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REVIEW

IgA and IgA-specific receptors in human disease: structural and functional insights into pathogenesis and therapeutic potential

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Abstract IgA antibodies play an important role in humoral immunity. IgA is the predominant antibody in mucosal secretions and the second most prevalent in the serum. It occupies a unique position among human antibodies in that it can both trigger and suppress inflammatory responses, depending on the situation. Recent structural and functional studies have revealed details of the structure of IgA and its interaction with key cell-surface receptors. We look at the role IgA and IgA receptors (particularly FcαRI) play in the pathogenesis of diseases such as IgA nephropathy and other autoimmune conditions. Finally, we address the potential of IgA as a therapeutic tool to either trigger specific inflammatory responses to destroy target cells or suppress inflammatory responses in the case of autoimmune diseases, and the promise of mucosal vaccines for eliciting specific IgA responses to pathogens in mucosal environments.

Keywords FcαRI · pIgR · TfR · IgA nephropathy · X-ray crystallography

Introduction

Immunoglobulin A (IgA) represents one of the five classes of human antibody (IgG, IgA, IgM, IgE, and IgD). Humans produce more IgA antibody per day than any other isotype; it is the second most prevalent antibody in the serum, while it is the predominant species in mucosal secretions [1]. There are several distinct forms of IgA: monomeric IgA, dimeric or polymeric IgA, and secretory IgA. Furthermore, there are two IgA subclasses in humans, IgA1 and IgA2. The IgA1 subclass contains extensive O-linked glycosylation in the hinge region connecting the Fc and Fab regions. In contrast, the IgA2 subclass has a truncated hinge region lacking O-linked glycosylation (see Fig. 1) [1]. The simple monomeric IgA form has two heavy and two light chains like all other antibody isotypes. Each IgA heavy chain features a C-terminal extension known as the tailpiece. The IgA tailpieces can form intermolecular disulfide bonds with a protein called the J chain, leading to the formation of dimeric (or occasionally polymeric) IgA (dIgA) [2]. In the serum, approximately 95% of IgA is in the monomeric form with the remaining 5% comprising dimeric or polymeric IgA [1]. A receptor called the polymeric Ig receptor (pIgR) expressed on the basolateral surface of mucosal epithelial cells specifically binds dIgA and transcytoses across the mucosal epithelial cell. During transcytosis, the ectodomain of pIgR forms a disulfide bond to dIgA, and the ectodomain is cleaved, releasing a covalent complex known as the secretory IgA (SIgA) [2].

Serum and secretory IgA have distinct immunological functions. Secretory IgA is responsible for immune exclusion in which SIgA binds to pathogens and prevents their adherence to and invasion of the mucosal epithelium. SIgA is not capable of triggering phagocytosis of pathogens [3, 4]. On the other hand, any pathogens that are able to breach the epithelial layer can be targeted by serum IgA [3]. In contrast to SIgA, serum IgA antibodies in immune complexes are very effective at initiating a wide range of inflammatory responses, including phagocytosis, antibody-dependent cellular cytotoxicity, oxidative burst, and cytokine release [1]. Inflammatory responses triggered by IgA are often mediated by the IgA-specific receptor FcαRI

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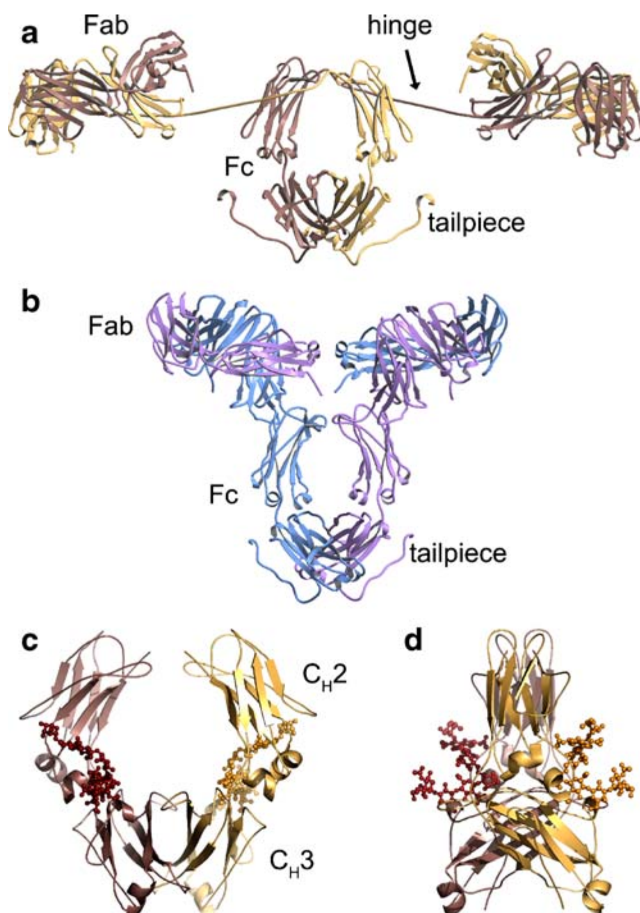

Fig. 1 Structural views of IgA1 and IgA2. Solution structure of (**a**) IgA1 and (**b**) IgA2 as determined by solution scattering [7, 8]. Note the extended conformation of the O-glycosylated hinge in IgA1, the compact conformation of IgA2, and the orientation of the tailpieces in both subclasses. (**c**) *Front view* and (**d**) *side view* of IgA1-Fc (Fcα) taken from the FcαRI:Fcα complex [9]. Note the location of the N-glycans, which are found on the external surface of the C_H2 and C_H3 domains and are highly solvent exposed, in contrast to N-glycans of IgG and IgE

(CD89) [5], although Fcα/μR can also mediate similar responses to IgA and IgM immune complexes [6].

