CHAPTER 3

Fc Receptors

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Abstract

The aggregation of cell surface Fc receptors by immune complexes induces a number of important antibody-dependent effector functions. It is becoming increasingly evident that the organization of key immune proteins has a significant impact on the function of these proteins. Comparatively little is known, however, about the nature of Fc receptor spatiotemporal organization. This review outlines the current literature concerning human Fc receptor spatial organization and physiological function.

Introduction

Like the T- and B-cell antigen receptors (TCR and BCR, respectively), Fc receptors for immunoglobulins (FcRs) belong to a group of cell surface glycoproteins known as the multichain immune recognition receptors (MIRRs). FcRs are key immune regulatory receptors, connecting humoral immune responses to cellular effector mechanisms. Our current understanding of Fc receptor function has been brought about by more than 25-years of work defining the molecular expression, functional outcomes following receptor cross-linking and the structures of these receptors complexed with ligand. This review focuses on human Fc receptor spatial organization and physiological function as it becomes increasingly evident that the organization of Fc receptors has a significant impact on their function. Further aspects of Fc receptor biology, such as the cellular expression, Ig subclass specificity and functional characterization have been extensively reviewed elsewhere[1-6] and are briefly overviewed in Tables 1-3.

Human Receptors for Immunoglobulin

The cross-linking and aggregation of FcRs are critically important for leukocyte activation. Key immunological functions such as macrophage phagocytosis, inhibition of B-cell activation, respiratory burst, pro-inflammatory cytokine secretion and antibody-dependent cellular cytotoxicity are all initiated as a result of Fc receptor aggregation. Receptors for all classes of immunoglobulins, including FcγR (IgG), FcεRI (IgE), FcαRI (IgA), FcμR (IgM) and FcδR (IgD), have been identified. This review examines the spatial organization and physiological functions of receptors for IgG, IgE and IgA.

Human IgG Receptors

There are three classes of receptors for human IgG (FcγRs) found on leukocytes: CD64 (FcγRI), CD32 (FcγRIIa, FcγRIIb, FcγRIIc) and CD16 (FcγRIIIa, FcγRIIIb) (Fig. 1, Table 1). FcγRI sets itself apart from FcγRII and FcγRIII as it binds ligand with high affinity (10^8-10^9 M^{-1}) and is

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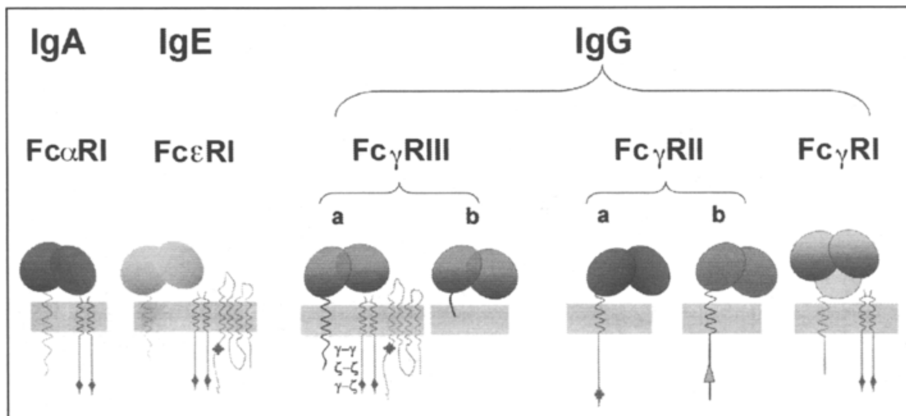

Figure 1. Schematic representation of the human Fc receptor family. All receptors exhibit two (or three), Ig-like domains and are arranged on the cell surface so that the immunoglobulin-binding surface is positioned away from the membrane (for FcγRI, there is no defined structure to date). With the exception of FcγRIIIb, which is a glycosylphosphatidyl inositol-anchored protein, all other Fc receptors are type I integral proteins containing cytoplasmic domains. The FcRs initiate activatory or inhibitory signaling processes via the signaling motifs intrinsic to the receptor (FcγRII) or found on the associated FcR γ–chain (FcγRI, FcγRIIIa, FcεRI), ζ–ζ homodimers or γ–ζ heterodimers (FcγRIIIa on NK cells). Signaling via the FcεRI is also mediated by the FcR β-chain which acts as an amplifier of the FcεRI activation signals. On the surface of mast cells, FcγRIIIa also associates with the FcR β-chain. Within the receptor cytoplasmic domain, immunoreceptor tyrosine-based activation motif (ITAM) is represented by diamonds and immunoreceptor tyrosine-based inhibition motif (ITIM) is represented by triangles.

