Fc Receptors

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Receptors for the Fc region of immunoglobulins link humoral responses to cellular activities within the immune system. Leucocyte Fc receptors exist as hetero-oligomeric complexes with unique ligand-binding α chains and promiscuous accessory subunits.

Advanced article

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Online posting date: 15th September 2008

Introduction

Receptors for the Fc region of immunoglobulins (FcRs) link humoral responses to cellular activities within the immune system. Based on their function, two general groups of FcR can be distinguished: those expressed predominantly by leucocytes that trigger antibody effector functions and those that primarily mediate transport of immunoglobulins across epithelial or endothelial surfaces (polyimmunoglobulin (poly-Ig) receptor and FcRn, although the latter was shown recently to have a function in leucocytes as well) (Nimmerjahn and Ravetch, 2007). This review will focus on the general characteristics of the human leucocyte FcRs for immunoglobulin G (IgG) (FcγR), IgA (FcαR), IgE (FcεR), IgM (FcμR) and IgD (FcδR) (**Figure 1**). **See also**: Antibodies; Antibody Classes

Most leucocyte FcRs exist as hetero-oligomeric complexes with unique ligand-binding α chains and promiscuous accessory subunits (ζ, γ or β chains). Within the FcR family, the immunoreceptor tyrosine-based activation motif (ITAM) plays an essential role in triggering biological functions. In addition, some FcRs contain inhibitory motifs within their cytoplasmic regions known as immunoreceptor tyrosine-based inhibitory motif (ITIM). In general, FcR crosslinking initiates a range of biological functions varying from activatory to inhibitory functions. The threshold for cell activation is set by the ratio of activating and inhibitory signalling when simultaneously triggered. A number of human Fc receptors have orthologues in the mouse. Although the murine FcR system differs from its human counterpart, our knowledge on FcR biology greatly benefited from murine studies, especially with mice with targeted inactivation of individual FcRs or transgenic for specific human FcR. **See also**: Lymphocyte Activation Signals: Transduction

ELS subject area: Immunology

How to cite:
Boross, Peter; van de Poel, Kees; Van de Winkel, Jan GJ; and, Leusen, Jeanette HW (September 2008) Fc Receptors. In: Encyclopedia of Life Sciences (ELS). John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0000916.pub2

FcγR

Leucocyte receptors for the Fc domain of IgG (FcγR) are members of the Ig supergene family and three classes have been described in humans: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) (**Figure 1**; Ravetch and Bolland, 2001). **See also**: Immunoglobulin Superfamily

FcγRI

Three genes have been characterized for the class I IgG receptor – Fcγ RIA, IB and IC. Only for FcγRIA functional protein expression has been shown. The prototypic FcγRI, has an extracellular region with three Ig-like domains, a transmembrane domain and a cytoplasmic tail. FcγRIa represents the sole leucocyte FcγR capable of binding monomeric IgG with high affinity $K_a = 10^8$–$10^9\,\mathrm{L\,mol^{-1}}$. The receptor shows specificity for the subclasses IgG3, IgG1 and IgG4, in decreasing affinity (**Table 1**).

FcγRIa is constitutively expressed at high levels on (progenitor) monocytes, and macrophages, and at low levels on polymorphonuclear leucocytes (PMNs) and on certain dendritic cell populations. Expression of FcγRIa is enhanced by interferon γ (IFNγ), granulocyte colony-stimulating factor (G-CSF) and interleukin 10 (IL-10), and is downregulated by IL-4 and IL-13 (**Table 2**). It exists as a hetero-oligomeric receptor complex with a ligand-binding α chain, and an FcR γ chain homodimer.

Although the FcR γ chain is important during FcγRI signalling, several studies have suggested an additional role for the α chain. Endocytosis and antigen presentation of endocytosed immunocomplexes is partly mediated by the α chain cytoplasmic tail (FcγRI-CY) (van Vugt *et al.*, 1999). Furthermore, deletion of FcγRI-CY abrogates the production of IL-6 upon receptor crosslinking. Although downstream signalling events have not been elucidated in detail, several proteins have been shown to interact with FcγRI-CY. The interacting proteins periplakin and filamin A, play a role in modulation of ligand binding

