When Therapeutic IgA Antibodies Might Come of Age

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Abstract
Background: Extensive efforts have been made in optimizing monoclonal immunoglobulin (Ig)G antibodies for use in clinical practice. Accumulating evidence suggests that IgA or anti-FcαRI could also represent an exciting avenue toward novel therapeutic strategies. Summary: Here, we underline that IgA is more effective in recruiting neutrophils for tumor cell killing and is potently active against several pathogens, including rotavirus, poliovirus, influenza virus, and SARS-CoV-2. IgA could also be used to modulate excessive immune responses in inflammatory diseases. Furthermore, secretory IgA is emerging as a major regulator of gut microbiota, which impacts intestinal homeostasis and global health as well. As such, IgA could be used to promote a healthy microbiota in a therapeutic setting. Key messages: IgA combines multifaceted functions that can be desirable for immunotherapy.

Introduction
Immunoglobulin (Ig)A is by far the most abundant immunoglobulin class in humans. Plasma cells produce around 3–5 g of IgA each day, much more than the combined production of all other isotypes [1]. Compared to other Ig classes, IgA has unique properties due to differences in its glycosylation patterns and molecular forms, compared to other isotypes, as well as the presence of more than 1 receptor.

Interestingly, the human IgA system differs substantially from that of rodents. While 2 IgA subclasses, IgA1 and IgA2, coexist in humans, murine and rat B cells produce only a single class of IgA. IgA antibodies are secreted in the intestinal and respiratory tract and are the main mediators of mucosal immunity. In humans, they are monomeric in serum but are present as dimers, termed secretory IgA (sIgA), at mucosal surfaces [2]. Moreover, the emerging field of mucosal immunology is shedding new light on IgA and in particular on its role in the maintenance of host/microbiota symbiosis. In the gut, IgA is able to neutralize pathogens as well as to establish and diversify commensal microbiota [3–7]. Serum IgA plays a dual role, triggering either pro-inflammatory or anti-inflammatory signaling pathways [8, 9]. Here, we review recent murine and human studies to evaluate the potential of IgA administration in immunotherapy.
Back to Basics

In humans, IgA exists as 2 closely related subclasses, IgA1 and IgA2, that differ by 13 additional amino acids in the hinge region of the IgA1 molecule [2]. While this difference might explain the increased susceptibility of IgA1 to bacterial proteases [10], this extended hinge region also confers to this subclass a T-shape that is beneficial for distant antigen recognition [11]. Both IgA subclasses are highly N-glycosylated in their CH1 and CH2 domains, with carbohydrates representing about 6% of their content. IgA1 harbors extra O-linked glycans consisting of N-acetylgalactosamine with galactose and sialic acids in the hinge region [12]. It is noteworthy that the glycan composition of the IgA1 hinge region is heterogeneous and that aberrant glycosylation is reportedly involved in the pathogenesis of IgA nephropathy [13].

IgA is present in 3 different forms, the most common in human serum being a monomer, whereas at mucosal sites, it is produced as polymeric molecules, foremost as dimeric IgA (dIgA). dIgA consists of 2 Ig molecules, linked tail-to-tail by an N-glycosylated 16 kDa protein called joining (J)-chain (J-chain) [14]. The presence of the J-chain is a prerequisite for IgA transcytosis across epithelial cells and its secretion at mucosal surfaces [15]. The polymeric Ig-receptor (pIgR), which is expressed on the basolateral pole of epithelial cells, binds to the J-chain and releases IgA into the lumen as sIgA. During this process, the pIgR ectodomain, referred to as the secretory component (SC), remains covalently attached to IgA [16]. The heavily N-glycosylated SC stabilizes IgA and prevents rapid proteolysis, thereby protecting the IgA against degradation in the hostile environment of the digestive tract [17, 18]. sIgA is also present in the mucous lining of the urogenital and respiratory tracts, as well as in saliva, milk, and tears [19].

