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FcγRIIB in autoimmunity and infection: evolutionary and therapeutic implications

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Abstract

FcγRIIB is the only inhibitory Fc receptor. It controls many aspects of immune and inflammatory responses, and variation in the gene encoding this protein has long been associated with susceptibility to autoimmune disease, particularly systemic lupus erythematosus (SLE). FcγRIIB is also involved in the complex regulation of defence against infection. A loss-of-function polymorphism in FcγRIIB protects against severe malaria, the investigation of which is beginning to clarify the evolutionary pressures that drive ethnic variation in autoimmunity. Our increased understanding of the function of FcγRIIB also has potentially far-reaching therapeutic implications, being involved in the mechanism of action of intravenous immunoglobulin, controlling the efficacy of monoclonal antibody therapy and providing a direct therapeutic target.

The receptors for the Fc region of IgG (FcγRs) are expressed by many immune cells (FIG. 1) and are important in both promoting and regulating the immune and inflammatory response to immune complexes. Most FcγRs are activating receptors and include the high-affinity receptor FcγRI and a family of low affinity receptors, including FcγRIIA, FcγRIIC, FcγRIIIA and FcγRIIIB in humans, and FcγRIII and FcγRIV in mice[1]. FcγRIIB is the only FcγR that has an inhibitory function.

IgG has an important role in defence against pathogens, as shown by the increased susceptibility to infection of patients with hypogammaglobulinaemia. The interaction between pathogen-bound IgG and activating FcγRs directly mediates pathogen clearance by antibody-dependent cell-mediated cytotoxicity (ADCC), degranulation of cytotoxic cells and phagocytosis, and indirectly through the release of cytokines and other inflammatory mediators[1]. FcγRs are also important in mediating IgG-associated pathogen toxin neutralization[2,3]. In addition to binding to IgG, FcγRs can also bind to pentraxins and acute-phase proteins, including serum amyloid P and C-reactive protein[4,5]; however, the physiological importance of these interactions remains to be determined.

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Cross-linking of activating FcγRs by immune complexes results in the phosphorylation of immunoreceptor tyrosine-based activating motifs (ITAMs) that are present either in the cytoplasmic domain of the receptor (FcγRIIA and FcγRIIC) or in the associated FcR common γ-chain (FcγRI and FcγRIIIA). This ITAM phosphorylation results in the activation of the signalling molecule SYK and the initiation of an activating signalling cascade[1].

It has long been known that the Fc fragments of IgG could suppress humoral immunity[6], an effect mediated by the specific interaction of these fragments with B cell-expressed FcγRIIB[7,8]. FcγRIIB is the only FcγR expressed by B cells[9], and if it is cross-linked to the B cell receptor (BCR) the B cell activation threshold is increased and antibody production decreased. FcγRIIB is also expressed by other immune cells, including dendritic cells (DCs), macrophages, activated neutrophils, mast cells and basophils[1,10,11]. When expressed by these cells, FcγRIIB inhibits the functions of activating FcγRs, such as phagocytosis and pro-inflammatory cytokine release. When expressed by follicular DCs (FDCs), FcγRIIB is important for trapping the antigen-containing immune complexes that are thought to be crucial for driving the germinal centre response[12,13]. This diversity of its expression and function underlies the importance of FcγRIIB in regulating defence against infection and susceptibility to autoimmune disease.

In humans and mice, three FcγRIIB isoforms have been identified[14-17]. Two of these, FcγRIIB1 and FcγRIIB2, encode membrane proteins that have an immunoreceptor tyrosine-based inhibitory motif (ITIM) within the cytoplasmic domain. FcγRIIB1 is the main isoform and is expressed by B cells and, at lower levels, by monocytes[18]. It has inhibitory functions and is not thought to mediate immune complex internalization. FcγRIIB2 is the main isoform expressed by myeloid-derived cells and can mediate endocytosis[19], a process dependent on a dileucine motif in its cytoplasmic domain[20,21]. Although FcγRIIB1 and FcγRIIB2 are encoded by the same gene, the FcγRIIB1 isoform is generated by alternative mRNA splicing that results in a 47-amino acid cytoplasmic insertion upstream of the ITIM, which inhibits endocytosis by preventing receptor accumulation in clathrin-coated pits[22]. FcγRIIB3 is a soluble isoform that lacks the transmembrane and first cytoplasmic domains[23], and it can inhibit the presentation of IgG-complexed antigen[24]. Another soluble form of FcγRIIB can be generated by cleavage of the two extracellular domains[25] and can suppress plasmablast production *in vitro*[26]. Thus, there are two soluble forms of FcγRIIB that can inhibit immune complexmediated immunity *in vitro*. However, remarkably little is known about their physiological role *in vivo*, and the remainder of this review will therefore focus on the membrane-bound isoforms. When studies do not differentiate between the isoforms (as is usually the case) they are referred to collectively as FcγRIIB.

In this Review, the regulation of FcγRIIB expression and function, as well as its role in controlling immune responses, is discussed. The signalling pathways downstream of FcγRIIB have been recently reviewed elswhere[1], and therefore we focus on the influence of FcγRIIB on cellular immunity, autoimmunity and responses to infection. Although FcγRIIB has a conserved and important role in regulating immunity in mice and humans, common genetic variants have been reported that result in diverse receptor expression and function within populations of both species. The effect of these variants on the predisposition to both

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autoimmunity and infection, and the potential evolutionary effects of the interplay between them, is discussed. Finally, we consider the effect that our increasing knowledge of the biology and function of FcγRIIB might have on the optimal use of current biological therapies, such as intravenous immunoglobulin (IVIG), and on the development of new therapeutic approaches.

The functions of FcγRIIB

The main function of FcγRIIB is to inhibit activating signals, which is achieved through co-ligation of FcγRIIB with either activating FcγRs or with the BCR by immune complexes (FIG. 2). This leads to phosphorylation of the cytoplasmic domain ITIM of FcγRIIB[27,28] by the Src-family kinase lYN[29]. This phosphorylation event is thought to require access of FcγRIIB to sphingolipid rafts in which activating FcγRs and the BCR reside following cross-linking[30,31]. Subsequent binding of SH2-domain-containing inositol phosphatases (SHIPs), in particular SHIP1, result in the dephosphorylation of downstream targets and inhibition of the activating signalling cascade[32,33].

FcγRIIB regulates B cell activation by increasing the BCR activation threshold and suppressing B cellmediated antigen presentation to T cells through the ITIM-dependent inhibitory mechanism described above (FIG. 2). FcγRIIB can interrupt immune synapse formation, which is important in early B cell activation[164], at least in part by altering BCR–lipid interactions and preventing antigen-induced BCR oligomerization[165]. In addition, cross-linking FcγRIIB in the absence of BCR ligation can induce apoptosis of mature B cells, independently of ITIM- and SHIP-mediated signalling. This induction of apoptosis depends on phosphorylation of a membrane proximal tyrosine residue (probably at position 269) of FcγRIIB by the tyrosine protein kinase ABL[34,35] and activation of the BCL-2 family members BH3-interacting-domain death agonist (BID) and BCL-2-antagonist of cell death (BAD)[36]. FcγRIIB is also expressed by pre-B cells, suggesting that it might contribute to central tolerance[37,38], although this is not supported by data from FcγRIIB-deficient mice[39].

Recent studies have shown that cross-linking FcγRIIB on plasma cells can also result in apoptosis. Terminally differentiated plasma cells express little or no BCR on the cell surface but express high levels of FcγRIIB; cross-linking FcγRIIB with immune complexes *in vitro* can induce apoptosis in a BCL-2-interacting mediator of cell death (BIM)-dependent manner[40]. A possible physiological role for this phenomenon is in regulating the long-lived bone marrow plasma cell population, as FcγRIIB-deficient mice have increased numbers of bone marrow plasma cells and no immune complex-mediated apoptosis; however, a causal link between these two observations has not been conclusively shown.

Inhibitory signalling has been shown in all cell types that express FcγRIIB with the exception of FDCs, in which only an immune complex-binding function for FcγRIIB has been observed. In contrast to FDCs in primary follicles, FDCs in germinal centres express high levels of FcγRIIB, and in fact FcγRIIB expression may be required for FDC activation[166]. The absence of FcγRIIB on germinal centre FDCs of knockout mice also impairs the trapping of immune complexes, resulting in impaired antibody and memory responses[12,13].

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FcγRIIB-deficient mice have elevated antibody levels in response to T cell-dependent antigens, and to a lesser extent T cell-independent antigens[41]. Transgenic overexpression of FcγRIIB by B cells leads to a decrease in T cell-dependent IgG responses, with little effect on IgM titres, whereas T cell-independent responses are unaffected[42]. The lack of effect of FcγRIIB on IgM titres in both FcγRIIB B cell transgenic[42] and FcγRIIB-deficient[40] mice could be because most of the short-lived extra-follicular plasmablasts responsible for the early production of IgM are generated before the IgG required to ligate FcγRIIB is produced (if antigen-specific IgG is indeed required for such feedback regulation). Another explanation might be that FcγRIIB-mediated suppression of IgG responses requires a level of cross-linking only achieved by FDC-associated immune complexes, thereby limiting the inhibitory effects of FcγRIIB to cells that develop in the germinal centre. Cross-linking of FcγRIIB may be decreased in T cell-independent responses dominated by IgG3, which has low affinity for FcγRIIB[43,44] (FIG. 1).

Thus, FcγRIIB is an important regulator of humoral immunity, although many of the details of this effect on B cells remain to be determined, a process that would benefit from cell-type specific knockout mice. FcγRIIB is particularly important in maintaining B cell tolerance in the periphery (see later), implicating variations in its expression and function in the pathogenesis of autoimmunity.