IgA structure in solution

Perkins and colleagues have used small-angle X-ray and neutron scattering to construct low-resolution models of both IgA1 and IgA2 in solution [7, 8]. These experiments are able to determine the relative orientation of domains within the intact antibodies in solution without the need for trapping the antibodies in crystalline form. Monomeric IgA1 is striking in that it adopts a roughly T-shaped conformation with long, extended hinge regions connecting the Fc and Fab regions (Fig. 1a) [8]. The extended nature of the hinge is due to its heavy O-glycosylation with five distinct O-linked glycan sites within the 23-residue hinge peptide. In contrast, IgA2 adopts a more compact structure [7], consistent with the 13-residue deletion in the hinge region that removes all potential O-glycosylation sites (Fig. 1b). The best-fit models from solution scattering data suggest that the tailpieces for both IgA1 and IgA2 are folded back toward the main body of the IgA Fc domains, rather than extending outward into the solution.

Crystal structure of IgA1-Fc

The crystal structure of an IgA1-Fc core fragment (called Fcα) lacking the hinge and tailpiece regions was recently solved in complex with FcαRI (Fig. 1c,d) [9]. This represented the first detailed view of the Fc portion of any IgA antibody. Although the overall structure resembles other IgG-Fc (Fcγ) and IgE-Fc (Fcε) structures, there are a few important differences. First, the C_H2 domains of Fcα are tethered together by an unusual pair of disulfide bonds connecting residue C299 in the DE loop of each C_H2 domain with C242 at the base of the hinge in the opposite heavy chain. It is interesting to note that C299 in Fcα corresponds to the conserved asparagine in Fcγ and Fcε to which the N-linked glycans are attached. In all Fc structures solved before Fcα, two N-linked glycan chains are found between the upper Fc domains. In contrast, on Fcα the N-linked glycans are linked to N263, found on the external surface of the C_H2 domain. Unlike the N-glycans in Fcγ and Fcε that are primarily buried between the two heavy chains, the Fcα N-glycans are solvent-exposed (Fig. 1d). The electron density in the crystal structure of the complex was not very well-defined for the Fcα N-glycans, and only one of the two branching oligosaccharides chains emanating from the core oligosaccharide could be resolved. As described below in more detail, the N-glycans (and O-glycans) of IgA1 were implicated in the pathogenesis of IgA nephropathy. It is potentially significant that the N-glycans of IgA1, unlike IgG and IgE, are highly solvent accessible and poised to interact with different IgA receptors.

IgA receptors in humans

There are several known receptors for IgA, although few were characterized in much detail. The best-known IgA receptors include the polymeric Ig receptor (pIgR) [10], FcαRI [11], and Fcα/μR [6]. Other IgA receptors include the transferrin receptor (TfR) [12], a secretory component receptor (SCR) on eosinophils [13], an IgA2-specific receptor expressed on M cells within Peyer's patches [14], and a receptor for SIgA and pIgA on natural killer cells [15]. Finally, there are a few lectin-like receptors that interact with specific glycan epitopes on IgA, including the asialoglycoprotein receptor (ASGPR) [16], galectin 1 [17], and an IgA1/IgD receptor on T cells [18].

pIgR is expressed on the basolateral surface of mucosal epithelial cells, and is specific for polymeric IgA or IgM. It is responsible for the transcytosis of polymeric IgA (and IgM) across the mucosal epithelium to form secretory IgA or IgM. pIgR has no inflammatory role and functions primarily in transcytosis, as far as is known [10]. FcαRI and Fcα/μR mediate inflammatory responses to IgA-immune complexes. FcαRI binds monomeric and polymeric IgA1 or IgA2, although it does not bind SIgA except in the presence of an integrin co-receptor [4, 19]. Clustering of FcαRI by IgA-immune complexes in the serum can trigger phagocytosis, respiratory burst, antibody-dependent cellular cytotoxicity and cytokine release [1]. Fcα/μR has sequence similarity to pIgR and is also specific for both IgA and IgM [6]. However, in terms of function, it more closely resembles FcαRI, as it activates phagocytosis of IgA-bound or IgM-bound antigens.

TfR, which is primarily responsible for iron homeostasis, was recently identified as a mesangial IgA1 receptor [12]. As described below, TfR was implicated in the pathogenesis of IgA nephropathy, along with FcαRI [20]. SCR is expressed on eosinophils and is specific for the secretory component of SIgA (secretory component is the ectodomain of pIgR that is covalently linked to pIgA). It triggers degranulation by eosinophils and may also be responsible for the ability of SIgA to degranulate basophils [13]. The M cell receptor is found within Peyer's patches, regions within the gut-associated lymphoid tissue responsible for antigen sampling [14]. This receptor specifically binds IgA2 via the C_H1 and C_H2 regions and is thought to be involved in gut antigen sampling via SIgA. ASGPR is not precisely an IgA-specific receptor; instead, it is specific for N-glycans and O-glycans on a large number of serum proteins, including IgA. It is expressed in the liver, and is responsible for the clearance of IgA from the serum [16]. ASGPR primarily interacts with IgA2 and therefore may be responsible for the increased prevalence of IgA1 in the serum [21]. This review will focus primarily on the receptors pIgR and FcαRI, for which both structural and functional data are available. Fcα/μR is described more fully in another chapter in this issue.

