

IGA Fc RECEPTORS

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■ **Abstract** The IgA receptor family comprises a number of surface receptors including the polymeric Ig receptor involved in epithelial transport of IgA/IgM, the myeloid specific IgA Fc receptor (Fc α RI or CD89), the Fc α / μ R, and at least two alternative IgA receptors. These are the asialoglycoprotein receptor and the transferrin receptor, which have been implicated in IgA catabolism, and tissue IgA deposition. In this review we focus on the biology of Fc α RI (CD89). Fc α RI is expressed on neutrophils, eosinophils, monocytes/macrophages, dendritic cells, and Kupffer cells. This receptor represents a heterogeneously glycosylated transmembrane protein that binds both IgA subclasses with low affinity. A single gene encoding Fc α RI has been isolated, which is located within the leukocyte receptor cluster on chromosome 19. The Fc α RI α chain lacks canonical signal transduction domains but can associate with the FcR γ -chain that bears an activation motif (ITAM) in the cytoplasmic domain, allowing activatory functions. Fc α RI expressed alone mediates endocytosis and recycling of IgA. No Fc α RI homologue has been defined in the mouse, and progress in defining the in vivo role of Fc α RI has been made using human Fc α RI transgenic (Tg) mice. Fc α RI-Tg mice demonstrated Fc α RI expression on Kupffer cells and so defined a key role for the receptor in mucosal defense. The receptor functions as a second line of antibacterial defense involving serum IgA rather than secretory IgA. Studies in Fc α RI-Tg mice, furthermore, defined an essential role for soluble Fc α RI in the development of IgA nephropathy by formation of circulating IgA-Fc α RI complexes. Finally, recent work points out a role for human IgA in treatment of infectious and neoplastic diseases.

INTRODUCTION

Fc receptors (FcR) belong to the immunoreceptor family, including T cell receptors, B cell receptors, and NK receptors, and their function is to recognize antigens. FcR are present on many cells and provide an essential link between humoral and cellular branches of the immune system. The interaction between antibodies and FcR provides antigen-(Ag) specific recognition to cells that express a given FcR. This interaction can initiate a variety of responses, varying from endocytosis, phagocytosis, transcytosis, exocytosis, superoxide generation, antibody-dependent cell

cytotoxicity (ADCC), and release of cytokine inflammatory mediators to modulation of cell survival. FcR have been recognized for all five human antibody classes. Receptors for immunoglobulin A (IgA) were described more than 25 years ago by Lawrence et al. who showed binding of an IgA1 myeloma protein and secretory IgA to blood neutrophils (1). Others, using red cell rosettes, identified IgA receptors on a subpopulation of lymphocytes (30%) (2–4), on blood monocytes, and on neutrophils (5). In this article, we address five types of receptors for IgA and focus on the biology of the myeloid cell Fc α RI (or CD89).

Biosynthesis and Structure of IgA

IgA-bearing B cells appear first during the eleventh week after birth, contrasting with those bearing IgG and IgM that are earlier in development (6). While both IgM and IgG plasma cells can usually be found by the fifteenth week of gestation, IgA-producing cells have not been observed before the thirty-second week (7). Serum IgA is usually undetectable at birth, and adult serum levels are not attained until around the time of puberty.

In adults, the majority of human plasma cells are committed to produce IgA, and IgA is thus by far the most abundant immunoglobulin (Ig) (9). More IgA is produced per day (66 mg/kg/d) than all other classes combined (10). IgA is also the most heterogeneous among the Ig, and IgA displays a T-shaped structure, which differs from the common Y-shape of other Ig (11). IgA is divided into closely related subclasses, IgA1 and IgA2, that basically differ by the absence of a 13-amino acid sequence in the hinge region of the IgA2 molecule (12). This difference explains resistance of IgA2 against the action of bacterial proteases (i.e., from *Streptococcus mutans*, *Neisseria meningitidis*, and *Haemophilus influenzae*) (13) and may underly the predominance of IgA2 in mucosal secretions. In serum, IgA constitutes one fifth of the total Ig pool due to a fast catabolism (half-life: 3–6 days), where it exists mainly in monomeric form and of the IgA1 subclass, with a minor percentage of polymeric IgA (pIgA).

Serum IgA is generated by B lymphocytes in the bone marrow and in some peripheral lymphoid organs (14, 15). In mucosal secretions (saliva, tears, colostrum, gastrointestinal fluids, nasal bronchial secretion, and urine), however, local plasma cells produce IgA as pIgA. This pIgA exists almost exclusively as dimers, joined by a polypeptide termed J-chain, and is linked to the secretory component (secretory IgA, SIgA). Recently, it has been proposed that secretory IgA comes from two sources, the B1 and B2 lymphocytes (16). The first one contributes about 25% of secretory IgA and is produced by B1 lymphocytes that develop in the peritoneal cavity. IgA derived from B1 lymphocytes has been proposed to represent a primitive system, a T lymphocyte-independent source of IgA, recognizing commensal bacteria. The second source, the B2 lymphocytes, represents the majority (75%) of lymphocytes in organized germinal centers of mucosal-associated lymphoid tissues (MALT) such as Peyer's patches. This IgA against exotoxins is T lymphocyte dependent. It should be noted, however, that animals deficient in

lymphotoxin α and lymphotoxin β receptors are devoid of both mesenteric lymph nodes and Peyer's patches, but can still produce IgA (17). Mucosal IgA is produced by plasma cells and transported from the baso-lateral epithelial compartment to the apical/luminal side. Dimeric IgA, containing the J-chain, is secreted in the lamina propria. It binds to and forms covalent complexes with the membrane-associated polymeric Ig receptor (pIgR) on the baso-lateral side of mucosal epithelial cells (18). The complex is actively transported through the epithelial cell to the apical/luminal side, where bound IgA is released by proteolytic cleavage from the pIgR, generating the so-called secretory component, which remains associated with dimeric IgA, forming altogether SIgA (19).

Interestingly, the IgA system differs substantially between three species studied in detail, human, mouse, and rabbit. Two IgA subclasses are recognized in humans, one class in mice, and 13 subclasses in rabbits (9, 20). Serum IgA is mostly monomeric in humans and polymeric in mice. Clearance via the hepatobiliary route plays an important role in mice but not in humans (9).

Functions of IgA

The mucosal surface encompasses more than 400 m² that is permanently in contact with multiple bacterial strains and other microorganisms. More than 70% of immune cells are mobilized daily to resist systemic infections, including antibody-secreting cells. SIgA plays a major role in the innate immune system preventing microorganisms and foreign proteins from penetrating the mucosal surfaces (21). It also neutralizes toxins and infectious organisms. SIgA antibodies have been proposed to act at three levels in the mucosal compartment. The first level is at the luminal side via a mechanism called immune exclusion (22, 23). SIgA can inhibit adherence of microorganisms by surrounding pathogens with a hydrophilic shell that is repelled by the mucin glycocalyx at mucosal surfaces (9, 24). In addition to this exclusion mechanism, two additional activities have been defined; one is the transport of IgA complexed with antigens that cross the epithelial cell barrier to the luminal side; the second is intracellular interception of viral antigens during transepithelial IgA transport (25–29). The third mechanism of protection by SIgA has been documented to be active at the stromal side. IgA/Ag complexes can be eliminated via the pIgR at the baso-lateral side of epithelial cells by transcytosis (30) or by Fc α R-bearing phagocytes (31, 32). The inability of SIgA to fix complement efficiently or to act as an opsonin is an advantage in secretions, where initiation of an inflammatory reaction would likely affect the most important component of local defense, the integrity of the mucosal surface (9). Whereas the role of secretory IgA is established in mucosal immunology, the function of serum IgA antibodies is mostly unknown. Studies on the ability of IgA antibodies to regulate humoral response are scarce. IgA was shown only in one report to enhance the induction of immunological memory to soluble Ag (34). IgG antibodies represent the most prominent component of secondary systemic immune responses to Ag, whereas IgA is rarely observed. The specificity of serum IgA in the human

antibody repertoire and IgA antigen selection remain poorly defined. Serum IgA is considered a “discrete housekeeper” because IgA immune complexes can be removed by the phagocytic system with little or no resulting inflammation. Moreover, monomeric serum IgA displays anti-inflammatory activity and is capable of inhibiting functions such as IgG-induced phagocytosis, bactericidal activity, oxidative burst, and cytokine release (9). Another argument in favor of anti-inflammatory properties of serum IgA is provided by selective IgA-deficient patients, the most common Ig deficiency (35). IgA deficiency has frequently been associated with allergy and autoimmunity. The molecular basis for this is not understood. Polymeric IgA and IgA-containing immune complexes (IC), in contrast, can efficiently trigger immune effector functions on blood leukocytes through IgA Fc receptors. In this context, interaction of serum IgA with Fc α RI on tissue phagocytic cells can act as a second line of defense in the case of bacterial infections following penetration through the mucosal barrier (12).

