

Fc receptors: Cell activators of antibody functions

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ABSTRACT

At the onset of an infection early defense systems, such as complement, get into action. Specialized leukocytes (white blood cells) of the innate immune system, including monocytes, macrophages, and neutrophils also participate as a first line of defense against infections. These early responses are rapid but not very specific and are usually not enough to clear completely many infections. The adaptive immune system is also needed to finish the job against many microorganisms. Antibody molecules, produced during the adaptive immune response, are crucial for preventing recurrent infections. Although, IgG antibodies are essential for controlling infections, these molecules do not directly damage the microorganisms they recognize. Today, it is established that leukocytes of the innate immune system are responsible for the protective effects of these antibodies. IgG molecules bind to their cognate antigens and are in turn recognized by specific receptors (Fc γ receptors) on the membrane of leukocytes. Crosslinking these receptors on the surface of leukocytes leads to activation of several effector cell functions. These effector functions are geared toward the destruction of microbial pathogens and the induction of an inflammatory state that is beneficial during infections. However, in autoimmune diseases, antibodies can direct these effector functions against normal tissues and cause severe tissue damage. In recent years, several factors that can modulate the IgG-Fc γ R interaction have been elucidated. In this review, we describe the main types of Fc γ receptors, and our current view of how antibody variants interact with these receptors to initiate different cell responses. In addition, new findings on the signaling role of individual Fc γ receptors are also discussed.

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1. INTRODUCTION

At the onset of an infection by different types of microorganisms, including viruses, bacteria, fungi, and protozoa, early defense systems, such as constitutive expression of antimicrobial peptides, and activation of complement get into action. These systems are rapid but not particularly specific. Specialized leukocytes (white blood cells) of the innate immune system, including monocytes, macrophages, and neutrophils also participate as a first line of defense against infections. These leukocytes can bind some microbial molecules, termed danger- and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively) via numerous receptors such as the Toll-like receptor family [1,2]. In this way, leukocytes recognize microorganisms directly and prevent a massive infection [3]. These early responses however, are usually not enough to clear completely many infections. The adaptive immune system is also needed to finish the job against many microorganisms. Antibody molecules, produced during the adaptive immune response, are crucial for preventing recurrent infections [4]. At the beginning of the adaptive response, antibodies belong to the IgM class. These antibodies present low affinity for microbial antigens, but they can easily activate the classical complement pathway. Complement deposited on microorganisms can induce phagocytosis via complement receptors [5,6], or it can induce bacterial lysis via the formation of the membrane attack complex [7]. At later times of the adaptive response, antibodies belong mainly to the IgG class. These antibodies are of higher affinity and of much greater specificity for their particular antigen. Thus, IgG antibodies are key for controlling many microorganisms, as demonstrated by immunodeficiency disorders,

with low production of this class of antibodies, in which there is increased susceptibility to microbial infections [4]. Although, IgG antibodies are essential for controlling infections, these molecules do not directly damage the microorganisms they recognize. Today, it is established that leukocytes of the innate immune system are responsible for the protective effects of these antibodies. IgG molecules bind to their cognate antigens via their two fragment antigen-binding (Fab) sites, and are in turn recognized by specific receptors on the membrane of leukocytes. These receptors bind the Fc (fragment crystallizable) domain of IgG; thus, they are named Fc γ receptors (Fc γ R) [8,9]. In this way, IgG antibodies are the bridge between the two arms of the immune system, bringing together the specificity of recognition of the adaptive immune system and the destructive potential of the cells of the innate immune system. Crosslinking these receptors on the surface of leukocytes leads to activation of several effector cell functions. Depending on the cell type, and also on the Fc γ receptor type, these functions include phagocytosis, cell degranulation, production of various cytokines and chemokines, antibody-dependent cell-mediated cytotoxicity (ADCC), and activation of genes [10]. These effector functions are geared toward the destruction of microbial pathogens and the induction of an inflammatory state that is beneficial during infections. However, in autoimmune diseases, antibodies can direct these effector functions against normal tissues and cause severe tissue damage [11,12]. It is then of great interest to understand how various Fc γ R are activated to induce these cellular functions. In recent years, several factors that can modulate the IgG-Fc γ R interaction have been described. These factors include, the particular IgG subclass [13] and the glycosylation pattern of the antibody [14]. In addition, other molecules, such as members of the pentraxin family can bind Fc γ R [15,16], and certain glycosylation variants of antibodies can bind other cell membrane receptors different from Fc γ R [17-19]. In this review, we describe the main types of Fc γ receptors, and our current view of how antibody variants interact with these receptors to initiate different cell responses. In addition, new findings on the signaling role of individual Fc γ receptors are also discussed.

2. Fc γ RECEPTORS

2.1. Structure

Antibodies represent an important bridge between the specificity of the adaptive immune system, and the highly destructive mechanisms of cells of the innate immune system. Antibodies bind to microorganisms via their antigen-binding sites, and to Fc receptors on the surface of leukocytes, via their carboxyl terminal Fc portion. Receptors for the Fc portion of various immunoglobulin (Ig)

classes have been described [20]. Fc Receptors for IgG (Fc γ R), for IgE (Fc ϵ R), and for IgA (Fc α R) are known [20]. Crosslinking of Fc γ receptors with their IgG antibody ligands triggers various functions in many cells of the immune system. These cell functions include phagocytosis, cell degranulation, production of various cytokines and chemokines, ADCC, and activation of genes [10,21].

Fc γ receptors are a family of glycoproteins, part of the IgG superfamily. They consist of an IgG binding α -subunit, that usually pairs with accessory γ chains, which are important for receptor signaling (**Figure 1**).

