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Receptors for the Fc portion of immunoglobulins (FcRs) account for most cell-mediated biological activities of antibodies. The majority of FcRs are encoded by a set of genes, clustered in the fcr locus, on chromosome 1 in humans and on chromosome 1 and 3 in mice. Eight (in humans) and six (in mice) new genes were found, intermixed with FcR genes in corresponding fcr loci, which encode FcR-like molecules (FcRLs). FcRs and FcRLs are genetically, phylogenetically, structurally, and functionally related. FcRs and FcRLs, however, markedly differ by their ligands, their tissue distribution, and, therefore, by the biological functions they control. A systematic comparison of their biological properties leads to the conclusion that FcRLs are not like FcRs. They altogether form a single family within the immunoreceptor family, whose members fulfill distinct but complementary roles in immunity by differentially controlling innate and adaptive responses.

From Fc Receptors to Fc Receptor-Like Molecules

The concept of receptors for the Fc portion of immunoglobulins arose in the 1960s to explain cell-mediated biological activities of antibodies. ’Opsonins’ indeed enabled antigen to enter phagocytic cells (Berken and Benacerraf, 1966); ’cytophilic’ antibodies sensitized tissues that released histamine upon antigen challenge (Bloch, 1967); distinct classes of antibodies differentially regulated secondary antibody responses (Henry and Jerne, 1968). These biological effects requiring the Fc portion of antibodies, the name ’Fc receptor’ (FcR) was coined (Paraskevas et al., 1972). FcRs for various antibody classes were identified as binding sites on a variety of cells (Vaughan and Boyden, 1964; Kulczycki and Metzger, 1974; Unkeless et al., 1988). FcRs were characterized functionally and biochemically (Holowka et al., 1980; Ernst et al., 1993; Pfefferkorn and Yeaman, 1994). Murine and human cDNAs encoding FcRs were cloned, sequenced, and expressed by transfection (Ravetch and Kinet, 1991); corresponding genes were located by the biological functions they control. A systematic comparison of their biological properties leads to the conclusion that FcRLs are not like FcRs. They altogether form a single family within the immunoreceptor family, whose members fulfill distinct but complementary roles in immunity by differentially controlling innate and adaptive responses.

From Genes Encoding FcRLs to Genes Encoding FcRs

Human (h) FcRs comprise ’classical FcRs,’ a receptor for IgA (FczRII) (Pfefferkorn and Yeaman, 1994), an MHC-related receptor (FcRn) (Simister and Rees, 1985), and a lectin-like receptor (FczRII) (Conrad, 1990). Genes that encode classical FcRs are within the FCR locus on chromosome 1, whereas the FCAR1 gene is in the leukocyte receptor complex (LRC) locus on chromosome 19 (Akula et al., 2014). The LRC locus
contains genes that encode the natural killer receptors (KIRs), the leukocyte Ig-like receptors (LILRs), and the leukocyte-associated Ig-like receptors (LAIRs), with which FcεR1 shows a higher sequence homology than with classical FcRs. FCERII, the gene that encodes hFcεRII, is also located on chromosome 19. Noticeably, genes encoding signaling homodimers shared by FcRs, NK receptors, and T cell receptors also lie in the same two loci. Genes encoding FcγRI and FcγRII are in the FCR locus, whereas genes encoding DAP10 and DAP12 are in the LRC locus. FcRn stands for neonatal FcR because this IgG receptor was first observed in newborn mice. FcRn is related neither structurally nor genetically with classical FcRs. It is an MHC class I molecule encoded by a gene of the MHC complex on chromosome 6 (Ghetie and Ward, 2000).

Mice have no equivalent of hFcεRI. Indeed, mouse genes encoding KIR-like molecules moved from the fc complex to chromosome X, and the fcrl gene is thought to have been lost during translocation (Woof and Kerr, 2006). Mouse (m) FcRs therefore comprise classical FcRs encoded by genes of the fcr locus, FcRn and FcεRI. The fcrl locus, however, was split into two fragments. The gene encoding mouse high-affinity IgG receptors (mFcγRI) is on chromosome 3, while other classical fcrl genes are on chromosome 1 (Akula et al., 2014). fcrl2, the gene that encodes mFcεRI, is on chromosome 8 (Conrad et al., 1993). The gene that encodes mFcRn is among other MHC-I genes, on chromosome 17.

Genes that encode FcRs are in the same loci as genes encoding classical FcRs in both species (Figure 1). All human FCRL genes are in the single human FCR locus on chromosome 1. Murine fcrl genes are distributed in the two murine fcr loci, on chromosomes 1 (fcrl and b) and 3 (fcrl1, fcrl5, fcrl6, and fcrls) (Davis et al., 2002; Akula et al., 2014).

Bioinformatic, genetic, and phylogenic analyses in mammals, birds, reptiles, amphibians, bony fishes, cartilaginous fishes, and lampreys unraveled that classical FcRs and FCRLs first appeared together and remained closely linked during evolution, as their complexity increased in parallel with that of immunoglobulins. Genes encoding the IgA/IgM poly-immunoglobulin receptor (pIgR), FCRLs, and FcγRI appear first within the fcr locus, as well as genes homologous to mammalian genes of the LRC locus in early bony fishes. Noticeably, genes encoding FCRLs were the ancestors of genes encoding FcRs for IgG (FcγRII, III, and IV) and IgE (FcεRI), while duplicated sequences from the pIgR gene provided sequences for genes encoding receptors for IgA/IgM (FcμR) and for IgM (FcμR) during early mammalian evolution (Akula et al., 2014). The majority of classical FcRs therefore derive from FCRLs.

**Structure and Biological Properties of FcRs and FCRLs**

Most FcRs and FCRLs are transmembrane molecules that generate intracellular signals when engaged by extracellular ligands. These biological properties depend (1) on the structure of their extracellular domains and their interactions with extracellular ligands and (2) on the signaling motifs in their intracytoplasmic domains and their ability to transduce signals across the plasma membrane and to generate productive signalosomes. The properties of nontransmembrane FCRLs are not well characterized.

**FcR and FCRL Structure**

Some FcRs are single-chain immunoglobulin-binding molecules. These include IgG receptors (FcγRIIA, FcγRIIB, FcγRIIC, and FcγRIIID), IgE receptors (FcεRI), IgM receptors (FcμR), and IgA/IgM receptors (pIgR and FcμR). Other FcRs are multichain receptors. They include IgA (FcαRI), IgE (FcεRI), and IgG (FcγRI, FcγRIIA, FcγRIIB, and FcγRIIC) receptors (Davenot, 2014). Multichain FcRs are composed of a specific immunoglobulin-binding subunit named FcRz and one or two common subunits. FcγRI is a disulfide-bonded homodimer shared by most multichain FcRs (Otolo et al., 1990). FcRβ is a tetraspanin that associates with multichain FcRs in mast cells and basophils (Kurosaki et al., 1992). Like other MHC-I molecules, FcRn associates with β2 microglobulin (Israel et al., 1995). FcγRI and β2 microglobulin are mandatory for the expression of multichain FcRs and FcRn, respectively. FcRβ is mandatory for the expression of FcεRI in mice. All FcRs are single-chain receptors. They comprise
six transmembrane molecules in humans (hFcRL1, 2, 3, 4, 5, 6) and three in mice (mFcRL1, 5, 6), two intracellular molecules (FcRLA and B) in both species, and one soluble molecule (mFcRLs) in mice (Li et al., 2014).

