Ann Hematol (1998) 76:231–248 © Springer-Verlag 1998

REVIEW ARTICLE

J.E. Gessner · H. Heiken · A. Tamm · R.E. Schmidt

The IgG Fc receptor family

Received: January 28, 1998 / Accepted: March 31, 1998

Abstract. IgG immune complexes are of central importance in the humoral immune system and strongly implicated in the pathogenesis of hematologic and rheumatic autoimmune disorders. Cross-linking of receptors for the Fc domain of IgG antibodies (FcγRs) triggers a wide variety of effector functions including phagocytosis, antibody-dependent cellular cytotoxicity, and release of inflammatory mediators, as well as immune complex clearance and regulation of antibody production. In this way, FcγR provide an essential feedback between the humoral and cellular immune response. In the past, significant advances have been made in the molecular dissection of FcγR function using cellular transfection systems. Current approaches designed to target and change individual FcγR genes in mice have given further insight into their specific contributions to systemic processes, also indicating them to be important immunoregulatory receptors involved in various disease states of allergy, autoimmunity, and inflammation. Future work on targeting FcγR binding sites in combination with humanized FcγR mouse models will lead to novel therapeutic strategies in the treatment of IgG-mediated human disease in which FcγR activation plays an integral part.

Key words Allergy · Autoimmunity · FcγR · IgG · Inflammation

This work was supported in part by grants GE 892/2–2 and GE 892/5–1 from the *Deutsche Forschungsgemeinschaft* and *Sonderforschungsbereich* 244 project A09.

J.E. Gessner (✉) · H. Heiken · A. Tamm · R.E. Schmidt
Department of Clinical Immunology, Hannover University Medical School, Carl-Neuberg Strasse 1, D-30625 Hannover, Germany (e-mail: Gessner.Johannes@MH-Hannover.de, Fax: (49)-511–532–5648)

Introduction

Cell surface receptors for the Fc domain of immunoglobulin (Ig) are known to be expressed on all cells of the immune system. Fc receptors (FcR) play an important role in immune regulation, as they serve to link antibody-mediated immune responses with cellular effector functions. Specific FcRs exist for all classes of immunoglobulin, including IgA (FcαR), IgD (FcδR), IgE (FcεR), IgG (FcγR), and IgM (FcμR). The primary structure of the genes and proteins of the FcαR, FcεR, and FcγR receptors has been resolved, revealing similarities in subunit composition and signal transduction with the T- and B-cell antigen receptors. In the case of FcγR, three distinct classes have been recognized: FcγRI, FcγRII, and FcγRIII, with different IgG binding affinities and IgG subclass specificities (for review see [1–3]).

All the FcγR belong to the Ig supergene family composed of unique ligand-binding a chains that consist of the C2 class of extracellular Ig domains. Within each FcγR receptor class multiple subtypes are known. The FcγRI and -III classes exist as oligomeric complexes together with γ and ζ chain homo- or heterodimers involved in cell activation through the conserved cytoplasmic signal transduction motif, termed immunoreceptor tyrosine-based activation motif (ITAM). Members of the FcγRII class such as FcγRIIA and FcγRIIB are different from other FcγR, in that they are monomeric receptors containing either activatory (ITAM) or inhibitory (ITIM) signaling motifs within their respective ligand-binding chains.

The structural heterogeneity of FcγR is reflected in a wide range of biological activities, including clearance of antigen/antibody immune complexes (IC), regulation of antibody production, enhancement of antigen presentation, antibody-dependent cell-mediated cytotoxicity (ADCC), phagocytosis, degranulation, and activation of inflammatory cells. Many of these responses may be unique for selected cell types based on differences in tissue-specific expression of FcγRs. Additional

diversity of individual FcγR receptor-mediated function is related to genetically determined polymorphisms (for review see [4]), to the generation of soluble FcγR (for review see [5]), and to synergisms with other receptor systems (for review see [6]).

FcγRs have been implicated to be involved in several rheumatic and autoimmune diseases. The specific contribution of each of the FcγR classes to many of these pathological events is still unclear. Recent studies using genetically altered FcγR mouse strains have been started to define more closely the functional significance of FcγRs for normal and pathological in vivo immune reactions. This review focuses on molecular aspects of human and murine FcγR structure and function and discusses the potential of FcγR knock-out mice as experimental models for human disease.

General characteristics of the IgG Fc receptor family (FcγR)

Three distinct classes of mouse and human FcγR have been defined: FcγRI, FcγRII, and FcγRIII. In the mouse each class is encoded by a single gene, whereas in the human being a total of eight genes have been identified: three genes for the high-affinity receptor FcγRI (A, B, C) and five genes for the two low-affinity receptors FcγRII (A, B, C) and FcγRIII (A, B). The human FcγR genes are located on chromosome 1, bands 1p13 and 1q21 (hFcγRI) and band 1q22 (hFcγRII and hFcγRIII) [7]. These regions are syntenic to mouse chromosomes 3 or 1, where the respective murine mFcγRI or mFcγRII and mFcγRIII genes have been mapped [8, 9]. The FcγR genes are derived from a common ancestral gene and are structurally related, containing conserved Ig-like extracellular (EC) domains and divergent transmembrane (TM) and cytoplasmic (C) regions [8]. The different organization in the TM/C domains, together with certain specificity of expression, accounts for the diverse functions of the different FcγR classes. An overview of the molecular heterogeneity and characteristics of FcγRs is shown in Figs. 1 and 3 and Tables 1–3.

FcγRI

Human FcγRI (CD64) is a 72-kDa glycoprotein which binds with high affinity ($K_a = 10^8$–$10^9 M^{-1}$) to monomeric as well as aggregated IgG, with a specificity for human IgG1 and IgG3. The interaction with IgG4 and particularly with IgG2 is much weaker. In contrast to other human FcγRs, hFcγRI does not interact with murine IgG2b, binding only mIgG2a and mIgG3 isotypes [2]. High affinity is a unique property for FcγRI, dependent on a third extracellular Ig domain not found in class II or III receptors [10].

Of the three hFcγRI genes (A, B, C), only hFcγRI-A encodes for the high-affinity receptor. The other two, i.e., the hFcγRI-B and hFcγRI-C genes, are characterized by in-frame stop codons in the third extracellular (EC3) exon [11]. hFcγRI-B-derived splice variants lacking the EC3 exon are capable of encoding a low-affinity hFcγRIb2 receptor isoform in vitro [12]. The existence and function of such a receptor isoform in vivo has not yet been demonstrated.

hFcγRIa is constitutively expressed on monocytes and macrophages and can be induced by IFN-γ on neutrophils, eosinophils, and glomerular mesangial cells [1–3, 13]. hFcγRIa expression is also induced by G-CSF on neutrophils and by IL-10 on mesangial cells [13, 14]. An IFN-γ-responsive region (GRR) within the hFcγRI-A gene promoter has been identified [15]. Induction by IFN-γ as well as by IL-10 and G-CSF involves the binding of STAT family members of activated transcription factors to the GRR [16–18].

The induction by IFN-γ, G-CSF, and IL-10 at sites of inflammation might be crucial to the function of hFcγRIa as a trigger molecule of phagocytosis and ADCC, as well as of endocytosis, leading to enhanced antigen presentation. hFcγRIa receptors lack signaling motifs in the cytoplasmic domain of their ligand-binding a chains [10]. Initiation of phagocytosis following ligand binding and receptor aggregation relies on tyrosine kinase activities recruited by the ITAM motif of the associated FcR γ-subunit [19, 20]. It is also suggested that the γ-subunit contributes to an improved IgG binding of hFcγRIa as well as to a more stable surface expression [21], whereas pseudopod formation occurring after binding of IgG-opsonized particles [22] and endocytosis of soluble immune complexes [23] are not strictly dependent on the γ-chain.

Murine FcγRI is a trypsin-sensitive 70-kDa glycoprotein expressed mainly on macrophages binding mIgG2a with high affinity ($K_a = 10^8 M^{-1}$) [1, 3]. mFcγRI seems not to interact with the other mIgG1, mIgG2b isotypes. The IgG-binding capacity for human IgG is not well defined. Similar to hFcγRIa, both features of high affinity and mIgG2a specificity are dependent on the presence of a third Ig domain [24]. Sequence comparison of mFcγRI and hFcγRIa has revealed a 65–75% identity in the three extracellular domains and the transmembrane region. However, the cytoplasmic domain is largely unrelated to hFcγRIa, containing as it does an additional stretch of 22 amino acids [25]. Within the cytoplasmic domain serine residues have been identified to be phosphorylated following stimulation of neutrophils by induction of protein kinase C [26]. A defective mFcγRI receptor lacking, in addition to extracellular mutations, most of its cytoplasmic tail is expressed in some mouse strains exemplified by nonobese diabetic (NOD) mice [27, 28]. This mutated mFcγRI has lost the capacity to internalize bound IgG2a. A similar functional impairment of IgG2a-FcγRI-triggered phagocytosis is seen in mice deficient in the FcR γ-chain. These data indicate that specific signals locate to

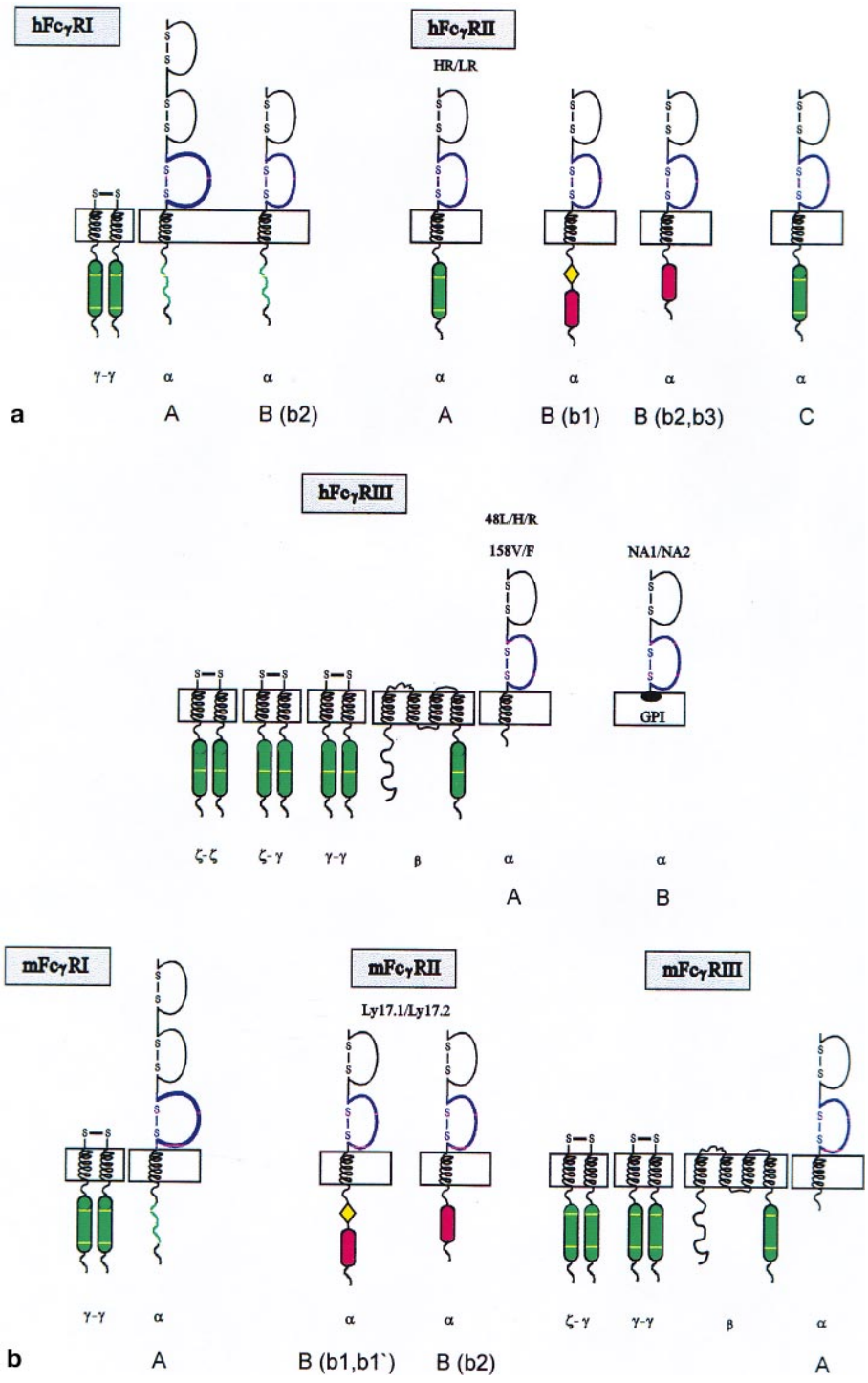

Fig. 1a,b. Schematic representation of the human (**a**) and mouse (**b**) IgG Fc receptor family (*FcγR*). All human and mouse FcγR classes I, II, and III are members of the immunoglobulin superfamily having two or three homologous extracellular Ig-like domains. The membrane-proximal Ig domains involved in ligand binding of IgG are shown in *blue*. With the exception of hFcγRIIIb, which is a GPI-anchored protein, all FcγRs are transmembrane molecules. Multiple genes in each receptor class, their alternative spliced products, and their individual subunits are referred to as *A*, *B*, and *C*; *b1*, *b1'*, *b2*, and *b3*; and α, β, γ, and ζ, respectively. Polymorphic variants are indicated (*HR/LR*, *NA1/NA2*, *48L/48R/48H*, *158F/158 V*, and *Ly17.1/Ly17.2*). Within the cytoplasmic tails distinct functional motifs involved in signal transduction are recognized. Activatory ITAM and inhibitory ITIM sequence motifs are indicated in *green* and *red*, respectively. In addition, the region responsible for inhibition of endocytosis present in human and mouse FcγRIIb1 is displayed in *yellow*

specialized cytoplasmic regions in the ligand-binding α-chain and the associated γ-subunit, which both might contribute to mFcγRI-triggered effector cell functions.