In humans, three classes of Fc γ R have been identified, Fc γ RI (CD64), Fc γ RII (CD32), and Fc γ RIII (CD16) (**Figure 1A**) [22]. Fc γ R are coded for by different genes and differ in their relative avidity for IgG, molecular structure, and cellular distribution. Fc γ RI α -subunit presents three Ig-like extracellular domains, and binds monomeric IgG [23]. In contrast, Fc γ RII and Fc γ RIII present two Ig-like extracellular domains, and bind only multimeric immune complexes. Fc γ RI, expressed on monocytes, macrophages, and interferon- γ (IFN- γ)-stimulated neu-

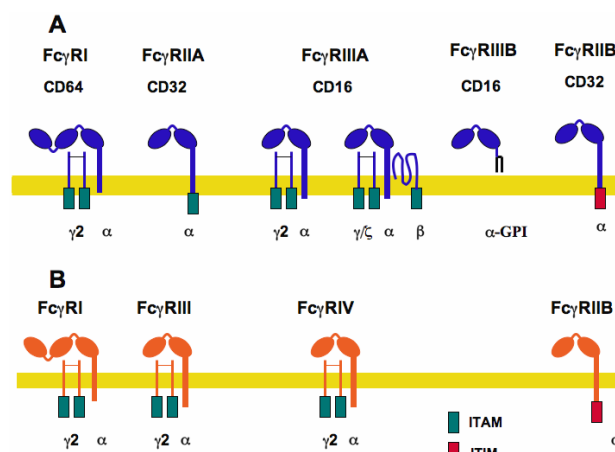


Figure 1. Fc γ Receptor family. (A) The human family of receptors for the Fc portion of immunoglobulin G (IgG) molecules comprises three members Fc γ RI, Fc γ RII, and Fc γ RIII. The IgG binding α -subunit in the high affinity Fc γ RI, possesses three immunoglobulin (Ig)-like extracellular domains. The α -subunit in the other low-affinity receptors presents only two Ig-like domains. Activating receptors contain an ITAM (immunoreceptor tyrosine-based activation motif) sequence within the α subunit (for Fc γ RIIA) or within the accessory γ and ζ chains. In contrast, Fc γ RIIB is an inhibitory receptor containing an ITIM (immunoreceptor tyrosine-based inhibition motif) sequence. Fc γ RIIIB is also an activating receptor, which is bound to the cell membrane via a glycosylphosphatidylinositol (GPI) anchor; (B) The murine family of receptors for the Fc portion of immunoglobulin G molecules comprises four members Fc γ RI, Fc γ RIIB, Fc γ RIII, and Fc γ RIV. Activating receptors (Fc γ RI, Fc γ RIII, and Fc γ RIV) contain an ITAM sequence within the accessory γ chains; while the inhibitory receptor (Fc γ RIIB) contains an ITIM sequence.

trophils, is associated with a dimer of the common Fc receptor (FcR) gamma-chain (also named FcR γ chain). Each γ chain contains tyrosine residues that are phosphorylated upon receptor activation and become docking sites for other signaling molecules. These tyrosine residues are found within a common motif known as ITAM, for immunoreceptor tyrosine-based activation motif [24, 25]. There are several isoforms of Fc γ RII, derived from its three genes and from alternative splicing. Fc γ RII isoforms are distributed differently on hematopoietic cells. Fc γ RIIA and Fc γ RIIC are found mainly in phagocytic cells (neutrophils, monocytes, and macrophages), whereas Fc γ RIIB is expressed mainly in B lymphocytes [22]. Fc γ RIIB expression is inducible in phagocytic leukocytes, for the negative regulation of cell functions, such as phagocytosis [8,26]. The human Fc γ RIIA is a particular receptor that does not have associated FcR γ chains. Fc γ RIIA contains an ITAM in its cytoplasmic portion, while Fc γ RIIB has a different tyrosine-containing motif involved in negative signaling. This motif is known as ITIM, for immunoreceptor tyrosine-based inhibition motif [27]. Fc γ RIII has two isoforms: Fc γ RIIIA is a receptor with a transmembrane portion and a cytoplasmic tail, associated with an ITAM-containing homodimer of FcR γ chains on macrophages, natural killer (NK) cells, and dendritic cells. Fc γ RIIIA expressed on basophils and mast cells associates with a heterodimer of γ/ζ chains and an extra β chain (**Figure 1A**) [22,23]. Fc γ RIIIB is present exclusively on neutrophils and it is a glycosylphosphatidylinositol (GPI)-linked receptor, lacking a cytoplasmic tail. No other subunits are known to associate with it, and its signaling mechanism remains unidentified (**Figure 1A**). It is also worth noting that human Fc γ RIIA and Fc γ RIIIB are exclusive receptors that are not found in other species [28].

In mice, several Fc γ receptors have also been described (**Figure 1B**). These receptors are very similar, yet not identical, to the human Fc γ R [8]. Fc γ RI is expressed on monocytes and macrophages, and it is also associated with a dimer of FcR γ chains, which contain the ITAM motifs involved in receptor signaling. Fc γ RIII is a receptor with a transmembrane portion and a cytoplasmic tail, associated with a dimer of FcR γ chains, containing ITAMs. This receptor is closer to the human Fc γ RIIA, as revealed by the genetic structure of FcRs in various species [13]. Fc γ RIV is also an activating receptor expressed together with a dimer of FcR γ chains [29], and it is closer to the human Fc γ RIIIA (**Figure 1B**). Fc γ RIV may be the most relevant activating Fc γ R in mice, due to its ability to bind IgG2a and IgG2b with higher affinity [13]. Fc γ RIIB is the negative receptor containing an ITIM motif in its cytoplasmic tail. It is expressed mainly in B lymphocytes but also in phagocytic leukocytes and dendritic cells. Fc γ RIIB, described first in B lymphocytes,

down regulates the activation signals from the B cell antigen receptor (BCR) to inhibit antibody production by the B cell [30]. This inhibitory receptor also helps to regulate initiation of other cell functions in phagocytic leukocytes and dendritic cells by creating, together with activating Fc γ receptors, a threshold for cell activation [13,31].