Except FcRRII whose extracellular domain is a C-type lectin, transmembrane FcRs and FcRLs have extracellular domains made of variable numbers of IgSF domains. Three receptors have IgSF domains of the V-type. There are five such domains in the pIgR and one in FcγRI and FcγRII. Other mouse and human FcRs have IgSF domains of the C2-type. Two have such two domains except FcγRI that has three. Human FcRL1 has three, FcRL2 and FcRL4 have four, FcRL3 has six, and FcRL5 has nine C2-IgSF domains. Mouse FcRL1 and FcRL6 have two and FcRL5 has five C2-IgSF domains. In both mice and humans, FcRLA and FcRLB also have IgSF domains, but these are intracellular, as well as a unique C-terminal mucin-like region (Li et al., 2014).

Most FcRs and FcRLs contain or are associated with subunits that contain tyrosine-based signaling motifs. In both humans and mice, one FcR only (FcγRIIB) contains an ITIM (Daén et al., 1995a). Except three low-affinity IgG receptors that are unique to humans (FcγRIIA and FcγRIIC, which contain an ITAM in their own intracytoplasmic domain, and FcγRIIB, which has no intracytoplasmic domain), most other human and murine FcRs are constitutively associated with the ITAM-containing FcRγ subunit. The FcRβ subunit also contains an ITAM. The more distant FcRs pgR, FcRγ, and FcγRIIα, as well as FcRn, have no known activation or inhibition motif. All transmembrane FcRs contain ITAMs and/or ITIMs in their intracytoplasmic domain. Human and mouse FcRL1 contain two ITAMs, whereas hFcRL4 contains two ITIMs. Human and mouse FcRL6 contain one ITIM only. Human and mouse FcRL5, as well as hFcRL2, contain two ITIMs and one ITAM. hFcRL3 contains one ITAM and one ITIM (Akula et al., 2014; Li et al., 2014).

**FcR and FcRL Ligands**

An ability to bind immunoglobulins defines FcRs. Due to their structural and genetic parenthood with FcRs, FcRLs were expected to bind immunoglobulins too. Three FcRLs, hFcRL4, hFcRL5, and the intracellular hFcRLA, do but, in spite of extensive search, other FcRLs do not. Instead, mFcRL5 and hFcRL6 bind MHC molecules. The remaining FcRLs are orphan receptors.

**Fc Receptors**

The affinity with which antibodies bind to FcRs depends both on the receptors and ligands. The binding of antibodies to FcRs is reversible and it obeys the mass action law. It is characterized by an affinity constant (\(K_a\)), calculated by dividing the association constant by the dissociation constant. The affinity constant is a characteristic of FcRs. One distinguishes two classes of FcRs. High-affinity FcRs have a \(K_a\) between 10^7 and 10^10 M^{-1} (Kulczycki and Metzger, 1974; Unkeless and Eisen, 1975). They can bind immunoglobulins as monomers, that is, not in complex with antigen. Low-affinity FcRs have a \(K_a\) between 10^3 and 10^5 M^{-1} (Bruhns et al., 2009). They cannot bind monomeric immunoglobulins. Both high- and low-affinity FcRs, however, bind immune complexes with a high avidity. A proportion of high-affinity FcRs are occupied in vivo, whereas low-affinity FcRs are not in spite of the high concentration of circulating immunoglobulins. They are therefore available for binding immune complexes. Occupied high-affinity FcRs, however, can be freed as bound antibodies dissociate (Mancardi et al., 2008). The dissociation constant therefore critically determines the availability of high-affinity FcRs.

High-affinity FcRs include IgA (FcγRIIA, in humans, and pgR in humans and mice), IgE (FcεRI, in humans and mice), and IgG receptors (FcγRI and FcγRn, in humans and mice, and FcγRIV, in mice only). Low-affinity FcRs 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 hFcγRII and III is further increased by polymorphisms in their extracellular domains (H131R in hFcγRIIA (Warmerdam et al., 1990), F158V in hFcγRIIA (Ravetch and Perussia, 1989), N43S, A27D, D82N, and V104I in FcγRIIB (Ory et al., 1989)). Altogether, 10 hFcγRs were described.

FcRs are not isotype-specific. Antibodies of several isotypes can bind to one FcR. Vice versa, several FcRs can bind antibodies of one isotype. Thus, every FcR can bind several subclasses of IgG, especially in humans where IgG1, IgG2, IgG3, and IgG4 bind similarly to hFcγRII, hFcγRIIA, B, and C; and hFcγRIIB and B (Bruhns et al., 2009). Also, mouse IgE can bind to mFcγRIIB and mFcγRIIA (Takizawa et al., 1992) and to FcγRIV (Mancardi et al., 2008).

The ability of immunoglobulins to bind to FcRs also depends on the glycosylation of their Fc portion (Arnold et al., 2007). Each heavy chain contains a covalently attached N-glycan at the highly conserved N297 residue in its CH2 domain. Point mutations of this glycosylation site abrogate the ability of IgG antibodies to bind to FcγRs, but not to FcRn (Ven et al., 2007). Other mutations that remove fucose residues from the glycan chain enhance the binding of antibodies to FcγRIIA (Natsume et al., 2005; Niwa et al., 2005). Recently, the Fc portion of immunoglobulins was found to oscillate between a ‘closed’ and an ‘open’ conformation which also determines their affinity for FcRs (Ahmed et al., 2014). Thus, when having a closed conformation, IgG binds preferentially to FcRI, whereas when having a closed conformation, they bind preferentially to FcRII (Pincetic et al., 2014).

**Fc- Like Molecules**

The majority of FcRLs have no known ligand. These include hFcRL1, hFcRL2, hFcRL3, hFcRL4, mFcRL1, mFcRL6, mFcRLA, and mFcRLB. The two types of ligands identified are immunoglobulins and MHC molecules. Only hFcRLs were found to have an affinity for immunoglobulins. hFcRL4 binds heat-aggregated IgA, and hFcRL5 binds IgG of the different subclasses (Li et al., 2014). Noticeably, IgG binds to hFcRL5 and to hFcγRs by different mechanisms. Binding indeed requires not only the Fc portion, but also the F(ab')2 moiety of intact IgG through two independent binding events. Like binding to FcRs, binding to hFcRL5 requires glycosylated IgG (Franco et al., 2013). Although intracellular, hFcRLA was also reported to have an affinity for IgA, IgM, and IgG. One human and one murine FcRL interact with MHC molecules. hFcRL6
has an affinity for MHC class II molecules and this affinity varies with the MHC-II haplotype (Schreeder et al., 2010). mFcRL5 has an affinity for an MHC-related viral protein. This MHC class I-like molecule encoded by the cowpox virus also binds to NKG2D on NK cells (Campbell et al., 2010).

**FcR and FcRL Signaling**

FcRs trigger signals when aggregated on cell membranes by antibodies and plurivalent antigens (Maeyama et al., 1986; Metzger, 1992). Although the result is the same, the sequence of events leading to receptor aggregation is different for high-affinity and low-affinity FcRs. Monomeric antibodies bind first to high-affinity FcRs that are aggregated later, 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 FcRs. FcRL signaling is not well documented, due to the paucity of natural ligands known. It was mostly investigated using anti-FcRL antibodies expected to mimic FcRL natural ligands, sometimes on FcRLs expressed by transfection in a murine B cell line.

**Fc Receptors**

FcRs can trigger activation signals and/or inhibition signals. The nature of signals primarily depends on molecular motifs contained in the intracytoplasmic domains of FcRs or of receptor subunits with which FcRs associate. ITAMs consist of two YxxL motifs separated by a 6-8 variable amino acid sequence (Reith, 1989). ITIMs consist of a single YxxL motif preceded by a loosely conserved often hydrophobic residue at position Y-2 (Vivier and Daëron, 1997). Internalization motifs enable FcRn and pIgR to transcytose IgG and/or IgA across polarized cells.

