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Fc Receptors in Immune Responses

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Introduction

Adaptive immune responses generate a variety of effector cells and molecules. Cells include T cells, endowed with various effector functions, and capable of secreting numerous cytokines upon cognate interactions with antigen-presenting cells. Molecules include antibodies that recognize specifically the antigen against which they were raised, and diffuse in the whole body through the bloodstream. At least quantitatively, antibodies are the major effector molecules of adaptive immunity.

Antibodies, however, have no biological activity by themselves. Their Fab portions can bind to antigens, but except in rare instances, binding to antigen has little or no biological consequences. Some therapeutic antibodies raised against receptors (Li et al., 2005) or ligands (Ellis and Hicklin, 2008) can prevent ligand–receptor interactions and some antireceptor antibodies can mimic agonists (Shan et al., 2000). It was recently shown, however, that to 'neutralize' bacterial toxins (Joller et al., 2010) or viruses (Mallery et al., 2010), antibodies require that their Fc portion binds to cellular receptors that transport immune complexes to intracellular compartments where they are degraded. For antibodies to affect antigens, they indeed not only need to bind to antigens through their Fab portions, but also to interact through their Fc portion with effector systems. These include soluble molecules such as components of the enzymatic cascade of Complement, and cells that express receptors for the Fc portion of antibodies (FcR).

The many cells of the myeloid lineage can exert a variety of biological activities without requiring to proliferate and/or to differentiate. As they are equipped with pattern-recognition receptors which enable them to interact with structures borne or secreted by microorganisms, myeloid cells are the effector cells of innate immunity. Unlike lymphoid cells, they have no antigen receptors. Most of them, however, express FcR. When binding to FcR, antibodies provide these cells, with B-cell receptor-like immunoreceptors and a bona fide immunological specificity (Daëron, 1997). As these antibodies, polyclonal in nature, have different specificities, one FcR-expressing cell can respond specifically to a wide repertoire of different antigens. When binding to FcR, specific antibodies thus enroll effector cells of innate immunity in adaptive immunity. It follows that both innate and adaptive immunity use the same effector cells.

FcR are indeed immunoreceptors of the third type. They 'recognize' neither native antigens as B-cell receptors (BCR) do, nor the association of antigen-derived peptides with major histocompatibility complex molecules, as T-cell receptors (TCR) do, but antigen–antibody complexes. Antibodies function as extracellular adapter molecules when their Fab and Fc portions bind simultaneously to specific epitopes on antigen and to FcR on cell membrane, respectively. BCR, TCR, and FcR are receptors for the three forms under which any given antigen can interact with and deliver signals to cells of the immune system. And, like other immunoreceptors, when engaged by specific ligands, FcR generate intracellular signals which modulate the biological activities of cells which express them. Some FcR activate, whereas others inhibit cellular responses.

Biological Properties of Fc Receptors

Structure of Fc Receptors

There are FcR for IgA (FcαR), IgG (FcγR and FcRn), and IgE (FcεR). There are also FcR for polymeric IgM and IgA (polyIgR). Many FcR names include a Roman number and a capital letter. Roman numbers refer to the binding affinity for immunoglobulins. FcRI and IV are high-affinity receptors; FcRII and III are low-affinity receptors. Capital letters refer to the genes that encode FcR (e.g., FcγRIIA, B, and C, and FcγRIIIA and B are encoded by three FcγRII genes and two FcγRIII genes, respectively, in humans). Human FcR are often referred to using the CD nomenclature. CD16 designate FcγRIII, CD32 FcγRII, CD16 FcγRI, CD23 FcεRII, and CD89 FcαRI (**Figure 1**).

Most FcR belong to the immunoglobulin superfamily (IgSF). They consist of an immunoglobulin-binding polypeptide made of 2–5 extracellular domains with a secondary structure that is typical of IgSF molecules, a hydrophobic transmembrane domain, and a nonstructured intracytoplasmic domain of variable length. Few FcR (FcγRIIA in humans; FcγRIIB and polyIgR in mice and humans) are single-chain receptors. Other FcR are multichain receptors composed of one immunoglobulin-binding subunit (FcRα) and one (FcRγ) or two (FcRγ and FcRβ) common subunits. FcRγ is a homodimer made of two disulfide bond-linked polypeptides highly conserved in mice and humans. Each polypeptide consists of a 5-amino-acid extracellular domain, a transmembrane domain, and a 42-amino-acid intracytoplasmic domain. FcRγ is shared by all multichain receptors. FcRβ is a 4-transmembrane domain polypetide that associates with multichain FcR expressed by mast cells and basophils. FcRn is a unique MHC class I–like molecule that binds the Fc portion of IgG instead of peptides (Burmeister et al., 1994).

Multichain FcR must associate with at least one specific subunit in order to be expressed. Most need FcRγ in order to reach the plasma membrane. Their intracytoplasmic domain indeed contains a retention site that sequesters the polypetide in the endoplasmic reticulum, unless it associates with FcRγ (Letourneur et al., 1995; Lobell et al., 1993). The expression of these receptors therefore depends on the tissue distribution of FcRγ, and FcRγ-deficient mice have no activating FcR (Takai et al., 1994). Mouse FcεRI, but not human FcεRI, also need to associate with FcRβ (Kinet, 1999). As FcRβ is expressed by mast cells and basophils only in both species, the expression of FcεRI is restricted to these cells in mice (Kinet et al., 1988), but not in humans (Gounni et al., 1994; Joseph et al., 1997; Gounni et al., 2001). Noticeably, mouse FcγRIIIA, the expression of which requires FcRγ but not FcRβ, associate with both subunits in mast cells (Kurosaki et al., 1992). FcRn do not associate with FcRγ but with β-2 microglobulin,

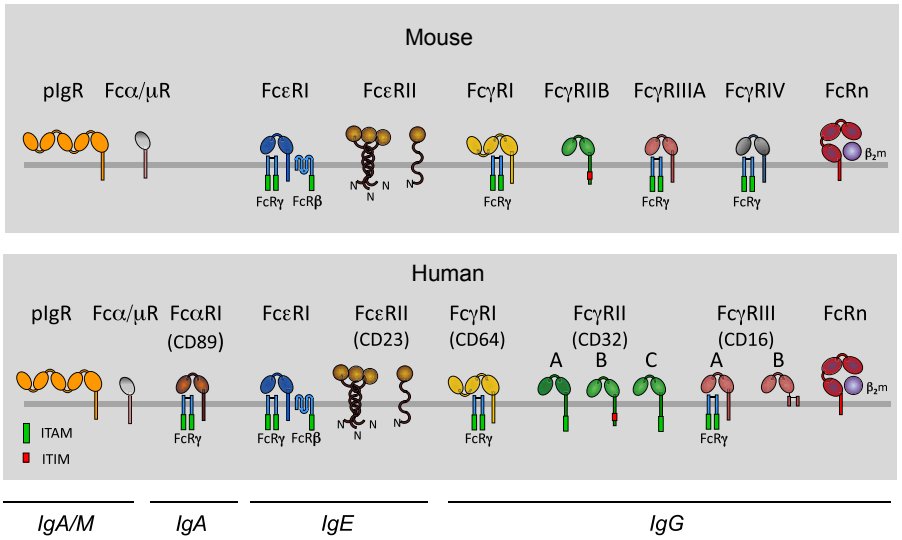

Figure 1 Murine and human receptors for the Fc portion of IgE, IgA, IgM, and IgG. This figure schematizes receptors for IgE, IgA, and IgG expressed by mouse and human cells of the hematopoietic lineage. Horizontal gray bars represent plasma membranes. Oval symbols represent immunoglobulin superfamily domains that constitute the extracellular domains of Fc receptors. Green boxes represent ITAM. Red boxes represent ITIM.

like other MHC-I molecules and this association is mandatory: β-2 microglobulin-deficient mice do not express FcRn.

