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Review Article

Regulation of murine hypersensitive responses by Fc receptors

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Abstract

Humoral and cellular immune responses communicate with each other via Fc receptors (FcR) expressed on various hematopoietic cells. Recent studies on several FcR knockout mice demonstrated pivotal roles of an IgG/FcγR system in the regulation of immune responses and the onset of hypersensitivity. The γ subunit of FcR is an essential component of the complex and is required for both receptor assembly and signal transduction. FcR γ chain-deficient mice have lost the functional expression of FcεRI, FcγRI, and FcγRIII and are unable to mount several types of hypersensitive reactions, including the skin Arthus reaction. In contrast, FcγRII-deficient mice exhibit augmented humoral immune responses and IgG-mediated anaphylaxis reactions. Thus, the regulatory system of murine hypersensitive responses involves both positive and negative signaling through FcR. In B cells, FcγRIIb modulates membrane Ig-induced Ca^{2+} mobilization by inhibiting Ca^{2+} influx through phosphorylation of its immunoreceptor tyrosine-based inhibition motif and recruitment of cytoplasmic phosphatases. Elucidation of the detailed mechanisms of negative regulatory signaling in the inflammatory effector cells by FcγRIIb as well as several groups of potent inhibitory molecules expressed on such cells should be valuable in the development of novel therapeutic procedures for allergic disorders.

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Introduction

Considerable progress has been made in the past decade in defining the genetic organization, molecular structures and detailed functions of Fc receptors (FcR) using molecular biological techniques.[1–5] In addition, a number of strains of mice that have manipulated FcR genes and mice with exogenous FcR genes have been developed. These include transgenic mice strains with a transgene for human FcγRI,[6] FcεRIα,[7] human FcRγ[8] or human FcγRIIIA or FcγRIIIB[9] and knockout mice strains lacking a gene for mouse FcεRIα,[10] FcεRII,[11–13] FcRγ,[14] FcγRII[15] or FcγRIII.[16] In particular, these gene knockout mice have proven to be highly useful for analyzing the physiological functions of individual FcR or its subunit molecules in the immune system.[17,18] The present review will focus mainly on new findings and observations derived from analysis of such gene knockout mice, emphasizing in particular the positive and negative regulatory functions of FcR in murine hypersensitive responses.

Structural features of FcR

Most ligand-binding α subunits of FcR belong to the immunoglobulin (Ig) superfamily and constitute a group of complex but highly related molecules (Table 1; Fig. 1). A total of eight genes have been identified for the human FcγRs: three genes for the high affinity IgG receptor FcγRI (*FcγRIA*, *FcγRIB* and *FcγRIC*)[19] and five

genes for the low affinity IgG receptors FcγRII (*FcγRIIA*, *FcγRIIB* and *FcγRIIC*)[20] and FcγRIII (*FcγRIIIA* and *FcγRIIIB*).[21] The low affinity FcγR genes and the genes for the FcεRIα and γ subunits, are clustered on chromosome 1q23. This region of 1q23 is syntenic to mouse chromosome 1, where single genes for these receptors are found.[22,23] The three FcγRI genes map to chromosome 1q21. The mouse FcγRI gene has been mapped on chromosome 3.

NOVEL FcR-RELATED MOLECULES

A receptor for IgA, FcαR, was found on the human monocytoid cell line U937[24] and on other cells, including glomerular mesangial cells[25] and monocytes[26] (Table 1; Fig. 1). A novel class of FcγR, Fcγ2R, was cloned from a cattle alveolar macrophage library[27] and has the ability to bind erythrocytes sensitized with IgG_2 but not IgG_1. A homology search for Fcγ2R indicated a