Activating FcRs are FczRI, FcαRI, FcγRI, FcγRIIA, FcγRIIC, FcγRIIIA, and FcγRIV. Upon receptor aggregation, ITAMs are phosphorylated by src family tyrosine kinases (Pribluda et al., 1994), which initiates the constitution of dynamic intracellular signalosomes (Kent et al., 1994). Not only activation signals are generated by activating FcRs, however. These, indeed, generate a mixture of positive and negative signals (Malbec et al., 2004), the dominant effect of which is activation under physiological conditions. Under other conditions, though, such as an excess of antigen that leads to a hyperaggregation of FcRs, negative signals overcome positive signals and, paradoxically, activating FcRs prevent cell activation (Gimborn et al., 2005).

Inhibitory FcRs are FcγRIIB (Daëron, 1997; Ravetch and Bolland, 2001). FcγRIIB generates inhibition signals only. Their inhibitory properties depend on the ITIM present in all murine and human FcγRIIB isoforms (Daëron et al., 1995a). Unlike activating receptors, FcγRIIB does not signal upon aggregation. They trigger negative signals when they are coaggregated with activating receptors by immune complexes (Daëron et al., 1995b). Under these conditions, the ITIM of FcγRIIB is phosphorylated by the same src family tyrosine kinase that phosphorylates ITAMs in activating receptors (Malbec et al., 1998). Phosphorylated FcγRIIB recruits 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 FcRs only (homoaggregation) is a rare situation. Different FcRs are coaggregated when IgG immune complexes interact with cells that coexpress different FcγRs or when pluri-isotypic immune complexes bind to cells that coexpress FcRs for several classes of antibodies. Even when cells express one type of FcR only (e.g., FcγRIIB in murine B cells or FcγRIIBA in murine NK cells), immune complexes can coengage FcRs with other immunoreceptors (BCR in B cells or NKR on NK cells). Heteroaggregation, that is, the coaggregation of different types of FcR or the coaggregation of FcRs with other immunoreceptors, is actually a rule, rather than an exception, under physiological conditions. Because there are FcRs 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 FcRs can be engaged at the cell surface to form heteroaggregates with a nonpredetermined composition. FcRs can thus generate a variety of signaling complexes, depending on the relative proportion of ITAM-containing and ITIM-containing receptors that are coengaged by immune complexes on any given cell (Daëron, 2014).

**FcR-Like Molecules**

Using specific antibodies that mimic FcRL ligands, FcRL signaling was found to obey similar rules as immunoreceptor signaling (Ehhardt and Cooper, 2011). The engagement of hFcRL1 or mFcRL1, which contains two ITAMs, generates activation signals. Like the BCR and the TCR, but unlike FcRs, FcRLs trigger both activation and proliferation signals. The engagement of the two-ITIM- and one-ITAM-containing hFcRL2, hFcRL5, and mFcRL5 generates a mixture of effects, the dominant effect of which is inhibition. Although it contains both activation and inhibition motifs, hFcRL5 does not signal upon aggregation. It requires to be coengaged with activating receptors for triggering negative signals. When hFcRL5 is coligated with BCR, the N-terminal hFcRL5 ITAM recruits the src kinase Lyn, which phosphorylates the ITIM, which in turn recruits the tyrosine phosphatase(s) SHP-1/2, which inhibits BCR signaling (Zhu et al., 2013). Unlike hFcRL5, when expressed in Ramos B cells, the two-ITIM-containing hFcRL4 was constitutively phosphorylated and associated with SHP-1/2, suggesting that it could exert a constitutive negative effect (Sohn et al., 2011).

**Tissue Distribution and Biological Functions of FcRs and FcRLs**

FcRs and FcRLs have no specific function per se. They transduce signals that trigger, inhibit, or generally speaking, control the functions of FcR- and FcRL-expressing cells. Responding cells are selected by the ligands their receptors interact with. Biological functions induced via FcRs and FcRLs therefore primarily depend on the tissue distribution of these receptors. Ultimately, they depend on the functional repertoires of FcR- and FcRL-expressing cells.

**Tissue Distribution of FcRs and FcRLs**

Except FcRn and pIgR, both FcRs and FcRLs are primarily expressed by cells of the hematopoietic lineage. FcRs, however,
are expressed mostly, though not only, by myeloid cells, whereas FcRLs are expressed mostly, if not only, by lymphoid cells, especially B lymphocytes.

**Fc Receptors**
Activating FcRs are expressed by myeloid cells of all types, that is, monocytes, macrophages, dendritic cells, polymorphonuclear cells of the three types, mast cells, etc. They are also expressed by NK cells (Perussia et al., 1989), NKT cells, and intraepithelial γ/δ T cells (Deusch et al., 1991; Sandor et al., 1992; Woodward and Jenkinson, 2001). FcγRIIA were also reported on a subset of murine CD8 T cells (Dhanji et al., 2005). Inhibitory FcRs are expressed by most myeloid cells and by B lymphocytes. Noticeably, human basophils express much higher levels of FcγRIIB than any other blood cells (Cassard et al., 2012). A few nonhematopoietic cells, such as some endothelial cells and some tumor cells (Cassard et al., 2002), also express FcRs. FcRn are expressed by many cells including epithelial cells, myeloid cells, and hepatocytes (Ghetie and Ward, 2000). The plgR is expressed by polarized epithelial cells, especially of the mammary gland and the gut (Kaetzel et al., 1991).

**FcR-Like Molecules**
FcRLs have a much more restricted distribution in both humans and mice (Li et al., 2014). FcR1–5 and FcRLA/B are expressed by B cells; FcR1 by all B cells, FcR2–5 by B cell subsets; hFcRLA/B by subsets of germinal center B cells, mFcRLA by peripheral B cells; the expression of mFcRLB is not known. hFcRL6 is not expressed by B cells, but by T cells and NK cells. hFcRL3 is also expressed by T and NK cells, besides by B cells. Finally mFcRLs and hFcRLs are expressed by melanocytes.

**Biological Functions of FcRs and FcRLs**
Biological responses induced by antibodies depend on the functional repertoire of Fc-expressing cells. The wide tissue distribution of FcRs therefore endows antibodies with a wide spectrum of biological functions. Antibodies, however, do not necessarily activate, they can as well inhibit those responses of cells that coexpress activating and inhibitory FcRs. FcRLs essentially regulate B cell functions. Noticeably, they appear to control differentially BCR- and TLR-dependent activation, proliferation, and differentiation of various B cell subsets.

**Fc Receptors**
FcRs control the internalization of immune complexes. All cell types pinocytose and endocytose, some phagocytose, and others can transcytose. Specific cells can exocytose. They release granules that contain cytotoxic, vasoactive, or proinflammatory mediators and proteases. Many cells can synthesize and secrete cytokines, chemokines, or growth factors. Immune responses being pluri-isotypic and cells of different types sharing FcRs for the same isotypes, antibodies select heterogeneous, rather than homogeneous cell populations, when in complex with antigen. These populations comprise a mixture of Fc-expressing cells that are present, were recruited, and/or proliferated locally. Biological processes in which FcRs are involved are therefore a result of those of many cells.

**FcR-Like Molecules**
FcRLs differentially control B cell functions. Activation signals generated by the two ITAM-containing human and murine FcR1 stimulate B cell proliferation, like signals generated by the BCR. Conversely, the ITAM + ITIM-containing FcR2–5 generally negatively regulate BCR signaling. However, when coligated with BCR, FcR3 inhibited activation signals, whereas it enhanced B cell activation, proliferation, and survival when coligated with TLR9 (Li et al., 2013). Likewise, the constitutive negative regulation of BCR signaling by FcR4 was accompanied by a positive regulation of TLR9 signaling (Sohn et al., 2011). Noticeably, while enhancing proliferation, the coligation of FcR3 and TLR9 inhibited plasma cell differentiation and antibody production (Li et al., 2014). When coengaged with BCR, mFcRL5 had antagonistic effects on Ca2+ responses and on MAPK activation, which differentially controlled BCR-dependent signals in B1 B cells and in marginal zone B cells (Zhu et al., 2013). These results altogether indicate that FcRLs which contain both ITAMs and ITIMs can differentially regulate (1) BCR- and TLR-dependent, that is, adaptive and innate signals, (2) activation versus proliferation and differentiation signals, and (3) B cell subsets.