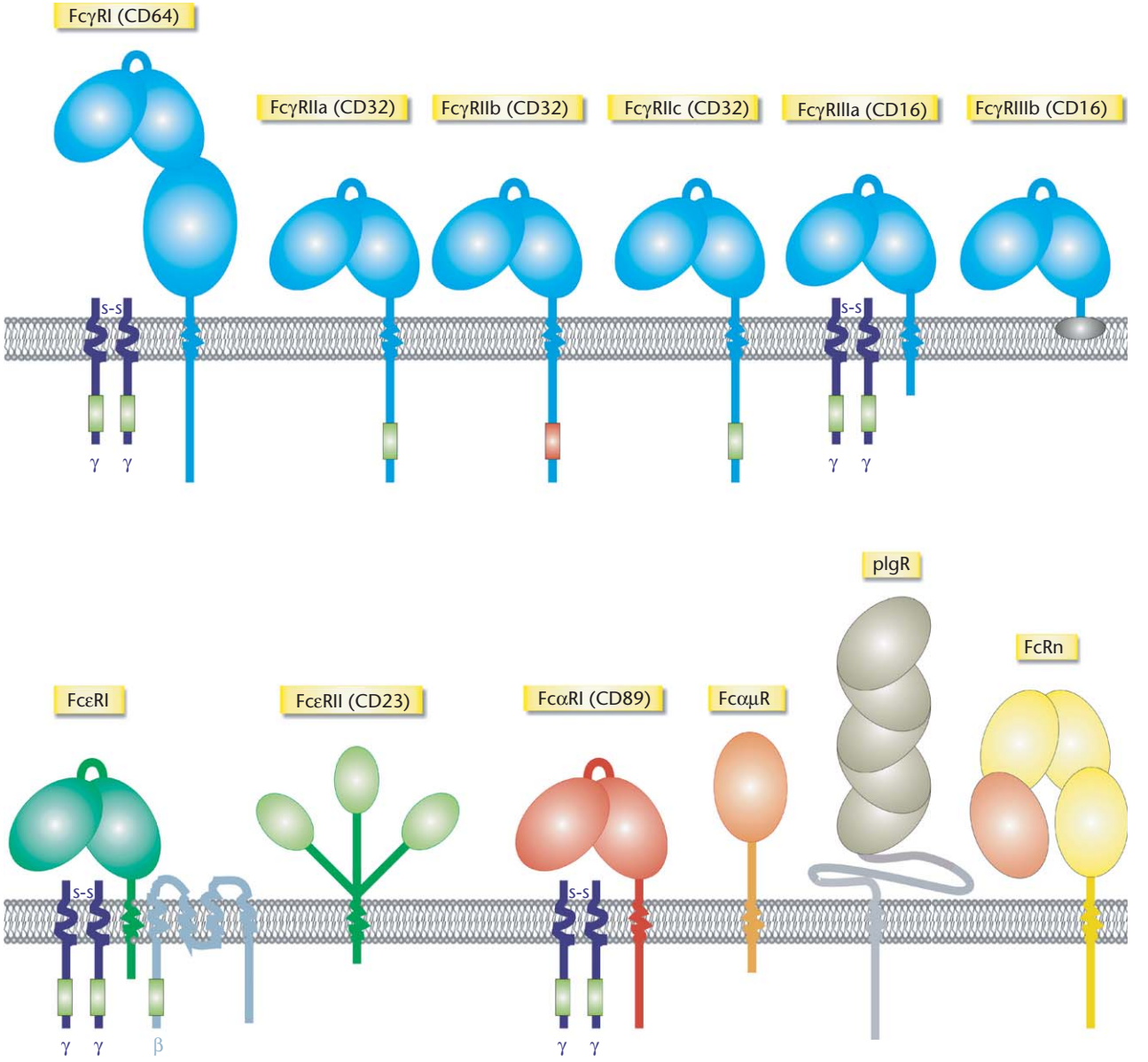

Figure 1 Schematic representation of human Fc receptors. The extracellular parts of most human Fc receptors are composed of varying amounts (1–5) of immunoglobulin domains. The two exceptions are the lectin family member FcεRII and the major histocompatibility complex (MHC) class I protein family member FcRn. Based on their function FcR can mediate activating signals via ITAM (green box) which consist of YxxLxxxxxxYxxL (Y = tyrosine, L = leucine, X = any amino acid). The ITAM can either be located on the intracellular part of the receptors (FcγRIIa and FcγRIIc) or on the associated γ chain (FcγRI, FcγRIIIa, FcεRI, FcαRI). Next to its role in signalling, the γ chain (in blue) is also essential for surface expression. The sole inhibiting FcR, FcγRIIb, bears an ITIM (red box) on its intracellular tail, which consists of Y/V/L/S/xYxxL/V (Y = tyrosine, V = valine, S = serine, L = leucine, X = any amino acid). FcγRIIIb is a glycosylphosphatidylinositol (GPI)-linked activating receptor that has no intracellular tail.

and stabilization of the receptor at the plasma membrane, respectively (Beekman *et al.*, 2004). The capacity to alter the affinity of the receptor for its ligand appears to be a feature shared among more Fc receptors, and is often referred to as 'inside-out' signalling. In general, this occurs when Fc receptor expressing cells are stimulated, for instance by cytokines, resulting in an activated cell with a higher capacity to bind immune complexes. A similar mechanism has been described for integrins.