TYPES OF IgA RECEPTORS

Fc receptors are defined by their specificity for the Fc fragment of immunoglobulin isotypes, and receptors for IgA are referred to as Fc α R (36). Although they are not structurally related, five types of IgA receptors are now recognized (Figure 1). Three of them are considered bona fide Fc α R. The first one, the polymeric Ig receptor, is involved in transport of IgM and polymeric IgA across epithelial barriers [reviewed in (18, 37)]. The second type is designated Fc α RI (or CD89) and is a receptor specific for IgA, capable of binding both human IgA1 and IgA2 subclasses (38, 39). The third receptor type is the recently described Fc α / μ R (40). The two alternative IgA receptors are the asialoglycoprotein receptor and the transferrin receptor (41, 42).

Fc α RI

Expression, Modulation, and Tissue Distribution

Expression of Fc α RI/CD89 begins at least as early as the promyelocyte stage in differentiation (43, 44). Fc α RI expression is restricted to cells of the myeloid lineage including neutrophils, eosinophils, most of monocytes/macrophages, interstitial dendritic cells, Kupffer cells, and cell lines corresponding to these cell types (31, 33, 43, 45, 46). Tonsillar, splenic, and alveolar macrophages do all express Fc α RI (43, 47, 48), in contrast to intestinal and genitourinary mucosal macrophages (44, 49). Fc α RI is neither expressed on cord blood–derived mast cells, erythrocytes, platelets, nor lymphoid cells, even after polyclonal or mitogenic stimulation (B. Pasquier, M. Arock & R. Monteiro, unpublished data). Fc α RI expression is constitutive and independent of the presence of IgA ligand because the receptor is expressed at similar levels on cells from patients deficient in IgA (50).

Several anti-Fc α RI (CD89) mouse and human monoclonal antibodies (mAb) have been generated (43, 51). Most of them recognize nonpolymorphic

TABLE 1 Location of IgA- and CD89 mAb binding sites within the Fc α RI extracellular domains

	EC1	EC2
IgA-binding site	+	–
anti-Fc α RI mAb	My43, 2E6, 2D11, 7G4, 2H8	A59, A62, A77, 7D7

determinants on Fc α RI (43). The CD89 mAb epitopes on Fc α RI have been characterized (52). Monoclonal Ab that bind in the EC1 domain of Fc α RI (e.g., My43) can block IgA binding, whereas those that bind in EC2 do not (Table 1). A3 mAb may recognize a binding site between both Fc α RI extracellular domains.

The level of Fc α RI expression on cells is estimated to be 57,000 per monocyte and 66,000 per neutrophil (44). A number of cytokines and other agents modulate Fc α RI expression, as summarized in Table 2. Fc α RI expression levels are upregulated on neutrophils in response to formyl-methionyl-leucyl-phenylalanine (FMLP), interleukin 8, and tumor necrosis factor α (TNF- α) (53–55). Receptor upregulation on neutrophils is rapid and results mainly from recruitment from intracellular pools (53). Fc α RI upregulation has been defined to occur via a Ca²⁺-dependent signaling pathway on neutrophils and eosinophils (45, 53); ionomycin upregulates Fc α RI expression on eosinophils but not on U937 cells. Expression of Fc α RI on monocytes and monocyte-like cell lines can be upregulated by phorbol esters, calcitriol, lipopolysaccharide (LPS), TNF- α , granulocyte-macrophage colony stimulating factor (GM-CSF), and IL-1 β (38, 54–57). Fc α RI is downregulated by transforming growth factor (TGF- β), interferon γ , suramin, and by its ligand (57–61). Indeed, in contrast to other FcR (such as Fc ϵ RI), Fc α RI expression is downregulated by polymeric IgA (61).

Genetics

Expression cloning of a cDNA encoding Fc α RI (CD89) was performed using a library made from U937 cells and the anti-Fc α RI mAb My43 (39). This clone was 1.6 kb long including an 861-bp open reading frame and a 711-bp 3'-UTR ending in a poly-A stretch. The latter includes an Alu sequence but lacks a classical

TABLE 2 Modulation of Fc α RI expression

Cell type	Increased expression	Decreased expression
Monocytes/macrophages	Calcitriol, PMA, TNF- α , IL-1 β , GM-CSF, LPS	TGF- β , IFN- γ , suramin, pIgA
Neutrophils	IL-8, TNF- α , GM-CSF, FMLP, ZAS, ionomycin	
Eosinophils	Ionomycin	

polyadenylation signal (39). The Fc α RI gene consists of 5 exons spanning approximately 12 kb (63). The first exon (S1) includes the 5'-UTR, an ATG translation initiation codon, and part of the leader peptide. The exon 2 (S2) is a mini-exon only 36 bp long, which codes for the leader peptide, including the predicted signal peptidase cleavage site. Exons EC1 and EC2 each encode a single extracellular Ig-like domain of 206 amino acids. The last exon, called TM/C, encodes the transmembrane domain and the cytoplasmic tail of 19 and 41 amino acids, respectively.

This Fc α RI single gene is located in the distal part of the q-arm on chromosome 19, at 19q13.4 (64) (Figure 2A). The molecular structure of Fc α RI classified this FcR as a member of the Ig gene superfamily (39). It is distantly related to other FcR genes (~20% homology), such as the Fc γ R and Fc ϵ RI genes, that are all located on chromosome 1 (65). Interestingly, Fc α RI is more homologous (~35%) to another family of receptors, the so-called leukocyte receptor cluster, that includes the killer-inhibitory/activatory (KIR/KAR)-related immunoreceptors, the Ig-like transcripts (ILTs), the leukocyte and monocyte/macrophage Ig-like receptors (LIRs, MIRs) (66–75). Fc α RI is also closely related to the bovine Fc γ 2R and human and mouse platelet-specific collagen receptor (GPVI) (77). Fc α RI and Fc γ 2R in fact constitute a separate group of FcR evolving from a common ancestral gene. These genes seem to have diverged from each other before the divergence of humans and cattle (76). It is noteworthy that no murine homologue for Fc α RI has been identified, in spite of intensive efforts to find one. Hybridization of murine cDNA libraries with a human Fc α RI cDNA did result in description of two new receptors called paired Ig-like receptors, PIR-A and PIR-B (78, 79). PIR ligands are so far unknown. Moreover, other uncharacterized IgA-binding molecules have been described on rat macrophages and rabbit lymphocytes (80, 81).

A 929 bp fragment of the Fc α RI promoter region has been characterized (82). Sequences between 59 and 197 bp downstream of the major transcription start site were shown to be essential for promoter activity. This sequence contains multiple consensus binding sites for transcription factors that function in myeloid gene expression, including three CCAAT enhancer-binding protein binding sites, an NF- κ B binding site, an Spl site, an Ets family protein binding site, and a Myb-binding site. Two polymorphisms have been identified (C-T transitions) at positions 114 bp upstream and 56 bp downstream of the transcription start site. Fc α RI promoter region carrying both -114T and +56T alleles exhibits a lower promoter activity than promoters harboring the C alleles at both sites (82).

