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Fcγ Receptors: Old Friends and New Family Members

Review

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Although cellular receptors for immunoglobulins were first identified nearly 40 years ago, their central role in the immune response was discovered only in the last decade. They are key players in both the afferent and efferent phase of an immune response, setting thresholds for B cell activation, regulating the maturation of dendritic cells, and coupling the exquisite specificity of the antibody response to innate effector pathways, such as phagocytosis, antibody-dependent cellular cytotoxicity, and the recruitment and activation of inflammatory cells. Moreover, because of their general presence as receptor pairs consisting of activating and inhibitory molecules on the same cell, they have become a paradigm for studying the balance of positive and negative signals that ultimately determine the outcome of an immune response. This review will summarize recent results in Fc-receptor biology with an emphasis on data obtained in in vivo model systems.

The mammalian immune system has evolved to defend the organism against pathogenic microbes, layering the specificity of adaptive responses on the ancestral pathways of innate immunity. This complexity exists to provide discrimination between self and nonself and to insure that immune responses are tightly regulated, thus avoiding autotoxicity and uncontrolled inflammation. Multiple checkpoints have been identified that function to insure an orderly progression through an immune response and thereby prevent the generation of self-destructive processes. A common theme that has emerged from the study of these checkpoints is the requirement for the establishment of discrete thresholds that define narrow windows of response. One mechanism to achieve these thresholds is for the coexpression of receptors with common ligand binding properties but divergent signaling capacities, coupling activating receptors with an inhibitory counterpart, thereby setting thresholds for immune cell activation (Ravetch, 2003). Immune complexes (IC) consisting of IgG antibodies have long been recognized to have potent immunoregulatory functions ranging from a strong enhancement to complete suppression of antibody responses (Heyman, 2000), in addition to their more overt roles as effector molecules for the elimination of foreign antigens. These divergent activities of IgGs can now be explained through the selective engagement of specific FcγRs on discrete cell types, which result in either arrest or progression of an immune response, determined by the specific checkpoint and threshold achieved. This review will focus on our current understanding of the diversity of these receptors and their in vivo biological function in both tolerance and immunity.

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In all mammalian species studied to date, four different classes of Fc receptors have been defined: FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcγRIV. Whereas FcγRI displays high affinity for the antibody-constant region and restricted isotype specificity, FcγRII and FcγRIII have low affinity for the Fc region of IgG but a broader isotype binding pattern (Ravetch and Kinet, 1991; Hulett and Hogarth, 1994), and FcγRIV is a recently identified receptor, conserved in all mammalian species (Figure 1) with intermediate affinity and restricted subclass specificity (Mechetina et al., 2002; Davis et al., 2002; Nimmerjahn et al., 2005). 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, on chromosome 13 in rats, and on chromosome 38 in dogs (Figure 1). Whereas only single copies of the low-affinity Fc-receptor genes are present in most species, duplications and diversification processes have led to the presence of multiple genes in the human genome (Qiu et al., 1990). Unfortunately, most likely due to their highly homologous sequences, many genome databases do not list these as separate genes but incorrectly as allelic versions of one gene.

Functionally, there are two different classes of Fc receptors: the activation and the inhibitory receptors, which transmit their signals via immunoreceptor tyrosine-based activation (ITAM) or inhibitory motifs (ITIM), respectively (Ravetch and Lanier, 2000). The paired expression of activating and inhibitory molecules on the same cell is the key for the generation of a balanced immune response. Additionally, it has only recently been appreciated that the IgG Fc receptors show significant differences in their affinity for individual antibody isotypes, rendering certain isotypes more strictly regulated than others (Nimmerjahn et al., 2005). This represents a second layer of complexity and is of major importance for understanding Fc-receptor-dependent antibody-mediated effector functions in vivo and for the design of antibody-based therapies. We will focus on recent key findings that define the specificity of IgG Fc receptors and their role in tolerance and immunity. We will only briefly mention developments in the rapidly evolving field of Fc-receptor homolog proteins; we direct the reader to several excellent recent reviews covering that topic in greater detail (Davis et al., 2002, 2005).

The Inhibitory Fcγ Receptor IIB

Fcγ receptor IIB (FcγRIIB) together with other receptors such as PIR-B, KIRs, CTLA-4, PD-1, CD5, and CD22, belong to the family of immune inhibitory receptors. These proteins can be found on a wide variety of immune effector cells, share similar properties, and are important regulators of their activating counterparts (Ravetch and Lanier, 2000). The loss of these negative regulators leads to imbalanced immune responses resulting in autoimmunity and overt autoimmune disease (Tivol et al., 1995; Penninger et al., 1995; Takai et al., 1996; O'Keefe et al., 1999; Nishimura et al., 1999; Bolland and Ravetch,

