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*Review*

# CD89: the Human Myeloid IgA Fc Receptor

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**Abstract.** CD89 (FcαRI) is the human myeloid IgA Fc receptor expressed on cells, such as neutrophils, eosinophils and monocytes/macrophages. Cross-linking of CD89 on these cells, by IgA-opsonised particles (e.g. bacteria, viruses) or anti-CD89 monoclonal antibodies, can trigger various immunological effector functions which are generally protective but may also cause harm to the body. CD89 is a transmembrane glycoprotein that binds both subclasses of IgA in all its molecular forms (i.e. monomeric, dimeric and secretory IgA) via a region of its membrane-distal EC1 domain. DNA studies have shown that the CD89 gene is located within the newly described leukocyte receptor cluster (LRC) on chromosome 19. CD89 is more closely related to the KIR and MIR proteins, whose genes are also found in the LRC, than to other human Fc receptors (FcRs). On myeloid cells, CD89 is able to associate with the immunoreceptor tyrosine-based activation motif (ITAM)-containing the FcR γ chain, which is responsible for intracellular signaling via CD89. Recently, it has been suggested that some cells express CD89 in a form that does not associate with the FcR γ chain. Although the biological relevance of this observation is not yet clear, it may explain certain anti-inflammatory/inhibitory effects attributed to IgA. Here we review current knowledge concerning the genetics, structure and biological function of CD89.

**Key words:** CD89; FcαR; FcαRI; IgA; Fc receptor; myeloid.

## Introduction

Receptors specific for the Fc regions of all immunoglobulin (Ig) isotypes (Fc receptors – FcRs) are expressed by most cells of the innate and adaptive immune systems. These isotype-specific FcRs enable antigen (Ag)-bound Igs and Ig-containing immune complexes (ICs) to trigger a diverse array of cellular effector functions, such as endocytosis, phagocytosis, augmentation of antigen presentation, superoxide production, antibody-dependent cellular cytotoxicity (ADCC), degranulation, and the release of various cytokines and other mediators of immunity[38, 83]. Terminally differentiated human B cells (plasma cells) produce five Ig classes: IgA, IgD, IgE, IgG, and IgM, with the vast majority (>80%) committed to IgA production[10]. Thus, more IgA is produced per day (66 mg/kg/day) than all other isotypes combined[10, 57]. In humans two subclasses of IgA (IgA1 and IgA2) exist, which are differentially distributed between the systemic and mucosal compartments. Serum IgA, predominantly monomeric IgA1, produced mainly by plasma cells located in lymph nodes, bone marrow and spleen, constitutes 15–20% of the total serum Ig pool[20, 45]. In external secretions, IgA produced by local plasma cells is the predominant isotype. The increased pre-

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valence of IgA2-producing plasma cells at exocrine effector sites results in more similar levels of IgA1 and IgA2 in secretions, particularly in the distal gut[20, 41, 45].

Local plasma cells secrete predominantly dimers and larger polymers of IgA (collectively called polymeric IgA – pIgA) that also contain a small peptide called the joining or J chain, responsible for controlling assembly of the secreted polymers[42]. The J chain, furthermore, allows binding of pIgA and pentameric IgM to the polymeric Ig receptor (pIgR), also called the transmembrane secretory component (SC)[11]. The pIgR transports pIgA and pentameric IgM through the mucosal epithelial cell to the apical membrane, where the ligand-binding portion of pIgR is cleaved and the complex is released into the lumen[72]. The portion of the pIgR remaining complexed to pIgA or pentameric IgM is called bound SC, and the released complexes are referred to as secretory IgA (SIgA) or secretory IgM (SIgM), respectively[68, 72]. Secretory IgA is the primary mediator of humoral immunity at mucosal surfaces, where the simple ability of SIgA to bind antigens leads to immune exclusion, preventing infections and influx of foreign Ags[16, 57, 102].

In addition to simply binding to Ags, the ability of various Ig isotypes to trigger secondary effector functions is the key to their effectiveness as antibodies. Activation of the complement system is considered one such important function. However, compared with IgM and IgG, IgA is a poor activator of complement and this is not considered important for the *in vivo* function of IgA[40, 95]. Therefore, IgA-mediated effector functions are believed to depend upon the interaction of IgA with specific IgA Fc receptors (FcαRs). Such receptors have been described on both myeloid and lymphoid cells and are presumed to function in the clearance of IgA-containing ICs and the control of IgA-mediated immune reactions.

In humans, the myeloid FcαR, CD89 (also termed FcαRI), represents the first extensively characterized IgA Fc receptor in terms of genetics, structure, biological function and cell expression pattern[66, 90]. Although experimental evidence suggests the existence of IgA receptors on human lymphoid cells, no such receptors have so far been characterized at the molecular level. Similarly, FcαRs from other species have not been identified, either. Therefore, this review will focus on current and emerging knowledge of CD89 and its role in immunity.