FcγRII

Human FcγRII (CD32) receptors are 40-kDa glycoproteins that bind, as low-affinity receptors, IgG in the form of immune complexes ($K_a = 10^7 M^{-1}$) with a specificity for hIgG1 and hIgG3. All hFcγRIIs show no detectable binding with hIgG4 but interact well with mIgG2a and mIgG2b. Binding to hIgG2 and mIgG1, which are normally not recognized by human FcγRs, depends on the high responder (HR)/low responder (LR) polymorphism of the hFcγRIIa receptor [2, 4]. The HR allotype which is determined by an Arg at position 131 interacts with hIgG2. In contrast, the LR allotype expresses for His at residue 131 and has the capacity to bind mIgG1. This polymorphism has been as-

Table 1 General characteristics of human Fcγ receptors

	hFγRI (CD64)	hFcγRII (CD32)	hFcγRIII (CD16)
Molecule	72 kDa	40–43 kDa	50–80 kDa
Genes	3 (A, B, C)	3 (A, B, C)	2 (A, B)
Alleles	IA: –	IIA: 2 (HR/LR)	IIIA: 3 (48L/R/H)
	IB: –	IIB: –	2 (158F/V)
	IC: –	IIC: –	IIIB: 2 (NA1/NA2)
Transcripts[a]	a1, a2	a1, a2	a1–a6, ΔEC2
	b1, b2, b3	b1, b2, b3	b
	c	c	
Isoforms[b]	hFcγRIa	hFcγRIIa1, hFcγRIIa2 (S)	hFcγRIIIa,
	(hFcγRIb2)	hFcγRIIb1, b2	(hFcγRIIIaΔEC2)
		(hFcγRIIc)	hFcγRIIIb (GPI)
Associated subunits[c]	FcR γ chain	–	FcR γ chain, FcR β chain TCR/CD3 ζ chain
Mabs[d]	22.2, 32.2, 197, 62, 44, 10.1	IIa: IV.3, CIKM5, 2E1, CIKM3	IIIa (48L): B73.1
		IIa-HR: 41H16	IIIa (158V): MEM154, 1D3
		IIb: 1A4, 8.7, 7.30	IIIb (NA1): MG38, B73.1
		IIa/b: KB61, 8.26, Ku79, AT10	IIIb (NA2): GRM1, PEN1
			IIIa/b: 3G8, DJ130c, Leu11a, LNK16, B88-9
Affinity for IgG (K_a)	10^8–10^9 M^{-1}	$<10^7$ M^{-1}	IIIa: 3×10^7 M^{-1} [e]
			IIIb: $<10^7$ M^{-1}
Specificity for hIgG	3=1>4>>>2	IIa (HR): 3>1>>2>4	IIIa/IIIb: 1=3>>>2, 4
		IIa (LR): 3>1=2>>>4	
		IIb1: 3>1>4>>2	

[a] A total of six variant FcγRI transcripts are evident, from which a1, b1, b2, c but not yet a2 or b3 have been published [11]. hFcγIIa transcripts lacking the EC2 coding sequences can be expressed by transfection as a hFcγRIIIa receptor variant with a single extracellular Ig domain [152]

[b] Parentheses indicate protein isoforms expressed after transfection but not yet verified in vivo [3, 12, 152]. All isoforms are transmembrane proteins, with the exceptions indicated as S (soluble) and GPI (glycosyl-phosphatidyl-inositol anchored)

[c] The FcR β chain can associate with the hFcγRIIIa $\alpha\gamma2$ receptor complex in the transfected murine P815 mastocytoma cell line. TCR/CD3 ζ chain associates as a homo- or heterodimer with hFcγRIIIa expressed by $\gamma\delta$ T cells and NK cells

[d] CD64, CD32, CD16 monoclonal antibodies characterized during the Fifth Leukocyte Typing workshop are listed [153–155]. Most CD64 mAbs recognize an epitope outside the ligand-binding domain. CD32 mAbs show differences in their patterns of reactivity, with preferential binding to either hFcγRIIa or hFcγRIIb, or both. The 41H16 mAb is specific for the FcγRIIa-HR allotype and reacts with all FcγRIIb isoforms [156]. The 1A4 mAb detects specifically an activation epitope of hFcγRIIb present on tonsilar CD19-positive B cells [157]. The 8.7, 7.30 mAbs preferentially bind to Daudi B cells rather than monocytic U937 cells [158]. CD16 mAb normally recognize both hFcγRIII isoforms but can show differences in their reactivity with distinct allotypes. A notable exception is MG38, which reacts exclusively with the NA1 form of hFcγRIIIb [159]. The 1D3 mAb, originally clustered to be specific for NA1 and NA2 of hFcγRIIIb, also demonstrates weak reactivity with the 158 V hFcγRIIIa [69]. The MEM154 mAb binding to an epitope at the ligand-binding site of hFcγRIIIb [160] also reacts with the 158 V hFcγRIIIa allotype [69]

[e] The medium affinity of hFcγRIIIa expressed by NK cells is dependent on the high-binding 158 V allotype [69, 161]

sociated with certain bacterial infections and with SLE [2, 4]. Extensive information has been gained in defining the IgG binding site of FcγRII [3]. The loop connecting F and G ß-sheets on the second extracellular Ig domain of FcγRII-A between residues Asn154 and Ser161 constitutes an IgG-binding structure [29]. In addition to this region, as the major site involved in the direct interaction with IgG, several amino acids located on the loops connecting B and C ß-sheets (Lys113, Pro114, Leu115, Val116) as well as C and 'E ß-sheets (Phe129, Arg/His131) influence hFcγRII-A/IgG interaction [30].

In contrast to the other hFcγRs, which are encoded by genes containing a single exon for the transmembrane and cytoplasmic region, three separate exons (C1–C3) have been discovered for the cytoplasmic tail and 3'UTR of the hFcγRII genes [8, 31]. Three separate genes, hFcγRII-A, hFcγRII-B, and hFcγRII-C, are known. Six different mRNAs (a1, a2, b1, b2, b3, and c) are transcribed encoding either soluble (a2) or transmembrane (a1) hFcγRIIa receptors as well as two hFcγRIIb isoforms [4, 32, 33]. The existence and function of the c1-transcribed hFcγRIIc receptor have not yet been demonstrated in vivo. The hFcγRIIb1 and hFcγRIIb2 receptors are identical except for a 19-amino acid insertion in hFcγRIIb1 encoded by the first intracytoplasmic (C1) exon. hFcγRIIb3 is almost identical to hFcγRIIb2 but lacks nucleotide sequences encoding for signal sequences by the S2 exon. The hFcγRIIb1-specific insertion negatively affects the internalization capacity of IgG [34].

hFcγRIIs are the most widely expressed FcγRs and are present on almost all leukocytes, including neutrophils, eosinophils, basophils, monocytes, macrophages, platelets, Langerhans cells, B cells, and some T-cell subsets [1–3]. In relation to the receptor classes I and III, their expression on monocytes and neutrophils is not up-regulated by cytokines. hFcγRIIa expressed on neutrophils and macrophages initiates phagocytosis, ADCC, and cellular activation [35–38], whereas

Table 2 Distribution and function of human Fcγ receptors

	hFcγRI (CD64)	hFcγRII (CD32)	hFcγRIII (CD16)
Expression			
Constitutive	Myeloid progenitors Monocytes Macrophages Dendritic cells	B cells, subpopulation of T cells Monocytes, macrophages Basophils, eosinophils Neutrophils, platelets, Langerhans cells, dendritic cells, endothelial cells	IIIa: NK cells, $\gamma\delta$ T cells, macrophages, subpopulation of monocytes IIIb: Neutrophils
Induced	Neutrophils Eosinophils Mesangial cells	–	IIIa: Mesangial cells, monocytes IIIb: Eosinophils
Regulation[a]	A: IFNγ, IL-10, G-CSF B: – C: IL-4, IL-3	A: – B: – C: IL-4	A: IFNγ, IL-10, G-CSF B: TGFβ C: IL-4
Functions	Endocytosis Antigen presentation ADCC Phagocytosis Respiratory burst Mediator release	IIa1: Endocytosis, antigen presentation, respiratory burst, phagocytosis, ADCC, mediator release IIb2: Endocytosis IIb1/2: Negative regulation of B-cell and mast-cell activation	IIIa: Endocytosis, antigen presentation, ADCC, apoptosis, phagocytosis, mediator release IIIb: Respiratory burst, IIIb: ADCC[b]

[a] *A* transcriptional induction, *B* post-transcriptional induction, *C* down-modulation
[b] Conflicting data in the literature (reviewed in [3])

Table 3 Characteristics of murine Fcγ receptors

	mFcγRI	mFcγRII	mFcγRIII
Molecule	70 kDa	40–60 kDa	40–60 kDa
Genes	1	1	1
Alleles	–	2 (Ly17.1/Ly17.2)	–
Isoforms	mFcγRI	mFcγRIIb1, b1′, b2, b3 (S)	mFcγRIIIa
Associated subunits	FcR γ chain	–	FcR γ chain, FcR β chain
Mabs	–	2.4G2 K9.361 (anti-Ly17.1)[a] K75.325 (anti-Ly17.2)[a]	2.4G2
Affinity for IgG (Ka)	$10^8\ M^{-1}$	$<10^7\ M^{-1}$	$<10^7\ M^{-1}$
Specificity for mIgG	2a>>>1, 2b, 3	1=2a=2b>>>3	1=2a=2b>>>3
Expression	Macrophages, mesangial cells[b]	b1: B cells, subset of T cells, early fetal thymocytes b2: Macrophages, mesangial cells[b] b1/b2: Mast cells, basophils, eosinophils	Macrophages, mast cells, neutrophils, eosinophils Mesangial cells[b] NK cells, $\gamma\delta$ T cells Early fetal thymocytes
Functions	ADCC, phagocytosis	b1: Capping, apoptosis[c], negative regulation of B-cell and mast-cell activation b2: Endocytosis, phagocytosis?[d], antigen presentation	ADCC, Antigen presentation, phagocytosis, degranulation Mediator release

[a] The FcγRII-specific anti-Ly17 antibodies distinguish between FcγRII and FcγRIII expression and functioning [162, 163]
[b] mRNAs for mFcγRI, mFcγRIIb2, and mFcγRIII are evident in mesangial cells
[c] Induction of apoptosis has been described for mFcγRIIb1 in B cells [164] and mFcγRII b1/b2 in eosinophils [165]
[d] There is some evidence that the endocytic mFcγRIIB2 is also involved in phagocytosis of opsonized particles [166]

hFcγRIIb expressed on B cells and mast cells delivers a negative signal modulating activatory BCR- and FcεRI-mediated responses, respectively [34, 39–41].

Specialized signaling motifs, an activatory ITAM in the cytoplasmic tail of hFcγRIIa versus an inhibitory ITIM in hFcγRIIb, are essential for the different functions of the hFcγRII isoforms. Mutational analyses have shown that tyrosine residues in both hFcγRIIa-ITAM and hFcγRIIb-ITIM are critical for the activation versus down-regulation events. ITAM motifs, found in hFcγRIIa and the FcR γ-chain as well as in the T- and B-cell antigen receptors, consist of two YXXL boxes interspaced by 7–12 amino acids [42]. Phosphorylation of both tyrosines by Src-family protein tyrosine kinases such as Lyn or Fyn, and by subsequent association with SH2 domains contained in tyrosine ki-

nases such as Syk, appears to be critical for activatory hFcγRIIa signaling [36, 43]. The ITIM motif is unique for all mouse and human FcγRIIb receptor isoforms not present in the other FcγR classes. It is part of a highly conserved 13-amino acid sequence with a consensus inhibitory I/LxYxxL motif encoded by the C3 exon and determines the ability to control ITAM-based signaling after co-cross-linking with the BCR, FcεRI, FcγRIIa, and FcγRIII receptors [40]. The functional significance of the ITIM motif is best studied in the murine system described below.

