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IgG Fc Receptors

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■ **Abstract** Since the description of the first mouse knockout for an IgG Fc receptor seven years ago, considerable progress has been made in defining the in vivo functions of these receptors in diverse biological systems. The role of activating FcγRs in providing a critical link between ligands and effector cells in type II and type III inflammation is now well established and has led to a fundamental revision of the significance of these receptors in initiating cellular responses in host defense, in determining the efficacy of therapeutic antibodies, and in pathological autoimmune conditions. Considerable progress has been made in the last two years on the in vivo regulation of these responses, through the appreciation of the importance of balancing activation responses with inhibitory signaling. The inhibitory FcR functions in the maintenance of peripheral tolerance, in regulating the threshold of activation responses, and ultimately in terminating IgG mediated effector stimulation. The consequences of deleting the inhibitory arm of this system are thus manifested in both the afferent and efferent immune responses. The hyperresponsive state that results leads to greatly magnified effector responses by cytotoxic antibodies and immune complexes and can culminate in autoimmunity and autoimmune disease when modified by environmental or genetic factors. FcγRs offer a paradigm for the biological significance of balancing activation and inhibitory signaling in the expanding family of activation/inhibitory receptor pairs found in the immune system.

INTRODUCTION

Fc receptors for IgG were identified over 35 years ago with the observation that IgG antibodies could be directly cytophilic for macrophages when presented as opsonized RBCs (1). This binding property of IgG antibodies was independent of the F(ab) region of the antibody and required only Fc interactions. Subsequent in vitro studies established the role of these receptors in triggering effector responses such as macrophage phagocytosis, NK cell ADCC, neutrophil activation, and the paradoxical inhibition of B cell activation by IgG immune complexes (2–6). Our current understanding of IgG FcRs has been greatly enhanced by the molecular cloning of the murine genes 15 years ago, followed soon after by their human counterparts and the recently described crystal structures for both the receptors

and ligand complexes defined in the last year (7–16). Two general classes of IgG FcRs are now recognized—the activation receptors, characterized by the presence of a cytoplasmic ITAM sequence associated with the receptor, and the inhibitory receptor, characterized by the presence of an ITIM sequence (Figure 1) (17–19). These two classes of receptors function in concert and are usually found coexpressed on the cell surface. Because activation and inhibitory receptors bind IgG with comparable affinity and specificity (17, 20), coengagement of both signaling pathways is thus the rule, setting thresholds for and ultimately determining the magnitude of effector cell responses. This appreciation of the balanced function of these receptors has been primarily developed through the analysis of mice deficient in either receptor or signaling pathway. This review focuses on these in vivo studies and the implications of those studies for the role of these receptors in maintaining tolerance, shaping the antibody repertoire, and determining the cellular outcome of engagement of FcRs by IgGs. The gene structures, cellular expression, binding affinities, polymorphisms, and subclass specificities of these receptors have been extensively reviewed in the past, and the reader is directed to those studies for further details (17, 18, 20, 21).

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ACTIVATION FcγRs

These molecules are characterized by the presence of an ITAM motif either intrinsic to the receptor, as in the case of the human FcγRIIA (a receptor not found in the mouse), or more commonly, as part of an associated subunit, the γ or ζ chain, as in FcγRI and FcγRIIIA, receptors conserved between mouse and human (17, 18, 20). (A neutrophil specific decoy receptor, FcγRIIIB, is additionally found in humans that binds IgG immune complexes without triggering activation.) Activation receptors bind IgG either with relatively high affinity (10^{-9}) for the case of FcγRI or with low affinity (10^{-6}), as is the case for FcγRIIA and IIIA (17, 20). Cross-linking of the ligand binding extracellular domain results in tyrosine phosphorylation of the ITAM by members of the src kinase family, with subsequent recruitment of SH2 containing signaling molecules that bind the phosphorylated ITAM, most notably the syk kinase family of molecules. Depending on the particular cell type activated by the Fc receptor, different kinases are involved in these signaling pathways. For instance, FcγRIIIA aggregation activates lck in NK cells, while FcγRIIA or FcγRIIIA activate lyn and hck in monocytic and mast cells (22, 23). Likewise, syk is activated in mast cells and macrophages, whereas the related kinase ZAP70 is activated in NK cells (24–26). Subsequent signaling pathways associated with cellular activation by FcγRs are similar to that observed for other ITAM-containing receptors such as the BCR and TCR (27, 28). Early events include the activation of PI3 kinase, the enzymatic activity of which leads to production of PIP_3 and recruitment of PH domain containing molecules, such as PLCγ and Tec kinases, through a PIP_3-PH domain interaction (29–31). Myeloid cells contain several Tec kinases, named Btk, Itk, and Emt (32), that can all be activated upon Fc receptor aggregation. The newly discovered