pIgR structure and function

The polymeric immunoglobulin receptor (pIgR) is a glycosylated type I transmembrane protein that transports pIgs from the basolateral surface of mucosal epithelia into mucosal secretions. pIgR consists of a 620-residue extracellular region containing five Ig-like domains, a transmembrane helix, and a 103-residue cytoplasmic tail. Human pIgR binds and transports both pIgA and pIgM [22]. Binding of human pIgA to pIgR takes place in two steps. In the first step, a noncovalent interaction occurs between the N-terminal pIgR domain (D1) and the C_H3, and possibly C_H2, domains of one of the Fc regions of dIgA [23, 24]. In the second step, a disulfide bond is formed between Cys467 in the extracellular C-terminal domain (D5) of human pIgR and residue C311 in the C_H2 domain of the second IgA molecule [25]. The pIg–pIgR complexes are then transcytosed to the apical surface of the mucosal epithelium where an unknown enzyme cleaves the extracellular domain of pIgR, releasing the pIg–pIgR complex from the membrane to form secretory Ig (SIg) [2]. The cleaved extracellular domain of human pIgR, also known as the secretory component (SC), is covalently attached via a disulfide bond to dIgA or noncovalently attached to pIgM [26, 27]. Free SC is also released into secretions [26].

Protection against microorganisms and bacterial toxins takes place at different stages of pIgR-mediated dIgA transport [1, 28]. First, SIgA can act via immune exclusion in the gut by binding and cross-linking microorganisms and inhibiting their adherence to the mucosal walls [1, 29, 30]. Second, SIgA can intercept and neutralize viral pathogens during transepithelial transport [31]. Third, dIgA can bind viruses and bacteria that have invaded the mucosal cell at the basolateral surface and pIgR can shuttle the antibody–antigen complex to the apical surface, removing the pathogen [32, 33]. Lastly, free SC in the absence of IgA can bind pathogens and bacterial toxins [34, 35].

The X-ray crystal structure of the N-terminal domain (D1) of human pIgR was recently solved (Fig. 2a) [36]. pIgR D1 folds as a V-type Ig-like domain with highly noncanonical conformations in the loops corresponding to the complementarity-determining regions (CDRs) in the epitope-binding sites of antibodies [36]. A single helical turn in CDR1 of D1 causes a hydrophobic residue (V29) that would typically be buried in Ig variable domains to instead become exposed to solvent, which is consistent with mutagenesis results implicating this region (T27, S28, N30, H32, and T33) as a dIgA binding site [37]. CDR2 consists of a very short, tightly turning loop containing a glutamic acid that may be required for IgM binding. It is interesting to note that only pIgR orthologs that bind pIgM (such as human and cow) have a charged residue in their CDR2 loops [22]. Unlike the CDR3 loop of antibody Ig domains, pIgR CDR3 folds back onto the body of D1, which precludes the dimerization mode observed for the V_H–V_L interface in antibody Fab fragments. Furthermore, binding experiments using surface plasmon resonance (SPR) spectroscopy showed that pIgR has significant affinity for J chain-containing dIgA and that the glycosylation state of the pIgR D1 did not affect binding [36]. Mutational studies have shown that D1 of pIgR interacts with residues in the DE and FG loops of the IgA C_H3 domain [38, 39], and that the CDR2 loop is most important for this interaction, although both CDR1 and CDR3 loops also play a role [40].