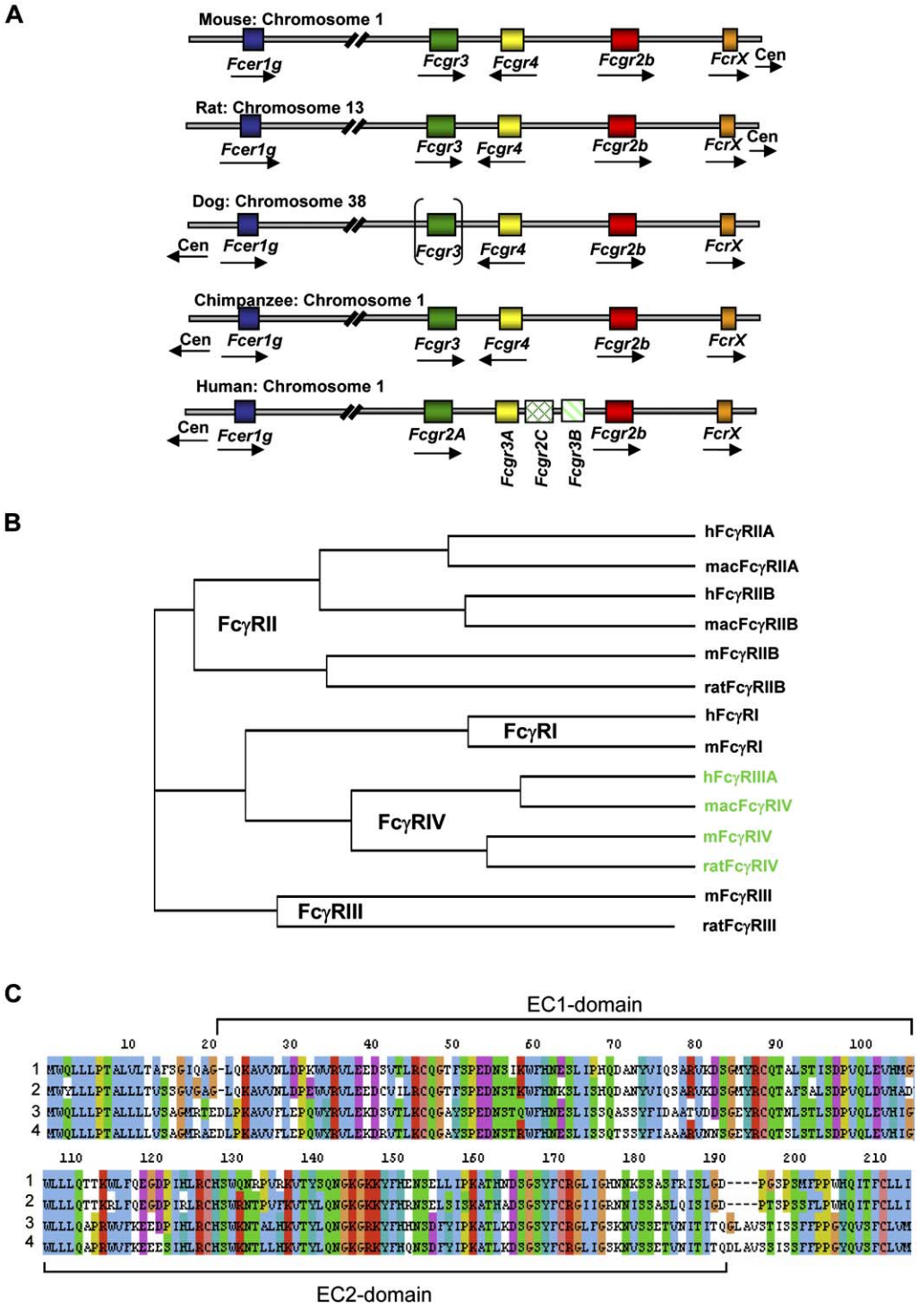


Figure 1. Genomic Organization of the Low-Affinity Fc-Receptor Genes

(A) The genomic organization of the Fc-receptor locus in mouse, rat, dog, chimpanzee, and humans is shown according to the ensembl database (http://www.ensembl.org). Colors indicate genes that were predicted to be orthologs. Based on these homologies, we are suggesting the indicated nomenclature. Arrows indicate the orientation of the gene. Cen indicates the localization of the centromer. Brackets indicate that the presence of the gene is assumed.

(B) Cladogram showing the alignment of selective Fcγ receptors of humans (h), macaques (mac), mice (m), and rats.

(C) Alignment of the FcγRIV-related proteins in humans, macaques, and rats. Colors indicate sequence homologies and the type of amino acids (red, basic; blue, small and hydrophobic; magenta, acidic; green, hydroxyl, amine, and weakly basic). 1, mouse FcγRIV (accession number, Q8R2R4); 2, rat FcγRIV (accession number, Q6XPU4); 3, human FcγRIIIA (accession number, P08637); 4, macaque FcγRIV (accession number, Q8SPW2). Abbreviations: EC1, EC2: extracellular domains 1 or 2 of FcγRIV.

2000). FcγRIIB is a single-chain receptor that carries an ITIM motif in its cytoplasmic domain, a hallmark of this inhibitory protein family. It functions through the recruitment of the inositol phosphatase SHIP through binding to an SH2 site generated on the FcγRIIB ITIM as a consequence of the transphosphorylation that is initiated upon its coligation to an ITAM-bearing receptor. With the exception of T cells and NK cells, FcγRIIB is expressed on all cells of the immune system, and it is the only classical Fc receptor on B cells where it regulates activating signals delivered by immune complexes retained on the FDC to the B cell receptor (BCR). Furthermore, several Fc-receptor-related molecules, e.g., FcRX and FcRH1-5, are expressed on human and mouse B cells. Despite significant sequence homology to classical Fc receptors, attempts to demonstrate antibody binding activity for these molecules have been unsuccessful, rendering FcγRIIB the only antibody binding Fc receptor on B cells. Nevertheless, these Fc-receptor-related molecules show a restricted expression pattern during different stages of B cell development and might become important new markers for defining B cell developmental stages or B cell malignancies (Davis et al., 2005).