Table 1. Genes and transcripts of Fc receptors (FcR) and FcR-related molecules

Species	CD	Gene	Chromosome*		Transcripts
			Human	Mouse (cM)	
Human	CD64	*FcγRIA*	1q21		FcγRIa
		FcγRIB	1q21		sFcγRIb1,† FcγRIb2
		FcγRIC	1q21		sFcγRIc
Mouse		*FcγRI*		3 (45.2)	FcγRI
Human	CD32	*FcγRIIA*	1q23		FcγRIIa1, sFcγRIIa2
		FcγRIIB	1q23		FcγRIIb1, FcγRIIb2, FcγRIIb3
		FcγRIIC	1q23		FcγRIIc
Mouse		*FcγRII*		1 (92)	FcγRIIb1, FcγRIIb1′, FcγRIIb2, sFcγRIIb3
Human	CD16	*FcγRIIIA*	1q23		FcγRIIIa
		FcγRIIIB	1q23		FcγRIIIb, sFcγRIIIb
Mouse		*FcγRIII*		1 (92.3)	FcγRIII
Human		*FcεRIα*	1q23		FcεRIα
Mouse		*FcεRIα*		1 (94.2)	FcεRIα
Human		*FcεRIβ*	11q13		FcεRIβ
Mouse		*FcεRIβ*		19 (8.0)	FcεRIβ
Human		*FcRγ*	1q23		FcRγ
Mouse		*FcRγ*		1 (93.3)	FcRγ
Human		*CD3ζ*	1q22-23		CD3ζ, CD3η
Mouse		*CD3ζ*		1 (87.2)	CD3ζ, CD3η
Human	CD23	*FcεRIIa, b*	19p13.3		FcεRIIa, sFcεRII, FcεRIIb
Mouse		*FcεRII*		8 (0.4)	FcεRII, sFcεRII
Human	CD89	*FcαR*	19q13.4		FcαRa1, FcαRa2, FcαRa3
Human		*poly-IgR*	1q31–q41		poly-IgR
Mouse		*poly-IgR*		?	poly-IgR
Human		*FcRn*	19q13.3		FcRn
Mouse		*FcRn*		7 (20.0)	FcRn
Human	CD158	*p58 KIR*	19q13.4		p58 KIR
		ILT	19q13.4		ILT
		LAIR-1	19q13.4		LAIR-1
Mouse		*gp49A*		10	gp49A
		gp49B		10	gp49B1, gp49B2
		p91A		7	p91A
		p91B		7	p91B
		p91C		7	p91C

*These data are available at http://www.genome.ad.jp

†s, soluble receptor.