One FcR (FcεRII) is a C-type lectin. Binding, however, does not involve the interaction of sugar residues in the Fc portion of IgE with the extracellular lectin domain of FcεRII. The binding affinity of monomeric FcεRII is relatively low. However, FcεRII are expressed as homotrimeric molecules which can bind IgE immune complexes with a high avidity.

High- and Low-Affinity Fc Receptors

Antibodies bind to FcR with a variable affinity (Hulett and Hogarth, 1994). The binding of antibodies to FcR is reversible and it obeys the mass action law. The affinity of FcR is characterized by an affinity constant Ka which is the quotient of an association constant (kon) divided by a dissociation constant (koff) (Figure 2). A proportion of high-affinity FcR, which can bind monomeric immunoglobulins in the absence of antigen, are occupied *in vivo* whereas low-affinity FcR, which can bind antibodies as multivalent immune complexes only, are not in spite of the high concentration of circulating immunoglobulins. Occupied high-affinity FcR, however, can be freed as bound antibodies dissociate. The dissociation constant therefore critically determines the availability of high-affinity FcR. In contrast, low-affinity FcR are generally available for immune complexes whenever they come close enough.

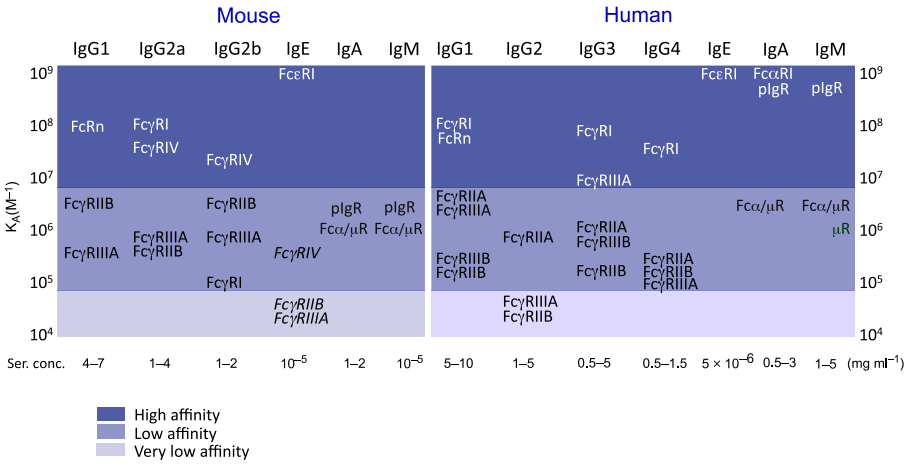

Figure 2 Affinity of mouse and human Fc Receptors for homologous IgE, IgA, and IgG subclasses. Affinity constants were determined by Plasmon resonance analysis (from Dierks et al., 1993; Hibbert et al., 2005; Nimmerjahn, F., Ravetch, J.V., 2005. Divergent immunoglobulin g subclass activity through selective Fc receptor binding. Science 310, 1510–1512; Mancardi, D.A., Iannascoli, B., Hoos, S., England, P., Daëron, M., Bruhns, P., 2008. FcgammaRIV is a mouse IgE receptor that resembles macrophage FcepsilonRI in humans and promotes IgE-induced lung inflammation. J. Clin. Invest. 118, 3738–3750; Bruhns, P., Iannascoli, B., England, P., Mancardi, D.A., Fernandez, N., Jorieux, S., Daëron, M., 2009. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. Blood 113, 3716–3725.). Figures under the table show the plasma concentrations of immunoglobulins of the various isotypes in both species.

High-affinity FcR include IgA (FcαRI, in humans, pIgR in humans and mice), IgE (FcεRI, in humans and mice), and IgG receptors (FcγRI and FcRn, in humans and mice, and FcγRIV, in mice only). Low-affinity FcR include IgE (FcεRII, in humans and mice) and IgG receptors (FcγRII and III, in humans and mice). Humans have three FcγRII (FcγRIIA, B, and C), and two FcγRIII (FcγRIIIA and B) whereas mice have one receptor of each type (FcγRIIB and FcγRIIIA) only. The diversity of human FcγRII and III is further increased by polymorphisms of selected residues in their extracellular domains. These are H_{131}R, in FcγRIIA (Warmerdam et al., 1990), F_{158}V in FcγRIIIA (Ravetch and Perussia, 1989), N_{65}S, A_{78}D, D_{82}N and V_{106}I in FcγRIIIB (Ory et al., 1989). Altogether, 10 FcγR were described in humans. One notices that FcR are not isotype-specific. Antibodies of several isotypes can bind to one FcR and, vice versa, several FcR can bind antibodies of one isotype.

The Ka of mouse and human FcεRI for IgE is 10^9–10^{10} M^{-1} (Kulczycki and Metzger, 1974; Metzger, 2004); those of human and mouse FcγR for human and mouse IgG subclasses, respectively, span from $\pm 10^5$ M^{-1} to 10^8 M^{-1} (**Figure 2**) (Bruhns et al., 2009). Low-affinity interactions were described between IgE and IgG receptors: Mouse IgE can bind to mouse FcγRIIB and FcγRIIIA with a Ka $\pm 2 \times 10^4$ M^{-1} (Takizawa et al., 1992) and to FcγRIV with a Ka $\pm 3 \times 10^5$ M^{-1} (Mancardi et al., 2008). Noticeably, the Ka of FcεRI is especially high not because the association constant is high but because the dissociation constant is extremely low. The result is that, in spite of their extremely low concentration in plasma, IgE remain bound to FcεRI for extended periods of time where they are ready to trigger mast cells and basophil activation when allergen comes. Another point to keep in mind is that even though their affinity is too low for monomeric immunoglobulins to bind, low-affinity FcR bind immune complexes with a high avidity.