FcγRIIB as a Regulator of B Cell Activation

As a consequence of its role in regulating BCR signals, which ultimately will decide whether a B cell proliferates, class switches, and matures into an antibody-secreting plasma cell, FcγRIIB has been suggested to play an important role in maintaining peripheral tolerance (Bolland and Ravetch, 1999; Ravetch and Lanier, 2000). When coligated with the BCR, it triggers two ITIM-dependent signaling pathways that inhibit cell activation and proliferation. While regulation of cell activation is dependent on the recruitment of SHIP to the ITIM motif, which ultimately leads to the inhibition of calcium-dependent signaling pathways, control of proliferation, however, seems to involve SHIP-independent signaling pathways, including the adaptor molecule Dok and MAP kinases (Bolland and Ravetch, 1999). Besides these ITIM-dependent signaling events, the isolated crosslinking of FcγRIIB on B cells leads to B cell apoptosis via ITIM- and SHIP-independent and c-Abl-family kinase-dependent pathways (Pearse et al., 1999; Tzeng et al., 2005). The capacity of FcγRIIB to trigger B cell apoptosis has been proposed to be another mechanism for controlling B cell responses and maintaining self tolerance by deletion of low-affinity or self-reactive B cells. This hypothesis was supported 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 (Takai et al., 1996; Bolland and Ravetch, 2000). It should be noted, however, that this autoimmune phenotype is strain dependent, indicating that other epistatic modifiers are involved in disease susceptibility and severity (Nguyen et al., 2002; Bolland et al., 2002). In line with this role of FcγRIIB in maintaining tolerance, autoimmune-prone mouse strains such as NZB, NOD, BXSB, and MRL express reduced levels of this receptor on activated and germinal-center B cells, which has been attributed to a polymorphism in the promoter of this gene (Jiang et al., 1999, 2000; Pritchard et al., 2000; Xiu et al., 2002). More recently, a similar polymorphism in the human FcγRIIB promoter that is linked to lupus has been identified. This polymorphism leads to decreased transcription and surface expression of FcγRIIB on activated B cells of human lupus patients (Blank et al., 2005). Additionally, a polymorphism in the transmembrane domain of FcγRIIB is linked to human lupus in several racial groups (Kyogoku et al., 2004; Siriboonrit et al., 2003; Chu et al., 2004). It has been suggested that this allelic variant of the inhibitory receptor loses its function due to the inability to associate with lipid rafts (Floto et al., 2005; Kono et al., 2005).

Although FcγRIIB is also expressed on other inflammatory immune effector cells such as neutrophils, monocytes, and macrophages, the fact that the autoimmunity observed in FcγRIIB-deficient animals is a B cell-autonomous phenotype is supported by several independent lines of evidence. First, transfer of FcγRIIB-deficient bone marrow into irradiated RAG or IgH knockout recipients leads to the development of autoimmunity. In these animals, the monocytic compartment still expressed FcγRIIB while it was absent from peripheral B cells (Bolland and Ravetch, 2000). Second, by increasing FcγRIIB expression on B cells to wild-type levels by retroviral transduction of bone marrow derived from the autoimmune-prone mouse strains NZM, BXSB, and FcγRIIB knockout mice, it was possible to restore tolerance and thus prevent the development of fatal autoimmune disease (McGaha et al., 2005). Interestingly, restoration of FcγRIIB expression to wild-type levels on approximately 40% of peripheral B cells was sufficient to prevent the development of autoantibodies and autoimmune glomerulonephritis, a result confirmed by the generation of mixed bone marrow chimeras (McGaha et al., 2005). The fact that it was not necessary to restore FcγRIIB function on all B cells highlights the threshold nature of autoimmunity. This finding has important implications for the design of therapeutic approaches, as it suggests that despite the complex nature of autoimmune diseases, therapeutic effects are achievable by targeting specific cell populations.

The B cell stage(s) at which FcγRIIB exerts its function as a gatekeeper of self tolerance has recently been defined. Autoreactive B cells can be generated at several stages during B cell development (Figure 2). There is accumulating evidence that FcγRIIB mediates its function during late stages of B cell maturation, thus representing a distal checkpoint. Through the analysis of an anti-DNA knockin model, it was established that the absence of FcγRIIB resulted in the expansion of IgG-positive plasma cells secreting autoreactive antibodies (Fukuyama et al., 2005). FcγRIIB deficiency did not impact on early events in the bone marrow like receptor editing, nor did it prevent the development of IgM-positive autoreactive B cells. After class switching to IgG, however, FcγRIIB was essential to prevent the expansion of autoreactive B cells and their maturation into plasma cells. Taking the considerably higher pathogenic potential of IgG compared to 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.

These results suggest a model in which several central and peripheral checkpoints prevent the emergence of autoreactive B cells and their maturation into plasma cells that could secrete pathogenic antibodies (Figure 2).