The FcR γ chain molecules are critical for stabilization of FcγRI surface expression, for signalling, and for ligand-binding affinity of the receptor. The FcR γ chain contains a conserved ITAM signalling motif in its cytoplasmic region, consisting of two YxxL boxes separated by seven amino acids. Upon FcγRIa cross-linking this ITAM is phosphorylated on both tyrosines by Src and Syk protein tyrosine family kinases, initiating signalling events. **See also**: Cytokines; Interferons; Myeloid

Table 1 General characteristics of human Fc receptors

	FcγR			*FcεR*							
	FcγRI	*FcγRII*	*FcγRIII*	*FcεRI*	*FcεRII*	*FcαRI*	*FcαμR*	*FcμR*	*FcδR*	*Poly-Ig*	*FcRn*
CD	CD64	CD32	CD16		CD23	CD89					
Genomic location	1q21.1	1q23-24	1q23-24	1q23	19q	19q13.4	1q32.3			1q31-41	19q13
Molecular weight	72 kDa	40 kDa	50–80 kDa	45–65 kDa	mFc εRII: 45 kDasFc εRII: 25 kDa	55–100 kDa	70 kDa	58–60 kDa			46 + 14 kDa
Genes	3	3	2	1	1	1	1			1	2
Isoforms	Ia1	IIa, sIIa2 IIb1, IIb2, IIc	IIIa, IIIb	Ia	IIa, IIb	Ia					
Ligand	IgG	IgG	IgG concanavalin A, *Escherichia coli*	IgE	CR2, IgE CR3	IgA, SIgA	IgM and IgA polymer	IgM	IgD	IgM and IgA polymer	IgG
Affinity ($L\,mol^{-1}$)	10^8–10^9	$<10^7$	IIIa: $\sim 3\times10^7$ IIIb: $<10^7$	10^9–10^{10}	10^6	5×10^7	IgM: 3×10^9 IgA: 3×10^8				pH dependent
Isotype specificity	3 > 1 ≫ 4	IIa-R131: 3 > 1 IIa-H131: 3 > 1–2 IIb1: 3 > 1 > 4	1–3[a]			1–2					
Accessory subunits	γ	γ	NK cells: ζ/γ Other cells: γ	Mast cells, basophils: β/γ chains Monocytes/ M ϕ: γ chain		γ		NK cells: ζ/γ			β2m

Notes: mFcεRII, membrane-expressed FcεRII; sFcεRII, soluble FcεRII and SIgA, secretory IgA. Polymorphisms of FcγRIII influence relative affinity for IgG subclasses.
[a]FcγRIIIa-158Valine has higher affinity for IgG1 and 3 than FcγRIIIa-158Phenylalamine and binds IgG4. FcγRIIIb has higher affinity for IgG1 and IgG3 than FcγRIIIb-NA2.

Table 2 Cell distribution and function of human Fc receptors

	Expression	Modulation	Functions
FcγRI	Monocytes, macrophages, CD34+ myeloid progenitor cells, dendritic cells, eosinophils, (PMN: IFNγ, G-CSF).	Upregulation: G-CSF, IFNγ, IL-10 Downregulation: IL-4, IL-13	Internalization, antigen presentation, superoxide generation, ADCC, phagocytosis, cytokine production
FcγRII	IIa: monocytes, macrophages, PMN, eosinophils, basophils, Langerhans cells, platelets, placental endothelial cells, T cells, subpopulation	Downregulation: IL-4	IIa: internalization, ADCC, phagocytosis, cytokine production, respiratory burst
	IIb: B cells, basophils, macrophages, eosinophils, dendritic cells, Langerhans cells IIc: NK cells		IIb1/IIb2: downmodulation of B cells, mast cells, macrophages IIb2: internalization
FcγRIII	IIIa: Macrophages, NK cells, (monocytes, subpopulation: TGFβ), subpopulation of T cells, Langerhans cells	Upregulation: TGFβ	IIIa: phagocytosis, ADCC, superoxide generation, cytokine production, induction of adhesion, apoptosis
	IIIb: PMN	Downregulation: IL-4	IIIb: superoxide generation, ADCC, degranulation
FcεRI	Mast cells, basophils, Langerhans cells, eosinophils, platelets, monocytes, dendritic cells	Upregulation: IgE	Release inflammatory mediators, anaphylaxis, fine-tuning of specific immune responses
FcεRII	IIa: B cells, follicular dendritic cells IIb: CD5+ B cells, T cells, eosinophils, mast cells, platelets, monocytes, Langerhans cells	Upregulation: IL-4, IL-13; IIa: downregulation by IFNα/γ; IIb: upregulation by IFNα/γ, TNFα downregulates FcεRII but upregulates sFcεRII; IIb: expression depends on IL-4	B-cell proliferation and differentiation, regulation of IgE production, antigen presentation, cell adhesion
FcαRI	Macrophages, monocytes, PMN, eosinophils	Upregulation: TNFα, IL-8, IL-1β, GM-CSF, LPS Downregulation: TGFβ	Phagocytosis, ADCC, oxidative burst, cytokine production, antigen presentation
FcαμR	FDCs, B cells, macrophages	Unknown	FDC: trapping of IgA and IgM immune complexes B cells, macrophages: endocytosis of IgM immune complexes
	IIb: CD5+ B cells, T cells, eosinophils, mast cells, platelets, monocytes, Langerhans cells	Downregulation: IFNα/γ (FcεRIIa), TNFα (mFcεRII3)	
FcμR	T cells, subpopulation, activated B cells, NK cells	Upregulation (B cells): IgM, PMA Downregulation (T cells): IgM	B-cell activation, downregulation of NK cell function
FcδR	T cells	Upregulation: IgD, IL-2, IL-4, IFNγ	Helper function in antibody production
Poly-Ig	Epithelial cells	Upregulation: IFNγ, TNF, IL-1, IL-4, diverse hormones, microbial factors	Transcytosis of IgA and IgM to mucosal surfaces
FcRn	Epithelial cells, placental syncytiotrophoblasts, endothelial cells		IgG transport to fetus, extending serum IgG half-life, phagocytosis