IgA: An Ig with Multiple Partners

IgA interacts with various host receptors including plgR [15, 20], transferrin receptor (CD71) [21], asialoglycoprotein receptor [22], dectin-1 [23], Fca/m receptor [24, 25], DC-SIGN [26, 27], and FcαRI (CD89) [28]. These interactions are mediated through the binding of glycans on the Fc part of the antibody or accessory molecules such as the J-chain or the SC. Of note, IgA also binds to several bacterial proteins, the main ones being IgA-binding M-like proteins of the serogroup A streptococci (Arp4 and Sir22), the β-antigen of serogroup B streptococci, and proteins of the superantigen-like (SSL) family of Staphylococcus aureus[29]. In the following sections, we briefly introduce dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN)/SIGNR1 and FcαRI since IgA interactions with these receptors may open novel therapeutic opportunities in infectious and autoimmune diseases.

DC-SIGN

DC-SIGN, whose counterpart is SIGNR1 in mice, belongs to the C-type lectin receptor family that is expressed at the surface of dendritic cells (DCs). DC-SIGN interacts with IgA glycan, notably mannose residues of the SC [26, 27]. sIgA binding to DC-SIGN/SIGNR1 induces tolerogenic DCs, which fail to produce IL-12 but produce large amounts of IL-10. Such sIgA-induced DCs promote the expansion of Foxp3+ regulatory T cells and prevent the development of experimentally induced autoimmune diseases in animal models, such as experimental autoimmune encephalomyelitis and type 1 diabetes [27, 30].

FcαRI

Although FcαRI is a member of the Fc receptor Ig superfamily, it shares only 20% sequence similarity with other Fc receptors such as FcγRs and FcεRI. The FcαRI gene is located on chromosome 19, within the leukocyte receptor cluster that encodes killer inhibitory receptors (KIR) and leukocyte Ig-like receptors (LIR), while other Fc receptors map on chromosome 1. FcαRI shows more sequence homology with KIR and LIR than with other Fc receptors [28, 31, 32]. Of note, mice lack FcαRI, which could explain why we are still lacking a comprehensive picture of IgA function in vivo. In humans, FcαRI is expressed on cells of the myeloid lineage (neutrophils, monocytes, eosinophils, and mostly macrophages) but not on mast cells or basophils [28, 33–35]. FcαRI expression has also been detected on human platelets [36]. FcαRI is still expressed in IgA-deficient (IgAd) patients, which implies that FcαRI expression is constitutive and independent of IgA. However, several mediators such as IL-8 [37], LPS, tumor necrosis factor-α [38], and granulocyte-macrophage colony-stimulating factor [39] are able to modulate its expression level. Moreover, both monomeric and polymeric IgA mediate FcαRI internalization, resulting in downregulation of its expression [40, 41]. Altered FcαRI expression has been described in various diseases including allergic disorders, arthritic diseases, such as ankylosing spondylitis, and bacterial infections [34, 42, 43].

All forms of IgA bind to FcαRI, albeit with different binding affinities. IgA-immune complexes, and mono-
meric IgA (mIgA) or dIgA, bind to FcαRI with comparable association rates, whereas, compared to IgA-immune complexes, mIgA and dIgA dissociation is faster, which results in low affinity (\(K_a \approx 10^{-6} \text{m}\)) interactions for the latter forms [44–46]. sIgA binding to FcαRI is partly hampered because of the presence of the SC [47]. However, complement receptor 3 can act as a co-receptor to enable increased sIgA binding [48–50]. It remains poorly described as of yet whether IgA1 and IgA2 differently bind to FcαRI, but it is noteworthy that altered glycosylation patterns of either IgA or FcαRI modify the strength of IgA-FcαRI interactions. For instance, impaired sialylation of FcαRI was reported to be associated with increased binding of IgA1 to FcαRI in patients with IgA nephropathy [51, 52].

