4
Fc Receptors for IgA

H. Craig Morton[1]

4.1. Introduction

Immunoglobulin A (IgA) is, by far, the most abundant immunoglobulin produced in humans and is also the most heterogeneous (Kerr, 1990; Woof and Mestecky, 2005) (see Chapter 1). Human serum IgA, produced by plasma cells in the bone marrow, lymph nodes, and spleen, is mainly monomeric (mIgA) and constitutes ~15–20% of the total serum Ig pool. However, IgA

[1] Laboratory of Immunohistochemistry and Immunopathology (LIIPAT), Institute of Pathology, Rikshospitalet University Hospital, 0027 Oslo, Norway. Present address: Institute of Marine Research, Nordnes 5817, Bergen, Norway.

predominates at the mucosa, as 80–90% of mucosal plasma cells produce this isotype (Brandtzaeg et al., 1999). In addition to IgA, mucosal plasma cells also express a small polypeptide called the joining chain (J-chain) that directs the assembly of dimers and larger polymers [collectively called polymeric IgA (pIgA)] (Johansen et al., 2000).

Following its secretion by plasma cells, and in order to fulfill its role as an important component of the human adaptive immune system, IgA interacts with a number of specific cellular receptors (Table 4.1). One of the most well characterized, and the primary focus of this chapter, is the IgA Fc receptor (FcR) expressed by cells of the myeloid lineage (called CD89 or FcαRI). Binding of IgA-coated targets to CD89 on myeloid cells can trigger a wide variety of cellular effector functions, including phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and the synthesis and release of cytokines and other inflammatory mediators. Another IgA FcR, critical for mucosal defense, is the polymeric immunoglobulin receptor (pIgR) (Kaetzel, 2005). The pIgR is a sacrificial receptor responsible for binding pIgA and transporting it into external secretions. The pIgA that has been transcytosed via this pathway is called secretory IgA (SIgA), and a portion of the pIgR [called secretory component (SC)] remains associated with the SIgA molecule (see Sect. 4.3.1). SIgA is thus the primary mediator of humoral immunity at mucosal surfaces, where it neutralizes pathogens and foreign antigens in a process known as immune exclusion. The pIgR will only be mentioned briefly here, but its structure and function are discussed extensively in Chapter 3. Three other IgA receptors—the asiaolglycoprotein receptor (ASGP-R), the transferrin receptor (TfR, CD71), and Fcα/μR—have been identified in humans. The ASGP-R is expressed in the liver and is thought to be involved in IgA catabolism. TfR has only recently been recognized as an IgA receptor and may be involved in the pathogenesis of the immune complex (IC) disease IgA nephropathy (IgAN). Fcα/μR is related to the pIgR and likewise binds both IgA and IgM. Its expression in human mesangial cells may also suggest a role for Fcα/μR in the pathogenesis of IgAN.

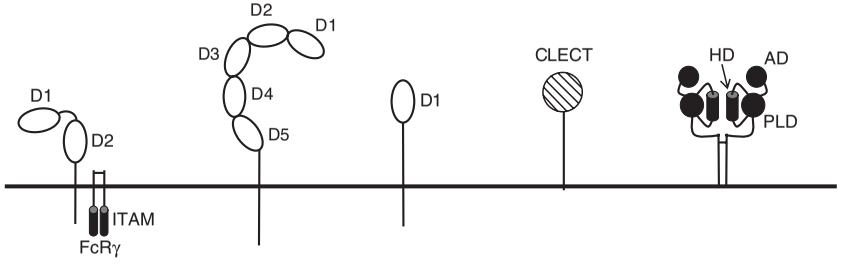
This chapter will discuss current and emerging knowledge of the five IgA receptors listed above and in Table 4.1. Interested readers are also directed to several other excellent reviews of this subject (Morton and Brandtzaeg, 2001; Monteiro and van de Winkel, 2003; Otten and van Egmond, 2004; van Egmond et al., 2001; Woof et al., 2005).

4.2. The Human Myeloid IgA FcR (CD89/FcαRI)

4.2.1. Protein Structure

CD89 is a type I transmembrane glycoprotein with an extracellular region composed of two Ig-like domains and a short cytoplasmic tail devoid of recognized signaling motifs (Maliszewski et al., 1990). CD89 can associate with

TABLE 4.1. Structures and characteristics of IgA receptors.