Cell Differentiation; Neutrophils; Signal Transduction: Overview

Owing to its high affinity for IgG, FcγRIa may be ligand-saturated under serum conditions. A role of FcγRIa for facilitation of antigen presentation has been proposed (Van Vugt *et al*., 1999). Furthermore, recent data suggests an important role for human FcγRI in antibody-mediated malaria therapies (McIntosh *et al*., 2007). Expression of FcγRIa increases in a variety of inflammatory and pro-inflammatory conditions; e.g. human immunodeficiency

virus (HIV) infection, sepsis and rheumatoid arthritis, indicating a role for this molecule under such conditions. Analysis of FcγRI-deficient mice revealed a role for FcγRI in hypersensitivity responses, arthritis, protection against bacterial infection and tumour killing.

Furthermore, because of both its unique phagocyte-restricted expression pattern and its potent capacity to trigger immune functions, FcγRIa has been proposed as an attractive target for immunotherapy (Thepen *et al*., 2000). **See also**: AIDS: Clinical Manifestations; Human Immunodeficiency Viruses (HIV); Rheumatoid Arthritis

FcγRII

Three genes have been identified for FcγRII (IIA, IIB and IIC) (**Figure 1**). Six transcripts, resulting from alternative splicing, have been documented, all encoding true isoforms. These molecules are conserved in their extracellular and transmembrane regions, but differ markedly in their cytoplasmic domains.

FcγRII molecules interact only with complexed or polymeric IgG, and family members are expressed on most types of blood leucocytes (**Table 2**). FcγRIIa crosslinking triggers activation, whereas FcγRIIb initiates inhibitory signals.

A genetic polymorphism in FcγRIIa at amino acid position 131 within the extracellular region (either histidine or arginine), results in different affinities for IgG isotypes (**Table 1**).

FcγRIIa crosslinking triggers functions varying from internalization, phagocytosis, cytokine production, antigen presentation, superoxide generation, to antibody-dependent cell-mediated cytotoxicity (ADCC). FcγRIIa is unique among leucocyte FcRs in that it contains a noncanonical ITAM directly in its cytoplasmic region. FcγRIIa can therefore transmit a phagocytic signal in the absence of other FcR subunits, and receptor crosslinking results in tyrosine phosphorylation of the α chain. FcγRIIa can, in addition, associate with the FcR γ chain on monocytes and macrophages. Both the α chain and the γ chain can activate signalling pathways, involving a variety of nonreceptor kinases (**Table 2**). Signalling via FcγRIIa has furthermore been shown to involve membrane molecules such as CD45, CD148 and the integrin complement receptor 3 (CR3) (CD11b/CD18). In eosinophils, granulocyte–macrophage CSF (GM-CSF) stimulation leads to an activated FcγRII with increased binding affinity. **See also**: Antibody-dependent Cell-mediated Cytotoxicity (ADCC); Immune Response: Regulation

FcγRIIa-His131 represents the sole leucocyte FcR capable of interaction with IgG2. The capacity to interact with this antibody subclass therefore depends on the individual's FcγRIIa genotype, and polymorphisms of FcγRIIa are now considered to be heritable risk factors for both infectious diseases (such as meningitidis and periodontitis) and autoimmune diseases (such as systemic lupus erythrematosus, SLE) (Van de Velde *et al*., 2006). Certain studies have shown an association of polymorphisms FcγRIIa-131-H with antibody therapy, whereas in other studies this was not confirmed. **See also**: Systemic Lupus Erythematosus

The FcγRIIb1 and IIb2 isoforms are unique in that they bear an ITIM within their cytoplasmic tails. An ITIM is a highly conserved (13 amino acid) motif containing one YxxL box, and FcγRIIb may inhibit cell activation triggered by receptors that signal via ITAM (B-cell receptor (BCR), FcεRI or FcγRIIa). Inhibition requires ITIM phosphorylation, and involves activation of the phosphatases SHP-1 (B cells), SHIP (mast cells and B cells) and the CD19 molecule on B cells. Furthermore, the FcγRIIb2 isoform proved effective in internalization of small immune complexes in contrast to FcγRIIb1 (Tarasenko *et al*., 2007).