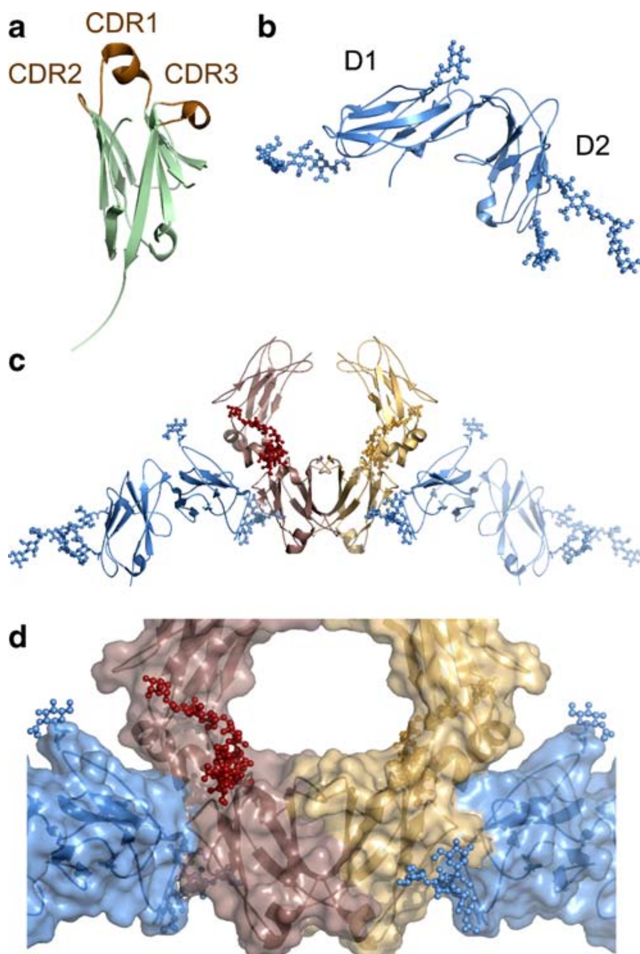

Fig. 2 Structural views of IgA receptors pIgR and FcαRI and the FcαRI:Fcα complex. (**a**) Crystal structure of the N-terminal domain of pIgR [36]. The CDR loops involved in binding dIgA are labeled. (**b**) Crystal structure of FcαRI, as seen in the FcαRI:Fcα complex [9]. Note the four N-linked glycosylation sites. (**c**) Crystal structure of the FcαRI:Fcα complex [9]. Two FcαRI molecules bind to a single Fcα dimer with D1 of each receptor contacting the C_H2–C_H3 interface on IgA1. (**d**) *Close-up view* of N-glycans in the FcαRI:Fcα complex. The IgA1 N-glycan (*red*) approaches within 8 Å of FcαRI but does not come into direct contact. In contrast, the N58 N-glycan of FcαRI (*blue*) does come into contact with IgA1

FcαRI inflammatory functions

The *FcαR* gene is found within the leukocyte receptor cluster on chromosome 19 [41]. This gene cluster includes genes encoding a number of different immune receptors, including the leukocyte imunoglobulin-like receptor (LIR) and killer cell immunoglobulin-like receptor (KIR) families, and also includes the collagen receptors GPVI and LAIR-1. Sequence analysis indicates that FcαRI and other receptors in the leukocyte receptor cluster contain one or more immunoglobulin-like (Ig) domains in their extracellular regions, similar to other Fc receptors found on chromosome 1, such as FcγRI, FcγRII, FcγRIII, and FcεRI. However, the receptors on chromosome 19 are only distantly related to those of chromosome 1. FcαRI is a glycosylated type I transmembrane receptor with two Ig-like domains in the extracellular region, a transmembrane helix, and a small cytoplasmic domain. An arginine in the transmembrane region of FcαRI forms a salt bridge with aspartate residues in two disulfide-linked FcR γ-chain co-receptors [42], which contain immunoreceptor tyrosine activation motifs (ITAM) capable of recruiting cytoplasmic signaling partners [43].

Clustering of the cell-surface FcαRI:γγ complex upon interaction with IgA-immune complexes leads to phosphorylation of the γ-chain and recruitment of SH2-containing downstream signaling molecules [1]. It seems likely that FcαRI signaling via the γ-chain resembles signaling by the T cell receptor via the ζ-chain in which orientation-independent receptor clustering, rather than formation of a specific oligomeric receptor conformation, activates the signaling cascade [44]. In addition to its role in signaling, the γ-chain governs the pathway of endocytosed FcαRI. Mutation of the intramembrane arginine in FcαRI abolishes the interaction with the γ-chain, and it alters the targeting of internalized FcαRI:IgA:antigen complexes [45]. Internalized complexes lacking γ-chain are directed to the recycling pathway and return IgA into the serum, whereas FcαRI:γ-chain:IgA:antigen complexes are targeted to the lysosome for degradation of the antigen [45]. It was also reported that a significant population of cell-surface FcαRI exists that is not associated with the γ-chain, suggesting that IgA catabolism or recycling by FcαRI is regulated by its interaction with the γ-chain [45]. Recent work showed that FcαRI is not simply tethered to γ-chain solely via intramembrane salt bridges, but that a more extensive interface exists between the transmembrane helices of FcαRI and the γ-chain dimer. Mutation of residues in these transmembrane regions of either FcαRI or γ-chain can abolish signaling [46, 47]. Clustering of FcαRI by IgA-immune complexes or anti-FcαRI monoclonal antibodies leads to shedding of the FcαRI ectodomain in a process that requires signaling via the γ-chain [48]. It is thought that this process may be responsible for fine-tuning the immune responses mediated through FcαRI. Furthermore, shedding of FcαRI by IgA1 was shown to have important implications on the development of IgAN symptoms, as described below [49].

FcαRI anti-inflammatory functions

Although secretory IgA is known to function by a passive mechanism and to have anti-inflammatory properties in the gut, serum IgA-immune complexes are able to trigger robust inflammatory responses via FcαRI [1]. However, it has long been noted that serum IgA itself has the capacity to diminish IgG-induced inflammatory responses. An intriguing recent report from Monteiro and colleagues [50]

showed that the anti-inflammatory effects of serum IgA (in the absence of antigen) are also mediated through FcαRI. Thus, FcαRI appears to be unique in its ability to function both as an activating and inhibitory receptor. In vitro studies using rat mast cells transfected with FcαRI revealed that when bound by serum IgA or anti-FcαRI Fab, FcαRI was able to inhibit the activation of inflammatory responses via FcεRI or FcγRs. This inhibition required the presence of the γ-chain and involved the recruitment of SHP-1 to FcαRI, which blocked signaling via Syk, LAT, and ERK [50]. Furthermore, in vivo studies using a murine IgE-mediated asthma model further confirmed this inhibitory effect of FcαRI, suggesting that IgA may play a protective role in allergy by suppressing inflammatory responses [50]. These results were surprising because inhibitory functions are typically mediated via immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing inhibitory receptors that co-aggregate with activating receptors. This is the first report of an ITAM receptor being able to transduce an inhibitory signal. FcαRI may therefore represent a new target for the design of anti-inflammatory therapies for asthma and allergy.