In addition to its effect on B cells, FcγRIIB inhibits FcγR-dependent internalization and presentation of antigen, as well as subsequent T cell priming, by DCs[45]. FcγRIIB also provides a basal level of inhibition to DC maturation, as blockade of immune complex binding to FcγRIIB, or FcγRIIB deficiency in DCs, results in DC maturation and type I interferon (IFN) production[46-48]. Healthy individuals have immune complexes in their serum[49] that induce DC maturation by binding activating FcγRs, unless this process was suppressed by FcγRIIB. In addition, a study has suggested that FcγRIIB expressed by DCs may deliver intact antigen to a non-degradative compartment, allowing its recycling to the cell surface where it could interact with the BCR and activate B cells[50].

In macrophages, engagement of FcγRIIB can reduce FcγR-mediated phagocytosis and cytokine release (including tumour necrosis factor (TNF), interleukin-6 (IL-6), IL-1α and neutrophil chemotactants)[51-53], as well as Toll-like receptor 4 (TLR4)-mediated activation[54] (FIG. 2). FcγRIIB may also have a non-inhibitory role in macrophage function by mediating endocytosis and non-inflammatory clearance of immune complexes from arthritic joints by macrophages[55].

FcγRIIB inhibits several aspects of mast cell and basophil function (FIG. 2), including degranulation, IL-4 production and histamine release induced through the Ige receptor[56-58], as well as stem cell factor (also known as KIT ligand)-mediated cell proliferation[59]. Resting human neutrophils express *FCGR2B2* mRNA[60,61] but express low levels of FcγRIIB2 on the cell surface[62]. In mouse neutrophils, cross-linking of activating FcγRs results in phagocytosis, superoxide production and enhanced neutrophil adhesion, rolling and migration[63-65], and it is likely that FcγRIIB inhibits all of these responses[51,66,67]. In humans, the precise role of FcγRIIB on neutrophils has not been defined.

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Regulation of FcγRIIB expression and function

Given that FcγRIIB has a central role in regulating immune responses, its function must be carefully controlled. FcγRIIB is expressed together with its activating counterpart (or counterparts) (either an activating FcγR or the BCR), and the ratio of binding to activating FcγRs and inhibitory receptors on a given cell (known as the A/I ratio) determines the activation threshold of the cell. This threshold can be influenced by factors that control cell surface expression of the receptor itself, its signalling capacity or its interaction with IgG.

Regulation of expression

The regulation of FcγRIIB expression is complex and differs depending on the cell type. For example, stimulation of B cells with IL-4 decreases *FCGR2B* mRNA and cell surface expression (in a signal transducer and activator of transcription 6 (STAT6)-dependent manner)[68,69], whereas in monocytes, IL-4 increases FcγRIIB expression[60,70]. This might be expected to increase antibody titres while reducing inflammatory cytokines production by macrophages in response to the resultant immune complexes. By contrast, IFNγ increases *FCGR2B* mRNA and cell surface expression by lipopolysaccharide-stimulated B cells[68] but decreases it on monocytes[60], which would polarize the immune response away from antibody production towards clearance of pathogens. It thus seems likely that the cytokine milieu is important in fine-tuning FcγRIIB expression in a cell- and context-specific manner.

Activation of complement may also affect FcγRIIB expression. In a mouse model of immune complex-induced alveolitis, the complement component C5a, an anaphylatoxin, was shown to directly upregulate FcγRIII and downregulate FcγRIIB expression by alveolar macrophages[71]. This regulation of FcγR expression would lower the activation threshold of macrophages and enhance the immune response to immune complexes, coordinating complement and phagocyte activation.

The transcription factors responsible for the regulation of *FCGR2B* expression are not well defined. The mouse *Fcgr2b* promoter contains a glucocorticoid response element, an AP4 binding site, an SP1 binding site, an e box (which is a binding site for helix–loop–helix factors) and an S box[72]. In addition, there are thought to be enhancer and repressor elements within the gene, particularly within demethylated regions in the third intron, which have an important role in control of *Fcgr2b* transcription[17,73,74].

Ubiquitylation of surface receptors, and their subsequent degradation, provides an important mechanism to control their expression and to regulate immune responses. A recent study showed that FcγRIIB may be a substrate for MARCH9, a membrane-associated RING-containing ubiquitin E3 ligase expressed by B cells, T cells and DCs[75].

Regulation of IgG–FcγRIIB interaction

All low-affinity FcγRs have two extracellular immunoglobulinlike domains termed D1 and D2; D2 interacts with the C_H2 domains of the IgG Fc region[76]. The affinity of this interaction differs with variations in the protein backbone of IgG and therefore with differing isotypes and with variations in the levels of glycosylation of the IgG Fc region. The variation in the binding affinity of activating and inhibitory receptors for IgG isotypes,

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that is the A/I ratio, differs by several orders of magnitude between isotypes in mice. IgG1 has the lowest A/I ratio (0.1), suggesting the activity of this isotype is strongly influenced by FcγRIIB, whereas the activity of IgG2a is much less affected, with an A/I ratio of 70 (REFS 43,44). In humans, FcγRIIB binds IgG1 with the highest affinity, followed by IgG3, IgG4 and IgG2 (REF. 77; reviewed in REF. 78) (FIG. 1). The C_H2 domains of IgG also contain an asparagine residue at position 297 that can be variably glycosylated. These sugar moieties vary in complexity, and this variation is associated with conformational changes in the Fc region[79] that may substantially alter their binding to FcγRs[80,81]. enrichment of α2,6-sialylated forms of mouse IgG1 results in a tenfold reduction in its affinity for FcγRIIB with the net effect of sialylation increasing the A/I ratio for IgG1 (REF. 81). It is clear that a crucial component in the regulation of FcγR-mediated immune responses involves not only the FcγRs, but also the IgG subclass involved and the nature and degree of IgG glycosylation.

Genetic variation in FcγRIIB

The human 1q23.3 locus contains five *FCGR* genes (*FCGR2A, FCGR2B, FCGR2C, FCGR3A* and *FCGR3B*) encoding the FcγRII and FcγRIII receptor families. There is high sequence similarity between these genes, in part due to an ancestral segmental duplication[82,83] that arose following the division of the great apes from new world monkeys[84,85]. The locus is complicated by the presence of at least three copy number variant (CNV) regions, two of which are common in Caucasians but do not seem to involve *FCGR2B*[62,86]. The homology in the region of the ancestral duplication is likely to facilitate CNV formation[87]. A similar complexity is seen in the mouse FcR locus, although the presence of CNVs has not been described.

In both species, genetic variation at the FcR locus exists within and between different populations. This combination of gene duplication, several common single nucleotide polymorphisms (SNPs) and CNVs is characteristic of regions involved in immune regulation. The generation and maintenance of such genetic diversity is thought to increase the probability of successful defence against varying pathogens. Such evolutionary plasticity has best been described at the MHC and killer cell immunoglobulin-like receptor loci[88], and the FcR locus seems to provide another, less complex, example. This genetic variability has implications for susceptibility to both autoimmunity and infection.

Variations in mice

Several variants in the putative promoter region and the demethylated region of intron 3 of *Fcgr2b* have been described, which together form three haplotypes in inbred strains of mice (FIG. 3) and are also found in wild mice (M.R.C. and K.G.C.S., unpublished observations). They include a 13-base-pair deletion that disrupts a putative AP4 binding site and an S box close to the transcription start site of *Fcgr2b*, as well as two deletions in intron 3. These variants were first described in several autoimmune-prone inbred strains of mice and were found to be associated with decreased expression and function of FcγRIIB[72,89,90]. Studies in congenic mouse strains have provided evidence they these variants may influence the expression of FcγRIIB by B cells[91,92], although the causative genetic variant and a direct link to autoimmune predisposition remain to be shown.

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In *Fcgr2b*, two coding variants have been identified, termed *Ly17.1* and *Ly17.2* (REF. 93) (FIG. 3). Despite resulting in amino acid exchanges in the extracellular D2 domain, there is no evidence of a detectable functional effect of these coding variants or of a consistent association with autoimmunity[94].

Human variations

Two promoter haplotypes have been described; the common −386G:−120T variant and the less common −386C:−120A variant[95] (FIG. 4). The −386C:−120A variant has been shown in one study to result in increased binding of the transcription factors GATA-binding protein 4 (GATA4) and Yin-Yang 1 (YY1) to the promoter[95] and in increased expression of FcγRIIB by monocytes, neutrophils and myeloid DCs[96], whereas, another study showed that −386C homozygosity decreased the transcription and surface expression levels of FcγRIIB in peripheral B cells compared with −386G homozygotes[97], creating an apparent paradox that awaits resolution.

Seven non-synonymous SNPs have been identified in human *FCGR2B*[98,99] (FIG. 4), but only one of these SNPs has been shown to occur at notable frequency. This non-synonymous T-to-C transition in exon 5 (rs1050501) results in the substitution of a threonine for isoleucine at position 232 within the transmembrane domain of FcγRIIB (referred to as FcγRIIB^{T232}). The FcγRIIB^{T232} variant is excluded from lipid rafts, leading to reduced phosphorylation by LYN, abnormal SHIP recruitment[100,101] and a decrease in FcγRIIB-mediated inhibition of both macrophage and B cell responses[100]. The frequency of the homozygous FcγRIIB^{T232} variant is subject to considerable ethnic variation and is lower in Caucasians (1%) than Africans (8–11%)[102] or Southeast Asians (5–7%)[98,103].

