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Fc Receptors and Fc Receptor-Like Molecules within the Immunoreceptor Family

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Abstract

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 on chromosomes and their exon/intron organization was elucidated (Qiu et al., 1990). The extracellular domains of FcRs were recognized as members of the immunoglobulin superfamily (IgSF) (Williams and Barclay, 1988); amino acid sequences enabling them to interact with antibodies, extracellularly (Hulett and Hogarth, 1994), and to signal, intracellularly (Daëron, 1997), were dissected; the 3D-structure of their extracellular domains in complex with immunoglobulin Fc portions was solved (Garman et al., 1998; Maxwell et al., 1999). Finally, a collection of genetically modified FcR knock out (KO), knock in (KI), and transgenic mice was generated that enabled FcR functions to be delineated *in vivo* (Smith et al., 2012). FcRs thus appeared as a family of functionally, structurally, and genetically related molecules that play major roles in antibody-dependent processes in physiology, in pathology, and, with the advent of passive immunotherapy, in therapeutics.

Genes encoding FcR-related molecules were unexpectedly discovered, clustered with human *FCR* genes (according to the usual typographic convention, protein names are in roman type, whereas gene names are in italics; names of human genes are in upper case, whereas names of murine genes are in lower case), in the early 1990s (Imboden et al., 1989; Seaman et al., 1991). Similar genes were found in the same clusters as mouse *fcr* genes (**Figure 1**). A whole family of putative Fc receptor-like molecules (FcRLs – the abbreviation 'FcRL' is used instead of 'FCRL' for consistency with 'FcR') thus emerged (Davis et al., 2001; Hatzivassiliou et al., 2001), whose existence was progressively confirmed (Li et al., 2014). As FcRLs originated from genetic studies, much less is known of their biological functions, compared to FcRs. A syntenic chromosomal linkage, a similar genetic organization, a common membership of the IgSF suggest that FcRLs may be functionally related to FcRs. Supporting this assumption, both FcRs and FcRLs possess immunoreceptor tyrosine-based activation motifs (ITAMs), like B cell and T cell receptors (BCR and TCR) for antigen (Reth, 1989), and/or immunoreceptor tyrosine-based inhibition motifs (ITIMs), like inhibitory receptors expressed by natural killer (NK) cells (Vivier and Daëron, 1997). FcRs and FcRLs therefore belong to the immunoreceptor family. Differences in their structure, ligands, and pattern of expression, however, indicate that FcRs and FcRLs play distinct, complementary roles.

I will discuss the genetic and phylogenetic relationships between FcRs and FcRLs; the structure and biological properties of FcRs and FcRLs; the tissue distribution and biological functions of FcRs and FcRLs; the roles of FcRs and FcRLs in health and disease; and the biological significance of FcRs and FcRLs within the immunoreceptor family.

From Genes Encoding FcRLs to Genes Encoding FcRs

Human (h) FcRs comprise 'classical FcRs,' a receptor for IgA (FcαRI) (Pfefferkorn and Yeaman, 1994), an MHC-related receptor (FcRn) (Simister and Rees, 1985), and a lectin-like receptor (FcεRII) (Conrad, 1990). Genes that encode classical hFcRs 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

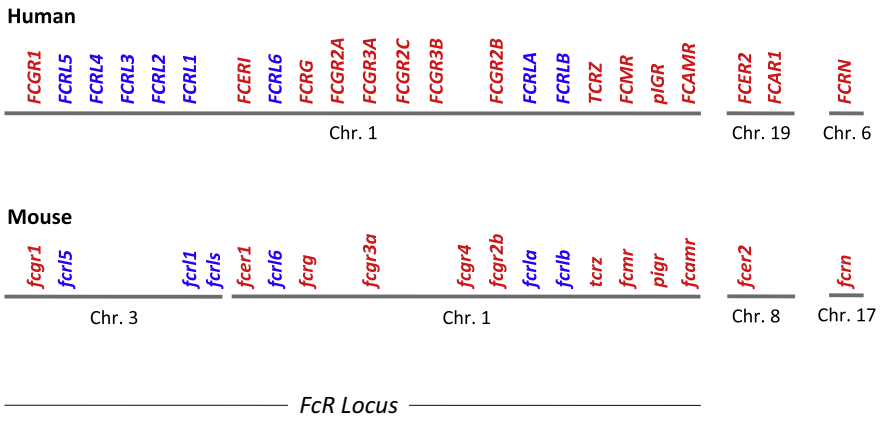

Figure 1 Human and murine Fc receptor (FcR) and Fc receptor-like molecule (FcRL) genes. Organization of the genes encoding FcRs (red) and FcRLs (blue) in humans and mice, on their respective chromosomes (Chr.) (Davis et al., 2002; Akula et al., 2014). The figure was not drawn at scale.