Crystal structure of FcαRI

The crystal structure of the human FcαRI ectodomain was solved alone and in complex with Fcα [9]. The FcαRI ectodomain is composed of two Ig-like domains oriented at approximately a 90° angle (Fig. 2b). Its overall structure closely resembles those of the related leukocyte Ig-like (LIRs) [51] and killer cell inhibitory receptors (KIRs) [52] and the platelet collagen receptor glycoprotein VI [53]. Although other Ig-like Fc receptors such as FcγRIIa, FcγRIIb, FcγRIII, and FcεRI also have tandem Ig-like domains oriented at an acute angle [54–57], the position of domain 1 (D1) is flipped over to the opposite side in FcαRI, LIRs, and KIRs relative to the other FcRs [9]. Ordered N-linked carbohydrate was observed at each of the four potential glycosylation sites in the IgA1-bound FcαRI ectodomain (in the free receptor, two N-glycans were observed in one molecule in the asymmetric unit, and the other two sites were observed in the second molecule).

Crystal structure of the FcαRI:Fcα complex

The structure of the FcαRI:Fcα complex showed that two FcαRI molecules bind a single Fcα dimer, consistent with prior analytical ultracentrifugation and SPR experiments (Fig. 2c) [9, 58]. Domain 1 of each FcαRI molecule interacts with residues in both the C_H2 and C_H3 domains of Fcα, as predicted by previous mutational work [59–63]. The binding interface is composed of a large hydrophobic patch surrounded by polar and charged residues that contribute potential hydrogen bonds [9]. The hydrophobic core in the binding interface consists of Fcα residues L257, L258, M433, L441, A442, F443 and the aliphatic portion of the R382 side chain packing against FcαRI residues Y35, L54, F56, G84, H85 and the aliphatic portion of K55. The surrounding residues that contribute hydrogen bonds include FcαRI R52, K55, R82, and Fcα R382. The binding interface observed in the crystal structure is consistent with prior mutational studies, although significant portions of the binding sites on both Fcα and FcαRI had not been previously identified.

Disease states linked to IgA

IgA nephropathy (IgAN)

IgA nephropathy (IgAN) is the most common form of glomerulonephritis, characterized by deposits of IgA1 in the glomerular mesangium. IgA1 deposition is followed by the infiltration of inflammatory immune cells, mesangial cell proliferation and mesangial matrix expansion [20]. IgAN, also called Berger's disease [64], affects approximately 1.3% of the population worldwide [65] and leads to renal failure in 20–30% of cases within 10–20 years of onset. Although clinically well-characterized by the deposition of blood (hematuria) and protein (proteinuria) into the urine, it is often a silent disease, which may go undetected for many years [20]. In IgAN patients who have had kidney transplants due to renal failure, mesangial IgA deposition often recurs after several years [66], suggesting that IgAN is actually a blood-borne disease with effects localized to the kidney.

IgA1 and FcαRI aberrations implicated in IgA nephropathy

IgAN patients display several major abnormalities in the IgA system: (1) increased levels of serum IgA and IgA-immune complexes (IC) [20] (2) increased ratio of polymeric (pIgA) to monomeric (mIgA) [67, 68] and (3) the generation of abnormally glycosylated IgA1 [69]. The enhanced levels (twofold to threefold) of serum IgA cannot fully explain IgA deposition in the kidneys of IgAN patients because AIDS and IgA myeloma are often associated with increased plasma levels of IgA yet do not typically cause mesangial IgA deposits [20]. The higher proportion of polymeric IgA1 in IgAN patient serum could have important implications given that mesangial deposits in IgAN are primarily composed of polymeric IgA1 [70]. A large number of alterations in IgA1 O-glycosylation and N-glycosylation were reported, including oversialylation [71] or undersialylation and undergalactosylation [72] of the O-glycans, and oversialylation [73] or truncation [74] of the

N-glycans. Furthermore, an overall decrease in the number of O-glycosylation sites in the IgA1 hinge region was reported in IgA1 [72].

Abnormal glycosylation events potentially alter a number of molecular events in IgAN. Oversialylated IgA1 has a reduced affinity for ASPGR, which would reduce clearance by the liver and therefore lead to higher serum IgA1 levels [75]. Undersialylation and undergalactosylation lead to the aggregation of IgA1 in a hinge-specific manner [76], and undergalactosylation of IgA1 leads to increased adhesion to extracellular matrix proteins [77]. Anti-IgA antibodies recognize epitopes on underglycosylated IgA1, and injection of enzymatically deglycosylated IgA1 in rats leads to mesangial deposits and recruitment of neutrophils to the mesangium [78]. Finally, IgA1 from IgAN patients was reported to show altered affinity for IgA receptors: either increased [79] or decreased [80] binding to FcαRI-expressing cells, and increased binding to transferrin receptor (TfR)-expressing cells [81].

An interesting feature of the IgA1 structure is the accessibility of its glycan moieties. The solution structure of intact IgA1 revealed that the O-glycosylated hinge region is highly extended (Fig. 1a), similar to other O-glycosylated mucin-like peptides such as the CD8 stalk [82]. Furthermore, the N-glycans on the IgA1 C_H2 domains are almost completely solvent exposed, unlike the C_H2 or C_H3 N-glycans on IgG or IgE, respectively (Fig. 1d). The exposed nature of these glycans could have important implications for their accessibility to lectin-like receptors. Furthermore, the propensity of undergalactosylated IgA1 to aggregate [76] is consistent with the exposed nature of the hinge region containing the affected O-glycans.