FcγRIIB and autoimmunity

Within the adaptive immune system, cells are generated with antigen receptors capable of recognizing selfantigen. During lymphocyte development mechanisms exist in the bone marrow to modify autoreactive B cells or to destroy or inactivate autoreactive cells (central tolerance); however, some autoreactive lymphocytes persist in the periphery. Thus, additional measures exist to limit autoreactivity in mature lymphocytes (peripheral tolerance)[104]. Failure of both central and peripheral tolerance leads to activation of the immune system against self-antigens, which is termed auto immunity. Autoimmune diseases may be tissue specific, such as type 1 diabetes, or may involve multiple organ systems, such as systemic lupus erythematosus (SLE) and they tend to be polygenic: there are many genes that contribute to disease susceptibility. *FCGR2B* is one of the genes thought to influence susceptibility to several autoimmune diseases in humans.

SLE

Abnormalities in B cell function and in the clearance and inflammatory response to immune complexes are characteristic features of SLE. As FcγRIIB is a key regulator of B cells, and low affinity FcγRs are central to the response to immune complexes, FcγRIIB might be expected to be involved in the pathogenesis of SLE and perhaps other autoimmune diseases.

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The most direct evidence for the role of FcγRIIB in SLE comes from studies involving genetically modified mice[1]. FcγRIIB deficiency renders normally resistant strains of mice susceptible to several antibody- or immune complex-dependent models of autoimmunity, including immune complex-mediated alevolitis[51] and glomerular basement membrane-specific antibody-mediated nephritis[67,105].

FcγRIIB-deficient mice backcrossed to a C57BL/6 background spontaneously develop hypergamma-globulinaemia, autoantibodies and an immune complex-mediated disease resembling SLE[106]; this does not occur on mice backcrossed to a BAlB/c background, indicating the importance of strain-specific epistatic effects on autoimmune susceptibility. The restoration of FcγRIIB expression levels on bone marrow cells of (NZB × NZW) F1 mice (a mouse model of spontaneous SLE) using an FcγRIIB-expressing retrovirus can prevent autoimmunity[107], and modest transgenic overexpression of FcγRIIB on B cells markedly reduces the development of SLE in MRL-*lpr* mice[42]. Thus, studies in genetically modified mice implicate FcγRIIB in the pathogenesis of auto immunity and the maintenance of B cell tolerance. Some uncertainty remains, however, owing to the possibility that neighbouring genes might be influencing the phenotype of FcγRIIB-deficient mice (see BOX 1).

FcγRIIB may also have an important role in determining susceptibility to spontaneous autoimmunity in several inbred strains of mice that develop a lupus-like disease; the major locus contributing to SLE susceptibility in the (NZB × NZW) F1 and BXSB mouse models of spontaneous SLE, excluding the MHC, is on distal chromosome 1 and contains the FcR region[108]. Furthermore, *Fcgr2b* promoter variants (FIG. 3) are present in polygenic models of SLE (MRL-*lpr*, (NZB × NZW) F1 and BXSB mice)[72,89,90,109]. Studies with congenic mice suggest, but do not prove, that variability in the *Fcgr2b* promoter can alter FcγRIIB expression by B cells and alter B cell and macrophage activation[72,91,92], consistent with a role in SLE pathogenesis. All of these studies, however, need to be interpreted in the light of the potential for other polymorphic genes in the locus to influence autoimmune susceptibility (BOX 1).

Collectively, these studies show a role for FcγRIIB in the control of the B cell-mediated immune responses. FcγRIIB is also important in the maintenance of peripheral B cell tolerance, and although the mechanisms underlying this are as yet not fully defined, possibilities include the induction of apoptosis of autoreactive germinal centre B cells, the exclusion of autoreactive B cells from B cell follicles[110] and the control of plasma cell development and apoptosis[40].

The polymorphism encoding FcγRIIB^{T232} in humans is associated with susceptibility to SLE in Southeast Asian populations[98,103,111] and in Caucasians[99]. This association is only seen when FcγRIIB^{T232} is homozygous; it is associated with an odds ratio of 1.73, making this one of the strongest genetic associations with SLE[99]. The increased frequency of FcγRIIB^{T232} in individuals of Southeast Asian and African descent may therefore contribute to the increased prevalence and/or severity of SLE, which has long been noted in these ethnic groups[112]. The effect of the *FCGR2B* promoter variant −386C:−120A on its

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expression is debated, but an association of the −386C:−120A haplotype with SLE in Caucasians has been shown by two studies[95,97].

Decreased expression of FcγRIIB has been observed in memory B cells from patients with SLE: this is perhaps due to a failure to upregulate FcγRIIB expression as B cells develop a memory phenotype[113]. Furthermore, low FcγRIIB expression by memory B cells and plasmablasts from patients with SLE with active, but not quiescent, disease has been described[96]. Decreased expression of FcγRIIB by DCs has also been observed in patients with SLE, together with an increased expression of activating FcγRs, thus substantially altering the A/I ratio in favour of cell activation[114]. These differences in expression may, at least in part, occur secondary to inflammation.

Thus, there is a consistent association between decreased FcγRIIB function and SLE, as determined by genetic association or cell surface expression, which may be due to various mechanisms (summarized in FIG. 5).

Rheumatoid arthritis

Collagen-induced arthritis (CIA) is a B cell-dependent mouse model of inflammatory arthritis that shares some features with rheumatoid arthritis. FcγRIIB deficiency increases both collagen-specific IgG titres and disease severity in CIA[52]. Consistent with this, FcγRIIB B cell transgenic mice show a reduction in disease severity and in collagen-specific IgG titres; however, this effect was not observed in FcγRIIB macrophage transgenic mice[42]. In addition to influencing CIA through it effects on antibody production, FcγRIIB may also limit cartilage destruction by inhibiting the production of matrix metalloproteinases[115].

Rheumatoid arthritis is a chronic inflammatory disease that results in a progressive, deforming polyarthropathy. Many patients have serum autoantibodies, particularly rheumatoid factor (an IgM autoantibody directed against the Fc portion of IgG), as well as antibodies directed against other autoantigens such as cyclic citrullinated peptide (CCP)[116]; it is thought these antibodies may contribute to disease pathogenesis through interactions with FcγRs. Several investigators have sought to identify an association between rheumatoid arthritis and the nonfunctioning variant receptor FcγRIIB^{T232}; Radstake *et al.* found no difference in the frequency of the polymorphism encoding FcγRIIB^{T232} between patients with rheumatoid arthritis and controls, but they did observe an association of the FcγRIIB^{T232} variant with increased radiological joint damage[117]. DCs from rheumatoid arthritis patients with the FcγRIIB^{T232} variant also showed an increase in immune complex-mediated inflammation *in vitro*. other investigators have observed higher expression of FcγRIIB by DCs from a subset of patients with low rheumatoid arthritis disease activity (in the absence of treatment) than patients with high disease activity[118].

Other autoimmune diseases

Anti-glomerular basement membrane (anti-GBM) disease, also known as Goodpasture's disease, is an antibody-mediated glomerulo nephritis that often leads to irreversible renal failure. one small study has shown an association between the polymorphism encoding

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FcγRIIB^{T232} and susceptibility to anti-GBM disease[86], which is consistent with findings in mouse models[67] but requires independent confirmation.

Multiple sclerosis is an autoimmune disease characterized by demyelination in the central nervous system. In a mouse model of multiple sclerosis, FcγRIIB deficiency was associated with an increase in disease severity and enhanced activation of myelin-specific T cells[119]. However, there are no studies to date examining the effect of the polymorphism encoding FcγRIIB^{T232} on susceptibility to multiple sclerosis in humans. Chronic inflammatory demyelinating polyneuropathy is characterized by recurrent episodes of an inflammatory polyneuropathy, and is thought to be mediated by autoantibodies. A recent study found that untreated patients expressed lower levels of FcγRIIB on monocytes and B cells[120].

Idiopathic thrombocytopenic purpura (ITP) is characterized by an often chronic antibody-mediated destruction of platelets. In a multivariate logistic regression analysis of data from 60 children with ITP, the presence of the FcγRIIB^{T232} variant predicted a chronic disease course[121]. of interest, a subset of patients with ITP was found to be infected with *Helicobacter pylori*, and this was associated with low surface expression of FcγRIIB on monocytes. *H. pylori* eradication led to an increase in platelet numbers and in the expression of FcγRIIB by monocytes, suggesting an intriguing link between infection and autoimmunity through the regulation of FcγRIIB expression[122].

Thus, to summarize, FcγRIIB affects susceptibility to several autoimmune diseases, particularly SLE, but also rheumatoid arthritis, anti-GBM disease and ITP.

FcγRIIB and infection

Many consider the primary role of the immune system to be defence against infection. Antibodies are a crucial component of this protective system; the interaction between pathogen-bound IgG and FcγR directly mediates pathogen clearance by ADCC, degranulation and phagocytosis and indirectly through the release of cytokines and other inflammatory mediators. FcγRIIB would be expected to control these functions, as well as the production of IgG by the B cell response itself, and it should thus have a notable, and perhaps complex, role in defence against infection.

Most work on FcγRIIB and infection has involved the study of *Streptococcus pneumoniae*, an encapsulated, gram positive organism, which is a major cause of pneumonia, peritonitis and meningitis in humans. The main defence against *S. pneumoniae* is through capsular polysaccharide- and cell wall phosphocholine-specific antibodies, which bind pneumococci and mediate FcγR-dependent phagocytosis by neutrophils and macrophages[123]. *In vitro*, macrophages from FcγRIIB-deficient mice incubated with opsonized *S. pneumoniae* show increased phagocytosis and production of cytokines such as TNF, and infected FcγRIIB-deficient mice showed reduced mortality from streptococcal peritonitis[53]. Mice that overexpress FcγRIIB on macrophages (but not B cells) are more susceptible to pneumococcal peritonitis and pneumonia[42,53]. However, if FcγRIIB-deficient mice were first immunized with a pneumococcal vaccine and then challenged with high doses of *S. pneumoniae*, mortality rates were increased and this was associated with an increase in pro-inflammatory cytokine production[53]. This suggests a role for FcγRIIB in the balance

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between efficient pathogen clearance and the prevention of the cytokine-mediated effects of sepsis.