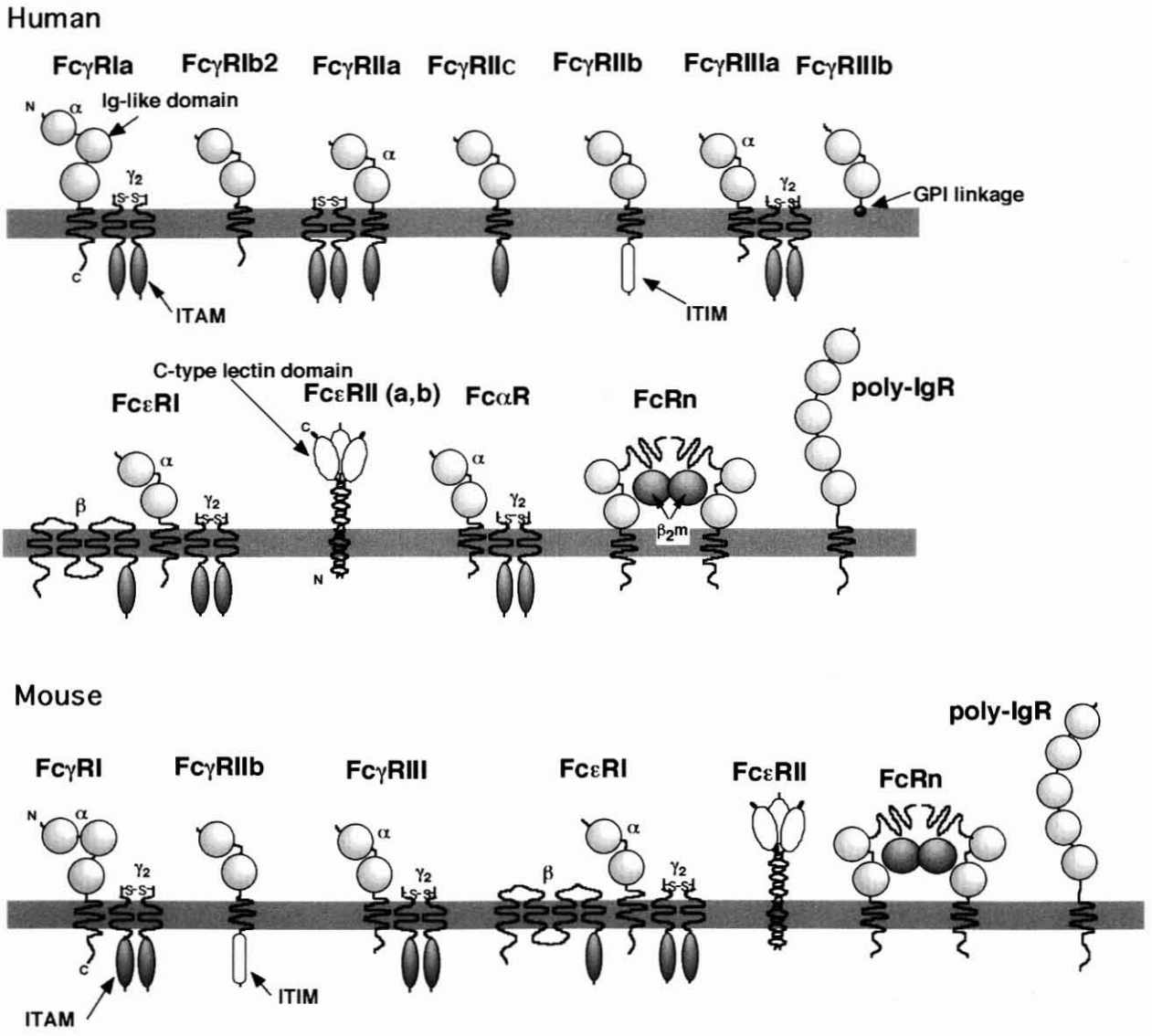

Fig. 1 Schematic structures of human and mouse Fc receptors (FcR) and those of the associating molecules. Minor differences among splicing variants within one type of FcR are not illustrated. FcRn, which participates in the transport of maternal IgG in neonatal gut, has a structural similarity to major histocompatibility complex class I molecules. Poly-Ig receptors recognize dimeric IgA and polymeric IgM and participate in the secretion of these molecules.

greater level of similarity with human FcαR than with any other FcR.[27] Recently, it was reported that human killer cell inhibitory receptors (KIR) found on natural killer (NK) cells as well as T cells show significantly high homology to human FcαR[28] (Fig. 2). The KIR are novel members of the Ig superfamily expressed exclusively on NK cells and on a subset of T cells. These molecules play a pivotal role in the recognition of polymorphic major histocompatibility complex (MHC) class I molecules on target cells and the delivery of the inhibitory signal to the cell interior by means of a mechanism involving phosphorylation of a specific tyrosine residue in their immunoreceptor tyrosine-based inhibitory motif (ITIM) and recruitment of a *src*-homology 2 (SH2)-containing tyrosine phosphatase 1 (SHP-1). Natural killer cells in humans and mouse also express C-type lectin-like receptors, such as a CD94/NKG2A complex in humans and a Ly-49 dimer in the mouse. Recent data have indicated that gp49B, a type I transmembrane glycoprotein belonging to the Ig superfamily