Transcripts, Protein Structure, and Ligand Binding

Several alternatively spliced Fc α RI transcripts have been identified by using RT-PCR (48, 83–85). Figure 2B summarizes the different Fc α RI transcripts. Full-length transcripts are denominated Fc α RI a.1, whereas spliced variants are defined as a.2, a.3, . . . Two of these transcripts, a.2 and a.3, specified proteins in *in vitro* translation experiments (48). *In vivo*, Fc α RI exists as at least two isoforms (a.1 and a.2) differing by a deletion in the extracellular domain (48). Whereas the a.1

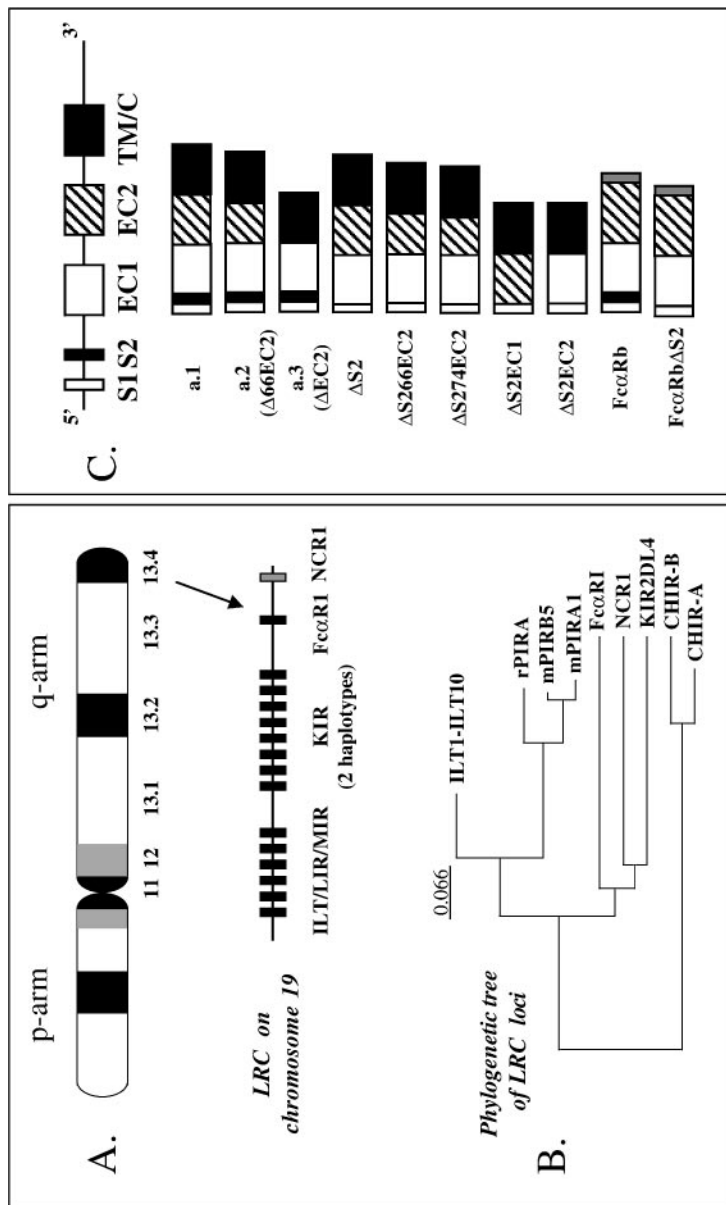


Figure 2 A. Location of the FcαRI (CD89) gene within the leukocyte receptor complex (LRC) on chromosome 19. B. Phylogenetic analysis of LCR. C. Schematic representation of FcαRI (CD89) gene intron-exon organization and FcαRI transcripts. ILT, Ig-like transcripts; LIR, MIR, the leukocyte and monocyte/macrophage Ig-like receptors; PIR, paired Ig-like receptors; KIR, killer inhibitory receptors; NCR1, natural cytotoxicity receptors; CHIR, chicken Ig-like receptors.

isoform is expressed on blood monocytes, neutrophils, eosinophils, cultured blood macrophages, and peritoneal macrophages, the a.2 isoform is found exclusively on alveolar macrophages (48). Another Fc α RI isoform, named Fc α RIb, is the product of an alternate splicing that skips the 3' splice site at the end of the EC2 exon, resulting in an extension of 23 new amino acids before reaching the stop codon, and thus potentially generating a "TM/C-less protein" (86). An Fc α RIb protein product was shown to represent a soluble protein in transfectants and was unable to associate with the FcR γ -chain. Whether this isoform is related to previously described Fc α RI soluble proteins is unclear. Native proteins corresponding to any of the other splice variants have not been identified. Whether this is due to "sterile transcripts" or to proteins not detected by CD89 antibodies is unknown.

Fc α RI a.1 represents a type I, 287-amino acid protein containing a 21 amino acid hydrophobic leader that is removed during processing to form the mature 266 amino acid Fc α RI a.1 full-length glycoprotein (39). Fc α RI is composed of two extracellular Ig-like domains, a predicted transmembrane region and a cytoplasmic tail devoid of recognized signaling motifs (Figure 3A). The protein core has a predicted M_r of 30 kDa and bears five potential N-linked glycosylation sites and several putative O-glycosylation sites. Mature cell surface Fc α RI display heterogeneous glycosylation with M_r ranging from 50 to 100 kDa, depending on the cell type (38, 43). Deglycosylation experiments using endoglycosydase F or O, indeed, confirmed a heterogeneous Fc α RI glycosylation with two molecular species, one of 32 and a second of 34 kDa, possibly attributable to inaccessibility of some carbohydrates (38, 43, 45). Fc α RI a.2 has a deletion in the extracellular domain of 22 amino acids and a backbone of 28 kDa (48). Another indication that Fc α RI a.1 exists in different glycosylated forms was obtained using the CD89 mAb A62 (43). This mAb recognizes a subpopulation of Fc α RI proteins with lower M_r (55–65 kDa) than the whole Fc α RI population (55–75 kDa) recognized by other CD89 mAb (A3, A59, A77, My43) on monocytes and neutrophils.

The Fc α RI binding site has been located in the membrane-distal EC1 domain (52, 65). This was demonstrated in experiments where point-mutations within EC1 greatly reduce IgA binding. A number of residues are potentially involved in IgA binding, located in the C strand (Y35), the C'-E region (R52), and the F-G loop (Y81, R82, I83, G84, H85, and Y86) (Figure 3B). This model predicts the F-G loop to be located at the bottom of EC1, apparently in a position close to the cell membrane. This represents a unique feature among the two-domain type FcR because Fc γ R and Fc ϵ RI both bind their respective Ig ligands via the membrane-proximal EC2 domains (88–90). It is noteworthy that the closely related bovine Fc γ 2R and p58 KIR molecules also bind ligand (bovine IgG2, and HLA molecules, respectively) via their EC1 domain (52, 91). The high degree of similarity between Fc α RI and p58 KIR proteins allowed a three-dimensional model of CD89 to be proposed based on the solved structure of KIR.

Fc α RI is a low-affinity receptor for IgA (K_a approximately $10^6 M^{-1}$). Rapid dissociation of the Fc α RI:IgA complex ($t_{1/2} \sim 25$ s) using recombinant soluble Fc α RI

suggests that monomeric IgA bind only transiently to cellular Fc α RI, whereas IgA immune complexes bind avidly (65). This confirms previous monocyte data showing polymeric IgA and IgA-IC to bind more efficiently to Fc α RI than monomeric IgA (50). Fc α RI binds IgA1 and IgA2 molecules at the boundary between the C α 2 and C α 3 domains (Figure 3B) (92, 93). Fc α RI glycosylation may also play a role because desialylated receptors bind five times more IgA (38). Another study documented full IgA glycosylation not to influence Fc α RI binding. Indeed, absence of N-glycans in C α 2 constructs does not impede binding to human neutrophil Fc α RI (94). The observation that SIgA binds transiently but specifically to Fc α RI (95) suggests that the binding site on IgA is not obstructed by a bound secretory component. Recent work defined a crucial role for complement receptor 3 (Mac-1, CD11b/CD18) in Fc α RI's capacity to bind SIgA, but not serum IgA (95a).