FcγRIIB deficiency is also associated with an increased resistance to *Staphylococcus aureus* in mice[66], and following nasal infection with *Mycobacterium tuberculosis*, FcγRIIB-deficient mice show decreased bacterial burden in lungs and spleen and enhanced protective pulmonary T helper 1 cell responses[124]. By contrast, FcγRIIB does not seem to be important in modulating phagocytosis of serum-opsonized *Salmonella enterica* subsp. enterica serovar Typhimurium (an intracellular bacterium) *in vitro*[125]. The role of FcγRIIB in defence against viral infections has not been examined in detail. one study using human papilloma virus-like particles (highly immunogenic, nonreplicative structures that mimic their virus counterparts in morphology and immunogenicity) showed decreased uptake of particles by DCs and decreased antiviral antibody and T cell responses in FcγRIIB-deficient mice compared with wild-type mice[126].

Therefore, FcγRIIB has a major effect on defence against some, but not all, microorganisms in mice. However, this effect is complex and can lead to different outcomes in different contexts even when the animals are infected by the same organism, as typified by the response to *S. pneumoniae*; in naive animals with primary infection, FcγRIIB ligation may dampen the immune response sufficiently to impair pneumococcal clearance resulting in a negative effect on survival. By contrast, in immune animals with pre-formed antibody, FcγRIIB ligation may be crucial to limit immune complex-associated inflammation and an excessive, pro-inflammatory cytokine storm, thus enhancing survival. This leads to the conclusion that regulation of FcγRIIB modulates not only pathogen clearance but also the inflammatory response to that pathogen, balancing the risks of infection with those of uncontrolled inflammation and septic shock.

In humans, *in vitro* studies have shown that expression of the functionally impaired FcγRIIB^{T232} variant is associated with increased phagocytosis of antibodyopsonized *S. pneumoniae* by monocyte-derived macrophages[100]. However, genetic studies have not shown an association between the polymorphism encoding FcγRIIB^{T232} and septicaemia in a large study of Kenyan children with bacterial sepsis[99]. This does not exclude the possibility that *FCGR2B* polymorphisms alter susceptibility to bacterial infection, and indeed genetic variants in *FCGR2B* have been associated with aggressive periodontitis[127]. Given the mouse data on FcγRIIB and pneumococcal infection[53], future genetic studies should use carefully stratified clinical cohorts, as FcγRIIB may have different effects on the immune and inflammatory response to different organisms in different clinical contexts, which could confound clinically heterogenous cohort studies. Moreover, the effect of the polymorphism encoding FcγRIIB^{T232} on disease may be influenced by epistatic interactions and linkage disequilibrium with genetic variants in other *FCGR* genes, particularly the neighbouring *FCGR3B* gene, which has common and functionally important CNV[62].

Ethnic differences in SLE, malaria and evolution

The incidence of SLE is at least two-fourfold higher in populations of African or Asian descent than in Caucasians[112] and, consistent with this, the frequency of the homozygous

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SLE-associated variant FcγRIIB^{T232} is higher in these populations; for example, in 10% of Kenyans and 6% of Vietnamese but 1% of europeans[99]. Thus, FcγRIIB^{T232} is common in areas where malaria is endemic (FIG. 4b), raising the possibility that decreased FcγRIIB function may provide a survival advantage against this disease[102].

Consistent with this hypothesis, FcγRIIB-deficient mice are resistant to *Plasmodium chabaudi chabaudi*, a model of the erythrocytic stage of human malarial infection[102]. Similarly, in humans, the expression of FcγRIIB^{T232} increased phagocytosis of antibodyopsonized *Plasmodium falciparum*-parasitized erythrocytes by monocyte-derived macrophages *in vitro*[102]. A large study in two cohorts has shown that homozygous expression of FcγRIIB^{T232} is associated with substantial protection against severe malaria in Kenyan children[99]. We propose that several mechanisms may contribute to this protective effect, including increased phagocytosis, malarial-specific antibody titres and TNF production[102,128,129] (FIG. 6).

The high mortality rate associated with malarial infection has resulted in its recognition as the strongest known force for evolutionary selection in the recent history of the human genome[130]. The most well recognized examples of this are the retention of sickle cell anaemia and thalassaemia traits: in Kenyan children from the Coast region of Kilifi, heterozygous and homozygous α-thalassaemia confers a protective effect against malarial infection[131]. Homozygous FcγRIIB^{T232} has a protective effect of similar magnitude to heterozygous α-thalassemia[99], and it thus could explain the higher frequency of FcγRIIB^{T232} in Africans and Southeast Asians. This might provide the first example of an immune poly morphism predisposing to polygenic autoimmunity, selected and retained by virtue of its protective effect in malaria infection, and beginning to provide an explanation for the ethnic differences seen in SLE susceptibility (FIG. 4b).

Therapeutic agents

Modification of FcγRIIB expression

Even a modest increase in the expression of FcγRIIB on B cells can ameliorate CIA and spontaneous SLE in mice[42]. *In vitro*, IL-4 treatment of monocytes from patients with rheumatoid arthritis altered the FcγR expression balance in favour of FcγRIIB and prevented IgG-induced TNF production by these cells[132]. These studies raise the possibility that careful cell-specific modulation of FcγRIIB expression may offer a new treatment strategy in autoimmune diseases (TABLE 1). There is also some evidence that two therapeutic agents in widespread use, IVIG and infliximab (Remicade; Centocor/Merck), may owe their efficacy, at least in part, to their effect on FcγRIIB expression.

FcγRIIB and IVIG

High dose IVIG is increasingly used to treat autoimmune diseases[133]. Proposed immunomodulatory mechanisms include the neutralization of pathogenic autoantibodies by anti-idiotypic antibodies, the modulation of cytokine production and the neutralization of the complement components C3a and C5a[133]. These effects are mainly F(ab′)$_2$ dependent, but studies in patients with ITP and in mouse models of auto immunity suggest that the Fc fragment may be as potent as whole IVIG preparations[134]. There is increasing evidence that

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FcγRIIB may have a central role in mediating this Fc-dependent effect. In FcγRIIB-deficient mice, IVIG is not effective in treating autoimmunity[81,135-137]. Following IVIG treatment of wild-type mice, FcγRIIB expression is upregulated on splenic macrophages[135], which, together with a decrease in expression of activating FcγRIV[137], might reduce macrophage activation and associated inflammation. More recent data extends this observation to humans, demonstrating an upregulation of FcγRIIB expression by monocytes and B cells following IVIG treatment of patients with chronic inflammatory demyelinating polyneuropathy[120].

Studies have suggested that IVIG indirectly increases FcγRIIB expression on effector macrophages through its direct effect on colony-stimulating factor 1 (CSF1)-dependent macrophages[138,139]. IVIG is ineffective in treating autoimmunity in *Csf1*-knockout mice, which are deficient in some subpopulations of monocytes and macrophages[138]. Furthermore, IVIG treatment of *Csf1*-knockout mice does not upregulate FcγRIIB expression on effector macrophages, suggesting that CSF1-dependent macrophages are required to mediate this effect[138]. other investigators have suggested that $CD11c^+$ splenocytes (a population that may be separate from, or contained in, the CSF1-dependent population) are required to 'sense' IVIG and that FcγRIII is required for 'sensing'[140]. However, once 'sensed', FcγRIIB expression was required for IVIG-mediated disease inhibition. Alternatively, IVIG may be sensed by DC-SIGN related 1 (SIGNR1), a C-type lectin that preferentially binds sialylated IgG (unlike FcγRs, which have decreased affinity for sialylated IgG). SIGNR1 is expressed by splenic marginal zone macrophages, and is a mouse homologue of human DC-SIGN[139]. It is estimated that ~5% of IVIG is fully glyco sylated[141]. De-glycosylation of IVIG abrogates its anti-inflammatory activity, whereas enrichment of IVIG for sialylated forms of IgG increases its anti-inflammatory activity effect 10-fold[81]. These intriguing results, which await full confirmation in human disease, are potentially of therapeutic importance. In an era where the demand for IVIG significantly outweighs supply, increasing the sialylation levels of IVIG may be a means of substantially improving efficacy.

FcγRIIB and infliximab

TNF upregulates the expression of activating FcγRIIA on neutrophils *in vitro*, and amplifies immune complex-induced activation of neutrophils *in vivo*. TNF blockade with infliximab in patients with rheumatoid arthritis led to a decrease in expression of FcγRIIA and an increased expression of FcγRIIB on neutrophils in some patients[142]. The increased expression of FcγRIIB was associated with a decrease in disease severity, suggesting that the efficacy of TNF blockade may be in part due to modulation of FcγRIIB expression levels.

Modification of antibody binding to FcγRIIB

FcγR interactions predict the efficacy of therapeutic monoclonal antibodies, such as the B cell depleting CD20-specific antibody rituximab (Rituxan/Mabthera; Genentech/Roche/Biogen Idec)[143]. Studies in Fcγ-chain-deficient mice have shown that the effect of many monoclonal antibodies that deplete immune cells depends on the presence of activating FcγRs, and that inhibitory FcγRIIB can be an important negative regulator of their effect *in vivo*[144-146]. The efficacy of cytotoxic antibodies may be improved by decreasing their

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interaction with FcγRIIB[45,47] or by increasing their binding affinity for activating FcγRs[147,148]. Modulation of the Fc glycosylation levels of monoclonal antibodies may provide a means of manipulating FcγR interaction and efficacy[43,80,149].