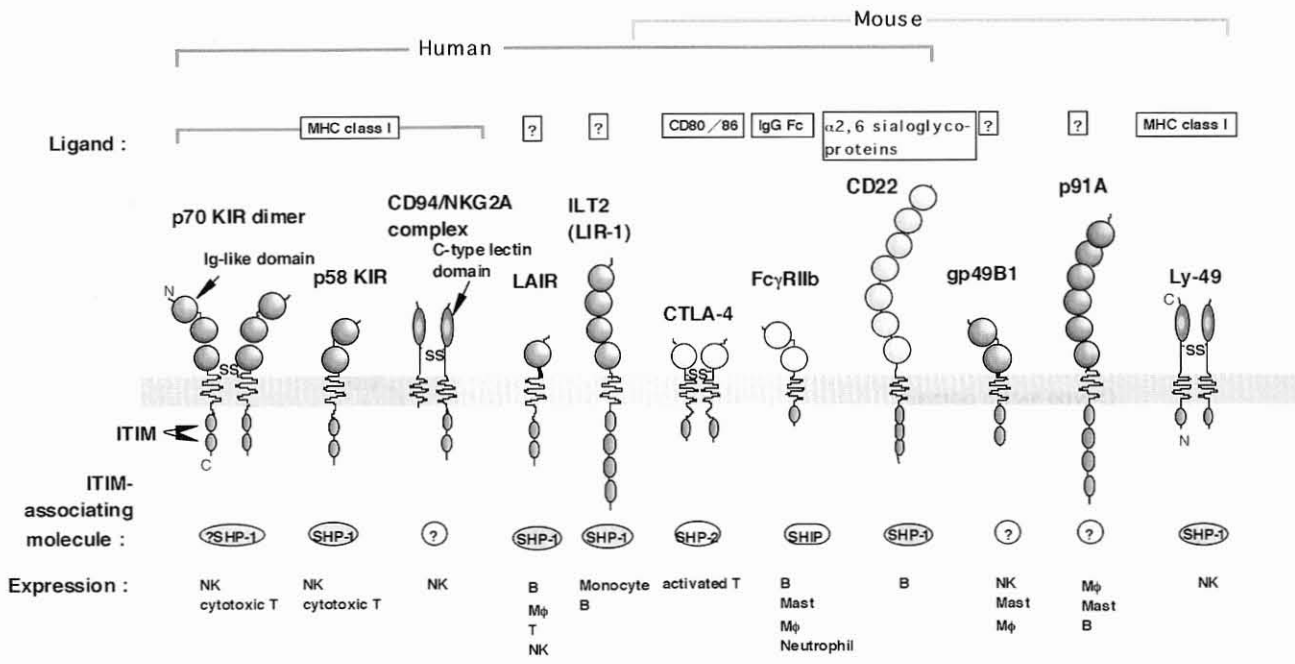

Fig. 2 Schematic structures of human and mouse immunoreceptor tyrosine-based inhibitory motif (ITIM)- or ITIM-like sequence-containing molecules expressed on various hematopoietic cells. Ligand, cell types and associating molecules to intracellular ITIM or ITIM-like motifs are shown in cases where they are known.

expressed on murine NK cells and mast cells, functions as an inhibitory molecule on these cells.[29-31] Thus, both human and mouse NK cells express Ig-related inhibitory receptors, in addition to C-type lectin-like molecules (Fig. 2).

Interestingly, several groups, including our own, have cloned novel KIR-like inhibitory molecules from mouse and humans expressed on various hematopoietic cells, such as B cells, macrophages and mast cells. They are murine p91A[32,33] or paired inhibitory receptor-B (PIR-B)[34] and human immunoglobulin-like transcripts (ILT)[35,36] and leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1)[37] (Fig. 2). They have one or a set of Ig-like extracellular domains, a transmembrane region and a cytoplasmic portion containing ITIM-like sequences. Although the physiological ligands for these receptors are not known, these molecules have been shown to be inhibitory to cell activation,[36,37] recruiting cytoplasmic phosphatases to the tyrosine-phosphorylated cytoplasmic motifs in a similar fashion to that of human KIR. Chromosomal locations of the human *p58 KIR, FcαR, LAIR-1* and *ILT* have been mapped within 19q13.4. The genes for human KIR and murine KIR-like molecules, human FcαR and bovine Fcγ2R may have evolved from a common ancestor.

Pivotal roles of FcR in stimulation of hypersensitive responses

Mast cells and basophils play a prominent role in anaphylaxis following activation by IgE and allergen. These cells of mouse origin express at least three types of receptors for IgE: FcεRI, FcγRII and FcγRIII. FcεRI binds monomeric IgE, whereas the two low affinity IgG receptors bind both IgG and IgE immune complexes.[38] To evaluate the relative contribution of these IgE receptors to the genesis of *in vivo* anaphylaxis, Dombrowicz *et al.*[10] have generated FcεRIα-deficient mice. Immunoglobulin E-mediated cutaneous and systemic anaphylaxis were tested in these mice. They injected mice with murine anti-dinitrophenyl (DNP) IgE into the ear or intravenously (i.v.) and then challenged mice with i.v. injections of antigen. The deposition of fibrin in the injected ear of mice or rectal temperature was measured as an index of the severity of passive cutaneous anaphylaxis (PCA) or of systemic anaphylaxis, respectively. The FcεRIα-deficient mice were resistant to cutaneous and systemic anaphylaxis triggered by IgE, verifying that FcεRI is essential for the onset of IgE-dependent anaphylaxis.

Initially identified as a subunit of FcεRI, FcRγ is also a

subunit of the FcγRI and, in a subset of T cells, functions as a subunit of the T cell receptor (TCR) complex.[39 43] It is also critical for transducing signals into the cell interior, which results in cellular activation[44,45] through tyrosine kinase Lyn- and Syk-activation pathways, mediated by the immunoreceptor tyrosine-based activation motif (ITAM).[46] Takai *et al.*[14] have generated a mouse strain genetically deficient in FcRγ. The ablation of this chain resulted in the almost complete loss of effector responses, such as antibody dependent cell-mediated cytotoxicity by NK cells, phagocytosis of IgG-opsonized particles by macrophages and IgE-dependent degranulation due to the loss of FcγRI, FcγRIII and FcεRI on these cells.