2.2. Cell Expression of Fc γ Receptors

Fc γ receptors are found on many cells of the immune system, including granulocytes such as neutrophils and eosinophils; phagocytes such as neutrophils, monocytes and macrophages; and lymphocytes such as natural killer cells and B cells [23]. The wide variety of cellular responses regulated by Fc γ receptors is consequently not surprising. Monocytes and macrophages express all types of activating Fc γ receptors, Fc γ RI, Fc γ RII, and Fc γ RIII in humans, and Fc γ RI, Fc γ RIII, and Fc γ RIV in mice (**Table 1**). Murine neutrophils express Fc γ RIII, and Fc γ RIV, whereas human neutrophils express Fc γ RIIA and Fc γ RIIIB. It is noteworthy to mention that human neutrophils have the two unique Fc γ R, not present in neutrophils of other species. Thus, care should be taken when analyzing data derived from mouse studies of neutrophil Fc γ R function, since conclusions may not necessarily apply to human neutrophils. NK cells exclusively express Fc γ RIIIA in humans and Fc γ RIII in mice. Dendritic cells (DCs) also express various Fc γ Rs, while B lymphocytes express mainly the inhibitory Fc γ RIIB (**Table 1**). Some T lymphocyte populations have also been reported to express Fc γ Rs [32-34], but the role for these receptors in T cell function or development remains unclear and requires further studies.

2.3. Fc γ Receptor Signaling

Crosslinking of activating Fc γ receptors with their IgG antibody ligands triggers various functions in many cells of the immune system. As mentioned before, all activating receptors contain ITAM motifs involved in receptor signaling. The exact activation mechanism is not completely clear, but at the initial molecular events involve activation of Src family kinases followed by activation of Syk (spleen tyrosine kinase) family kinases.

The model for the initial steps of activating Fc γ R signaling is as follows: Upon crosslinking, the receptor associates with lipid rafts. Lipid rafts are small regions of the plasma membrane that are enriched in cholesterol and sphingolipids [35]. There, the receptor co-localizes with Src kinases. These kinases phosphorylate tyrosines within the ITAM. Phosphorylated tyrosines then become docking sites for Syk. This kinase then phosphorylates multiple substrates, including phosphatidylinositol 3-kinase (PI 3-K), phospholipase C γ (PLC γ), and the adap-

Table 1. Fc gamma receptors.

Human			
Receptor	Principal antibody ligand	Affinity for ligand^a	Cell distribution
Fc γ RI (CD64)	IgG1 and IgG3 > IgG4 > IgG2	High (Kd ~ 10 ⁸ M ⁻¹)	Macrophages Neutrophils Eosinophils Dendritic cells
Fc γ RIIA (CD32)	IgG1 > IgG2 and IgG3 > IgG4	Low (Kd ~ 2 × 10 ⁶ M ⁻¹)	Macrophages Neutrophils Mast cells Eosinophils Platelets Dendritic cells
Fc γ RIIB (CD32)	IgG1 > IgG2 and IgG3 > IgG4	Low (Kd ~ 2 × 10 ⁶ M ⁻¹)	Macrophages Neutrophils Mast cells Eosinophils Dendritic cells B Cells
Fc γ RIIIA (CD16A)	IgG1 and IgG3	Low (Kd ~ 5 × 10 ⁵ M ⁻¹)	Macrophages Mast cells Basophils NK cells Dendritic cells
Fc γ RIIIB (CD16B)	IgG and IgG3	Low (Kd ~ 2 × 10 ⁵ M ⁻¹)	Neutrophils
Mouse			
Receptor	Principal antibody ligand	Affinity for ligand^b	Cell distribution
Fc γ RI	IgG2a	High Kd ~ 1.6 × 10 ⁸ M ⁻¹	Monocytes Macrophages Dendritic cells
Fc γ RIIB	IgG1 IgG2a IgG2b	Low Kd ~ 3.3 × 10 ⁶ M ⁻¹ Kd ~ 0.4 × 10 ⁶ M ⁻¹ Kd ~ 2.2 × 10 ⁶ M ⁻¹	B Cells Dendritic cells
Fc γ RIII	IgG1 IgG2a IgG2b	Low Kd ~ 0.3 × 10 ⁶ M ⁻¹ Kd ~ 0.7 × 10 ⁶ M ⁻¹ Kd ~ 0.6 × 10 ⁶ M ⁻¹	Monocytes Macrophages Neutrophils NK cells Dendritic cells
Fc γ RIV	IgG2a IgG2b	Low Kd ~ 2.9 × 10 ⁷ M ⁻¹ Kd ~ 1.7 × 10 ⁷ M ⁻¹	Monocytes Macrophages Neutrophils Dendritic cells

^aData from [64,65]; ^bData from [29,61].

or molecules SLP76 (SH2-domain-containing leukocyte protein of 76 kDa) and LAT (linker for activation of T cells) [36] (**Figure 2**). These molecules organize and activate several signaling pathways, depending on the cell type, leading to particular cellular responses and to transcriptional changes (**Figure 2**). For example, SLP76 seems to be important for Fc γ R signaling in neutrophils [37], while it seems to be dispensable in macrophages and NK cells [38,39]. LAT is another adaptor that seems to participate in many Fc γ R-mediated functions (**Figure 2**). LAT was reported to be constitutively associated with the common Fc γ chain in monocytes [40], and to be important for efficient phagocytosis in macrophages [40]. Clearly, further studies are needed to identify the particular adaptor used by each type of Fc receptor in the various leukocytes, and to connect this to a unique cell

response.