The affinity with which IgG binds to FcγR further depends on the glycosylation of their Fc portion (Arnold et al., 2007). Each heavy chain contains a single covalently attached biantennary N-glycan at the highly conserved N_{297} residue in its CH2 domain. Point mutations of this glycosylation site abrogate the ability of IgG antibodies to bind to FcγR. If engineered with such a mutation (e.g., N_{297}Q), aglycosylated antibodies therefore no longer engage FcγR (Veri et al., 2007) and they can be used as blocking-only molecules. Aglycosylated antibodies against specific receptors or ligands can prevent receptor–ligand interactions without engaging FcγR. Noticeably, N_{297} mutations do not affect the binding of IgG to FcRn. Aglycosylated antibodies are therefore similarly protected from degradation as glycosylated antibodies. Other mutations that remove fucose residues from the glycan chain were found to enhance the binding of modified antibodies to FcγRIIIA, irrespectively of the polymorphism that affects this receptor (Natsume et al., 2005; Niwa et al., 2005).

Fc Receptor Signaling

FcR trigger no signal when binding immunoglobulins. They signal when aggregated on the cell membrane by antibodies and plurivalent antigens (Maeyama et al., 1986; Metzger, 1992). Although the result is the same, the sequence of events that lead to receptor aggregation is different for high-affinity and low-affinity FcR. Monomeric antibodies bind first to high-affinity FcR that are aggregated when a plurivalent antigen binds to receptor-bound antibodies. Antibodies bind first to antigen, generating immune complexes that can bind to and, therefore, simultaneously aggregate low-affinity FcR.

FcR can trigger activation signals and/or inhibition signals. The nature of signals primarily depends on molecular motifs contained in the intracytoplasmic domains of FcR or of receptor subunits with which FcR associate. Two such motifs were identified. *Immunoreceptor tyrosine-based activation motifs* (ITAM) consist of two YxxL motifs separated by a 6–8 variable amino acid sequence (Reth, 1989). *Immunoreceptor tyrosine-based inhibition motifs* (ITIM) consist of a single YxxL motif preceded by a loosely conserved often hydrophobic residue at position Y-2 (Vivier and Daëron, 1997). Other motifs, such as di-leucine internalization motif found in mouse FcγRIIB were also identified. Finally, intracytoplasmic motifs of FcRn and pIgR enable these receptors to transcytose IgG and/or IgA trough epithelial cells.

Activating FcR are FcαRI, FcεRI, FcγRI, FcγRIIA, FcγRIIC, FcγRIIIA, and FcγRIV. FcγRIIA and FcγRIIC are the only single-chain receptors that possess an ITAM. FcαRI, FcεRI, FcγRI, FcγRIIIA, and FcγRIV associate with the common FcR subunit FcRγ (Daëron, 1997). FcRγ contains two ITAM (Orloff et al., 1990); FcRβ contains one ITAM. Upon receptor aggregation, ITAM are phosphorylated by src family tyrosine kinases (Pribluda et al., 1994), which initiates the constitution of dynamic intracellular signalosomes (Kent et al., 1994) in which activation signals are dominant over inhibition signals (Malbec et al., 2004).

Inhibitory FcR are the members of one family of low-affinity receptors for IgG, referred to as FcγRIIB (Daëron, 1997; Ravetch and Bolland, 2001). FcγRIIB are encoded by a single gene that generates two (FcγRIIB1 and FcγRIIB2 in humans) or three (FcγRIIB1, FcγRIIB1′, and FcγRIIB2 in mice) isoforms of membrane receptors, by alternative splicing of sequences encoded by the first intracytoplasmic exon (Hibbs et al., 1986; Lewis et al., 1986; Ravetch et al., 1986; Latour et al., 1996). The inhibitory properties of FcγRIIB depend on an ITIM (Daëron et al., 1995), encoded by the third intracytoplasmic exon of the *fcgr2b* gene, present in the intracytoplasmic domain of all murine and human FcγRIIB isoforms. Unlike activating receptors, FcγRIIB trigger no intracellular signal upon aggregation. They trigger negative signals when they are coaggregated with activating receptors by immune complexes (Daëron et al., 1995). Under these conditions, the ITIM of FcγRIIB is phosphorylated by the same src-family tyrosine kinase that phosphorylates ITAM in activating receptors (Malbec et al., 1998). Phosphorylated FcγRIIB recruit inhibitory molecules that are brought into signalosomes. This renders inhibition signals dominant over activation signals (Lesourne et al., 2005; Daëron and Lesourne, 2006).

The aggregation of identical FcR only (homoaggregation) is a rare situation in physiology. Even when cells express one type of FcR only (e.g., FcγRIIB in murine B cells, or FcγRIIIA in murine NK cells), immune complexes can coengage FcR with other immunoreceptors (BCR in B cells, or NKR on NK cells). Several FcR are coaggregated when IgG immune complexes interact with cells that coexpress several FcγR or with

cells that coexpress FcR for several classes of antibodies. Heteroaggregation, i.e., the coaggregation of different types of FcR or the coaggregation of FcR with other immunoreceptors, is actually a rule, rather than an exception, under physiological conditions. Because there are FcR for all antibody classes, because immune complexes contain more than one class of antibody, and because most cells express more than one type of FcR, various combinations of FcR can be engaged at the cell surface to form heteroaggregates with a nonpredetermined composition. FcR can thus generate a variety of signaling complexes, depending on the relative proportion of receptors of the various types that are coengaged by immune complexes.

Biological Responses Induced by Fc Receptors

Activating FcR can trigger a variety of cellular responses. These include the transcytosis of immunoglobulins through polarized cells, the endocytosis of soluble immune complexes, the phagocytosis of particulate complexes, the exocytosis of preformed granular mediators, including vasoactive amines, proteolytic enzymes, and/or cytotoxic molecules, the production of newly formed lipid-derived proinflammatory mediators or the secretion of newly transcribed cytokines, chemokines, and growth factors. Differing from other immunoreceptors, which induce both cell activation and proliferation, FcR induce cell activation only. Activating FcR do not induce unique biological responses, but biological activities that can be induced by other receptors in the same cell.

Biological Functions of Fc Receptors

The nature of biological responses triggered by antibodies via FcR primarily depends on the cell type. They are indeed determined by the functional repertoire of the cell and, therefore, by the tissue distribution of FcR (**Figure 3**).

Tissue Distribution of Fc Receptors

FcR are essentially expressed by myeloid cells of all types. Some are expressed by some lymphoid cells such as B cells, NK cells, and NKT cells. A few nonhematopoietic cells, such as some endothelial cells and some tumor cells, also express FcR. FcRn are expressed by epithelial cells, and by monocytes, macrophages, dendritic cells, and neutrophils (Zhu et al., 2001).

Activating FcR are expressed by myeloid cells and by lymphoid cells with no classical antigen receptor (i.e., NK cells (Perussia et al., 1989) and intraepithelial γ/δ T cells of the intestine (Woodward and Jenkinson, 2001; Deusch et al., 1991; Sandor et al., 1992)). They are not expressed by mature T and B lymphocytes. Lymphocytes therefore do not express more than one type of antigen receptor, and activating FcR do not interfere with lymphocyte activation triggered by clonally expressed antigen receptors. Interestingly, however, activating FcR is transiently expressed by pre-B and pre-T cells, before they express a functional BCR or TCR, respectively (Sandor and Lynch, 1992). Low levels of FcγRIIIA were, however, reported to be expressed on a subset of murine CD8 T cells and to efficiently trigger antibody-dependent cell-mediated cytotoxicity (Dhanji et al., 2005).