Less is known about potential FcαRI aberrations in IgAN. Impaired endocytosis of FcαRI in IgAN was described [83], leading to increased IgA recycling and higher serum IgA levels. Furthermore, FcαRI with increased N-glycosylation levels and potential FcαRI splice variants were reported in IgAN patients [84], although their significance in the pathogenesis of IgAN is unknown. The crystal structure of FcαRI complexed with Fcα revealed that one N-glycan attached to N58 of FcαRI does come into contact with Fcα (Fig. 2d) [9], suggesting that alterations in the glycosylation profile of FcαRI could play a role in modulating the FcαRI:IgA interaction.

Role of the FcαRI–IgA interaction in a mouse model of IgA nephropathy

In a study by Monteiro and colleagues, circulating soluble FcαRI ectodomain bound to IgA1 was found in 40% of IgAN patients but not in patients with other diseases of the immune system or kidney [49]. To determine the role that FcαRI plays in the pathogenesis of IgAN, they generated several transgenic mouse lines expressing human FcαRI on monocytes and macrophages (mice do not express an FcαRI homolog) [49]. The transgenic mice developed essentially all the symptoms of IgAN, including mesangial IgA deposits, infiltration of macrophages in the mesangial and interstitial areas, hematuria, and proteinuria. $Rag2^{-/-}$ SCID mice (expressing no FcαRI or IgA) injected with serum from the FcαRI-transgenic mice also developed IgAN symptoms, indicating that the cause of disease was blood-borne. Depletion of FcαRI from the transgenic mouse serum before injection into the $Rag2^{-/-}$ SCID mice led to less pronounced IgAN symptoms. Finally, an FcαRI-transgenic SCID mouse (expressing FcαRI but no IgA) did not develop IgAN symptoms unless IgAN patient-derived human IgA1 was injected. These elegant experiments revealed that soluble FcαRI and IgA together were required for the development of IgAN-like symptoms. It should be pointed out that mouse IgA is predominantly polymeric (unlike human IgA1) and has fewer N-glycosylation sites than human IgA1.

Interaction of the transferrin receptor with the IgA1 immune complexes in the glomerulus

An IgA-specific receptor was reported on kidney mesangial cells [85]. This receptor was distinct from other known IgA receptors such as FcαRI, pIgR, or ASGPR because these are not expressed on mesangial cells [86, 87]. Recently, Moura et al. demonstrated that, unexpectedly, TfR is a mesangial IgA receptor [12]. TfR specifically binds IgA1 but not IgA2 with clear preference for polymeric IgA1. Deletion of either O-glycans or N-glycans of IgA1 abolished binding to TfR [81]. It is interesting to note that TfR is overexpressed on mesangial cells in patients with IgAN relative to healthy controls [88], and IgAN patient-derived IgA1 bound more tightly to TfR-expressing cells [81]. These results suggest that TfR may be responsible for trapping IgA1 in the mesangium, leading to the well-known mesangial IgA1 deposits that are hallmarks of IgAN.

Model for IgA1-receptor interactions in IgAN

In a current model for IgAN, the altered glycosylation or polymerization state of circulating IgA1 leads to higher affinity for, and increased shedding of, the FcαRI ectodomain, resulting in tightly associated circulating FcαRI:IgA1 immune complexes. These circulating FcαRI:IgA1 complexes are bound by mesangial cell TfR, leading to IgA1 deposition in the mesangium [20]. Although the role of FcαRI is unclear, it may be that the presence of soluble FcαRI in circulating IgA1 immune complexes favors their deposition due to either the increased size of the complex or due to the N-glycans of FcαRI itself binding to lectin-like mesangial receptors.

N-glycans in the FcαRI:Fcα crystal structure

Given the aberrant N-glycosylation and O-glycosylation of IgA1 in IgAN patients, and the reported abnormalities in N-glycosylation of FcαRI in some cases, the contribution of glycans to the FcαRI:Fcα binding interface is of significant interest. The O-glycosylated hinge is located far from the FcαRI binding site on IgA1, and thus the O-glycans would not be expected to affect the binding of FcαRI. In the crystal structure of the FcαRI:Fcα complex described above, N-glycans were observed at all potential N-linked glycosylation sites of both FcαRI and Fcα in the complex [9]. Of the four sites on FcαRI, the N-glycan attached to FcαRI N58 extends toward the C_H3 domain of Fcα and forms two potential hydrogen bonds with E348 of Fcα (Fig. 2d, see the *blue* N-glycans) The crystallized FcαRI ectodomain was expressed in insect cells, yielding high-mannose N-glycans. Therefore, the complex N-glycans found on the natural human receptor might interact more extensively with IgA1. Another interesting feature of FcαRI glycosylation is that the two N-glycans on the C-terminal domain extend outward from the complex by up to 28 Å (Fig. 2c), resulting in an overall width of the FcαRI:Fcα complex of 193 Å. The large dimensions of the complex, combined with the long polysaccharides extending out on either end, could contribute to the trapping of circulating soluble FcαRI:IgA1 complexes in the mesangium of the kidney in IgAN, particularly if lectin-like receptors are involved.

In the FcαRI:Fcα crystal structure, the N-glycans of Fcα do not contact FcαRI, although they approach within 8 Å of the receptor (Fig. 2d, see the *red* N-glycans) [9]. The CHO cell-expressed Fcα that was crystallized has complex carbohydrate similar to that found on human proteins, so it should represent a close approximation to the N-glycans on normal human IgA1. However, the electron density was rather weak for the N-glycans and as a result, only one branch of the biantennary oligosaccharide was visible. It is therefore possible that IgA1 N-glycans could play a role in interacting with FcαRI in vivo, and further structural work is needed to address this issue.