adaptor molecules SLP-76 and BLNK link Syk activation with Btk and PLCγ responses in FcR-dependent macrophage activation (33). Ultimately, activation of PLCγ leads to generation of IP3, DAG, and sustained calcium mobilization. The significance of this activity for FcR function has been appreciated by the analysis of PLCγ2-deficient mice, which are defective for FcγRIII-dependent NK cell function (34). An example of some of the possible signaling pathways activated by FcγRIII aggregation is shown in Figure 2. Cellular phenotypes associated with FcγR activation receptors include degranulation, phagocytosis, ADCC, transcription of cytokine genes, and release of inflammatory mediators (2–4). In general, these phenotypes are indicative of the central role of these receptors in mediating inflammatory responses to cytotoxic IgGs or IgG immune complexes.

Activation FcγRs are found on most effector cells of the immune system, notably monocytes, macrophages, NK cells, mast cells, eosinophils, neutrophils, and platelets, while absent from lymphoid cells. In general, activation and inhibitory FcγRs are coexpressed on the same cell, a physiologically important means of setting thresholds for activating stimuli, because the IgG ligand will coengage both receptors. The ratio of expression of these two opposing signaling systems will determine the cellular response. It is, therefore, not surprising that these receptors are modulated in their expression during the differentiation and development of effector cells and by cytokine activation of these cells (17, 35, 36).

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INHIBITORY FcγR

In both mouse and human, a single gene for an inhibitory FcγR, FcγRIIB, encodes a single chain glycoprotein characterized by a ligand-binding extracellular domain highly homologous to its activation counterparts, but containing the distinctive inhibitory or ITIM sequence in its cytoplasmic domain. The inhibitory FcR binds IgG with low affinity (10^{-6}), interacting with immune complexes only at physiological concentration of antibody (17, 20). The prototype six amino acid ITIM cytoplasmic sequence, I/V/L/SxYxxL/V, in which x denotes any amino acid, has been found in a growing number of receptors, most notably the NK inhibitory molecules that bind MHC class I (19, 37–40). The inhibitory activity of FcγRIIB, embedded in the cytoplasmic domain of the single chain FcγRIIB molecule, was defined as a 13 amino acid sequence AENTITYSLLKHP, shown to be both necessary and sufficient to mediate the inhibition of BCR-generated calcium mobilization and cellular proliferation (41, 42). Significantly, phosphorylation of the tyrosine of this motif was shown to occur upon BCR coligation and was required for its inhibitory activity (42). This modification generated an SH2 recognition domain that is the binding site for the inhibitory signaling molecule SHIP that leads to the abrogation of ITAM activation signaling by hydrolyzing the membrane inositol phosphate PIP3, itself the product of receptor activation (Figure 3) (43). In the absence of PIP3, binding proteins of the PH domain class (e.g. Btk and PLCγ) are released from the membrane and a sustained calcium signal is blocked by

preventing influx of extracellular calcium through the capacitance-coupled channel (44, 45). FcγRIIB phosphorylation also leads to an arrest of BCR triggered proliferation by potentially perturbing the activation of MAP kinases and preventing the recruitment of the anti-apoptotic protein kinase, Akt (46–49).