Inhibitory FcR (FcγRIIB) are expressed by most myeloid cells and by B lymphocytes. NK cells and T cells, which do not express FcγRIIB, express other inhibitory receptors involved in cell–cell interactions (Long, 1999). FcγRIIB have a more restricted tissue distribution in humans than in mice.

Biological Functions of Fc Receptors

The biological functions of FcR depend on the functional repertoire of individual FcR-expressing cells. All cell types can endocytose, some only can phagocytose, and even less can transcytose. Some cells can expel granules that contain cytotoxic mediators, other cells granules that contain vasoactive or

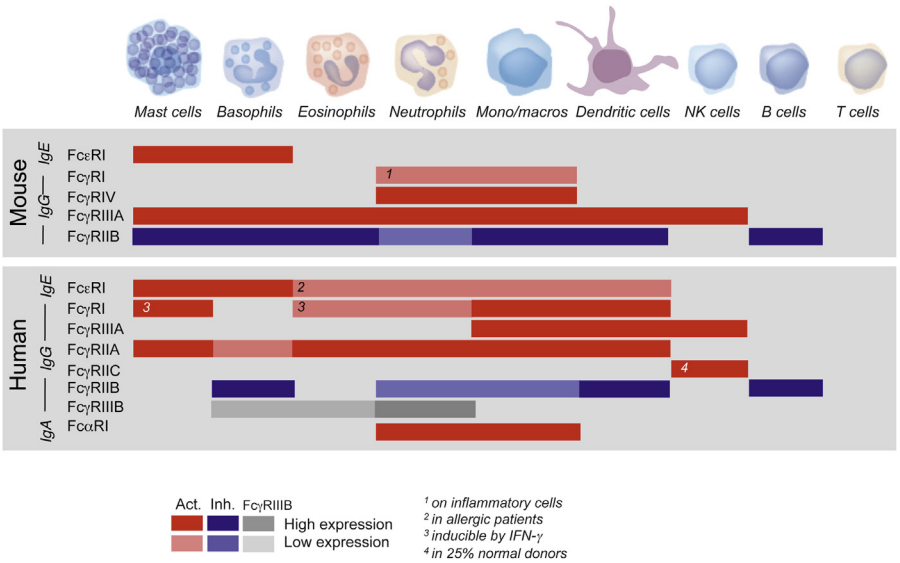

Figure 3 Tissue distribution of mouse and human Fc receptors for IgE, IgA, and IgG. The figure shows the relative expression of activating (red) and inhibitory (blue) IgE, IgG, and IgA receptors by murine and human cells of the hematopoietic lineage. Gray bars show the expression of FcγRIIIB.

proinflammatory mediators. Many cells can synthesize cytokines, chemokines, or growth factors of different types. FcR therefore are involved in a variety of biological functions. These include pathogen clearance, toxin neutralization, antigen capture at the initiation of antigen presentation, cytotoxicity, and inflammatory responses. Biological functions, however, are not ensured by single cells but by cell populations. These consist of a mixture of various cell types that are either present or recruited by chemokines and/or that proliferate in response to growth factors, at the site of the reaction. The composition of such populations depends on time and location. Biological functions in which FcR are involved are therefore a resultant of the biological properties of the many cells that are engaged in the reaction at a given place and at a given time. They are pleiotropic and dynamic.

In Vivo Functions of Fc Receptors

For the above reasons, the roles played by FcR can be poorly understood on the basis of *in vitro* investigations. A variety of *in vivo* models have therefore been developed to investigate FcR in physiology and in pathology. Most were established in mice.

In some models, anti-FcR antibodies are simply injected intravenously. Ideally, anti-FcR antibodies are expected to block the binding site of FcR and prevent them to bind antibodies or immune complexes. Sometimes, however, they can mimic immune complexes and trigger biological responses. In many cases, because they possess an unaltered Fc portion, anti-FcR antibodies engage FcR expressed by neighbor cells with not well-mastered consequences, including the depletion of cells that express targeted FcR.

A whole panoply of FcR-deficient mice have been generated that have permitted major progress in FcR biology. Investigating the roles of individual FcR using such KO mice revealed some unique properties of some FcR. It also revealed the functional redundancy of many FcR. FcRγ-deficient mice, which lack all activating FcR, unraveled the essential roles played by these receptors in normal and pathological antibody-dependent processes. Likewise, FcγRIIB-deficient mice permitted to identify the many biological responses that are negatively regulated by these receptors. Neither FcRγ-deficient mice nor FcγRIIB-deficient mice, however, were devoid of problems due to compensatory reactions occurring during development or to long-term consequences of a regulation loss. Cell-type-specific inducible FcR deficiencies based on the use of the Cre-Lox system have been developed to overcome these problems. If these mice are indeed invaluable for studying mouse biology, they do not enable one to draw conclusion on human biology. Indeed, mouse and human FcR are not identical and many have different tissue distributions.

Several teams have therefore generated humanized transgenic mice that express human FcR. Transgenes in which a human FcR is placed under the control of its own promoter hopefully result in mice that express that FcR with the same tissue distribution as in humans. When such transgenic mice are made in normal mice, the human FcR is expressed in addition to endogenous murine FcR, making it difficult to determine the respective roles of human and murine FcR. Transgenic mice made in FcR-deficient mice are more informative. Unless they are used to assess the effect of passively administered human antibodies in short-term assays, one limitation is that mouse immunoglobulins do not bind identically to human and to murine FcR. To bypass this difficulty, such mice are being constructed using mice in which the locus containing C_H genes have been replaced by the whole or a part of the human homolog. Based on these various mouse models, a whole set of data have accumulated on the roles played by FcR in health and disease.

Fc Receptors in Health and Disease

FcR are critical molecules of the immune system as they mediate most biological activities of antibodies, i.e., of the main effectors of the so-called humoral immunity. As they are ubiquitously expressed, and as antibodies circulate in the bloodstream, FcR are involved in a wide array of biological activities in physiology and pathology. These activities have been essentially investigated in immunized animals. They are likely to concur to homeostasis in physiology, but they are not readily accessible to investigation under these conditions. They were thus more thoroughly documented in pathological conditions. FcR are critical in protective immune responses against pathogens. FcR also contribute to generate pathological processes. They can trigger the release of potentially harmful – in some cases, life-threatening – inflammatory mediators, and induce destructive cytotoxic mechanisms, but (or therefore?) their activating properties are tightly controlled by regulatory mechanisms. As a consequence, immune responses are normally nonpathogenic. For those reasons, FcR can be either valuable tools or exquisite targets in passive immunotherapy.

Fc Receptors in Physiology

Although individuals who lack FcγRI, FcγRIIA, FcγRIIIA, FcεRI, or FcαRI displayed no obvious phenotype (Ceuppens et al., 1988; de Haas et al., 1995), important physiological roles could be assigned to FcR. Some FcR control the amount and the transport of immunoglobulins; others critically control adaptive immune responses.