## Genetics

In 1990, a 1.6 kb cDNA clone encoding CD89 was isolated from phorbol myristate acetate-stimulated U937 cells[54]. This cDNA clone included a 39 bp 5'-untranslated region (UTR), an 861 bp open reading frame, and a 711 bp 3'-UTR ending in a poly-A stretch. The 3' UTR is AT-rich, includes an Alu sequence, but lacks a polyadenylation signal[54]. Recent analysis of a cosmid clone containing the CD89 gene (FCAR) revealed a polyadenylation signal ~1.8kb downstream of the stop codon (Fig. 1)[106]. Sequence comparisons showed CD89 to be a member of the Ig gene superfamily, related to human FcγR and FcεR[54]. Uniquely amongst FcR genes, however, the CD89 gene is located on chromosome 19, at position 19q13.4 (Fig. 1). Most human, mouse and rat FcγR and FcεRI α chain genes mapped so far are located on chromosome1[43, 83]. The CD89 gene consists of 5 exons spanning ~12 kb[23]. The first exon (S1) includes the 5'-UTR, an ATG translation initiation codon, and a large part of the leader peptide. Exon 2 (S2) is 36 bp long and encodes the remaining part of the leader peptide, including the predicted signal peptidase cleavage site. A similar mini-exon is found in all other FcγR genes and FcεRIα chain genes. In these genes, however, the S2 mini-exon is only 21bp in size[43, 83]. Exons EC1 and EC2 each encodes a single extracellular Ig-like domain, while the TM/C exon encodes a short extracellular segment, the transmembrane domain, and a short cytoplasmic tail. DNA sequence analysis, and the existence of a 36bp S2 mini-exon, identified the CD89 gene as a more distantly related member of the Ig receptor gene family[23, 43, 54].

Interestingly, CD89 is more closely related to the bovine Fcγ2R than to other FcRs. In fact, CD89 and Fcγ2R appear to constitute a separate group of FcRs, suggesting that these two genes diverged from each other before the divergence of humans and cattle[120]. Recently, it has been shown that CD89 and bFcγ2R are members of a new gene family that apparently evolved from a common ancestral gene. Other human genes belonging to this family include the natural killer cell inhibitory/activatory receptors (KIRs, KARs), the Ig-like transcripts (ILTs), the leukocyte and monocyte/macrophage Ig-like receptors (LIRs, MIRs), LAIR-1, and HM18[3, 8, 18, 19, 48, 59, 73, 87, 109]. The genes that encode these proteins are located close to the CD89 gene within the so-called leukocyte receptor cluster on chromosome 19q13.4[109, 112, 114]. Several murine members of the same gene family have also been described[44, 110].

In addition to the normal full length CD89 mRNA, numerous alternatively spliced CD89 transcripts have been isolated by reverse transcriptase polymerase chain reaction (RT-PCR) from human cells (Fig. 1)[64, 76, 78, 101]. Recently it was claimed that the CD89 gene includes