composed of three Ig-like domains. FcγRII and FcγRIII are composed of two Ig-like domains and bind IgG with low to intermediate affinity (10^6-10^7 M^{-1}). For some time, the division of Fc receptor into classes has been largely based around ligand specificity and affinity. However, more recently this classification has been expanded by key in vivo analyses that describe Fc receptors as having either an activating or inhibitory function, characterized by the presence of an immunoreceptor tyrosine-based activation[7] or inhibition[8] motifs (ITAM or ITIM, respectively) within the cytoplasmic domain of the receptor or by association with ITAM-containing signaling subunits, the FcR γ-chain or the ζ–chain homodimers. Upon receptor cross-linking, FcγRI, FcγRIIa and FcγRIIIa all initiate activation processes via ITAMs in the noncovalently associated γ-chain (FcγRI, FcγRIII) or via intrinsic ITAMs (FcγRIIa,[9] FcγRIIIc[10]). Notably, for FcγRIIIa, γ–ζ heterodimers or ζ–ζ homodimers are also capable of inducing activatory signals upon FcγRIIIa, cross-linking on the surface of natural killer (NK) cells.[11-13] FcγRIII on mast cell is also known to associate with the FcR β-chain of the FcεRI oligomeric complex.[14] The ITAM found in FcγRIIa differs from the canonical ITAM with 12 amino acids (rather than 7 residues) separating the essential tyrosine residues within the signaling motif.[9] The intracellular signaling pathways following activatory receptor cross-linking are induced by the phosphorylation of tyrosine residues within the ITAM via the cooperative recruitment of nonreceptor tyrosine kinase, src, which in turn induces the recruitment of Src homology 2 (SH2) domain-containing signaling molecules such as the syk kinase to the phosphorylated ITAM. These early events in the signaling pathway induce the phosphorylation of numerous intracellular substrates leading to the generation of inositol triphosphate (IP3), diacylglycerol (DAG) and intracellular calcium mobilization or, depending on the cell type activated, the induction of gene expression (reviewed by refs. 2,3,15).

Unlike all other FcRs, FcγRIIb is a negative regulator of activation. This low-affinity receptor shares a high degree of homology with the activatory FcγRIIa molecule, but contains the ITIM sequence (I/V/L/SxYxxL/V) within the cytoplasmic domain.[16] Two isoforms of FcγRIIb are

Table 1. Molecular and functional characteristics of human FcγRs

	FcγRI	FcγRII	FcγRIII
CD	CD64	CD32	CD16
Isoforms	FcγRIa	FcγRIIa, FcγRIIb1, FcγRIIb2, FcγRIIc	FcγRIIIa, FcγRIIIb
Alleles		FcγRIIa HR; FγRIIa LR	FcγRIIIb NA1; FcγRIIIb NA2
Affinity for monomeric IgG	High, (10^8-10^9 M^{-1})	Low, (10^6 M^{-1})	Low, (10^6-10^7 M^{-1})
Human IgG isotype specificity	3 > 1 > 4 >> 2	FcγRIIa HR; 3 = 1 >> 2 > 4 FcγRIIa LR; 3 = 1 = 2 >> 4 FcγRIIb; 3 > 1 > 4 > 2	1 = 3 >> 2, 4
Cellular distribution	Monocytes, neutrophils, macrophages	FcγRIIa; monocytes, neutrophils, macrophages, eosinophils, basophils, platelets, dendritic cells FcγRIIb; B-cells, monocytes, macrophages, mast cells FcγRIIc; NK-cells	FcγRIIIa; subpopulations of monocytes, NK cells, macrophages, mast cells FcγRIIIb; neutrophils,
Associated signaling subunit	FcR γ-chain, but not absolutely required for expression	none known to date; signaling motif located within cytoplasmic domain	FcγRIIIa; FcR γ-chain or γζ heterodimer on NK-cells FcγRIIIb; none, is a GPI-anchored protein and uses FcγRIIa to signal
Functional characteristics	Phagocytosis, endocytosis ADCC, cytokine release	FcγRIIa; phagocytosis, ADCC, cytokine release, endocytosis (FcγRIIb1 incapable of this function). FcγRIIb; blockade of BCR-induced B-cell activation	Phagocytosis, endocytosis ADCC, cytokine release
Polymorphisms	FcγRI 'null' family	FcγRIIa, HR, LR; influences IgG2 and mouse IgG1 binding FcγRIIb, I232T; raft exclusion	FcγRIIIa; F176, V176; influences IgG1, IgG3 binding FcγRIIIb; NA1, NA2; influences phagocytosis
Modulation of expression	IFN-γ , IL-10, G-CSF↑ TGF-β, IL-4 ↓	FcγRIIa; IL-4 ↓ FcγRIIb2; IFN-γ ↓, IL-4 ↑	IFN-β, GM-CSF, G-CSF↑ TGF-β, IL-4, TNF-α (FcγRIIIb only) ↓