In mice the mFcγRII gene is structurally related to hFcγRII-B. Activatory mFcγRIIa receptors are not present in the murine system. mFcγRII-B exist in four isoforms generated by cell-type-specific alternative splicing of TM- and/or C1-encoding exons of the transcript classes b1, b1' in B cells and b2, b3 in macrophages [44]. mFcγRIIb3 receptors lacking TM and C1 sequences are released as soluble receptors by macrophages [45]. mFcγRIIb2 receptors lacking C1 sequences are preferentially expressed by myeloid cells and mediate endocytosis of immune complexes, leading to an enhancement of antigen presentation [46]. The mFcγRIIb1' isoform contains a 19-amino acid insertion encoded by the 5' part of the C1 exon, indicating that this isoform is the murine homologue of hFcγRIIb1 [47]. It is coexpressed with and functionally equivalent to mFcγRIIb1, which has a longer, 47-amino acid-encoded C1 insertion. The presence of C1 sequences in the B-cell-specific mFcγRIIb1/b1' receptors is not required to modulate BCR activation signals, but selectively prevents mFcγRII-mediated endocytosis and antigen presentation [48, 49]. The characteristic C1 insertion contributes to the formation of caps in response to mFcγRIIb1 cross-linking. It has been concluded that this feature is important to B-cell function, ensuring that mFcγRIIb1 is in close proximity to the BCR and other costimulatory factors such as MHC class II and CD19 [48].

Coligation of mFcγRIIb1 with the antigen receptor on B cells inhibits the influx of extracellular calcium and abrogates the proliferative signal [48, 50, 51]. Phosphorylation of the FcγRIIb ITIM tyrosine is critical to its inhibitory mechanism (see Fig. 3), leading to the recruitment of SH2-domain containing phosphatases, namely the tyrosine-phosphatase SHP-1 and the phosphatidylinositol (3,4,5) P_3 5' inositol phosphatase SHIP [52–54]. Although SHP-1 and SHIP are both implicated in FcγRIIb signaling, their relative roles remain controversial [55, 56]. A potential role for SHP-1 was originally suggested in studies on SHP-1 in B cells, where SHP-1-deficient (moth-eaten) B cells did not demonstrate antiproliferative activity on FcγRIIb engagement [52]. The involvement of a tyrosine phosphatase like SHP-1 may explain the selective decrease in the tyrosine phosphorylation of CD19 [54]. The dephosphorylation of CD19 gives rise to a corresponding decrease in the level of associated PI3 K, suggesting that inhibition of calcium influx and IP3 production may result from default PI3 K activation [57, 58]. The finding that inhibitory signaling by mFcγRIIb does not require SHP-1 in SHP-1-deficient mast cells led to the identification of SHIP [59]. Later on, the preferential association of mFcγRIIb1 with SHIP was also demonstrated in B cells [53, 60]. It has been proposed that SHIP recruitment attenuates a proapoptotic signal initiated by mFcγRIIb1 coligated with the BCR [60, 61].

FcγRIII

Human FcγRIII (CD16) receptors are extensively glycosylated proteins showing heterogeneity with an apparent molecular weight of 50–80 kDa. hFcγRIII binds IgG in the form of immune complexes, with a specificity for hIgG1 and hIgG3 and minimal binding of hIgG4 and hIgG2 [1–3, 62]. Several amino acids on the membrane-proximal Ig domain of hFcγRIII (Gln126, Arg156, Lys162, Val164) are involved in IgG binding [63]. Molecular modeling located these amino acids to the FG loop (Lys162, Val164), the CC' loop (Gln126), and the F β-sheet, providing one discontinuous binding site for IgG [64]. The Lys162, Val164 residues on the FG loop seem to form the main IgG-interactive site of FcγRIII (Fig. 2).

Two separate genes encoding hFcγRIII (III-A and III-B) have been mapped within a distance of 200 kb from the hFcγRII gene complex [8]. Sequence conservation of about 97% identity has been described between both coding and flanking regions of each gene [65, 66]. hFcγRIII-A and hFcγRIII-B encode almost identical proteins but contain amino acid differences responsible for distinct post-translational modifications such as N-linked glycosylation and membrane expression [65]. The presence of serine at position 185 of hFcγRIIIb is essential to create a signal for attachment to a glycosylphosphatidylinositol (GPI) anchor [1–3]. The hFcγRIIIa contains a phenylalanine instead of a serine at that position, resulting in a transmembrane receptor isoform with a cytoplasmic tail of 25 amino acids. This transmembrane hFcγRIIIa receptor requires additional subunits, the FcR γ-chain and/or the CD3 ζ-chain, for efficient cell surface expression, protecting the hFcγRIIIa ligand-binding α-chain against degradation in the endoplasmic reticulum [1–3]. In addition, recent studies suggest that the FcR γ-chain might be responsible for the medium affinity of hFcγRIIIa compared with the low affinity of hFcγRIIIb [21].

Several polymorphisms on hFcγRIII that influence the binding of IgG have been described [4, 67–69]. On neutrophils, the hFcγRIIIb exists in two allelic forms, NA-1 and NA-2, which differ by four amino acids in the membrane-distal Ig domain [4]. Individuals homozygous for NA2 show a lower phagocytic capacity by hFcγRIIIb compared with NA1 [67]. On NK cells and monocytes, two polymorphisms have been recognized for hFcγRIIIa [68, 69]. The first represents a triallelismus in the membrane-distal Ig domain, predicting a

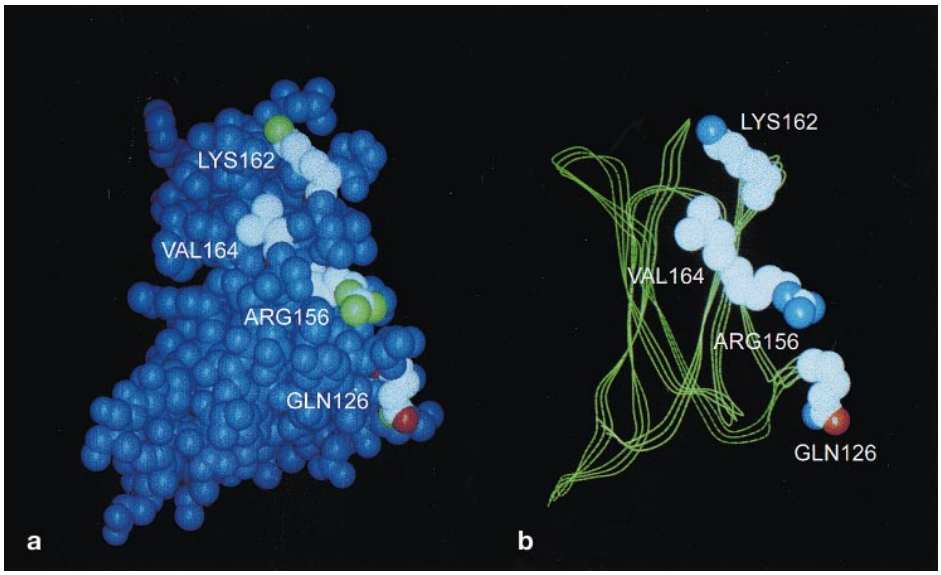

Fig. 2a,b. Three-dimensional-model of the putative IgG-binding site on FcγR exemplified for hFcγRIII-B. Amino acid residues involved in IgG binding are colored. Space-filling (**a**) and ribbon diagram (**b**) presentations imply that these residues are located on the FG loop and the GFC surface of the membrane-proximal domain of hFcγRIII-B. Similar structural determinants are involved in interactions with IgG by hFcγRII receptors [28, 29]

leucine (L) to arginine (R) or histidine (H) at residue position 48. The second is localized in the membrane-proximal Ig domain near the ligand-binding site, predicting a phenylalanine (F) to valine (V) at residue position 158. Compared with FF homozygotes, hFcγRIIIa expressed in 158VV-positive individuals bound more IgG1 and IgG3, despite identical levels of receptor expression and irrespective of the amino acid present on position 48 [68]. The difference in high binding (158VV) versus low binding (158FF) has direct functional as well as clinical consequences. In a recently published case, two children suffering from recurrent viral infections were genotyped to carry the hFcγRIIIa-48HH-158VV high-binding allele [68, 70]. Moreover, the initial analysis of 200 patients with SLE indicates a strong association of the low-binding phenotype with disease, especially nephritis, and a corresponding under-representation of the homozygous high-binding phenotype [69].

The hFcγRIIIa is constitutively expressed on macrophages, NK, and γδ T cells and can be induced by IFN-γ on glomerular mesangial cells [1, 2, 71–73]. hFcγRIIIb is the most abundant receptor on neutrophils and can be induced by IFN-γ on eosinophils [1, 74]. The molecular basis for the differential tissue-specific expression patterns has been analyzed both in vitro and in vivo [75, 76]. Reconstitution studies in transgenic mice locate the regulatory gene elements sufficient for NK cell (FcγRIII-A) versus neutrophil (FcγRIII-B) restriction to the 5'flanking region of both genes. Enhancer and silencer structures as well as separate promoters reside within the 5'flanking regions [75]. In the case of hFcγRIII-A, simultaneously active promoters control for the initiation of multiple transcript classes a1–a6 in NK cells [66, 75]. As revealed by RT-PCR analysis, most of them encode for identical hFcγRIIIa receptor molecules. A notable exception is the a4 transcript, containing divergent sequences [77].

While the GPI-anchored hFcγRIIIb isoform is expressed on the cell surface as a monomeric protein, the hFcγRIIIa receptor complex requires the presence of dimeric γ or ζ subunits for assembly and signal transduction. Through their differential requirements for these associated signaling molecules, the hFcγRIII isoforms mediate different functions. hFcγRIIIa on NK cells mediates ADCC (Fig. 3) and all other antibody-dependent responses, where it represents the only FcγR [78] (for review see [79]). Furthermore, hFcγRIIIa triggering of IFN-γ-activated mesangial cells results in the secretion of IL-6. It has been suggested that the appearance of this receptor on normally FcγR-negative mesangial cells is critical for the initiation and progression of chronic glomerular inflammation [73]. Cross-linking of hFcγRIIIb on neutrophils leads to cellular activation [80]. The hFcγRIIIb receptor, like other GPI-anchored proteins, associates with Src-family tyrosine kinases, especially with hck [81]. The activation of hck might contribute to the increase in calcium mobilization and the induction of the respiratory burst [82]. Down-regulation of these intracellular events involves the tyrosine phosphatase CD45 [83]. The interaction with other cell surface receptors is important for the achievement of a full effector response. Cooperation of hFcγRIIIb with hFcγRIIa and CR3 is necessary for efficient phagocytosis, ADCC, and degranulation [6, 84, 85]. In an in vitro model of immune vasculitis hFcγRIIIb-mediated activation of neutrophils appeared to be critical for the pathogenesis of cryoglobulin-induced leukocytoclastic vasculitis [86].

mFcγRIII was first classified as an mFcγRII protein because it reacted with the same anti-FcγRII/III mAb 2.4G2 and shared with mFcγRII identical binding characteristics, interacting with mIgG1, mIgG2b, and mIgG2a in the form of immune complexes [87]. mFcγRIII is now defined as a class-III receptor by virtue of its similarity to hFcγRIIIa in structure, function,