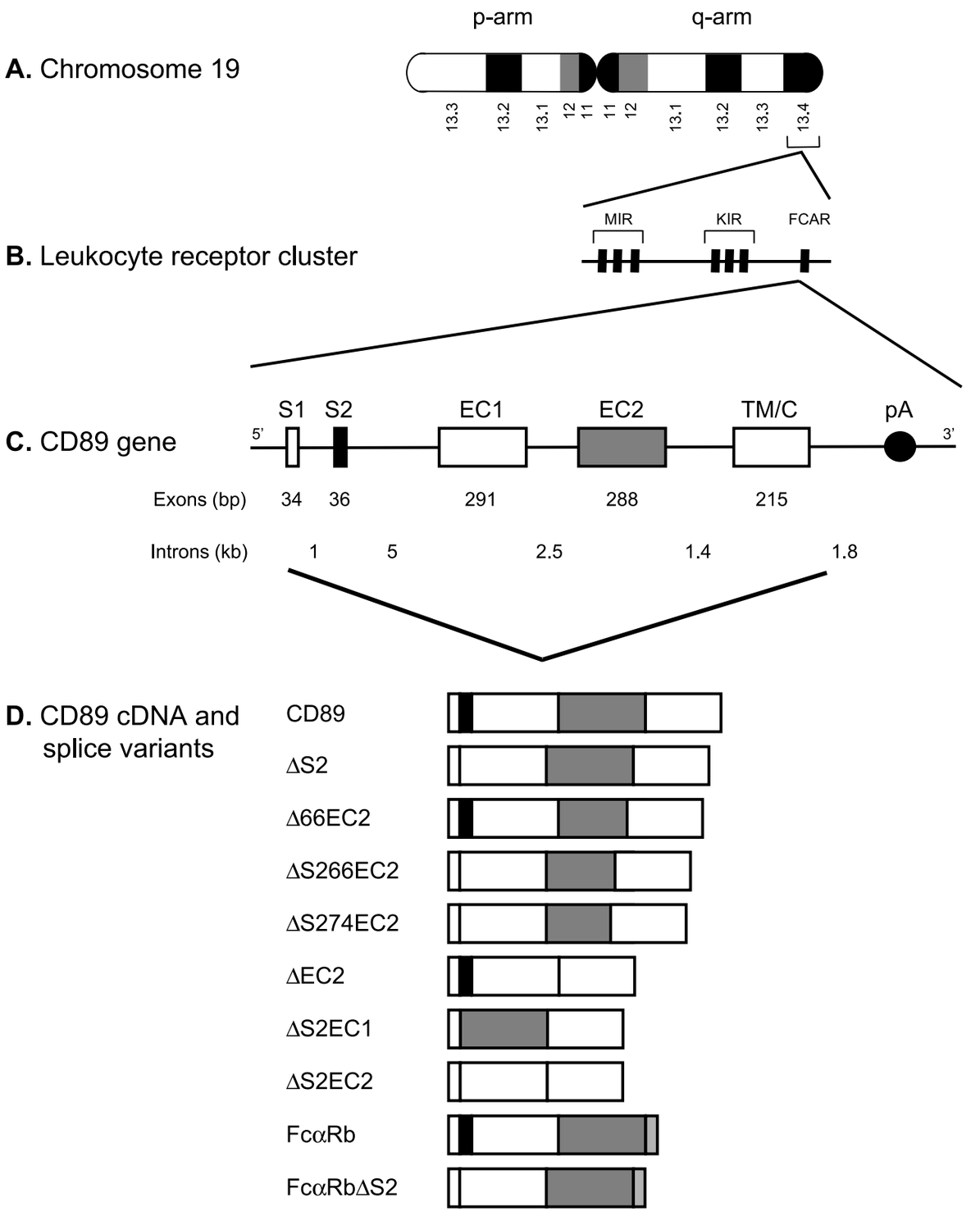


**Fig. 1. A.** Location of the leukocyte receptor complex on chromosome 19q13.4. EC1 and EC2 – extracellular domains 1 and 2; TM – transmembrane region; Cyt – cytoplasmic tail. **B.** Location of the CD89 gene (FCAR) within the leukocyte receptor complex which also contains the KIR and MIR genes. **C.** Intron-exon organization of the CD89 gene. **D.** Structure of CD89 cDNA and isolated splice variants. The putative S3 exon has been shown to be a pseudo-exon, therefore variants encoding this exon have been omitted[19, 39]. Please also note that several of the transcripts shown have been isolated by different investigators and have been given alternative names. Thus the Δ66EC2 variant has also been named FcαR a. 2[37], and the ΔEC2 variant FcαRIa2 or FcαR a. 3[37, 38]

an additional exon, S3, and that its transcription is correlated with the occurrence of IgA nephropathy (IgAN), a disease characterized by a high level of circulating IgA and IgA-containing ICs (see below)[101]. However, it has since been shown that the S3 exon is a non-functional pseudo-exon possessing stop codons in all reading frames[106]. A novel CD89 isoform (FcαRb), which appears to result from skipping the 3' splice site at the end of the EC2 exon, has also been isolated. Exon EC2 is thus extended by 23 new amino acids before reaching a new stop codon[104]. The protein product of FcαRb has been expressed in transfectants and shown to be unable to associate with the FcR γ chain (see below) and it may, in fact, code for a predominantly soluble form of CD89[104]. Whether this isoform is related to a newly described soluble form of CD89 is unknown[108]. While alternatively spliced mRNA transcripts of other human FcR (FcγR and FcεRIα) genes that generate biologically relevant isoforms have been reported, the biological role of the described CD89 splice variants remains obscure[38].

## Protein Structure, Ligand-Binding and Signaling

The 1.6kb CD89 cDNA encodes a 287-amino-acid protein[54]. A 21-amino-acid hydrophobic leader sequence is removed during processing to form the mature 266-amino-acid transmembrane glycoprotein. CD89 consists of two extracellular Ig-like domains followed by a stretch of hydrophobic amino acids representing the predicted transmembrane domain and a short cytoplasmic tail devoid of recognized signaling motifs (Fig. 2A). The protein core of CD89 has a predicted molecular mass of 30 kDa with differential glycosylation at the six potential N-linked sites, and the probability of additional O-glycosylation contributing to the variable size observed for the mature receptor (55–110 kDa).