A polymorphism of FcγRIIb, FcγRIIbT_{232}, encodes a single amino acid substitution (from isoleucine to threonine) at position 232 within the transmembrane domain. This polymorphism leads to exclusion of FcγRIIb from specialized membrane domains, called lipid rafts, and is thereby unable to inhibit activating FcRs. Its presence is strongly associated with SLE and with inflammatory diseases, whereas it is more often found in regions where malaria is endemic and therefore increased effector responses are favourable (Tarasenko *et al*., 2007).

The third gene, FcγRIIc, probably results from an unequal crossover event between genes IIa and IIb, and encodes a protein which resembles FcγRIIa intracellularly and FcγRIIb extracellularly. The majority of people (91%) do not express FcγRIIc due to a single nucleotide polymorphism (SNP) in intron 3 that results in a stop codon. The remaining 9% have a functional receptor, bearing its own signalling motif that is able to mediate ADCC. The presence of a functional FcγRIIc variant is associated with idiopathic thrombocytopenic purpura (ITP), due to disruption of balanced immunity (Breunis *et al*., 2008).

FcγRIII

This receptor class is encoded by two genes FcγRIIIA and FcγRIIIB (**Figure 1**). FcγRIIIa has two extracellular Ig-like domains, and a 25-amino acid cytoplasmic tail, with medium affinity for IgG ($K_a = 3 \times 10^7\ \mathrm{L\,mol^{-1}}$). Expression and function of this receptor is dependent upon association with the FcR γ chain on monocytes and macrophages, or with γ or ζ chains on natural killer (NK) cells.

Expression of FcγRIIIA is upregulated by transforming growth factor β (TGFβ), and downregulated by IL-4. The ligand-binding chain of FcγRIIIA has recently been reported to be active in initiating calcium fluxes. Biological function of this receptor, however, is critically dependent on either the ζ and/or γ accessory chains (Ravetch and Bolland, 2001). **See also**: Transforming Growth Factor beta (TGFβ)

FcγRIIIa has been shown to be polymorphic and two allotypes have been defined that differ by a single amino acid at position 158 (either valine or phenylalanine). The allotypes exhibit different capacities to bind IgG1, IgG3 and IgG4, and preliminary evidence has been provided for

skewing of the FcγRIIIa polymorphism in SLE patients (Van Sorge *et al*., 2003).

The FcγRIIIa-V158 variant of this polymorphism is associated with better outcome in monoclonal antibody treatment of non-Hodgkin lymphoma. Recently, copy number variation (CNV) has been described in FcγRIIIA gene (Breunis *et al*., 2008).

The FcγRIIIb subclass exhibits low affinity for IgG, and is expressed exclusively on PMNs. Two allotypes and one gene duplication exist that are designated FcγRIIIb-NA1, IIIb-NA2 and IIIb-SH, respectively. FcγRIIIb has two extracellular Ig-like domains, and is uniquely anchored to the outer leaflet of the lipid bilayer by a glycosylphosphatidylinositol linkage. FcγRIIIb has been suggested to interact with either FcγRIIa, the integrin CR3 (CD11b/CD18), or accessory signalling molecules localized in lipid rafts to confer signalling ability (Vidarsson and Van de Winkel, 1998). FcγRIIIb crosslinking can trigger a variety of activation events including superoxide generation, degranulation and ADCC. FcγRIIIb can be released into serum upon cell activation or apoptosis induction through serine protease cleavage. The level of soluble FcγRIIIb in the circulation reflects the total body mass of neutrophils (Van der Pol and Van de Winkel, 1998).

FcγRIIIb bears the neutrophil antigen (NA) polymorphism, which has been implicated in alloimmune and autoimmune neutropenias and blood transfusion reactions. The FcγRIIIb-NA1 exhibits higher affinity for immune-complexed IgG1 and IgG3 than IIIb-NA2, and IgG1- and IgG3-opsonized particles are more efficiently phagocytosed via the IIIb-NA1 allotype. In addition, it has been shown that the FcγRIIIb allelic polymorphism is of clinical importance for progression of periodontal disease (Van der Pol and Van de Winkel, 1998). Interestingly, low copy numbers of FcγRIIIB has been found to associate with systemic – but not organ-specific – autoimmune diseases in humans and rats, possibly owing to decreased clearance of apoptotic cells. **See also**: Blood Groups and Transfusion Science; Neutropenia

FcαR

Receptors for the Fc domain of IgA (FcαR) are members of the Ig supergene family. Genetic analyses suggest these molecules to be more distantly related to FcγR and FcεR. One class of IgA receptors has been characterized in humans and is designated FcαRI (CD89) (Monteiro and van de Winkel, 2003).