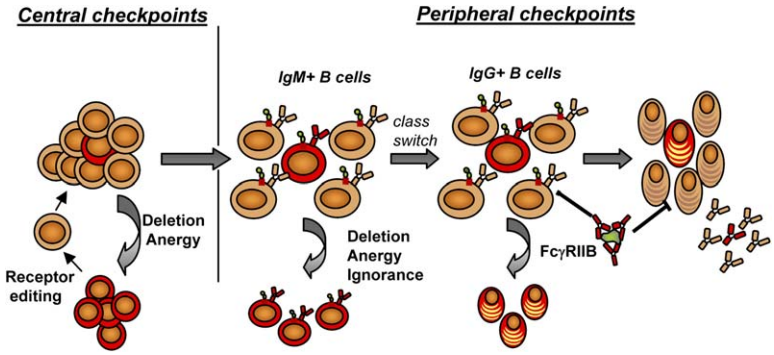


Figure 2. Checkpoints Regulating Self-Reactive B Cells during Development

During early B cell development, central checkpoints delete B cells with an autoreactive B cell receptor (shown in red) in the bone marrow. Some of these autoreactive B cells can be rescued by ongoing BCR rearrangements (receptor editing). Autoreactive B cells that escape into the periphery or are generated de novo during the germinal center reaction are controlled by peripheral checkpoints such as deletion or rendering harmful cells anergic. FcγRIIB represents a late checkpoint that controls the expansion of IgG- positive autoreactive cells and their differentiation into plasma cells.

Central checkpoints including receptor editing, deletion, and anergy of self-reactive BCR species insure that the majority of B cells with an autoreactive BCR are deleted in the bone marrow (Meffre et al., 2000; Goodnow et al., 2005; Grimaldi et al., 2005); this occurs independently of FcγRIIB. It is widely accepted, however, that this process is incomplete and self-reactive cells can escape into the periphery, in a background-dependent manner. Thus, Balb/c mice are more efficient in editing than C57Bl/6 mice, making the later a more permissive strain for the development of autoimmunity. Consistent with this observation, FcγRIIB-deficient mice on the Balb/c background did not develop spontaneous autoimmunity; in contrast, this deficiency of an inhibitory receptor on the C57Bl/6 background resulted in the emergence of a highly penetrant, fatal lupus-like disease. Moreover, autoreactive B cells can be generated de novo in the periphery during the germinal center reaction (Ray et al., 1996; Bona and Stevenson, 2004). Therefore, additional checkpoints are of major importance to prevent the accumulation of autoreactive cells in the periphery. Furthermore, the expansion of class-switched self-reactive antibodies that can trigger a wide variety of inflammatory effector functions needs to be tightly regulated (Dijstelbloem et al., 2001; Ravetch and Bolland, 2001). Here, FcγRIIB might serve as the final barrier to prevent these B cells with potentially harmful BCR specificities from maturing into plasma cells that would otherwise induce tissue pathology by secretion of large amounts of self-reactive antibodies.

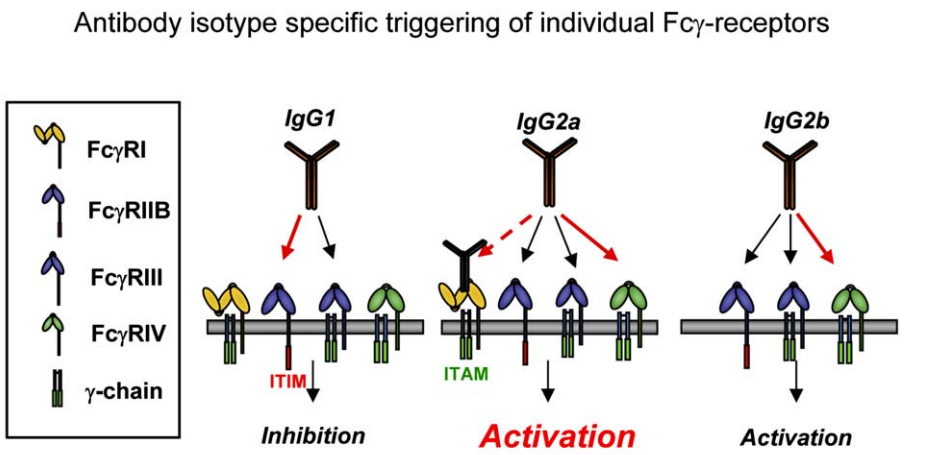
FcγRIIB on Dendritic Cells

While FcγRIIB appears to function in a B cell-autonomous manner to regulate autoreactive cells in the periphery, another cell type where FcγRIIB may play an important role in regulating immunity and tolerance are the dendritic cells (DC). Depending on their maturation state, DCs can either tolerize or activate naive T cells (Steinman et al., 2003). Several groups have shown that immune complexes can function as potent mediators of DC maturation and can enhance efficient antigen presentation of endocytosed antigen (Regnault et al., 1999; Dhodapkar et al., 2002; Rafiq et al., 2002; Groh et al., 2005). FcγRIIB expression on DCs controls immune complex-mediated DC maturation, as DCs derived from FcγRIIB-deficient mice showed an enhanced potential to generate antigen-specific T cell responses in vitro and in vivo (Kalergis and Ravetch, 2002). Those studies suggested that in the steady state, FcγRIIB could function to prevent spontaneous maturation of DCs and that manipulation of this pathway could result in optimized immunotherapeutic and vaccination strategies by overcoming this negative regulatory effect of FcγRIIB on DCs.