Receptor	FcαR1	Polymeric Ig receptor (pIgR)	Fcα/μR	Asialoglycoprotein receptor (ASGP-R)	Transferrin receptor (TfR)
Receptor structure[a]					
Type	Type I	Type I	Type I	Type II	Type II
CD designation	CD89	—	—	—	CD71
HUGO designation	*FCAR*	*PIGR*	*FCAMR*	*ASGR1*	*TFRC*
Reference sequences					
mRNA	NM 02000	NM 002644	NM 032029	NM 001671	NM 003234
Protein	NP 01991	NP 002635	NP 114418	NP 001662	NP 003225
Structures	1OVZ (CD89)	1XED (D1 only)	N.D.	N.D.	1CX8 (TfR)
	1UCT (CD89)				1SUV (TfR+Tf)
	1OW0 (CD89+Fcα)				1DE4 (TfR+HFE)
Chromosomallocation	19q13.4	1q31-q41	1q32.1	17p13.2	3q29
Ligands	mIgA, pIgA	pIgA, IgM	IgA, IgM	Desialylated glycoproteins	Transferrin, HFE, pIgA1

[a]D, domain; CLECT, C-type lectin domain; HD, helical domain; AD, apical domain; PLD, protease-like domain, HFE, hemochromatosis protein; N.D., not done.

the FcR γ-chain (FcRγ_2), a specialized signaling dimer with two cytoplasmic immunoreceptor tyrosine-based activation motifs (ITAMs) in its cytoplasmic domains. Co-expression of FcRγ_2 is not required for surface expression of CD89 in transfectants. However, when CD89 transgenic (CD89Tg) mice were crossed with FcRγ_2 knockout mice, surface expression of CD89 was abolished (van Egmond et al., 1999). The ability of CD89 to trigger cell-mediated effector functions like phagocytosis, respiratory burst, and cytokine release is critically dependent on its association with FcRγ_2 (Morton et al., 1995; van Egmond et al., 1999).

CD89 associates with FcRγ_2 via a basic arginine residue in its transmembrane (TM) domain (Morton et al., 1995). A recent study demonstrated that lateral transfer of this positive charge in an Arg209Leu/Met210Arg mutant of human CD89 completely abrogated FcRγ_2-dependent signaling (Bakema et al., 2006). It is now understood that the possession of a basic TM residue, which facilitates association with signaling molecules like FcRγ_2, is a characteristic of activating receptors. This charged-based mechanism for the pairing of ligand-binding chains with specialized signaling molecules appears to be an evolutionary successful approach that is utilized by numerous activating receptors expressed on hematopoietic cells (Feng et al., 2005).

Recently, the crystal structure of the ectodomain of CD89 has been solved (Ding et al., 2003; Herr et al., 2003a). The two Ig-like domains of CD89 are orientated at ~90° to one another, and this orientation most closely resembles that seen in the leukocyte Ig-like receptor B1 (LILRB1, also called LIR-1/CD85j) and the killer cell Ig-like receptors (KIRs). However, the relative orientation of the extracellular Ig-like domains of CD89 is opposite to that previously observed for the other Ig-superfamily FcRs such as FcγRIIa, FcγRIIb, FcγRIII, and FcεRI (Herr et al., 2003a; Woof and Burton 2004).

4.2.2. Evolution

It is now apparent that CD89 has followed a slightly different evolutionary pathway to the other Ig-superfamily FcRs. CD89 is actually more closely related to receptors encoded by genes located on a region of chromosome 19, at position 19q13.4, known as the leukocyte receptor complex (LRC) (Martin et al., 2002). In contrast, the genes of the other Ig-superfamily FcRs are located on chromosome 1 (Hulett and Hogarth, 1994). Interestingly, the genes encoding the pIgR and Fcα/μR are also located on chromosome 1 (see Sects. 4.3.1 and 4.3.2).

In addition to the CD89 gene (*FCAR*), the LRC includes genes for the LILRs, KIRs, NKp46 (also called natural cytotoxicity receptor 1, NCR1), platelet glycoprotein VI (GPVI), and leukocyte-associated Ig-like receptor-1 and -2 (LAIR-1 and LAIR-2). Although they display a wide variety of functions, LRC-encoded receptors display a relatively high level of sequence and structural homology, strongly suggesting that they have evolved from a common ancestor (Nikolaidis et al., 2005; Volz et al., 2001). Although the closest relatives of the LRC-encoded proteins are the Ig-superfamily FcRs, genomic

analysis suggests that the ancestors of these two gene families diverged before the separation of birds and mammals (Nikolaidis et al., 2005). To date, CD89 orthologues have been described in chimpanzees (Morton et al., 2005), macaques (Rogers et al., 2004), cattle (Morton et al., 2004), horses (Morton et al., 2005), and rats (Maruoka et al., 2004). Although IgA is also found in birds, an avian orthologue of CD89 has not been described.