The inhibitory Fc γ RIIB is the negative receptor containing an ITIM motif in its cytoplasmic tail instead of an ITAM sequence [41]. It was described first in B lymphocytes, where it down regulates the activation signals from the B cell antigen receptor (BCR) (**Figure 3A**) to inhibit antibody production by the B cell [30]. Contrary to the activating receptors that engage several kinases, this inhibitory receptor signals by activation of phosphatases. Inositol 5-phosphatase (SHIP1) is the main enzyme activated upon crosslinking of Fc γ RIIB and BCR (**Figure 3B**) [27]. This phosphatase binds via its SH2 domain, to the phosphorylated tyrosines within the ITIM sequence of Fc γ RIIB. SHIP1 transforms phosphatidylinositol-3,4,5-triphosphate (PIP₃) the main product of PI 3-K, into phosphatidylinositol-3,4-bisphosphate (PIP₂); pre-

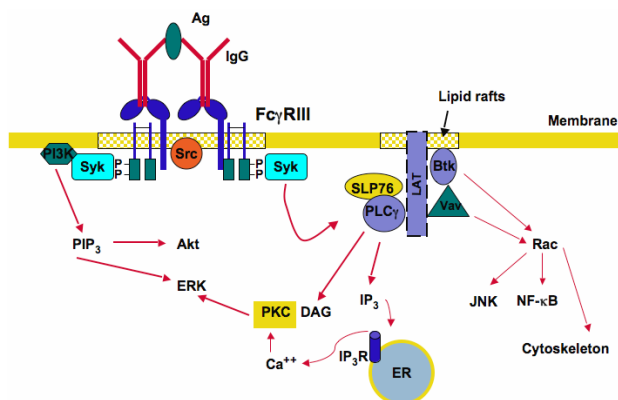


Figure 2. Activating Fc γ receptor signaling. Fc γ R cross-linking by immunoglobulin (IgG) bound to antigen (Ag), induces activation of Src family kinases and Syk family kinases in lipid rafts. These enzymes associate with phosphorylated tyrosines in the ITAM sequences. Syk then phosphorylates enzymes such as phosphatidylinositol 3-kinase (PI 3-K), phospholipase C γ (PLC γ), and the adaptor molecules SLP76 (SH2-domain-containing leukocyte protein of 76 kDa) and LAT (linker for activation of T cells). PI 3-K produces phosphatidylinositol-3,4,5-triphosphate (PIP $_3$), which leads to activation of Akt and extracellular signal-regulated kinase (ERK). PLC γ produces inositoltrisphosphate (IP $_3$) and diacylglycerol (DAG). These second messengers cause calcium release from the endoplasmic reticulum (ER), and activation of protein kinase C (PKC), respectively. PKC leads to activation of ERK. Vav activates GTPases of the Rho and Rac family, which are involved in the regulation of the actin cytoskeleton. Other enzymes such as Bruton's tyrosine kinase (Btk) also activate the GTPase Rac to induce activation of nuclear factors such as JNK and NF- κ B. P represents a phosphate group. IP $_3$ R, receptor for IP $_3$.

venting in this way the stimulation of key activating enzymes such as Akt, Btk, and PLC γ (**Figure 3B**).

2.4. Coexpression of Fc γ Receptors and Threshold for Cell Activation

As indicated above, different leukocytes express more than one activating Fc γ R (**Table 1**), and most of these cells also express at the same time the inhibitory Fc γ RIIB. NK cells are particular leukocytes in this respect, because they only express Fc γ RIIA in humans and Fc γ RIII in mice. The coexpression of both activating and inhibitory Fc γ R results in simultaneous triggering of activating and inhibitory signal transduction pathways (**Figure 4A**). Thus, a particular cell will respond when the sum of activating and inhibiting signals reach a threshold of activation that is determined by the relative expression of both types of Fc γ R (**Figure 4B**). The importance of the inhibitory Fc γ RIIB in regulating many IgG-mediated responses in different leukocytes was made evident in Fc γ RIIB-deficient mice, which showed enhanced activity of many IgG-mediated cell responses including: phagocytosis, immune complex-mediated inflammation, IgG-