Regulation of Immunoglobulin Levels

FcRn-deficient mice have abnormally low serum IgG (Israel et al., 1996; Ghetie et al., 1996), in spite of having normal B-cell functions (Roopenian et al., 2003). The reason is that FcRn protect IgG antibodies from degradation (Raghavan et al., 1993; Huber et al., 1993) (Junghans and Anderson, 1996). This phenomenon explains why the half-life of IgG is about 22 days (Spiegelberg and Fishkin, 1972), whereas that of IgM, IgA, and IgE is only 5, 3, and 1 day, respectively (Butler, 1983). Inversely, FcεRII keep the plasma concentration of IgE low. FcεRII-deficient mice have high IgE levels because FcεRII downregulates the production of IgE (Yu et al., 1994).

Transport of Immunoglobulins

Transcytosis of immunoglobulins across polarized cells can be induced by several FcR.

FcRn contribute to the passage of IgG from tissues to blood. FcRn expressed by human proximal kidney cells (Haymann et al., 2000; Kobayashi et al., 2002) may lower the elimination

of IgG through urine by reabsorbing filtered IgG (Lobo et al., 2004). It has been also suggested that FcRn expressed by the mammary gland recycles colostral IgG into blood (Cianga et al., 1999). Mouse hepatocytes (Borvak et al., 1998; Telleman and Junghans, 2000) and human alveolar epithelial cells (Spiekermann et al., 2002) also express FcRn. Fc-coupled proteins administered in the airways reach the blood in an Fc-dependent manner (Low et al., 2005; Bitonti et al., 2004). When expressed in the intestine, FcRn were found both to deliver IgG into the lumen and to absorb immune complexes back (He et al., 2008; Yoshida et al., 2004). During pregnancy, the trans-placental transfer of maternal immunoglobulins to the fetus confers a protection to the fetus whose humoral responses are inefficient (Palmeira et al., 2012). IgG is the only immunoglobulin class that crosses the human placenta and ensures humoral protection (Kim et al., 2009). FcRn expressed by the syncytiotrophoblast and the fetal intestine (Shah et al., 2003; Simister, 2003) are mandatory for maternal IgG to be transferred to fetuses (Simister and Rees, 1985). FcγRIIB expressed by human placental endothelium were believed to contribute to IgG transport. Recent studies in FcγRIIB-deficient mice, however, demonstrated that FcγRIIB are dispensable (Mohanty et al., 2010). Altogether, these reports underline the unique role of FcRn in IgG transport.

IgA and, to a lesser extent, IgM are transcytosed by pIgR. These receptors are mandatory for IgA secretion: pIgR-deficient mice have no detectable IgA in the mucosal compartment (Johansen et al., 1999). Ig transport by pIgR is remarkably efficient, especially through the mammary gland. Mature breast milk is especially rich in IgA and IgM (Brandtzaeg, 1983). The concentration of IgA in human milk can reach 32 g l^{-1} (Kuo et al., 2010). IgA antibodies are thought to protect the intestinal mucosa (Brandtzaeg et al., 1989).

Finally, FcεRII have been shown to transport IgE or IgE-immune complexes through enterocytes (Yang et al., 2000). FcεRII also selectively transport IgE into colostrum (Hine et al., 2010).

Antigen Presentation

Antibodies can function as potent adjuvants. These properties depend on FcR expressed by different cell types involved in different conditions through different mechanisms.

The uptake of antigen–IgG antibody complexes through dendritic cell FcR may indeed contribute to both the cross presentation (Machy et al., 2000) and the MHC class II presentation (Heyman, 1990) of antigen to T cells. The engagement of activating FcγR on dendritic cells, by antigen–antibody complexes, was shown to induce the activation and maturation of dendritic cells (Regnault et al., 1999) and to promote antigen-specific CD8 responses *in vivo* (Schuurhuis et al., 2002). Indeed, dendritic cells that lack activating FcR are unable to trigger MHC class I and class II presentation and thus to initiate an efficient antitumor response (Desai et al., 2007). As it requires that specific IgG antibodies have been produced before, IgG-induced enhancement of immune responses is likely to promote efficient memory responses rather than primary responses.

The enhancing effect of IgG antibodies in antigen presentation is under the control of inhibitory receptors (Wernersson et al., 1999). The coengagement of FcγRIIB, with activating FcR was indeed shown to suppress immune complex-induced dendritic cell maturation and to dampen antigen presentation (Kalergis and Ravetch, 2002). It is therefore thought that, under physiological conditions, FcγRIIB interfere with the processing of antigen internalized as immune complexes via activating FcR, and it was indeed shown that cross-priming by self Ag on dendritic cells can be negatively regulated by FcγRIIB. FcγRIIB may thus have an important role in the maintenance of peripheral T-cell tolerance (Desai et al., 2007).

Noticeably, if FcγRIIB expressed by dendritic cells can inhibit antigen presentation, FcγRIIB expressed by follicular dendritic cells promote T-independent B-cell activation by antigens that display repetitive epitopes (Mond et al., 1995). Follicular dendritic cells can trap immune complexes in secondary lymphoid tissues, and these complexes are periodically arranged like epitopes on T-independent antigens (Szakal et al., 1985). FcγRIIB expressed by follicular dendritic cells can be engaged by the Fc portion of antibodies present in immune complexes and prevent them from binding to B cell FcγRIIB (El Shikh et al., 2006). In the absence of FcγRIIB on follicular dendritic cells, immune complexes can coengage the BCR with FcγRIIB on B cells and inhibit B-cell activation. Antigen in immune complexes bound by follicular dendritic cells are thus far more potent inducers of antibody responses than free antigen. This phenomenon has been demonstrated both *in vitro* (Tew et al., 2001) and *in vivo* (Wu et al., 2008). Supporting this point of view, the blockade of FcγRIIB expressed by follicular dendritic cells inhibited the ability of immune complexes to induce T-independent responses (El Shikh et al., 2009).

IgE antibodies were also found to be potent adjuvants for adaptive immune responses. IgE-induced enhancement was abrogated in FcεRII-deficient mice. IgE immune complexes can indeed efficiently present antigen to T cells when interacting with FcεRII expressed by B cells (Getahun et al., 2005). IgE-induced enhancement affects all classes of antibodies (Westman et al., 1997). Although FcεRII are expressed by both types of cells, B cells but not follicular dendritic cells are involved. This explains that enhancement is antigen specific: only FcεRII-expressing B cells that possess the specific BCR receive cognate T cell help leading to antibody production (Hjelm et al., 2006).