Uniquely amongst two-domain FcRs, CD89 binds its ligand via the membrane-distal EC1 domain[67, 115]. Furthermore, point mutation of residues within the F-G loop of EC1 abolished or greatly reduced IgA-binding[115]. Conversely, FcγRII, FcγRIII and FcεRI all bind their respective Ig ligands via their membrane-proximal EC2 domains[38]. Interestingly, the closely related bFcγ2R and p58 KIR proteins also bind their ligands (bIgG2 and HLA molecules, respectively) via their EC1 domains[67, 116]. The high degree of similarity between CD89 and p58 KIR proteins has allowed a three-dimensional model of CD89 to be proposed based on the solved structure of the KIR (Fig. 2B)[26, 115]. This model predicts that the F-G loop is located at the bottom of the EC1 domain, apparently in a position close to the cell membrane. Because the ligand-binding regions of FcRs and KIRs are located at accessible sites on top of the molecule (albeit in EC2), it seems likely that CD89 may have a more upright structure than the KIR to ensure that the F-G loop is accessible for IgA-binding[26, 30, 55, 97].

The affinity of CD89 for IgA1, IgA2 and SIgA is estimated to be ~$5\times10^7$ $M^{-1}$, which in view of the normal serum concentration of IgA suggests that the receptor is saturated *in vivo*[56, 99]. Domain-swap and mutational studies of IgA have mapped its CD89-binding site at or close to the Cα2-Cα3 boundary (Fig. 2C)[14, 79]. The fact that SIgA and monomeric IgA bind CD89 with similar affinity suggests that the binding site is not obstructed by a bound SC or J chain[40]. A new model for IgA1 has also suggested that this isotype has more of a T shape than the traditional Y shape of IgG (Fig. 2C)[6]. Thus, even with this confirmation it seems the Fab arms do not hinder the CD89-binding site in IgA.

Like many activatory receptors (including other FcRs, ILTs, and LIRs), CD89 can associate with the FcR γ chain, a specialized immunoreceptor tyrosine-based activation motif (ITAM)-containing signaling molecule[18, 65, 77, 86]. Association between CD89 and the FcR γ chain depends on charged residues located within their transmembrane domains (Fig. 2A)[51, 65]. Evidence from transfectant model systems suggests that CD89-mediated signaling, including recruitment of protein tyrosine kinases (PTKs) and subsequent activation of the intracellular signaling cascade, is accomplished by association with the FcR γ chain (see below). Interestingly, however, not all CD89 molecules appear to associate with the FcR γ chain[51, 86]. Neutrophils, monocytes and the monocytic cell line U937 apparently express two forms of the receptor: CD89 alone and CD89/FcR γ chain (CD89/$\gamma_2$). Although both forms of CD89 bind IgA with similar affinity, and IgA complexes are endocytosed with similar kinetics, the intracellular fate of the internalized complexes differed[51, 85]. Experimental data suggest that IgA complexes endocytosed via CD89 alone may be recycled, while those internalized via CD89/$\gamma_2$ are degraded and sorted for antigen presentation[51]. Thus, because endocytosis can occur in the absence of the FcR γ chain, the ITAM motifs contained therein are not essential for this function. Presumably, as yet uncharacterized motifs within the cytoplasmic tail of CD89 are sufficient to trigger the internalization process.

The signaling cascade triggered via the FcR γ chain has to some extent been unraveled in molecular terms.