known, FcγRIIb1 and FcγRIIb,2 which are distinguished from each other by the insertion of a 19-amino-acid sequence within FcγRIIb1,[17] which renders the receptor incapable of endocytosis (unlike FcγRIIb2).[18] FcγRIIb1 is found on B lymphocytes while FcγRIIb2 expression is restricted to myeloid cells. The cytoplasmic ITIM is sufficient to inhibit a number of key immunological processes. When coligated with receptors containing the cytoplasmic ITAM sequence, both FcγRIIb1 and FcγRIIb2 are negative regulators of cellular activation. FcγRIIb is also known to modulate cellular responses triggered by coaggregation with either the BCR or the high-affinity IgE receptor (FcεRI).[8]

The expression of FcγRs on the surface of leukocytes has been well documented (Table 1 and reviewed by ref. 1), with the receptor expression levels differentially modulated by cytokine secretion during immune responses. Cytokines, such as interferon gamma (IFN-γ) and granulocyte colony stimulating factor, both increase the expression of FcγRI and FcγRIII (reviewed by ref. 1). Interleukin 10 (IL-10) is known to induce the up-regulation of FcγRI, whereas IL-4 inhibits expression of all activatory receptors.[19-21] Interestingly, FcγRIIb2 expression is decreased by IFN-γ, while IL-4 up regulates the receptor level.[22] Transforming growth factor-β (TGF-β) has been known to modulate the expression of FcγRIII on the surface of monocytes.[21] Recently, it was demonstrated that myeloid cells cultured in the presence of TGF-β have reduced expression of FcγRI and FcγRIII with a concomitant reduction in the levels of detectable FcR γ-chain.[23] Interestingly, TGF-β has also been reported to inhibit the expression of FcεRI on mast cells, with TGF-β affecting the rate of mRNA translation of the FcεRI β-chain.[24] This cytokine has long been recognized as having an immunosuppressive phenotype with these later studies helping to elucidate the molecular mechanisms by which this cytokine can exert such effects on varying cell types. It has been suggested that through the ability to differentially regulate FcγR expression, cytokines may potentially act to modulate effector cell functions in an autocrine and paracrine manner.[25] As the activatory and inhibitory FcγRs are often co-expressed within the cell and bind ligand with comparable affinities, the regulation of FcγR expression is biologically significant. The numerous in vivo studies of mice null for a particular FcR gene encoding the FcR γ-chain (reviewed by refs. 3,26-28), or carrying the FcγRIIa transgene,[29,30] have identified that disruptions in the balance of activatory and inhibitory receptors results in potent pathological responses as well as possible increased susceptibility to infection (reviewed by ref. 25).

Human IgE Receptor

The FcεRI is a complex of three distinct polypeptides and comprises the ligand-binding α subunit and two signaling subunits, FcR β- and γ chains. Two isoforms of the FcεRI complex are