Cytokines can influence IgA binding to Fc α RI. Both IL-4 and IL-5 increase IgA ligand binding to Fc α RI, without effects on receptor expression, suggesting that cytokine stimulation regulates Fc α RI avidity (96). The increase in Fc α RI's avidity for IgA induced by cytokines seems mediated by a cytokine-induced inside-out signaling mechanism. This involves PI 3 kinase and phosphorylation of a serine residue (S263) in Fc α RI's cytoplasmic tail (97, 98).

Whether or not mouse IgA binds to human Fc α RI is controversial. Initial studies used erythrocytes coated with mouse IgA myeloma MOPC-315 to detect human IgA receptors (4). Later studies by others failed to observe binding of mouse IgA to human Fc α RI (93). However, recent evidence for binding of dimeric, but not monomeric, mouse IgA to human Fc α RI comes from experiments using macrophages from human CD89 transgenic (Tg) mice (99). Macrophages from human CD89-Tg SCID mice allow detection of mouse IgA binding, which is inhibited by the CD89 mAb My43 (99). These Tg mice, furthermore, form IgA complexes with soluble human Fc α RI, culminating in the development of IgA nephropathy in six-month-old mice, supporting interaction between mouse IgA and human Fc α RI.

Two types of soluble Fc α RI have been described. The first type is generated by proteolysis via an FcR γ -chain-dependent pathway (100). This soluble form, a slightly glycosylated 30-kDa protein with a 25-kDa backbone, was shown to be covalently associated with polymeric IgA, which circulates in serum of normal individuals (101). The molecular nature and function of this 30-kDa Fc α RI remains unclear. A second soluble Fc α RI type was described in serum from patients with IgA nephropathy (IgAN) (99). Studies with metabolically labeled cells from IgAN patients revealed a glycosylated soluble Fc α RI form of 50–70 kDa with a 24-kDa protein core (99). Production of this latter soluble Fc α RI is induced by polymeric IgA from Fc α RI transfected cells. IgA-induced shedding was indicated by the loss of reactivity with an antibody raised against Fc α RI cytoplasmic tail. These data indicate that cleavage of the Fc α RI extracellular domain may occur, resulting in release of IgA/Fc α RI complexes into circulation.

Signal Transduction

Fc α RI is a member of the multichain immune recognition receptor (MIRR) family. Signaling is dependent on association of Fc α RI with the FcR γ -chain subunit, forming the trimer Fc α RI α / γ γ (102). The FcR γ -chain was initially described as a component of Fc ϵ RI and Fc γ RI, expressed on mast cells and monocytes, respectively (36). The FcR γ -chain contains a so-called ITAM (immunoreceptor tyrosine-based activation motif) signaling motif (103). The Fc α RI α -FcR γ interaction is strong and depends on oppositely charged residues in their transmembrane regions (104, 105). However, Fc α RI can be expressed either associated, or non-associated with FcR γ (so called γ -less receptor) on monocytes or neutrophils (Figure 4). Although the basis for this partial association of Fc α RI to FcR γ remains unknown, it is possible that due to the positively charged Arginine at position 209 Fc α RI may associate with another—as yet uncharacterized—molecule. Notably, colostrum neutrophils express only γ -less Fc α RI, despite large amounts of intracellular FcR γ -chain (95). While γ -less Fc α RI represent the majority of cell surface receptors, the level of Fc α RI- γ 2 is upregulated by phorbol esters and interferon- γ on monocytes (105). Importantly, human Fc α RI cannot be expressed *in vivo* in mice deficient in the FcR γ -chain, contrasting with *in vitro* data using transfectants (106) (M. Arcos-Fajardo and R. Monteiro, unpublished). This discrepancy may be attributable to species-specific differences in Fc α RI assembly.

Cross-linking of IgA bound to Fc α RI triggers the receptor's redistribution into glycosphingolipid- and cholesterol-rich domains or "rafts" in the cell membrane that serve as signaling platforms important for recruitment of signaling effectors (107, 108). FcR γ -ITAM's are initially phosphorylated by the Src kinase lyn, which leads to recruitment of a number of tyrosine kinases including Syk, Blk, Btk, PI-3 kinase, and PLC- γ 2 (Figure 4). Recruitment and phosphorylation of Syk and Btk are modulated by cell stimulation with interferon- γ and/or phorbol ester, indicating that activation of these tyrosine kinases through Fc α RI may depend on the level of cell priming at inflammatory sites (110).

Fc α RI cross-linking triggers calcium release from intracellular stores in neutrophils (112) and induction of NADPH oxidase activity that is sensitive to inhibition by PI 3-kinase inhibitors (113). Fc α RI can also associate with Grb2, Shc, SHIP (SH2-containing inositol phosphatase-1), and SLP-76 (SH2-containing leukocyte protein of 76 kDa), suggesting the formation of adaptor complexes to regulate signalling (111). Recently, it has been shown that IgA can also activate the ERK1/2 MAP kinase pathway on PMA-treated alveolar macrophages (114) and serine/threonine kinases such as protein kinase C (PKC) α , PKC ϵ , and protein kinase B (PKB) α (115).

Biological Function

FcR participate in many aspects of host defense through engagement with antibodies complexed to antigens. FcR ligation by immunoglobulins can initiate a plethora of biological processes, including phagocytosis, antigen presentation,

ADCC, superoxide generation, and the release of cytokines and inflammatory mediators (116). FcR ligation can also modulate the activation status of cells, and consequently immune responses (117).

The cellular functions promoted by Fc α RI depend mostly on FcR γ -chain-mediated tyrosine kinase activation. In this context, it has been shown using transfectants that only Fc α RI molecules associated with FcR γ can induce Ca²⁺ release, IL-2 release, degranulation, or IgA degradation (104, 105). However, both types of Fc α RI, Fc α RI- γ 2, and γ -less Fc α RI perform endocytosis at similar rates (105). Although γ -less Fc α RI are unable to mediate downstream functions, they recycle internalized IgA complexes and protect them from degradation. Cells expressing the two forms of Fc α RI (Fc α RI- γ 2 and γ -less Fc α RI) may play a regulatory role, either by degrading IgA antibody complexes or by recycling serum IgA to achieve serum homeostasis, possibly depending on receptor clustering size (105). Recently, it has been shown that Fc α RI- γ 2 complexes mediate antigen presentation in IIA1.6-cell transfectants expressing Fc α RI plus either wild-type FcR γ -chain, a γ -chain in which the ITAM was altered by a Y to F mutation, or a γ -chain in which the ITAM was substituted with the ITAM of Fc γ RIIA (118). The results indicated that signaling-competent ITAM was not required for endocytosis of IgA-ovalbumin. Antigen presentation, however, was impaired by ITAM changes. Signaling-competent FcR γ -chain ITAM appeared necessary for transport of ligated Fc α RI to lamp-1(+) late endocytic compartments, for remodeling and/or activation of those compartments, and also for efficient degradation of IgA complexes. Moreover, Fc α RI ligation activated efficient processing of nonreceptor-targeted antigen. The results suggest FcR γ -chain signaling to activate the antigen processing (118).