FcαRI

Although multiple transcripts have been described, only one FcαRI transcript specifying two extracellular Ig-like domains, a transmembrane domain and a short cytoplasmic tail, has been identified on myeloid cells (**Figure 1**). FcαRI is expressed on monocytes/macrophages, mesangial cells, neutrophils and eosinophils (**Table 2**). The receptor binds both IgA1 and IgA2, and secretory IgA (SIgA), with medium affinity ($K_a = 5 \times 10^7\ L\ mol^{-1}$) (**Table 1**). Its expression can be upregulated by tumour necrosis factor α (TNFα), IL-8, IL-1β and lipopolysaccharide (LPS), and downregulated by TGFβ. Addition of GM-CSF, IL-3 or IL-5 can rapidly increase ligand-binding capacity without effects on receptor expression levels, known as inside-out regulation. (De)phosphorylation of the intracellular Serine 263 of the FcαRI α chain seems to be crucial in this process (Bracke *et al*., 2001).

FcαRI exists as a hetero-oligomeric receptor complex containing the FcR γ chain homodimer. The ligand-binding chain of FcαRI is devoid of recognized signalling motifs, and requires the FcR γ chain for signal transduction. A charge-based interaction underlies the assembly of the functional FcαRI/γ chain complex. A positively charged arginine residue at position 209 in the transmembrane domain of FcαRI was shown to be essential for interaction with a negatively charged aspartic acid in the transmembrane region of the FcR γ chain. In addition, the orientation of FcαRI α chain to the γ chain homodimer was also found to be important suggesting the involvement of additional amino acids in the interaction.

Triggering of FcαRI induces phosphorylation of cellular proteins including Src and Syk family protein tyrosine kinases, and increases in intracellular free Ca^{2+}, resulting in phagocytosis, ADCC, superoxide generation, cytokine production, antigen presentation and inflammatory mediator release (**Tables 2**). **See also**: Protein Kinases

Conversely, in the absence of sustained aggregation by IgA-immune complexes FcαRI itself may act as an inhibitory modulator acting on Fcγ and Fcε receptor activation or induce apoptosis. IgA Fc receptor I signals apoptosis through the FcR γ ITAM and affects tumour growth.

Interestingly, FcαR is an effective cytotoxic trigger molecule, as shown by efficient ADCC of various tumour targets. The FcαRI molecule is now considered an excellent target for immunotherapies of malignant and infectious diseases. Furthermore, FcαRI is thought to play an important role in the removal of IgA immune complexes, and defective FcαRI-mediated endocytosis has been postulated to contribute to the pathogenesis of IgA nephropathy, alcoholic liver cirrhosis and the acquired immune deficiency syndrome (AIDS) (Monteiro and van de Winkel, 2003). **See also**: Tumours: Immunotherapy

FcεR

Two classes of receptors for the Fc domain of IgE (FcεR) have been described: FcεRI and FcεRII (CD23). FcεRI belongs to the Ig supergene family, whereas FcεRII is a member of the lectin family (**Figure 1**).

FcεRI

FcεRI is expressed on mast cells, basophils, Langerhans cells, eosinophils, platelets, monocytes and dendritic

cells and binds IgE with high affinity ($K_a > 10^{10}\,L\,mol^{-1}$) (**Table 1**). Owing to the high ligand affinity, FcεRI stably associates with monomeric IgE on the mast cell surface, where it readily responds to foreign allergens. The molecule is composed of two extracellular Ig-like domains, a transmembrane domain and a cytoplasmic tail. On mast cells and basophils the ligand-binding α chain of FcεRI is associated with both the FcR β and γ chains, whereas on monocytes and macrophages an FcεRI/γ chain complex is expressed (**Table 1**). **See also**: Basophils; Macrophages; Mast Cells

Activation of FcεRI on mast cells and basophils results in release of inflammatory mediators, including preformed granular mediators, lipid mediators and cytokines, and is considered important for host defence against invading parasites (**Table 2**). Upon receptor engagement, phosphorylation of the FcR β and γ chains is essential for downstream signalling. Phosphorylated ITAM tyrosine of the γ chain specifically recruits Syk family protein tyrosine kinases, whereas the β subunit preferentially associates with Lyn. FcεRI β subunit functions as a signalling amplifier via enhancing FcR γ chain tyrosine phosphorylation. Exposure of mast cells to IgE augments surface expression of FcεRI. Interestingly, already the binding of monoclonal IgE without ligand induces a variety of signals such as survival, granule release and *de novo* synthesis of inflammatory cytokines. FcεRI signalling is under negative regulation by CD31, CD81 and FcγRIIb. FcγRIIb-mediated downregulation of FcεRI requires coaggregation, and recruitment of the phosphatases SHIP, SHP-1 and SHP-2.