In evolutionary terms, FcRγ_2 and other homologous signaling adapter molecules (i.e., CD3ζ, DAP10, and DAP12) are much older than the activating receptors with which they associate (Abi-Rached and Parham, 2005). Therefore, this suggests that when activating receptors possessing a polar TM residue arose during evolution, they were able to use pre-existing signaling pathways. In addition, these ancient signaling molecules might also have influenced the evolution of activating receptors by selecting for variants with which they were able to associate (Abi-Rached and Parham, 2005; Feng et al., 2005).

4.2.3. Genomics

FCAR consists of five exons spanning ~12-kb (de Wit et al., 1995) and lies at the telomeric end of the LRC close to *NCR1* and *GPVI*. On the centromeric side of *FCAR* lie two clusters of genes encoding the KIRs, LILRs, LAIR-1 and LAIR-2. Synteny mapping has revealed a region on mouse chromosome 7 that appears to represent the murine LRC. A murine homologue of *FCAR* is not found in this region (or anywhere else in the mouse genome), thus explaining why a CD89 homologue has not been identified in mice (Martin et al., 2002).

Characterization of the *FCAR* promoter has mapped elements responsible for the myeloid specific expression of CD89 to a 259-bp region directly prior to the translation initiation site (Shimokawa et al., 2000). The transcription factors CCAAT/enhancer-binding protein α (C/EBPα) and GA-binding protein (GABP) have been shown to bind to sites within this core promoter and to regulate CD89 transcription (Shimokawa and Ra, 2003).

Transcription of *FCAR* gives rise to a variety of differently spliced mRNA transcripts. A full-length cDNA clone encoding CD89 was first isolated by Maliszewski and co-workers in 1990 (Maliszewski et al., 1990), and numerous alternatively spliced transcripts have since been described (Morton and Brandtzaeg, 2001; Monteiro and van de Winkel, 2003). At least one of these splice variants (FcαRb) might encode a soluble form of CD89 (van Dijk et al., 1996). The relationship between FcαRb and soluble forms of CD89, which have been detected in serum covalently linked to IgA, is unknown (Launay et al., 2000; van der Boog et al., 2002).

Recent genetic analysis has identified several single-nucleotide polymorphisms (SNPs) within *FCAR*. The activity of *FCAR* promoter constructs carrying T alleles at two polymorphic sites (positions −311 and −142 relative to the ATG translation initiation codon) was reduced approximately twofold when compared to those carrying C alleles (Shimokawa

et al., 2000). One Japanese study has since shown that the frequencies of the −311C/C and −142C/C genotypes is significantly increased in IgAN patients (Tsuge et al., 2001). These authors recently reported that these SNPs were also associated with increased risk for chronic hepatitis C (Watanabe et al., 2006). However, a second study of a different population of Japanese IgAN patients failed to find a significant association between these SNPs and IgAN (Narita et al., 2001). Four other SNPs (−340G/A, 363A/G, 376G/A, and 844A/G) have been described in *FCAR* (Jasek et al., 2004), and the 363A/A genotype has been linked to a susceptibility to aggressive periodontitis (Kaneko et al., 2004).

4.2.4. Distribution

CD89 is expressed at high levels by circulating neutrophils and monocytes (Hamre et al., 2003; Monteiro et al., 1992, 1993). Eosinophils express much lower levels of CD89 compared to neutrophils, but CD89 expression is reported to be increased on the eosinophils of patients suffering from allergic rhinitis and/or asthma (Monteiro et al., 1993).

In contrast to blood monocytes, intestinal macrophages resident in the lamina propria do not express CD89. These macrophages still retain effective phagocytic and bactericidal activity but do not secrete pro-inflammatory cytokines and lack receptors for IgG (FcγRs), lipopolysaccharide (LPS) (CD14), complement (CR3, CR4, C5aR), interleukin (IL)-2 (CD25), and IL-3 (CD123) (Smith et al., 2005). Thus, intestinal macrophages appear ideally adapted to promoting the anti-inflammatory environment of the gut (see below) while still retaining effective host defense functions. In contrast to gut macrophages, varying levels of CD89 expression have been detected on several other macrophage populations, including those from the peritoneal cavity, the lungs (alveolar macrophages), and the liver (Kupffer cells) (Hamre et al., 2003; Ouadrhiri et al., 2002; Patry et al., 1996; van Egmond et al., 2000).

