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Review

# Fc receptors and their interaction with complement in autoimmunity

Reinhold E. Schmidt, J. Engelbert Gessner*

*Abteilung für Klinische Immunologie, Medizinische Hochschule Hannover, Labor für Molekulare Immunologie, Carl-Neuberg-Str. 1, Hannover 30625, Germany*

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**Abstract**

Genetic studies in mice indicate a crucial role for Fc receptors (FcR) in antibody-mediated autoimmune diseases. Like other immune regulatory receptor pairs, the FcR system is constituted by activating and inhibitory receptors that bind the same ligand, the Fc portion of Ig. Analyses of animal models have shown that the inhibitory Fc receptor, FcγRIIB can suppress antibody-mediated autoimmunity, whereas activating-type FcR, such as FcγRIII promote disease development. This review summarizes recent advances of FcR, as obtained from gene deletion studies in mice, and highlights the importance of factors that interact with FcR in autoimmunity. There is emerging evidence for an indispensable role of the complement component C5a in the regulation of FcR and the sensing of FcR-dependent effector cell responses. On the other hand, FcR might be alternatives to serum complement in the generation of C5a at sites of inflammation. Thus, FcR and complement interact with each other at the level of C5a by linking regulatory events with effector cell activities in autoimmunity. This connecting pathway is now proposed to be a promising new therapeutic target for the treatment of inflammation and autoimmune disease in both mice and humans.


*Keywords:* Autoimmune disease; Complement; Fc receptors; Inflammation

**Contents**



* Corresponding author. Tel.: +49 511 532 3621; fax: +49 511 532 5648.
*E-mail address:* Gessner.Johannes@MH-Hannover.de (J.E. Gessner).

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## 1. Introduction

During the last years, with the advent of mice genetically ablated in cellular receptors for IgG Fc (FcγR) and with their use in various disease models, our insight on the mechanisms that trigger antibody-induced autoimmune pathologies has been greatly extended. Starting from the initial knowledge that FcγR can mediate cellular effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis, FcγR are now considered in a much broader sense as important immune regulators linked to autoimmunity. FcγR are constituted by activating and inhibitory receptors that bind the same Fc portion of IgG. In this review, we will provide an overview on FcγR-mediated regulation in autoimmunity and discuss novel interacting factors and pathways that are capable of tuning the FcγR regulatory system, thereby providing a basis for the regulation of the immune effector response in inflammation and autoimmune diseases.

## 2. IgG Fc receptors

Receptors for the Fc part of IgG (FcγR) provide a critical link between the humoral and cellular arms of the immune response. FcγR can trigger effector mechanisms such as ADCC, phagocytosis, release of toxic oxygen metabolites and inflammatory mediators, and facilitate antigen presentation. As has been extensively reviewed in the past, several of these responses may be unique for selected cell types based on differences in tissue-specific FcγR expression [1–4]. Diversity of FcγR-mediated functions is also related to genetically determined polymorphisms [5], the generation of soluble FcγR [6], and synergisms with other receptor systems [7].

Three classes of leukocyte FcγR are currently distinguished, FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) that differ in cell distribution, function and affinity for IgG isotypes. In mice, FcγRI and FcγRIII are both the activating receptors, forming multimeric complexes together with their signal transduction subunit, the FcRγ-chain, characterized by the presence of an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic tail [8,9]. FcγRI (FcγRIA in humans) is mainly expressed on monocytes and macrophages. Induction of FcγRI expression on neutrophils and eosinophils by IFNγ, IL-10 and G-CSF as seen in humans, however, is not observed in mice. FcγRI binds monomeric, as well as complexed IgG, with a specificity for IgG2a and IgG2b, but not IgG1 [10]. High affinity ($K_a = 10^8\ M^{-1}$) is a unique property for FcγRI, dependent on a third extracellular Ig-like domain not present in the FcγRII and FcγRIII receptors [11]. FcγRIII (the murine homolog of human FcγRIIIA) is a low-affinity receptor for complexed IgG1, IgG2a and IgG2b but not IgG3. Thus, FcγRIII is the principal activatory IgG1 receptor in mice [12]. The second low-affinity FcγR, 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 complexed IgG. In contrast to FcγRIII, however, FcγRIIb1 and FcγRIIb2 are monomeric receptors that contain an immunoreceptor tyrosine-based inhibition motif (ITIM) responsible for mediating inhibitory rather than activatory functions [13–15]. In addition, FcγRIIb2, which has a 47-amino acid deletion in its cytoplasmatic domain, mediates endocytosis and facilitates the clearance of IC, while FcγRIIb1 lacks endocytosis. FcγRIIb2 and FcγRIII are coexpressed on neutrophils, macrophages and mast cells. Among lymphocytes, the b1 isoform of FcγRIIB is present on B cells, while NK cells express FcγRIII. FcγRIIB does not trigger cellular activation to aggregated IgG, unless the ligand coengages FcγRIIB and ITAM containing activation receptors, such as the BCR on B cells, FcγRIII and FcεRI on mast cells, and FcγRI and/or FcγRIII on macrophages [16].

The balanced signaling through activating and inhibitory FcγR regulates the activity of various cells in the immune system. Many aspects of the initial events of distinct cell signaling by FcγR were elucidated during the last years, demonstrating that FcγR 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 FcγRIII (and FcγRI) by IgG triggers ITAM-dependent cell activation that is initiated by SRC-family protein kinase-mediated phosphorylation of tyrosine residues in the FcRγ-ITAM motif [9,17]. 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 phosphatidylinositol 3-kinase (PI-3K) and phospholipase Cγ (PLCγ), which are involved in $Ca^{2+}$ mobilization, stimulation of mitogen-activated protein kinase (MAPK), and reorganization of the cytoskeleton. This activation pathway can be inhibited by co-aggregation of FcγRIIB through phosphorylation of its ITIM motif by the SRC-family kinase Lyn that then results in the recruitment of SH2-domain-containing phosphatases, including SHP1, SHP2 and the inositol polyphosphate 5′ phosphatase (SHIP) [18–20]. SHIP is thought as the primary effector of FcγRIIB-inhibition in macrophages and mast cells. The main substrate of SHIP is phospatidylinositol-3,4,5-trisphosphate, which is formed by the action of PI3K. Thus, FcγRIIB inhibition of FcγRIII-mediated cell activation is likely to be mediated by a SHIP-dependent blockade in the generation of IP3 and DAG second messengers (Fig. 1).

The activating FcγRIII and the inhibitory FcγRIIB bind IgG IC with comparable affinity and specificity. These two opposing signaling pathways act in concert, thus determining the magnitude of effector cell responses in IC inflammation and autoimmune disease. In fact, in non-inflamed tissues, the ratio of activating to inhibitory FcγR is low, while it is highly increased in an inflamed environment [21]. Several factors have been shown to modulate this ratio in vitro: IFNγ increases it through upregulation of activating FcγRIII (and FcγRI) and downregulation of the unique inhibitory