IgE- and antigen-specific mast cell activation and mediator production is thought to be critical in allergic disorders, associated with exaggerated production of IgE antibodies to environmental allergens. The importance of FcεRI in allergy and hypersensitivity is indicated by the protection from these diseases in mice lacking FcεRI and the enhanced reaction in mice deficient for negative regulatory molecules of FcεRI, such as FcγRIIb or SHIP. The fact that IgE upregulates FcεRI expression may have potential for modulation of effector cell functions in IgE-dependent allergic reactions for immunological responses to parasites.

FcεRII

FcεRII (CD23) is a low-affinity receptor for IgE ($K_a < 10^7\,L\,mol^{-1}$). Besides binding IgE, FcεRII also binds to CD21, CD11b/CD18 and CD11c/CD18 on monocytes. FcεRII consists of a *C*-terminal extracellular domain, a transmembrane domain, and a cytoplasmic tail. Unlike the IgG, IgA and high-affinity IgE Fc receptors, FcεRII has no Ig-like domains and represents a member of the calcium-dependent animal lectin family. Two isoforms have been described, which differ in their 5′ untranslated region and in the first six amino acids of the cytoplasmic tail that have different cellular distribution (**Table 2**).

There is also a soluble FcεRII described (sFcεRII) that can be released from cells into serum. **See also**: B Lymphocytes; Follicular Dendritic Cells (B Lymphocyte Stimulating)

Expression of FcεRII and levels of secreted sFcεRII are under complex regulation of cytokines, mainly IL-4, IL-13, IFNs and TNF α (**Table 2**). **See also**: Interleukins

FcεRII has been proposed to function in B-cell proliferation, differentiation, regulation of IgE production, antigen presentation and cell adhesion. On monocytes and macrophages, FcεRII mediates phagocytosis and IgE-dependent cytotoxicity.

FcμR and FcδR

Receptors for IgM (FcμR) and IgD (FcδR) have been identified, although structure–function analyses are still limited.

FcαμR

FcαμR is a functional Fc receptor that binds both IgM and IgA polymers but not their monomeric forms. It is expressed as a 125-kDa homodimer and is structurally more related to the polymeric Ig receptor (pIgR) than to other FcRs (**Figure 1**). The expression pattern of FcαμR in humans is more restricted than in mice that have no FcαR. It is predominantly expressed on follicular dendritic cells (FDCs), suggesting a role in trapping of IgM and IgA immune complexes and in presenting intact antigens to B cells. That human mesangial cell lines express FcαμR transcripts together with the abundant expression of FcαμR messenger ribonucleic acid (mRNA) found in the kidney suggests that FcαμR might be involved in IgA nephropathy (Shibuya and Honda, 2006).

FcμR

Functional FcμRs that bind the IgM Fc fragment have been reported on subpopulations of B, T and NK cells. FcμR is expressed on activated B cells, as a glycosylphosphatidylinositol-linked receptor. FcμR represents an activation antigen throughout pre-B and B-cell stages in differentiation, and expression is increased after exposure of B cells to IgM or the phorbolester phorbol myristate acetate (PMA). The precise role of FcμR on B cells is not known but a potential role in B-cell responses by its ability to bind both secreted IgM molecules and neighbouring membrane-bound IgM molecules has been proposed.

FcδR

Immunoglobulin receptors for IgD (FcδR) can bind IgD via both the Fd and Fc regions. Receptors for IgD have been documented on subpopulations of T cells, and their expression is under regulation by cytokines. FcδRs are not thoroughly investigated, but they may function as lectins and seem to require calcium for binding IgD. FcδRs are proposed to play a role in T-cell helper responses for antibody production. **See also**: Lectins

Polymeric Ig receptor

The pIgR is expressed at the basolateral surface of secretory epithelial cells and ensures efficient secretion of polymeric IgA (pIgA) and IgM (pIgM) at mucosal surfaces. After binding its ligand at the basolateral surface, pIgR transcytoses to the apical surface, where its extracellular, ligand-binding domain is cleaved off and released as the secretory component (SC) bound to pIgA forming SIgA. The role of SC in SIgA is mainly stabilizing but free SC released from unloaded pIgR has direct antimicrobial function. Mice deficient for pIgR lack mucosal IgA and have reduced protection to influenza infections but not to bacterial infections (Kaetzel, 2005).

FcRn

The neonatal Fc receptor for IgG (FcRn) transfers antibodies from mother to her fetus. FcRn uniquely binds IgG in a pH-dependent manner, not on physiological pH (7.4) but only in acidic environment of endocytic vacuoles. It is classically expressed on epithelial cells, placental syncytiotrophoblasts and endothelial cells, but recently expression was shown in leucocytes as well. Upon internalization of IgG into endosomes, these vesicles are gradually acidified thereby allowing IgG to bind to FcRn present in this compartment. Subsequent fusion of the vesicle with membranes at the fetal side of the syncytiotrophoblasts, results in dissociation of IgG at local physiological pH (Roopenian and Akilesh, 2007). FcRn plays a crucial role in prolonging the half-life of serum IgG antibodies by recycling. In addition, recent data show an additional role for FcRn in enhancing phagocytosis (Vidarsson *et al*., 2006).