In addition to its expression on B cells, where it is the only IgG Fc receptor, FcγRIIB is widely expressed on effector cells such as macrophages, neutrophils, and mast cells, missing only from T and NK cells (17, 20). FcγRIIB displays three separable inhibitory activities, two of which are dependent on the ITIM motif and one independent of this motif. Coengagement of FcγRIIB to an ITAM-containing receptor leads to tyrosine phosphorylation of the ITIM by the lyn kinase, recruitment of SHIP, and the inhibition of ITAM-triggered calcium mobilization and cellular proliferation (43, 50, 51). However, inhibition of calcium mobilization and arrest of cellular proliferation, while both ITIM-dependent processes, are the result of different signaling pathways. Calcium inhibition requires the phosphatase activity of SHIP to hydrolyse PIP_3 and the ensuing dissociation of PH domain containing proteins like Btk and PLCγ (Figure 3) (44, 45, 52). The net effect is to block calcium influx and prevent sustained calcium signaling. Calcium-dependent processes such as degranulation, phagocytosis, ADCC, cytokine release, and proinflammatory activation are all blocked. Arrest of proliferation in B cells is also dependent upon the ITIM pathway, through the activation of the adaptor protein dok and subsequent inactivation of MAP kinases (47, 48). The role of SHIP in this process has not been fully delineated, although it can affect proliferation in several ways. SHIP, through its catalytic phosphatase domain, can prevent recruitment of the PH domain survival factor Akt by hydrolysis of PIP_3 (46, 49). SHIP also contains PTB domains that could act to recruit dok to the membrane and provide access to the lyn kinase that is involved in its activation. Dok-deficient B cells are unable to mediate FcγRIIB triggered arrest of BCR-induced proliferation, while retaining their ability to inhibit a calcium influx, demonstrating the dissociation of these two ITIM-dependent pathways (48).

The third inhibitory activity displayed by FcγRIIB is independent of the ITIM sequence and is displayed upon homo-aggregation of the receptor. Under these conditions of FcγRIIB clustering, a proapoptotic signal is generated through the transmembrane sequence (Figure 4). This proapoptotic signal is blocked by recruitment of SHIP, which occurs upon coligation of FcγRIIB to the BCR, due to the Btk requirement for this apoptotic pathway. This novel activity has been reported only in B cells and has been proposed to act as a means of maintaining peripheral tolerance for B cells that have undergone somatic hypermutation (Figure 4) (53).

FcγRs IN THE AFFERENT RESPONSE

The ability of IgG immune complexes to influence the afferent response has been known for over 50 years and can be either enhancing or suppressive, depending on the precise combination of antibody and antigen and the mode of

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administration (54). Recent studies have attempted to define the molecular mechanisms behind these activities using defined mouse strains with mutations in activation or inhibitory FcRs. Direct effects on B cells stem from the ability of the inhibitory FcγRIIB molecule to influence the state of B cell activation and survival by providing a means to discriminate between those rare somatically hypermutated germinal center B cells that have high-affinity cognate antigen binding from the predominant population with low-affinity and potentially cross-reactive specificities. Because antigen is retained in the form of immune complexes on follicular dendritic cells (FDC), it can interact with B cells either through FcγRIIB alone, resulting in apoptosis, or by coengaging FcγRIIB with BCR, favoring survival, as summarized in Figure 4. Support for a role of FcγRIIB in the maintenance of peripheral tolerance comes from the observation that FcγRIIB-knockout mice on the C57Bl/6 background develop autoimmune disease in a B cell–autonomous manner (55). Those animals develop anti-DNA and antichromatin antibodies and then succumb to a fatal, autoimmune glomerulonephritis at 8 months of age. The phenotype is strain-dependent and is not seen in Balb/c or 129 strains of mice. FcγRIIB thus acts as a genetic susceptibility factor for autoimmune disease, under the control of epistatic modifiers, to suppress the emergence of autoreactivity and maintain peripheral tolerance. Further support for this conclusion is provided by the observations that autoimmune strains of mice, like B/W F1, have reduced surface expression of FcγRIIB attributed to DNA polymorphisms in the promoter region of the gene encoding this receptor (56, 57). This reduced expression of FcγRIIB is thus suggested to contribute to the increased susceptibility of these animals to the development of autoantibodies and autoimmune disease.