FcγRIIB as a therapeutic target

A monoclonal antibody against FcγRIIB (hu2B6-3.5; MacroGenics) has been used to direct monocyte- or macrophage-induced cytotoxicity against B cell lymphoma cells[150] and plasma cells from patients with systemic lightchain amyloidosis[151]. FcγRIIB cross-linking on B cells, plasma cells and myeloma cell lines[40] can induce apoptosis *in vitro*, and thus FcγRIIB-specific antibodies might show efficacy in B and plasma cell malignancies. These antibodies might also provide a means of targeting plasma cells in antibody-driven autoimmune diseases.

Cross-linking FcγRIIB activating receptors could therapeutically harness its inhibitory effect. This is being investigated in allergy, where FcγRIIB cross-linking with IgE-antigen complexes or FcεRI has been used to inhibit IgE-mediated histamine release from human mast cells and basophils *in vitro* and in mouse models[152,153]. These observations have recently extended to non-human primates[154,155]. Moreover, the possibility that bispecific antibodies could co-ligate specific antigen and FcγRIIB raises the prospect of autoantigen-specific suppression of humoral immunity.

The soluble FcγRIIB3 isoform has been shown to inhibit the effects of immune complexes *in vitro*[24,26]. A more recent study of soluble FcγRIIB in (NZB × NZW) F1 mice showed therapeutic efficacy, slowing the progression of nephritis and prolonging survival[156] and prompting its use in human trials in SLE.

Conclusion and future direction

FcγRIIB, identified as the mediator of Fc fragment-induced B cell suppression over 30 years ago, is now known to be widely expressed and to control key aspects of immunity. Variation in its complex and often subtle regulation is crucially involved in determining susceptibility to autoimmunity and defence against infection. Better understanding of this variation is beginning to provide insight into the evolution of disease susceptibility and to open new opportunities for therapy.

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Glossary

Immune complexes Complexes of antigen bound to antibody and, sometimes, components of the complement system. The number of circulating immune complexes is increased in some autoimmune disorders

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	(particularly SLE) in which they may be deposited in tissues causing inflammation and tissue damage.
Antibody-dependent cell-mediated cytotoxicity (ADCC)	A mechanism by which FcR-expressing cells kill other cells, such as virus-infected target cells, that are coated with antibodies. The Fc portions of the coating antibodies interact with the FcγR, thereby initiating a signalling cascade that results in the induction of apoptosis of the antibody-coated cell.
Acute-phase proteins	A group of proteins, the plasma concentration of which changes in response to trauma, inflammation and infection. C-reative protein is the prototypical acute-phase protein and binds phosphocholine on pathogens and apoptotic cells, opsonizing them for disposal by phagocytes by FcγR binding.
FcR common γ-chain	A membrane-associated signal adaptor protein that contains an ITAM. It is shared by FcγRI and FcγRIIIA, as well as other receptors, including collagen receptor glycoprotein IV, NKp46, ILT1 (also known as LIR7) and osteoclast-associated immunoglobulin-like receptor (OSCAR).
Follicular DCs (FDCs)	Cells with a dendritic morphology that are present within B cell follicles in secondary lymphoid tissues such as lymph nodes and spleen. They display intact antigens that are held in immune complexes on their surface, accessible to B cells. FDCs are of non-haematopoietic origin and are not related to ‘conventional’ DCs.
Germinal centre	A lymphoid structure that arises in B cell follicles in secondary lymphoid organs, such as spleen and lymph node, after immunization with, or exposure to, a T cell-dependent antigen. It is specialized for facilitating the development of high-affinity, long-lived plasma cells and memory B cells.
Intravenous immunoglobulin (IVIG)	A preparation of human polyclonal IgG obtained from pooled plasma samples taken from thousands of healthy blood donors. It is used as a replacement therapy for individuals with hypogammaglobulinaemia, but is also increasingly used, at much higher doses, to treat autoimmune diseases. IVIG is licensed for the treatment of idiopathic thrombocytopenic purpura, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy and Kawasaki disease, and is also used in the treatment of other autoimmune diseases, including multiple sclerosis and ANCA-associated vasculitis.
Central tolerance	Immune tolerance to self antigens that is imposed during lymphocyte development in the thymus (T cells) or the bone marrow (B cells). B cells expressing a BCR that recognizes self antigen must undergo further rearrangement of antigen-receptor

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	genes to become self tolerant or they are deleted or rendered anergic. This process does not eliminate all autoreactive lymphocytes and therefore mechanisms exist in the periphery to maintain tolerance in mature lymphocytes (peripheral tolerance).
T cell-dependent antigens	Antigens that require T cell–B cell interactions to activate B cells and produce an antibody response.
Ubiquitin E3 ligase	An enzyme that is required to attach the molecular tag ubiquitin to proteins. Depending on the position and number of ubiquitin molecules that are attached, the ubiquitin tag can target proteins for degradation in the proteasomal complex, sort them to specific subcellular compartments or modify their biological activity.
Copy number variant (CNV)	A genomic variant characterized by differences in the number of copies of specific repeated DNA fragments that range from 1 kb to several mb long and can contain entire genes.
Haplotype	A set of single nucleotide polymorphisms (SNPs) or other genetic variants in a gene or locus that are inherited together.
Systemic lupus erythematosus (SLE)	A multisystem autoimmune disease characterized by hypergammaglobulinaemia and the development of autoantibodies, including those specific for nuclear self antigens such as DNA. These antibodies form immune complexes that become deposited in tissues, including the kidneys and skin. Deposited immune complexes initiate an inflammatory response causing tissue damage. SLE is a polygenic disease, that is multiple, common polymorphisms confer disease susceptibility.
(NZB × NZW) F1 mice	The F1 generation of the cross between NZB mice and NZW mice. (NZB × NZW) F1 mice spontaneously develop a disease that closely resembles the human disease SLE.
MRL–*lpr* mouse	A mouse strain that spontaneously develops glomerulonephritis and other symptoms of SLE. The *lpr* mutation causes a defect in CD95 (also known as FAS), preventing apoptosis of activated lymphocytes. The MRL background contributes other disease-associated genetic variants.
Collagen-induced arthritis (CIA)	A model of rheumatoid arthritis. CIA develops in susceptible rodents and primates after immunization with cartilage-derived type II collagen.
Sickle cell anaemia	Sickle cell anaemia is an autosomal recessive disease in which the gene encoding the β-globin chain has a mutation resulting in an amino acid change (a valine for a glutamic acid at position 6), which leads to erythrocytes that are rigid and sickle shaped. Patients develop anaemia and sickle crises, which significantly

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	shorten life expectancy. Heterozygotes are protected from malaria infection, resulting in the retention of this mutation in populations exposed to malaria.
Thalassaemia	Thalassaemia is an autosomal recessive genetic disorder, in which there is a mutation in the gene encoding either the α- or β-globin chains that make up haemoglobin. This leads to reduced globin chain (and hence haemoglobin) synthesis, causing anaemia of variable severity. Carriers of the thalassaemia mutations (thalassaemia trait) are protected from malaria infection. This selective advantage is thought to contribute to the persistence of this potentially harmful mutation in the human genetic pool.
Anti-idiotypic antibody	An antibody that is directed against the antigen-specific binding site of an immunoglobulin or a T cell receptor and therefore may compete with antigen for binding.

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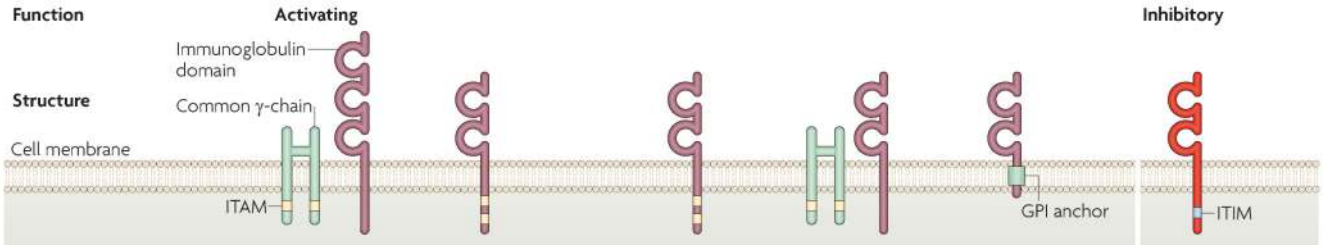
Box 1

FcγRIIB and spontaneous SLE in mice

Fcgr2b is found in a region of distal chromosome 1 that contains both the low affinity Fc receptors for IgG (FcγRs) and several other immunologically important genes, such as those encoding signalling lymphocytic activation molecule (SLAM) and complement receptor 2 (CR2). Therefore, studies on the association between naturally occurring FcγRIIB variants and spontaneous systemic lupus erythematosus (SLE), as well as the phenotype of FcγRIIB-deficient mice, have to be interpreted carefully. This region has been linked with SLE in mice, although initial fine-mapping studies suggested that the FcγR region did not contribute to disease susceptibility (however, this region was of NZW origin, and a role for the NZB haplotype was not excluded)[157]. Studies using congenic mice with genomic regions containing the NZW-derived *Fcgr2b* allele have shown evidence of abnormal FcγRIIB expression and immune function, but not spontaneous autoimmunity[92] (although, in a polygenic disease, any single polymorphism would be expected to act in concert with other genetic variants before exerting a measurable effect on disease susceptibility). Consistent with this, a recent study has shown that the FcγR interval in NZB mice can combine with the SLAM locus to increase SLE susceptibility[158]. Thus, the importance of FcγRIIB in controlling SLE has been unequivocally shown by abrogation of SLE through partial restoration of FcγRIIB expression[107] and transgenic overexpression of FcγRIIB on B cells[42] and, in addition, genetic evidence demonstrates that the FcγR region contributes to the pathogenesis of SLE[158]. Nonetheless, careful studies of the immunological and pathological implications of naturally occurring FcγRIIB variants are still required, preferably using C57BL/6 embryonic stem cell ‘knock-in’ mice to exclude the possible influence of neighbouring genetic variation present in congenic regions.