Summary and Future Directions

Over the last decade, knowledge about FcR structure and function has increased dramatically. The function of each FcR is now known to be determined by the specificity of its ligand-binding α chain, a family of accessory subunits and several key intracellular signalling molecules. The cell type, cytokine milieu and communication with other FcRs or other membrane molecules have decisive effects on Fc receptor-mediated responses. Since Fc receptors are crucial in the mechanism of action of therapeutic antibodies, current efforts are aimed at modulating antibody interaction with activating or inhibiting FcγRs or with FcRn to change its serum half-life. In the future, replacing the mouse FcRs with its human counterpart will provide a valuable platform for *in vivo* testing of therapeutic antibodies.

References

Beekman JM, Bakema JE, van de Winkel JG and Leusen JH (2004) Direct interaction between FcgammaRI (CD64) and periplakin controls receptor endocytosis and ligand binding capacity. *Proceedings of the National Academy of Sciences of the USA* **101**(28): 10392–10397.

Bracke M, Lammers JW, Coffer PJ and Koenderman L (2001) Cytokine-induced inside-out activation of FcalphaR (CD89) is mediated by a single serine residue (S263) in the intracellular domain of the receptor. *Blood* **97**(11): 3478–3483.

Breunis WB, van Mirre E, Bruin M *et al*. (2008) Copy number variation of the activating FCGR2C gene predisposes to idiopathic thrombocytopenic purpura. *Blood* **111**(3): 1029–1038.

Kaetzel C (2005) The polymeric immunoglobulin receptor: bridging innate and adaptive immune responses at mucosal surfaces. *Immunological Reviews* **206**: 83–99.

McIntosh RS, Shi J, Jennings RM *et al*. (2007) The importance of human FcgammaRI in mediating protection to malaria. *PLoS Pathogens* **3**(5): e72.

Monteiro RC and van de Winkel JG (2003) IgA Fc receptors. *Annual Review of Immunology* **21**: 177–204.

Nimmerjahn F and Ravetch JV (2007) Fc-receptors as regulators of immunity. *Advances in Immunology* **96**: 179–204.

Ravetch JV and Bolland S (2001) IgG Fc receptors. *Annual Reviews in Immunology* **19**: 275–290.

Roopenian DC and Akilesh S (2007) FcRn: the neonatal Fc receptor comes of age. *Nature Reviews. Immunology* **7**(9): 715–725.

Shibuya A and Honda S (2006) Molecular and functional characteristics of the Fcalpha/muR, a novel Fc receptor for IgM and IgA. *Springer Seminars in Immunopathology* **28**(4): 377–382.

Tarasenko T, Dean JA and Bolland S (2007) FcgammaRIIB as a modulator of autoimmune disease susceptibility. *Autoimmunity*. **40**(6): 409–417.

Thepen T, van Vuuren AJ, Kiekens RC *et al*. (2000) Resolution of cutaneous inflammation after local elimination of macrophages. *Nature Biotechnology* **18**(1): 48–51.

Van de Velde NC, Mottram PL and Hogarth PM (2006) FcgammaRII and multi-system autoimmune disease. *Springer Seminars in Immunopathology* **28**(4): 329–338.

Van der Pol W-L and Van de Winkel JGJ (1998) IgG receptor polymorphisms: risk factors for disease. *Immunogenetics* **48**: 222–232.

Van Sorge NM, van der Poll WL and van de Winkel JG (2003) Fcgamma polymorphisms: implications for function, disease susceptibility and therapy. *Tissue Antigens* **61**(3): 189–202.

Vidarsson G, Stemerding AM, Stapleton NM *et al*. (2006) FcRn: an IgG receptor on phagocytes with a novel role in phagocytosis. *Blood* **108**(10): 3573–3579.

Vidarsson G and Van de Winkel JGJ (1998) Fc receptor and complement receptor mediated phagocytosis in host defence. *Current Opinion in Infectious Diseases* **11**: 271–278.

van Vugt MJ, Kleijmeer MJ, Keler T *et al*. (1999) The FcgammaRIa (CD64) ligand binding chain triggers major histocompatibility complex class II antigen presentation independently of its associated FcR gamma-chain. *Blood* **94**(2): 808–817.

Further Reading

van Egmond M (2007) FcαRI: a case of multiple personality disorder? *Blood* **109**: 1–2.

Honda Z (2006) Fcepsilon- and Fcgamma-receptor signalling in disease. *Springer Seminars in Immunopathology* **28**(4): 365–375.