Similar to the above-described situation, the expression of CD89 by different dendritic cell (DC) populations is still controversial. Monocyte-derived DCs (Mo-DCs) generated *in vitro* retain low levels of CD89 (Geissmann et al., 2000; Heystek et al., 2002), but the situation *in vivo* is less clear. Although Langerhans cells do not express CD89 *in vivo* (Geissmann et al., 2000; Hamre et al., 2003), expression was detected on both DR^+ and DR^- cells in the dermis (Geissmann et al., 2000). As these cells were also $CD68^+$, it is unclear whether they were "true" DCs or macrophages. However, functionally, this distinction might be superfluous, as skin DCs and macrophages can display similar phenotypic characteristics, especially during inflammation (Kiekens et al., 2001). However, even if DCs *in vivo* lack functional levels of CD89, they have been reported to be capable of binding and internalizing SIgA at least partly via the mannose scavenger receptor (Heystek et al., 2002).

4.2.5. IgA Binding

The interaction between IgA and CD89 is quite distinct from that between IgG and IgE and their respective FcRs. CD89 binds IgA via its N-terminal membrane-distal domain 1 (D1) (Morton et al., 1999; Wines et al., 1999, 2001), whereas FcγRIIIb (CD16) and FcεRI bind their ligands via residues located in the membrane proximal domain (D2) and near the D1–D2 interface (Woof and Burton 2004). The FcR-binding sites within the Ig molecules themselves are also quite distinct. CD89 binds IgA at the Cα2–Cα3 interface, whereas FcγRs bind to the lower hinge region at the amino terminal of the IgG Cγ2 domain, and FcεRI binds IgE at the analogous Cε2–Cε3 linker region (Woof and Burton, 2004).

Results from earlier mutagenesis experiments have been confirmed and extended by resolution of the crystal structure of CD89 in complex with the Fc region of IgA (Herr et al., 2003a; Wines et al., 1999, 2001). The IgA-binding site of CD89 involves residues in the B-C loop, the D strand, the D-E loop, and the F-G loop of D1. The CD89–IgA interface is composed of a central hydrophobic core flanked by several charged residues (Herr et al., 2003a; Woof et al., 2005). Previously, it was shown that mutation of CD89 residues Tyr-35 (in the B-C loop) and Arg-82 (in the F-G loop) to alanine abolished IgA binding (Wines et al., 2001). The molecular basis for this ablation is revealed by the crystal structure of the complex, which shows that Tyr-35 lies at the center of the hydrophobic patch on CD89 and forms a potential hydrogen bond to the Leu-257 of IgA. Similarly, Arg-82 forms a hydrogen bond with Leu-256.

A further unique characteristic of CD89-IgA binding is the stoichiometry of the interaction. A conformational change occurs in the Fc regions of IgG and IgE after interaction with one FcR, preventing the binding of a second FcR to the other heavy chain (Kato et al., 2000). However, recent structural and biochemical analysis have shown that the receptor-binding sites on both IgA heavy chains remain accessible and are each able to bind one CD89 molecule (Herr et al., 2003a, 2003b). This unique 2:1 stoichiometry raises some interesting questions regarding our understanding of FcR signaling, as it is usually assumed that FcR-mediated cellular effector functions can be triggered by as few as two antibody molecules bound to an antigen (Segal et al., 1977). Therefore, several potential explanations (which are not mutually exclusive) have been put forward to explain why soluble mIgA molecules in serum do not trigger CD89-mediated cellular activation (Herr et al., 2003a). First, the cytoplasmic regions of the CD89 molecules might be too far apart to trigger downstream signaling. Second, the relatively high concentration of IgA in serum might favor the formation of 1:1 complexes, which would presumably prevail until displaced by larger multivalent immune complexes. Finally, the lateral movement of CD89 within the cell membrane might be restricted by elements of the cytoskeleton that might need to undergo rearrangement before CD89 can aggregate and signal.