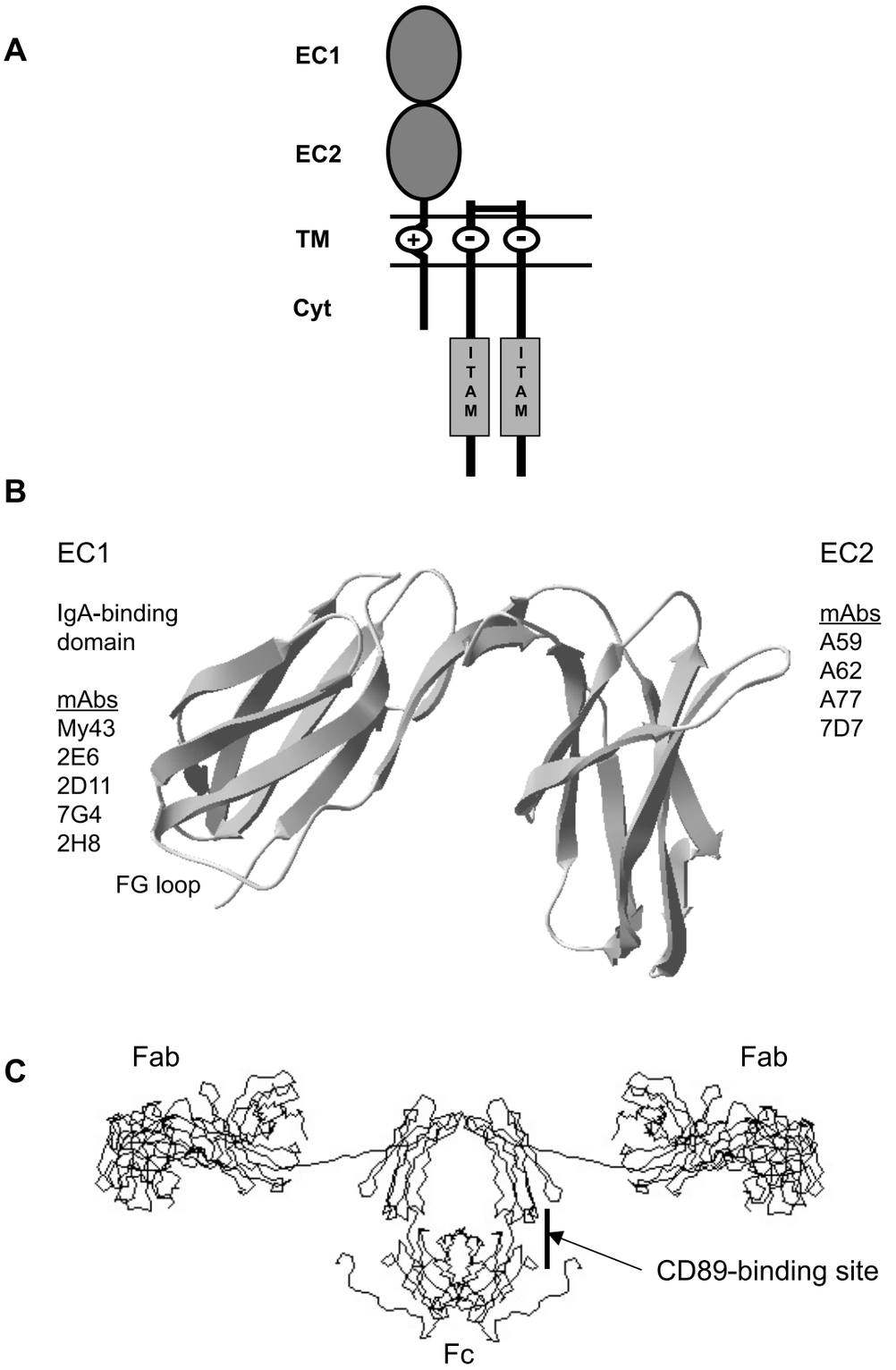


**Fig. 2. A.** Structure of the CD89/FcR γ chain signaling complex. **B.** Model for CD89 generated by the Swiss-Model automated protein--modeling server (GlaxoWellcome Experimental Research, Geneva) with the p58 KIR (PDB ID code: 1NKR) coordinates as a template. The FG loop, which contains residues critical for interaction with IgA, is indicated. Domain-specific mAbs are listed beside their respective domains. **C.** Model for human IgA1 (PDB ID code: 1IGA) showing the CD89-binding site

