Although immunoglobulin (Ig) A is commonly recognized as the most prevalent antibody subclass at mucosal sites with an important role in mucosal defense, its potential as a therapeutic monoclonal antibody is less well known. However, IgA has multifaceted anti-, non- and pro-inflammatory functions that can be exploited for different immunotherapeutical strategies, which will be the focus of this review.

Introduction

In the human body, more immunoglobulin (Ig) A is produced per day (66 mg kg⁻¹day⁻¹) than all other antibody isotypes combined. Moreover, in addition to being the most prominent antibody class at mucosal sites, IgA is the second prevalent antibody in the circulation. Although notable breakthroughs in understanding the role of IgA and IgA receptors have been achieved in the last decade, IgA is generally, but erroneously, still considered to be primarily a non-inflammatory antibody that helps to maintain homeostasis in the mucosa. However, through different expression forms and interaction with several distinct receptors, IgA can passively and actively inhibit or initiate inflammatory responses. The prototypic myeloid IgA Fc receptor FcαRI (CD89) plays a key role in several of these processes. As such, the role of IgA and FcαRI in immunity and their potential for immunotherapeutical strategies deserve re-evaluation. Because the potential of IgA as an anti-inflammatory agent was recently reviewed in ref-
a 16 kDa joining J-chain (Fig. 1B)\[^9,19,20\] Dimeric IgA, containing J-chains bind to the polymeric Ig receptor (pIgR), which is expressed on the basolateral membrane of epithelial cells, after which it is transported through epithelial cells and released into the lumen as secretory IgA (SIgA).\[^20-22\] IgA is secreted via this route into the mucosal lining of the gastro-intestinal, uro-genital and respiratory tracts, as well as into tears, saliva and milk. Apical cleavage of the pIgR ensures that a part of this receptor, referred to as secretory component (SC), remains attached to IgA (Fig. 1C), which stabilizes IgA and prevents rapid breakdown in the hostile environment of the gut lumen.

IgA Receptors

Another notable difference between human and animal IgA systems is the diversity of IgA receptors between species, which complicates comparisons. The existence of receptors for IgA was initially proposed after binding of IgA1 myeloma protein and SIgA to blood neutrophils was observed.\[^24\] Currently, multiple types of cellular IgA receptors that can either bind the Fc tail, carbohydrate side chains or accessory molecules like the J-chain and SC, including pIgR,\[^19,25\] Fcα/μ receptors,\[^26\] asialoglycoprotein-receptors,\[^27\] transferrin receptors (TFR, CD71),\[^28\] SC receptors,\[^29\] M cell receptors,\[^30\] have been identified in both rodents and humans. The functions of a number of these receptors have not yet been completely elucidated, but do not seem to differ greatly between species, although subtle variations can be observed. The major divergence is the lack of the myeloid FcαRI in mice. Several bacterial IgA proteins that bind to sites in IgA that overlap with the binding site of FcαRI have also been described, e.g., IgA-binding M-like proteins Arp4, Sir22, b-antigen and members of the staphylococcal superantigen-like proteins (SSL) family.\[^31\] As such, a main role for FcαRI in immune defence is supported, since bacterial evolution has led to development of molecules that interfere with IgA binding to FcαRI, resulting in an important evasion strategy for pathogens to escape IgA-mediated phagocytosis.

Figure 1. Schematic model of (A) monomeric human IgA1, IgA2m(1) and IgA2m(2), (B) dimeric IgA2 and (C) secretory IgA2. Heavy chains are depicted in light and dark orange, whereas light chains are shown in brown. J-chains or secretory component (SC) are indicated by blue or red, respectively. IgA1 contains O-linked oligosaccharides in the hinge region, which are depicted as white circles, whereas N-linked oligosaccharides are shown as black circles. For clarity, glycosylation of J-chain and secretory component has been omitted.
Thus far, FcαRI has been identified in primates, horses, cattle and rats, but not in mice, which is likely attributable to a gene translocation in the LRC locus.35-39 FcαRI expression begins at the promyelocyte stage in differentiation and is restricted to cells of the myeloid lineage, including neutrophils, eosinophils, monocytes and most macrophages (alveolar, tonsilar and splenic, but not macrophages from the small intestine). FcαRI is furthermore expressed on Kupffer cells and on interstitial and monocye-derived dendritic cells.40-48 Expression has recently been described on human platelets as well, but FcαRI is not observed on mast cells or basophils.49 FcαRI expression is constitutive and independent of its ligand, which is demonstrated in IgA deficient patients who still express FcαRI.50 However, expression levels can be modulated by cytokines (depending on cell type),54 or adaptor protein binding to the intracellular domain of FcαRI,51 which can induce either de novo synthesis or transport from intracellular stores to the cell surface.52,53