If FcγRIIB indeed functions in vivo to maintain peripheral tolerance, then its loss should allow for the emergence of autoantibodies when otherwise resistant animals are challenged with potentially cross-reactive antigens. This hypothesis has been validated in models of collagen-induced arthritis and Goodpasture's syndrome. FcγRIIB-deficient mice, on the nonpermissive H-2^b haplotype, develop arthritis when immunized with bovine type II collagen (58). The loss of FcγRIIB thus bypasses the requirement for the specific H-$2^{q,r}$ alleles previously demonstrated to be required in this model by allowing FcγRIIB-deficient autoreactive B cell clones to expand and produce pathogenic autoantibodies. When the permissive DBA/1 strain (H-2^q) is made deficient in FcγRIIB, autoantibody development is augmented and disease is greatly enhanced. In a similar manner, immunization of H-2^b mice deficient in FcγRIIB with bovine type IV collagen results in cross-reactive autoantibodies to murine type IV collagen, with dramatic pathogenic effects (59). These mice develop hemorrhagic lung disease and glomerulonephritis with a "ribbon deposition" pattern of immune complexes in the glomuli of affected animals. These characteristics are indicative of Goodpasture's syndrome, a human disease not previously modeled in an animal species.

Immune complexes can either enhance or suppress the humoral response depending on the kind of Fc receptor engaged and the cell type involved. Expression

of the inhibitory FcγRIIB on B cells provides a mechanism for the suppressive effects of immune complexes on antibody production, particularly during the germinal center reaction when immune complexes retained on FDCs interact with somatically hypermutated B cells. The enhancing property of immune complexes on the afferent response is likely to arise from the expression of FcRs on antigen presenting cells, like dendritic cells (60–62). DCs express all three classes of IgG FcR. While in vitro studies have suggested that triggering of activation FcRs can induce DC maturation, the in vivo significance of this pathway has not been established (63). The ability of FcRs, particularly FcγRI, to internalize ICs could provide a mechanism for enhanced presentation and augmented antibody responses, while the presence of the inhibitory FcγRIIB molecule appears to reduce the enhancing effect (64, 65). Mice deficient in RIIB display enhanced antibody responses to soluble antibody-antigen complexes, in some cases dramatically so (66), which is likely to result from enhanced presentation. In addition, in vitro studies suggest that internalization through specific FcRs on APCs may influence the epitopes presented and T cell response generated as a result (63). At the present time there is a growing body of data to suggest that FcRs are indeed involved in enhancing the afferent response, by influencing antigen presentation and cognate T cell interactions. It is also possible that FcRs function on APCs in the establishment of tolerance by influencing the differentiation of DCs and their capacity to induce either anergy or T cell activation. The precise role of each Fc receptor expressed on APCs will require conditional knockouts of these molecules on specific DC populations to resolve the contribution of these systems to the generation of an appropriate antibody response.

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FcRs IN THE EFFERENT RESPONSE

The first FcR knockout to be described was for the common activation subunit, the γ chain, required for surface assembly and signaling of FcγRI and FcγRIII as well as FcεRI (67). Mice deficient in the γ chain were systematically studied in diverse models of inflammation and found to be unable to mediate IgG-triggered inflammatory responses, attributed to the loss of the low-affinity activation receptor FcγRIII (67–73). This was further confirmed by the analysis of FcγRIII-deficient mice constructed by deletion of the receptor α-chain (74, 75). Subsequent studies on mice deficient in the inhibitory FcγRIIB molecule established the opposing action of this receptor, such that mice deficient in that receptor displayed enhanced B cell responses, autoimmunity, and augmented IgG-mediated inflammation (55, 58, 59, 71,76–78). The general finding, discussed in detail below, illustrates that IgGs initiate their effector responses in vivo through coengagement of activating and inhibitory FcRs. The physiological response is thus the net of the opposing activation and inhibitory signaling pathways each receptor triggers and is determined by the level of expression of each receptor and the selective avidity of the IgG ligand.

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TYPE I—IMMEDIATE HYPERSENSITIVITY