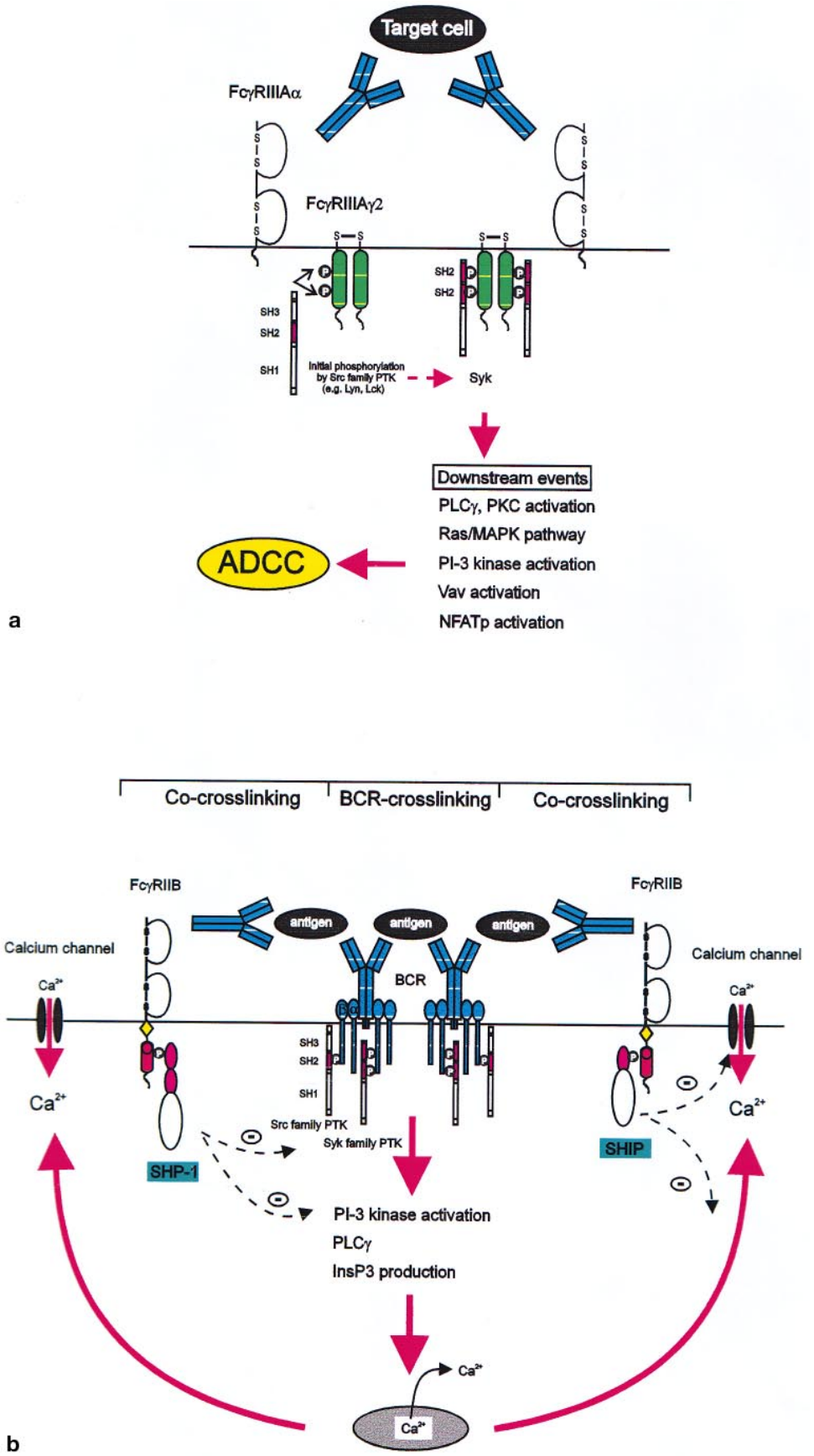

Fig. 3a,b. Positive (**a**) and negative (**b**) signal transduction pathways initiated upon engagement of FcγR. **a** FcγR activation induced by receptor cross-linking is the crucial first step in triggering the signaling cascade, which, in the case of hFcγRIII-A on NK cells, culminates in the destruction of IgG-coated target cells through ADCC. hFcγRIII-A cross-linking results in the binding and activation of *Src family PTKs*, inducing tyrosine phosphorylation of the ITAM motif in the accessory FcR γ-chain cytoplasmic domain. This phosphorylation induces binding and activation of *Syk*, followed by several downstream events leading to the cellular response of *ADCC*. The broken arrow indicates that activation of Syk may be sufficient to trigger ADCC even in the absence of known Src-family PTK (discussed in [79]). **b** Down-modulation of BCR-dependent activation signals by FcγRII-B. Co-cross-linking results in tyrosine phosphorylation of the ITIM motif in FcγRII-B, leading to the recruitment and activation of phosphatases such as *SHIP* and *SHP-1*. These phosphatases can interact with different substrates involved in BCR-mediated activation which result in inhibition of the influx of extracellular calcium and B-cell proliferation. There are some indications for the primacy of SHIP over SHP-1 (see text)

and cell distribution [1, 3]. mFcγRIII is expressed as a multimeric complex with dimeric γ-chains on NK cells, mast cells, macrophages, and neutrophils, as well as on mesangial cells [1, 3, 88]. Additional mFcγRIII receptor complexes, namely an αγζ structure and a tetrameric $\alpha\beta\gamma_2$ form, are known in NK cells and mast cells, respectively [89]. mFcγRIIIb receptors similar to the GPI-linked hFcγRIIIb on human neutrophils are not present in the murine system. mFcγRIII is the only FcγR on mature NK cells, where it mediates ADCC. In addition to mFcγRII, mFcγRIII expression has been demonstrated on early fetal thymocytes containing progenitor cells of NK and T cells, suggesting a role of mFcγRIII in NK cell development [90]. mFcγRIII is coexpressed with mFcγRI and mFcγRII on macrophages. Triggering of phagocytosis by activated macrophages is mediated mainly by mFcγRIII rather than mFcγRII. mFcγRIII-mediated endocytosis and antigen presentation are dependent on the ITAM motif of the associated FcR γ-chain [46, 91, 92].

mFcγRIII is coexpressed with the high-affinity receptor for IgE, FcεRI, in mast cells. Both receptors associate with the same FcR β and γ subunits and differ only in terms of their relative ligand-binding α-chains responsible for the interaction with either IgE or IgG. It has been shown that the β-subunit acts as an amplifier of signal transduction triggered by the ITAM motif of the common FcR γ-chain [93]. Evidence of competition between the FcεRI and FcγRIII α-chains for the FcR β and γ subunits has been described. In the absence of the FcεRI α-chain, an increased association of FcγRIII with the β and γ subunits leads to an up-regulation of cell surface expression of FcγRIII [94, 95]. Under such conditions, IgG-dependent mast cell activation responses of degranulation and anaphylaxis mediated by mFcγRIII are enhanced [94].

In vivo role of FcγR assessed in mouse mutants

The structural heterogeneity of FcγRs, combined with an overlapping pattern of expression on effector cells, has made it difficult to dissect the specific functions of individual receptors in in vivo immune responses. This problem has been addressed in genetic knock-out mice in which one or more FcγRs have been disrupted by targeted deletion. KO mice for FcR γ-chain, FcγRII, and FcγRIII show defined specific defects in their immune responses, making them useful as models for evaluating the distinct roles of individual FcγRs in host defense and IgG-triggered diseases (Table 4).

FcR γ-chain KO

Mice deficient in the common γ-chain constituted the first FcγR mutant strain with which the relative contribution of several structurally related Fc receptors to normal and pathological in vivo immune responses was studied [96]. Functional defects in the expression of FcγRIII on NK cells, FcγRI and FcγRIII on macrophages, and FcγRIII and FcεRI on mast cells are evident in these FcR γ KO mice. Macrophage effector function to phagocytose distinct IgG-opsonized particles appears to be completely absent in FcR γ chain-deficient mice, despite the normal binding activity of IgG1 and IgG2b subclasses. This may indicate that IgG1/IgG2b-dependent phagocytosis is normally mediated by mFcγRIII rather than mFcγRII. The FcγRI-specific binding activity of IgG2a-coated erythrocytes is undetectable, suggesting FcR γ to be critical in facilitating either surface expression or ligand binding of the high-affinity FcγRI.

The cytotoxic activity of FcγR-expressing effector cells is affected by the disruption of the FcR γ-chain gene. The ability to mediate antibody-mediated tumor cytotoxicity is impaired in FcR γ-negative NK cells and macrophages in vitro. Most importantly, FcγRI- and FcγRIII-dependent ADCC appears to be a dominant pathway of melanoma tumor rejection in vivo [97]. This finding clearly suggests that increasing the efficiency of antibody-mediated cytotoxicity may be a key step in tumor rejection. Current clinical trials approach this issue by developing bispecific molecules directed at tumor cells and either FcγRI or FcγRIII on immune effector cells [98–100].

The role of FcγR in the pathology induced by infections has been described in FcR γ-chain KO mice [101, 102]. The report by Yuan et al. [102] demonstrates that the antibody-mediated modulation of *Cryptococcus neoformans* (an encapsulated fungus that infects immunosuppressed individuals and is responsible for the death of 6–8% of AIDS patients) infection is IgG subclass dependent, and that FcγRs – most likely FcγRIII – are essential for IgG1-mediated passive protection against this pathogen. Importantly, phagocytosis of *C. neoformans* opsonized by IgG3 occurs even in the absence of the FcR γ-chain. Together with the observation that FcγRI is the mouse IgG3 receptor [103], this finding suggests another additional IgG3/FcγRI-mediated signal transduction pathway that is not dependent on the common FcR γ-chain.

The analysis of type I and III hypersensitivity immune reactions demonstrates the central role for the γ-chain-associated FcεRI and FcγRIII receptors in the initiation of IgE- and IgG-mediated immunity. Both receptors mediate degranulation and release of inflammatory mediators by mast cells when cross-linked with IgE and IgG immune complexes, respectively. FcR γ-chain-deficient mice fail to respond to IgE stimulation, as assessed by early and late mast cell activation responses. In the model of IgE-dependent passive cutaneous anaphylaxis (PCA), the characteristic increase in vascular permeability occurs in control but not in FcR γ KO mice [96]. A similar phenotype was originally described in FcεRI α-chain-deficient mice, indicating that FcεRI is the dominant FcR necessary for the initiation of IgE-dependent anaphylactic reactions [95]. Sensitiza-

Table 4 Phenotypic characteristics of FcγR mouse mutants (*n.p.* not published)

	KO		
	FcR γ	FcγRIII	FcγRII
a) Effector cell functions in vitro			
1) FcR off-signal (B cells)	n.d.	n.d.	Abrogated [59, 117]
2) ADCC (NK cells)	Abrogated [96]	Abrogated [107]	n.d.
3) Degranulation (mast cells)			
IgG mediated	n.d.	Abrogated [107]	Enhanced]59, 117]
IgE mediated	Abrogated [96]	n.d.	Enhanced [59, 117]
4) Phagocytosis (macrophages)			
IgG1 dependent	Abrogated [96]	Abrogated [108–109)	n.d.
IgG2a dependent	Abrogated [96]	Reduced [140]	n.d.
IgG2b dependent	Abrogated [96]	Not affected [107]	n.d.
B) Immune responses in vivo			
1) Type-I hypersensitivity			
– Active systemic anaphylaxis	Abrogated [94, 104]	n.d.	n.d.
– Passive anaphylaxis, IgG	Abrogated]94, 104]	Abrogated [107]	Enhanced [117]
– Passive anaphylaxis, IgE	Abrogated [94, 104]	Not affected [107]	n.d.
2) Type-II hypersensitivity			
– Hemolytic anemia (AIHA)			
IgG1 induced	n.d.	Abrogated [140]	n.d.
IgG2a induced	Abrogated [141]	Reduced [140]	n.d.
– Thrombocytopenia (ITP)	Abrogated [141]	n.d.	n.d.
– Melanoma tumor rejection	Abrogated [97]	n.d.	n.d.
3) Type-III hypersensitivity			
– reserve passive Arthus reaction	Abrogated [105]	Reduced [107]	n.d.
– Arthus reaction after CVF treatment	Abrogated [105]	Abrogated [107]	n.d.
– Mast cell reconstitution	Abrogated [106]	n.d.	n.d.
– Cryoglobulin-induced skin vasculitis	n.d.	Abrogated (n.p.)	n.d.
– Autoimmune glomerulonephritis	Abrogated [128]	n.d.	n.d.
4) Humoral immune response			
– Serum Ab production	Not affected [168]	n.d.	Elevated [117, 168]
– Follicular IC deposition	Enhanced [169]	n.d.	n.d.
– Ab affinity maturation	Not affected [169]	n.d.	n.d.
– B cell tolerance	Not affected [168]	n.d.	Not affected [168]

tion for active systemic anaphylaxis not only induces an IgE response, but also results in the production of antigen-specific IgG1 antibodies. In a recent study, the relative importance of IgE and FcεRI versus IgG1 and FcγR in the pathogenesis of active or IgE- or IgG1-dependent passive anaphylaxis was therefore assessed by analyzing the cardiopulmonary changes and mortalities in both FcR γ-chain and FcεRI α-chain KO mice [104]. These results indicate that IgE and FcεRI contribute in part to the pathophysiology of active systemic anaphylaxis, but they clearly demonstrate that the mortality associated with active anaphylaxis is dependent on FcγRs, most likely FcγRIII but not FcεRI.

The significance of defective FcR γ-chain expression has been further evaluated in the experimental system of the reverse Arthus reaction. This model of IgG immune complex-mediated pathogenesis is characterized by edema, hemorrhage, and neutrophil infiltration, resulting from the subcutaneous formation of immune complexes. A strong reduction of the Arthus reaction in the skin for all three parameters measured is observed in FcR γ KO mice as compared with control mice [105]. Differential in vivo reconstitution experiments have further identified the mast cell expressing FcγRIII to be a very important cell type for triggering the initial phase of this type-III inflammatory reaction [106].

FcγRIII KO

Studies with KO mice deficient for the ligand-binding α chain of FcγRIII support the critical role of this receptor in IgG inflammatory disease states [107]. FcγRIII mutant mice show a functional defect in the expression of FcγRIII and exhibit impaired antibody-mediated responses, including loss of NK cell-mediated ADCC [107], neutrophil IgG1-dependent phagocytosis [108], and mesangial cell-mediated release of inflammatory cytokines (Gessner and Radeke, unpublished). Phagocytosis of IgG1- but not IgG2a- and IgG2b-opsonized particles by macrophages is strongly diminished. These data indicate that, in addition to FcγRIII, the other FcγRs normally expressed by macrophages might contribute to phagocytosis, but apparently with different IgG isotype specificities [109]. On the other hand, IgG-mediated mast cell degranulation appeared to be exclusively dependent on FcγRIII. Studies with mast cell-deficient mice indicate that the mast cell might be a crucial effector cell type, not only in IgE- but also in IgG-

dependent anaphylaxis [110, 111]. Moreover, the contribution of FcγRIII in in vivo IgG-mediated PCA reactions has been suggested in studies with IgE-deficient mice [112]. The activation of FcγRIII with the 2.4G2 mAb in normal mice results in physiological changes that are similar to those observed in active anaphylaxis [94]. FcγRIII-deficient mice are resistent to IgG-dependent PCA, thus providing direct in vivo evidence for the activatory role of FcγRIII on mast cells in this process [107].

