When Therapeutic IgA Antibodies Might Come of Age

Delphine Sterlin, Guy Gorochov

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Delphine Sterlin PharmD, PhD[1,2] and Guy Gorochov MD, PhD[1*]

Affiliations

1. Sorbonne Université, Inserm, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), AP-HP Hôpital Pitié-Salpêtrière, 75013 Paris, France
2. Unit of Antibodies in Therapy and Pathology, Institut Pasteur, UMR1222 Inserm, F-75015 Paris, France.

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Corresponding author :
Guy Gorochov
Centre d'Immunologie et des Maladies Infectieuses
83 boulevard de l'hôpital
75013 Paris, France
Tel : +33 1.42.17.75.07
Fax : +33 1.42.17.74.90
e-mail : guy.gorochov@sorbonne-universite.fr

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Abstract

Background

Extensive efforts have been made in optimizing monoclonal IgG 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 on 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 to 5 grammes 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 one receptor.

Interestingly, the human IgA system differs substantially from that of rodents. While two IgA subclasses, IgA_1 and IgA_2, 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 human, 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 two 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 harbours extra-O-linked glycans consisting of N-acetylgalacosamine 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 three 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. Dimeric IgA consists of two Ig molecules, linked tail-to-tail by a 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]. Secretory IgA 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 pIgR [15,20], transferrin receptor (TfR, CD71) [21], asialoglycoprotein-receptor [22], Dectin-1 [23], Fcα/μ receptors [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 *S. aureus* [29]. In the following sections, we briefly introduce DC-SIGN/SIGNR1 and FcαRI since IgA interactions with these receptors may open novel therapeutic opportunities in infectious and autoimmune diseases.

DC-SIGN

Dendritic Cell-Specific ICAM-3 Grabbing Nonintegrin (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]. Secretory IgA 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 leucocyte receptor cluster (LRC) that encodes killer-inhibitory receptors (KIR) and leucocyte 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 that 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 patients, which implies that FcαRI expression is constitutive and independent of IgA. However, several mediators such as IL-8 [37], lipopolysaccharides (LPS), tumor necrosis factor-α (TNF-α) [38] and granulocyte-macrophage colony-stimulating factor (GM-CSF) [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 monomeric (mIgA) or dimeric IgA (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 ($Ka \approx 10^{-6}M$) 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 to increased binding of IgA1 to FcαRI in patients with IgA nephropathy [51,52].

Recently, it has been demonstrated that FcαRI-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 (NET) [61]. Alternatively, it has been shown that monomeric IgA, which does not cross-link FcαRI, propagates inhibitory signals through the formation of "inhibisomes" that contain signaling molecules [8,62]. Inhibisomes interfere in Fcγ-chain signaling through a process called inhibitory ITAM (ITAMi), leading to a downregulation 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 monomeric IgA 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 (Figure 2). 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 gastro-intestinal pathogens such as *Salmonella Typhimurium* [5], *Shigella flexnerii* [4], *Clostridiodes difficile* [69], as well as 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 and 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 proteosomal degradation in a process antibody-dependent intracellular neutralization

[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 immunisation 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 two current oral vaccines Rotarix® (GlaxoSmithKline Biologicals) and RotaTeq® (Merck) were licensed for use in 2006. Although of different composition, their effectiveness is similar in the prevention of severe rotavirus gastroenteritis [86,87]. Seroconversion rates for serum anti-rotavirus IgA are around 95% after the administration of two 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 three distinct serotypes [90–92]. However, mucosal IgA titers induced by the two 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 ten years, major efforts have been undertaken to develop new mucosal adjuvants such as TLR agonists [95,96], and toxin derivatives (ADP-ribosyl transferase enterotoxins, 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 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.* showed that high levels of serum specific IgA likely mitigated the protective effect of the vaccine [112]. 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 (FFP), 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 two patients with relapsing *Campylobacter jejuni* infection demonstrated that repeated infusions of FFP 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 IgA-deficient patients (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 -that 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 gammaglobulins 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 the 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 (Figure 1). Plasma-derived IgA, which is mainly

monomeric IgA1 might not have the same protective effect as dimeric IgA2 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 (CDC), antibody-dependent cellular phagocytosis (ADCP) and (ADCC) [126]. 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 (Figure 1). In this respect, results from *in vitro* experiments have shown that IgA is superior in triggering ADCC by neutrophils, as compared to IgG [127–130]. Experimental *in vivo* models have been greatly improved with the generation of FcαRI transgenic mice [131,132], permitting to demonstrate the potent anti-tumor activity of anti-EGFR IgA2 antibodies in various solid tumor models [127]. In a mouse lymphoma model, anti-CD20 IgA2 elicited powerful anti-tumor effects, subsequent to the recruitment of and recruited neutrophils to the tumor site [129,133].

Unfortunately, IgA class antibodies have a short half-life, likely related by their resistance to the process of recycling [134,135] 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 (Figure 2). For instance, IgA molecules with increased sialylation and deletion of terminal galactose residues on glycan exhibited longer serum half-life, as compared to wild type IgA, offering a promising format for immunotherapy [136,137]. Meyer et al. developed another

strategy to increase IgA half-life via its fusion to an albumin-binding domain [138]. 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 [134,139]. Besides pharmacokinetics, combinations of IgA and CD47-SIRPα-blocking agents have provided evidence [140] that targeting phagocytosis checkpoint inhibitors enhanced IgA function, as already demonstrated for IgG antibodies [141].