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 FcαRI shows a higher sequence homology than with classical FcRs. *FCER2*, 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 FcRγ and TCRξ 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 hFcαRI. Indeed, mouse genes encoding KIR-like molecules moved from the *lrc* complex to chromosome X, and the *fcarl* 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 FcεRII. The *fcr* locus, however, was split into two fragments. The gene encoding mouse high-affinity IgG receptors (mFcγRI) is on chromosome 3, while other classical *fcr* genes are on chromosome 1 (Akula et al., 2014). *fcer2*, the gene that encodes mFcεRII, 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 FcRLs 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 (*fcrla 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 FcRγ appeared 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 (FcγRI, II, III, and IV) and IgE (FcεRI), while duplicated sequences from the *pigr* gene provided sequences for genes encoding receptors for IgA/IgM (FcαμR) 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 FcγRIIIB), IgE receptors (FcεRII), IgM receptors (FcμR), and IgA/IgM receptors (pIgR and FcαμR). Other FcRs are multichain receptors. They include IgA (FcαRI), IgE (FcεRI), and IgG (FcγRI, FcγRIIIA, FcγRIV, and FcRn) receptors (Daëron, 2014). Multichain FcRs are composed of a specific immunoglobulin-binding subunit named FcRα and one or two common subunits. FcRγ is a disulfide-bonded homodimer shared by most multichain FcRs (Orloff 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 β-2 microglobulin (Israel et al., 1995). FcRγ and β-2 microglobulin are mandatory for the expression of multichain FcRs and FcRn, respectively. FcRβ is mandatory for the expression of FcεRI in mice. All FcRLs 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 FcεRII 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 FcμR and FcαμR. Other mouse and human FcRs have IgSF domains of the C2-type. All have two such 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 (Daëron 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 FcγRIIIB, 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 pIgR, FcμR, and FcαμR, as well as FcRn, have no known activation or inhibition motif. All transmembrane FcRLs contain ITIMs and/or ITAMs 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 10^5 and $10^7\,M^{-1}$ (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 (FcαRI, in humans, and 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 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 ($H_{131}R$ in hFcγRIIA (Warmerdam et al., 1990), $F_{158}V$ in hFcγRIIIA (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 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 FcγR can bind several subclasses of IgG, especially in humans where IgG1, IgG2, IgG3, and IgG4 bind similarly to hFcγRI; hFcγRIIA, B, and C; and hFcγRIIIA and B (Bruhns et al., 2009). Also, mouse IgE can bind to mFcγRIIB and mFcγRIIIA (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 N_{297} 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 (Veri et al., 2007). Other mutations that remove fucose residues from the glycan chain enhance the binding of antibodies to FcγRIIIA (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, IgE bind preferentially to FcεRI, whereas when having a closed conformation, they bind preferentially to FcεRII (Pincetic et al., 2014).

FcR-Like Molecules

The majority of FcRLs have no known ligand. These include hFcRLl, hFcRL2, hFcRL3, hFcRLB, mFcRLl, 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 (Reth, 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 FcαRI, FcεRI, 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 FcγRIIIA 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 (Ehrhardt 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). FcγRIIIA 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 pIgR 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). FcRL1–5 and FcRLA/B are expressed by B cells: FcRL1 by all B cells, FcRL2–5 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 FcR-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 FcR-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 FcRL1 stimulate B cell proliferation, like signals generated by the BCR. Conversely, the ITAM + ITIM-containing FcRL2–5 generally negatively regulate BCR signaling. However, when coligated with BCR, FcRL3 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 FcRL4 was accompanied by a positive regulation of TLR9 signaling (Sohn et al., 2011). Noticeably, while enhancing proliferation, the coligation of FcRL3 and TLR9 inhibited plasma cell differentiation and antibody production (Li et al., 2014). When coengaged with BCR, mFcRL5 had antagonistic effects on Ca^{2+} 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 pIgR 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 FcγRIIB-deficient mice (Heyman et al., 2001), nor in mice lacking all FcγRs (Karlsson et al., 1999).

