibodies are linked with enhanced pathogenic effects in FcγRII-deficient mice, but are inefficient in the absence of the FcRγ-chain[16, 17].

Type III hypersensitivity. The classical model of the IC-mediated inflammation is the Arthus reaction, which

was originally described by Maurice Arthus precisely one century ago. He reported an inflammatory response characterized by perivascular edema, infiltration of neutrophils and tissue damage that followed repeated injections of heterologous serum in the skin. Today, the most commonly used experimental model is termed the "passive reverse Arthus reaction", owing its name to the use of preformed IgG antibodies. In a desired tissue antibodies given locally meet the related antigen given systemically. In this passive immunization model, the role of FcγRs for mediating the efferent function of the immune response was extensively studied using FcγR--deficient mice. The IC inflammation was abrogated in FcRγ-deficient mice[43], largely depending on the function of FcγRIII[25], and augmented in FcγRII mutant mice[41, 46]. Reconstitution of mast cell-deficient $kit^{W}/kit^{W\text{-}v}$ mice with FcγRIII-negative mast cells demonstrated the critical role of FcγRIII-dependent mast cell activation in the cutaneous Arthus reaction, as well as in immune vasculitis[5, 44, 50]. Due to the accessability of cellular and soluble components of the inflammatory response, the Arthus reaction was also extensively studied at other tissue sites, including lung and peritoneum[31]. In the lung model of hypersensitivity pneumonitis, the FcγRIII on alveolar macrophages but not mast cells is responsible for neutrophil recruitment in the alveolar space via the induced secretion of TNF-α and IL-1ß, as well as of CXC chemokines macrophage inflammatory protein 2 (MIP-2) and cytokine-induced neutrophil chemoattractant (KC, the murine homologue to human IL-8), which is further enhanced in mice lacking the inhibitory FcγRII[12, 14, 42].

Defective FcγR-mediated clearance of ICs and correlation to certain FcγR polymorphism has been described in patients suffering from SLE and severe GN. NZB/NZW F1 mice spontaneously develop IC-GN resembling nephritis in SLE. Although FcRγ-deficient NZB/NZW F1 mounted comparable levels of anti-DNA antibodies as NZB/NZW F1 $\gamma^{+/+}$ mice, and although IC and C3 were deposited similarly in the glomeruli, NZB/NZW F1 $\gamma^{-/-}$ mice showed only minimal pathology and normal life expectancy[13]. In a passive model of glomerular injury, both FcRγ and FcγRIII mutant mice display a strongly abrogated recruitment of neutrophil effector cells, indicating an essential contribution of the renal FcγRIII. FcγRIII-mediated production of MCP-1 and MIP-2 chemokines and cellular infiltration depends on the downregulation of the constitutively expressed FcγRIIb2 on glomerular mesangial cells[38]. Lack of FcγRIIb2 can exacerbate the kidney injury, as is also seen in a model of collagen--induced Goodpasture's syndrome[35].

FcγR and Complement

Complement is an important contributor to actions of the innate immune system and is involved in autoimmune diseases in various ways. ICs can activate the classical pathway of complement activation, which leads to inflammatory responses comparable to inflammation induced by IC-FcγR interaction. IC-triggered complement cleavage can enhance phagocytosis via C3b interaction with various complement receptors. Moreover, C3b at the surface of RBCs acts as an important transport mechanism for clearing ICs from the intravascular space.

The combined involvement of both, complement components and FcγRs, was investigated recently in several models of autoimmune disease in mice. Participation of complement in the type II hypersensitivity model of AIHA appeared minimal in earlier studies (summarized in reference[27]), but this may have been due to the selection of the antibody. Investigation of a panel of isotype class-switch variants of anti-RBC antibodies revealed that involvement of complement depends on the IgG isotype, in particular IgG3 antibodies. Moreover, the high pathogenic activity of IgG2b antibodies appeared to rely on the synergistic action of complement and FcγRs, as demonstrated in C3/FcRγ-double mutant mice[3]. Similarly, antibody-induced hypopigmentation in another type II hypersensitivity model of autoimmune vitiligo was dependent on the action of either C3 or FcRγ, with abrogation of disease pathology present only in $FcR\gamma^{-/-}$ $C3^{-/-}$ chimeric mutants[47].

Genetic deletion of the complement receptor for the anaphylatoxin C5a (C5aR) leads to a marked attenuation in the Arthus reaction in various tissues[10], which was consistent with earlier experiments with complement depletion by cobra venom factor. In cutaneous and pulmonary IC inflammation, C5aR deficiency offered the same level of protection as FcγRIII deficiency. Since either FcγR or complement could trigger only a minor response if the other pathway was dysfunctional, both pathways appeared to act synergistically[6]. Recently, a mechanism of how C5aR and FcγRIII interact in IC inflammation can operate in synergy was clarified. Apart from its action as a chemoattractant for neutrophils, C5a-C5aR interaction on alveolar macrophages augments the expression of FcγRIII and downregulates the expression of FcγRII thus shifting the balance towards activation through FcγRIII[42]. Consistent with this finding, FcγRIII and C5aR were found to be equally indispensable for dis-

ease pathology in a model of autoimmune arthritis based on the formation of anti-GPI antibodies in transgenic K/BxN T cell receptor mice[28].