The absolute requirement of FcγRIII in the experimental model of the reverse Arthus reaction has been analyzed. Interestingly, the degree of impairment of the Arthus reaction in the skin varied considerably among individual FcγRIII-deficient mice, supporting the critical role of FcγRIII in this process but indicating that additional factors also play a role [107, 113]. Thus depletion of complement components C3 and C5 by cobra venom factor (CVF) is necessary to achieve a complete block of the Arthus reaction in all FcγRIII KO mice [107]. This is different from what has been observed in the FcR γ KO model, in which complement appears to play a secondary role [105]. Variations in the genetic background may differently influence the relative contribution of the complement-mediated pathway in the FcR γ-chain- and FcγRIII-deficient strains of mice. In a recent experiment, the genetic deletion of the complement components C3 and C4 did not result in a diminished responsiveness of type II and III IgG-triggered inflammation [114]. The distinction between complement and FcγRIII as primary triggers of tissue injury is therefore very important, with major therapeutic implications for human disease. Obviously, however, additional studies with well-defined mouse mutants in distinct strain backgrounds using different experimental protocols for the induction of inflammation are necessary to characterize all the determinants involved in immune complex-mediated disorders. This issue has recently been addressed in mice who are deficient in the C5a receptor gene, by analyzing three models of immune complex injury. Quantitative differences are evident, with a key role for C5aR in the initiation of IgG-hypersensitivity reaction in the lung, but a synergistic action of C5aR and FcγRs, most likely FcγRIII, in the skin and peritoneum [115].

FcγRII KO

Despite their widespread distribution, the biological role of FcγRII receptors is not fully understood. Reconstitution studies have suggested that FcγRII can inhibit activation through ITAM-containing receptors [40]. In vitro, coligation of FcγRII with the antigen receptor on B cells and with FcεRI and FcγRIII on mast cells inhibits B-cell proliferation and receptor-triggered degranulation, respectively [51, 116]. The significance of this inhibitory pathway for in vivo immune responses has been investigated in FcγRII-deficient mice. These mice show a functional defect in the expression of the FcγRIIb1 receptor on B cells and of the FcγRIIb2 receptor on macrophages and mast cells [117]. The in vivo consequences on B cells were determined by immunization with thymus-dependent and thymus-independent antigens. FcγRII-deficient mice display elevated immunoglobulin levels to these antigenic stimulations for IgM, IgG, and IgA as compared with normal mice. Thus, defective FcγRII function may contribute to the development of autoimmunity. However, the observation of only a partial reduction of IgG immune complex-dependent feedback inhibition to regulate antibody production indicates that additional mechanisms are probably involved in antibody homeostasis [117]. A potential candidate gene is the CD22 lectin-like membrane protein known to associate with the B-cell antigen receptor. Antibody clustering of CD22 before BCR ligation increases the proliferative capacity of B cells [118]. CD22-deficient mice have been independently generated by several groups [119–122]. In one study, immunization with T-cell-dependent antigens resulted in augmentation of the humoral response [119]. Thus, both FcγRII and CD22 might have the potential to act as negative regulators of the humoral immune response in vivo. Phosphatase recruitment to the ITIM domains of FcγRII and CD22 upon coengagement with the BCR is critical for inhibition. The SH2-containing tyrosine phosphatase SHP-1 recruited by CD22 can suppress BCR signaling, whereas the inositol polyphosphate 5-phosphatase SHIP contributes to the inhibitory effects of FcγRII. Studies on double CD22/FcγRII-deficient mice with mutations in their ITIM domains will be helpful to test the possibility that synergisms may be sufficient for uncontrolled antibody production and the development of autoimmune disease.

In addition to B cells, FcγRII modulates IgE- and IgG-triggered mast cell functions via FcεRI and FcγRIII, respectively [59, 117]. This inhibitory role has been clearly shown in vivo for IgG-mediated passive cutaneous anaphylaxis (PCA) reactions in FcγRII-deficient mice. Significant augmentation of the PCA response triggered by FcγRIII on mast cells is observed at antibody concentrations five to ten times lower than in normal mice [117]. IgE-mediated PCA reactions have not been analyzed. Repression of IgE-triggered degranulation is evident in normal as well as mast cells derived from SHP-1-defective *me/me* mice [123] but absent in FcγRII-deficient mice.

FcγRIIb2 expressed on macrophages is functionally different from FcγRIIb1 on B cells in its ability to mediate endocytosis of immune complexes in vitro [48]. However, the contribution of FcγRIIb2 to macrophage phagocytic function in vivo is less clear. FcγRIIb2 engagement on macrophages from FcγRIII-deficient mice by SRBCs opsonized with a bispecific antibody has revealed phagocytosis [107]. On the other hand, FcRγ-deficient mice who still express FcγRIIb2 have completely lost their phagocytic activity [96]. FcγR-mediated phagocytosis in FcγRII-deficient mice has not

yet been analyzed. Therefore, it remains unclear to what extent FcγRIIb2 contributes to phagocytosis in vivo.

FcγR KO as experimental models for human disease

In general, the molecular mechanisms by which IgG autoantibodies and immune complexes can trigger autoimmune disease are due to autoantibody production, immune complex deposition, and complement activation. One very important additional pathway in disease development may depend on the interaction of IgG directly with effector cells through FcγRs. As described before, the elimination of individual FcγRs greatly influences the pathology in the cutaneous Arthus reaction, the murine model of type-III inflammation. Cutting out the functional expression of FcγRIII by deletion of either the α or the γ chain results in a diminished reaction, whereas the deficiency of the counteractive FcγRII leads to enhanced responsiveness. In FcγRIII, but not FcRγ mutant animals complement can partly compensate for the loss of FcγRIII function as the primary trigger during the initial phase of the Arthus reaction. Both KO strains are characterized by a high degree of genetic heterogeneity, which may account for the variation in complement activation. The predominant pathway through which an autoantibody or immune complex triggers disease may further depend on the nature of the self-antigen or the tissue site of sustained immune complex deposition. Thus, several clinical outcomes are possible.

Glomerulonephritis

Glomerulonephritis (GN) is a severe complication of the renal involvement which is the major cause of pathology and death in patients suffering from systemic lupus erythematosus (SLE). In such cases, immune complexes may be formed outside the glomerulus under the control of the cellular immune system as a reaction to foreign or self-antigens and captured by the glomerular structures from the circulation [124]. The mechanisms of fixation of antigen-antibody aggregates in the glomerulus have been explained by either charge-dependent (GBM, matrix) or specific, low-affinity FcR-dependent binding [125]. During initiation of a glomerular inflammatory or autoimmune reaction, these events may also precede the invasion of leukocytes [126], and the presence of local FcR-bearing glomerular cells has been postulated for quite some time. Two different cell types may be distinguished in the mesangial area, bone marrow-derived resident macrophages and the mesenchyme-derived mesangial cell [127].

It has been demonstrated that, upon stimulation, cultured human glomerular mesangial cells can express hFcγRIIIa in association with FcRγ [73]. Binding of immune complexes to FcγRIII on mouse and human MC leads to the production of mediators of inflammation such as IL-6, MCP-1, and CSF-1 [73, 88]. More recent data on the expression of other FcγRs indicate the induction of hFcγRI on human MC by IFN-γ and IL-10 [13]. A similar expression profile is observed on mouse MC, which are able to coexpress FcγRI and FcγRIII upon activation (Gessner and Radeke et al., unpublished). Thus, it appears very likely that triggering of either FcγRI, FcγRIII, or both on mesangial cells by IgG complexes is essential in the initiation of autoimmune GN. This hypothesis is supported by studies in which FcR γ-chain KO mice with the FcγRIII and FcγRI deficiencies are crossed into the lupus-prone NZB/NZW genetic backgrounds. In resulting F1-hybrids complete protection from the spontaneous development of severe nephritis is observed [128]. Deposition of immune complexes along with complement C3 occurs in the mesangial space of FcR γ mutant B/W mice, indicating that complement activation is not sufficient to initiate glomerular disease but is more important than FcγRI/III in the clearance of immune complexes. This latter finding may explain clinical data from human beings which show that deficiencies in complement increase the risk of SLE. A reduction in immune complex clearance due to defective complement would increase immune complex deposition, which then could enhance FcγRI/III-mediated activation of glomerular mesangial cells, thereby leading to the initiation and progression of chronic glomerular inflammation.

Immune vasculitis

Immune vasculitis (IV) is another immune complex disease which may require the initial binding of IgG aggregates to FcγRs [129]. Cryoglobulin-induced activation of neutrophils triggered by hFcγRIIIb plays a contributory role in the pathogenesis of leukocytoclastic vasculitis [86], the dominant lesion of type-I cryoglobulinemia in human beings [130]. Clinical symptoms of type-I cryoglobulinemia include cold urticaria, Raynaud's phenomenon, cutaneous ulcers, and gangrene of the fingers and toes upon exposure to cold [131]. Conventionally, cryoglobulins are classified as type I or type II. Type-I cryoglobulins are usually monoclonal IgM, IgG, or IgA immunoglobulins, whereas type-II cryoglobulins are rheumatoid factors which form cryoprecipitating complexes with polyclonal IgG [132]. In this light, intermediate-sized IgG-containing rheumatoid factor complexes from patients with rheumatoid arthritis (RA) can interact with FcγRIII on NK cells and other mononuclear cells [133]. IgG rheumatoid factor cryoglobulins resembling those found in sera or synovial fluids from RA patients are spontaneously produced in MRL-*lpr* but not in other strains of lupus-prone mice [134]. The injection of hybridomas secreting pathogenic cryoglobulins with anti-IgG2a rheumatoid

factor activity obtained from MRL-*lpr* mice induces GN and skin leukocytoclastic vasculitis in association with cryoglobulinemia in normal mice [135]. The induction of immune vasculitis but not GN is critically dependent on immune complex formation due to the anti-IgG2a rheumatoid factor activity of cryoglobulins of the IgG3 subclass [136, 137]. Interestingly, FcγRIII KO mice crossed to the MRL background are protected from the development of skin vascular lessions (Izui and Gessner et al., unpublished). Although the significance of these results needs to be tested further and extended, it may help to explain the immunopathological effects and clinical features of human cryoglobulinemia as a primary disorder or secondary to lymphoproliferative diseases.

Autoimmune hemolytic anemia

Autoimmune hemolytic anemia (AIHA) is one of the oldest recognized autoimmune disease in human patients. It is characterized by the production of autoreactive anti-red blood cell antibodies, which are responsible for the immune destruction of RBC, causing AIHA. Mice of the NZB inbred strain spontaneously develop AIHA resembling its human counterpart. A number of NZB-derived pathogenic anti-mouse RBC (aMRBC) have been described, demonstrating the aMRBC response to be quite heterogeneous in terms of antigen specificity, pathogenic potential, and the mechanisms responsible for the anemia observed [138]. Differences in the cytotoxic activities of two IgG1 aMRBC autoantibodies demonstrate FcR-dependent and FcR-independent pathogenic pathways in the development of AIHA [139]. One antibody, 31–9D, causes anemia after injection into normal mice due to a marked sequestration of agglutinated erythrocytes in spleens and livers. The second antibody, 105–2H, which recognizes a distinct antigenic epitope, induces anemia as a result of rapid FcγR-mediated erythrophagocytosis [139]. The 105–2H-induced anemia can be completely prevented by treatment with the anti-FcγRII/III mAb 2.4G2 [139]. FcγR engagement occurs also in the case of another 34–3C aMRBC. The pathogenic mechanism of the 34–3C and 105–2H mAbs, which recognize the same antigenic epitope on erythrocytes, is mediated either by FcγRIII, which interacts exclusively with the IgG1 isotype (105–2H), or by FcγRIII and FcγRI, which both contribute to the binding and phagocytosis of the IgG2a isotype (34–3C) [140, 141]. Additional evidence for the important role of individual FcγRs has been obtained in FcR γ mutant mice by the use of a polyclonal rabbit aMRBC serum [141]. In this model, FcR γ KO mice are resistant to the pathogenic effects, preventing the outcome of AIHA.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) and autoimmune neutropenia (AIN) are two other autoimmune diseases in which the production of autoreactive antibodies leads to destruction of IgG-coated platelets or neutrophils by the mononuclear phagocyte system. The efficacy of intravenous IgG (IVIG) in the treatment of ITP and AIN has been attributed to FcγR blockade [142–145], because the administration of either purified Fc fragments or the anti-hFcγRIII mAb 3G8 successfully restores platelet numbers in ITP patients refractory to conventional therapies [146, 147]. Furthermore, clinical trials with humanized anti-FcγR monoclonal antibodies are now being considered for ITP patients (for review see [98]). Experimental evidence for the direct involvement of FcγRs has been obtained from in vivo animal studies. The (NZW × BXSB) F_1 (W/BF_1) mouse strain is used as a model for ITP, showing a spontaneous thrombocytopenia and the appearance of autoreactive anti-platelet antibodies [148]. When injected into nonautoimmune mice, the W/BF_1–derived pathogenic IgG1 autoantibody 6A6, induces a rapid transient thrombocytopenia [149]. FcR γ-chain KO mice are resistant to these pathogenic effects of 6A6, due to their deficiency in FcγRIII [141].

Conclusions and perspectives

Within the past few years significant progress has been made in defining the physiological role of FcγRs. The elucidation of the primary structure, accompanied by the molecular dissection of FcγR function using various cellular transfection systems, has provided important information on the relationship between the structure of a specific isoform and triggered effector function. From these studies it has become clear that the structural heterogeneity of FcγRs, determined by unique structural features of their transmembrane and cytoplasmic domains, influences the specificity of a particular response induced by FcγRs to cross-linking by IgG immune complexes. Conserved tyrosine residues within unique ITAM- (or ITIM- in the case of FcγRIIB) signaling motifs play a central role in the FcγR-triggered activation (or inhibition) of effector cells.