Both cutaneous and systemic models of passive anaphylaxis, induced by IgE, were studied in FcRγ chain–deficient mice and were found to be absent, fully consistent with the observations obtained in FcεRI–α chain deficient mice, confirming the role of the high-affinity IgE receptor in mediating IgE-induced anaphylactic responses (67, 79). FcγRIIB deficient mice, challenged in this model, displayed an unexpected enhancement of IgE-mediated anaphylaxis, suggesting a physiological interaction between this inhibitory receptor and FcεRI (80). The molecular basis for this modulation of FcεRI signaling by FcγRIIB has not been determined, although previous studies have indicated that IgE can bind with low affinity to FcγRII/III, suggesting a mechanism for coengagement of these receptors (81, 82). In addition to FcεRI, mast cells also express the IgG FcRs RIIB and RIII (82). Passive systemic anaphylaxis induced by IgG was attenuated in FcRγ chain–deficient and FcγRIII-deficient mice, indicating the capacity of IgG and FcγRIII to mediate mast cell activation in vivo (80, 83). FcγRIIB deficient mice were enhanced in IgG-induced anaphylaxis (76, 80). Surprisingly, active anaphylaxis, induced by immunization with antigen in alum, was enhanced in FcεRI-deficient mice and FcγRIIB-deficient mice and attenuated in FcRγ– and FcγRIII-deficient mice (83, 84). These animals all displayed antigen specific antibodies of both the IgE and IgG classes, indicating that the active anaphylaxis seen, which was FcγRIII dependent and FcεRI independent, was primarily attributed to IgG antibodies. The enhancement of anaphylactic responses in FcεRI animals resulted from the increased expression of FcγRIII on mast cells in these mice, normally limited by the availability of the common γ chain. In the absence of FcεRI α chain, FcRγ chain is available to associate with FcγRIII–α chain and assemble on the cell surface as a functional signaling receptor (84). These studies indicated the importance of the γ chain in regulating the level of surface expression of FcεRI and FcγRIII. Since γ chain is also associated with other members of the activation/inhibition paired receptors expressed on mast cells, such as PIRA/PIRB (85, 86), the intracellular competition between these diverse α subunits and the common γ chain will determine the level of surface expression of individual receptors and thus their ability to respond to specific biological stimuli. The absolute level of surface expression of FcRs on mast cells is clearly of therapeutic significance in both IgE- and IgG-mediated inflammatory responses; modulation of γ chain expression could thus represent a new therapeutic avenue for intervention in diseases like anaphylaxis and asthma.

TYPE II INFLAMMATION—CYTOTOXIC IgG

Cytotoxic IgGs are found in a variety of autoimmune disorders and have been developed for therapeutic indications in the treatment of infectious and neoplastic diseases. The mechanisms by which these antibodies trigger cytotoxicity in vivo

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have been investigated in FcR knockout mice. Anti-RBC antibodies trigger erythrophagocytosis of IgG opsonized RBCs in an FcR-dependent manner; γ chain–deficient mice were protected from the pathogenic effect of these antibodies, while complement C3 deficient mice were indistinguishable from wild-type animals in their ability to clear the targeted RBCs (69, 87, 88). FcγRIII plays the dominant role in this process for IgG1, 2a and 2b isotypes of antibodies; IgG3 antibodies were not pathogenic, consistent with its minimal engagement by FcRs. Experimental models of ITP, using mouse IgG2a antiplatelet antibodies to trigger thrombocytopenia, yielded similar results; FcRγ-deficient or FcγRIII-deficient mice were protected from the pathogenic activity of these antibodies, while C3-deficient mice were fully susceptible to antibody induced thrombocytopenia (87, 88). FcγRIIB-deficient mice were indistinguishable from wild-type animals in their ability to mediate anti-RBC or antiplatelet clearance, indicating that the specific effector cells involved in clearance were not expressing significant levels of this inhibitory receptor constitutively (89) (A Samuelsson, JV Ravetch, unpublished results). In other models of cytotoxic antibody responses, the dependence of activation FcRs was similar to the cases cited above. In a model of *Cryptococcus neoformans*-induced disease, passive immunization with mouse IgG1, 2a and 2b antibodies resulted in protection in wild-type, but not FcRγ chain– or FcγRIII-deficient animals; IgG3 antibodies enhanced disease in wild-type and FcR-deficient strains, again indicating that a distinct pathway, not requiring known FcγRs, is involved in IgG3 antibody–mediated internalization of this pathogen (90). While IgG3 antibodies have been reported to bind to FcγRI in vitro (91), the studies cited above indicate that different receptors are involved in vivo for IgG3 activity in this type of experimental system.

IgG antibodies raised to mouse glomerular basement membrane preparations induce acute glomerulonepthritis in wild-type, but not FcRγ– or FcγRIII-deficient animals (78, 92). FcγRIIB-deficient animals displayed enhanced disease in this model, indicating that the effector cells involved were constitutively expressing significant levels of FcγRIIB (78). Similar results were obtained when DBA/1 animals were immunized with bovine type II collagen to induce arthritis. Deficiency of FcRγ chain protected the mice from the pathogenic effects of the anticollagen antibodies generated in these mice (93). As mentioned above, deficiency of FcγRIIB in the DBA/1 CIA model resulted in enhanced disease, through increased autoantibody production and elevated effector responses (58).