FcαRI consists of two extracellular Ig-like domains, a 19 aa transmembrane region and a short (41 aa) cytoplasmic tail. For most functions, association with the common γcR chain is necessary (see below).54-58 In addition to the full length FcαRI, several splice variants on the mRNA level have been described, and at least two other isoforms exist in vivo. One isoform (FcαRIα.2) is exclusively expressed on alveolar macrophages and differs by a deletion in the extracellular domain (EC) 2, whereas the transmembrane/ intracellular domains are deleted in the other isoform (FcαRβ), resulting in a soluble receptor.44,45 Furthermore, several polymorphisms have been described of which the Ser-248/Gly-248 polymorphism—which is located in the intracellular domain—has functional consequences and is associated with systemic lupus erythematosus.60

The FcαRI binding site for IgA is located in the extracellular domain EC1,61-63 which is different compared to FcεRI and FcγRs, as these FcRs bind their ligands in EC2. Residues Y35 (in the BC loop), R52, R53, L54, K55 (in the D strand), F56, W57, N58 (in the DE loop), Y81, R82, I83, G84, H85 and Y86 (in the FG loop) within EC1 are involved in IgA binding.62,64,65 The two EC domains are oriented at approximately 90° relative to each other. Although a number of conformational changes have been observed within the FcαRI-EC1 domain (in the D-strand, DE and FG loop) after binding to IgA, the orientation of the EC domains does not change significantly. FcαRI is a heavily glycosylated protein harbouring six N-glycosylation sites and several putative O-linked glycosylation sites.41 Deglycosylation of FcαRI N58 increases IgA binding.66 Recently, it was described that the pentraxin C-reactive protein (CRP) can bind to FcαRI, which induces cellular activation. However, the pentraxin-binding site on FcαRI is distinct from that of IgA.67

Crystallographic studies demonstrated that one IgA molecule can simultaneously bind two FcαRI molecules (Fig. 2).61,62 This is in contrast to FcγRIII and FcεRI, for which a 1:1 stoichiometry with their respective ligands was described, again emphasizing the dissimilarities between FcαRI and other members of the Fc receptor family.68-72 Because of partial overlap of the IgA binding site for FcαRI and pIgR, binding of SlgA to FcαRI is (partly) hampered due to steric hindrance of SC, although binding is increased when complement receptor 3 acts as co-receptor.62,63,73 Still, SlgA is a poorer opsonin compared with dimeric or monomeric IgA, and is therefore mostly considered as a non-inflammatory variant of IgA. In contrast, dimeric IgA can potentely trigger inflammatory functions through cross-linking of FcαRI,74,75 and can thus be considered a pro-inflammatory antibody. However, monomeric IgA probably represents the most interesting form of IgA, as either anti-inflammatory or potent pro-inflammatory responses are induced, depending on the mode of interaction with FcαRI (Fig. 2).