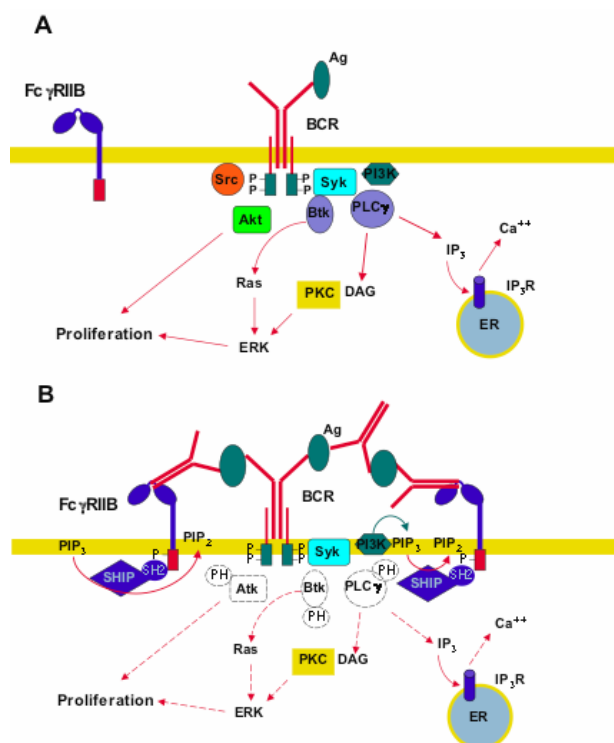


Figure 3. Inhibitory Fc γ RIIB signaling. (A) Upon binding of antigen (Ag) to the B cell antigen receptor (BCR), Src family kinases and Syk family kinases get activated and become associated to the phosphorylated tyrosines in the ITAM sequences of the receptor. Syk then participates in activation of enzymes such as phosphatidylinositol 3-kinase (PI 3-K), Bruton's tyrosine kinase (Btk), and phospholipase C γ (PLC γ). Btk leads to activation of Ras and extracellular signal-regulated kinase (ERK), which together with Akt induce cell proliferation. PLC γ produces inositoltrisphosphate (IP $_3$), which causes calcium release, and diacylglycerol (DAG), which causes activation of protein kinase C (PKC). PKC also leads to cell proliferation via ERK; (B) After antigen recognition by both the inhibitory Fc γ RIIB and the BCR, crosslinking of the receptors leads to phosphorylation of the ITIM sequence. Then, inositol 5-phosphatase (SHIP1) binds to the phosphorylated tyrosines within the ITIM via its SH-2 domain. SHIP1 transforms phosphatidylinositol-3,4,5-triphosphate (PIP $_3$) the main product of PI 3-K, into phosphatidylinositol-3,4-bisphosphate (PIP $_2$); preventing in this way the stimulation of key activating enzymes (dashed lines). P represents a phosphate group. IP $_3$ R, receptor for IP $_3$. ER, endoplasmic reticulum.

mediated passive and active anaphylaxis, and IgE-mediated anaphylaxis [42,43]. They also showed enhanced dendritic cell maturation, and antigen presentation [44-46]. These results thus confirmed that Fc γ RIIB regulates initiation of cell functions by generating, together with activating Fc γ receptors, a threshold for cell activation [31, 47].

2.5. Genetic Structure and Polymorphisms

Analysis of Fc γ R genes in different species has identified

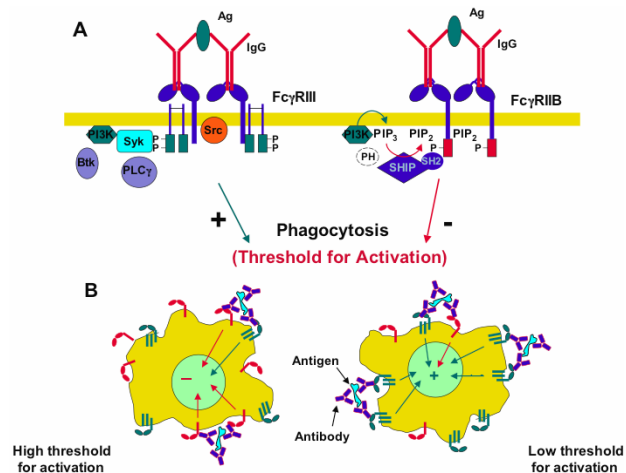


Figure 4. Threshold for activation. (A) The coexpression of both activating and inhibitory Fc γ receptors results in simultaneous triggering of activating and inhibitory signaling pathways, which will result in a threshold for activation of a specific cell response such as phagocytosis; (B) A particular cell will respond when the sum of signals from activating receptors (green), and inhibitory receptors (red) reach a threshold of activation that is determined by the relative expression of both types of Fc γ R.

orthologous receptors between mice and humans. The similarities come from gene localization and also from sequence homology of the extracellular portion of the receptors [8,13]. Therefore, the high affinity receptors Fc γ RIA and FcRI, the low affinity receptors Fc γ RIIA and Fc γ RIII, and also the low affinity receptors Fc γ RIIIA and Fc γ RIV cluster in the same area of chromosome 1 (**Figure 5**). Similarly, the inhibitory Fc γ RIIB gene maps to the same chromosome region, both in mice and humans (**Figure 5**). In addition, the human Fc γ RIIA and mouse Fc γ RIII, as well as the human Fc γ RIIIA and mouse Fc γ RIV, present high sequence homology in their extracellular domains [13]. Despite this similarity, the receptors are not equivalent, since important differences have been detected between mice and human responses to IgG. For example, the human Fc γ RI binds the IgG1 and IgG3 subclasses with high affinity, while the mouse Fc γ RI only binds IgG2a with high affinity (**Table 1**). In addition, the mouse Fc γ RIV is also able to bind IgE, while the human Fc γ RIIIA is not [48,49].

In addition, there are several polymorphisms in the human Fc γ RII and Fc γ RIII. For Fc γ RIIA two allelic variants exist expressing either arginine or histidine at position 131 [50,51]. For Fc γ RIIIA also allelic variants exist expressing either valine or phenylalanine at position 158 [52,53]. Similarly, for Fc γ RIIIB on neutrophils, two isoforms exist, the NA1 and NA2 allotypes [54]. These isoforms differ by five nucleotides and four amino acids, with NA2 containing two additional N-linked glycosylation sites. These differences affect the capacity of Fc γ RIIIB

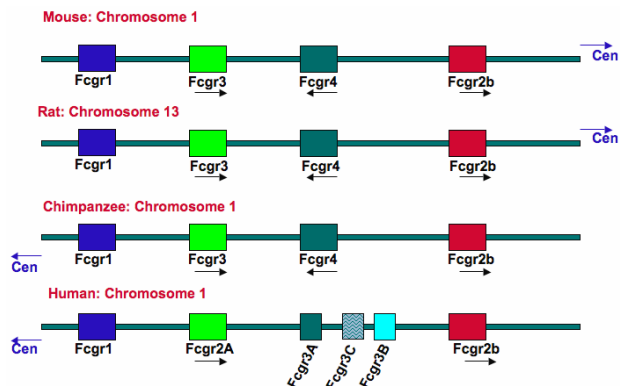


Figure 5. Genomic organization of the Fc γ -receptor locus for various species. Figure modified from [13]. Data from the ensembl database (<http://www.ensembl.org>). Cen, centromer.

to interact with human IgG. Therefore, neutrophils from individuals who are homozygous for the NA1 allele have better phagocytosis of IgG-opsonized targets than do neutrophils from NA2-homozygous individuals [55,56]. These multiple Fc γ R and their allelic variants vary greatly in their affinity for different IgG classes [57]. Thus, a great interest exists to understand how different IgG molecules engage different Fc γ R to activate the multiple cell responses associated with antibodies Fc γ receptor signaling.