Table 2. Molecular and functional characteristics of human FcεR

	FcεR
CD	No CD antigen number assigned as yet
Isoform	FcεRI
IgE specificity	Human IgE, rat IgE, mouse IgE
Affinity for monomeric IgE	High (10^{10} M^{-1})
Cellular distribution	Monocytes (activated), mast cells, basophils, Langerhan cells, eosinophils
Receptor forms	$\alpha\beta\gamma_2$, detected on the cell surface of mast cells and basophils $\alpha\gamma_2$ detected on the surface of monocytes, macrophages, Langerhan and dendritic cells
Functional characteristics	Degranulation, phagocytosis, endocytosis ADCC, release of histamine and leukotriene, cytokine production

known. Monocytes, macrophages, Langerhans and dendritic cells express the αγ2 complex, while mast cells and basophils express the classical $\alpha\beta\gamma_2$ complex (Fig. 1, Table 2). The α, β and γ chains are maintained within the plasma membrane by a combination of hydrophobic and electrostatic noncovalent interactions (reviewed extensively by ref. 4). Signaling and cellular activation are initiated by the high-affinity binding of specific multivalent antigens to receptor-bound IgE, thus inducing receptor clustering. Upon clustering, the nonreceptor tyrosine kinase lyn, constitutively associated with the FcεRI β-chain, trans-phosphorylates the ITAMs of both γ- and β-chains and stimulates further recruitment of lyn and trans-phosphorylation of receptors within the cluster. Phosphorylation of the ITAM allows lyn to phosphorylate syk which in turn initiates the phosphorylation of a number of key intracellular substrates, thus leading to a number of different functional outcomes. These outcomes include the release of intracellular calcium stores; antigen presentation; degranulation and release of histamine, leukotrienes, cytokines and other inflammatory mediators from mast cells; or anti-parasitic responses following activation of eosinophils. In cells expressing the $\alpha\gamma_2$ complex, it is the membrane-associated lyn that orchestrates the phosphorylation of the FcR γ-chain and the activation of syk. However, the level of activation and functional outcomes (calcium signaling and degranulation) occur at reduced levels compared to αβγ2 complexes. The FcεRI β-chain has been shown to act as an amplifier of the FcεRI activation signals mediated through the FcR γ-chain.[31]

Human IgA Receptor

There are several well-characterized receptors for human IgA: the polymeric Ig receptor (pIgR), Fcα/μR and FcαRI.[5,6] This review will only focus on the leukocyte Fc receptor for IgA, FcαRI (CD89) (Fig. 1, Table 3). The FcαR gene is found in the leukocyte receptor cluster on chromosome 19 which is known to also encode the leukocyte immunoglobulin-like receptor (LIR) and killer cell immunoglobulin-like receptor (KIR). These immunoreceptors are only distantly related to the leukocyte FcR gene family which is located on chromosome 1. However, despite this notable difference, the FcαR does share structural similarities with the other members of the FcR family. FcαRI is a type I integral membrane protein consisting of two Ig-like domains, a transmembrane region and a short cytoplasmic tail. On the cell surface, FcαRI noncovalently associates (via a transmembrane domain interface containing the crucial arginine residue) with the FcR γ-chain[32-34] which transduces activatory signals upon receptor clustering by IgA-immune complexes. The intracellular signaling pathway following FcαRI cross-linking is induced by the phosphorylation of tyrosine residues within the FcR γ-chain ITAM, results in the phosphorylation of intracellular intermediates and culminates in a number of different functional outcomes including phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), cytokine release and respiratory burst.

The FcαRI receptor is set apart from other FcRs by three features. First, there is no known mouse homolog of the FcαRI protein. FcαRI is the only Ig-like receptor identified as binding IgA immune complexes. In mice, a gene translocation between chromosomes 1 and X is thought to

Table 3. Molecular and functional characteristics of human FcαR

	FcαR
CD	CD89
Isoform	FcαRI
IgA specificity	Serum and secretory forms of IgA1 and IgA2
Affinity for monomeric IgA	Low (10^7 M^{-1})
Cellular distribution	Monocytes (activated), mast cells, basophils, Langerhan cells, eosinophils
Receptor forms	α, $\alpha\gamma_2$
Functional characteristics	Phagocytosis, endocytosis, respiratory burst and cytokine release, ADCC