FcRγ-deficient mice did not respond to various experimental induction protocols of inflammatory reactions.[14,47,48] For example, bone marrow-derived cultured mast cells isolated from FcRγ-deficient mice lack IgE binding, as a result of the loss of FcεRI.[14] Consistent with the loss of these *in vitro* mast cell functions, PCA reaction mediated via FcεRI and IgE on mast cells *in vivo* was ablated in the FcRγ-deficient mice,[14] agreeing with the observations from FcεRIα-deficient mice described earlier.[10]

Mast cells and basophils can be activated *in vitro* and *in vivo* by non-IgE stimuli.[49] Oettgen *et al.*[50] have reported that IgE knockout mice were able to mount systemic anaphylaxis at a similar magnitude to that of wild-type mice on antigen challenge, suggesting that the type I hypersensitivity reaction is inducible upon crosslinking between FcγRII/III on mast cells by IgG immune complexes as well as crosslinking of FcεRI via IgE and antigen, in agreement with the phenotypes of FcγRIIb-deficient mice[15] described later.

FcRγ-deficient mice were shown to be resistant to the development of experimental autoimmune hemolytic anemia induced by rabbit anti-mouse red blood cell IgG antibodies.[47] This resistance was primarily a consequence of ineffective erythrophagocytosis, resulting from the lack of FcγR on phagocytes. Therefore, it was suggested that FcR play an important role in the pathogenesis of antibody induced type II hypersensitivity.[47]

The type III hypersensitivity response is caused by the deposition of an immune complex. As an experimental model of this type of response, one injects antibody into the skin and administers the antigen i.v. followed by assessment of skin inflammation, such as edema, hemorrhage and neutrophil infiltration after 2–24 h (reverse passive Arthus reaction). This induction scheme is interpreted as the local formation of immune complex, complement activation via the classical pathway and triggering of the inflammatory cascade. Sylvestre and Ravetch[48] re-evaluated this cascade using FcRγ-deficient mice and found that the Arthus reaction is not able to be induced without FcγR. Mice were injected i.v. with ovalbumin (OVA) and then given i.d. injections of anti-OVA IgG. The FcRγ knockout mouse showed a distinct reduction in edema, hemorrhage and neutrophil infiltration. Therefore, the inflammatory deficit observed in the mutant mice can be attributed to the lack of FcR in these animals.[48] Sylvestre *et al.* then examined the Arthus reaction in complement-deficient mice and found that the magnitude of the reaction was comparable to that of wild-type animals,[51] confirming that the complement system is not essential and that FcγR are the primary initiators of the Arthus reaction in the skin. Using differential reconstitution of the mast cell-deficient mouse strain W/W^v with mast cells derived from wild-type or FcRγ-deficient mice, Sylvestre and Ravetch[52] further demonstrated that the Arthus reaction in FcRγ-deficient mice was shown to be reconstituted by such mast-cell transfer. Therefore, it was confirmed that the tissue mast cells from FcRγ-deficient mice are primary candidates of this unresponsiveness to type III hypersensitivity induced in skin and the effector molecule that is responsible for the initiation of this type of reaction is FcγRIII. This notion has been verified using FcγRIIIα-deficient mice generated by Hazenbos *et al.*[16] Strikingly, the mice exhibited an impaired Arthus reaction. These data support the notion that FcγRIII play a dominant role in the type III hypersensitive response induced in the skin.

Negative immune regulation by FcgRIIb

Negative signaling through FcγRIIb

FcγRIIb is unique among other FcR, both structurally and functionally. This receptor molecule does not associate with an FcRγ homodimer and possesses an ITIM.[53] When B cells are stimulated with anti-Ig $F(ab')_2$, the cells proliferate efficiently due to crosslinking of surface Ig, but intact anti-Ig antibody fails to do so. This phenomenon has been interpreted as indicating that FcγRIIb molecules on B cells bind the Fc portion of the antibody and form co-crosslinkages between the antigen receptor and FcγRIIb via an anti-Ig antibody. This observation suggests that FcγRIIb on B cells may inhibit antibody production in immune response *in vivo*.[54] Amigorena *et al.*[55] and Muta *et al.*[56] transfected FcγRII-deficient A20 B lymphoma cell line, IIA1.6, with FcγRIIb and observed that anti-Ig antibody that crosslinks