**FcRs and FcRLs in Health and Disease**

**In Physiology**
Due to their cellular expression, FcRs control the many biological functions of myeloid cells, while FcRLs primarily regulate B cell activation and antibody responses.

**Fc Receptors**
FcRs mediate most biological activities induced by antibodies. They are not readily accessible to investigation in physiology. FcRs were, however, shown to protect and transport immunoglobulins and to control adaptive immune responses.

FcRn protects IgG from degradation (Huber et al., 1993; Raghavan et al., 1993; Junghans and Anderson, 1996). It also transports IgG across the gut (Yoshida et al., 2004; He et al., 2008) and maternal IgG across the placenta (Palmeira et al., 2012). The plgR transcytoses IgA and IgM, especially through the mammary gland (Johansen et al., 1999).

Activating FcRs enhance MHC-I and II presentation of tumor antigens (Desai et al., 2007), while FcγRIIB dampens dendritic cell maturation and antigen presentation (Wernersson et al., 1999; Kalergis and Ravetch, 2002). FcγRIIB therefore contribute to peripheral T cell tolerance (Desai et al., 2007). Conversely, FcγRIIB expressed by follicular dendritic cells can ‘present’ T-independent antigens to B cells (Szakal et al., 1985; Mond et al., 1995). Follicular dendritic cell FcγRIIB also prevent the Fc portions of IgG immune complexes from coengaging FcγRIIB with BCR and inhibit B cell activation (Tew et al., 2001; El Shikh et al., 2006; Wu et al., 2008).

Unlike immune responses to soluble antigen that are enhanced by IgG antibodies (Hjelm et al., 2006), immune responses to particulate antigens such as erythrocytes are suppressed by minute amounts of IgG antibodies. This observation has provided the rationale for injecting Rh– mothers of Rh+ babies with anti-RhD antibodies to prevent hemolytic disease of the newborn. FcγRIIB-dependent negative regulation,
however, does not account for feedback regulation by antibodies, which was altered neither in FcγRIIIB-deficient mice (Heyman et al., 2001), nor in mice lacking all FcRs (Karlssson et al., 1999).

IgE antibodies are potent adjuvants (Getahun et al., 2005). When interacting with FcγRI on B cells, IgE immune complexes present antigen to T cells and enhance antibody responses of all classes (Westman et al., 1997). This enhancement is antigen-specific because only FcγRII-expressing B cells that possess the specific BCR receive cognate T cell help (Hjelm et al., 2006).

**FcR-Like Molecules**

Little is known of the roles played by FcRLs in physiology. Reasons are the limited knowledge on FcRL ligands, but also the small number of genetically engineered mice with altered fcrl genes available. Only transgenic mice with a targeted disruption of the fcrla and fcrlb genes, which encode the intracytoplasmic FcRs with no known ligand, were published. FcRLA-deficient mice displayed an enhanced secondary (but not primary) IgG1 antibody response to a T-dependent particulate antigen like sheep erythrocytes. Responses to T-independent antigens or to soluble T-dependent antigens (particulate antigen like sheep erythrocytes. Responses to T-independent antigens or to soluble T-dependent antigens like sheep erythrocytes. Responses to T-independent antigens or to soluble T-dependent antigens were unaffected (Wilson et al., 2010). FcγRIIB-deficient mice displayed an enhanced IgG1 response to nitrophenylated chicken γ-globulins. However, due to unexpected deletions of regulatory sequences, fcrlb−/− mice also had a reduced FcγRIIB expression that could account for the observed hyperresponsiveness (Masuda et al., 2010).

**In Pathology**

**Fc Receptors**

FcRs can both protect, as in infectious diseases, and be pathogenic, as in inflammatory diseases. FcRs are involved in protection against infections. Legionella (Joller et al., 2010), Salmonella (Tobar et al., 2004), and Toxoplasma (Joiner et al., 1990) are phagocytosed via FcRs. The neutralization of Bacillus anthracis toxin depends on FcRs (Abboud et al., 2010). Fcγ-receptor-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. FcγRIIB polymorphisms are associated with clinical malaria (Adu et al., 2012), and FcγRI protected from plasmodium in mouse models (McIntosh et al., 2007). Instead of being protective, antibodies may favor infection. Anti-Spike antibodies can prevent the severe acute respiratory syndrome (SARS) coronavirus from entering epithelial cells, they enable FcγR-expressing cells to be infected (Jaume et al., 2011). Likewise, anti-HIV antibodies can use FcRs to infect monocytes (Jouault et al., 1991; Fust, 1997).

The role of mast cell and basophil FcγRI is well known in allergy. FcγRIIIB-deficient mice are resistant to IgE-induced passive systemic anaphylaxis (PSA) (Dombrowicz et al., 1993); IgE-induced PSA in hFcγRII-expressing transgenic mice (Dombrowicz et al., 1996; Fung-Leung et al., 1996). IgG1 antibodies can also trigger passive cutaneous anaphylaxis (PCA) when engaging mFcγRIIAla (Hazenbos et al., 1996), and FcγRIV expressed by neutrophils accounted for active systemic anaphylaxis (ASA), together with FcγRIIA (Jonsson et al., 2011). FcγRIIIB-deficient mice display enhanced anaphylaxis (Takai et al., 1996; Uijie et al., 1999). Both hFcγRI and hFcγRIIAla triggered IgG-induced PSA and ASA in transgenic mice (Jonsson et al., 2012; Mancardi et al., 2013). Human mast cell FcγRIIA account for IgG-induced PCA (Zhao et al., 2006). When coengaged on human basophils, FcγRIIA and FcγRIIB inhibit cell activation. Consequently, basophils failed to be activated by IgG immune complexes, and IgG immune complexes that coengaged FcRs with FcR inhibition IgE-dependent basophil activation (Cassard et al., 2012).

FcγRIIB-deficient C57BL/6 mice develop a systemic lupus erythematosus (SLE)-like disease when aging (Ravetch and Bolland, 2001). Anti-platelet antibody-induced thrombocytopenia was prevented in FcγRIIB-deficient mice (Fossati-Jimack et al., 1999). mFcγRIIIA, and IV were found to contribute to platelet depletion (Fossati-Jimack et al., 1999; Nimmerjahn et al., 2005; Nimmerjahn and Ravetch, 2005), SLE (Seres et al., 1998), hemolytic anemia (Meyer et al., 1998; Syed et al., 2009), glomerulonephritis (Fuji et al., 2003), and arthritis (Ioan-Facsinay et al., 2002; Bruhns et al., 2003; Mancardi et al., 2011). hFcγRIIA induced thrombocytopenia purpura (Reilly et al., 1994) or arthritis (Pietersz et al., 2009) in transgenic mice. Antimyelin antibodies found in multiple sclerosis and anti-dopaminergic neurons antibodies found in Parkinson disease (McRae-Degueurce et al., 1988) are thought to activate FcR-expressing phagocytic cells. Fcγ-receptor-deficient mice indeed displayed less or milder lesions in murine models of Alzheimer (Das et al., 2003), Parkinson (He et al., 2002), multiple sclerosis (Robbie-Ryan et al., 2003), and ischemic stroke (Komine-Kobayashi et al., 2004). Conversely, FcγRIIB-deficient mice had an enhanced disease susceptibility.

**FcR-Like Molecules**

FcRs have been involved in three types of diseases, infectious diseases, autoimmune diseases, and proliferative diseases, which are linked to B cell abnormalities.