A dramatic example of the importance of these pathways in determining the in vivo activity of cytotoxic antibodies was obtained in models of antitumor antibody response. In a syngenic murine model of metastatic melanoma, an IgG2a antimelanocyte antibody was able to reduce tumor metastasis in wild-type animals but was ineffective in FcRγ-deficient mice (94). In the absence of FcγRIIB, the activity of the antibody was enhanced 50-fold, indicating that the in vivo cytotoxic activity of the antibody was the net of activation and inhibitory receptor engagement (77). Identical results were obtained in xenograft models in nude mice, using human breast carcinoma or lymphoma lines and either murine IgG1 or humanized

IgG1 antibodies. A point mutation that eliminated FcR binding abolished the in vivo cytotoxic activity of the antibodies, while not affecting the in vitro growth inhibitory activity, again illustrating the difference between in vivo and in vitro mechanisms (77). The conclusions that can be drawn from these studies support a dominant role for FcγRIII in mediating cytotoxicity by IgG antibodies. FcγRIIB restricts the effector response in those situations where the effector cell expresses this inhibitory molecule. Through manipulation of IgG-Fc receptor interactions at either the receptor or antibody interface, cytotoxic antibodies can either be enhanced in their activity for therapeutic benefit in infectious and neoplastic disease or blocked in their ability to trigger effector responses as a means of treating IgG antibody mediated, organ-specific autoimmune diseases, or attenuating adverse side effects observed with some therapeutic antibodies. The availability of crystallographic data on these interactions will clearly guide the design of antibodies to optimize specific Fc-FcR interactions.

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TYPE III RESPONSES—IMMUNE COMPLEX–MEDIATED INFLAMMATION

The classic example of this reaction, the Arthus reaction, has been studied in a variety of FcR and complement-deficient animals. The initial studies were performed using the cutaneous reverse passive Arthus reaction, in which antibody was injected intradermally and antigen given intravenously. An inflammatory response developed within 2 h, characterized by edema, hemorrhage, and neutrophil infiltration. This reaction was performed in a variety of complement-deficient and FcR-deficient animals (68, 87). The results from several independent studies confirmed the initial observations, that IgG immune complexes triggered cutaneous inflammatory reactions even in the absence of complement but displayed an absolute requirement for FcγRIII activation (75). FcγRIIB modulated the magnitude of the response, with enhanced Arthus reactions observed in FcγRIIB-deficient strains (76). The effector cell in the cutaneous reaction was determined to be the mast cell, as demonstrated by the use of mast cell–deficient strains and by mast cell reconstitution studies (95). The generality of this result was demonstrated in similar reactions performed in the lung, illustrating the FcR dependence and relative complement independence of this response (71). Thus, all studies have observed an absolute dependence on FcR expression in the Arthus reaction. However, some studies have reported partial attenuation of the Arthus reaction in mouse strains deficient in C3 and have suggested a synergistic involvement of both FcRs and early components of the complement cascade (96–98). It is more likely that the partial attenuation of the Arthus reaction reported in those studies is the result of IgM contamination in commercial IgG preparations of antibodies used or the effects of traumatic insult, two conditions in which complement has been demonstrated to be involved in effector cell activation. Deficiency in C5a or its receptor has also been reported to result in a partial reduction in the magnitude of the

response in IC-induced lung inflammation (98). The conclusions consistent with these data on the Arthus reaction in the mouse is the strict requirement for the activation FcγRIII in initiating IgG immune complex inflammation, once again limited in its response by the expression of the inhibitory FcγRIIB. C5a activation may be a distal response to FcγRIII engagement in some specific models as one of downstream effector molecules involved in the later stages of the inflammatory response.