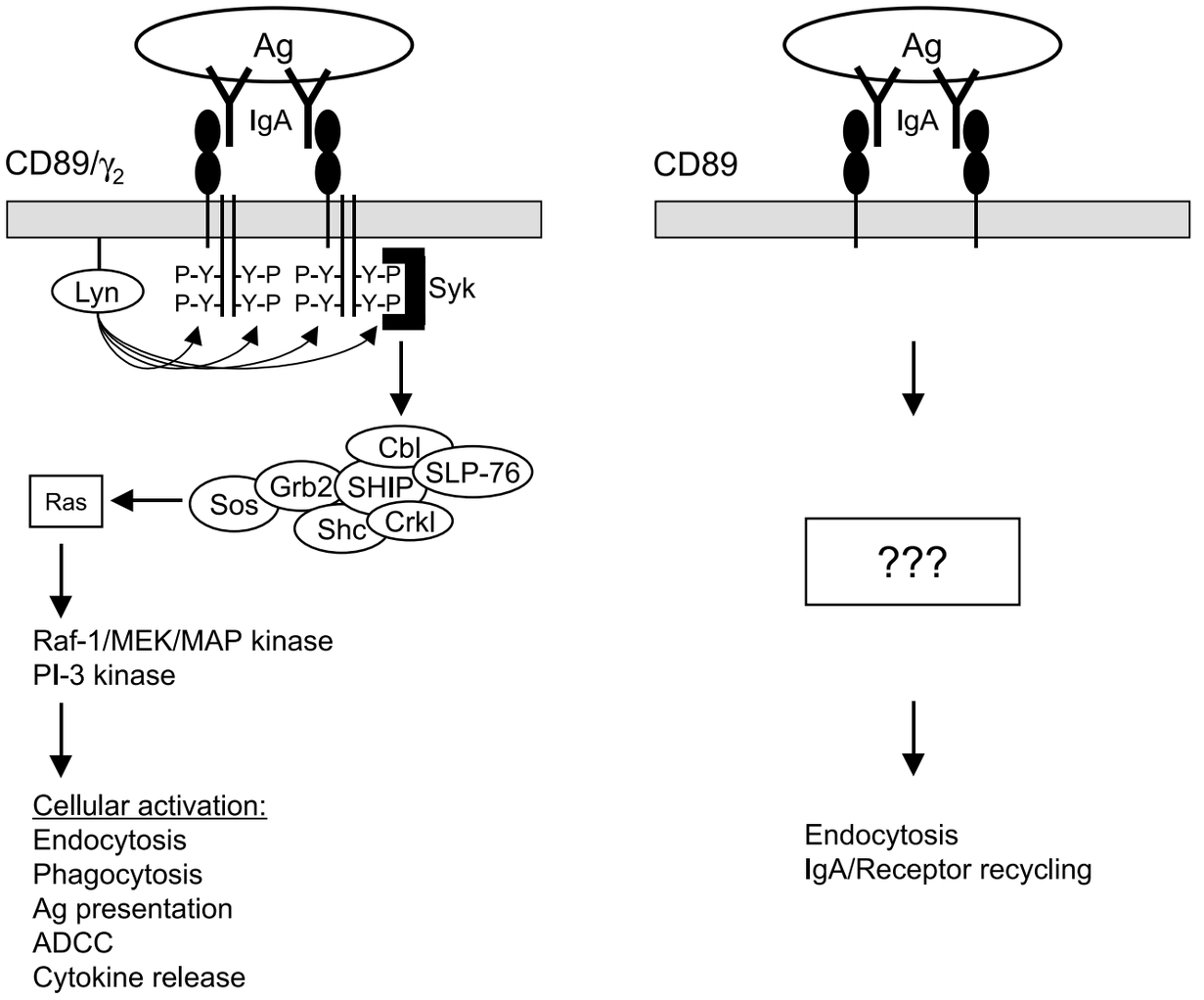


**Fig. 3.** Signaling pathways and cellular responses following CD89/$\gamma_2$ and CD89 aggregation. For CD89/$\gamma_2$, cross-linking triggers phosphorylation (P) of the tyrosine (Y) residues within the FcR γ chain ITAMs by the Src PTK Lyn. Syk then binds to the phosphorylated ITAM and becomes activated. The signal cascade continues with the recruitment of numerous adaptor proteins (Grb2, Shc, Crkl, Cbl, SLP-76), the lipid metabolizing enzyme SHIP, and the GTPase Sos to the complex. Sos converts GDP-Ras to GTP-Ras, which subsequently activates the Raf-1/MEK/MAP and PI-3 kinase signaling pathways. In the case of CD89 alone, nothing is as yet known about the intracellular signals triggered upon cross-linking

The ITAM signaling motifs, consisting of two YxxL boxes and present in the cytoplasmic tail of the FcR γ chain, were shown to be crucial for triggering cellular activation[13]. Phosphorylation of tyrosine residues within these motifs by PTKs is necessary for the potentiation of the signaling cascade. FcR cross-linking results in phosphorylation of the ITAM motifs by a Src family PTK. The next step is the association of a Syk family PTK with the (phosphorylated) ITAM, resulting in the recruitment and phosphorylation/activation of a number of downstream proteins, including protein kinase C (PKC) and the mitogen-activated protein (MAP) kinases[88]. In the case of CD89/$\gamma_2$, cross-linking by IgA complexes or anti-CD89 monoclonal antibodies (mAbs) triggers phosphorylation of the FcR γ chain ITAMs by the Src PTK Lyn[35]. Syk is then able to bind to the phosphorylated ITAM and subsequently becomes activated by phosphorylation (probably by Lyn). In some studies, phosphorylation of the tec family PTK Btk has also been observed[47, 50]. The signal transduction cascade continues via numerous adaptor proteins (Grb2, Shc, SHIP, CrkL, Cbl, SLP-76), resulting in the recruitment of the GTPase Sos to the complex. Sos converts GDP-RAS to GTP-RAS, which subsequently activates the Raf-1/MEK/MAP kinase and PI-3 kinase signaling pathways (Fig. 3)[74].