When binding to integrins on B cells, the HIV envelope protein gp120 upregulates FcγRI expression, which inhibits B cell proliferation (Jelicic et al., 2013). The expression of FcγRI is also upregulated in chronic infection by viruses such as HIV and hepatitis C virus (Charles et al., 2008; Moir et al., 2008).

SNPs in FcγRI-L1-5 have been associated with several autoimmune disorders including rheumatoid arthritis, SLE, and Graves’ disease. One SNP, the T164C variant, which affects an NF-kB-binding site in the FCRL3 promoter, enhances FcγRII expression (Kochi et al., 2005), making FCRL3 an autoimmune susceptibility candidate gene (Chistiakov and Chistiakov, 2007).

FcγRI-L1-5 are upregulated in most B cell proliferative disorders including lymphoid leukemias, Burkitt, follicular, diffuse B cell, and mantle cell lymphomas (Li et al., 2014). FcγRI is normally expressed by marginal zone B cells, is expressed in marginal zone leukemias. FcγRII was associated with IGHV-unmutated aggressive chronic lymphoid leukemias.
In Therapeutics

Fc Receptors

Therapeutic antibodies against cancer use FcRs as tools. The antitumor activities of Rituximab, a humanized anti-CD20 antibody that has been approved for B cell malignancies, and of Trastuzumab, an anti-HER2 antibody used in breast, ovary, and lung cancer, depend on FcγRs (Clynes et al., 2004; Clynes et al., 2001). The therapeutic effects of these mAbs were increased by enhancing their affinity for FcγRn, which enhances their half-life (Ward and Ober, 2009), and by removing fucose residues from their Fc portion, which increases their affinity for activating FcγRIIA (Natsume et al., 2005; Niwa et al., 2005).

Therapeutic antibodies against autoimmune or allergic inflammation use FcRs either as tools or as targets. Therapeutic strategies have been developed, aiming at coengaging FcεRs (et al., 2005; Niwa et al., 2005). FcεRs increases their affinity for FcεRI by removing fucose residues from their Fc portion, which increases their affinity for activating hFcγRIIA (Natsume et al., 2005; Niwa et al., 2005).

All FcRs, some single-chain FcRs, and the subunits with which multisubunit FcRs associate contain tyrosine-based signaling motifs. This makes the FcR/FcRL family a member of the wider immunoreceptor family which, itself, belongs to the IgSF. The immunoreceptor family, defined as gathering receptors that use ITAMs and/or ITIMs for signaling, contains also B cell and T cell receptors for antigens, as well as an increasing number of activating and inhibitory receptors (Daéron et al., 2008). The majority of FcRs are ITAM-containing activating receptors; only one is an ITIM-containing inhibitory receptor. FcRs contain ITAMs only, ITIMs only, or ITAMs and ITIMs. FcRs may therefore have more subtle regulatory effects than Fcs. When engaged by immune complexes, however, Fcs form heteroaggregates in which variable numbers of ITIM- and ITAM-containing receptors generate mixtures of positive and negative signals (Daéron, 2014), as FcRs that contain both ITAMs and ITIMs do, when engaged by their ligands.

FcRs and FcRLs have markedly different tissue distributions. FcRs are expressed by myeloid cells and by some lymphoid cells, including B cells and NK cells. FcRs are expressed by lymphoid cells, primarily B cells, but also T and NK cells. Myeloid cells thus express a variety of activating and inhibitory FcRs, but no FcRLs. B lymphocytes express a variety of activating and inhibitory FcRs, as well as inhibitory FcRs, but no activating FcRs. NK cells and some T cells express activating and inhibitory FcRLs, as well as activating FcRs but no inhibitory FcRs. FcRs and FcRLs therefore control different functions of different cell types. When engaged by antigen–antibody complexes, Fcs use the many cells of the innate immune system for adaptive immune responses (Daéron, 2014), whereas FcRs differentially control responses of cells of the innate immune system (but also of NK cells) to adaptive and innate signalings (Li et al., 2014).

Finally, FcRs and FcRLs are also the relatives of other members of the immunoreceptor family encoded by genes of the LRC locus. These include LILRs A and B, ILTs, KIRs and KIRL, and NCR1, whose genes are all on chromosome 19, with FCAR1 in humans, and LIRA, PIRA/B, NCR1, whose genes are on chromosome 7, and KIRL genes on chromosome X in mice (Akula et al., 2014). The vast majority of these receptors contain ITIMs, some contain ITAMs, and a minority contain both. Being expressed by myeloid cells, B cells, T cells, and NK cells, but also a variety of nonhematopoietic cells, these receptors are involved in a multitude of immune and nonimmune responses (Daéron et al., 2008). It follows that altogether, receptors of the immunoreceptor family, among which FcRs and FcRLs are major, complementary, regulators of innate and adaptive responses.

FcRL-Like Molecules

FcRs are potential therapeutic targets in B cell malignancies. Toxin-conjugated anti-FcRL1 mAbs have been used as an anti-pan-B cell (BCR and TCR) depleting reagent (Du et al., 2008), while FcRL5, which is expressed by plasma cells, has been specifically targeted in multiple myeloma (Elkins et al., 2012). FcRLs are also potential therapeutic tools in infectious diseases. Knocking-down FcRL4 (as well as other inhibitory receptors) in chronic viral infections indeed restored BCR-dependent B cell proliferation and HIV-specific antibody responses (Kardava et al., 2011).

FcRs and FcRLs among Immunoreceptors

FcRs are more than Fc receptor-like molecules. FcRs and FcRLs indeed form a single family that shares genetic, structural, and functional properties. Genes encoding FcRs all lie in the FCR locus that contains the vast majority of genes encoding FcRs on chromosome 1. Likewise, genes encoding mFcRLs all lie in the fcr locus, even though one segment of this locus was translocated to chromosome 3. Importantly, fcrl genes were the ancestors of genes encoding FcγRI, FcγRII, FcγRIII, FcγRIV, and FcεRI, that is, the majority of classical FcRs, which appeared with early mammals during evolution. These receptors account for most properties of IgG and IgE antibodies in humans and mice. FcRs and FcRLs, however, differ by their ligands. Most FcRLs do not bind immunoglobulins whereas, by definition, all FcRs do.

All FcRs, some single-chain FcRs, and the subunits with which multisubunit FcRs associate contain tyrosine-based signaling motifs. This makes the FcR/FcRL family a member of the wider immunoreceptor family which, itself, belongs to the IgSF. The immunoreceptor family, defined as gathering receptors that use ITAMs and/or ITIMs for signaling, contains also B cell and T cell receptors for antigens, as well as an increasing number of activating and inhibitory receptors (Daéron et al., 2008). The majority of FcRs are ITAM-containing activating receptors; only one is an ITIM-containing inhibitory receptor. FcRs contain ITAMs only, ITIMs only, or ITAMs and ITIMs. FcRs may therefore have more subtle regulatory effects than Fcs. When engaged by immune complexes, however, Fcs form heteroaggregates in which variable numbers of ITIM- and ITAM-containing receptors generate mixtures of positive and negative signals (Daéron, 2014), as FcRs that contain both ITAMs and ITIMs do, when engaged by their ligands.

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See also: B Cell Activation: T Cell–Dependent B Cell Activation.

Signal Transduction: Signal Transduction by the B Cell Antigen Receptor; Signaling Pathways Downstream of TLRs and IL-1 Family Receptors; TCR Signaling: Proximal Signaling.

Structure and Function of Diversifying Receptors: Structure, Function, and Spatial Organization of the B Cell Receptor.

References

Abboud, N., Chow, S.K., Saylor, C., et al., 2010. A requirement for FcgammaR in antibody-mediated bacterial toxin neutralization. J. Exp. Med. 207, 2395–2405.