IgE antibodies are potent adjuvants (Getahun et al., 2005). When interacting with FcεRII 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 FcεRII-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 FcRLs 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 were unaffected (Wilson et al., 2010). FcRLB-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). 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. FcγRIIIB 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. If 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 FcεRI is well known in allergy. FcεRI-deficient mice are resistant to IgE-induced passive systemic anaphylaxis (PSA) (Dombrowicz et al., 1993); hIgE induce PSA in hFcεRI-expressing transgenic mice (Dombrowicz et al., 1996; Fung-Leung et al., 1996). IgG1 antibodies can also trigger passive cutaneous anaphylaxis (PCA) when engaging mFcγRIIIA (Hazenbos et al., 1996), and FcγRIV expressed by neutrophils accounted for active systemic anaphylaxis (ASA), together with FcγRIIIA (Jonsson et al., 2011). FcγRIIB-deficient mice display enhanced anaphylaxis (Takai et al., 1996; Ujike et al., 1999). Both hFcγRI and hFcγRIIA 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 FcγRs with FcεRI inhibited 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 FcRγ-deficient mice (Fossati-Jimack et al., 1999). mFcγRI, IIIA, 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 (Fujii 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. FcRγ-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). Inversely, FcγRIIB-deficient mice had an enhanced disease susceptibility.

FcR-Like Molecules

FcRLs 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 FcRL4 expression, which inhibits B cell proliferation (Jelicic et al., 2013). The expression of FcRL4 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 FcRL1-5 have been associated with several autoimmune disorders including rheumatoid arthritis, SLE, and Graves' disease. One SNP, the $T_{169}C$ variant, which affects an NF-κB-binding site in the *FCRL3* promoter, enhances FcRL3 expression (Kochi et al., 2005), making *FCRL3* an autoimmune susceptibility candidate gene (Chistiakov and Chistiakov, 2007).

FcRL1–5 are upregulated in most B cell proliferative disorders including lymphoid leukemias, Burkitt, follicular, diffuse B cell, and mantle cell lymphomas (Li et al., 2014). FcRL4, which is normally expressed by marginal zone B cells, is expressed in marginal zone leukemias. FcRL2 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., 2000; Manches et al., 2003). The therapeutic effects of these mAbs were increased by enhancing their affinity for FcRn, which enhances their half-life (Ward and Ober, 2009), and by removing fucose residues from their Fc portion, which increases their affinity for activating hFcγRIIIA (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 FcεRI or FcεRI-bound IgE with mast cell or basophil FcγRII to prevent allergy (Zhu et al., 2002; Tam et al., 2004). FcγRIIB indeed exerts a dominant inhibitory effect on FcγRIIA and FcεRI in human basophils (Cassard et al., 2012). Anti-FcγRI (Ericson et al., 1996) and anti-FcγRIIIA antibodies (Clarkson et al., 1986) reduced symptoms in idiopathic thrombocytopenia. Anti-IgE antibodies (Omalizumab) used in asthma (Busse et al., 2001), rhinitis (Casale et al., 2001), and chronic urticaria (Kaplan et al., 2008) deplete plasma IgE (Djukanovic et al., 2004) and downregulate FcεRI on basophils and mast cells. Their efficacy was markedly enhanced, by increasing their affinity for FcγRIIB (Chu et al., 2012).

Initially conceived as a substitutive treatment of immunodeficiencies, intravenous Immunoglobulins (IVIG) proved efficient in arthritis, idiopathic thrombocytopenia, or SLE (Bayary et al., 2006). IVIG Fc had similar effects as intact IVIG, suggesting a role of FcRs (Anthony and Ravetch, 2010). The therapeutic effect of IVIG was enhanced by increasing their concentration in sialic acid–rich immunoglobulins (Kaneko et al., 2006). The mechanism underlying this phenomenon remains unclear.

FcR-Like Molecules

FcRLs 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

FcRLs are more than Fc receptor-*like* molecules. FcRs and FcRLs indeed form a single family that shares genetic, structural, and functional properties. Genes encoding hFcRLs 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 mammalians 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 FcRLs, 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 (Daëron et al., 2008). The majority of FcRs are ITAM-containing activating receptors; only one is an ITIM-containing inhibitory receptor. FcRLs contain ITAMs only, ITIMs only, or ITAMs and ITIMs. FcRLs may therefore have more subtle regulatory effects than FcRs. When engaged by immune complexes, however, FcRs form heteroaggregates in which variable numbers of ITIM- and ITAM-containing receptors generate mixtures of positive and negative signals (Daëron, 2014), as FcRLs 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. FcRLs 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 FcRLs, 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, FcRs use the many cells of the innate immune system for adaptive immune responses (Daëron, 2014), whereas FcRLs differentially control responses of cells of the adaptive 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 (Daëron 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.

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.

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