The telomeric region of chromosome 1 derived from the 129 strain of mouse is similar to that in autoimmune-prone strains of mice[157] including NZB mice[72], and thus the phenotype of FcγRIIB-deficient mice made with 129 mouse-derived embryonic stem cells[41] might be influenced by carry-over of adjacent 129 mouse-derived regions despite backcrossing[106]. C57BL/6 mice congenic for the 129 mouse-derived region develop autoimmunity[159,160], which may explain why mice that are deficient in closely linked genes, such as SAP, CR2 and C1q, develop similar phenotypes[161-163]. Thus, although it is likely that *Fcgr2b* contributes to spontaneous SLE in mice (in concert with other variants) and to the autoimmune phenotype of FcγRIIB-deficient mice, the analysis of FcγRIIB-deficient mice made with C57BL/6 embryonic stem cells, and/or autoimmune-associated variant ‘knock-in’ C57BL/6 mice, will be necessary to formally prove this association.



		FcγRI	FcγRIIA	FcγRIIC	FcγRIIIA	FcγRIIIB	FcγRIIB
Name							
Expression	Lymphoid	Not expressed	Not expressed	NK cell	NK cell	Not expressed	B cell and plasma cell
	Myeloid	Monocyte, DC and macrophage	Monocyte, DC, platelet and macrophage	Not expressed	Monocyte, DC and macrophage	Not expressed	Monocyte, DC and macrophage
	Granulocyte	Neutrophil and eosinophil	Neutrophil	Not expressed	Not expressed	Neutrophil, mast cell and eosinophil	Neutrophil, basophil and mast cell
IgG binding affinity		IgG1>>>IgG2, IgG3 and IgG4	IgG1 and IgG3>> IgG2>IgG4	IgG1>IgG3>> IgG4>IgG2	IgG1>>IgG2 and IgG3 >IgG4	IgG1 and IgG3>> IgG2 and IgG4	IgG1>IgG3>> IgG4>IgG2

Figure 1. Structure, cellular distribution and IgG isotype-binding affinity of human activating and inhibitory FcγRs

Human Fc receptors for IgG (FcγRs) differ in function, affinity for the Fc fragment of antibody and in cellular distribution. There are five activating FcγRs: the high-affinity receptor FcγRI, which can bind monomeric IgG, and four low-affinity receptors (FcγRIIA, FcγRIIC, FcγRIIIA and FcγRIIIB), which bind only immune-complexed IgG. Cross-linking of activating FcγRs by immune complexes results in the phosphorylation of immunoreceptor tyrosine-based activating motifs (ITAMs) that are present either in the cytoplasmic domain of the receptor (FcγRIIA and FcγRIIC), or in the associated FcR common γ-chain (FcγRI and FcγRIIIA), resulting in an activating signalling cascade. FcγRIIIB is a glycosylphosphatidylinositol (GPI)-linked receptor that has no cytoplasmic domain. FcγRIIB is the only inhibitory FcγR. It is a low affinity receptor that binds immune-complexed IgG and contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic domain. FcγRIIB cross-linking by immune complexes results in ITIM phosphorylation and inhibition of the activating signalling cascade. FcγRs differ in their cellular expression; myeloid cells express FcγRI, FcγRIIA and FcγRIIIA, whereas granulocytes express FcγRI, FcγRIIA and FcγRIIIB. In such cells, immune complex-mediated activation of these receptors is negatively regulated by FcγRIIB. FcγRIIB is the only FcγR expressed by B cells and negatively regulates B cell receptor activation by immune-complexed antigen. FcγRs bind different IgG subtypes with differing affinity. For example, in the case of FcγRIIB, binding affinity is highest for IgG1, followed by IgG3, which in turn has higher affinity than IgG4 followed by IgG2. The ratio of binding of an IgG subtype to activating FcγRs and inhibitory FcγRIIB is known as the A/I ratio, and it determines the activation threshold of the cell. DC, dendritic cell; NK, natural killer.

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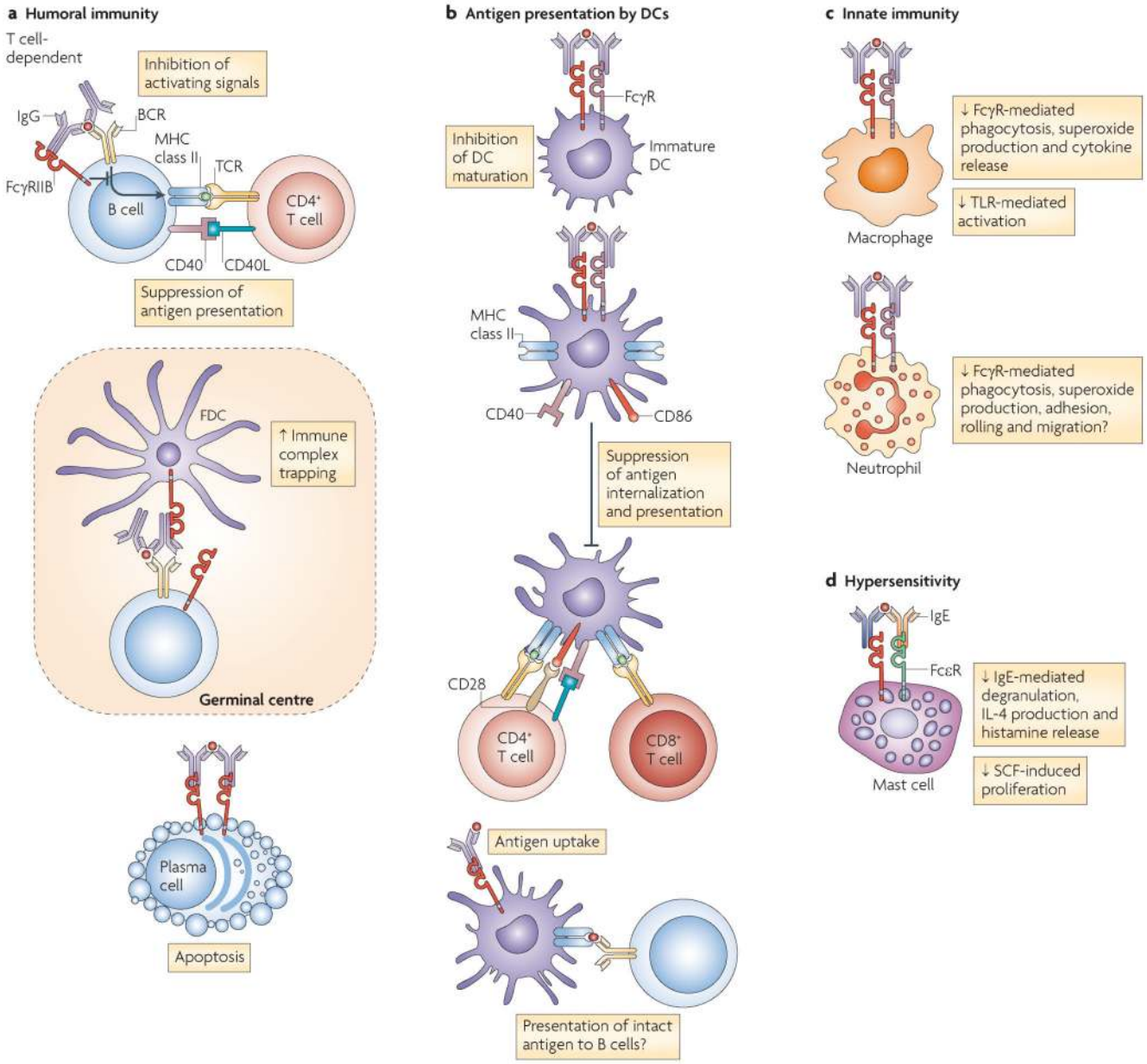

Figure 2. The functions of FcγRIIB

a | Fc receptor IIB for IgG (FcγRIIB) has an important role in controlling humoral immunity by regulating B cell activation, localization of B cells in the germinal centres, as well as plasma cell survival. FcγRIIB regulates B cell activation by increasing the B cell receptor (BCR) activation threshold and suppressing B cell-mediated antigen presentation to T cells. Follicular dendritic cells (FDCs) express FcγRIIB, which is thought to be important for trapping immune-complexed antigen for presentation to germinal centre B cells. The absence of FcγRIIB on germinal centre FDCs results in impaired antibody and memory responses. Terminally differentiated plasma cells express little or no BCR but express high levels of FcγRIIB, and cross-linking FcγRIIB with immune complexes *in vitro* can induce apoptosis. **b |** FcγRIIB influences antigen presentation by inhibiting FcγR-dependent

internalization of immune-complexed antigen by DCs, as well antigen presentation to both CD4+ and CD8+ T cells (cross-presentation). FcγRIIB is also thought to provide a basal level of inhibition to DC maturation, as blockade of immune complex binding to FcγRIIB results in DC maturation and type I interferon production. There is also a possibility that FcγRIIB may deliver intact antigen to a non-degradative compartment, allowing its recycling to the cell surface where it could interact with the BCR and activate B cells. **c** | FcγRIIB can also influence innate immunity: in macrophages, FcγRIIB cross-linking inhibits FcγR-mediated phagocytosis and cytokine release (including tumour necrosis factor, interleukin-6 (IL-6) and IL-1α), as well as Toll-like receptor 4 (TLR4)-mediated activation. In neutrophils, cross-linking of activating FcγRs results in phagocytosis, superoxide production and enhanced neutrophil adhesion, rolling and migration, all of which are probably inhibited by ligating FcγRIIB. **d** | FcγRIIB also inhibits IgE-induced mast cell and basophil degranulation, thus contributing to hypersensitivity responses. FcεR, Fc recpetor for IgE; SCF, stem cell factor.