With the recent generation of monoclonal antibodies that specifically block immune complex binding to human FcγRIIB, it has become possible to test this hypothesis. Incubation of human dendritic cells with an FcγRIIB blocking antibody was sufficient to induce DC maturation by immune complexes normally present in plasma, as suggested by the upregulation of costimulatory molecules and the enhanced generation and activation of tumor-specific T cells (Dhodapkar et al., 2005; Boruchov et al., 2005). This indicates that blocking the inhibitory Fc receptor on DCs might indeed be a strategy for generating stronger and probably longer lasting immune responses. It should be noted, however, that immature DCs are continuously tolerizing self-reactive T cells that escape negative selection in the thymus. Systemic administration of an FcγRIIB blocking antibody might perturb this pathway and lead to expansion of autoreactive cells. To test this hypothesis, the development of novel animal models with targeted deletion of Fc receptors in dendritic cells or other selective cell populations will be essential. Additionally, mice and man differ in the specific FcRs they express on DCs. Animals carrying the human Fc receptors in place of their mouse counterparts will be important preclinical tools for assessing the in vivo activity of blocking antibodies for human Fc receptors. In summary, these studies suggest that FcγRIIB may function as an important regulator of DC activation by setting thresholds that prevent the spontaneous maturation of dendritic cells (Figure 3) and thereby promote steady-state tolerance. This activity, on one hand, prevents the activation and expansion of self-reactive T and B cells but on the other may limit the generation of strong antitumor or pathogen-specific immune responses. Manipulation of this pathway thus offers an approach to enhanced vaccines and immunotherapeutics.

FcγRIIB Controls Innate Immune Effector Cell Activation

In addition to its autoregulatory role 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



	IgG1 (A/I)	IgG2a (A/I)	IgG2b (A/I)
FcγRIII/FcγRIIB	0.1	1.6	0.5
FcγRIV/FcγRIIB	n.a.	70	7

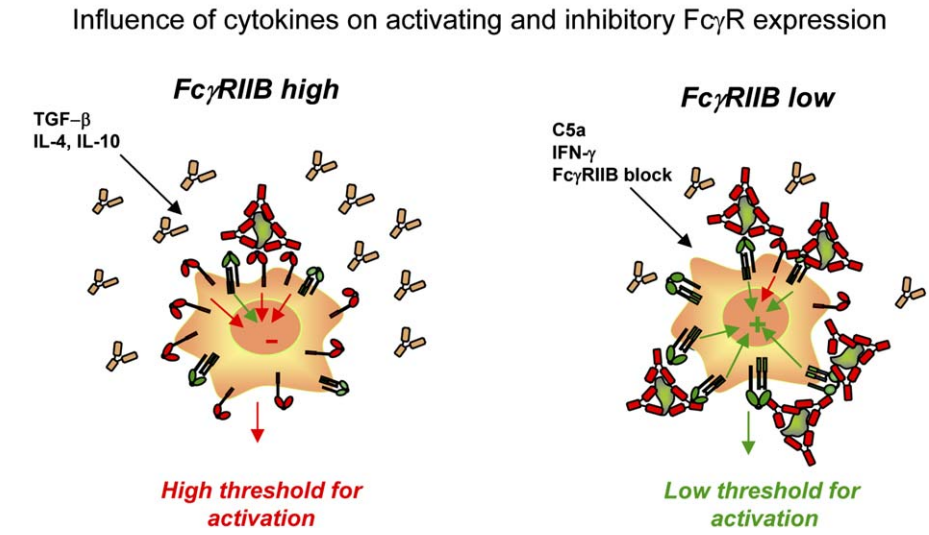


Figure 3. Factors that Influence Fc-Receptor-Dependent Activities of Antibody Isotypes

(A) Individual antibody isotypes have different affinities for activating and inhibitory Fc receptors (see text). Red arrows indicate preferential interactions of the indicated antibody isotypes with cellular Fc receptors; black arrows indicate lower affinity interactions. In the case of IgG2a, the broken red arrow indicates that the interaction might be blocked as FcγRI is continuously occupied with monomeric IgG2a. The table summarizes the actual A/I ratios based on the affinities of the individual Fc receptors for the respective antibody isotypes.

(B) The ratio of activating to inhibitory Fc receptors on immune cells such as DCs, macrophages, and neutrophils is regulated by exogenous factors. Cytokines like IL-4, IL-10, or TGF-β upregulate FcγRIIB, thereby setting high thresholds for cell activation, whereas inflammatory mediators downregulate the inhibitory (shown in red) and upregulate the activating (shown in green) Fc receptors. For therapeutic approaches, FcγRIIB-mediated inhibition might be circumvented by using FcγRIIB-blocking antibodies.

response (Ravetch and Bolland, 2001; Dijstelbloem et al., 2001). On these cell types, FcγRIIB is coexpressed with activating Fc receptors of varying affinities and isotype specificities and negatively regulates activating signals delivered by these receptors. This role of FcγRIIB is apparent in animals deficient in this receptor. Lack of FcγRIIB leads to enhanced immune complex-mediated inflammation and phagocytosis as demonstrated by an enhanced Arthus reaction, systemic IgG- and IgE-induced anaphylaxis, anti-GBM glomerulonephritis, immunothrombocytopenia (ITP), hemolytic anemia, collagen-induced arthritis, and IgG-mediated clearance of pathogens and tumor cells. 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. As will be discussed below, the magnitude of FcγRIIB modulation is strictly isotype dependent and predictable based on the relative affinities of IgG subtypes for activating and inhibitory receptors.