Regulation of Antibody Responses to Particulate Antigens by IgG Antibodies

Unlike immune responses to soluble antigen, immune responses to particulate antigens can be suppressed by minute amounts of IgG antibodies. Suppression can thus affect an ongoing antierythrocyte immune response, whether primary or secondary. This observation has provided the rationale for injecting Rh^- mothers who have given birth to Rh^+ babies with anti-RhD antibodies, as a mean to prevent hemolytic disease of the newborn. Unexpectedly, FcγRIIB-dependent negative regulation appears not to account for feedback regulation by antibodies. This regulation was indeed unaltered not only in FcγRIIB-deficient mice (Heyman et al., 2001), but also in mice lacking all FcγR (Karlsson et al., 1999). Unlike responses to particulate antigens, responses to soluble antigens are markedly enhanced by IgG antibodies (Hjelm et al., 2006).

Fc Receptors in Protective Antibody Responses

The protective role of antibodies is well known in infection. The best evidence is provided by vaccines. Antibodies are indeed responsible for the protective effect of the overwhelming majority of vaccines. The contribution of FcR is however poorly known. Neutralizing antibodies are indeed thought to account for protection and, in most cases, other mechanisms have not been investigated.

Specific antibodies are produced and detected in the bloodstream of humans and mice following bacterial or viral infection (Jancar and Sanchez Crespo, 2005). Antiviral antibodies may profoundly affect viral infection by FcR-dependent mechanisms. It was recently reported that the neutralizing effect of antibodies requires more than binding and depends on the interaction of the Fc portion of antibodies with a unique intracellular FcR named TRIM 21 (Mallery et al., 2010). Classical activating FcR are needed to clear influenza virus (Huber et al., 2001). Noticeably, the engagement of activating FcγR by unrelated immune complexes was found to inhibit the replication of HIV-1 in primary human macrophages (David et al., 2006).

Antibodies also protect from bacterial infection (Hangartner et al., 2006). They are well known to neutralize bacterial toxins. Surprisingly, the neutralization of *Bacillus anthacis* toxin was found to depend on the engagement of FcR (Abboud et al., 2010). FcR are also involved in the clearance of invading bacteria. The phagocytosis of microbes such as *Legionella* (Joller et al., 2010), *Salmonella* (Tobar et al., 2004), or *Toxoplasma* (Joiner et al., 1990) is enhanced in the presence of specific antibodies and FcR. Interestingly, the presence of specific IgA is sufficient to decrease bacterial load, suggesting that immunoglobulin classes other than IgG contribute to antibacterial immunity (Williams et al., 2004). FcRγ-deficient mice fail to control *Leishmania major* (Padigel and Farrell, 2005) or *Mycobacterium tuberculosis* (Maglione et al., 2008) infection. Conversely, FcγRIIB-deficient mice display an enhanced resistance to these bacteria. Which, among activating FcR, account for antimicrobial activities has been poorly investigated. FcγRIIIA seem to play a predominant role (Thomas and Buxbaum, 2008). FcγRI-deficient mice, however, are more susceptible to *Bordello pertussis* infection (Ioan-Facsinay et al., 2002). Patients with febrile infections display elevated levels of FcγRI and FcγRII, especially on neutrophils (Leino et al., 1997).

Finally, recent evidence supports the involvement of FcR-dependent mechanisms in parasitic infection. FcγRIIIB polymorphisms are associated with clinical malaria in Ghana (Adu et al., 2012). FcγRI have been reported to control plasmodium infection in mouse models (McIntosh et al., 2007).

Fc Receptors in Pathogenic Antibody Responses

Infectious Diseases

In some instances, rather than being protective, antibodies favor or aggravate infection. Antibodies against a viral protein named Spike that enables the severe acute respiratory syndrome coronavirus to enter into and to infect epithelial cells can prevent these cells from being infected. Antispike antibodies, however, were recently found to enhance the infection of human immune cells through their interaction with FcγR (Jaume et al., 2011). Likewise, antibodies may enhance HIV infection. Indeed, FcR can bind antibody in complex with the gp120 protein of HIV (Fust, 1997). FcR aggregation that ensues enables the internalization of antibody–HIV complexes and, as a consequence, monocytes infection (Jouault et al., 1991).

In some cases, FcR themselves can facilitate bacterial infection. Some bacteria indeed interact directly with FcR expressed by immune cells. *Escherichia coli* K1 express the outer membrane protein A (OmpA), which binds to FcγRI and prevents the phosphorylation of the FcRγ subunit (Mittal et al., 2010). When *E. coli* is bound through OmpA to FcγRI-expressing macrophages, bacteria can enter the cell. Transfer experiments demonstrated that macrophage FcγRI are mandatory for *E. coli* infection and meningitis symptoms. FcγRI-deficient mice are indeed resistant to *E. coli* infection.

Cancer

An increased susceptibility to spontaneous tumor formation was reported neither in FcRγ-deficient nor in activating FcγR-deficient mice. Some tumors were, however, found to alter FcR expression and, possibly, thus escape immune surveillance. Myeloma-induced downregulation of activating FcR on immune cells may decrease FcR-dependent antitumor mechanisms. Other studies reported an upregulation of FcγRIIB in lymphoma cells (Callanan et al., 2000). An ectopic expression of FcγRIIB was also observed in tumor cells such as melanoma cells (Cassard et al., 2002). The role of FcγRIIB expressed by tumor cells is not known.

Allergy

It is well established that FcεRI initiate allergic reactions when receptor-bound IgE are aggregated by a plurivalent allergen on mast cells or basophils. FcεRI-deficient mice indeed fail to develop IgE-induced passive systemic anaphylaxis (PSA) (Dombrowicz et al., 1993), or as passive cutaneous anaphylaxis (PCA) (Dombrowicz et al., 1993), and mast cells are critical for both reactions (Wershil et al., 1987; Arimura et al., 1990). Human FcεRI can also trigger PCA (Fung-Leung et al., 1996) and PSA (Dombrowicz et al., 1996) induced by human IgE in transgenic mice. FcεRI expressed by eosinophils (Tanaka et al., 1995), monocytes (Maurer et al., 1994), alveolar macrophages (Ochiai et al., 1996), neutrophils (Gounni et al., 2001), and platelets (Joseph et al., 1997) in patients with high IgE levels may increase allergic symptoms.

Although it has been known since the 1950s, IgG antibodies, especially of the IgG1 subclass, were recently rediscovered to induce PSA in mouse models (Miyajima et al., 1997). FcγRIIIA are the only activating receptors that bind IgG1, and these receptors were demonstrated to be critical using FcγRIIIA-deficient mice. Other recent studies confirmed the predominant role of FcγRIIIA in anaphylaxis (Jonsson et al., 2011). FcγRIV, however, a receptor that binds IgG2 only, was recently demonstrated to contribute to active systemic anaphylaxis (ASA), together with FcγRIIIA (Jonsson et al., 2011). The expression of FcγRIV is restricted to neutrophils and monocytes/macrophages, and both cell types were found to contribute to systemic anaphylaxis (Jonsson et al., 2011; Strait et al., 2002). FcγRIIIA, however, play a predominant role in anaphylaxis because they bind not only IgG2 but also IgG1

antibodies that are produced in much higher amounts than IgG2, and because they are expressed by mast cells and basophils (Mancardi et al., 2011). FcγRIIIA-expressing mast cells are indeed mandatory for PCA (Hazenbos et al., 1996). One study reported the involvement of FcγRI in PCA (Ioan-Facsinay et al., 2002). There is, however, no convincing evidence for a major role of FcγRI in anaphylaxis. FcγRIIB can inhibit IgG1-induced PCA. FcγRIIB-deficient mice indeed display markedly increased anaphylaxis compared to wild type mice (Takai et al., 1996; Ujike et al., 1999).