**Table 1.** Modulation of CD89 expression levels

| Cell type | Increase of CD89 expression | Decrease of CD89 expression | No effect on CD89 expression |
|---|---|---|---|
| Neutrophils | IL-8, TNF-α, FMLP, ZAS, ionomysin | | GM-CSF, IFN-γ |
| Monocytes/macrophages | IL-1β, TNF-α, LPS, GM-CSF, calcitriol | TGF-β, suramin | IL-3/4/6, IFN-γ |
| Eosinophils | Ionomycin, **IL-4/5**, GM-CSF | | IL-1α/β, TGF-β, IL-2/3/**4**/**5**/6, G-CSF, GM-CSF, IFN-α/β/γ, Con A, PMA |

For definition of the abbreviations used see text (except: ZAS – zymosan activated serum; G-CSF – granulocyte-colony stimulating factor, IFN-α/β/γ – interferon α/β/γ, Con A – concanavalin A). Bold letters signifies that the data are contradictory.

## Expression and Modulation

Expression of CD89 is restricted to cells of the myeloid lineage: neutrophils, monocytes/macrophages, eosinophils, and cell lines corresponding to these cell types. Lymphoid cells do not express any detectable CD89 protein or mRNA[54, 60, 62, 63]. CD89 expressed on neutrophils, monocytes and U937 cells has a molecular mass of 55–75 kDa, whereas eosinophil FcαR is larger (70–100 kDa) due to more extensive glycosylaton[2, 62, 63]. A number of CD89-specific monoclonal antibodies (mAbs) exist and their binding sites within CD89 have been localised (see Fig. 2B)[60, 67, 93]. In general, mAbs that bind in the EC1 domain of CD89, are able to block IgA-binding, while those that bind to EC2 do not[67].

Various cytokines and other factors can modulate surface expression of CD89 (Table 1)[66]. CD89 is upregulated on neutrophils in response to formyl-methionyl-leucyl-phenylalanine (FMLP), interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α)[36, 37, 71]. Interestingly, this upregulation is unaffected by inhibitors of protein synthesis, suggesting the existence of an intracellular pool of CD89[36]. The CD89 levels can be modulated by $Ca^{2+}$-dependent signaling processes in both neutrophils and eosinophils[36, 62]. The expression of CD89 on monocytes and monocyte-like cell lines can be upregulated by Calcitriol, lipopolysaccharide (LPS), TNF-α, granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-1β, and downregulated by suramin and transforming growth factor-β (TGF-β)[7, 31, 84, 92].

## Biological Function

Triggering of cellular effector functions is a critical step in many immune reactions, and Ig-FcR interactions are often vitally important for the outcome of this process[81, 82]. Thus, stimulation of neutrophils with aggregated serum IgA or SIgA triggers a respiratory burst that can be primed by prior treatment with FMLP. Monomeric IgA and pIgA, as well as the anti-CD89 mAb My43, can induce a similar response if a cross-linking secondary mAb is used[32, 53, 89, 93, 98, 99]. Although monocytes express lower levels of CD89 relative to other FcγRs, stimulation with serum IgA or SIgA triggers production of superoxide at levels comparable to those generated via IgG[91]. Similarly, IgA2-containing ICs trigger neutrophil activation more effectively than ICs with IgG[122]. IgA-coated particles also trigger efficient eosinophil degranulation and release of eosinophil-derived neurotoxin[1]. However, reports that SIgA is a powerful stimulator of eosinophil degranulation is complicated by the observation that eosinophils also possess a receptor specific for SC (in addition to CD89)[46, 69].

Neutrophils efficiently bind and phagocytose IgA-opsonized bacteria and yeast particles, but priming with GM-CSF or IL-8 (resulting in increased IgA binding) was necessary for phagocytosis of IgA-coated latex beads[12, 32, 71, 111, 119]. Similarly, treatment of monocytes with IL-1, TNF-α, GM-CSF or LPS increased CD89 expression levels and promoted IgA-mediated phagocytosis[92]. Likewise, eosinophils bind serum IgA-coated beads poorly unless primed with GM-CSF, IL-4 or IL-5, which presumably upregulate CD89 expression[9]. Somewhat puzzlingly, however, an earlier report saw no effect of these cytokines on the expression level of CD89 on eosinophils[62].

CD89 has also proven to be an efficient trigger molecule for ADCC in a number of *in vitro* test systems. Effector cells have been stimulated to lyse target cells such as bacteria, *Schistosoma mansoni* schistosomula, and erythrocytes in an IgA-dependent manner[17, 25, 52]. Recently, the therapeutic potential of CD89 has been demonstrated by the use of bispecific antibodies comprising anti-CD89 mAb A77 F(ab') and

anti-tumor antigen mAb F(ab'), which were shown to trigger ADCC and phagocytosis of tumor cells by CD89-positive effector cells[21, 103].