Interestingly, a combination of these last two theories might help to explain some previous observations regarding the ability of cytokines to modulate IgA binding by neutrophils and eosinophils. Nearly 20 years ago it was shown that granulocyte monocyte-colony stimulating factor (GM-CSF) and granulocyte-colony stimulating factor (G-CSF) could rapidly switch the binding of IgA to neutrophils from low to high affinity without increasing receptor expression and that this switch was associated with the enhancement of IgA-mediated phagocytosis (Weisbart et al., 1988). Similarly, IgA binding by eosinophils has been shown to be modulated by a cytokine-induced "inside-out" signaling pathway involving phosphatidylinositol 3 kinase (PI 3-kinase) (Bracke et al., 2000, 2001). Reduced IgA binding was also seen following disruption of the cytoskeleton (Bracke et al., 2001). Furthermore, whereas truncation of the cytoplasmic domain of CD89 or mutation of serine 263 (S263) to alanine resulted in constitutive high-affinity binding, mutation of S263 to aspartate (mimicking the phosphorylated state) reduced the affinity of CD89 for IgA (Bracke et al., 2001). Taking these results and their own observations on the stoichiometry of the binding interaction into account, Herr et al. (2003b) have proposed a model for the cytokine-induced increase in CD89–IgA affinity. They proposed that, in unstimulated cells, CD89 is phosphorylated on S263 and its lateral movement in the plasma membrane is restricted via cytoskeletal interactions. Two receptors are therefore prevented from binding to a single IgA molecule. However, following cytokine stimulation, a signal is transmitted via PI 3-kinase, which results in dephosphorylation of S263 causing either a redistribution of CD89 molecules or a change in their orientation, thus allowing two receptors to bind one IgA molecule. In this way, the bivalent binding of one IgA with two CD89 molecules would produce an increase in avidity and, therefore, a higher apparent affinity without increasing receptor expression.

More recently, Pasquier et al. (2005) presented evidence that the 1:1 complexes formed between CD89 and IgA might actually play a more active role than previously thought. Their experiments showed that binding of mIgA or anti-CD89 Fab fragments to CD89 could inhibit activating responses triggered by the cross-linking of other FcRs for IgG or IgE. Thus, these authors suggested that their observations might help to explain the inhibitory effect of IgA that has been seen in some experimental systems (Kerr 1990). Further studies into this interesting phenomenon are clearly needed.

A recent study utilized surface plasmon resonance to investigate the association of mIgA versus pIgA with CD89 (Oortwijn et al., 2007). These authors concluded that the initial association of mIgA and pIgA with CD89 is similar, whereas mIgA dissociates more rapidly than does pIgA. Given the large excess of circulating mIgA over pIgA in humans, mIgA should compete effectively with pIgA for binding to CD89, thus preventing receptor aggregation and consequent cellular activation.

4.2.6. Signaling

Aggregation of CD89/FcRγ_2 by IgA complexes or anti-CD89 monoclonal antibodies (mAbs) triggers their redistribution into detergent-insoluble lipid rafts (Lang et al., 1999, 2002). Such lipid rafts have been shown to provide protection to the Src family PTK Lyn from dephosphosphorylation and inactivation by a transmembrane tyrosine phosphatase. In the raft environment, Lyn is able to phosphorylate the FcRγ_2 ITAMs (Gulle et al., 1998). Syk is then recruited to the phosphorylated ITAMs and subsequently becomes activated by phosphorylation (probably also by Lyn). In some studies, phosphorylation of the tec family PTK Btk has also been observed (Lang et al., 1999; Launay et al., 1998). 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 (Park et al., 1999).

However, not all CD89 molecules appear to associate with FcRγ_2 (Launay et al., 1999; Saito et al., 1995). Neutrophils, monocytes, and the monocytic cell line U937 apparently express two forms of the receptor: CD89 alone and CD89/FcRγ_2. Although both forms of CD89 bound IgA with similar affinity and IgA complexes were endocytosed with similar kinetics, the intracellular fate of the internalized complexes differed (Launay et al., 1999). Experimental data suggest that IgA complexes endocytosed via CD89 alone might be recycled, whereas those internalized via CD89/FcRγ_2 are degraded and sorted for antigen presentation (Launay et al., 1999). Therefore, signaling via FcRγ_2 is not essential for endocytosis and presumably as-yet uncharacterized motifs within the cytoplasmic tail of CD89 are required to trigger this process.

The role of FcRγ_2 signaling in CD89-mediated antigen presentation was investigated by transfecting the A20 B cell line with CD89 and either wild-type FcRγ_2 or FcRγ_2 in which the ITAM motif was mutated (Lang et al., 2001; Lang and Lang, 2006). These investigators found that cells expressing wild-type but not mutant FcRγ_2 presented CD89-targeted OVA antigen to OVA-specific T-cell hybridomas in the context of MHC class II. Cross-linking of CD89 with soluble IgA–OVA complexes resulted in translocation of phosphatidylinositol-dependent protein kinase 1 and protein kinase Bα to MHC II peptide-loading compartments, a mechanism that appeared to link FcRγ_2 signaling with efficient presentation of OVA peptides by MHC class II. A possible role for CD89/FcRγ_2-mediated presentation of IgA-linked antigen by DCs was suggested by the report that CD89 expression was upregulated during *in vitro* maturation of human myeloid DCs isolated from peripheral blood (Pasquier et al., 2004). These investigators further demonstrated that CD89 cross-linking by IgA–antigen complexes resulted in upregulation of MHC class II and costimulator expression. However, a recent study demonstrated that presentation of CD89/IgA-targeted antigen by DCs from CD89 transgenic mice was inefficient (Otten et al, 2006). In conclusion, various cell types appear to be capable

of processing IgA-bound antigens internalized via CD89/FcRγ_2; however, the *in vivo* significance of this phenomenon remains to be demonstrated.