Recently, it has been demonstrated that FcαR-mediated signaling can initiate either pro-inflammatory responses or inhibitory signals as a mechanism to dampen excessive immune responses [8, 53]. In this sequence of events, IgA-immune complexes first cross-link FcαRI whose cytoplasmic tails are linked to the Fcγ chains. Then, kinases from the src family phosphorylate the tyrosines in the immunoreceptor tyrosine-based activation motif (ITAM) of the Fcγ chain, which, in turn, induce the recruitment of other tyrosine kinases, thereby facilitating the activation of various targets such as PI3K and phospholipase C-γ [54–56]. Together, these signaling pathways trigger a variety of cellular processes, such as release of pro-inflammatory mediators, the induction of antibody-dependent cellular cytotoxicity (ADCC), phagocytosis, antigen presentation, or the generation of respiratory bursts [57–60]. Functional responses following FcαRI activation may also differ depending on cell type and is targeted. For instance, FcαRI activation in neutrophils can lead to the formation of neutrophil extracellular traps [61]. Alternatively, it has been shown that mIgA, which does not cross-link FcαRI, propogates inhibitory signals through the formation of “inhibisomes” that contain signaling molecules [8, 62]. Inhibisomes interfere in Fcy chain signaling through a process called inhibitory ITAM (ITAMI), leading to a down-regulation of pro-inflammatory cytokine release, chemotaxis, IgG-mediated phagocytosis, and oxidative burst activity [37, 63–66]. In line with these results, it has been proposed that IgA-opsonized pathogens cross-link FcαRI, resulting in the generation of pro-inflammatory responses, whereas, in contrast, circulating mIgA antibodies induce inhibitory signals that prevent excessive immune responses [67].
IgA Therapy in Infectious Diseases

For years, sIgA has been described as a first barrier against pathogens at mucosal surfaces (Fig. 1). sIgA can agglutinate bacteria, disturb bacterial motility, neutralize bacterial toxins, and also inhibit bacterial adherence to epithelium, thereby preventing pathogen dissemination to the circulation [3–5, 68, 69]. These potent effects of IgA have been assessed against multiple gastrointestinal pathogens such as Salmonella typhimurium [5], Shigella flexneri[4], Clostridiodes difficile [69], and against some viruses. In particular, IgA exerts a neutralizing action on Sendai virus, human immunodeficiency virus, and influenza virus [70–74]. We have recently shown that IgA is more effective than IgG at neutralizing SARS-CoV-2 [75]. Mallery et al. described an alternative way for the neutralization of intracellular viruses through IgA binding to tripartite motif-containing 21 (TRIM 21), which is expressed in various tissue types and not just immune cells. After binding, TRIM 21 targets the virus-IgA complex for proteasomal degradation in an antibody-dependent intracellular neutralization process [76–78]. IgA also mediates protection against microbial infection via its interaction with the FcαRI. It has been demonstrated that infusion of antigen-specific IgA in human FcαRI transgenic mice, but not wild-type mice, results in an enhanced clearance of Mycobacterium tuberculosis or Bordetella pertussis[79, 80]. Based on these observations, passive transfer of specific IgA and active immunization may be effective strategies to fight viral and bacterial infections.

The rotavirus vaccine is viewed as a model system for understanding the therapeutic potential of intestinal IgA in gastrointestinal viral infections. Before and during the development of this vaccine, several correlative studies demonstrated that rotavirus-specific IgA is one of the major effector molecules that confers long-term immunity in humans as well as in animal models [81–85]. The 2 current oral vaccines Rotarix® (GlaxoSmithKline Biologicals) and RotaTeq® (Merck) were licensed for use in 2006. Although of different compositions, their effectiveness is similar in the prevention of severe rotavirus gastroenteritis [86, 87]. Seroconversion rates for serum antibody to rotavirus IgA are around 95% after the administration of 2 doses of the vaccine and duration of protection and vaccine efficacy may be predicted by serum IgA titers [88]. Importantly, higher child mortality has been associated with lower levels of vaccine-induced IgA [89].

Vaccine-induced IgA has played a major role in the worldwide eradication of poliovirus. Both the inactivated polio vaccine, used in developed world, and live, attenuated, oral poliovirus vaccine, mostly used in low- and middle-income countries, induce strong specific IgA responses that neutralize the 3 distinct serotypes [90–92]. However, mucosal IgA titers induced by the 2 vaccines greatly differ. The inactivated polio vaccine, which is delivered by intramuscular injection, fails to trigger intestinal IgA responses and is therefore less efficient [93]. This discrepancy points out the difficulties to ensure the generation of mucosal IgA antibodies and furthermore underscores the need to develop adequate vaccine adjuvants and delivery systems. Current injectable vaccines use alum as adjuvant, which is not effective to trigger class-switching toward the production of IgA [94]. In the last 10 years, major efforts have been undertaken to develop new mucosal adjuvants such as TLR agonists [95, 96], and toxin derivatives (ADP-ribosyltransferase enterotoxins and adenylate cyclase toxins) [97, 98]. These efforts stem from earlier studies that established key principles for the mucosal adjuvants mode of action, such as cholera toxin [99, 100]. sIgA itself might deliver an antigen to the mucosal tissue and elicit a strong humoral response. Recently, it has been shown that administration of p24gag (from HIV)-sIgA complexes in the nasal cavity elicits both humoral and cellular immune responses, which confer protection against HIV intranasal challenge [101].