The significance of the FcR pathway in initiating immune complex inflammation in autoimmune disease was established by investigating a spontaneous murine model of lupus, the B/W F1 mouse. The Arthus reaction results predicted the absolute requirement of activation FcγR in initiating inflammation and tissue damage in immune complex diseases like lupus. The FcRγ chain deletion was backcrossed onto the NZB and NZW strains for eight generations and the intercrossed progeny were segregated into B/W FcR$\gamma^{-/-}$ and FcR$\gamma^{+/-}$. Anti-DNA antibodies and circulating immune complexes developed in all animals; immune complex and complement C3 deposition was similarly observed in all animals. However, mice deficient in the common γ chain showed no evidence of glomerulonephritis and had normal life expectancy, while mice heterozygous for the γ chain mutation developed glomerulonephritis and had reduced viability as has been described for B/W F1 animals (70). Reconstitution studies have confirmed that disease segregates with bone marrow derived cells expressing FcRγ, suggesting a model in which the IgG immune complexes deposited in the kidney triggered inflammation by FcR activation of bone marrow derived, circulating effector cells, most likely monocytes (RA Clynes, JV Ravetch, unpublished results). These results indicate that intervention in the effector stage of immune complex diseases, like lupus, would be accomplished by blocking FcγRIII activation to prevent initiation of effector cell responses. Early components of complement seem not to be required for initiating the inflammatory reponses, whereas later components like C5a may be downstream of FcR activation. Whether species selectivity exists favoring one pathway in rodents (FcRs) and another in humans (complement) remains to be determined, but such selectivity is unlikely given the conservation of both systems in a wide variety of species.

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CONCLUSIONS

Receptors for the Fc portion of IgG play a significant role in vivo in maintaining peripheral tolerance by deleting autoreactive B cells, which can arise during somatic hypermutation in germinal centers, in augmenting T cell responses by enhancing antigen presentation by dendritic cells, and in mediating the coupling of antigen recognition to effector cell activation. Central to the correct functioning of these responses is the balance that is maintained through the pairing of activation and inhibitory receptors that coengage the IgG ligand; perturbations in either component result in pathological responses. Studies in mice deficient in individual

FcRs have provided the necessary insights for defining comparable activities in human autoimmune diseases and suggest ways in which manipulation of the IgG-FcR interaction may lead to new classes of therapeutics for the treatment of these diseases. Conversely, engineering of therapeutic antibodies targeted to eliminate infectious or neoplastic disease will likely benefit from optimization of their Fc domains for interaction with specific Fc receptors.

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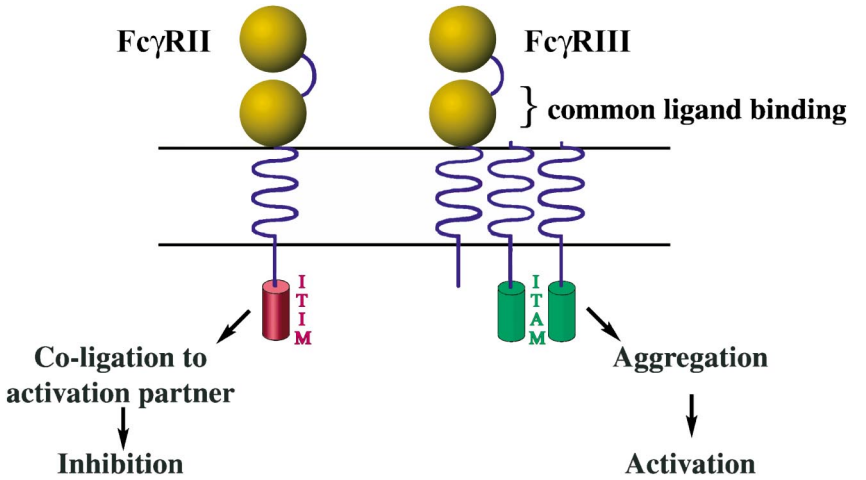

Figure 1 Schematic representation of an activation/inhibitory Fc receptor pair.