A further function of IgA is to trigger the release of various cytokines and inflammatory mediators through interaction with CD89. It has been shown that unprimed monocytes secrete IL-1β, TNF-α, IL-6, IL-8, leukotrienes $C_4$ and $B_4$, and prostaglandin $E_2$ following triggering of CD89 with IgA-containing ICs or anti-CD89 mAb[22, 27, 28, 75, 80]. However, some reports also detail the down-regulation of monocyte TNF-α and IL-6 secretion by IgA[117, 118]. This disparity probably reflects the activation level of the isolated effector cells. IIA1.6 B cells transfected with CD89/FcR γ chain secrete IL-2 following stimulation with IgA or anti-CD89 mAb[65]. IgA is also reported to induce secretion of activated collagenase and lactoferrin from neutrophils[5, 121].

It has also recently become clear that under certain circumstances CD89 may work together with complement receptors to ensure efficient triggering of many cellular effector functions. IgA-containing ICs mediate a slow release of lactoferrin from neutrophils, which becomes much faster if the ICs also contain complement factors such as C3b and iC3b[121]. Similarly, phagocytes were found to require both specific IgA and complement to trigger efficient binding, uptake and killing of *Streptococcus pneumoniae*[39]. In both these studies the complement receptors involved were identified as CR1 and CR3. Furthermore, when transgenic mice expressing CD89 were crossed with CR3 deficient animals, phagocytosis was unaffected, but lysis of target cells was abolished[105].

## Role in Disease

Endocytosis via CD89 has been proposed to be important for the removal of potentially harmful IgA-containing ICs from the bloodstream[61, 94]. Recently, a defect in CD89-mediated endocytosis has been proposed to contribute to the pathogenesis of diseases such as IgAN, Sjögren's syndrome (SS), alcoholic liver cirrhosis and HIV infection, which are all characterized by a high serum concentration of pIgA and increased levels of circulating IgA-containing ICs[33, 34, 61, 94]. In addition, it appears that the O-linked glycans of IgA1 are different in IgAN patients and that the IgA from these patients shows a reduced affinity for CD89, which may contribute to the increased serum IgA levels[58, 107]. Similarly, in SS, over-sialylation of IgA may explain its reduced binding to CD89, its inefficient clearance and its high serum levels[4]. Defective clearance of IgA-containing ICs could lead to their deposition in the mesangium, where they may trigger chronic kidney damage[29]. Such deposition of IgA-containing ICs in the kidneys might be mediated by CD89 expressed on the mesangial cells[66]. However, this theory remains controversial because some investigators have failed to detect expression of CD89 mRNA or protein in these cells, while others have reported easily detectable levels of both CD89 and FcR γ chain[24, 100, 113].

It was mentioned above that eosinophils express a highly glycosylated form of CD89. The same report showed that eosinophils from some allergic patients expressed higher levels of CD89 than those from normal individuals[62]. More recently, atopic asthmatics were shown to have elevated levels of specific IgA in sputum against both allergens and bacterial antigens[70]. Taken together, these data point to a role for IgA and CD89 in the pathogenesis of atopic allergy and extrinsic asthma. Further research is clearly needed to define the roles of IgA, CD89, and the putative SC receptor on eosinophils for the degranulation of these cells as a component of the allergic reaction.

## Future Perspectives

In terms of signaling via CD89, it would be interesting to know whether CD89 can associate with molecules other than the FcR γ chain, such as the family of molecules related to the FcR γ chain and recently shown to associate (via charged transmembrane residues) with the KIR/KAR proteins[15, 49]. It is tempting to speculate that, while activation signals generated by CD89 are transmitted via the FcR γ chain, anti-inflammatory/inhibitory actions of CD89 may be attributed either to non-association with the FcR γ chain or, indeed, association with an as yet uncharacterized immunoreceptor tyrosine-based inhibitory motif-containing accessory molecule. It would also be advantageous to understand how the IgA-CD89 interaction takes place at the cell surface. Uniquely (for human FcRs), CD89 binds to the Cα2/Cα3 region of IgA via its EC1 domain. Current structural models for both molecules do not easily suggest how this interaction proceeds (Fig. 2); perhaps CD89 adopts a more upright conformation than the related KIR proteins. Crystallographic data will probably be needed to truly answer this question. A more detailed three-dimensional structure of CD89 should also reveal the stoichiometry of IgA-CD89 complexing, i.e. do two (or more) CD89 molecules associate at the cell surface prior to or during the interaction

with IgA? Interestingly, several investigators have reported that FcγRII forms dimers to bind one IgG molecule, and it is suggested that KIR proteins may also be associated on the cell surface[55, 96, 97].

## Conclusions

In this review we have described current knowledge on the structure and function of the only well-defined human IgA Fc receptor, CD89. This receptor appears to play an important role in immune defense by linking the humoral IgA response to powerful cellular effector mechanisms. Further studies will no doubt seek to exploit the CD89-IgA interaction for the design of antibody-based therapeutics, including recombinant variants of IgA and bispecific anitbodies.

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