lead to a loss of the equivalent FcαR gene.[35,36] Second, the nature of ligand-binding by the FcαRI and other FcRs differs significantly.[37,38] Site-directed mutagenesis of FcαRI identified domain 1 (D1) as the focal point of interaction with ligand (see below).[37] Homology modeling and biosensor analysis suggested that the stoichiometry of FcαR:IgA interaction is 2:1,[38] which was confirmed by crystallographic analysis of the FcαRI:IgA complex.[39] The crystal structure of the receptor:ligand complex demonstrated that FcαRI has a folding topology similar to other FcR proteins.[39] However, the relative orientation of domains 1 and 2 is opposite to that observed for the FcR family. Finally, the third unique feature of FcαRI is its capacity to induce negative cellular regulation following activation via the associated FcRγ-chain ITAM[40] (reviewed by ref. 41). The binding of complexed IgA to FcαRI is well documented as inducing numerous inflammatory cell functions that are crucial to immune regulation. However, binding of monomeric IgA (serum IgA) can inhibit IgG-mediated activation of myeloid cells, thereby exerting an anti-inflammatory function through FcαRI.[40] Both in vitro and in vivo analyses of binding of serum IgA or anti-FcαRI Fab fragments to FcαRI demonstrated a dual signaling role for this receptor. Moreover, it has been postulated that this dual function is regulated by the avidity of ligand: receptor interactions, whereby low avidity binding causes inhibition of receptor signaling and high avidity interaction induces cellular activation.[41]

Interaction between Fc Receptor and Immunoglobulin

The determination of receptor structures has allowed us to closely examine the interaction with ligand and better understand how these interactions may impact on cellular activation.

The orientation of FcγRII, FcγRIII, FcεRI and FcαRI extracellular D1 and D2 is highly conserved across the leukocyte receptor family: an acute angle (approximately 50-90 degrees) separates the Ig domains and the ligand binding surface is positioned away from the cell membrane.[39,42-46] Notably, for FcαRI, the relative D1-D2 orientation is also bent (approximately 90 degrees), but the orientation of the domains is opposite to that of other FcRs.[38,39] To date there are no structural data for FcγRI. Mutagenesis studies have identified that D2 is crucial for the interaction with ligand, while D3 is responsible for the high affinity interaction between FcγRI and ligand.[45,47]

For FcγRII, FcγRIII and FcεRI, the B-C, C'-E and F-G loops of D2 as well as the D1 and D2 linker region and the D2 C' β strand have been shown to directly interact with the lower hinge region of immunoglobulin.[42-44,48-50] Based on the crystal structures of FcγRIIIa and FcεRI complexed with their ligands, the receptor-ligand interaction is known to involve a combination of salt bridges, hydrogen bonds and hydrophobic interactions. The interface between FcγRIII and IgG Fc is dominated by hydrogen-bonding interactions within one Ig-heavy chain as well as hydrophobic interactions occurring at the binding interface of the other Ig-heavy chain.[43,44] Hydrogen-bonding networks are thought to contribute to the stability of receptor:ligand complexes as evident from alanine scanning mutagenesis of FcγRIIa which found that mutation of His134 culminates in the loss of Ig binding, probably due to the loss of key hydrogen bonds between receptor and ligand.[42,49] For the FcεRI:IgE interaction, two binding sites within the FcεRI D2 domain involve overlapping but non-identical sets of IgE residues.[46] The binding surface dominated by potential salt bridges, hydrogen bonds and extensive hydrophobic interactions is much larger than that of the FcγRIII. The extensive hydrophobic and electrostatic interactions have been suggested to contribute to the observed differences in high-ligand affinity for FcεRI compared to the lower affinity for FcγRIII.[43] A comparative analysis of FcR crystal structures[43,44,46] has formed the basis of a model that describes the mode of interaction between receptor and ligand. Receptor tryptophan residues and a proline residue within the Ig-CH_2 domain form a proline sandwich that acts as the primary site of receptor: ligand interaction followed by the interaction between the hinge proximal peptide sequences (Leu234-239)[51] within Ig and the D2 loop regions (B-C, C'-E and F-G) of the receptor. Mutagenesis studies of the hinge peptide sequence have highlighted the crucial importance of this region for the interaction with FcRs.[45,52-54]

The structure of FcαRI:IgA1-Fc[39] demonstrated that the B-C loop, D strand and the D-E and F-G loops of D1 form the ligand-binding site. Also, the FcαRI:IgA1-Fc structure confirmed

that the stoichiometry of the complex is 2:1 whereby two FcαRI molecules bind the IgA at each Cα2-Cα3 junction.[38,39] This is strikingly different when compared with the determined 1:1 stoichiometry of the receptor-ligand complexes of FcγRIII and FcεRI.[55,56] Dimerization of the FcαRI molecules within the receptor:ligand complex is unlikely to induce spontaneous activation as the C-termini are separated by 124Å which is too far to initiate trans-phosphorylation of the receptors.[39] It is also speculated that the rapid kinetics of receptor:ligand interaction may also prevent receptor-mediated cellular activation.[39]