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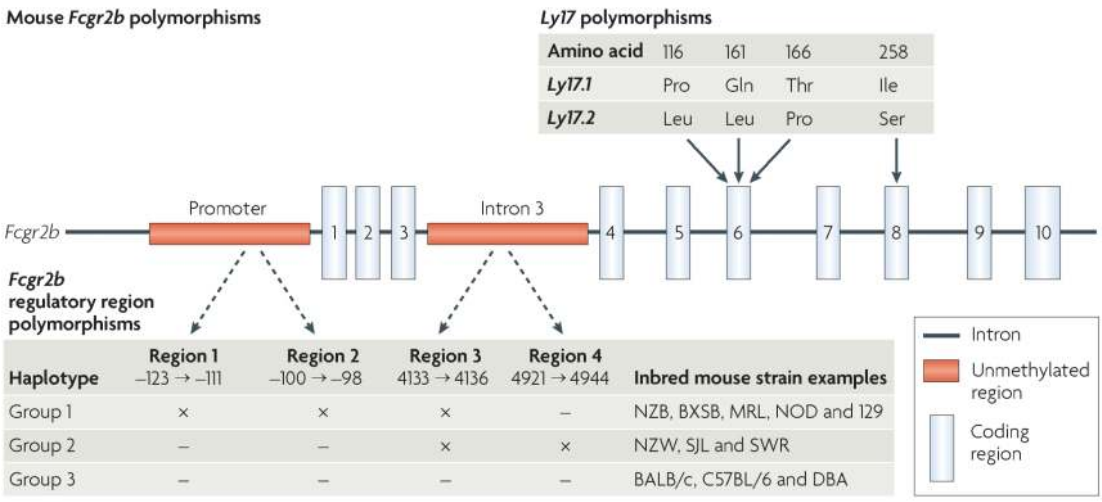

Figure 3. Mouse *Fcgr2b* polymorphisms

Fcgr2b polymorphisms include the *Ly17* polymorphisms, which are found in the coding region that comprises the *Ly17* haplotype. These include three single nucleotide polymorphisms (SNPs) within exon 6 and one in exon 8 that appear to have no effect on receptor function. Regulatory region polymorphisms identified within the promoter region and intron 3 form 3 haplotypes and vary between different strains of inbred mice. In the promoter there is a 13 base pair deletion (region 1) and a 3 base pair deletion (region 2). In intron 3, there is a 4 base pair deletion at nucleotide 4133 to 4136 (region 3) and a 24 base pair deletion at nucleotide 4921 to 4944 (region 4). Inbred strains with the group 1 haplotype (NZB, BXSB, MRL, non-obese diabetic (NOD) and 129 mice) have region 1, region 2 and region 3 deletions (×), have decreased expression of FcγRIIB by macrophages and activated B cells and are prone to autoimmune disease. The precise contribution of deletions in the promoter and intron 3 to autoimmune susceptibility in these strains has yet to be determined. Inbred strains with the group 2 haplotype have a promoter with no deletions but have deletions in region 3 and 4 of intron 3 (which may contain enhancer and repressor elements). Inbred strains with the group 3 haplotype do not have deletions in either the promoter or intron 3 and include BALB/c and C57BL/6 mice.

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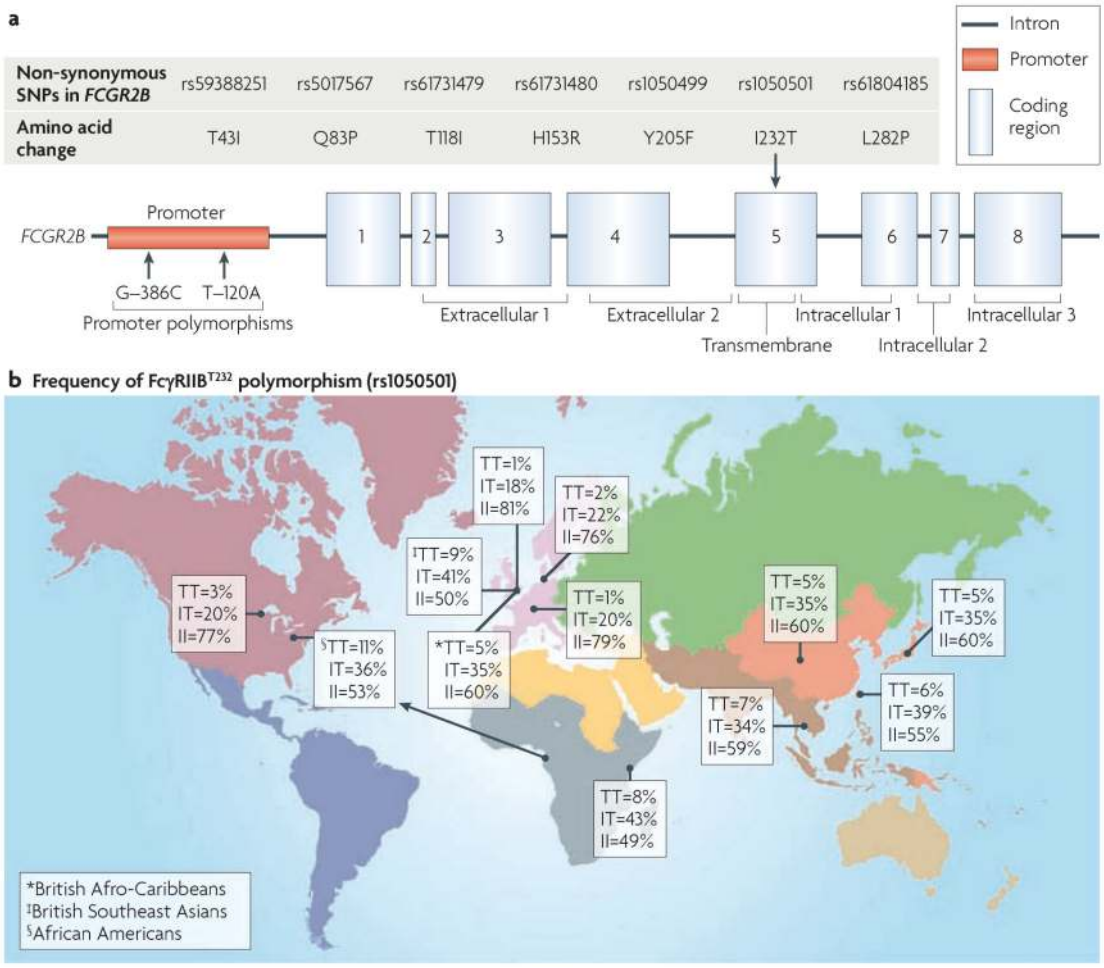

Figure 4. Human *FCGR2B* polymorphisms

a | Several single nucleotide polymorphisms (SNPs) have been identified within the promoter and coding regions of *FCGR2B*. In the promoter, there are two SNPs at nucleotides −386 and −120. These SNPs form two haplotypes, a common −386G:−120T haplotype and a less common −386C:−120A haplotype. These haplotypes may alter transcription factor binding and expression. Seven non-synonymous SNPs have been identified in the human *FCGR2B* gene but only one has been studied in detail. This non-synonymous T-to-C transition (rs1050501) in exon 5 of the gene results in the substitution of a threonine for isoleucine at position 232 within the transmembrane domain of FcγRIIB (FcγRIIB^{T232}). The FcγRIIB^{T232} variant is excluded from lipid rafts and has notably impaired inhibitory function. The polymorphism that encodes FcγRIIB^{T232} has been associated with increased susceptibility to systemic lupus erythematosus (SLE) in both Southeast Asian and Caucasian populations. **b** | The frequency of the FcγRIIBT232 variant in different populations varies substantially. It is uncommon in Caucasians (1% homozygosity) but more common in populations found in areas of malarial endemicity such as Africa and Southeast Asia (5–11% homozygosity) suggesting that decreased FcγRIIB function may provide a survival advantage against this disease. This might provide the first example of an immune polymorphism predisposing to polygenic autoimmunity, selected and

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retained by virtue of its protective effect in malaria infection, and thus it is beginning to provide an explanation for the ethnic differences seen in SLE susceptibility.