Adu, B., Dobot, D., Adukpo, S., et al., 2012. Fc gamma receptor IIB (FcgammaRIIB) polymorphisms are associated with clinical malaria in Ghanian children. PLoS One 7, e46197.

Ahmed, A.A., Giddens, J., Pincetic, A., et al., 2014. Structural characterization of antifilamin immunoglobulin G Fc proteins. J. Mol. Biol. 426, 3166–3179.

Akula, S., Mohammadamin, S., Hellman, L., et al., 2014. Fc receptors for immunoglobulins and their appearance during vertebrate evolution. PLoS One 9, e96903.

Anthony, R.M., Ravetch, J.V., 2010. A novel role for the IgG Fc glycan: the inflammatory immunoglobulin G Fc proteins. J. Mol. Biol. 408, 363–369.

Anthony, R.M., Ravetch, J.V., 2010. A novel role for the IgG Fc glycan: the inflammatory immunoglobulin G Fc proteins. J. Mol. Biol. 408, 363–369.

Bennett, E.P., 1997. Fc receptor biology. Annu. Rev. Immunol. 15, 203–234.

Berken, A., Benacerraf, B., 1966. Properties of antibodies cytophilic for macrophages. J. Exp. Med. 123, 119–144.

Blox, K.J., 1967. The anaphylactic antibodies of mammals including man. Prog. Allergy 10, 84–150.

Bruhns, P., larnascsoi, B., England, P., et al., 2009. Specificity and affinity of human Fc gamma receptors and their polymorphic variants for human IgG subclasses. Blood 113, 3716–3725.

Bruhns, P., Samuelsson, A., Pollard, J.W., Ravetch, J.V., 2003. Colony-stimulating factor-1-dependent macrophages are responsible for NIG protection in antibody-induced autoimmune disease. Immunology 188, 573–581.

Busse, W., Corren, J., Lanier, B.Q., et al., 2001. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J. Allergy Clin. Immunol. 108, 87–94.

Campbell, J.A., Davis, R.S., Lilly, L.M., et al., 2010. Cutting edge: FcR-like 5 on innate B cells targets a putative pMHC class I-like immunoevasin. J. Immunol. 185, 28–32.

Cassard, L., Cohen-Solal, J.F., Galinha, A., et al., 2002. Modulation of tumor growth by inhibitory Fc gamma RIIa receptor expressed by human melanoma cells. J. Clin. Invest. 110, 1549–1557.

Cassatt, L., Jones, M., Arnaud, S., Dairon, M., 2012. Fcgamma receptors inhibit mouse and human basophil activation. J. Immunol. 189, 2995–3006.

Charles, E.D., Green, R.M., Manukian, S., et al., 2008. Clonal expansion of immunoglobulin M+CD27+ B cells in HIV-associated mixed cryoglobulinemia. Blood 111, 1344–1356.

Chistikov, D.A., Chistikov, A.P., 2007. Is FCR3 a new general autoimmune gene? Hum. Immunol. 68, 375–383.

Chu, S.Y., Horton, H.M., Pong, E., et al., 2012. Reduction of total IgE by targeted immunoglobulin E knock-out mice. J. Neurosci. 23, 8532–8538.

Davis, R.S., Dennis Jr., G., Odem, M.R., et al., 2002. Fc receptor homologs: newest members of a remarkably diverse Fc receptor gene family. Immunol. Rev. 190, 123–136.

Davis, R.S., Wang, Y.H., Kubagawa, H., Cooper, M.D., 2001. Identification of a family of Fc receptor homologs with preferential B cell expression. Proc. Natl. Acad. Sci. U.S.A. 98, 9772–9777.

Daś, D.D., Dubroka, N., Conolly, C., et al., 2009. Regulation of high-affinity IgE receptor-mediated mast cell activation by murine low-affinity IgG receptors. J. Clin. Invest. 95, 577–585.

Daś, R., Lesourene, R., 2006. Negative signaling in Fc receptor complexes. Adv. Immunol. 89, 39–86.

Das, P., Howard, V., Looobrock, N., et al., 2003. Amyloid-beta immunization effectively reduces amyloid deposition in Fc gamma RIIB knockout mice. J. Neurosci. 23, 8532–8538.

Deacon, D.D., Warner, B.O., Flores, M., et al., 2007. Fc gamma receptor on dendritic cells enforces peripheral tolerance by inhibiting effector T cell responses. J. Immunol. 178, 6217–6226.

Deusch, O., Pfeffer, K., Reich, K., et al., 1991. Phenotypic and functional characterization of human TCR gamma delta+ intestinal intraepithelial lymphocytes. Curr. Top. Microbiol. Immunol. 173, 279–283.

Dhajli, S., Tse, K., Teh, H.S., 2005. The low affinity Fc receptor for IgG functions as an effective cytolytic receptor for self-specific CD8 T cells. J. Immunol. 174, 1253–1258.

Djakonovic, R., Wilson, S.J., Kraft, M., et al., 2004. Effects of treatment with anti-immunoglobulin G antibody omalizumab on airway inflammation in allergic asthma. Am. J. Respir. Crit. Care Med. 170, 583–593.

Dombrowicz, D., Bini, A.T., Flambard, V., et al., 1996. Anaphylaxis mediated through a humanized high affinity IgE receptor. J. Immunol. 157, 1645–1651.

Dombrowicz, D., Flambard, V., Bigman, K.K., Koller, B.H., Kinel, J.P., 1993. Abolition of anaphylaxis by targeted disruption of the high affinity immunoglobulin G receptor alpha chain gene. Cell 75, 969–976.

Du, X., Nagata, S., Ise, T., Stetler-Stevenson, M., Pacstan, I., 2000. FcR5L on chronic inflammatory immunoglobulin G proteins. J. Clin. Immunol. 20, S127–S135.

El Shikh, M.E., El Sayed, R., Szakal, A.K., Tew, J.G., 2006. Follicular dendritic cell Fc gamma RIIB engagement via immune complexes induces the activated FDC phenotype with secondary follicle development. Eur. J. Immunol. 36, 2715–2724.

Elkins, K., Zheng, B., Go, M., et al., 2012. FcR5L as a target of antibody-drug conjugates for the treatment of multiple myeloma. Mol. Cancer Ther. 11, 2222–2232.

Ehrhardt, G.R., Cooper, M.D., 2011. Immunoregulatory roles for fc receptor-like molecules. Curr. Top. Microbiol. Immunol. 350, 89–104.

El Shikh, M.E., El Sayed, R., Szakal, A.K., Tew, J.G., 2006. Follicular dendritic cell (FDC)-FcgammaRIIB engagement via immune complexes induces the activated FDC phenotype with secondary follicle development. Eur. J. Immunol. 36, 2715–2724.

Ernst, L.K., Duchemin, A.M., Anderson, C.L., 1993. Association of the high-affinity receptor for IgG Fc gamma RII with the gamma subunit of the Fc epsilon receptor. Proc. Natl. Acad. Sci. U.S.A. 90, 6023–6027.

Fossati-Jimack, L., Reinger, L., Chicheportiche, Y., et al., 1999. Expression of a family of Fc gamma RII receptors in human immune cells. Haematol. 92, 718–724.

Franco, A., Damdinsuren, B., Ise, T., et al., 2013. Human Fc receptor-like 5 binds intact IgG via mechanisms distinct from those of Fc receptors. J. Immunol. 190, 5739–5746.

Fujii, T., Hamano, Y., Ueda, S., et al., 2003. Predominant role of FcgammaRII in the induction of accelerated nephrotic glomerulonephritis. Kidney Int. 64, 1406–1416.

Fung-Leung, W.P., De Sousa-Hitlizer, J., Ishaque, A., et al., 1996. Transgenic mice expressing the human high-affinity immunoglobulin G E receptor alpha chain respond to human IgE in mast cell degranulation and in allergic reactions. J. Exp. Med. 183, 49–56.