Fc α RI mediates phagocytosis of IgA-opsonized bacteria and yeast particles, and priming of neutrophils and monocytes represents an essential step in phagocytosis of IgA-coated particles. This has been demonstrated using GM-CSF; and IL-8 on neutrophils (55, 119–122); IL-1, TNF- α , GM-CSF, or LPS on monocytes (57); and GM-CSF, IL-4, or IL-5 on eosinophils (96). Priming-induced increases in IgA-mediated phagocytosis have been attributed to either modulation of the number of Fc α RI molecules on the cell surface or an increase of Fc α RI avidity for ligand.

Another function initiated by Fc α RI is antibody-dependent cell-mediated cytotoxicity (or ADCC). Cells primed by IgA antibodies mediate lysis of target cells such as bacteria, *Schistosoma mansoni schistosomula*, erythrocytes, as well tumor cells (123–126). This has been the basis for the development of therapeutic approaches targeted to Fc α RI. CD89-targeted bispecific antibodies direct highly effective reverse ADCC and phagocytosis of tumor cells by Fc α RI expressing cells (127–129).

In vitro data indicate that under certain conditions Fc α RI cooperates with complement receptors CR1 and CR3 to improve the efficiency of different cellular effector functions. Immune complexes containing IgA and C3b/iC3b induce faster release of lactoferrin from neutrophils than do IgA immune complexes alone (130). In another study, leukocytes required IgA and complement to kill *Streptococcus pneumoniae* (131). More recently it was demonstrated that human Fc α RI

transgenic mice back-crossed to CR3^{-/-} animals were unable to initiate extracellular lysis of target cells (106, 132).

Activation through Fc α RI depends on receptor clustering on the cell surface. Studies with unprimed monocytes showed Fc α RI cross-linking to result in induction of IL-6 and TNF- α release (133). Also, Fc α RI triggering on monocytes by CD89 mAb or by IgA immune complexes induces secretion of IL-1 β , IL-8, leukotrienes C4 and B4, and prostaglandin E2, as well as superoxide release (134–138). Similarly, aggregated serum IgA and cross-linked monomeric, polymeric IgA, SIgA, or CD89 mAb My43 trigger a respiratory burst inducing superoxide release in neutrophils (120, 139–142). Both subclasses of IgA, IgA1 and IgA2, can initiate these functions. It is noteworthy that IgA2 immune complexes trigger neutrophil activation more efficiently than do IgG complexes (143). A similar trend was observed in studies with FcR-directed bispecific antibodies, documenting Fc α RI-directed antibodies to be superior to Fc γ R-directed BsAb in facilitating lysis of CD20-positive tumor cells (129). IgA antibodies potently induce lysis of lymphoma and solid tumor targets and are far more effective than IgG anti-tumor antibodies in recruiting neutrophils, the most populous type of tumor-cytolytic cells in blood (144, 145). IgA therapeutic molecules also do not interact with down-modulatory types of FcR, such as Fc γ RIIb (117), in contrast to IgG antibodies. In addition, work with recombinant SIgA molecules directed to *S. mutans* documented these molecules to be longer lived at mucosal sites than IgG, and to effectively prevent oral bacterial colonization in humans (146). These data suggest IgA antibodies to represent attractive candidates for immunotherapy of neoplastic and infectious disorders (147).

On eosinophils, Fc α RI aggregation seems required for degranulation and release of eosinophil-derived neurotoxin following triggering by SIgA-coated beads (148). However, since other less-well characterized receptors for secretory component have been described on eosinophils (149), it is difficult at this time to attribute these effects conclusively to Fc α RI.

Role of Fc α RI in Mucosal Defense

The observation that intestinal macrophages fail to express Fc α RI (49) may point to a programmed anti-inflammatory system for protection of mucosal integrity. In this context, CD15⁺ colostrum neutrophils express Fc α RI at levels similar to those on blood neutrophils. Most colostrum neutrophils (70%), however, bear SIgA on their surface, whereas blood cells do not. The former cells do express Fc α RI alone and fail to release superoxide products or kill bacteria in an Fc α RI-dependent way, indicating that γ -less Fc α RI exhibit anti-inflammatory properties (95). By contrast, colostrum mononuclear cells are able to kill enteropathogenic *Escherichia coli* opsonized with colostrum IgA via Fc α RI (150).

Recently a differential regulation has been documented for the Fc α RI a.2 isoform on human alveolar macrophages at the level of the ERK1/2 pathway (114). It was observed that S-IgA and p-IgA downregulate the LPS-increased

respiratory burst in alveolar macrophages through an inhibition of ERK1/2 activity. Both these IgA ligands, however, induce an increase in respiratory bursts associated with upregulated ERK1/2 phosphorylation on PMA-treated cells.

Analysis of the *in vivo* role of Fc α RI was made possible by generation of two types of transgenic mice. One model, in which the Fc α RI transgene was placed under control of a CD11b promoter, resulted in high human Fc α RI expression levels on monocytes and macrophages (99). In a second model, created with the use of a cosmid clone bearing the human Fc α RI gene under its own regulation, a preferential expression on neutrophils was observed (106). In both models, Fc α RI transgenic mice express CD89 only on myeloid cells, similarly as in humans. However, because the cosmid-generated Fc α RI transgenic (Tg) mice contain the endogenous regulatory sequences, it was possible to modulate Fc α RI expression on macrophages and Kupffer cells (33, 151). These mice helped to determine the role of Fc α RI in mucosal infections including studies with *S. pneumoniae* and *Bordetella pertussis*. In both cases, Fc α RI transgenic mice could be protected against pneumonia and sepsis (152) (G. Vidarsson & J.G.J. van de Winkel, unpublished).

Kupffer cells express Fc α RI in humans and have been proposed as essential for the clearance of bacteria passing the mucosal barrier (33). The Fc α RI-Tg mice demonstrated that Fc α RI plays a key role in mucosal defense. Indeed, *in vivo* studies show that Fc α RI-expressing Kupffer cells vigorously ingest *E. coli*, opsonized with human serum IgA. Notably, these studies revealed human SIgA to be incapable of initiating phagocytosis. This was also observed *in vitro* for other pathogens, including *Staphylococcus aureus*, *Candida albicans*, *B. pertussis*, and *S. pneumoniae* (33, 153–155, 155a). Based on these results one can propose that SIgA may function as an “antiseptic coating” at the mucosa by avoiding bacterial adherence and invasion of microorganisms. Binding of antigens to SIgA, thus, does not initiate inflammatory processes, qualifying this class of antibody as non-inflammatory (Figure 5A).

Under pathological conditions, characterized by disruption of the mucosal barrier with production of inflammatory mediators, primed Kupffer cells or dendritic cells expressing Fc α RI may play an important role either as a second line of defense against bacterial infection or by arming the immune system to respond to external antigens (Figure 5B) (33). In this context, upregulation of Fc α RI associated with FcR γ -chain on monocytes from patients with septic shock by gram-negative bacteremia has been reported. This confirms a possible role of this receptor in immunity against bacterial infections (156).

Fc α RI is expressed on immature dendritic cells but is undetectable by immunohistochemical methods on human epithelial LC (31), suggesting that LC may neglect IgA immune complexes within the epithelium in the absence of a breakdown of the epithelial barrier. Fc α RI downregulation may be mediated by TGF β 1, which surrounds mucosal areas. This is demonstrated when *in vitro* (31, 60) Fc α RI is active in Ag-binding and Ag-uptake, permitting internalization of the ligand by immature DC, which triggers overexpression of the costimulatory molecule CD86,

and of MHC class II molecules at the plasma membrane, which increases their allostimulatory activity and triggers IL-10 production (31) (Figure 5C). IL-10 has been found to mediate IgA1 and 2 isotype switching (157). Fc α RI⁺ interstitial-type dendritic cells may well play a role in mounting specific immune responses against mucosa-derived antigens bound to SIgA; activation of dendritic cells via Fc α RI may positively feed-back on IgA production. It should be mentioned, however, that a recent report confirms Fc α RI expression by immature dendritic cells but claims SIgA binding to these cells is mediated not by Fc α RI, but rather via carbohydrate-recognizing receptors such as mannose receptor (46).