Administration via the nasal route has been extensively examined as an alternative strategy to induce sIgA that may protect against respiratory infections. These studies came to fruition when the Food and Drug Administration (FDA) approved the cold-adapted, live attenuated influenza vaccine in 2002, a vaccine that ensures stronger protection than the parenteral inactivated vaccines [102–104]. Vaccination via the nasal mucosa induces polymeric sIgA that showed greater ability to neutralize virus than monomers. In addition, elevated sIgA serum levels correlated with vaccine efficacy [105–108]. Intranasal vaccination offers many practical benefits such as needle-free delivery and easy self-administration [109]. However, using the nasal route to mimic the natural infection with the aim to induce mucosal immunity requires novel approaches to evaluate the quality and quantity of IgA response, which, at present however, are not correctly implemented. For instance, the approval of novel influenza vaccines is still based on the results of hemagglutination inhibition tests, which only measure IgG in serum [107].

Although we and others pointed out the beneficial effects of vaccine-induced IgA responses [110, 111], several studies revealed a potential drawback of this approach. In the RV144 trial, which tested the efficacy of a
vaccine against HIV, Haynes et al. [112] showed that high levels of serum specific IgA likely mitigated the protective effect of the vaccine. In a secondary analysis, they demonstrated that antigen-specific serum IgA antibodies partially interfere with the binding of vaccine-induced IgG to HIV-1, thereby inhibiting ADCC [113]. Recently, these results have been reproduced with human samples in vitro, as well as in vivo in a macaque vaccine trial [114, 115]. Future research is needed to define to which extent different forms of IgA may differentially affect vaccine efficacy. It is, for instance, presently unclear as to which kind of humoral response would optimally protect against COVID-19, and whether anti-SARS-CoV-2 vaccine regimens should consider boosting the IgA response.

**IgA Replacement Therapy**

Patients with primary antibody deficiency (PAD) have decreased immunoglobulin levels, which makes them more susceptible to infections [116]. The use of IgG replacement therapy successfully reduces the frequency of severe bacterial infections. However, non-respiratory and upper respiratory tract infections persist, especially in patients with low IgA and IgM levels [117–119]. Hence, it could be suggested to treat IgA/IgM-deficient patients with IgA and/or IgM replacement therapy. While most of the currently used Ig preparations contain only IgG, a limited number of IgA-enriched preparations are commercially available, such as fresh frozen plasma, Pentaglobin®, and Trimodulin [120]. Next, we will discuss the efficacy of these preparations in preventing infections.

Although the protective role of IgA in infections has been extensively reported in the literature, few studies have addressed the efficacy of IgA replacement in clinical practice [120, 121]. The first case reports of 2 patients with relapsing *Campylobacter jejuni* infection demonstrated that repeated infusions of fresh frozen plasma led to detectable serum IgA levels and a complete recovery from infection [122]. These findings were corroborated by a study reporting the successful treatment of recurrent *C. jejuni* infections in PAD patients using Pentaglobin®, which is an IgA- and IgM-containing Ig preparation [123]. Finally, treatment with Trimodulin (BT-588), which contains twice the quantity of IgA, as compared to Pentaglobin®, tended to limit secondary infections in patients with severe community-acquired pneumonia [124]. Of note, there are no reports on the treatment of selective IgAd, which is the most common PAD, with a prevalence reaching 1:600 in the Western hemisphere [125]. This is likely to be due to reactions to Ig products and the emergence of anti-IgA antibodies that may preclude substitutive IgA therapy in patients with selective IgAd. Anaphylactic reactions to IgG infusions, which previously contained a small amount of IgA, have indeed been attributed to the appearance of anti-IgA antibodies in patients lacking IgA [121]. However, a detailed review of the literature reporting reactions in IgAd patients treated with gamma globulins identified only 27 patients that developed life-threatening reactions, whereas around 50 patients exhibited detectable anti-IgA antibodies without any symptoms [121]. These results question the relevance of anti-IgA antibodies and rather suggest that IgAd patients might tolerate the presence of heterologous IgA. Large studies are required to assess the safety and therapeutic effects of IgA-enriched products in preventing infections in general, and in IgAd in particular. Furthermore, IgA preparations need to be improved in order to mimic the various forms of IgA that are active at the mucosal surfaces (Fig. 1). Plasma-derived IgA, which is mainly mIgA1, might not have the same protective effect as dIgA2 to limit respiratory and intestinal infections.