4.2.7. Effector Functions of CD89 and the Role of IgA

The IgA system in humans is relatively compartmentalized, with mIgA and SIgA being differentially distributed between the systemic and mucosal compartments, respectively. The high concentration of mIgA in serum is a feature unique to humans and other primates, as other mammals have only low levels of pIgA in serum. Thus, the function of human serum IgA and its relationship with SIgA has been the source of debate for many years (Conley and Delacroix 1987).

In the gut (and other mucosal areas), where SIgA predominates, the immune system is under tight control (Sansonetti, 2004). Here, under normal conditions, inflammation is actively avoided and, instead, tolerogenic signals predominate. Therefore, the primary function of SIgA is considered to be the protection of the mucosae by the immune exclusion of commensal and pathogenic bacteria. In this way, SIgA protects against the possibility of a damaging inflammatory reaction at these delicate areas. The observation that macrophages resident in the gut lamina propria are still phagocytically active but do not secrete inflammatory cytokines and have down-regulated many of their activating receptors (including CD89; see Sect. 4.2.4) supports the concept of a non-inflammatory gut environment (Smith et al., 2005). It has recently been shown that SIgA is apparently unable to trigger phagocytosis by Kupffer cells *in vivo* or neutrophils *in vitro* (van Egmond et al., 2000; Vidarsson et al., 2001). Although the molecular basis for these observations is still unclear, they appear to define a novel anti-inflammatory role for SIgA.

Serum IgA, however, is able to trigger phagocytosis by neutrophils and monocytes (Morton and Brandtzaeg, 2001). Serum IgA-coated bacteria were also phagocytosed by CD89$^+$ Kupffer cells in G-CSF-treated CD89Tg mice (van Egmond et al., 2000). Therefore, it has been proposed that bacteria that are able to invade the gut mucosae enter the portal circulation, where they become opsonized with serum IgA and are subsequently phagocytosed by activated Kupffer cells (Otten and van Egmond, 2004; van Egmond et al., 2000). This observation appears to support earlier speculation that the role of serum IgA is to reinforce the first line of defense provided by SIgA at the mucosae (Conley and Delacroix, 1987).

In contrast to phagocytosis, serum IgA and SIgA are both able to trigger respiratory burst activity by neutrophils and monocytes (Monteiro and van de Winkel, 2003; Morton and Brandtzaeg, 2001; Otten and van Egmond, 2004). The ability of SIgA to trigger neutrophil respiratory burst was shown to be dependent on the coexpression of CR3 (Mac-1, CD11b/CD18) (van Spriel et al., 2002). Experiments suggested a direct interaction between CR3 and SC, but no detectable association between CR3 and CD89 was observed.

Recently, the therapeutic potential of CD89 against tumor cells has been demonstrated both with the use of recombinant IgA and with bispecific

antibodies (Dechant et al., 2002; Valerius et al., 1997). Moreover, recombinant reagents, targeted to CD89, have been shown to effectively trigger neutrophil-mediated effector functions against several pathogenic microorganisms, including *Candida albicans*, *Bordetella pertussis*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* (Hellwig et al., 2001; Valerius et al., 1997; van der Pol W.L. et al., 2000; Vidarsson et al., 2001).

4.3. Alternative IgA Receptors

4.3.1. The Polymeric Immunoglobulin Receptor (pIgR)

The pIgR [also known as the membrane secretory component (SC)] is expressed at high levels on the basolateral membrane of secretory epithelial cells (see Chapter 3). Here, the pIgR binds J-chain-containing pIgA or IgM molecules, which are then endocytosed and transported through the cell to the apical membrane, where the pIgR is cleaved and the complex released into the external secretions. The fragment of pIgA remaining bound is called the SC and the released Igs are referred to as SIgA or SIgM. Interestingly, unoccupied receptors are also transcytosed, resulting in the release of free SC at the apical surface, suggesting that this protein might have a biological role distinct from its association with IgA (see Chapter 8).

The pIgR is a heavily glycosylated transmembrane protein, containing five extracellular Ig-like domains. The pIgR gene (*PIGR*) is located on chromosome 1, close to the Fcα/μR gene (see Sect. 4.3.2). The pIgR initially binds to pIgA or IgM via a noncovalent interaction mediated by a specific motif in D1 of the pIgR. For IgA, but not IgM, a covalent disulfide bond between D5 of the pIgR and the Cα2 domain of IgA is formed during transcytosis and provides extra stabilization for SIgA.