Allergy and asthma

Various studies have indicated that mucosal and systemic production of allergen-specific IgA occurs in patients with asthma and/or allergic rhinitis [89–91]. At sites of allergic inflammation where basophils and eosinophils play an active role, mucous secretions contain large amounts of SIgA [92]. In vitro studies using immobilized SIgA and mIgA showed that SIgA but not mIgA can induce histamine release from human basophils [93]. SIgA-mediated basophil degranulation may therefore play an important role in the exacerbation of allergic inflammation at the mucosal surface. Eosinophils can also trigger allergic responses in asthma via respiratory burst, which produces superoxide anions and reactive oxygen species [94]. In a recent study, IgA—particularly the secretory form—was shown to potently induce NADPH oxidase activity and eosinophil degranulation in an FcαRI-dependent process [95]. Furthermore, when incubated with SIgA in vitro, blood eosinophils release large amounts of eosinophil cationic protein, eosinophil peroxidase, eosinophil derived neurotoxin, and various cytokines [96].

Conversely, despite the ability of SIgA to activate eosinophils, there is evidence that IgA can also suppress inflammatory responses in asthma and allergy [97]. Chronic obstructive pulmonary disease was associated with a decrease in secretory IgA levels, apparently due to the downregulation of pIgR on bronchial epithelial cells [97]. Children with low IgA levels showed higher likelihood of asthma, otitis media and allergy, and the severity of allergic responses was elevated relative to children with intermediate or high IgA levels [98]. Furthermore, pretreatment of mice with allergen-specific monoclonal IgA prevented airway hyperresponsiveness and the infiltration of eosinophils upon allergen challenge [99].

Ankylosing spondylitis (AS)

Ankylosing spondylitis (AS) is a chronic inflammatory form of arthritis that affects the spinal joints. Patients with AS have elevated levels of serum monomeric IgA1 [100, 101]. AS may represent an abnormal IgA response to bacterial infection, as elevated jejeunal SIgA levels can be reduced by treatment with the antibiotic sulfasalazine [102]. Furthermore, increased levels of IgA1 and IgA2 specific to *Klebsiella pneumoniae* were reported in AS patients [103]. Recently, FcαRI expression was found to be downregulated in blood phagocytes of AS patients with increased serum IgA [104]. The increased levels of serum IgA and IgA-IC could be explained by altered FcαRI-mediated endocytosis and increased recycling of IgA towards the cell surface [100]. It is interesting to note that AS patients who also display IgA deficiency were shown to have particularly severe AS [100]. This suggests that IgA and IgA-IC may not be directly involved in the pathogenesis of AS and that instead, increased serum IgA may actually serve a protective role against joint inflammation.

Celiac disease

Celiac disease is a gastrointestinal disorder triggered by immune responses to wheat proteins, particularly gliadins that are modified by the tissue enzyme transglutaminase in genetically susceptible individuals. IgA and IgG antibodies

to gliadin show cross-reactivity to tissue transglutaminase, inducing inflammatory responses that eventually cause a loss of villi within the intestinal epithelium, leading to poor nutrient absorption [105]. In addition, IgA antibodies to a variety of food allergens were found in patients with celiac disease [106]. IgA autoantibodies in celiac disease are often associated with dermatitis herpetiformis in which IgA is deposited in affected skin [107]. Although IgA antibodies can be helpful in the diagnosis of celiac disease, the link between IgA and pathogenesis is unclear, as the disease appears to be primarily T cell-mediated [105]. Furthermore, it was shown that IgA deficiency is associated with a tenfold risk of celiac disease, suggesting that, as for ankylosing spondylitis, IgA may play a protective role [108].

Other disease states with elevated or aberrant IgA populations

A number of diseases, including alcoholic cirrhosis, AIDS, IgA myeloma, Sjögren's syndrome and Henoch–Schönlein purpura, exhibit elevated levels of serum IgA. However, the relevance of increased IgA to disease pathogenesis is unknown. In alcoholic cirrhosis and AIDS the increased IgA levels may be associated with aberrant expression of FcαRI and defective FcαRI-mediated endocytosis [79, 109]. In the autoimmune disease Sjögren's syndrome, characterized by lymphoid cell infiltration of lacrimal and salivary glands, the N-glycans of monomeric IgA1 are oversialylated [110], which could presumably affect the FcαRI–IgA interaction and alter recycling of IgA. Furthermore, in Henoch–Schönlein purpura (HSP), a form of systemic vasculitis, IgA deposits form in affected blood vessels [111]. In HSP patients who have renal involvement, undersialylation [112] and undergalactosylation [113] of IgA1 O-glycans were reported, leading to IgA1 deposition in the glomerulus, in a manner similar to IgAN. Indeed, HSP and IgAN may actually represent different degrees of the same disease with HSP being the more severe form and IgAN being only the renal manifestation of HSP.

Therapeutic approaches based on IgA-receptor interactions

Anti-tumor immunotherapy

Antibody-based immunotherapy has become an effective treatment for a number of different cancers. Therapeutic monoclonal antibodies (mAb) can induce tumor cell death by a variety of mechanisms. Some act by simply cross-linking antigens on tumor cells, leading to apoptosis, cell cycle arrest or the inhibition of cell proliferation [114]. Others act indirectly via FcR-mediated effector functions of immune cells such as phagocytosis, Ab-dependent cellular cytotoxicity and enhanced presentation of tumor antigens [115].