Fc α / μ R

A mouse Fc receptor for IgA and IgM, designated Fc α / μ R, recently described (40, 158), represents a type I transmembrane protein of 503 amino acids containing four potential sites for N-linked glycosylation. The receptor has only one extracellular loop, which contains a conserved motif present in the first EC loop of human, bovine, and murine pIgR, suggesting an ancestral link. Fc α / μ R has a human homologue, and both bind IgM as well as IgA with intermediate affinity. The human Fc α / μ R gene is located at chromosome 1q 32.3 near several other FcR genes. Fc α / μ R is constitutively expressed on the majority of murine B lymphocytes and macrophages. Cross-linking Fc α / μ R by soluble IgM or IgM-coated microparticles triggers receptor internalization. Fc α / μ R, furthermore, mediates B lymphocyte endocytosis of IgM-coated *S. aureus*. Fc α / μ R has been proposed to play a role in the primary stages of antimicrobial immune responses (40). Moreover, Fc α / μ R is expressed on mature, but not immature, B lymphocytes and acquires the ability to bind IgA and IgM antibodies after B lymphocyte stimulation (158). This receptor is abundantly expressed in secondary lymphoid organs such as lymph nodes, appendix, and intestine, suggesting a role in systemic and mucosal immunity (158). More recently, Fc α / μ R transcripts have been shown in human mesangial cells, which were in addition markedly upregulated by proinflammatory cytokines such as IL-1 (159), suggesting a regulatory role for this receptor during inflammation.

ALTERNATIVE IgA RECEPTORS

Asialoglycoprotein Receptor (ASGP-R)

The liver plays an important role in maintaining homeostasis through regulation of IgA catabolism. The ASGP-R expressed on hepatocytes (41, 160) recognizes terminal Gal residues on serum glycoproteins, including IgA, and conveys bound ligand for intracellular degradation. Studies performed in primates revealed that a minority of proteins bound and internalized by ASGP-R escape degradation and are transported into bile in intact form (161). The ASGP-R is proposed to be involved in IgA clearance from the blood (162). The major pathway for IgA2 clearance was recently shown to be mediated by the liver ASGP-R. Liver-mediated

uptake through the ASGP-R was suppressed in ASGP-R-deficient mice. Notably, only a small percentage of IgA1 is cleared through this pathway. Clearance of IgA1 lacking the hinge region, with its associated O-linked carbohydrate, was more rapid than that of wild-type IgA1. The rapid clearance of IgA2, and not IgA1, through the liver may contribute to the higher serum levels of IgA1, relative to IgA2 (158).

Transferrin Receptor (TfR)

Transferrin receptor, TfR (or CD71), selectively binds IgA1 (42). In contrast to Fc α RI, this IgA receptor is not fully expressed on mature blood leukocytes, but it is well-expressed on cultured renal mesangial cells. Highly purified polymeric IgA1 (free of transferrin) binds better to TfR than does monomeric IgA1 (I.C. Moura & R. Monteiro, unpublished).

Human T and B lymphocytes have been observed to bind human IgA (2–4, 164–166). IgA binding proved dependent on T lymphocyte proliferation, and the TfR mediated the interaction with IgA (42). TfR is an IgA receptor expressed on B lymphocyte cell lines, such as Daudi cells (42). It is possible that the TfR mediates the earlier described IgA1 binding to T cells, mediated by O-linked carbohydrate moieties within the IgA1 (and IgD) hinge region (167, 168). It remains unclear whether TfR binds IgD (169).

Secretory Component Receptor (SCR)

A receptor specific for secretory component (SC) with a M_r of 15 kDa has been isolated from eosinophils (149). This molecule binds SC and SIgA, but not serum IgA, and triggers degranulation and release of eosinophil cationic protein and peroxidase. Thus, the existence of two types of IgA receptors capable of binding SIgA, Fc α RI and the SC receptor, may underlie SIgA's potency to trigger eosinophil degranulation (148). SIgA also induces basophil degranulation in an Fc α RI-independent manner and may express SCR as well (170).

Other IgA Receptors

Recently, a mouse IgA receptor was described on Peyer's patch M cells, an epithelial cell located exclusively within the follicle-associated epithelium overlying mucosa-associated lymphoid tissues (170a). Although the molecular nature of this receptor remains unknown, it is interesting that this murine molecule can bind human IgA2 but not human IgA1. Furthermore, in contrast to Fc α RI, the IgA binding to the M-cell receptor was dependent on C α 1 and C α 2 domains.

INVOLVEMENT OF IgA RECEPTORS IN PATHOLOGY

IgA-associated diseases are characterized by increased serum IgA levels, often paralleled by IgA tissue deposition. These disorders include IgA nephropathy (IgAN), ankylosing spondylitis, Sjögren's syndrome, alcoholic liver cirrhosis (ALC), HIV infection, and dermatitis herpetiformis.

Abnormal Fc α RI endocytosis is potentially harmful due to impaired removal of IgA-containing immune complexes from blood. Defective Fc α RI endocytosis rates, and increased IgA recycling toward the cell surface, have been demonstrated on blood phagocytes from patients with IgAN and ALC (171, 172). As a consequence, cells from these patients express high IgA levels.

In IgAN, an altered O-linked glycosylation, a decreased galactosylation and altered sialylation, has been observed in a subpopulation of serum IgA1 (173). Macromolecular IgA complexes that escape clearance by IgA receptors may be trapped in the mesangium in IgAN (173). It remains unclear, however, whether abnormally glycosylated IgA1 in IgAN patients influences its capacity to bind to Fc α RI, ASGPR, or TfR. Some studies suggest IgA binding to Fc α RI to be favored in IgAN patients because increased amounts of IgA bound to blood monocytes and neutrophils were observed. In addition, purified IgA from these patients binds better to normal monocytes than IgA from healthy volunteers (61). Notably, another study documented a reduced affinity of patient IgA for Fc α RI-transfected B cells (174). The fact that mouse B cells may express up to three IgA receptor types, pIgR (175), Fc α / μ R (40), and TfR (42), complicates interpretation of these latter data.

Studies in IgAN patients, and patients with other IgA-associated disease including HIV infection, ALC, and spondyloarthropathies, indicate reduced Fc α RI expression levels on circulating monocytes and (to a lesser degree) on neutrophils, (61, 172, 176, 177). Other investigators did not observe a decreased monocyte Fc α RI expression using indirect immuno fluorescence (178). Addition of IgA has a negative effect on Fc α RI expression, possibly due to shedding of Fc α RI's extracellular domain (99). The demonstration of soluble Fc α RI in serum of IgAN patients and not in serum from healthy controls supports this hypothesis. In addition, metabolically labeled cells from IgAN patients released a glycosylated Fc α RI form of 50–70 kDa with a 24-kDa protein core. Production of soluble Fc α RI was also induced by polymeric IgA from Fc α RI-transfected cells. IgA-induced Fc α RI-shedding was indicated by the loss of reactivity with an antibody specific for Fc α RI's cytoplasmic tail. These results indicate that cleavage of the Fc α RI extracellular domain can occur, resulting in release of IgA/Fc α RI complexes into the circulation. Cleavage may be promoted by Fc α RI aggregation with cell surface protease(s). IgA-induced receptor shedding in IgAN patients may amplify the molecular size of immune complexes and could include IgA–IgG rheumatoid factors, or IgA–fibronectin complexes (173).