For FcγRIIa, a receptor:ligand complex structure has not been defined. However, the crystal structure of the unligated FcγRIIa revealed the receptor can form a crystallographic dimer.[42] Mutagenesis of the dimer interface highlighted the functional importance of Ser129 which is predicted to make a main chain contact between adjacent receptor molecules. Dimerization of FcγRIIa is speculated to bring the cytoplasmic domains sufficiently close (Fig. 2A) to initiate trans-phosphorylation of the cytoplasmic ITAMs, thereby mediating downstream signaling processes common to the MIRR family (see above). However, dimerization of FcγRIIa alone was unable to induce signal transduction,[57] supporting the well-established dogma that aggregation of FcγRIIa is required to induce cellular activation.[58] This work demonstrates that receptor spatial organization is a crucial aspect of receptor activation. Prior to ligand-induced aggregation, the organized association of FcγRIIa dimers is an essential component of the receptor signaling cascade.

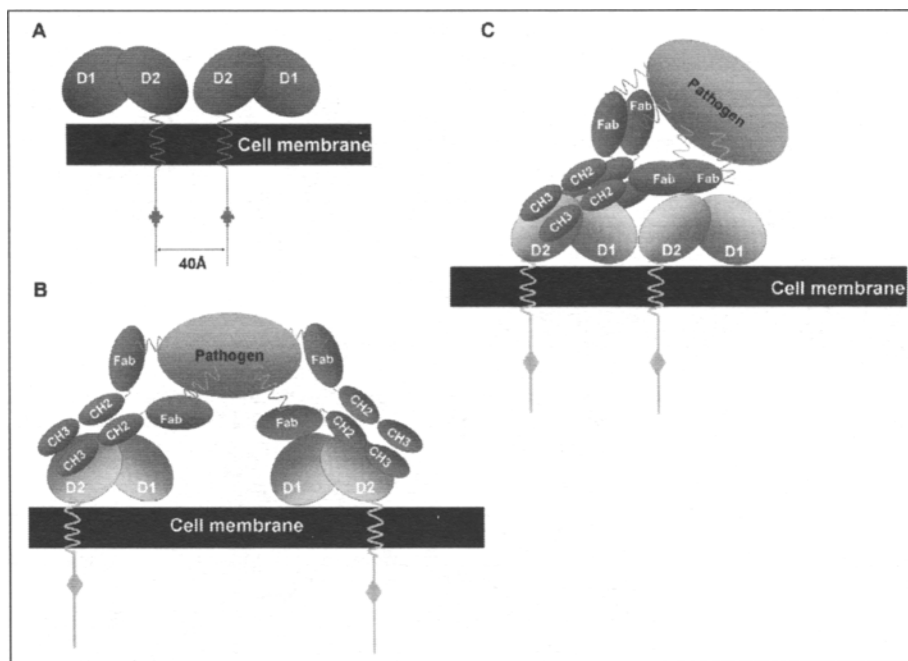

Figure 2. Models of FcγR spatial organization. A) FcγRIIa dimerization. The dimerization of FcγRIIa[42] brings the cytoplasmic domains of this receptor within approximately 40 Å of each other which is sufficiently close to initiate transphosphorylation of the cytoplasmic ITAM and is speculated to contribute to receptor activation. FcγRIII-ligand induced models of activation.[43] B) The model of simple avidity assumes binding of multiple antibodies clusters receptors in close proximity and induces activation. C) An alternative model of activation proposes that binding of oligomeric antigens leads to the formation of an ordered receptor-ligand aggregation which contributes to the receptor activation complex. Panels B and C are adapted from Radaev et al.[43]

Two models of receptor activation have been outlined based on the FcγRIII:ligand structural data (Figs. 2B and 2C).[43] The avidity model (Fig. 2B) suggests that the multiple binding of oligomeric antigen by antibodies binds and clusters the FcRs to induce activation. The second model (Fig. 2C) suggests that the binding of oligomeric antigens leads to the formation of an ordered receptor-ligand aggregation as a distinct event in the activation process. Considering structural data and examples of ordered aggregation of immunological proteins, it has been suggested that the ordered receptor cluster model may also be a plausible mechanism for activation.[43] Despite the recent studies[43,57] showing that receptor organization is a crucial aspect of receptor function and ultimately cellular activation, it remains to be elucidated in detail how FcRs become organized within the cell membrane following ligand binding.