The Activating Fcγ Receptors

In contrast to the single-chain inhibitory Fc receptor, activating FcγRs (with the exception of human FcγRIIA) cannot transmit activating signals in the absence of an accessory chain, the common γ chain (γ chain), that carries an ITAM motif required for triggering cell activation. Aggregation of activating receptors by immune complexes leads to tyrosine phosphorylation of the ITAM motif by members of the Src-kinase family and subsequent recruitment of SH2-containing kinases such as members of the Syk-kinase family. These early events ultimately lead to the recruitment of phosphatidylinositol 3-kinase (PI3-K) and phospholipase-Cγ (PLCγ), which trigger protein kinase C (PKC) activation and sustained calcium elevation (Ravetch, 2003). Moreover, the γ chain plays a major role in the assembly of activating FcRs, mediating cell-surface expression of activating Fc receptors. FcγRI, FcγRIII, and FcγRIV are dependent on γ chain expression; thus, deletion of this receptor subunit leads to the functional loss of all activating Fc receptors and several other non-FcR-related proteins such as PIR-A and NK cell cytotoxicity receptors (Moretta et al., 2001; Ravetch, 2003). Expectedly, γ chain knockout animals were demonstrated to have significant defects in antibody-dependent effector cell responses such as phagocytosis of ICs, ADCC, and inflammatory responses (Takai et al., 1994; Sylvestre and Ravetch, 1994; Clynes and Ravetch, 1995; Park et al., 1998; Zhang et al., 2004). In contrast to these dramatic effects in γ chain knockout mice, deletion of the individual activating Fcγ receptors I or III resulted in less pronounced phenotypes, especially for effector responses involving the IgG2a and IgG2b antibody isotypes.

The only IgG isotype that could consistently be assigned to an individual activating Fc receptor in vivo was IgG1. Here the deletion of the low-affinity receptor FcγRIII abrogated IgG1-mediated effector functions in various models like arthritis, glomerulonephritis, IgG-dependent anaphylaxis, IgG-mediated hemolytic anemia, and immunothrombocytopenia (Hazenbos et al., 1996; Meyer et al., 1998; Fossati-Jimack et al., 2000; Ji et al., 2002; Bruhns et al., 2003; Fujii et al., 2003; Nimmerjahn et al., 2005). Importantly, however, under many circumstances, such as host response to viral or bacterial infections (Coutelier et al., 1987; Schlageter and Kozel, 1990; Markine-Goriaynoff and Coutelier, 2002; Taborda et al., 2003), antibody-mediated cytotoxicity, or antibody-based therapy (Kipps et al., 1985; Fossati-Jimack et al., 2000; Uchida et al., 2004; Nimmerjahn et al., 2005; Nimmerjahn and Ravetch, 2005), the most potent antibody isotypes were of the IgG2a and IgG2b isotype. Therefore, a thorough understanding of how these isotypes exert their function was essential.

Considering the isotype specificities of the high-affinity FcγRI (binding exclusively IgG2a) and the low-affinity FcγRIII (binding IgG1, IgG2a, and IgG2b) (Ravetch and Kinet, 1991; Hulett and Hogarth, 1994), these two receptors seemed to be the obvious candidates responsible for IgG2a and IgG2b effector functions. Although there was some suggestion that FcγRI and III might participate in a limited fashion in IgG2a-mediated effector responses (Ioan-Facsinay et al., 2002; Barnes et al., 2002), the majority of studies concluded that IgG2a- and IgG2b-triggered effects occur independently of these two receptors, but in a γ chain-dependent manner (Hazenbos et al., 1996; Meyer et al., 1998; Fossati-Jimack et al., 2000; Uchida et al., 2004; Nimmerjahn et al., 2005). Especially in the case of IgG2a, these results seemed to be surprising, as FcγRI shows a high affinity for this isotype (K_A: 10^8–10^9 M^{-1}). However, the increased affinity allowed this receptor to bind monomeric IgG2a as efficiently as immune complexes (ICs), indicating that newly generated ICs would be expected to have only limited access to FcγRI (Figure 3A).

The dominant view, therefore, suggested that other effector mechanisms such as activation of the complement cascade might mediate the in vivo effects of these isotypes. Indeed, IgG2a and IgG2b can efficiently activate the complement cascade in vitro (Duncan and Winter, 1988). However, several studies with mice deficient in a variety of complement proteins such as C2, C3, or C4 failed to demonstrate a major involvement of the complement cascade (Ravetch and Clynes, 1998; Uchida et al., 2004; Nimmerjahn and Ravetch, 2005). On the other hand, deletion of the γ chain abrogated IgG2a and IgG2b effector functions in a variety of passive models of cytotoxicity, strongly arguing for the existence of other γ-chain-dependent Fc receptors. Genomic analysis of the recently assembled mouse database identified one gene that showed 63% overall amino acid identity to human FcγRIIIA and an even greater identity in the antibody binding extracelluar domain and was called Fc-receptor-like 3 (Fcrl3), CD16-2, or FcγRIV (Mechetina et al., 2002; Davis et al., 2002; Nimmerjahn et al., 2005). This gene has now been shown to be a bona fide IgG Fc receptor and is called FcγRIV to designate that fact.