FcγR Polymorphisms

In addition to animal models of disease, cross-sectional analysis of FcγR polymorphisms in disease populations offers an intriguing tool for linking gene, FcγR function and disease pathophysiology in humans. A number of studies have been performed in various countries, in particular in SLE patients, presenting a large variety of potential links. The main persistent finding that was made across different racial backgrounds, is related to the R/H131 polymorphism of the FcγRIIa isoform, which is not expressed in mice[30]. The RR phenotype, which poses a risk for SLE development, seems to have a weaker affinity to IgG2 subclass molecules[20]. With FcγRIIa mediating endocytosis, an impaired clearance of IC may contribute to the overload of IC observed in SLE patients. An impaired FcγR-dependent IC clearance of the liver has been recently demonstrated[18]. In contrast to the functional defects of activating FcγRs that are commonly considered to lead to an impaired IC clearance, mutations of FcγRIIb may lead to an uncontrolled upregulation of antibody production by B cells. Mouse strains prone to autoimmune responses were shown to have distinct patterns of polymorphisms in their FcγRIIb gene together with a downregulation of FcγRIIb upon antigen stimulation of B cells[29]. Recently, the association of a single nucleotide polymorphism of the FcγRIIb gene with SLE was found in a Japanese population of SLE patients[32].

Also other FcγR-related mutations and polymorphisms have been implicated in the pathogenesis of SLE, but none of them could be consistently found in all disease populations investigated[21, 24, 33]. The fact that these polymorphisms were not uniformely detected in all disease populations does not necessarily exclude their contribution to the development of SLE. Other genes and gene products may interfere with the role of FcγR-mediated IC clearance, such as deficiencies of several complement components of the early part of the activation pathway. Several complement component deficiencies were shown to be associated with SLE, likely due to an impaired IC clearance by C3b[49].

A skewed distribution of FcγR polymorphisms was also found in other autoimmune diseases, suggesting an involvement of FcγRs in their pathogenesis. As in SLE, a reduced IC clearance associated with homozygosity for the FcγRIIa R131 (RR) allotype seems to pose a risk for heparin-induced or idiopathic thrombocytopenia[11, 52]. Interestingly, the RR genotype of the FcγRIIa gene was shown to be a risk factor for severity and propensity to relapse in patients with Wegner's granulomatosis if it was combined with homozygosity of the F158 allele of the FcγRIIIa gene[19]. The impaired clearance hypothesis does not appear to apply to all autoimmune diseases. The HH allotype of FcγRIIa, which is related to a higher binding affinity, was associated with increased disease susceptibility and severity in myasthenia gravis and Guillain-Barre syndrome[39, 48]. Enhanced binding of cross-linked autoantibodies to FcγRs may contribute to autoimmune disease with an augmented proinflammatory response in these diseases.

Concluding Remarks

New insights into the function of FcγRs have broadened the view of how FcγRs can be involved in the pathophysiology of autoimmune diseases. This includes not only the efferent part of the immune system, from antibody-dependent cytotoxicity to the clearance of antibodies, but also includes a role in the afferent functions, such as antigen presentation and antibody production. However, a detailed knowledge of the functions of FcγRs as demonstrated in animal models frequently lacking certain FcγRs does not easily translate to a role in human autoimmune diseases. Studies on FcγR gene polymorphisms have already provided some concepts as to the contribution of activating FcγRIIa isoforms to autoimmune diseases by an impaired IC clearance. Yet much remains to be elucidated in the *in vivo* functions of FcγR polymorphisms in humans. Moreover, the interplay with other parts of the immune system, as the complement system, together with the varying associations of FcγR polymorphisms in genetic population studies suggests that autoimmune diseases have a multigenic etiology. Again, the knowledge of FcγR functions will help to dissect the potentially contributing gene loci.

What conclusions can be drawn from the knowledge of FcγR functions for the therapy of autoimmune diseases? Modifying the function of FcγRs *in vivo* may be beneficial in the course of the disease, with FcγRs being part of the primary etiology of part of the effector function of the erroneous immune response. The efficacy of intravenous immunoglobulin (IVIG) in some autoimmune diseases appears, at least in part, to be based on the competition with autoantibodies in the binding to FcγRs, thus attenuating FcγR-mediated inflammation. Moreover, neutralization of C3a and C5a by IVIG may

prevent the enhanced expression of activating FcγR thus preventing the susceptibility to autoimmune antibodies[4]. Recent developments may lead to more specific interventions. Antibodies against the Fc part of immunoglobulins or against binding sites of activating FcγRs can attenuate the proinflammatory response induced by autoantibodies. Soluble FcγRs may bind to circulating IC. An intriguing approach would be to activate the inhibitory FcγRIIb, thus modulating the activation of phagocytic effector cells by autoantibodies.

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Received in July 2003
Accepted in August 2003