surface FcγRIIb with membrane Ig inhibits Ca^{2+} mobilization in that cell line. It was shown that FcγRIIb modulates membrane Ig-induced Ca^{2+} mobilization by inhibiting Ca^{2+} influx without changing the pattern of tyrosine phosphorylation.[56,57] The 13 amino acid sequence including ITIM in the cytoplasmic domain of FcγRIIb was both necessary[55] and sufficient[56] for this effect. The inhibitory motif in FcγRIIb controls B cell activation by inhibiting a Ca^{2+} signaling pathway triggered through ITAM of Ig-α and Ig-β as a result of recruitment of novel SH2-containing proteins that interact with the tyrosine-phosphorylated ITIM.[56] Cambier *et al.*[58] showed one of the SH2-containing proteins as a cytoplasmic protein tyrosine phosphatase, SHP-1. Daeron *et al.*[53] have reported that the inhibition signaling through FcγRIIb is a more general mechanism of immunosuppression in a variety of cells, including B cells, T cells and mast cells, showing that FcγRIIb inhibit FcεRI- and T cell receptor-dependent cell activation as well as B cell receptor pathways. Recently, Ono *et al.*[59] have shown that the inhibitory signaling by FcγRIIb does not require SHP-1 in mast cells and results in the recruitment of the SH2-domain-containing inositol polyphosphate 5-phosphatase, SHIP,[60] to the tyrosine-phosphorylated 13-amino-acid inhibitory motif of FcγRIIb in both B cells and mast cells. Furthermore, Ono *et al.*[61] have generated SHP-1- or SHIP-deficient B cell lines to determine their ability to mediate inhibitory signaling. They found that two distinct classes of inhibitory responses are defined. The FcγRII class of inhibitory signaling is dependent on SHIP. In contrast, KIR requires SHP-1 for its inhibitory signaling.

Enhanced hypersensitive responses in FcγRII-deficient mice

Crosslinking stimulation of surface IgM on splenic B cells using intact anti-μ IgG resulted in the marked proliferative response in B cells from FcγRII-deficient mice but not in those cells from wild-type mice, confirming the role of FcγRIIb on B cells as a negative regulator of signaling through the antigen receptor *in vitro*.[15] The FcγRII-deficient mice showed higher antibody titers than those of wild-type mice when they were immunized with T-dependent as well as T-independent antigens. The number of anti-sheep erythrocyte IgM and IgG plaque-forming cells in splenocytes from FcγRII-deficient mice were higher than those of wild-type mice, especially in the secondary immune response. Therefore, it was shown that FcγRIIb negatively regulates antibody production *in vivo*.[15]

Bone marrow-derived cultured mast cells from FcγRII-deficient mice were stimulated by crosslinking FcεRI with IgE and anti-IgE or FcγRII/III with anti-FcγRII/III monoclonal antibody 2.4G2 and anti-rat IgG and their degranulation was estimated *in vitro*.[15] Interestingly, although mast cells from wild-type mice did not degranulate upon crosslinking of surface FcγRIIb and FcγRIII with 2.4G2 and anti-rat IgG, mast cells from the mutant animals responded significantly on the same crosslinking stimulus. *In vitro* observations by Daeron *et al.*[49,53] are consistent with these data. Immunoglobulin G-induced PCA reactions in FcγRII-deficient mice were augmented several-fold over those in wild-type mice.[15] These observations in FcγRII-deficient mice provide an indication of the mechanism responsible for the onset of hypersensitive responses. It is clear that IgE antibody works very efficiently as a triggering molecule through its binding to the high-affinity receptor for IgE, FcεRI, on immune cells such as mast cells and basophils. Similarly, the IgG immune complex-induced positive switching through FcγRIII is also present, but is attenuated in normal situations because FcγRIIb is co-expressed simultaneously with FcγRIII on most effector cells and this receptor delivers abortive or negative signaling upon co-engagement with FcγRIII. In FcγRII-deficient mice this negative switching does not operate so that the FcγRIII-mediated signaling cascade will work effectively.