FcγRIV: A Family Member with Distinct Activity

The FcγRIV gene is located on mouse chromosome 1 tightly linked to FcγRIIB and FcγRIII (Figure 1). A prediction of ortholog proteins in other species shows that there are related proteins in humans (FcγRIIIA), chimpanzees, macaques, rats, dogs, cats, pigs, and cows (Figure 1 and not shown), with the highest level of similarity to the rat (80%) and the human ortholog. It requires γ chain for its surface expression and, as has been described for other γ-chain-dependent Fc receptors, crosslinking of FcγRIV by immune complexes induces activating signaling pathways leading to sustained calcium flux (Ravetch and Bolland, 2001; Nimmerjahn et al., 2005).

FcγRIV is highly expressed on neutrophils, monocytes, macrophages, and dendritic cells and is undetectable on mast cells, NK cells, and T and B cells. Similar to other activating Fc receptors, inflammatory stimuli (LPS) and TH-1 cytokines (IFN-γ) can upregulate FcγRIV; in contrast, TH-2 cytokines IL-4, IL-10, or TGF-β downregulate FcγRIV cell-surface expression. After induction of DC maturation, FcγRIV, together with other activating Fc receptors, is downregulated. An important difference between mouse FcγRIV and the human FcγRIIIA is that FcγRIV is not expressed on NK cells. Human neutrophils do not express FcγRIIIA but rather FcγRIIA as their dominant activating FcγR.

The ligand specificity for FcγRIV revealed that it bound IgG2a and IgG2b with intermediate affinity (K_A: $2–3 \times 10^7$ M^{-1}), but not IgG1 or IgG3 antibody isotypes.

Importantly, this higher affinity was not sufficient to enable stable binding to monomeric IgG, leaving it accessible for immune complex binding. Comparison of the affinity of IgG2a and 2b for FcγRIV and FcγRIIB revealed a 1–2 order of magnitude higher affinity for the activation receptor as compared to its inhibitory counterpart, thus predicting that these subclasses would be significantly less sensitive to FcγRIIB-mediated negative regulation (Figure 3A). Moreover, even if coexpressed with FcγRIII, IgG2a and IgG2b ICs would preferentially engage FcγRIV due to its 20–40 times higher affinity and due to the strong FcγRIIB-imposed negative regulation of FcγRIII. Consistent with this notion, blocking FcγRIV function in vivo greatly impaired the pathogenic effects of IgG2a and IgG2b antibodies in passive models of antibody-mediated platelet depletion or tumor cell destruction (Nimmerjahn et al., 2005; Nimmerjahn and Ravetch, 2005). It will be important to determine the role of FcγRIV in other passive and active models of antibody-mediated cytotoxicity and inflammation, where FcγRI- and FcγRIII-independent effects have been observed, such as anti-CD20 antibody-mediated B cell depletion, hemolytic anemia, or certain models of glomerulonephritis and arthritis.

These studies suggest that even if several activating Fc receptors with the same isotype specificity are present on the same cell, only those Fc receptors will be engaged that show the optimal affinity for the respective isotype (Figure 3A). Therefore, IgG1 immune complexes will trigger only FcγRIII, as it is the only activating Fc receptor that can bind IgG1; IgG2a and IgG2b, despite their ability to bind FcγRI (in the case of IgG2a) or FcγRIII (in the case of IgG2a and 2b), will functionally be dependent on FcγRIV as FcγRI will be occupied by monomeric IgG2a and the low affinity of FcγRIII will not result in productive engagement at normal serum concentration of these isotypes. These same principles also apply for the human system, where it has been shown that human FcγRIIIA has a higher affinity for IgG1 as compared to human FcγRIIA. In addition, the presence of allelic variants that show differential affinities for the specific antibody isotypes further supports this concept (Dijstelbloem et al., 2001).

Another Layer of Complexity: Isotype-Specific Negative Regulation by FcγRIIB and the Influence of Cytokines