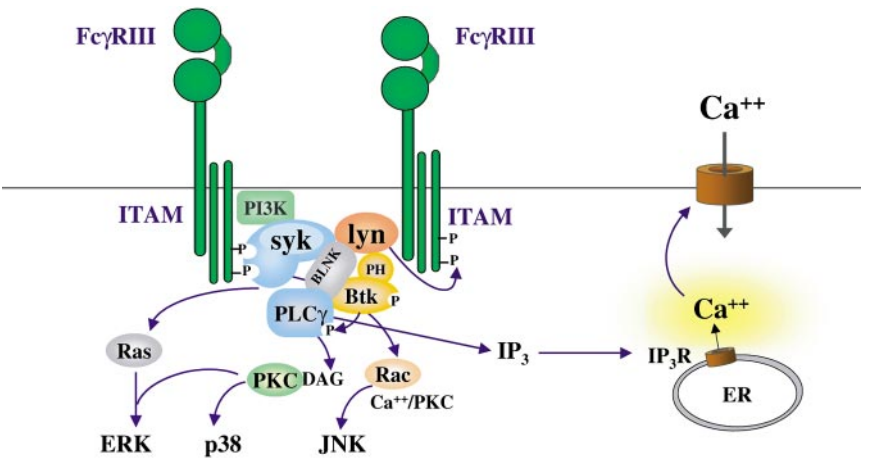

Figure 2 Cellular activation by FcγRIII aggregation. This figure shows an example of the possible signaling pathways initiated upon FcR ITAM phosphorylation.

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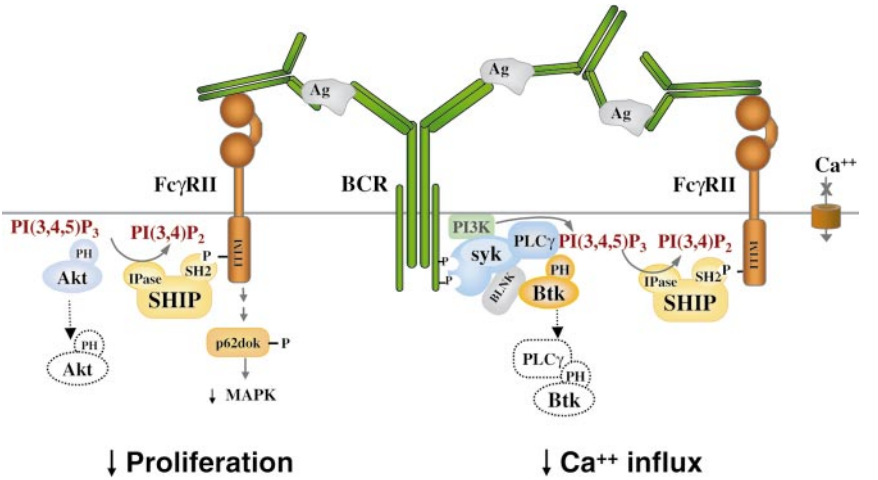

Figure 3 Signaling pathways triggered by BCR-FcγRII co-ligation. Cellular activation is inhibited by recruitment of the inositol phosphatase SHIP to the FcγR phosphorylated ITIM.

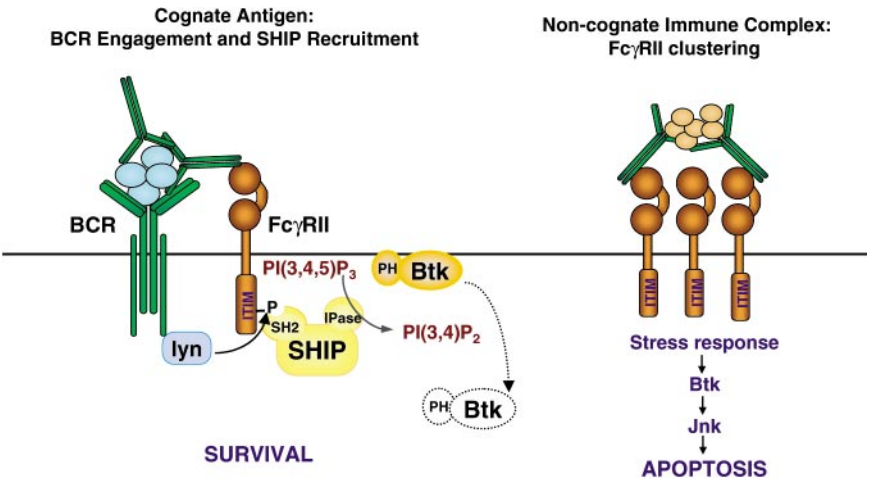

Figure 4 A model for the role of FcγRIIB in affinity maturation of germinal center B cells.