Unlike the well-established role of FcγR in experimental anaphylaxis, the role of FcγR in human allergies is far from being clear. Recent studies nevertheless demonstrated the ability of human FcγR to induce allergic reactions using transgenic mice ((Jonsson et al., 2012) and Mancardi et al., 2013). Both human FcγRI and FcγRIIA triggered IgG-induced PSA and ASA. FcγRIIA expressed by mast cells were also responsible for IgG-induced PCA. A mouse deficient for all endogenous FcγR and transgenic for all human FcγR underwent anaphylaxis following an injection of aggregated human IgG (Smith et al., 2012). Finally, the transfer of human neutrophils expressing FcγRIIA could restore anaphylaxis in resistant mice, suggesting that not only human FcγRIIA, but also human neutrophils, can trigger IgG-induced anaphylaxis (Jonsson et al., 2011). It was recently found that IgG receptors expressed by human basophils function as inhibitors of cell activation. As a consequence, basophils failed to be activated by IgG immune complexes, and IgG immune complexes that coengaged FcγR with FcεRI on basophils inhibited IgE-dependent basophil activation in all normal donors tested (Cassard et al., 2012).

Autoimmune Diseases

FcR are involved in most antibody-dependent autoimmune diseases. Although IgA or IgE can account for some autoimmune disorders such as nephropathy (Coppo et al., 1992) and bullous pemphigoid (Fairley et al., 2007), respectively, and although IgM-induced complement-dependent autoimmunity was reported, most pathogenic autoantibodies are of the IgG class. FcγRIIB-deficient C57BL/6 mice spontaneously develop autoimmune diseases when aging. Anti-DNA and anti-chromatin antibodies are found in these mice, which usually succumb at 8 months of age, due to fatal autoimmune glomerulonephritis (Ravetch and Bolland, 2001). Thus, FcγRIIB seem to contribute to peripheral tolerance (Bolland and Ravetch, 2000). Inversely, all activating FcγR contribute to the development of autoimmune diseases. Antiplatelet-induced idiopathic thrombocytopenic purpura (ITP) was prevented in FcRγ-deficient mice (Fossati-Jimack et al., 1999). FcγRI (Nimmerjahn and Ravetch, 2005), FcγRIIIA (Fossati-Jimack et al., 1999), and FcγRIV (Nimmerjahn et al., 2005) were demonstrated to contribute to platelet depletion using FcR-deficient mice. Each of these receptors was sufficient to induce ITP, suggesting a redundant role of activating FcγR (Nimmerjahn and Ravetch, 2005). The involvement of FcγRI, FcγRIIIA, and FcγRIV was also reported in systemic lupus erythematosus (SLE) (Seres et al., 1998), experimental hemolytic anemia (Meyer et al., 1998; Syed et al., 2009), glomerulonephritis (Fujii et al., 2003), and arthritis (Bruhns et al., 2003; Ioan-Facsinay et al., 2002; Mancardi et al., 2011). The role of FcγRI in arthritis is however controversial as the blockade of FcγRIIIA and FcγRIV in wild type mice abolished symptoms and neutrophil infiltration in the joints (Mancardi et al., 2011). The role of human FcR in experimental autoimmune diseases has been investigated in transgenic mice. Human FcγRIIA induced ITP (Reilly et al., 1994) or arthritis (Pietersz et al., 2009). The expression of human FcγRI in mice lacking activating FcR restored arthritis symptoms (Mancardi et al., submitted). The contribution of IgA and human FcαRI in glomerulonephritis is well established (Launay et al., 2000). All FcR seem to play a redundant role in antibody-induced autoimmunity. Most of these FcR are expressed by mouse monocytes/macrophages and by neutrophils, the two cell types that are responsible for the phagocytosis of opsonized particles. Macrophages and neutrophils are mandatory for autoimmune diseases such as arthritis (Solomon et al., 2005; Wipke and Allen, 2001), lung inflammation (Skokowa et al., 2005), and thrombocytopenia (Tan et al., 2003). Slight differences were observed when autoimmune reactions were induced by different subclasses of mouse IgG. IgG2b-induced autoimmune hemolytic anemia (AHA) was dependent on FcγRIIIA and FcγRIV, whereas IgG2a-induced AHA was dependent on FcγRIIIA, FcγRIV, and FcγRI (Baudino et al., 2008). AHA induced by low dose of autoantibodies seems to be induced only by FcγRIIIA. Altogether, these data demonstrated the crucial role of every FcR in autoantibody-induced reactions. The role of FcR in human autoimmunity is highlighted by the successful use of IVIg and specific blocking antibody (see below).

FcR may also be involved in autoimmune disorders of the central nervous system (CNS) (Okun et al., 2010). Antimyelin antibodies were found in multiple sclerosis, and anti-dopaminergic neurons antibodies in Parkinson's disease (McRae-Degueurce et al., 1988). These antibodies are thought to induce inflammation by activating FcR-expressing phagocytic cells. Many cells of the CNS express FcR, and immune cells are recruited from the bloodstream into the brain in these disorders. FcRγ-deficient mice displayed a decreased phagocytosis in a model of Alzheimer disease (Das et al., 2003), less lesions and elimination of tyrosine hydroxylase-positive cells in a model of Parkinson's disease (He et al., 2002), and a reduced mortality in a model of ischemic stroke (Komine-Kobayashi et al., 2004). Interestingly, FcγRIIB-deficient mice had an enhanced disease susceptibility, whereas mice lacking IgG activating FcR were protected in a mouse model of multiple sclerosis (Robbie-Ryan et al., 2003). Furthermore, the reconstitution of resistant mice with FcγRIIIA-expressing bone marrow–derived mast cells, restored symptoms. In conclusions, the mechanism of autoantibodies production and deposition in CNS disorders is poorly documented, but the pathogenicity of these antibodies seems largely mediated by FcR.