Recent work in human Fc α RI Tg mice modeled the development of IgAN (99). Human Fc α RI interacts with mouse polymeric IgA to form complexes that are deposited in the renal mesangium of Fc α RI Tg mice. Whereas other animal models, such as the ddY, HIGA mice, and uterogloblin knockout mice, only show some signs of IgAN (173), human Fc α RI transgenic mice developed mesangial IgA deposition, hematuria, mild proteinuria, and macrophage infiltration around the renal glomeruli (99). The disease can be transferred to wild-type recipients by infusion of serum IgA/soluble Fc α RI complexes from Tg mice. To examine the

contribution of IgA, a model of SCID-Fc α RI Tg mice was created. These mice do not develop IgAN spontaneously, but develop manifestations of IgAN upon injection of IgA from IgAN patients. Interestingly, IgA from healthy subjects did not result in IgAN in SCID-Fc α RI Tg mice, suggesting that abnormally glycosylated IgA coupled with Fc α RI participates in IgAN pathogenesis. Circulating complexes containing IgA and soluble Fc α RI may well be involved in the development of IgAN (99, 179).

Overexpression of a mesangial IgA1 receptor, the TfR (CD71), has also been found in patients with IgAN (42), and may well mediate the (selective) deposition of IgA1 complexes in kidneys. Deposited mesangial IgA1 complexes may trigger inflammation via the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- α , with consequent fibrosis and renal impairment (179, 180). This hypothetical cycle of events could thus account for progression and chronicity of disease. This picture may yet be more complicated, as Fc α / μ R transcripts have also been found in human mesangial cells, which are upregulated by pro-inflammatory cytokines such as IL-1 (150).

Enhanced Fc α RI surface expression has been observed on eosinophils of allergic patients (45) and on monocytes from patients with gram-negative bacteremia (156). Increased levels of IgA antibodies against allergen and bacterial antigens have been documented in sputum of atopic asthmatic individuals (181). Whether increased Fc α RI expression exerts a protective or harmful role in these diseases remains to be established.

CONCLUSIONS

Receptors for IgA play a significant role in vivo in maintaining the integrity of immune responses in systemic and mucosal compartments. In this review we summarized the current knowledge of five types of IgA receptors, focusing on Fc α RI (CD89). This receptor appears to play an important role in immunity by linking the IgA response to powerful cellular effector mechanisms. A role for select IgA receptors has been implicated in a variety of pathological conditions. Recent studies support a role for IgA antibodies and Fc α RI-directed molecules as therapeutics for human disease.

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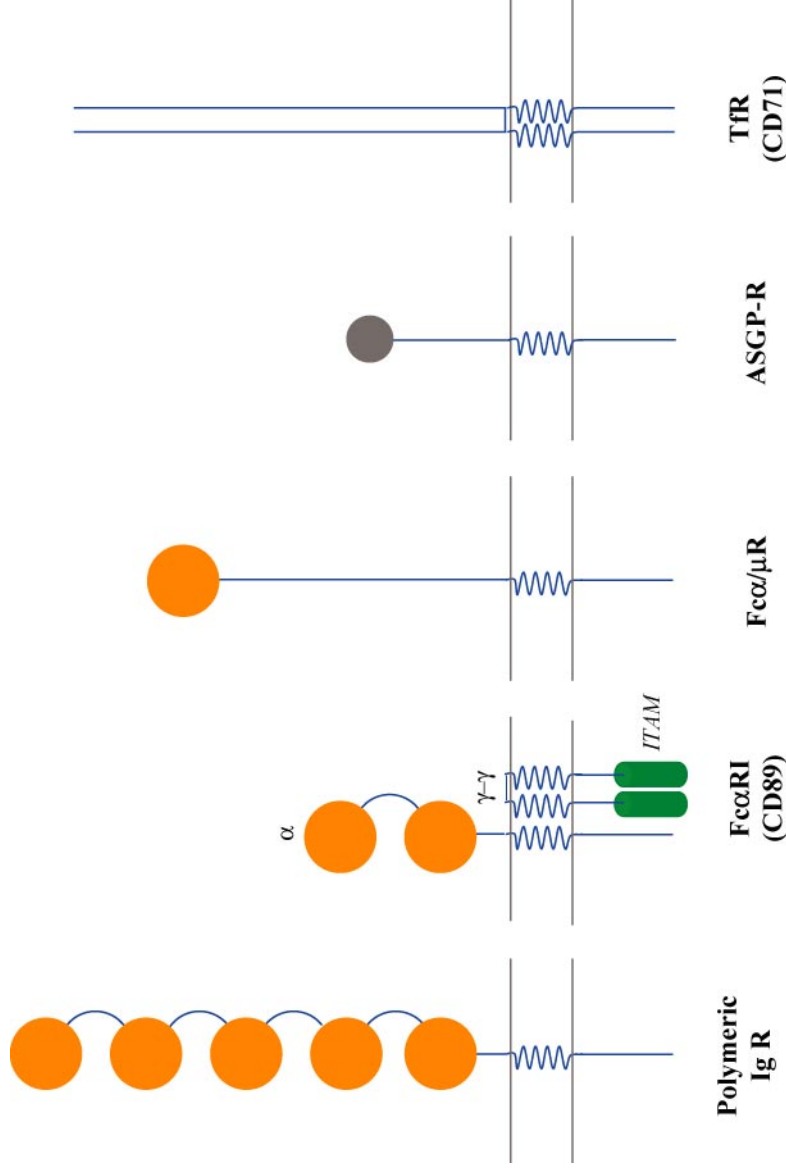


Figure 1 The human IgA receptor family. Orange circles are schematic representations of extracellular Ig-like domains (for an example of a three-dimensional structure see CD89 in Figure 3B). pIgR, polymeric Ig receptor; Fc α RI, the myeloid IgA Fc receptor; Fc α / μ R, the IgA/IgM Fc receptor; ASGP-R, the asialoglycoprotein receptor; TtR, the transferrin receptor.