Spatial Organization of FcRs

Studies of FcR spatial arrangements have centered on the translocation of the FcRs to detergent-resistant microdomains and the analysis of ligand-binding subunit association with signaling subunits whereas the physical protein:protein interactions between the FcRs have been measured in a limited number of studies. Ligand-dependent aggregation of FcRs initiates the receptor translocation to detergent-resistant microdomains (DRMs, or lipid rafts). The DRMs have been shown to bring key enzymes and signaling proteins in close proximity to the FcRs including FcγRIIa, FcεRI and FcαRI to initiate downstream processes.[59-61] For FcγRIIa, palmitoylation of the Cys208 residue within the juxtamembrane region is critical to the receptor localization within the DRM.[59] Notably, the equivalent mutation in the FcR γ-chain had little effect on FcαRI function, suggesting that different factors control DRM localization of the FcR γ-chain.[62] Only recently, the importance of FcγRII association with DRMs was reinforced by the data showing that the systemic lupus erythematosus (SLE)-associated FcγRIIb allele carrying the Ile232Thr polymorphism is not localized in lipid rafts.[63,64] The exclusion of FcγRIIb from DRMs results in failure to inhibit the activatory signals generated in rafts by FcγRI cross-linking[63] as well as activatory signals from the BCR,[64,65] highlighting that the localization of FcγRs to DRMs is crucial for receptor organization and regulatory functions. Association of FcRs (in particular, FcεRI) with DRMs is extensively reviewed elsewhere.[66]

Within the cell membrane, FcR organization is thought to be mediated by transmembrane domain interactions (reviewed by refs. 34, 67-71). For example, in FcεRI, charged residues within the transmembrane domain act as a focal point of association between the ligand-binding α-chain and the FceRI β or FcR γ signal transduction subunits.[72] The FcγRIII and FcγRI transmembrane domains also contain the charged residues[67,73] necessary for interaction with the FcR γ-chain. Notably, despite reported association of FcγRII with the FcR γ-chain, this association is not required for FcγRII expression or signaling function.[9,74] Considering the absence of charged residues within the FcγRII transmembrane domain and the data on FcγRII dimerization, it is difficult to rationalize this association. It also remains to be determined if FcγRII associates with any other signaling subunits, such as the FcR β-chain or an FcR β-chain-like molecule. As this particular signaling subunit is known to amplify signals,[31] one may speculate on the possible recruitment of such a molecule to form a complex with FcγRII.

FcR spatial organization within the cell membrane is not well-studied and only limited studies have examined the physical interaction between FcRs themselves or with associated proteins. Using protein-fragment complementation assays to monitor receptor-dependent reassembly of complementary, nonfunctional fragments of the enzyme, dihydrofolate reductase (DHFR),[75] it was determined that FcγRIIa is organized in such a manner that the receptors are in close association with each other.[57] Using fluorescence recovery after photobleaching (FRAP) technique, FcγRIIa has also been observed to have lateral mobility within the cell membrane whereby the diffusion of receptors become diminished with the progressive truncation of the cytoplasmic domain,[76] suggesting that the cytoplasmic tail can be critically important for receptor spatial organization. Studies of FcR:ligand complexes have shown a 1:1 stoichiometry for FcγRIII[55] and FcεRI[56]. However, the stoichiometry between FcR ligand-binding and signaling subunits has not been analyzed in these

studies. Fluorescence correlation spectroscopy data describing the real-time interaction between FcεRI and the src family tyrosine kinase lyn within intact cells, demonstrated that there are possibly multiple associations between FcεRI and lyn.[77] Recent stoichiometric measurements of the activating NKG2D receptor associated with the DAP10 signaling homodimer, found that the receptor is dimerized at the cell membrane, forming a hexameric protein complex.[78] Physiologically, the association of the NKG2D receptor and DAP10 signaling molecules may facilitate the phosphorylation of up to four ITAM motifs, potentially improving the sensitivity of NKG2D signaling. The stoichiometry of other key immunological receptors such as the BCR[79] and TCR[80] complexes has also been undertaken, thus proving that spatial arrangements are not always as predicted.

Physiological Function of Fc Receptors

The tissue-specific expression of FcRs and the pairing of activation and inhibitory receptors[3,25,27,28] are a crucial part of processes such as phagocytosis, endocytosis, release of inflammatory mediators, as well as the inhibition of cellular activation (Table 1).