FcεRII Deletion

FcεRII-deficient mouse lines have been generated independently by three groups.[11–13] In the case of mice generated by Yu *et al.*,[11] immunization with T-dependent antigens in alum adjuvant with *Bordetella pertussis* leads to increased and sustained specific IgE and IgG_1 antibody titers compared with controls. These authors proposed that murine FcεRII possibly acts as a negative feedback component of IgE regulation.[11] In contrast, a FcεRII-deficient mouse generated by Fujiwara *et al.*[13] displayed normal lymphocyte differentiation and could mount normal antibody responses, including IgE responses, following immunization with T-dependent antigens in complete Freund's adjuvant. The inconsistency may arise from differences in the genetic background of mice and differences in the immunization protocol.

Concluding remarks

Recent advances in understanding the regulatory mechanisms of FcR on murine hypersensitive responses are due to various reasonable results that are consistent with

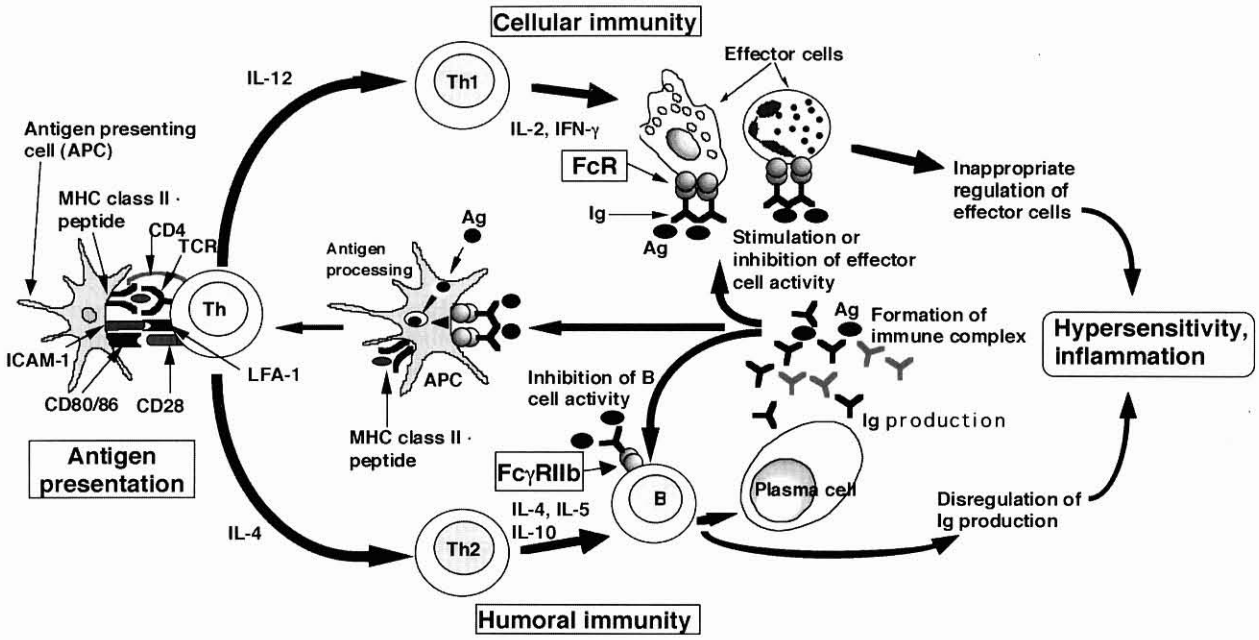

Fig. 3 A hypothetical model for the regulation of hypersensitive responses by FC receptors (FcR). Th1 and Th2 induce cellular and humoral immune responses, respectively. These two processes are cross-regulated by cytokines, antibodies and FcR. This hypothetical model postulates that deregulation by FcR could be an important factor for the onset of hypersensitivity.

preceding *in vitro* data as well as to unexpected observations in FcR-deficient mice. Using FcRγ-, FcεRIα- or FcγRIIIα-deficient mice, the mechanisms of initiating several types of hypersensitivity cascades have been re-evaluated. It has been shown that the binding of IgE to FcεRI and the binding of the IgG immune complex to FcγRIII on effector cells are pivotal events that lead to IgE-induced anaphylaxis and the IgG-induced skin Arthus reaction, respectively. In contrast, it has been proposed that suppression of these activation events through FcγRIIb could be a potent means of maintaining homeostasis and controlling inappropriate effector cell activation (Fig. 3). Elucidation of biochemical nature of the inhibitory cascades, as well as detailed physiological roles of FcγRIIb and novel molecular families, such as gp49B, p91A/PIR-B, ILT and LAIR-1, will be challenging fields in the next several years.

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