At mucosal surfaces, immune exclusion by SIgA antibodies provides a first line of defense against pathogens. IgA undergoing pIgR-mediated transcytosis has also been implicated in the intracellular neutralization of LPS and virus and also in the transport of Ags (possibly even whole bacteria) out of the lamina propria and into the lumen (Johansen and Brandtzaeg, 2004; Phalipon and Corthesy 2003) (see Chapter 7). However, it appears that some microorganisms might in fact be able to exploit their ability to bind to the pIgR to infect epithelial cells (Kaetzel, 2001), although whether this actually happens *in vivo* is still unclear (Phalipon and Corthesy, 2003).

4.3.2. Fcα/μR

Fcα/μR is a transmembrane glycoprotein with one extracellular Ig-like domain that is able to bind both IgA and IgM (Shibuya et al., 2000; McDonald et al., 2002). Its ligand-binding site consists of a motif within its single

Ig-like domain that is highly homologous to the ligand-binding motif of the pIgR (Shibuya and Honda, 2006). The Fcα/μR gene (*FCAMR*) is located close to the pIgR gene (*PIGR*) on human and mouse chromosome 1, suggesting common ancestry (Shimizu et al., 2001). In the mouse, flow cytometry showed that Fcα/μR was expressed by the majority of B-cells and macrophages, but not by T-cells, natural killer (NK) cells, or granulocytes (Shibuya et al., 2000). Fcα/μR mRNA has been detected in primary human mesangial cells, which has led to speculation that this receptor might be involved in the kidney deposition of IgA-containing immune complexes (IgA-ICs) in IgAN (see Sects. 4.3.3 and 4.4.2).

4.3.3. Transferrin Receptor (CD71)

Transferrin receptor (TfR) is a disulfide-linked homodimeric type II transmembrane receptor that binds two proteins critical for iron metabolism: transferrin (Tf) and the hereditary hemochromatosis protein (HFE). Recently, it has been shown that TfR is also able to bind IgA (Moura et al., 2001). TfR has been reported to bind only human IgA1 (not IgA2 or SIgA), and it binds pIgA1 better than mIgA1 (Moura et al., 2004). Current evidence suggests that the TfR interacts mainly with the O-linked hinge region carbohydrate moieties of pIgA1, but that the N-linked sugar chains might also be involved (Moura et al., 2004). Thus, it has been suggested that TfR might represent the receptor for IgA1 O-linked glycans previously identified on human T-cells (Monteiro and van de Winkel, 2003; Rudd et al., 1994; Swenson et al., 1998). Significantly, TfR has been found to be expressed on human mesangial cells (HMCs) and cell lines. More importantly, TfR expression has been shown to be increased on HMCs in renal biopsies from IgAN patients and to colocalize with IgA deposits (Haddad et al., 2003; Moura et al., 2001). TfR has also been shown to preferentially bind the aberrantly glycosylated IgA1, which is a characteristic of IgAN (Moura et al., 2004) (see Sect. 4.4.2). Furthermore, HMCs stimulated with pIgA1 upregulate TfR expression, begin to proliferate, and secrete IL-6 and transforming growth factor (TGF)-β (Moura et al., 2005). Together, these results suggest that TfR is an important IgA FcR on HMCs and, as such, might be involved in the initiation of renal damage thought to be triggered by IgA-IC deposition in the kidney.

4.3.4. Asialoglycoprotein Receptor

The liver has been identified as the major site of IgA catabolism in humans. Here, IgA binds, in a calcium-dependent manner, to the ASGP-R expressed on the surface of hepatocytes. The ASGP-R binds the exposed terminal Gal or GalNAc residues of desialylated IgA, resulting in its internalization and eventual delivery to lysosomes for degradation (Stockert, 1995). Thus, ASGP-R is important for the regulation of the serum levels of IgA.

4.3.5. Other IgA Receptors

Many studies have noted that human T- and B-cells express receptors for IgA (Kerr et al., 1995; Morton et al., 1996). However, because CD89 is not expressed on these cell types, other novel IgA receptors, such as the recently described Fcα/μR and TfR, might explain some of these earlier reports.

A receptor for IgA has been described on several intestinal epithelial cell lines (Kitamura et al., 2000). These cells were shown not to express CD89, and the receptor was shown to be distinct from pIgR, as it was able to bind monomeric IgA. The possibility that IgA was binding to the ASGP-R was also discounted.