Based on the recognition of FcγRIV as a highly conserved member of the IgG FcR family, the affinity of the individual Fc receptors for the respective antibody isotypes has been readdressed (Nimmerjahn et al., 2005). These studies predict that, depending on the antibody isotype, individual activating Fc receptors will be differentially regulated by the low-affinity inhibitory Fc receptor IIB (Figure 3A). Based on these affinities, IgG1 would be expected to be the most strictly regulated IgG isotype with a ratio of FcγRIII to FcγRIIB (A/I-ratio) affinity of 0.1 (Figure 3A). In contrast, due to the higher affinity of FcγRIV, these ratios are 70 or 7 for IgG2a and IgG2b, suggesting that these isotypes should be more potent in vivo. Consistent with this hypothesis, it has been observed that in many model systems where isotype switch variants were used, the IgG2a and IgG2b variants were more potent than IgG1or IgG3 (Kipps et al., 1985; Fossati-Jimack et al., 2000; Nimmerjahn and Ravetch, 2005). Moreover, deletion of the inhibitory Fcγ receptor impacted most strongly on antibodies of the IgG1 isotype (Clynes et al., 2000; Nimmerjahn and Ravetch, 2005). The in vivo activity of an IgG antibody, therefore, can be predicted based on its A/I ratio. While there are several factors that can influence these basic A/I ratios, such as basal expression levels of activating versus inhibitory receptors and the modulation of these ratios by cytokines, the magnitude of those components are of secondary significance when compared to the contribution of affinity. Thus, IgG2a antibodies are relatively insensitive to these effects, while IgG1 is quite sensitive to modest changes in A/I ratios. For example, in active models of antibody-mediated inflammation, the steady-state ratios will be changed in favor of the activating Fc receptors (Figure 3B). Inflammatory mediators, such as IFN-γ and C5a, can upregulate activating Fc receptors and at the same time reduce FcγRIIB expression levels (Guyre et al., 1983; Shushakova et al., 2002). Under these circumstances, autoreactive IgG1 antibodies are capable of causing severe damage. In contrast, TH-2 cytokines like IL-4, IL-10, or TGF-β upregulate the inhibitory Fc receptor and decrease expression of the activating Fc receptors on innate immune effector cells (Okayama et al., 2000; Pricop et al., 2001; Radeke et al., 2002; Tridandapani et al., 2003; Nimmerjahn et al., 2005). Under these conditions, isotypes that have a low or moderate A/I ratio (IgG1 and IgG2b) would be expected to lose more activity than those with a high ratio, such as IgG2a. High-dose intravenous γ globulin (IVIG) provides a compelling example of the generality of this concept. The antiinflammatory activity of this preparation has recently been shown to be linked to its ability to upregulate FcγRIIB expression on effector macrophages in models of ITP and rheumatoid arthritis (RA). For IgG1, this modulation alone is sufficient to convert a pathogenic antibody to a nonpathogenic isotype, consistent with the low A/I ratio for this subclass in which modest changes in FcγRIIB expression will raise the threshold required for effective IgG1 crosslinking of FcγRIII. It should be noted, however, that cytokine-mediated regulation of FcR expression is cell type-specific. IL-4, for example, while upregulating FcγRIIB expression on myeloid cells, downregulates FcγRIIB expression on activated B cells (Rudge et al., 2002).

Recent data suggest that this paradigm holds true for human IgG antibodies as well. Human clinical trials with antibodies directed against tumor cell-surface proteins, such as CD20, revealed that patients with the high-affinity FcγRIIIA or FcγRIIA alleles, resulting in a higher A/I ratios, responded significantly better to antibody therapy with increased survival and time to relapse (Cartron et al., 2002; Weng and Levy, 2003; Weng et al., 2004). The challenge for future antibody-based immunotherapeutic approaches will be to select or, preferably, design antibody isotypes that can trigger effector functions such as ADCC reactions even under nonfavorable A/I ratios. A critical factor in such Fc engineering is knowledge of the FcR-expression profile of the relevant effector cells mediating the biologically relevant response and the impact of both disease and therapy on the modulation of these receptors. Moreover, knowledge of the dominant antibody isotypes involved in an autoimmune disease

might be predictive for the involvement of a specific activating Fc receptor, thereby allowing the identification of therapeutic targets. Thus, since murine lupus models display a dominance of IgG2a and IgG2b subclasses, it is tempting to speculate that FcγRIV is the responsible activating Fc receptor in these disease models, as well. It seems likely that in human lupus, where IgG1 and IgG3 isotypes dominate the anti-DNA response, and IgG2 and IgG3 are the major isotypes in kidney immune complex deposits, multiple activating Fc receptors are responsible for antibody-mediated inflammation (Maddison, 1999; Tsao, 2003). Indeed, allelic variants of human FcγRIIA and IIIA that change the affinity of these receptors for IgG isotypes have been suggested to be risk factors for developing lupus in certain populations (Tsao, 2003).

The regulation of FcR expression by cytokines is coupled to the regulation of isotypes by these same cytokines. Thus, TH1 cytokines such as IFN-γ induce class switching to IgG2a, whereas TH2-type cytokines (IL-4) induce class switching to IgG1 (Coffman et al., 1989; Finkelman et al., 1990). 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 of expression levels of the responsible activating versus inhibitory Fc receptors.

Conclusions

Research in the field of Fc-receptor biology over the last decade has established the in vivo role of these receptors during various phases of an immune response. With the identification of mouse FcγRIV, a more complete and consistent picture of Fc-receptor biology in the mammalian system emerges and previously conflicting results can now be explained. It has become clear that the efficiency of therapeutic as well as the pathogenicity of autoimmune antibodies will be determined by the strength of the interaction with cellular Fc receptors. Factors that influence this interaction are the actual affinity of antibody isotypes for Fc receptors and the expression level of the activating/inhibitory receptor pairs. Analysis of murine model systems has established that despite the complex nature of these interactions, it is clearly possible to manipulate their outcome. The challenge for the future will be to translate this knowledge into optimized therapeutic approaches. In the case of the inhibitory Fc receptor, these therapeutic scenarios might include enhancing inhibitory Fc-receptor expression on B cells to suppress the generation of autoreactive plasma cells or blocking FcγRIIB activity on dendritic cells to generate stronger antitumor or antipathogen immune responses. Activating Fc receptors can be similarly manipulated such that blocking their activity in the case of destructive autoimmune processes would be desirable or enhancing antibody binding to these receptors to obtain stronger antibody-dependent cellular cytotoxicity reactions for the elimination of infected or malignant cells.

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