Fc Receptors as Therapeutic Tools

Therapeutic approaches have been developed, based on the ability of FcR to induce phagocytosis and/or antibody-dependent cell-mediated cytotoxicity (ADCC). To this aim, one can use antibodies directed against antigen expressed by target cells. Once opsonized, these cells interact with FcR-expressing cells, and they are phagocytosed or killed by ADCC. Such

therapeutic antibodies are used in cancer, bacterial infection, and some autoimmune disorders. Thus, the passive administration of specific IgG antibodies protects wild type mice, but not FcRγ-deficient mice infected with *Cryptococcus neoformans* (Yuan et al., 1998). Likewise, the injection of antitumor antibodies can lead to a significant reduction of tumor mass in wt mice (Nimmerjahn and Ravetch, 2005), but not in FcRγ-deficient mice (Clynes et al., 1998). FcγRIIIA seem to play a predominant role in antitumor activity (Albanesi et al., 2012). FcγRI (Bevaart et al., 2006) and FcγRIV (Nimmerjahn and Ravetch, 2005), however, have been reported to participate to the reaction. Noticeably, no enhanced rejection was observed in FcγRIIB-deficient mice. Human FcγRI triggered tumor clearance in transgenic mice injected with a humanized antibody (Mancardi et al., Blood, in press). This suggests that human FcR may be responsible for the antitumor effect of therapeutic antibodies. Several monoclonal antibodies such as Rituximab and Trastuzumab that are used in the clinics exert their therapeutic effects through FcR (Albanesi and Daëron, 2012). Rituximab is a humanized anti-CD20 antibody that has been approved for B-cell malignancies. It indeed kills CD20-expressing transformed B cells (Manches et al., 2003), and this antitumor activity is partially mediated by FcR. Rituximab is also used to treat rheumatoid arthritis patients. Indeed, it eliminates autoimmune B cells that are responsible for the production of pathogenic antibodies (Shaw et al., 2003; Edwards et al., 2004). Trastuzumab is an anti-HER2 antibody. It binds to breast, ovary, and lung cancer cells. In addition to blocking cell proliferation by preventing receptor dimerization (Yakes et al., 2002), Trastuzumab also induces tumor destruction by engaging FcR through its Fc portion (Clynes et al., 2000). Antibodies that target molecules expressed by dendritic cells can enhance antigen presentation and, therefore, T-cell dependent cytotoxicity against tumor cells through. This effect was reported to involve FcγRIIB (Li and Ravetch, 2011).

The efficacy of therapeutic antibodies can be markedly improved (1) by increasing their half-life, (2) by enhancing their affinity for activating FcR, and (3) by decreasing their affinity for inhibitory FcR. Mutations have been described, which enhance the affinity of therapeutic antibodies for FcRn (Ward and Ober, 2009). As a consequence, the plasma concentration of these mutant antibodies is increased (Dall'Acqua et al., 2006). Other mutations that remove fucose residues from the glycan chain in the Fc portion of antibodies enhanced the affinity of these antibodies for human FcγRIIIA (Natsume et al., 2005; Niwa et al., 2005), but also for mouse FcγRIV (Nimmerjahn and Ravetch, 2005).

Fc Receptors as Therapeutic Targets

One clinical trial used blocking anti-FcγRI antibody as a treatment of idiopathic thrombocytopenia. This antibody markedly reduced symptoms (Ericson et al., 1996). The disease was however not abolished, suggesting that FcR other than FcγRI participate to pathogenesis. Supporting this conclusion, the administration of anti-FcγRIIIA antibodies to patients had some therapeutic effect (Clarkson et al., 1986). These antibodies can function as blocking-only antibody when engineered with a $N_{297}Q$ point mutation. This mutation prevents the glycosylation of the antibody, which can no longer engage FcR (Veri et al., 2007). Such aglycosylated antibodies against either specific receptors or ligands can prevent receptors–ligand interactions without engaging FcR.

Intravenous immunoglobulins (IVIG) consist of pools of IgG from thousands of normal donors. Initially conceived as a substitutive treatment of immunodeficiencies, IVIG proved efficient in several other pathologic conditions. High doses of IVIG had indeed antiinflammatory effects and they became an efficient treatment of several autoimmune diseases such as arthritis, ITP, or SLE (Bayary et al., 2006). This effect can be reproduced with IVIG Fc fragments, suggesting that FcR contribute to the antiinflammatory effect of IVIG (Anthony and Ravetch, 2010). The therapeutic effect of IVIG can be enhanced by increasing their concentration in sialic acid–rich immunoglobulins (Kaneko et al., 2006). The mechanism underlying this phenomenon remains unclear. Divergent hypotheses point out a role for FcRn, activating FcR, or FcγRIIB, which can be saturated, blocked, or upregulated, respectively, by IVIG (Nimmerjahn and Ravetch, 2007).

Therapeutic approaches of allergic disease mainly focus on IgE and/or FcεRI. Recombinant soluble FcεRI has been proposed to ameliorate allergic symptoms (Gavin et al., 1995). These recombinant molecules are expected to compete with endogenous FcεRI for IgE and, indeed, an injection of a sufficient amount may decrease IgE. Another strategy was to target membrane FcεRI with proapoptotic molecules, to induce the internalization of the complex and the subsequent killing of FcεRI-expressing cells (Belostotsky and Lorberboum-Galski, 2004). Omalizumab is a humanized monoclonal antibody directed against the FcεRI-binding site of IgE. It was developed to prevent mast cell and basophil sensitization by IgE. Omalizumab was however found to form IgE–anti-IgE complexes that are rapidly degraded, so that serum IgE becomes undetectable (Djukanovic et al., 2004). As the half-life of FcεRI is markedly reduced in the absence of receptor-bound IgE, basophils and mast cells have a reduced FcεRI expression. In spite of some side effects (Vichyanond, 2011), Omalizumab efficiently reduces the severity of symptoms in allergic diseases such as asthma (Busse et al., 2001), seasonal rhinitis (Casale et al., 2001), and chronic urticaria (Kaplan et al., 2008). Experimental therapeutic approaches have been developed, aiming at coengaging FcεRI or FcεRI-bound IgE with mast cell or basophil FcγRII (Zhu et al., 2002; Tam et al., 2004). FcγRIIB were indeed found to exert a dominant inhibitory effect on FcγRIIA and FcεRI in human basophils (Cassard et al., 2012).

Conclusion

Finally, antibody-dependent effector functions in immune responses depend on a variety of parameters. (1) They depend on the availability and on the nature of antibodies. Antibodies are present in relatively high concentrations in blood and hematopoietic organs, but in relatively low concentrations in peripheral tissues, such as skin. Local concentrations of antibodies can however be high, such as IgE in nasal polyps that contain IgE-secreting plasma cells (Takhar et al., 2005). The isotopic composition of immune complexes at a given time and at a given place is also critical. (2) They depend on FcR that are expressed by any given cell at a given time. High-affinity FcR

may be occupied, at least in part, by antibodies of different specificities. Some FcR are inducible only; others are constitutively expressed but can be up- and downregulated by cytokines. The relative expression of FcR, especially of activating vs inhibitory FcR, on myeloid cells that are present at the same site is a critical parameter. (3) They depend on the tissue distribution of FcR. FcR-expressing cells have different functional repertoires. They may be present in low numbers and in defined proportions at the initiation of responses and be recruited in high numbers and different proportions in inflammatory infiltrates. In any case, FcR are central in all antibody-dependent reactions. They are therefore both potent potential tools and privileged targets for immunotherapy.

See also: Antigen Presentation; Evolution of the Immune System; Natural Killer Cells; Platelets; Structure and Function of Immunoglobulins; V(D)J Recombination, Somatic Hypermutation, and Class Switch Recombination; White Blood Cells and Lymphoid Tissue.

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