**IgA mediated FcαRI signalling and cellular functioning.** Monomeric serum IgA binds with moderate affinity to FcαRI (Ka = -106 M-1) in the boundaries of Ca2 and Ca3, whereas IgA immune complexes bind avidly.61,62,64,65,76 Residues within IgA involved in FcαRI binding are L256, L257, L258 in α-helix of
AB loop of Ca2 and within Ca3: E348 (A-strand), R382, L384 (C-strand), S387, E389 (CC’ loop), M433, H436 (F-strand), E437, A438, L439, P440, L441, A442 (FG loop), F443, T444 and Q445 (G strand).62-77 IgA Fc glycosylation is not critical for binding to FcαRI.14,78 Immune complexes with optimal binding contain five to six molecules of IgA per complex.79 On monocytes and eosinophils, inside-out signalling is involved in binding, which entails that stimulation of these cells with cytokines rapidly modulates binding capacity in response to intracellular signals, without affecting receptor expression levels.80-83 Thus, in a resting state FcαRI exhibits low capacity to interact with IgA-immune complexes, but ligand binding capacity increases profoundly after stimulation with cytokines like granulocyte/macrophage-colony stimulating factor, and interleukin (IL) 4 or 5, but surface receptor expression is not augmented. This process critically depends on the intracellular domain of FcαRI and the presence of an intact cytoskeleton, but does not require FcRγ chain. It further involves activation of phosphoinositide-3-kinase (PI-3K), intracellular phosphorylation of Serine 263 of FcαRI and binding of the serine/threonine phosphatase protein PP2A. Inside-out signalling is likely not influenced by the Ser-248/Gly-248 polymorphism.

Binding of IgA-immune complexes (containing either monomeric IgA or dimeric IgA) induces pro-inflammatory responses, which requires association of FcαRI with the FcRγ chain subunit.54,74 FcαRI contains a positively charged amino acid on position 209 that associates with an opposite negatively charged amino acid of the FcRγ chain, which is necessary, but not sufficient, for tethering FcαRI to FcRγ chain. For this, a more extensive interface between both transmembrane regions is required.54-58 FcαRI can also be expressed in the absence of FcRγ chains, which has been described for transfected cell lines, and selective monocyte and neutrophil populations (Fig. 2). Functionality of FcαRI “γ-less” receptors is limited to ligand binding (inside-out signalling) and receptor internalization,85-87 although Gly248-FcαRI can trigger IL-6 production in the absence of FcRγ chain.88

After cross-linking of FcαRI by IgA-immune complexes, Src kinase Lyn phosphorylates the tyrosines within the associated FcRγ chain immunoreceptor tyrosine-based activation motifs (ITAM). The phosphorylated tyrosines then serve as “docking” sites for recruitment of other tyrosine kinases, including Syk, Blk, Btk, PI-3K and PLC-γ. FcαRI can also associate with members of the Ras/Raf1 pathway, e.g., Grb2, Shc and SHIP.84 Dissimilarities in signalling pathways are induced at inflammatory sites by diverse stimuli and vary between different cell types, but result in pro-inflammatory cellular processes like phagocytosis, antigen presentation, antibody-dependent cellular cytotoxicity (ADCC), superoxide production or cytokine release.

Recently, a new type of intricacy was elucidated for IgA-mediated FcαRI signalling, as it was demonstrated that non-targeted monomeric serum IgA transduces inhibitory signals through FcαRI, which diminishes signalling through other activating Fc receptors.89,90 The ability of monomeric serum IgA to downregulate IgG-mediated phagocytosis, chemotaxis, bacterial activity, oxidative burst activity and cytokine release has been described for some time, but the mechanisms were poorly understood.91-97 Pasquier, et al. unravelled the underlying molecular mechanism by showing that SHP-1 is recruited to FcαRI-associated FcRγ chain, which blocks activating signals via Syk, induced by other Fc receptors.89 This inhibitory capacity through FcRγ chain ITAM is referred to as ITAMi. Thus, both IgA-induced activating and inhibitory signals depend on FcαRI-FcRγ chain ITAM, but differ in the recruitment of tyrosine kinases versus tyrosine phosphatases, respectively (Fig. 2). As such, it has been proposed that cross-linking of FcαRI during infection with IgA-opsonized pathogens results in pro-inflammatory responses, whereas naturally occurring serum IgA (not complexed with an antigen) induces inhibitory signals through FcαRI to dampen excessive immune responses (initiated by other Ig-immune complexes). Therapeutic strategies to target ITAMi with monomeric IgA have recently been reviewed by Monteiro, et al.5,6