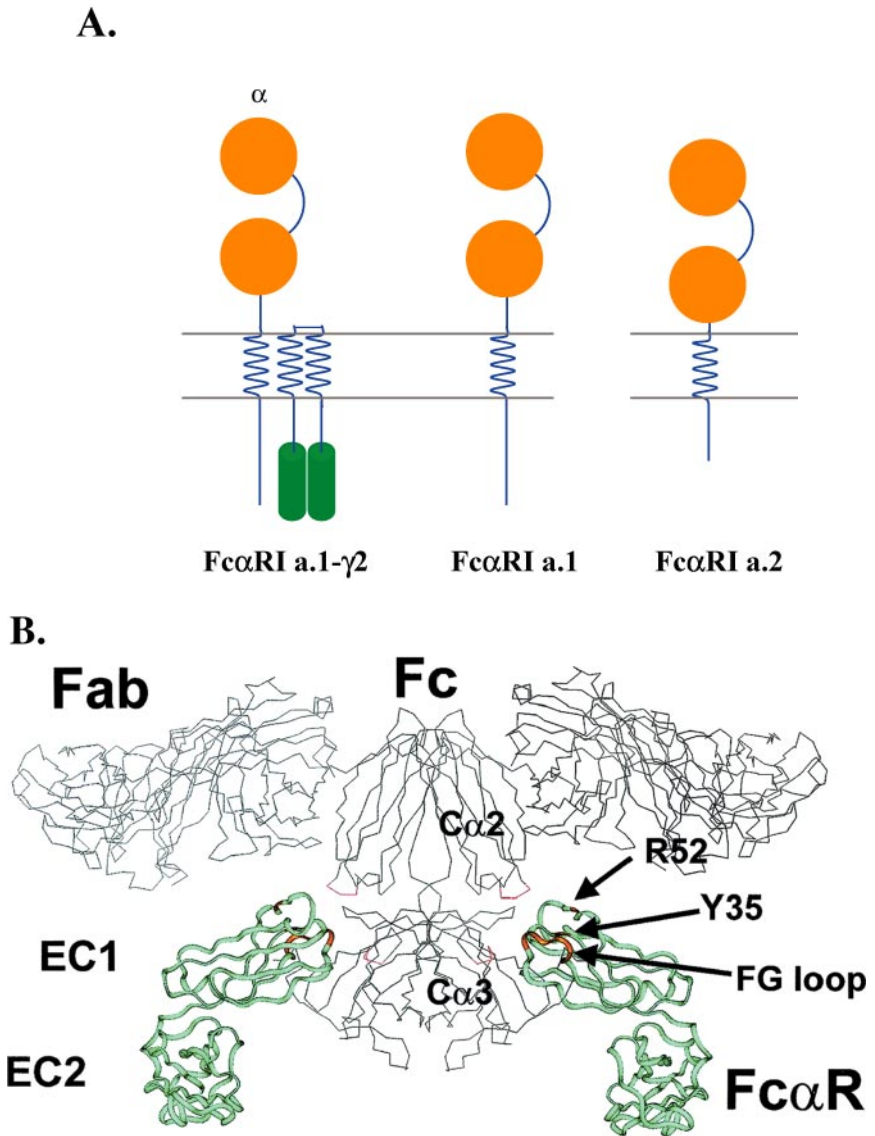


Figure 3 (A) Schematic model for Fc α RI (CD89) structure. Fc α RI a.1 can be expressed associated or not associated with the FcR γ -chain. Fc α RI a.2 has a deletion of 22 amino acids in the EC domain near the membrane. (B) Automated protein-modeling for Fc α RI (CD89) indicating residues important for ligand binding [modified from Wines et al. (87)]. Copyright 2001. *The American Association of Immunologists, Inc.*

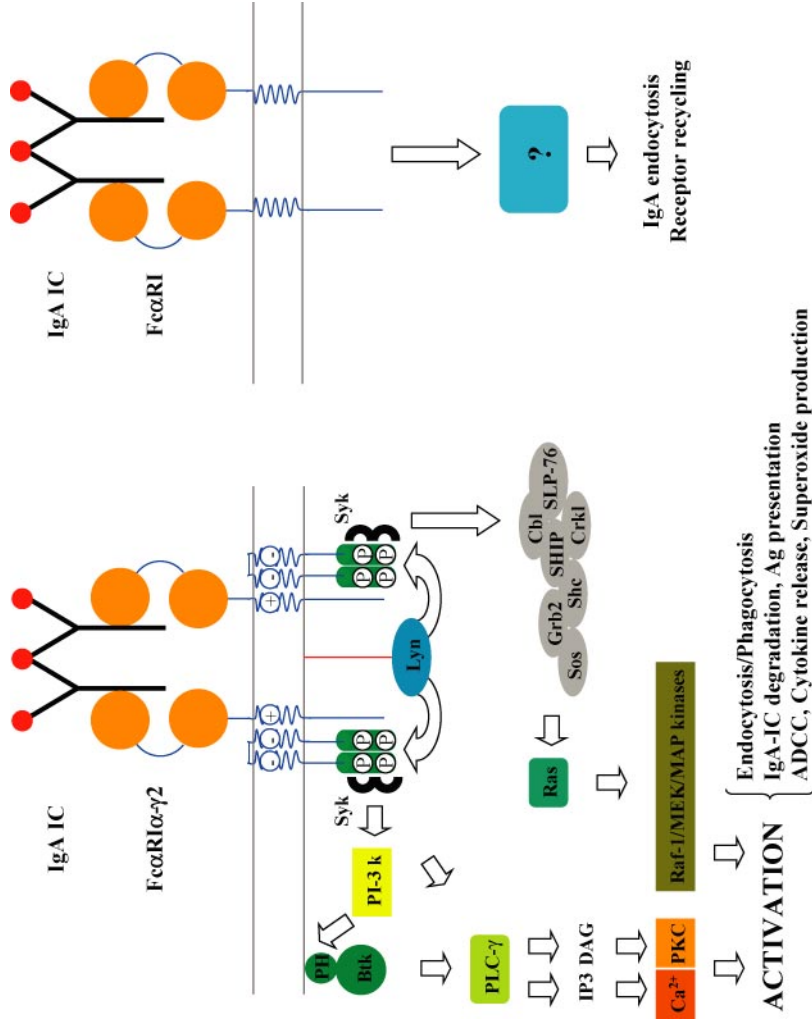


Figure 4 Signaling pathways triggered by Fc γ RI (CD89). Schematic model for IgA-mediated cellular activation depending on clustering of Fc γ RI- γ 2 complexes. Signaling through Fc γ -unassociated Fc γ RI molecules is unclear. IgA IC, IgA immune complexes.

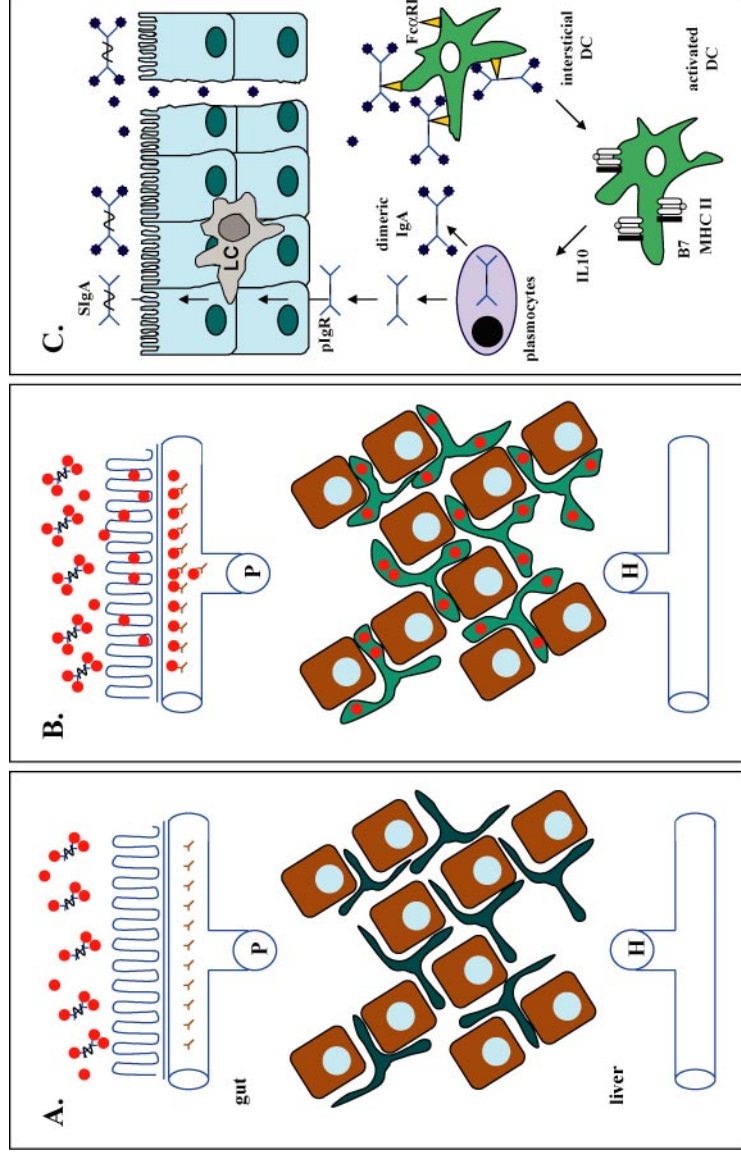


Figure 5 Model for the role of $Fc\alpha RI$ in mucosal defence. (A) Protection of mucosal surface by SIgA. (B) $Fc\alpha RI$ as a gatekeeper against bacterial infections. Upon disruption of the epithelial barrier, pathogens are exposed to serum IgA. Inflammatory cytokines induce Kupffer cell $Fc\alpha RI$, which filter the portal blood via $Fc\alpha RI$ -mediated phagocytosis. P, portal vein, H, hepatic vein. Small red circles represent bacteria. (C) $Fc\alpha RI$ -mounted immune response following disruption of epithelial barrier. Small blue circles represent environmental antigens and yellow triangles, the $Fc\alpha RI$. MHC, major complex of histocompatibility; B7, costimulatory molecule; LC, Langerhans cells; DC, dendritic cells.

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