Phagocytosis and endocytosis are both initiated by the cross-linking and aggregation of receptors on the cell surface of macrophages and neutrophils. Both are crucial processes responsible for the clearance of antibody-coated particles[81] or small soluble complexes[82] from the circulation, subsequent antigen presentation and for the killing of pathogens. While phagocytosis and endocytosis are fundamentally similar, they are functionally distinct. This difference is based not only on the size of particle ingested but also on the cytoskeleton requirements. Phagocytosis requires the assembly of F-actin structures whereas endocytosis is dependent on clathrin and the ubiquitylation of cytoplasmic lysine residues.[83] Phagocytosis has been extensively studied using the aggregation of FcRs to map the processes that underpin this function. All activatory FcγRs[84], the glycosylphosphatidyl inositol (GPI)-anchored FcγRIIIb,[85] FcαRI,[5,6] and FcεRI[4] have phagocytic function. Differences in the phagocytic function of the FcγRs appear to be affected by the recruitment of tyrosine kinases[67,86-88] via direct association with the receptor ITAM or through FcR γ-chain association. Interestingly, both phagocytosis and endocytosis are also modulated by the sequences within the cytoplasmic tails of FcγRs.[89] The FcγRI cytoplasmic tail possesses no intrinsic signaling function and the modulation of phagocytosis and endocytosis is known to occur via intracellular sequences[89] or via the association with the intracellular protein periplakin.[90] It remains to be elucidated if other FcγRs associate with intracellular nonsignaling proteins and what (if any) effect this has on the spatial organization of the receptor within the cell.

While processes such as FcR-mediated phagocytosis and endocytosis are recognized as essential effector functions that culminate in antigen presentation, FcR activation is also a potent inducer of pro-inflammatory cytokines, in particular IL-1[91] and TNF-α.[92] The deleterious effects of these cytokines in vivo are noted in the extensive literature outlining the efficacy of anti-cytokine therapies for the treatment of diseases such as rheumatoid arthritis (RA) (reviewed by ref. 93). For RA patients, the treatment can involve the combination of steroids and antagonists of TNF-α function[94] and to date over one million patients receive anti-TNF-α treatments.[93] Interestingly, FcγRIIa transgenic mice[29] develop spontaneous autoimmune disease and are hypersensitive to antibody-induced inflammatory reactions, demonstrating that this receptor plays a critical role in the modulation of inflammatory reactions in vivo.[30] As the structure of FcγRIIa has a spatial arrangement that potentially sets it apart from other FcRs, the development of small chemical entities or monoclonal antibodies that block receptor function could make this receptor a valid target for immunotherapy. Therapies designed to block immune complex binding to FcγRIIa are strengthened by findings that immune complex-mediated inflammatory reactions can be blocked using recombinant soluble FcγRIIa.[95] For FcεRI, it has been well established that this receptor plays a crucial role in IgE-mediated allergic responses.[4] The activation of FcεRI on the cell surface of mast cells and basophils triggers cellular degranulation and release of pro-inflammatory histamine from the granules. The potency of FcεRI in immediate allergic responses is demonstrated in mice null for the FcεRI α-or FcR γ-chains showing no immediate hypersensitivity reactions (reviewed by ref. 1). IgA nephropathy (IgAN), is the most common form of glomerulonephritis which affects

a vast number of people globally and can lead to renal failure. It has been suggested that impaired FcαRI function or changes in the IgA antibody contribute to the pathology of this disease.[5,6]

Concluding Comments

Receptors for the Fc portion of immunoglobulins are a diverse family of cell surface glycoproteins capable of connecting humoral immune responses to cellular effector mechanisms. Elucidation of receptor structures together with physiological studies using FcR gene knock-out mice or FcR transgenics have provided useful insights to the nature of receptor spatial organization on the cell surface as well as the physiological involvement of these receptors in disease. The balance between activatory and inhibitory receptor functions is crucial to immune homeostasis as disruptions to this balance are often evident by the ensuing potent pathological responses. The recent analyses of receptor organization within the cell add significantly to the exciting field of Fc receptor function, highlighting that the spatial organization of receptors is a critically important aspect of receptor function and cellular activation. However, much work still needs to be done to elucidate the precise organization of the Fc receptors within the cell and what changes of the receptor arrangement occur upon activation.

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