**IgA mAbs and Targeted Therapy**

Research to investigate the potential of IgA mAbs for immunotherapeutic approaches is mostly based on in vitro experiments, as in vivo studies have been hampered by the lack of adequate mouse models. Because mice do not express FcαRI, experiments need to be performed in FcαRI transgenic mice.89 Furthermore, as traditional hybridoma technology has yielded murine antibodies, it has been difficult to generate suitable IgA mAbs because murine IgA binds poorly to human FcαRI. Alternatively, IgA mAbs have been produced by re-cloning IgG mAbs, use of phage display derived antibodies, or by transgenic plant technology. Additionally, chemically-linked FcαRI bispecific antibodies (BsAb) have been used. The latter are generated from the backbones of two IgG mAbs that recognize either the extracellular domain of FcαRI or the antigen of interest. The generation of human IgA knock-in mice in which the first gene (encoding IgM) downstream of the joining genes is exchanged for a human IgA knock-in gene (α1KI mice) was recently described in reference 99. As such, homozygous α1KI mice produce human IgA instead of murine IgM, which will allow the generation of a continuous source of antigen-specific human IgA mAbs. The availability of these novel models combined with the existence of human FcαRI transgenic mice for testing will greatly facilitate future in vivo research.

**IgA for prevention and treatment of infectious diseases.** Mucosal sites, where IgA is the most prominent antibody class, are critical interfaces that separate the interior of the body and the outside world. At these sites, a fine balance must exist between mounting effective immunological defense against pathogenic microorganisms and avoiding responses against commensal microbial and environmental antigens.11 SlgA plays an important role as the first line of defense by forming an anti-septic covering for the mucosa, hereby inhibiting adherence of microorganisms. Other mechanisms of displayed by SlgA include the ability to agglutinate microbes, interfere with bacterial motility by interacting with their flagella, and neutralize bacterial products such as enzymes and toxins. Whereas antibodies usually offer little protection against intracellular pathogens, dimeric IgA has the
intriguing ability to neutralize viruses intracellularly by intersecting virus particles and interfere with virus replication or assembly when in transit through an infected epithelial cell. IgA-virus complexes can subsequently be excreted into the lumen. Addition of specific anti-viral IgA to the basolateral surface of polarized epithelial cells was shown to reduce virus titers of Sendai virus, rotavirus, influenza and human immunodeficiency virus.100-104 Furthermore, polymeric IgA against toxin A of Clostridium difficile was able to prevent destruction of the epithelial monolayer.105 Importantly, mice were protected against rotavirus, a diarrhea causing pathogen, when IgA mAbs were given systemically, but not when IgA was presented via the lumen of the intestinal tract, which supports the hypothesis that IgA transcytosis is required for viral inactivation in vivo.106 Moreover, these data also suggest that systemically delivered IgA, transported via the pIgR route, is not hampered by locally produced mucosal IgA. Similarly, either passive transfer with specific IgA mAbs or oral immunization eliciting increased production of mucosal IgA was demonstrated to prevent Helicobacter felis, Helicobacter pylori, influenzaa, or Shigella flexneri infection.

The protective effect of IgA is presumably even more pronounced in humans due to the presence of FcαRI. Both IgA that was purified from immune sera of patients with Bordetella pertussis infection and BsAb directed against Bordetella Pertussis and FcαRI enhanced bacterial clearance in lungs of human FcαRI transgenic mice.116 Furthermore, Escherichia coli bacteria that had been opsonised with human serum IgA were efficiently phagocytosed by FcαRI-expressing Kupffer cells in the liver of transgenic mice in vivo, which also supports a role for IgA in systemic clearance of pathogens.45 It was recently demonstrated that passive transfer of human IgA mAbs against the α-crystallin of Mycobacterium tuberculosis protected human FcαRI transgenic mice, but not FcαRI-negative littermates against Mycobacterium tuberculosis infection.117 Mycobacterium tuberculosis infection of human whole blood culture or isolated monocytes was reduced in the presence of IgA, albeit with high interdonor variability.