Functional dissection of the in vivo immune response in FcγR KO mouse mutants indicates an essential role of FcγRs in systemic anaphylaxis (type-I hypersensitivity), where the anaphylactic mortality can be attributed primarily to the FcγRIII/IgG1-dependent as opposed to the FcεRI/IgE-dependent pathway. In addition, it is now realized that FcγR-dependent mechanisms contribute significantly to inflammatory type-II (induced by self-reactive autoantibodies) and type-III (induced by IgG immune complexes) hypersensitivity reactions, generally attributed to complement activation. These studies are of major relevance, in that they demonstrate the involvement of FcγRs as important

immunoregulatory receptors in the pathogenesis of allergy, autoimmunity, and inflammation.

The potential of inhibiting the pathophysiological effects of FcγRs by blocking studies is being considered for future therapeutic modalities. Approaches involving the targeting of FcγR-binding sites (reviewed in [63]) in combination with humanized FcγR mouse models [76, 150, 151] will be very useful for the development of novel strategies in the treatment of IgG-mediated human disease in which FcγR activation plays an integral part. Initial results of clinical trials for several FcγR-directed immunotherapies have already shown positive effects (reviewed in [98]), encouraging further studies in this direction.

References

1. Ravetch JV, Kinet J-P (1991) Fc receptors. Annu Rev Immunol 9:457–492
2. van de Winkel JGJ, Capel PJA (1993) Human IgG Fc receptor heterogeneity: molecular aspects and clinical implications. Immunol Today 14:215–221
3. Hulett MD, Hogarth PM (1994) Molecular basis of Fc receptor function. Adv Immunol 57:1–127
4. De Haas M, Vossebeld PJM, von dem Borne AEGK, Roos D (1995) Fcγ receptors of phagocytes. J Lab Clin Med 126:330–341
5. Fridman WH, Teillaud J-L, Bouchard C, Teillaud C, Astier A, Tartour E, Galon J, Mathiot C, Satres C (1993) Soluble Fcγ receptors. J Leuk Biol 54:504–512
6. Jones SL, Brown EJ (1996) Functional cooperation between Fcγ receptors and complement receptors in phagocytes. In: van de Winkel JGJ, Capel PJA (eds) Human IgG Fc receptors. Springer, Berlin Heidelberg New York, pp 149–163
7. Ravetch JV (1994) Fc receptors: rubor redux. Cell 78:553–560
8. Qiu WQ, de Bruin D, Brownstein BH, Pearse R, Ravetch JV (1990) Organization of the human and mouse low-affinity FcγR genes: evidence for duplication and recombination. Science 248:732–735
9. Oakley RJ, Howard TA, Hogarth PM, Tani K, Seldin MF (1992) Chromosomal mapping of the high-affinity Fcγ receptor gene. Immunogenetics 35:279–282
10. Allen JM, Seed B (1989) Isolation and expression of functional high-affinity Fc receptor complementary DNAs. Science 243:378–381
11. Ernst LK, van de Winkel JGJ, Chiu I-M, Anderson CL (1992) Three genes for the human high-affinity Fc receptor for IgG (FcγRI) encode four distinct transcription products. J Biol Chem 267:15692–15700
12. Porges AJ, Redecha PB, Doebele R, Pan LC, Salmon JE, Kimberly RP (1992) Novel Fcγ receptor I family gene products in human mononuclear cells. J Clin Invest 90:2102–2109
13. Uciechowski P, Schwarz M, Gessner JE, Schmidt RE, Resch K, Radeke HH (1998) Interferon-γ induces the high-affinity Fc receptor class I for IgG (CD64) on human glomerular mesangial cells. Eur J Immunol (submitted)
14. Kerst JM, van de Winkel JGJ, Evans AH, de Haas M, Slaper-Cortenbach IC, de Wit TP, von dem Borne AE, van der Schoot CE, van Oers RH (1993) Granulocyte colony-stimulating factor induces hFcγRI (CD64 antigen)-positive neutrophils via an effect on myeloid precursor cells. Blood 81:1457–1464
15. Pearse RN, Feinmann R, Ravetch JV (1991) Characterization of the promoter of the human gene encoding the high-affinity IgG receptor: transcriptional induction by γ-interferon is mediated through common DNA response elements. Proc Natl Acad Sci U S A 88:11305–11309
16. Pearse RN, Feinman R, Shuai K, Darnell Jr. JE, Ravetch JV (1993) Interferon γ-induced transcription of the high-affinity Fc receptor for IgG requires assembly of a complex that induces the 91-kDa subunit of transcription factor ISGF3. Proc Natl Aacad Sci U S A 90:4314–4318
17. Finbloom DS, Winestock KD (1995) IL-10 induces the tyrosine phosphorylation of tyk2 and Jak1 and the differential assembly of STAT1a and STAT3 complexes in human T cells and monocytes. J Immunol 155:1079–1090
18. Bovolenta C, Gasperini S, Cassatella MA (1996) Granulocyte colony-stimulating factor induces the binding of STAT1 and STAT3 to the IFNγ response region within the promoter of the FcγRI/CD64 gene in human neutrophils. FEBS Letters 386:239–242
19. Indik ZK, Hunter S, Huang MM, Pan XQ, Chien P, Kelly C, Levinson AI, Kimberly RP, Schreiber AD (1994) The high-affinity Fcγ receptor (CD64) induces phagocytosis in the absence of its cytoplasmic domain: the γ subunit of FcγRIIIA imparts phagocytic function to FcγRI. Exp Hematol 22:599–606
20. Pfefferkorn L, Swink SL (1996) Intracluster restriction of Fc receptor γ-chain tyrosine phosphorylation subverted by a protein-tyrosine phosphatase inhibitor. J Biol Chem 271:11099–11105
21. Miller KL, Duchemin A-M, Anderson CL (1996) A novel role for the Fc receptor γ subunit: enhancement of FcγR ligand affinity. J Exp Med 183:2227–2233
22. Lowry MB, Duchemin A-M, Robinson JM, Anderson CL (1998) Functional separation of pseudopod extension and particle internalization during Fcγ receptor-mediated phagocytosis. J Exp Med 187:161–176
23. Davis W, Harrison PT, Hutchinson MJ, Allen JM (1995) Two distinct regions of FcγRI initiate separate signaling pathways involved in endocytosis and phagocytosis. EMBO J 14:432–441
24. Hulett MD, Osman N, McKenzie IFC, Hogarth PM (1991) Chimeric Fc receptors identify functional domains of the murine high-affinity receptor for IgG. J Immunol 147:1863–1868
25. Sears D, Osman N, Tate B, McKenzie IFC, Hogarth PM (1990) Molecular cloning and expression of the mouse high-affinity Fc receptor for IgG. J Immunol 144:371–378
26. Quilliam AL, Osman N, McKenzie IFC, Hogarth PM (1993) Biochemical characterization of murine FcγRI. Immunology 78:358–363
27. Gavin AL, Hamilton JA, Hogarth PM (1996) Extracellular mutations of non-obese diabetic mouse FcγRI modify surface expression and ligand binding. J Biol Chem 271:17091–17099
28. Prins J-B, Todd JA, Rodrigues NR, Ghosh S, Hogarth PM, Wicker LS, Gaffney E, Podolin PL, Fischer PA, Sirotina A, Peterson LB (1993) Linkage on chromosome 3 of autoimmune diabetes and defective Fc receptor for IgG in NOD mice. Science 260:695–698
29. Hulett MD, Witort E, Brinkworth RI, McKenzie IFC, Hogarth PM (1994) Identification of the binding site of the human low-affinity receptor for IgG FcγRII. Enhancement and ablation of binding by site-directed mutagenesis. J Biol Chem 269:15287–15293
30. Hulett MD, Witort E, Brinkworth RI, McKenzie IFC, Hogarth PM (1995) Multiple regions of human FcγRII (CD32) contribute to the binding of IgG. J Biol Chem 270:21188–21194
31. Warmerdam PAM, Nabbon NMJM, van de Graaf SAR, van de Winkel JGJ, Capel PJA (1993) The human low-affinity immunoglobulin G Fc receptor IIC gene is a result of an unequal crossover event. J Biol Chem 268:7346–7349
32. Brooks DG, Qiu WQ, Luster AD, Ravetch JV (1989) Structure and expression of a human IgG FcRII (CD32): functional heterogeneity is encoded by the alternatively spliced products of multiple genes. J Exp Med 170:1369–1386

33. Rappaport EF, Cassel DL, Walterhouse DO, McKenzie SE, Surrey S, Keller MA, Schreiber AD, Schwartz E (1993) A soluble form of the human Fc receptor FcγRII-A: cloning, transcript analysis and detection. Exp Hematol 21:689–696
34. Budde P, Bewarder N, Weinrich V, Schulzeck O, Frey J (1994) Tyrosine-containing sequence motifs of the human immunoglobulin G receptors FcRIIb1 and FcRIIb2 essential for endocytosis and regulation of calcium flux in B cells. J Biol Chem 269:30636–30644
35. Kolanus W, Romeo C, Seed B (1992) Lineage-independent activation of immune system effector function by myeloid Fc receptors. EMBO J 11:4861–4868
36. Kiener PA, Rankin BM, Burkhardt AL, Schieven GL, Gilliland LK, Rowley RB, Bolen JB, Ledbetter JA (1993) Cross-linking of Fcγ receptor I (FcγRI) and receptor II (FcγRII) on monocytic cells activates a signal transduction pathway common to both Fc receptors that involves the stimulation of p72 syk protein tyrosine kinase. J Biol Chem 268:24442–24448
37. Edberg JC, Lin C-T, Lau D, Unkeless JC, Kimberly RP (1995) The Ca^{2+} dependence of human Fcγ receptor-initiated phagocytosis. J Biol Chem 270:22301–22307
38. Indik ZK, Park J-G, Hunter S, Schreiber AD (1995) The molecular dissection of Fcγ receptor-mediated phagocytosis. Blood 86:4389–4399
39. Van den Herik-Oudijk IE, Capel PJA, van der Bruggen T, van de Winkel JGJ (1995) Identification of signaling motifs within human FcγRIIa and FcγRIIb isoforms. Blood 85:2202–2211
40. Daëron M, Latour S, Malbec O, Espinosa E, Pina P, Pasmans S, Fridman WH (1995) The same tyrosine-based inhibition motif, in the intracytoplasmic domain of FcγRIIB, regulates negatively BCR-, TCR-, and FcR-dependent cell activation. Immunity 3:635–646
41. Sarmay G, Koncz G, Gergely J (1996) Human type II Fcγ receptors inhibit B cell activation by interacting with the p21(ras)-dependent pathway. J Biol Chem 271:30499–30504
42. Cambier JC, Daëron M, Fridman W, Gergely J, Kinet J-P, Klausner R, Lynch R, Malissen B, Pecht I, Reinherz E, Ravetch JV, Reth M, Samelson L, Sandor M, Schreiber A, Seed B, Terhorst C, van de Winkel J, Weiss A (1995) New nomenclature for the Reth motif (or ARH1/TAM/ARAM/YXXL). Immunol Today 16:110
43. Bewarder N, Weinrich V, Budde P, Hartmann D, Flaswinkel H, Reth M, Frey J (1996) In vivo and in vitro specificity of protein tyrosine kinases for immunoglobulin G receptor (FcγRII) phosphorylation. Mol Cell Biol 16:4735–4743
44. Ravetch JV, Luster AD, Weinshank R, Kochan J, Pavlovec A, Portnoy DA, Hulmes J, Pan YCE, Unkeless JC (1986) Structural heterogeneity and functional domains of murine immunoglobulin G Fc receptors. Science 234:718–725
45. Tartour E, de la Salle H, de la Salle C, Teillaud C, Camoin L, Galinha A, Latour S, Hanau D, Fridman WH, Sautes C (1993) Identification, in mouse macrophages and serum, of a soluble receptor for the Fc portion of IgG (FcγR) encoded by an alternatively spliced transcript of the FcγRII gene. Int Immunol 5:859–868
46. Amigorena S, Lankar D, Briken V, Gapin L, Viguier M, Bonnerot C (1998) Type II and III receptors for immunoglobulin G (IgG) control the presentation of different T cell epitopes from single IgG-complexed antigens. J Exp Med 187:505–515
47. Latour S, Fridman WH, Daëron M (1996) Identification, molecular cloning, biologic properties, and tissue distribution of a novel isoform of murine low-affinity IgG receptor homologous to human FcγRIIB1. J Immunol 157:189–197
48. Amigorena S, Bonnerot C, Drake J, Choquet D, Hunziker W, Guillet JG, Webster P, Sautes C, Mellman I, Fridman WH (1992) Cytoplasmic domain heterogeneity and functions of IgG Fc receptors in B-lymphocytes. Science 256:1808–1812
49. Miettinen HM, Rose JK, Mellman I (1989) Fc receptor isoforms exhibit distinct abilities for coated pit localization as a result of cytoplasmic domain heterogeneity. Cell 58:317–326
50. Choquet D, Partiseti M, Amigorena S, Bonnerot C, Fridman WH, Korn H (1993) Cross-linking of IgG receptors inhibits membrane immunoglobulin-stimulated calcium influx in B lymphocytes. J Cell Biol 121:355–363
51. Muta T, Kurosaki T, Misulovin Z, Sanchez M, Nussenzweig MC, Ravetch JV (1994) A 13-amino-acid motif in the cytoplasmic domain of FcγRIIB modulates B-cell receptor signaling. Nature 368:70–73
52. D'Ambrosio D, Hippen KL, Minskoff SA, Mellman I, Pani G, Siminovitch KA, Cambier JC (1995) Recruitment and activation of PTP1 C in negative regulation of antigen receptor signaling by FcγRIIB1. Science 268:293–297
53. Chacko GW, Tridandapani S, Damen JE, Liu L, Krystal G, Coggeshall KM (1996) Negative signaling in B lymphocytes induces tyrosine phosphorylation of the 145-kDa inositol polyphosphate 5-phosphatase, SHIP. J Immunol 157:2234–2238
54. Kiener PA, Lioubin MN, Rohrschneider LR, Ledbetter JA, Nadler SG, Diegel ML (1997) Co-ligation of the antigen and Fc receptors gives rise to the selective modulation of intracellular signaling in B cells. J Biol Chem 272:3838–3844
55. Scharenberg AM, Kinet J-P (1996) The emerging field of receptor-mediated inhibitory signaling: SHP or SHIP? Cell 87:961–964
56. Cambier JC (1997) Inhibitory receptors abound? Proc Natl Aacad Sci U S A 94:5993–5995
57. Hippen KL, Buhl AM, D'Ambrosio D, Nakamura K, Persin C, Cambier JC (1997) FcγRIIb1 inhibition of BCR-mediated phosphoinositide hydrolysis and Ca^{2+} mobilization is integrated by CD19 dephosphorylation. Immunity 7:49–58
58. Toker A, Cantley LC (1997) Signalling through the lipid products of phosphoinositide-3-OH kinase. Nature 387:673–676
59. Ono M, Bolland S, Tempst P, Ravetch JV (1996) Role of the inositol phosphatase SHIP in negative regulation of the immune system by the receptor FcγRIIB. Nature 383:263–266
60. Ono M, Okada H, Bolland S, Yanagi S, Kurosaki T, Ravetch JV (1997) Deletion of SHIP or SHP-1 reveals two distinct pathways for inhibitory signaling. Cell 90:293–301
61. Ravetch JV (1997) Fc receptors. Curr Opin Immunol 9:121–125
62. Simmons D, Seed B (1988) The Fcγ receptor of natural killer cells is a phospholipid-linked membrane protein. Nature 333:568–570
63. Tamm A, Schmidt RE (1997) IgG binding sites on human Fcγ receptors. Int Rev Immunol 16:57–85
64. Tamm A, Kister A, Nolte KU, Gessner JE, Schmidt RE (1996) The IgG binding site of human FcγRIIIB receptor involves CC' and FG loops of the membrane-proximal domain. J Biol Chem 271:3659–3666
65. Ravetch JV, Perussia P (1989) Alternative membrane forms of FcγRIII (CD16) on human NK cells and neutrophils: cell-type-specific expression of two genes which differ in single nucleotide substitutions. J Exp Med 170:481–491
66. Gessner JE, Grussenmeyer T, Kolanus W, Schmidt RE (1995) The human low-affinity immunoglobulin G Fc receptor III-A and III-B genes: molecular characterization of the promoter regions. J Biol Chem 270:1350–1361
67. Salmon JE, Edberg JC, Kimberly RP (1990) Fcγ receptor III on human neutrophils. Allelic variants have functionally distinct capacities. J Clin Invest 85:1287–1295
68. Koene HR, Kleijer M, Algra J, Roos, D, von dem Borne AEGK, de Haas M (1997) FcγRIIIa-158 V/F polymorphism influences the binding of IgG by natural killer cell FcγRIIIa, independently of the FcγRIIIa-48L/R/H phenotype. Blood 90:1109–1114