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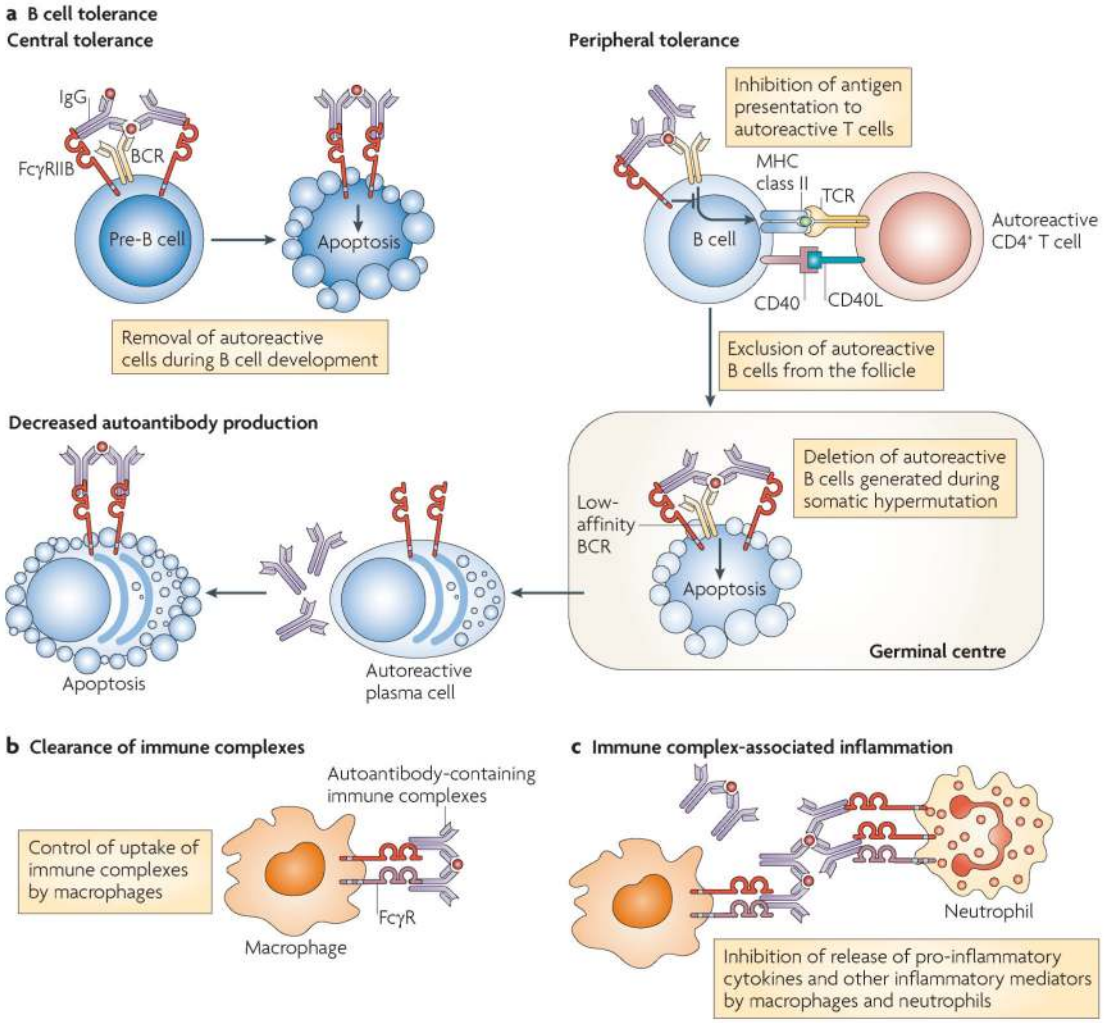

Figure 5. Potential mechanisms by which FcγRIIB might contribute to the pathogenesis of systemic lupus erythematosus

a | Fc receptor IIB for IgG (FcγRIIB) is important for the maintenance of B cell tolerance through inhibition of B cell activation, promotion of the exclusion of autoreactive cells from follicles and perhaps by mediating apoptosis of autoreactive B cells and plasma cells. *In vitro*, FcγRIIB cross-linking in pre-B cells can result in apoptosis. This has been proposed as a possible mechanism for the removal of autoreactive B cells that arise during development; however, studies in FcγRIIB-deficient mice do not confirm the importance of this mechanism in central tolerance *in vivo*. FcγRIIB operates at several stages during later peripheral B cell development, potentially inhibiting B cell receptor (BCR)-mediated activation of autoreactive B cells. In addition, it may be important for the follicular exclusion of low-affinity autoreactive B cells. Autoreactive B cells may arise during somatic hypermutation and affinity maturation. It has been proposed that FcγRIIB cross-linking in the absence of BCR ligation may mediate apoptosis of such autoreactive follicular B cells and may also be important for deleting autoreactive plasma cells. **b** | Breakdown of B cell tolerance and the emergence of autoantibodies does not necessarily result in autoimmune disease, as there are mechanisms that function to clear circulating immune complexes,

preventing them from becoming deposited in tissues. Immune complex clearance is, in part, mediated by binding and internalization by activating FcγRs (particularly on macrophages of the reticuloendothelial system of the liver and spleen). FcγRIIB may enhance or inhibit FcγR-mediated immune complex internalization by phagocytes (depending on the isoform expressed) thus modulating the amount of circulating immune complex present. **c |** Tissue-deposited immune complexes may initiate inflammation owing to ligation of activating FcγRs on infiltrating macrophages and neutrophils. Pro-inflammatory cytokine release and neutrophil degranulation in response to immune complexes is negatively regulated by FcγRIIB. Thus, FcγRIIB dysfunction might contribute to the pathogenesis of systemic lupus erythematosus at several stages, including the breakdown of self-tolerance, decreased disposal of immune complexes and a failure to modulate the inflammatory response to deposited immune complexes. TCR, T cell receptor.

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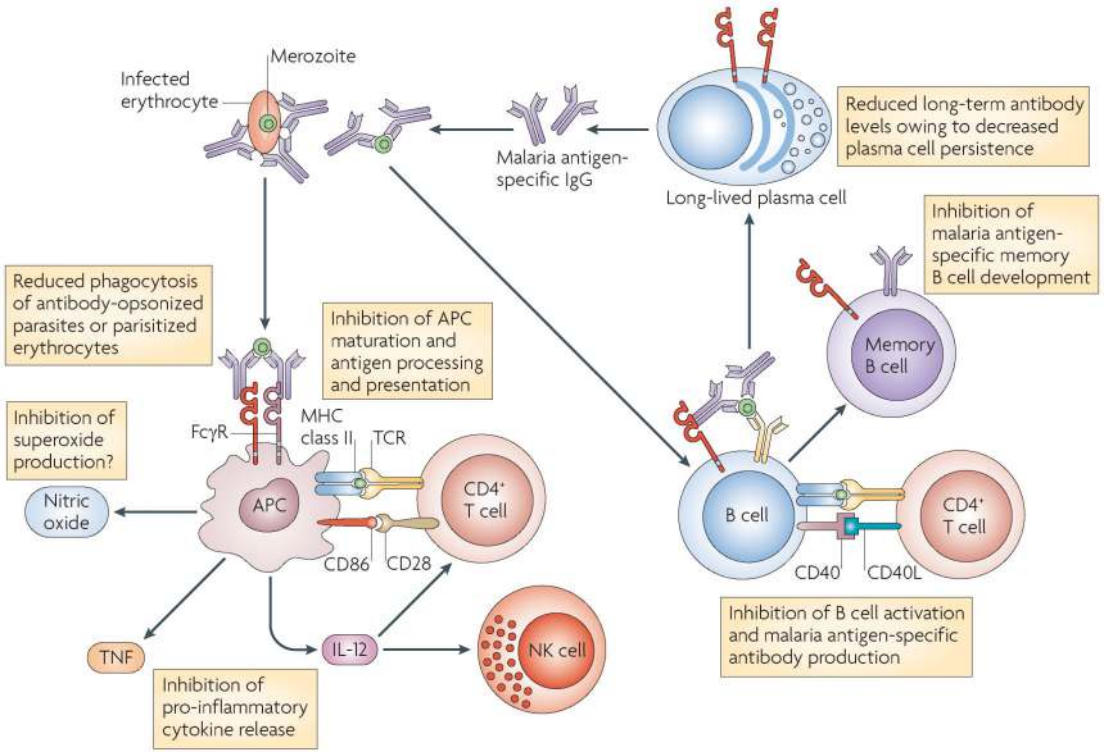

Figure 6. The proven and potential roles of FcγRIIB in defence against malarial infection

Fc receptor IIB for IgG (FcγRIIB) regulates phagocytosis of parasites and parasitized erythrocytes, antigen presentation to T cells and the production of malarial antibodies by B cells. Macrophages are important in the immune response to malaria, both as antigen-presenting cells (APCs) and phagocytes. In particular, FcγR-mediated phagocytosis is crucial for the elimination of parasitized erythrocytes in mouse malarial models. FcγRIIB inhibits FcγR-mediated phagocytosis of antibody-opsonized parasitized erythrocytes or opsonized merozoites. Subsequent presentation of malarial antigens to T cells may also be potentially modulated by FcγRIIB. Cytokines are important in the immune response to malarial parasites. Tumour necrosis factor (TNF) promotes macrophage phagocytosis and enhances killing of intra-erythrocytic *Plasmodium falciparum* in humans. FcγRIIB inhibits the production of TNF from macrophages following FcγR-mediated phagocytosis of antibody-opsonized parasitized erythrocytes. IL-12 is crucial for the development of interferon-γ (IFNγ)-mediated protection to mouse malarial infections and for the production of TNF, and its release may also be modulated by FcγRIIB. Antibodies form an important defence to the erythrocytic stages of malaria (as shown by the passive transfer of protective IgG in mice and humans). FcγRIIB-deficient mice generate enhanced levels of malaria-specific IgG following infection with Plasmodium chabaudi chabaudi, suggesting that FcγRIIB may have a role in regulating antibody responses to malarial parasites in humans. IL, interleukin; NK, natural killer; TCR, T cell receptor.

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Table 1
Current and future therapeutic exploitation of FcγRIIB

Therapeutic strategy	Clinical effect	Refs
Modulation of FcγRIIB expression on effector cells	IVIG indirectly increases FcγRIIB expression on 'effector' cells	138,139
	Infliximab (Remicade; Centocor/Merck) blocks TNF, leading to increased FcγRIIB expression on monocytes	142
Modulation of IgG-binding to FcγRIIB	Decrease in affinity of depleting monoclonal antibodies for FcγRIIB increases efficacy	45,47
Use of FcγRIIB as a direct therapeutic target	Monoclonal antibody directed against FcγRIIB allowing co-crosslinking of FcγRIIB may induce apoptosis of B cells and plasma cells in lymphoma, myeloma or autoimmunity	40,150,151
	A bispecific antibody that binds antigen-specific BCR and FcγRIIB potentially allows targeted inhibition of autoreactive B cells	-
	Therapeutic antibody targeting IgE receptor can inhibit mast cell degranulation and may be useful in the treatment of allergy	152-155
	Soluble FcγRIIB may inhibit immune complex-mediated immune activation and has shown efficacy in a mouse model of SLE	156

BCR, B cell receptor; FcγR, Fc receptor for IgG; IVIG, intravenous immunoglobulin; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.