Neutrophilic granulocytes (neutrophils) are also likely involved in efficient IgA-mediated protective responses against pathogens. We recently demonstrated that monomeric and dimeric IgA have the unique ability to induce neutrophil migration directly,75 whereas other antibody isotypes such as IgG and IgM induce neutrophil migration indirectly, through activation of the classical complement pathway (generating the chemottractants C3a and C5a). However, after cross-linking of FcαRI, neutrophils release LTβ4, which is a potent neutrophil chemottractant. A self-contained neutrophil migration loop will thus be initiated until the infectious agent has been eliminated.

To date, enhanced uptake of Escherichia coli, Streptococcus pneumonia, Staphylococcus aureus, Pseudomonas gingivalis, Candida albicans, Bordetella Pertussis and Neisseria meningitidis by neutrophils in the presence of specific IgA or FcαRI BsAb targeting specific pathogens has been demonstrated.45,75,112,114-116 Both monomeric and dimeric IgA proved effective in mediating phagocytosis by either neutrophils or Kupffer cells, but opsonic activity was reduced after binding of SC, which is consistent with a more anti-inflammatory role of SlgA.45,74 It was furthermore recently demonstrated that a specific anti-(gp41 x FcαRI) BsAb effectively directed neutrophils to destroy HIV-infected target cells.117 Additionally, a BsAb targeting FcαRI and surfactant protein D, which demonstrated a broader binding to a great variety of pathogens via its carbohydrate recognition domain, induced uptake of Escherichia coli, Candida albicans and influenza virus by neutrophils.118

Thus, therapies aimed to passively or actively increase specific IgA antibody titers against pathogens may significantly add to the arsenal of agents that fight (mucosal) infection. For instance, mucosal administration with transgenic plant SlgA afforded specific protection in humans against oral streptococcal colonization.119 Furthermore, mucosal administration of an HIV-1 vaccine demonstrated both resistance to the virus and elicited virus-specific IgA with HIV-1 transcytosis-blocking properties in monkeys.120

**Targeting FcαRI for anti-tumor immunotherapy.** FcαRI was proposed as a novel trigger molecule for mAb-based anti-cancer therapy more than 10 years ago.121,122 However, because mice do not express an FcαRI homologue, it has proven difficult to test the efficacy of human IgA anti-tumor mAbs in vivo.123 This has seriously hampered the collection of in vivo data on the effects of targeting FcαRI. Nevertheless, in vitro experiments using therapeuetic IgA1, IgA2, dimeric IgA, chimeric IgA and FcαRI BsAb targeting FcαRI have yielded promising results.119,121,122,124-137 For instance, IgA mAbs were demonstrated to engage a different cell population as effector cells compared to IgG mAbs. It was demonstrated that neutrophils from healthy donors or (FcγRII-expressing) neutrophils from donors who had been treated with granulocyte-colony stimulating factor (G-CSF) triggered tumour cell killing much more effectively in the presence of anti-(HER2/ neu x FcαRI) BsAb or anti-EpCAM IgA mAbs compared with an IgG counterpart. The superior ability of FcαRI to induce neutrophil-mediated tumour cell killing has now been demonstrated for a multitude of tumour-associated antigens, including HER2/ neu (on breast carcinoma), EpCAM (colon carcinoma), EGFR (epithelial carcinoma and renal cell carcinoma), HLA class II (B cell lymphoma), CD30 (T and B cell lymphoma) and carcinoembryonic antigen (CEA) in vitro. Notably, neutrophils were unable to kill malignant B cells via anti-CD20 IgG1 mAbs, but the addition of FcαRI targeting enabled this “antigen restriction” to be overcome, as tumour cells were efficiently killed in the presence of anti-(CD20 x FcαRI) BsAb.112,121,122,124-133,135-137