3. IgG-MEDIATED CELL FUNCTIONS

3.1. Fc γ Receptor Affinity for IgG

A single antibody molecule does not bind to Fc γ receptors. However, antigen-antibody complexes promote many low affinity interactions between Fc γ R on the surface of leukocytes and antibody complexes. The low affinity of antibodies for individual leukocyte Fc γ R prevents receptors from binding antibodies in the absence of antigen, thus reducing the chance of immune cell activation when there is not an infection. Immune complexes induce the crosslinking of Fc γ R to activate the many different antibody-mediated cell responses. Immune complexes are clearly of different kinds, since they are formed by different classes of antibodies, and *in vivo* studies have suggested that the different IgG classes have different activities. For example, IgG2b/c was better in eliminating B cells [58] and T cell lymphomas [59] than IgG1. Likewise, using class-switch variants of anti-erythrocyte antibodies it was found that IgG2a and IgG2b were better in mediating phagocytosis of opsonized erythrocytes than IgG1 and IgG3 [60,61]. Also, poliomyelitis induced by infection with lactate dehydrogenase-elevating virus (LDV) was delayed much better by IgG2a anti-LDV antibodies than any other IgG class of anti-LDV antibodies [62]. In addition, the severity of glomerular inflammation was greater for IgG2a, followed by

IgG2b and finally IgG1 [63]. All these reports confirmed that different IgG classes mediate different cellular responses *in vivo* through Fc γ receptors.

Because, immune complexes of different kinds induce different cell responses, there has been a great interest in determining which type of IgG binds to which Fc γ R and what particular receptor is involved in mediating the activity of particular IgG classes. Early studies showed that there is a high affinity receptor for IgG (Fc γ RI), which binds preferably to IgG1 in humans and IgG2a in mice [64,65]. This receptor is saturated with serum IgG on leukocytes in the blood. As mentioned before, the other receptors have only low affinity and can bind to IgG only in the form of immune complexes (Table 1) [64,65]. In addition, it was clearly established that most Fc γ R have a binding preference for IgG1 and IgG3 over the other classes of IgG (Table 1). Similarly, in mice it was found that IgG1 binds only to Fc γ RIII, while IgG2a binds to all types of activating Fc γ R, and IgG2b binds to Fc γ RIII and Fc γ RIV. IgG3 does not seem to bind significantly to any of the Fc γ R (Table 1) [29,61]. In agreement with these data, IgG1 activity was lost in mice deficient in Fc γ RIII [61,66]. For IgG2a and IgG2b, however the correlation with particular Fc γ receptors is not as simple. In some model systems the activity of these IgG classes was lost in Fc γ RIII-deficient mice, while it was not in others [13]. In a model of autoimmune hemolytic anemia, IgG2a-mediated response was highly dependent on Fc γ RIII, but also Fc γ RI and Fc γ RIV contributed to the development of severe anemia [67]. In another model of arthritis, mice deficient in Fc γ RI showed reduced cartilage destruction, and impaired protection from a bacterial infection, indicating the prominent role of Fc γ RI in IgG2a-dependent immune functions [68]. Thus, IgG2a used all activating Fc γ receptors with important contribution from Fc γ RI and Fc γ RIII. Similarly, for IgG2b a particular interaction with a particular Fc γ receptor cannot be clearly established. In models of IgG2b-dependent B cell depletion [69], and nephrotoxic nephritis [70], inhibition of Fc γ RIV prevented B cell destruction and kidney inflammation, suggesting a central role for Fc γ RIV in IgG2b-mediated functions. However, in models of IgG2b-dependent autoimmune hemolytic anemia [67], acute glomerular inflammation [63], or acute lung injury [71], Fc γ RIV and also Fc γ RIII were important for the activity of this IgG class. Thus, an order of activity is observed among the different IgG classes, and a preference of engagement with particular Fc γ receptors.

Part of the mechanism used to create this IgG-Fc γ R selectivity is revealed by studies that measured the affinities of IgG classes toward both activating Fc γ receptors and the inhibitory Fc γ RIIB [13]. In this way, it was found that IgG1 has higher affinity for the inhibitory Fc γ RIIB than for the activating Fc γ RIII (Figure 6A),

generating a high threshold for activation. In contrast, IgG2a and IgG2b have higher affinity for the activating Fc γ RIV than for the inhibitory Fc γ RIIB (Figure 6B), generating a lower threshold for activation. Thus, certain classes of IgG, such as IgG1, are more dependent on the signaling from the inhibitory receptor. In agreement with this view, deletion of the inhibitory Fc γ RIIB increased IgG1 activity in models of platelet depletion and tumor cell killing [61]. It is important to note that this model for IgG-Fc γ R selectivity is not static and can be modulated by other factors, such as the pattern of Fc γ R expression on the different leukocytes (Table 1), and cytokines that can modify Fc γ R expression (Figure 7). Thus, Th1-type cytokines such as interferon- γ , and the anaphylatoxin C5a upregulate activating Fc γ Rs expression and down-regulate Fc γ RIIB expression [72,73], whereas Th2-type cytokines, such as interleukin (IL)-4, IL-10, and transforming growth factor-beta (TGF- β) upregulate Fc γ RIIB expression [8,74].