**IgA in Anti-Tumor Therapy**

Therapeutic antibodies used in the treatment of various cancers eliminate tumor cells by a combination of both direct and indirect effects, which include complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and ADCC [132]. While IgG antibodies dominate the therapeutic field, it should be noted that IgA monoclonal antibodies are also effective in killing tumor cells through the activity of FcαRI-expressing macrophages and neutrophils (Fig. 1). In this respect, results from in vitro experiments have shown that IgA is superior in triggering ADCC by neutrophils, as compared to IgG [133–136]. Experimental in vivo models have been greatly improved with the generation of FcαRI transgenic mice [137, 138], permitting to demonstrate the potent anti-tumor activity of anti-EGFR IgA2 antibodies in various solid tumor models [133]. In a mouse lymphoma model, anti-CD20 IgA2 elicited powerful anti-tumor effects, subsequent to the recruitment of neutrophils to the tumor site [135, 139].

Unfortunately, IgA class antibodies have a short half-life, likely related by their resistance to the process of recycling [140, 141] and also their asialoglycoprotein-receptor-mediated liver clearance via terminal galactose interaction [22], so far hinders their use as therapeutic
antibodies. Recent glyco-engineering strategies significantly improved the pharmacokinetic properties of recombinant IgA (Fig. 2). For instance, IgA molecules with increased sialylation and deletion of terminal galactose residues on glycan exhibited longer serum half-life, compared to wild-type IgA, offering a promising format for immunotherapy [126, 130]. Meyer et al. [127] developed another strategy to increase IgA half-life via its fusion to an albumin-binding domain. This small protein subunit, expressed in various gram-positive bacteria, allows the binding of the fused protein to albumin, then to the FcRn. In humans, recycling of albumin and IgG1 through FcRn extends their serum half-life to 19 and 21 days, respectively [140, 142]. Besides pharmacokinetics, combinations of IgA and CD47-SIRPα-blocking agents have provided evidence [143] that targeting phagocytosis checkpoint inhibitors enhanced IgA function, as already demonstrated for IgG antibodies [144].

**IgA Therapy in Inflammatory Diseases**

IgA binding to the FcαRI propagates inhibitory signals that result in anti-inflammatory responses. Thus, FcαRI targeting could represent a promising strategy for the treatment of various inflammatory diseases [145]. Indeed, administration of mIgA to FcαRI transgenic mice was found to result in the prevention and resolution of experimentally induced arthritis. Similarly, in patients with rheumatoid arthritis, mIgA is able to inhibit pro-inflammatory cytokine production and chemotaxis of myeloid cells in vitro [9]. Alternatively, anti-FcαRI Fab fragments can drive ITAMi-induced inhibitory signaling and have proven their therapeutic potential in models of kidney inflammation [146, 147]. Pasquier et al. [8] also demonstrated that pretreatment of FcαRI transgenic mice with anti-FcαRI drastically reduced the development of bronchial inflammation. Taken together, these findings suggest that FcαRI targeting could represent a new and promising tool in preventing or treating inflammatory diseases (Fig. 1).

**Outlook**

Research and development efforts provided meaningful improvements in IgA half-life [126, 130] and IgA production, underlining the feasibility of commercial-scale IgA production [126, 128]. Since IgA is the predominant antibody fighting pathogens at the mucosal surfaces, recent studies also developed exciting tools for orally deliverable IgA. Entire sIgA or chimeric IgA have been already introduced in food or produced in plants fit for human consumption. Strikingly, these formulations are able to neutralize bacterial toxins in vitro or prevent gastrointestinal infections in animals [148–150]. Since cost hurdles might impede mAb IgA drug commercialization, future work should focus on simple and low-cost manufacturing.
processes. Finally, in order to capitalize on the advantages of IgA and IgG isotypes, the engineering of either cross-isotype molecules [129] or bispecific antibodies [151, 152] might be considered for therapeutic applications.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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