Furthermore, neutrophil accumulation and destruction of HER2/neu expressing breast carcinoma colonies in a three-dimensional culture system was only observed in the presence of anti-(HER2/neu x FcαRI) BsAb, but not in the presence of a counterpart FcγRII BsAb.132 Similar results were observed when colon carcinoma colonies were targeted with anti-EpCAM IgA, but not IgG mAb (Fig. 3A), which is likely the result of LTβ4 release after cross-linking of FcαRI.75,132 Enhanced neutrophil migration may therefore underlie increased ADCC after targeting with IgA mAb or FcαRI BsAb compared with IgG mAb or FcγRII BsAb. However, it was additionally demonstrated that immature bone marrow neutrophils were not capable of killing tumour cells via FcγRII, whereas FcαRI efficiently induced
Figure 3. For figure legend, see page 7.
ADCC.\textsuperscript{134} Thus, alternatively the amplitude of signals mediated through Fc\textgammaRI or Fc\textgammaR may differ, since it was reported that interaction of Fc\textalphaRI with Fc\textgammaR is stronger due to an electrostatic interaction that is absent for Fc\textgammaR.\textsuperscript{55}

Treatment with G-CSF in order to mobilize neutrophils from the bone marrow combined with targeting Fc\textgammaRI may improve clinical responses in cancer patients compared to results observed in unsuccessful trials that utilized therapeutic Fc\textgammaRI BsAb to enlist neutrophils as effector cells. An additional attractive feature of recruiting neutrophils as effector cells is that targeting Fc\textalphaRI on neutrophils induced necrotic and autophagic tumour cell death in vitro.\textsuperscript{138} Because therapeutic IgG mAb facilitate natural killer (NK) cell-mediated apoptosis of tumour cells, targeting neutrophils as effector cells may represent a supplementary approach to kill tumour cells with mutations in apoptotic pathways.

**Future Perspectives: IgA in Therapeutic Antibody Development!**

Today, IgG mAbs are dominating the therapeutic antibody field because they have extended plasma half-life, efficiently activate complement and recruit NK cells for ADCC. Moreover, extensive time and effort is invested in optimizing IgG mAbs to fine-tune desired effector functions. Nonetheless, an accumulating amount of data indicates that IgA mAbs (or Fc\textalphaRI BsAb) represent a promising addition to therapeutic strategies, especially in situations when IgG is less suitable, e.g., IgA responses will be likely more effective when active or passive mucosal immunity is required. Additionally, IgA mAbs are superior in recruiting neutrophils for antibody-mediated tumour cell killing, and may be a good alternative to overcome apoptosis resistance in tumour cells.

It must be noted that there are several challenges to the development of therapeutic IgA mAbs. First, the general miscomprehension of IgA as a non-inflammatory antibody needs to be rescinded, as many investigators have not really appreciated how powerful an inflammatory antibody IgA can be under the right circumstances. Second, adequate mouse models are urgently needed. The recent generation of human IgA knock-in mice and the availability of human Fc\textalphaRI transgenic mice should greatly facilitate progress of therapeutic IgA mAb development. Third, the lack of established models for high IgA production and purification has hampered generation of IgA mAbs. However, the development of the human \alpha\textkI mouse model will allow hybridoma technology for specific human IgA production,\textsuperscript{99} and advantages towards development of IgA-specific purification techniques have recently been established.\textsuperscript{139-141} The knowledge generated during optimizing IgG mAbs may furthermore significantly accelerate generation of effective IgA mAbs. For instance, IgA mAbs may require protein modulation to increase its plasma half-life, which is approximately a week.\textsuperscript{142} This suggests less favourable pharmacokinetics compared to IgG, as the half-life of IgG is 1 to 3 weeks depending on the isotype. Another feature of IgA antibodies is the incapability of activating the classical complement pathway. This may be advantageous in certain situations, but may hamper therapeutic efficacy in other approaches. Since it has been demonstrated that the glycan moieties of IgA can activate the MBL complement pathway, glyco-engineering may be used to optimise IgA mAbs, although it may be challenging to manufacture heavily glycosylated proteins.

The functions of different IgA forms range from mere neutralization to active immune suppression or pro-inflammatory responses, and these differences can be exploited in the design and generation of IgA mAbs with specific desired therapeutic functional activity (Fig. 3B). We thus anticipate that IgA mAbs will be a prominent part of the arsenal of therapeutic mAbs in the future.

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