3.2. Each Fc γ R Initiates Particular Signaling Pathways That Lead to Unique Cell Responses

All the reports previously described have confirmed that different IgG classes mediate different cellular responses *in vivo* by engaging particular Fc γ receptors depending on the relative affinity of these receptors for a particular

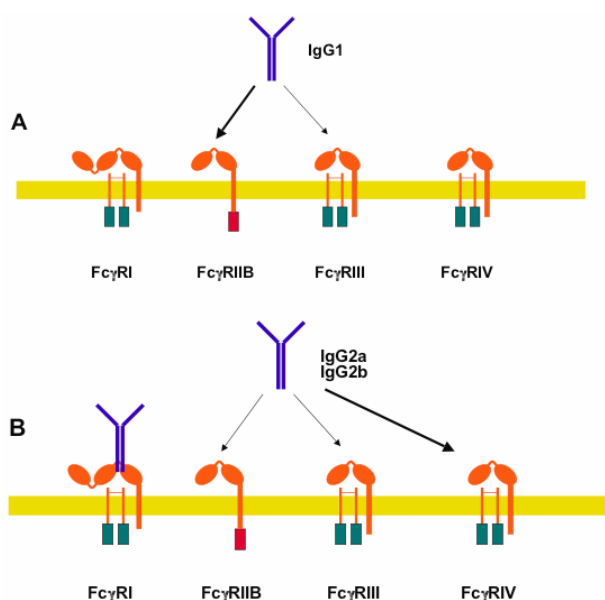


Figure 6. Relative preference of IgG classes for murine Fc γ receptors. (A) IgG1 has higher affinity for the inhibitory Fc γ RIIB (thick arrow) than for the activating Fc γ RIII (thin arrow); (B) In contrast, IgG2a and IgG2b have higher affinity for the activating Fc γ RIV (thick arrow) than for the inhibitory Fc γ RIIB (thin arrow). Thus, certain classes of IgG, such as IgG1, are more dependent on signaling from the inhibitory receptor.

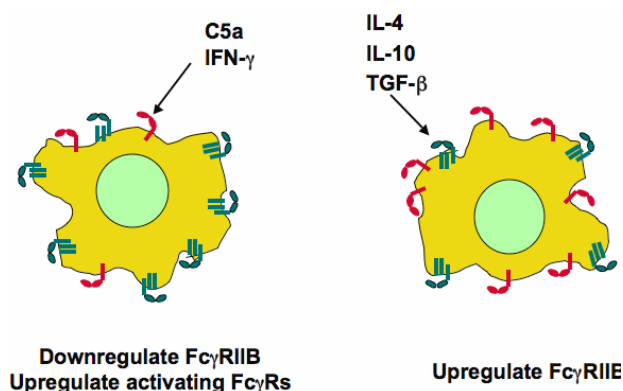


Figure 7. Cytokines can modify Fc γ R expression. Th1-type cytokines such as interferon- γ IFN- γ , and the anaphylatoxin C5a upregulate activating Fc γ R (green) expression and downregulate Fc γ RIIB (red) expression, whereas Th2-type cytokines, such as interleukin (IL)-4, IL-10, and transforming growth factor-beta (TGF- β) upregulate Fc γ RIIE expression.

IgG class. However, these findings do not explain what cell response is activated in response to a particular type of Fc γ receptor. One possibility is that each leukocyte is already programmed to respond in a certain way when immune complexes crosslink its Fc γ receptors. Another possibility is that each Fc γ R signals differently to initiate a particular cell response. The first possibility is not very likely because a particular leukocyte can respond with various cell functions, and also because the same class of IgG induces different responses in different leukocytes. The idea that each Fc γ R is able to initiate a particular cell response is supported by recent reports where individual Fc γ R were crosslinked on human neutrophils. As described above, human neutrophils express only two Fc γ R, Fc γ RIIA and Fc γ RIIB [28]. These receptors are different in the way they are anchored to the cell membrane. Fc γ RIIA has a typical transmembrane and cytoplasmic tail containing an ITAM for signaling. In contrast, Fc γ RIIB is a GPI-linked receptor, lacking a cytoplasmic tail, and its signaling mechanism remains unidentified. However, early reports indicated that both Fc γ R are capable of signaling and inducing particular responses [75]. More recently, it was found that Fc γ RIIA, but not Fc γ RIIB could induce an increase in L-selectin expression [76]. Opposite to this, Fc γ RIIB, but not Fc γ RIIA, was able to activate β 1 integrins [77]. In addition, when the major cell response of neutrophils, arguably phagocytosis, was examined, Fc γ RIIA was the predominant Fc γ R mediating this response. Fc γ RIIB contribution to phagocytosis was minimal [78]. In complete contrast, Fc γ RIIB signaling to the neutrophil nucleus was much more efficient than Fc γ RIIA signaling. Fc γ RIIB, but not Fc γ RIIA, promoted a robust increase in phosphorylated ERK in the nucleus, and also efficient phosphorylation of the nuclear factor Elk-1 [79]. Interestingly, the Fc γ RIIA

signaling pathway resembles the classical ITAM-mediated pathway (Figure 2) [5], while Fc γ RIIB signaling pathway remains a mystery (Figure 8). Taken together, these reports strongly support the hypothesis that each Fc γ R is capable of initiating particular signaling pathways that lead to unique cell responses.