Fust, G., 1997. Enhancing antibodies in HIV infection. Parasite 115 Suppl. 1, S127–S140.

Garman, S.C., Kinet, J.P., Jardetzky, T.S., 1998. Crystal structure of the human high-affinity IgE receptor. Cell 95, 951–961.
IgE enhances antibody and T cell responses in vivo via CD22. B cells. J. Immunol. 175, 1473–1482.

Getahun, A., Hjelm, F., Heyman, B., 2005. Molecular Aspects of Innate Immunity: IgE-mediated antibody transport across epithelial cells revealed by electron tomography. Nature 455, 542–546.

Heyman, B., Dahlstrom, J., Diaz De Stahl, T., et al., 2001. No evidence for a role of SHIP in immune activation. J. Immunol. 167, 41–68.

Huber, A.H., Kelley, R.F., Gastinel, L.N., Bjorkman, P.J., 1993. Crystallization and stoichiometry of binding of a complex between a rat intestinal Fc receptor and Fc. J. Mol. Biol. 230, 1077–1092.

Jenner, N., Jonas, P., 1968. Competitor of IgG and IgM antigens in the regulation of the primary immune response. J. Exp. Med. 128, 135–152.

Herzenberg, L.A., Herzenberg, L.A., 1980. Association of the immune response. Scand. J. Immunol. 64, 177–184.

Holowka, D., Hartmann, H., Kanellopoulos, J., Metzger, H., 1980. Association of the immune response. Scand. J. Immunol. 64, 177–184.

Huber, A.H., Kelley, R.F., Gastinel, L.N., Bjorkman, P.J., 1993. Crystalization and stoichiometry of binding of a complex between a rat intestinal Fc receptor and Fc. J. Mol. Biol. 230, 1077–1083.

Hulet, M.D., Hogarth, P.M., 1994. Molecular basis of Fc receptor function. Adv. Immunol. 57, 1–127.

Imboden, J.B., Eriksson, E.C., McCutcheon, M., Reynolds, C.W., Seaman, W.E., 1989. Identification and characterization of a cell-surface molecule that is selectively induced on rat lymphokine-activated killer cells. J. Immunol. 143, 3100–3103.

Isbell, C., Janeway, C.A., Jr., 1993. Identification and characterization of a cell-surface molecule that is selectively induced on rat lymphokine-activated killer cells. J. Immunol. 143, 3100–3103.

Kochi, Y., Yamada, R., Suzuki, A., et al., 2005. A functional variant in FCRL3, encoding a Fc receptor-like protein, is associated with rheumatoid arthritis and several autoimmune diseases. Nat. Genet. 37, 478–485.

Kominami-Kobayashi, M., Chos, N., Mochizuki, H., et al., 2004. Dual role of Fcgamma receptor in transient focal cerebral ischemia in mice. Stroke 35, 958–963.

Kuczyński Jr., A., Metzger, H., 1974. The interaction of IgE with rat basophilic leukemia cells. II. Quantitative aspects of the binding reaction. J. Exp. Med. 140, 1676–1695.

Kurosaki, T., Gander, I., Wirthmueller, U., Ravetch, J.V., 1992. The beta subunit of the Fc epsilon RI is associated with the Fc gamma RIII on mast cells. J. Exp. Med. 175, 447–451.

Lessmann, E., Kuppig, S., Krystal, G., Huber, M., 2005. SHIP down-regulates FcepsilonR1-induced degranulation at supraoptimal IgE or antigen levels. J. Immunol. 174, 507–516.

Hazenbos, W.L., Gessner, J.E., Hofhuis, F.M., et al., 1996. Impaired IgG-dependent anaphylaxis and Arthus reaction in Fc gamma RIII (CD16) deficient mice. Immunity 5, 181–188.

Kalergis, A.M., Ravetch, J.V., 2002. Inducing tumor immunity through the selective engagement of Fc gamma RIIb receptors on dendritic cells. J. Exp. Med. 195, 1653–1659.

Kaneko, Y., Nimmerjahn, F., Ravetch, J.V., 2006. Anti-inflammatory activity of immunoglobulin G resulting from Fc signaling. Science 313, 670–673.

Kaplan, A.P., Joseph, K., Maykut, R.J., Geis, G.P., Zeldin, R.K., 2008. Treatment of chronic autoimmune uveitis with omalizumab. J. Allergy Clin. Immunol. 122, 569–573.

Karlsson, M.C., Wernersson, S., Diaz de Stahl, T., Gustavsson, S., Heyman, B., 1999. Efficient IgG-mediated suppression of primary antibody responses in Fc gamma receptor-deficient mice. Proc. Natl. Acad. Sci. U.S.A. 96, 2244–2249.

Kert, U.M., Mao, S.Y., Wofsy, C., et al., 1995. Dynamics of signal transduction after antigen cross-presentation: studies on the type I receptor for IgG. Proc. Natl. Acad. Sci. U.S.A. 91, 3087–3091.

Kochi, Y., Yamada, R., Suzuki, A., et al., 2005. A functional variant in FCRRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmune diseases. Nat. Genet. 37, 478–485.

Kominami-Kobayashi, M., Chos, N., Mochizuki, H., et al., 2004. Dual role of Fcgamma receptor in transient focal cerebral ischemia in mice. Stroke 35, 958–963.

Kuczyński Jr., A., Metzger, H., 1974. The interaction of IgE with rat basophilic leukemia cells. II. Quantitative aspects of the binding reaction. J. Exp. Med. 140, 1676–1695.

Kurosaki, T., Gander, I., Wirthmueller, U., Ravetch, J.V., 1992. The beta subunit of the Fc epsilon RI is associated with the Fc gamma RIII on mast cells. J. Exp. Med. 175, 447–451.

Lessmann, E., Kuppig, S., Krystal, G., Huber, M., 2005. SHIP down-regulates FcepsilonR1-induced degranulation at supraoptimal IgE or antigen levels. J. Immunol. 174, 507–516.

Kalergis, A.M., Ravetch, J.V., 2002. Inducing tumor immunity through the selective engagement of Fc gamma RIIb receptors on dendritic cells. J. Exp. Med. 195, 1653–1659.

Kaneko, Y., Nimmerjahn, F., Ravetch, J.V., 2006. Anti-inflammatory activity of immunoglobulin G resulting from Fc signaling. Science 313, 670–673.

Kaplan, A.P., Joseph, K., Maykut, R.J., Geis, G.P., Zeldin, R.K., 2008. Treatment of chronic autoimmune uveitis with omalizumab. J. Allergy Clin. Immunol. 122, 569–573.

Karlsson, M.C., Wernersson, S., Diaz de Stahl, T., Gustavsson, S., Heyman, B., 1999. Efficient IgG-mediated suppression of primary antibody responses in Fc gamma receptor-deficient mice. Proc. Natl. Acad. Sci. U.S.A. 96, 2244–2249.

Kert, U.M., Mao, S.Y., Wofsy, C., et al., 1995. Dynamics of signal transduction after antigen cross-presentation: studies on the type I receptor for IgG. Proc. Natl. Acad. Sci. U.S.A. 91, 3087–3091.
Meyer, D., Schiller, C., Westermann, J., et al., 1998. FcgammaRIII (CD16)-deficient mice show IgG isotype-dependent protection to experimental autoimmune hemolytic anemia. Blood 92, 3997–4002.

Moir, S., Ho, J., Malaspina, A., et al., 2008. Evidence for HIV-associated B cell exhaustion in a dysfunctional memory B cell compartment in HIV-infected viremic individuals. J. Exp. Med. 205, 1797–1805.

Mund, J.J., Lees, A., Snapper, C.M., 1995. T cell-independent antigens type 2. Annu. Rev. Immunol. 13, 655–692.