M-cells are specialized epithelial cells able to transport mucosal Ags across the intestinal epithelium and deliver them to the underlying Ag-presenting cells. Both human and murine M-cells have been reported to specifically bind IgA. The murine M-cell IgA receptor was shown to bind IgA with or without SC and recognizes a site spanning domains Cα1 and Cα2 of IgA (Mantis et al., 2002) (see Chapter 9).

Natural killer cells were found to specifically bind human pIgA and SIgA, but not to express CD89 or mannose receptor (Mota et al., 2003). The binding was not inhibited by L-fucose, D-galactose, D-glucose, D-mannose, or *N*-acetyl-D-glucosamine, suggesting that NK cells bind IgA via its protein backbone, not via sugar moieties present on IgA or SC.

4.4. IgA and IgA Receptors in Disease

4.4.1. CD89 Dysfunction

As mentioned earlier, eosinophils from some allergic patients express higher levels of CD89 than those from normal individuals (Monteiro et al., 1993). As atopic asthmatics have been shown to have elevated levels of specific IgA in sputum against both allergens and bacterial antigens (Nahm et al., 1998), this might suggest a role for IgA and CD89 in the pathogenesis of atopic allergy and extrinsic asthma.

CD89 has also been proposed to be important for the removal of potentially harmful IgA-ICs from the circulation via endocytosis. In diseases such as IgAN, Sjogren's syndrome, alcoholic liver cirrhosis, and human immunodeficiency virus (HIV) infection, which are characterized by high serum concentrations of pIgA and increased levels of circulating IgA-ICs, decreased CD89 expression levels and/or endocytotic rates have been noted (Grossetete et al., 1995, 1998; Monteiro et al., 1995; Silvain et al., 1995). Failure to clear IgA-ICs is proposed to lead to their deposition in the kidneys (see Sect. 4.4.2), where they are associated with inflammation and chronic tissue damage.

4.4.2. IgA Nephropathy (IgAN)

IgAN is the most common form of primary glomerulonephritis worldwide. This disease is characterized by the deposition of granular IgA-ICs in the glomerular mesangium, and approximately half of IgAN patients have elevated levels of IgA1 and/or IgA1-ICs in serum. Current evidence suggests that the basic abnormality in IgAN lies not in the kidney but, rather, involves a defect within the IgA immune system itself (van der Boog et al., 2005). Several studies have now shown that there is an under-galactosylation of the O-linked carbohydrate moieties in the IgA1 hinge region and that this might contribute to the formation and reduced clearance of IgA1-ICs (van der Boog et al., 2005). Recently, it was proposed that a soluble form of CD89 could be released into the serum of IgAN patients following interaction with abnormal IgA and thus contribute to the formation of IgA-ICs (Launay et al., 2000). Evidence in support of this theory was obtained from a CD89 transgenic mouse model that spontaneously developed IgAN-like symptoms (Launay et al., 2000). However, because the presence of IgA-CD89-ICs do not appear to be specific for IgAN (van der Boog et al., 2003) and the ability of CD89 to bind murine IgA is disputed, the potential involvement of CD89 in the pathogenesis of IgAN is still controversial (van der Boog et al., 2004).

Elevated serum levels of IgA1 and/or IgA1-ICs are not sufficient to cause mesangial deposition, and it is likely that a specific receptor for IgA is involved (Gomez-Guerrero et al., 2002). The identity of the mesangial cell IgA receptor has been hotly disputed for many years, but studies from several groups have now excluded CD89, ASGP-R, and pIgR (van der Boog et al., 2005). Similarly, although Fcα/μR mRNA is expressed in mesangial cells, this receptor does not seem to be involved in IgA deposition (van der Boog et al., 2005). Recently, however, an upregulation of TfR on mesangial cells of IgAN patients has been described (Moura et al., 2001). In addition, TfR has been shown to bind abnormally glycosylated IgA1 and IgA1-ICs more efficiently than normal IgA (Monteiro 2005; van der Boog et al., 2005). Taken together, these data suggest that TfR might turn out to be the elusive mesangial cell IgA receptor and thus be involved in the pathogenesis of IgAN.

4.5. Concluding Remarks

This chapter summarizes current knowledge concerning the structure and function of the five recognized types of IgA receptors, with special emphasis on the activating receptor CD89. The interplay between IgA and its receptors plays a critical role in immune defense in both the systemic and mucosal compartments. However, dysfunction of the IgA system has also been implicated in the pathogenesis of a number of diseases, especially IgAN. Future studies should help to elucidate the biological role of the newly described IgA receptors Fcα/μR and TfR and to further increase our understanding of the function of CD89 *in vivo*.

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