4. EFFECT OF ANTIBODY GLYCOSYLATION ON Fc RECEPTOR FUNCTION

All antibodies are glycoproteins with various carbohydrate side chains attached to the protein backbone. The immunoglobulin classes IgM, IgA, and IgE have several exposed carbohydrate side chains. In contrast, IgG molecules have one carbohydrate side chain. This carbohydrate (sugar) side chain is important for IgG function. Deletion of the sugar side chain results in an altered conformation of the antibody molecule and in deficient binding to Fc γ receptors [80]. This carbohydrate domain is heterogeneous in its sugar composition. More than 30 different glycosylation variants of IgG can be found in serum of a healthy human or mouse individuals [14]. This heterogeneity is formed by variable addition of sugar residues such as sialic acid, N-acetylglucosamine, galactose and fucose in straight or branching patterns. Although heterogeneous, the pattern of glycosylation seems to change in various physiological conditions. For example, terminal galactose and sialic acid residues were reduced in active autoimmune disease [18,81], while they were increased during pregnancy [82,83]. It is not clear what these changes in the glycosylation pattern

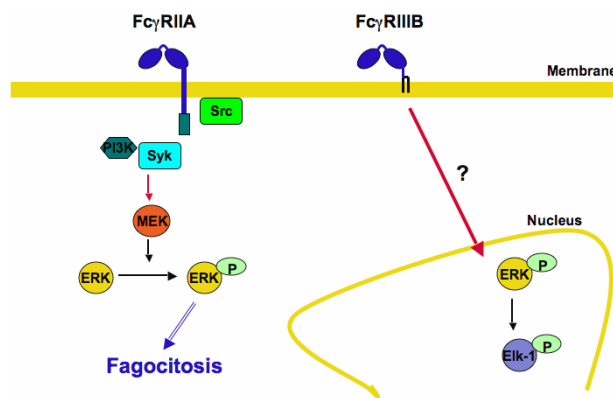


Figure 8. Each Fc γ R initiates particular signaling pathways leading to unique cell responses. In human neutrophils, Fc γ RIIA activates the classical ITAM-mediated signaling pathway leading to efficient phagocytosis. In contrast, Fc γ RIIB promotes a robust increase in phosphorylated ERK in the nucleus, and also efficient phosphorylation of the nuclear factor Elk-1. The Fc γ RIIB signaling pathway remains a mystery. P represents a phosphate group; Syk, spleen tyrosine kinase; PI 3-K, phosphatidylinositol 3-kinase; MEK, ERK kinase; ERK, extracellular signal-regulated kinase.

represent, but it seems that they can modulate IgG activity [84]. In contrast, IgG antibodies with reduced fucose residues presented higher affinity for human Fc γ IIIa and its mouse ortholog Fc γ RIV and showed improved antibody-dependent cellular toxicity against various tumor cells [61,85,86]. IgG antibodies with high levels of terminal sialic acid presented lower affinity for Fc γ receptors and also reduced inflammatory activity [18,87, 88]. In addition, IgG antibodies with abundant sialic can bind to other cellular receptors different from Fc receptors. SIGNR-1 (specific ICAM-3 grabbing nonintegrin related 1) and its human ortholog DC-SIGN (dendritic cell specific ICAM-3 grabbing nonintegrin) were identified as receptors for sialic acid rich IgG [87]. Moreover, this subpopulation of antibodies was also suggested to be responsible for the anti-inflammatory activity of intravenous Ig (IVIg) therapy, because in SIGNR-1 knockout mice, IVIg did not show an anti-inflammatory effect in a model of rheumatoid arthritis [87]. IVIg therapy that consists on administration of high doses of pooled serum IgG from many different donors has been used for many years to treat various autoimmune diseases such as rheumatoid arthritis and thrombocytopenia [19]. In addition, it has been reported that IVIg therapy can change the threshold for activation of cells by upregulation of the inhibitory Fc γ RIIB and downregulation of activating Fc γ R in some mouse models and in patients with chronic inflammatory demyelinating polyneuropathy [70,89,90]. Thus, glycosylation patterns are critical for binding to particular Fc γ receptors and other novel antibody receptors. These reports underline the need of further studies on antibody-Fc receptor interactions to better understand the multiple effects of antibody molecules.

5. NEW LIGANDS FOR Fc γ RECEPTORS

Antibodies are the bona fide ligands for Fc receptors. However, some recent reports have identified other molecules different from IgG that can bind Fc γ receptors and can also activate the cell functions characteristic of antibodies. Two members of the pentraxin superfamily [91], which are multimeric cyclic proteins, are reported to bind human and mouse Fc γ receptors. These pentraxins are C-reactive protein (CRP) and serum amyloid P (SAP) [92-95]. These proteins are usually not found in serum of healthy individuals, but they are rapidly expressed in large amounts during inflammation and microbial infections. CRP and SAP are capable of binding to several microorganisms including bacteria and fungi and thus targeting them for phagocytosis by neutrophils and macrophages [92,96]. These reports suggest that these pentraxin proteins behave like antibodies recognizing foreign antigens on pathogens and directing them to cells of the innate immune system [16]. In support of this idea, it was also found that Fc γ receptor uptake of CRP-opsonized

Streptococcus pneumoniae increased the immune response against these bacteria [95]. Moreover, CRP also seems to have an anti-inflammatory effect mediated by Fc γ receptors. In Fc γ R-deficient mice, administration of CRP did not protect from nephrotoxic nephritis or immune thrombocytopenia [94,97].

6. CONCLUSION

Fc Receptors expressed in a wide variety of leukocytes are capable of activating in response to various antibodies different cellular responses of great importance for host defense and for immune regulation. The different subclasses of IgG antibodies are recognized by Fc γ receptors with different affinities. Also singular Fc γ receptors seem to activate particular cell responses. This provides two ways for modulating cellular responses. In addition, expression of both activating and inhibitory Fc γ receptors establishes a threshold for activation of innate immune cells. Thus, Fc γ receptors are responsible of controlling the intensity of the immune response and of preventing unnecessary activation of innate immune cells, which might damage normal tissues. Novel glycosylation variants of IgG that bind Fc γ receptors with different affinities have been identified and also the anti-inflammatory activity of intravenous IgG therapy. Finally, novel receptors for antibody variants and novel Fc γ receptor ligands are been recognized. These new information together with new studies on IgG-Fc γ receptor interactions will certainly help us to develop new ways of controlling not only antibody-mediated effector functions directed against pathogens and tumors, but also the exaggerated antibody-mediated cell responses associated with auto-immunity.

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