69. Wu J, Edberg JC, Redecha PB, Bansal V, Guyre PM, Coleman K, Salmon JE (1997) A novel polymorphism of FcγRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. J Clin Invest 100:1059–1070
70. De Vries E, Koene HR, Vossen, JM, Gratama JW, von dem Borne AEGK, Waaijer JLM, Haraldsson A, de Haas M, van Tol MJD (1996) Identification of an unusual Fcγ receptor IIIa on natural killer cells in a patient with recurrent infections. Blood 88:3022–3029
71. Uciechowski P, Gessner JE, Schindler R, Schmidt RE (1992) FcγRIII activation is different in CD16+ cytotoxic T lymphocytes and natural killer cells. Eur J Immunol 22:1635–1638
72. Braakman E, van de Winkel JGJ, van Krimpen BA, Jansze M, Bolhuis RLH (1993) CD16 on human γδ T lymphocytes: expression, function and specificity for mouse IgG-isotypes. Cell Immunol 143:97–107
73. Radeke HH, Gessner JE, Uciechowski P, Mägert H-J, Schmidt RE, Resch K (1994) Intrinsic human glomerular mesangial cells can express receptors for IgG complexes (hFcγRIII-A) and the associated FcRI γ-chain. J Immunol 153:1281–1292
74. Hartnell A, Kay AB, Wardlaw AJ (1992) IFN-γ induces expression of FcγRIII (CD16) on human eosinophils. J Immunol 148:1471–1478
75. Gessner JE, Grussenmeyer T, Dumbsky M, Schmidt RE (1996) Separate promoters from proximal and medial control regions contribute to the natural killer cell-specific transcription of the human FcγRIII-A (CD16-A) receptor gene. J Biol Chem 271:30755–30764
76. Li M, Wirthmueller U, Ravetch JV (1996) Reconstitution of human FcγRIII cell type specificity in transgenic mice. J Exp Med 183:1259–1263
77. Gessner JE, Grussenmeyer T, Schmidt RE (1995) Differentially regulated expression of human IgG Fc receptor class III genes. Immunobiology 193:341–355
78. Werfel T, Uciechowski P, Tetteroo PAT, Kurrle R, Deicher H, Schmidt RE (1989) Activation of cloned human natural killer cells via FcγRIII. J Immunol 142:1102–1106
79. Leibson PJ (1997) Signal transduction during natural killer cell activation: inside the mind of a killer. Immunity 6:655–661
80. Hundt M, Schmidt RE (1992) The glycosylphosphatidylinositol-linked Fcgamma receptor III represents the dominant receptor structure for immune complex activation of neutrophils. Eur J Immunol 22:811–816
81. Stefanova I, Horejsi V, Ansotegui IJ, Knapp W, Stockinger H (1991) GPI-anchored cell-surface molecules complexed to protein tyrosine kinases. Science 254:1016–1019
82. Zhou M-J, Lublin DM, Link DC, Brown EJ (1995) Distinct tyrosine kinase activation and Triton X-100 insolubility upon FcγRII and FcγRIIIB ligation in human polymorphonuclear leukocytes. J Biol Chem 270:13553–13560
83. Hoffmeyer F, Witte K, Gebhardt U, Schmidt RE (1995) The low-affinity FcγRIIa and FcγRIIIb on polymorphonuclear neutrophils are differentially regulated by CD45 phosphatase. J Immunol 155:4016–4023
84. Boros P, Odin JA, Muryoi T, Masur SK, Bona C, Unkeless JC (1991) IgM anti-FcγR autoantibodies trigger neutrophil degranulation. J Exp Med 173:1473–1482
85. Kushner BH, Cheung N-KV (1992) Absolute requirement of CD11/CD18 adhesion molecules, FcRII, and the phosphatidylinositol-linked FcRIII for monoclonal antibody-mediated neutrophil antihuman tumor cytotoxicity. Blood 79:1484–1490
86. Hundt M, Zielinska-Skowronek M, Schmidt RE (1993) Fcγ receptor activation of neutrophils in cryoglobulin-induced leukocytoclastic vasculitis. Arthritis Rheum 36:974–982
87. Unkeless JC, Fleit H, Mellman IS (1981) Structural aspects and heterogeneity of immunoglobulin Fc receptors. Adv Immunol 31:247–270
88. Hora K, Satriano JA, Santiago A, Mori T, Stanley ER, Shan Z, Schlondorff D (1992) Receptors for IgG complexes activate synthesis of monocyte chemoattractant peptide 1 and colony-stimulating factor 1. Proc Natl Acad Sci U S A 89:1745–1749
89. Kurosaki T, Gander I, Ravetch JV (1992) The β subunit of the FcεRI is associated with the FcγRIII on mast cells. J Exp Med 175:447–451
90. Rodewald H-R, Moingeon P, Lucich JL, Dosiou C, Lopez P, Reinherz EL (1992) A population of early fetal thymocytes expressing FcγRII/III precursors of T lymphocytes and natural killer cells. Cell 69:139–150
91. Amigorena S, Salamero J, Davoust J, Fridman WH (1992) Tyrosine-containing motif that transduces cell activation signals also determines internalization and antigen presentation via type III receptors for IgG. Nature 358:337–341
92. Bonnerot C, Amigorena S, Choquet D, Pavlovich K, Choukroun V, Fridman WH (1992) Role of associated γ-chain in tyrosine kinase activation via murine FcγRIII. EMBO J 11:2747–2757
93. Lin S, Cicala C, Scharenberg A, Kinet J-P (1996) The atopy-associated FcεRIβ chain gene: the encoded subunit functions as an amplifier of FcεRI γ-mediated cell activation signals. Cell 85:985–995
94. Dombrowicz D, Flamand V, Miyajima I, Ravetch JV, Galli SJ, Kinet J-P (1997) Absence of FcεRI α chain results in upregulation of FcγRIII-dependent mast cell degranulation and anaphylaxis. J Clin Invest 99:915–925
95. Dombrowicz D, Flamand V, Brigman KK, Koller BH, Kinet J-P (1993) Abolition of anaphylaxis by targeted disruption of the high-affinity immunoglobulin E receptor α chain gene. Cell 75:969–976
96. Takai T, Li M, Sylvestre DL, Clynes R, Ravetch JV (1994) FcR γ chain deletion results in pleiotropic effector cell defects. Cell 76:519–529
97. Clynes R, Takechi Y, Moroi Y, Houghton A, Ravetch JV (1998) Fc receptors are required in passive and active immunity to melanoma. Proc Natl Acad Sci U S A 95:652–656
98. Deo YM, Graziano RF, Repp R, van de Winkel JGJ (1997) Clinical significance of IgG Fc receptors and FcγR-directed immunotherapies. Immunol Today 18:127–135
99. Hartmann F, Renner C, Jung W, Deisting C, Juwana M, Eichentopf B, Kloft M, Pfreundschuh M (1997) Treatment of refractory Hodgkin's disease with an anti-CD16/CD30 bispecific antibody. Blood 89:2042–2047
100. Weiner LM, Clark JI, Davey M, Li WS, Garcia de Palazzo I, Ring DB, Alpaugh RK (1995) Phase I trial of 2B1, a bispecific monoclonal antibody targeting c-erbB-2 and FcγRIII. Cancer Res 55:4586–4593
101. Jankovic D, Cheever AW, Kullberg MC, Wynn TA, Yap G, Caspar P, Lewis FA, Clynes R, Ravetch JV, Sher A (1998) CD4+ T cell-mediated granulomatous pathology in schistosomiasis is downregulated by a B cell-dependent mechanism requiring Fc receptor signaling. J Exp Med 187:619–629
102. Yuan RR, Clynes R, Oh J, Ravetch JV, Scharff M (1998) Antibody-mediated modulation of Cryptococcus neoformans infection is dependent on distinct Fc receptor functions and IgG subclasses. J Exp Med 187:641–648
103. Gavin AL, Barnes N, Dijstelbloem HM, Hogarth PM (1988) Identification of the mouse IgG3 receptor: implications for antibody effector function at the interface between innate and adaptive immunity. J Immunol 160:20–23
104. Miyajima I, Dombrowicz D, Martin TR, Ravetch JV, Kinet J-P, Galli SJ (1997) Systemic anaphylaxis in the mouse can be mediated largely through IgG1 and FcγRIII. J Clin Invest 99:901–914
105. Sylvestre DL, Ravetch JV (1994) Fc receptors initiate the Arthus reaction: redefining the inflammatory cascade. Science 265:1095–1098