Naturae, A., Wakitani, M., Yamanoe-Ohnuki, N., et al., 2005. Fucose removal from complex-type oligosaccharide enhances the antibody-dependent cellular cytoxicity of single-gene-encoded antibody comprising a single-chain antibody linked to the antibody constant region. J. Immunol. Methods 306, 93–103.

O'Neill, L.J., Bevilaqua, P., Chizzonite, J., et al., 1989. Antigen receptor tail clue. Nature 338, 383.

Ory, P.A., Goldstein, I.M., Kwoh, E.E., Clarkson, S.B., 1989. Characterization of polymorphic human leukocyte antigen class I. J. Exp. Med. 170, 1327–1337.

Pietersz, G.A., Mottram, P.L., van de Velde, N.C., et al., 2009. Inhibition of destructive inflammation by a novel human FCR gamma-LAT-dependent generation of C5a. Clin. Diagn. Lab. Immunol. 16, 3430–3434.

Pietersz, G.A., Mottram, P.L., van de Velde, N.C., et al., 2009. Inhibition of destructive inflammation by a novel human FCR gamma-LAT-dependent generation of C5a. Clin. Diagn. Lab. Immunol. 16, 3430–3434.

Pribluda, V.S., Pribluda, C., Metzger, H., 1994. Transphosphorylation as the mechanism of the low affinity FcR with distinct IgG subclass specificity. Immunity 23, 41–51.

Pribluda, V.S., Pribluda, C., Metzger, H., 1994. Transphosphorylation as the mechanism of the low affinity FcR with distinct IgG subclass specificity. Immunity 23, 41–51.

Raghothama, K.G., Srivastava, R.K., Mekhjian, H.S., 1987. In vivo and in vitro activation of murine gamma/delta T cells induces the expression of IgA, IgM, and IgG Fc receptors. J. Immunol. 148, 2363–2369.

Scheeder, D.M., Cannon, J.P., Wu, J., et al., 2010. Cutting edge: FcR-like 6 is an MHC class II receptor. J. Immunol. 185, 23–27.

Seeman, W.E., Niemi, E.C., Stark, M.R., et al., 1991. Molecular cloning of gp42, a cell-surface molecule that is selectively induced on rat natural killer cells by interleukin 2: glycolipid membrane anchoring and capacity for transmembrane signaling. J. Exp. Med. 173, 251–260.

Simister, N.E., Rees, A.R., 1985. Isolation and characterization of an Fc receptor from neonatal rat small intestine. Eur. J. Immunol. 15, 735–738.

Smith, P., Dilillo, D.J., Bourjazoso, S., Li, F., Ravetch, J.V., 2012. Mouse model recapitulating human FcgammaR receptor structural and functional diversity. Proc. Natl. Acad. Sci. U.S.A. 109, 6181–6186.

Sohn, H.W., Krueger, P.D., Davis, R.S., Pierce, S.K., 2011. FcRn4 acts as an adaptive to innate molecular switch dampening BCR signaling and enhancing TLR signaling. Blood 118, 6332–6341.

Syed, S.N., Konrad, S., Wiege, K., et al., 2009. Both FcgammaRIV and FcgammaRII are essential receptors mediating type II and type III autoimmune responses via FcRgamma-LAT-dependent generation of C5a. Eur. J. Immunol. 39, 3343–3356.

Szakal, A.K., Gieringer, R.L., Kosiak, M.H., Tew, J.G., 1985. Isolated follicular dendritic cells: cytochemical antigen localization, Norsamins, SEM, and TEM morphology. J. Immunol. 134, 1349–1359.

Takai, T., Ono, M., Hikida, M., Ohrnori, H., Ravetch, J.V., 1996. Augmented humoral and anaphylactic responses in Fc gamma RI–deficient mice. Nature 379, 346–349.

Takizawa, F., Adamczewski, M., Kinet, J.P., 1992. Identification of the low affinity Fc receptor for immunoglobulin E on mouse mast cells and macrophages as Fc gamma RI and Fc gamma RII. J. Exp. Med. 176, 469–475.

Tan, S.W., Demiesie, S., Thomas, D., Daillont, M., 2004. A bispecific antibody against human IgE and human FcgammaRIIIa that inhibits antigen-induced histamine release by human mast cells and basophils. Allergy 59, 772–780.

Tew, J.G., Wu, J., Fakher, M., Szakal, A.K., Qin, D., 2001. Follicular dendritic cells: beyond the necessity of T-cell help. Trends Immunol. 22, 361–367.

Tober, J.A., Gonzalez, P.A., Kalergis, A.M., 2004. Salmonella escape from antigen presentation can be overcome by targeting bacteria to Fc gamma receptors on dendritic cells. J. Immunol. 170, 4038–4045.

Ukle, A., Ishikawa, Y., Ono, M., et al., 1999. Modulation of immunoglobulin (Ig) E-mediated systemic anaphylaxis by low-affinity Fc receptors for IgE. J. Exp. Med. 189, 1573–1579.

Unkeless, J.C., Eisen, H.N., 1975. Binding of monomeric immunoglobulin to Fc receptor on human lymphocytes. J. Immunol. 108, 1319–1327.

Unkeless, J.C., Scigliano, E., Freedman, V.H., 1988. Structure and function of human immunoglobulin G1. Immunol. Cell Biol. 87, 3.

Unkeless, J.C., Scigliano, E., Atkinson, V.H., 1988. Structure and function of human immunoglobulin G1. Immunol. Cell Biol. 87, 3.

Veri, M.C., Gorlatov, S., Li, H., et al., 2007. Monoclonal antibodies capable of mononuclear immunoglobulins to Fc receptors of mouse macrophages. J. Exp. Med. 142, 1520–1533.

Unkeless, J.C., Scigliano, E., Freedman, V.H., 1988. Structure and function of human immunoglobulin G1. Immunol. Cell Biol. 87, 3.

Vaughan, R.B., Boyden, S.V., 1964. Interactions of macrophages and erythrocytes. Immunology 7, 118–126.

Veri, M.C., Gorlatov, S., Li, H., et al., 2007. Monoclonal antibodies capable of mononuclear immunoglobulins to Fc receptors of mouse macrophages. J. Exp. Med. 142, 1520–1533.

Veri, M.C., Scigliano, E., Freedman, V.H., 1988. Structure and function of human immunoglobulin G1. Immunol. Cell Biol. 87, 3.

Warner, D., David, D., Tew, J.G., 1984. Characterization of the many faces of FcRn. Chapter 4 Adv. Immunol. 103, 77–103.

Woof, J.M., Kerr, M.A., 2006. The function of immunoglobulin A in immunity. J. Immunol. 170, 497–506.

Wu, Y., Sukumar, S., El Shikh, M.E., et al., 2008. Immune complex-bearing follicular dendritic cells deliver a late antigenic signal that promotes somatic hypermutation. J. Immunol. 180, 281–290.
Yoshida, M., Claypool, S.M., Wagner, J.S., et al., 2004. Human neonatal Fc receptor mediates transport of IgG into luminal secretions for delivery of antigens to mucosal dendritic cells. Immunity 20, 769–783.

Zhao, W., Kepley, C.L., Morel, P.A., et al., 2006. Fc gamma RIIa, not Fc gamma RIIb, is constitutively and functionally expressed on skin-derived human mast cells. J. Immunol. 177, 694–701.

Zhu, D., Kepley, C.L., Zhang, M., Zhang, K., Saxon, A., 2002. A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation. Nat. Med. 8, 518–521.

Zhu, Z., Li, R., Li, H., Zhou, T., Davis, R.S., 2013. FCRL5 exerts binary and compartment-specific influence on innate-like B-cell receptor signaling. Proc. Natl. Acad. Sci. U.S.A. 110, E1282–E1290.