A number of studies showed that therapeutic antibodies able to trigger immune responses via FcαRI show exciting potential. These antibodies can either be intact IgA or bispecific antibodies (BsAb) that recognize both the ectodomain of FcαRI and the tumor antigen of interest [116]. In a comparison of hapten-directed antibodies of different human isotypes, IgA2 was found to be more effective than IgG isotypes at recruiting neutrophils and inducing tumor cell death [116]. Similarly, an IgA1 antibody against EpCAM proved more effective than IgG1 at recruiting neutrophils to kill EpCAM-positive, solid tumor cells [117]. A comparison of bispecific antibodies targeting FcαRI or FcγRs in humans and transgenic mice showed that FcαRI was the most effective FcR at triggering tumor cell killing and enhanced migration of neutrophils into tumors [118]. Upon granulocyte colony-stimulating factor (G-CSF) treatment, immature neutrophils are mobilized from the bone marrow and mediate tumor cell lysis via FcαRI but are incapable of tumor cell killing via the FcγR [118]. Since neutrophils constitute the most abundant cytotoxic cells in humans, improved neutrophil recruitment may enhance tumor cell lysis in whole blood, especially when tumor cells are complement-resistant or when neutrophils were primed by G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) [119].

Anti-inflammatory therapy

FcαRI has the unique ability to mediate either activating or inhibitory inflammatory responses depending on the nature of its interactions with IgA [50]. Monoclonal Fabs targeting the FcαRI ectodomain or engineered IgA constructs could therefore play a valuable therapeutic role in inhibiting inflammatory processes in autoimmune disorders or allergy and asthma. For example, leukocyte infiltration, a key characteristic of asthma, was markedly inhibited by treatment with anti-FcαRI mAb in a murine model of IgE-triggered asthma [50]. The key advantage of this approach is that the inhibitory response mediated via FcαRI extends to both IgG-specific and IgE-specific receptors, suggesting the potential for widespread anti-inflammatory effects.

Mucosal vaccines

In the gut, secretory IgA plays an important role in immune exclusion and pathogen clearance, as described above. However, there is also evidence that specific mechanisms are in place for sampling gut antigens complexed with

SIgA. Antigen sampling occurs in discrete patches of organized gut-associated lymphoid tissue (GALT) such as the Peyer's patches of the distal ileum [120, 121]. Specialized cells called microfold or M cells in the Peyer's patches mediate transcytosis of antigens and microbes across the gut epithelial layer and delivery to lymphoid and dendritic cells found in a pocket in the basolateral surface of the M cell. Upon antigen capture, immature dendritic cells then migrate from the GALT to lymphoid organs for antigen presentation to naïve T cells [120, 121]. Thus, both systemic and mucosal immune responses can be generated by mucosal antigens, and the GALT represents a potential avenue for vaccination. A particularly attractive possibility is the development of oral vaccines that can lead to both mucosal and systemic responses.

There are a couple of important aspects related to IgA when discussing mucosal vaccination. First, vaccines capable of inducing a strong pathogen-specific SIgA response in the mucosae could be very effective at preventing infection because for most pathogens, the initial adherence and invasion occur via the respiratory, genitourinary or gastrointestinal tissues. Furthermore, it was demonstrated that protection against reinfection by various pathogens is better correlated with levels of specific SIgA antibodies than with serum antibodies [122]. A prime example of this is the oral polio vaccine in which efficacy was correlated with the production of mucosal anti-polio IgA [123]. Intranasal vaccination with capsular polysaccharides against *S. pneumonaie*, influenza and adenoviruses was also found to elicit a protective SIgA response [122, 124]. However, despite the promise of this type of approach, mucosal vaccines are limited due to the difficulty in eliciting a response to nonreplicating agents, probably because of their rapid clearance/degradation in the gut [97, 120]. A second avenue of investigation involves using SIgA itself as a carrier for inducing immunity via the gut. M cells express a receptor for SIgA that can transcytose SIgA or SIgA-complexed antigens [14]. Targeting this receptor could be an effective approach for developing an oral vaccine. For example, Corthésy et al. created antigenized SIgA by inserting a linear epitope from *Shigella flexneri* invasin B into the secretory component and reconstituting into SIgA [125]. This antigenized SIgA was able to immunize mice, as shown by the production of both serum and mucosal antibodies specific for invasin B.

Conclusions

Recent studies have provided significant insights into IgA-mediated processes in health and human disease. Structural data on intact IgA1 and IgA2 in solution have highlighted unusual aspects of these antibodies, such as the extended O-glycosylated hinge of IgA1 and the compact conformation of IgA2. Furthermore, crystallographic studies on pIgR, FcαRI, and the FcαRI:IgA1-Fc complex have revealed the nature of the IgA-binding sites and have revealed highly solvent-exposed N-glycans in IgA1 with possible implications for IgA nephropathy. Functional studies have elucidated the intriguing dual nature of IgA in which it is capable of both activating and inhibiting inflammatory responses via FcαRI. This duality is observed in many of the disease states in which IgA was implicated. Additional research will be needed to better understand how FcαRI can distinguish between activating and inhibitory signals and to develop new strategies for the control of these processes for therapeutic use. Finally, recent results have provided exciting glimpses into the potential uses of IgA and its receptors for novel therapies to fight cancer, ameliorate autoimmune diseases, or immunize patients in a straightforward manner through the use of oral vaccines.

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