106. Sylvestre DL, Ravetch JV (1996) A dominant role for mast cell Fc receptors in the Arthus reaction. Immunity 5:387–390
107. Hazenbos WLW, Gessner JE, Hofhuis FMA, Kuipers H, Meyer D, Heijnen IAFM, Schmidt RE, Sandor M, Capel PJA, Daëron M, van de Winkel, JGJ, Verbeek JS (1996) Impaired IgG-dependent anaphylaxis and Arthus reaction in FcγRIII (CD16) deficient mice. Immunity 5:181–188
108. Hazenbos WLW, Heijnen IAFM, Meyer D, Hofhuis FMA, de Lavalette CR, Schmidt RE, Capel PJA, van de Winkel JGJ, Gessner JE, van den Berg TK, Verbeek JS (1988) Murine IgG1-complexes trigger immune effector functions predominantly via FcγRIII (CD16). J Immunol (submitted)
109. Schiller C, Meyer D, Schmidt RE, Gessner JE (1997) Anti-Ly-17 antibodies can be used for functional FcγRII blocking in mice. Immunobiology 197:294
110. Wershil BK, Mekori YA, Marukama T, Galli SJ (1987) ^{125}I-fibrin deposition in IgE-dependent immediate hypersensitivity reactions in mouse skin: demonstration of the role of mast cells using genetically mast cell-deficient mice locally reconstituted with cultured mast cells. J Immunol 139:2605–2614
111. Zhang Y, Ramos SF, Jakschik BA (1991) Augmentation of reverse Arthus reaction by mast cells in mice. J Clin Invest 88:841–846
112. Oettgen HC, Martin TR, Wynshaw-Boris A, Deng C, Drazen JM, Leder P (1994) Active anaphylaxis in IgE-deficient mice. Nature 370:367–370
113. Colten HR (1994) Drawing a double-edged sword. Nature 371:474–475
114. Sylvestre DL, Clynes R, Ma M, Warren H, Carroll M, Ravetch JV (1996) Immunoglobulin G-mediated inflammatory responses develop normally in complement-deficient mice. J Exp Med 184:2385–2392
115. Höpken UE, Lu B, Gerard NP, Gerard C (1997) Impaired inflammatory responses in the reverse Arthus reaction through genetic deletion of the C5a receptor. J Exp Med 186:749–756
116. Daëron M, Malbec O, Latour S, Arock M, Fridman WH (1995) Regulation of high-affinity IgE receptor-mediated mast cell activation by murine low-affinity IgG receptors. J Clin Invest 95:577–585
117. Takai T, Ono M, Hikida M, Ohmori H, Ravetch JV (1996) Augmented humoral and anaphylactic responses in FcγRII-deficient mice. Nature 379:346–349
118. Doody GM, Justement LB, Delibrias CC, Matthews RJ, Lin J, Thomas ML, Fearon DT (1995) A role in B cell activation for CD22 and the protein tyrosine phosphatase SHP. Science 269:242–244
119. O'Keefe TL, Williams GT, Davies SL, Neuberger MS (1996) Hyperresponsive B cells in CD22-deficient mice. Science 274:798–801
120. Otipoby KL, Andersson KB, Draves KE, Klaus SJ, Farr AG, Kerner JD, Perlmutter RM, Law C-L, Clark EA (1996) CD22 regulates thymus-independent responses and the life span of B cells. Nature 384:634–637
121. Sato S, Miller AS, Inaoki M, Bock CB, Jansen PJ, Tang MLK, Tedder TF (1996) CD22 is both a positive and negative regulator of B lymphocyte antigen receptor signal transduction: altered signaling in CD22-deficient mice. Immunity 5:551–562
122. Nitschke L, Carsetti R, Ocker B, Kohler G, Lamers MC (1997) CD22 is a negative regulator of B-cell receptor signalling. Curr Biol 7:133–143
123. Shultz LD, Schweitzer PA, Rajan TV, Yi T, Ihle JN, Matthews RJ, Thomas ML, Beier DR (1993) Mutations at the murine moth-eaten locus are within the hematopoietic cell protein-tyrosine phosphatase (Hcph) gene. Cell 73:1445–1454
124. Radeke HH, Resch K (1992) The inflammatory function of renal glomerular mesangial cells and their interaction with the cellular immune system. Clin Invest 70:825–842
125. Couser WG (1985) Mechanisms of glomerular injury in immune-complex disease. Kidney Int 28:569–583
126. Tipping PG, Neale TJ, Holdsworth SR (1985) T-lymphocyte participation in antibody-induced experimental glomerulonephritis. Kidney Int 27:530–537
127. Sterzel RB, Lovett DH (1988) Interactions of inflammatory and glomerular cells in the response to glomerular injury. Contemp Issues Nephrol 18:137–173
128. Clynes R, Dumitru C, Ravetch JV (1998) Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis. Science 279:1052–1054
129. Smiley JD, Moore SE (1989) Immune-complex vasculitis: role of complement and IgG-Fc receptor functions. Am J Med Sci 298:267–277
130. Franklin EC (1980) The role of cryoglobulins and immune complexes in vasculitis. J Allergy Clin Immunol 66:269–273
131. Ng YC, Schifferli JA (1988) Clearance of cryoglobulins in man. Springer Semin Immunopathol 10:75–89
132. Finn AF jr, Gorevic PD (1990) Pathogenic paraproteins: gammopathies and cryoglobulinemia. Curr Opin Rheumatol 2:652–660
133. Hendrich C, Kuipers JG, Kolanus W, Hammer M, Schmidt RE (1991) Activation of CD16 positive effector cells by rheumatoid factor complex. Arthritis Reum 34:423–431
134. Shibata T, Berney T, Spertini F, Izui S (1992) Rheumatoid factors in mice bearing the lpr or gld mutation. Selective production of rheumatoid factor cryoglobulins in MRL/MPJ-lpr/lpr mice. Clin Exp Immunol 87:190–195
135. Berney T, Fulpius T, Shibata T, Reininger L, van Snick J, Shan H, Weigert M, Marshak-Rothstein A, Izui S (1992) Selective pathogenicity of murine rheumatoid factors of the cryoprecipitable IgG3 subclass. Int Immunol 4:93–99
136. Reininger L, Berney T, Shibata T, Spertini F, Merino R, Izui S (1990) Cryoglobulinemia induced by a murine IgG3 rheumatoid factor: skin vasculitis and glomerulonephritis arise from distinct pathogenic mechanisms. Proc Natl Acad Sci U S A 87:10038–10042
137. Fulpius T, Spertini F, Reininger L, Izui S (1993) Immunoglobulin heavy chain constant region determines the pathogenicity and the antigen-binding activity of rheumatoid factor. Proc Natl Acad Sci U S A 90:2345–2349
138. Izui S, Reininger L, Shibata T, Berney T (1994) Pathogenesis of autoimmune hemolytic anemia in New Zealand black mice. Crit Rev Oncol/Hematol 17:53–70
139. Shibata T, Berney T, Reininger L, Chiche Portiche Y, Ozaki S, Shirai T, Izui S (1990) Monoclonal anti-erythrocyte autoantibodies derived from NZB mice cause hemolytic anemia by two distinct pathological mechanisms. Int Immunol 2:1133–1141
140. Meyer D, Schiller C, Westermann J, Izui S, Hazenbos W, Verbeek JS, Schmidt RE, Gessner JE (1998) FcγRIII (CD16) deficient mice demonstrate IgG isotype-dependent protection to experimental autoimmune hemolytic anemia. Blood (submitted)
141. Clynes R, Ravetch JV (1995) Cytotoxic antibodies trigger inflammation through Fc receptors. Immunity 3:21–26
142. Imbach P, Barandun S, d'Apuzzo V, Baumgartner C, Hirt A, Morell A, Rossi E, Schöni M, Vest M, Wagner HP (1981) High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1:1228–1230
143. Schmidt RE, Budde U, Schäfer G, Stroehmann I (1981) High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura. Lancet 2:475–476
144. Pollack S, Cunningham-Rundles C, Smithwick EM, Barandun S, Good RA (1982) High-dose intravenous gammaglobulin for autoimmune neutropenia. N Engl J Med 307:243–246
145. Bussel J, Lalezari P, Hilgartner M, Partin J, Fikrig S, O'Malley J, Barandun S (1983) Reversal of neutropenia with intravenous gammaglobulin in autoimmune neutropenia of infancy. Blood 62:398–403

146. Debre M, Bonnetr MC, Fridman WH, Carosalla E, Phillipe N, Reinert P, Vilmer E, Kaplan C, Teillaud JL, Griscelli C (1993) Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet 342:945–949
147. Clarkson SB, Bussel JB, Kimberly RP, Valinsky JE, Nachman RL, Unkeless JC (1986) Treatment of refractory immune thrombocytopenic purpura with an anti-Fc gamma receptor antibody. N Engl J Med 314:1236–1238
148. Oyaizu N, Yasumizu R, Miyama-Inaba M, Nomura S, Yoshida H, Miyawaki S, Shibata Y, Mitsuoka S, Yasunaga K, Morii S, Good RA, Ikehara S (1988) (NZW× BXSB) F_1 mouse. A new animal model of idiopathic thrombocytopenic purpura.J Exp Med 167:2017–2022
149. Mizutani H, Engelman RW, Kurata Y, Ikehara S, Good RA (1993) Development and characterization of monoclonal antiplatelet autoantibodies from autoimmune thrombocytopenic purpura-prone (NZW× BXSB) F_1 mice. Blood 82:837–844
150. Heijnen IA, van Vugt MJ, Fanger NA, Graziano RF, de Wit TP, Hofhuis FM, Guyre PM, Capel PJA, Verbeek JS, van de Winkel JGJ (1996) Antigen targeting to myeloid-specific human FcγRI/CD64 triggers enhanced antibody responses in transgenic mice. J Clin Invest 97:331–338
151. Kwack K, Verbeek JS, van de Winkel JGJ, Capel PJA, Nambu M, Hagen M, Weinstock JV, Lynch RG, Sandor M (1995) Functional consequences of the interaction between T-cell antigen receptors and FcγRs on T cells. Immmunol Lett 44:139–143
152. Dumbsky M, Schmidt RE, Gessner JE (1997) Molecular characterization of variant FcγRIII (CD16) transcripts. Immunol Lett 56:401
153. Guyre PM, von dem Borne AEGK (1995) CD64 cluster workshop report. In: Schlossman SF, Boumsell L, Gilks W (eds) Leukocyte typing V: White cell differentiation antigens. Oxford University Press, London, pp 874–875
154. van de Winkel JGJ, Anderson CL (1995) CD32 cluster workshop report. In: Schlossman SF, Boumsell L, Gilks W (eds) Leukocyte typing V: White cell differentiation antigens. Oxford University Press, London, pp 823–826
155. Schmidt RE (1994) CD16 cluster workshop report. In: Schlossman SF, Boumsell L, Gilks W (eds) Leukocyte typing V: White cell differentiation antigens. Oxford University Press, London, pp 805–806
156. Gosselin EJ, Brown MF, Anderson CL, Zipf TF, Guyre PM (1990) The monoclonal antibody 41H16 detects the Leu-4 responder form of human FcγRII. J Immunol 144:1817
157. Budde P, Weinrich V, Sondermann P, Bewarder N, Kilian A, Schulzeck O, Frey J (1994) Specificity of CD32 mAb for FcγRIIa, FcγRIIb1, and FcγRIIb2 expressed in transfected mouse B cells and BHK-21 cells. In: Schlossman SF, Boumsell L, Gilks W (eds) Leukocyte typing V: White cell differentiation antigens. Oxford University Press, London, pp 828–832
158. Ierino FL, Hulett MD, McKenzie IFC, Hogarth PM (1993) Mapping epitopes of human FcγRII (Cdw32) with monoclonal antibodies and recombinant receptors. J Immunol 150, 1794–1803
159. de Haas M, Kleijer M, Roos D, von dem Borne AEGKr (1995) Characterization of mAb of the CD16 cluster and six newly generated CD16 mAb. In: Schlossman SF, Boumsell L, Gilks W (eds) Leukocyte typing V: White cell differentiation antigens. Oxford University Press, London, pp 811–814
160. Tamm A, Schmidt RE (1996) The binding epitopes of human CD16 (FcγRIII) monoclonal antibodies. Implications for ligand binding. J Immunol 157:1576–1581
161. Vance BA, Huizinga TWJ, Wardwell K, Guyre PM (1993) Binding of monomeric human IgG defines an expression polymorphism of FcγRIII on large granular lymphocyte/ natural killer cells. J Immunol 151:6429–6439
162. Holmes KL, Palfree RGE, Hammerling U, Morse HC (1985) Alleles of the Ly-17 alloantigen define polymorphisms of the murine IgG Fc receptor. Proc Natl Acad Sci U S A 82:7706–7710
163. Schiller C, Meyer D, Schmidt RE, Gessner JE (1997) Murine low-affinity Fcγ receptors can be distinguished by anti-Ly-17 antibodies. Immunol Lett 56:401
164. Ashman RF, Peckham D, Stunz LL (1996) Fc receptor offsignal in the B cell involves apoptosis. J Immunol 157:5–11
165. de Andrés B, Mueller AL, Blum A, Weinstock I, Verbeek S, Sandor M, Lynch RG (1997) FcγRII (CD32) is linked to apoptotic pathways in murine granulocyte precursors and mature eosinophils. Blood 90:1267–1274
166. Daëron M, Malbec O, Latour S, Bonnerto C, Segal DM, Fridman WH (1993) Distinct intracytoplasmic sequences are required for endocytosis and phagocytosis via murine FcγRII in mast cells. Int Immunol 5:1393–1401
167. Dastych J, Hardison MC, Metcalfe DD (1997) Aggregation of low-affinity IgG receptors induces mast cell adherence to fibronectin: requirement for the common FcR γ-chain. J Immunol 158:1803–1809
168. Whitmer KJ, Romball CG, Weigle WO (1997) Induction of tolerance to human g-globulin in FcR γ- and FcγRII-deficient mice. J Immunol 159:644–649
169. Vora KA, Ravetch JV, Manser T (1997) Amplified follicular immune complex deposition in mice lacking the Fc receptor γ-chain does not alter maturation of the B cell response. J Immunol 159:2116–2124