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 [142]. Indeed, administration of monomeric IgA to FcαRI transgenic mice was found to result in the prevention and resolution of experimentally induced arthritis. Similarly, in patients with rheumatoid arthritis, monomeric IgA is able to inhibit pro-inflammatory cytokine production by 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 [143,144]. Pasquier et al. also demonstrated that pretreatment of FcαRI transgenic mice with anti-FcαRI drastically reduced the development of bronchial inflammation [8]. Taken together, these findings suggest that FcαRI targeting could represent a new and promising tool in preventing or treating inflammatory diseases (Figure 1).

Outlook

Research and development efforts provided meaningful improvements in IgA half-life [136,137] and IgA production, underlining the feasibility of commercial scale IgA production [136,145]. 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 gastro-intestinal infections in animals [146–148]. Since costs 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 [149], or bispecific antibodies [150,151] might be considered for therapeutic applications.

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Author contributions

DS prepared the figures and wrote the manuscript. GG wrote and reviewed the manuscript.

References

1 Jonard PP, Rambaud JC, Dive C, Vaerman JP, Galian A, Delacroix DL. Secretion of immunoglobulins and plasma proteins from the jejunal mucosa. Transport rate and origin of polymeric immunoglobulin A. J Clin Invest. 1984 Aug;74(2):525–35.

2 Kerr MA. The structure and function of human IgA. Biochem J. 1990 Oct;271(2):285–96.

3 Forbes SJ, Eschmann M, Mantis NJ. Inhibition of Salmonella enterica serovar typhimurium motility and entry into epithelial cells by a protective antilipopolysaccharide monoclonal immunoglobulin A antibody. Infect Immun. 2008 Sep;76(9):4137–44.

4 Forbes SJ, Bumpus T, McCarthy EA, Corthésy B, Mantis NJ. Transient suppression of Shigella flexneri type 3 secretion by a protective O-antigen-specific monoclonal IgA. MBio. 2011;2(3):e00042-00011.

5 Bioley G, Monnerat J, Lötscher M, Vonarburg C, Zuercher A, Corthésy B. Plasma-Derived Polyreactive Secretory-Like IgA and IgM Opsonizing Salmonella enterica Typhimurium Reduces Invasion and Gut Tissue Inflammation through Agglutination. Front Immunol. 2017;8:1043.

6 Kawamoto S, Maruya M, Kato LM, Suda W, Atarashi K, Doi Y, et al. Foxp3(+) T cells regulate immunoglobulin a selection and facilitate diversification of bacterial species responsible for immune homeostasis. Immunity. 2014 Jul;41(1):152–65.

7 Slack E, Balmer ML, Fritz JH, Hapfelmeier S. Functional flexibility of intestinal IgA - broadening the fine line. Front Immunol. 2012;3:100.

8 Pasquier B, Launay P, Kanamaru Y, Moura IC, Pfirsch S, Ruffié C, et al. Identification of FcalphaRI as an inhibitory receptor that controls inflammation: dual role of FcRgamma ITAM. Immunity. 2005 Jan;22(1):31–42.

9 Rossato E, Ben Mkaddem S, Kanamaru Y, Hurtado-Nedelec M, Hayem G, Descatoire V, et al. Reversal of Arthritis by Human Monomeric IgA Through the Receptor-Mediated SH2 Domain-Containing Phosphatase 1 Inhibitory Pathway. Arthritis & Rheumatology (Hoboken, NJ). 2015 Jul;67(7):1766–77.

10 Batten MR, Senior BW, Kilian M, Woof JM. Amino acid sequence requirements in the hinge of human immunoglobulin A1 (IgA1) for cleavage by streptococcal IgA1 proteases. Infect Immun. 2003 Mar;71(3):1462–9.

11 Bonner A, Almogren A, Furtado PB, Kerr MA, Perkins SJ. The nonplanar secretory IgA2 and near planar secretory IgA1 solution structures rationalize their different mucosal immune responses. J Biol Chem. 2009 Feb;284(8):5077–87.

12 Toraño A, Tsuzukida Y, Liu YS, Putnam FW. Location and structural significance of the oligosaccharides in human Ig-A1 and IgA2 immunoglobulins. Proceedings of the National Academy of Sciences of the United States of America. 1977 Jun;74(6):2301.

13 Mestecky J, Tomana M, Moldoveanu Z, Julian BA, Suzuki H, Matousovic K, et al. Role of aberrant glycosylation of IgA1 molecules in the pathogenesis of IgA nephropathy. Kidney Blood Press Res. 2008;31(1):29–37.

14 Krugmann S, Pleass RJ, Atkin JD, Woof JM. Structural requirements for assembly of dimeric IgA probed by site-directed mutagenesis of J chain and a cysteine residue of the alpha-chain CH2 domain. The Journal of Immunology. 1997 Jul;159(1):244–9.

15 Johansen FE, Pekna M, Norderhaug IN, Haneberg B, Hietala MA, Krajci P, et al. Absence of epithelial immunoglobulin A transport, with increased mucosal leakiness, in polymeric immunoglobulin receptor/secretory component-deficient mice. J Exp Med. 1999 Oct;190(7):915–22.

16 Stadtmueller BM, Huey-Tubman KE, López CJ, Yang Z, Hubbell WL, Bjorkman PJ. The structure and dynamics of secretory component and its interactions with polymeric

immunoglobulins. Elife. 2016 Mar;5. DOI: 10.7554/eLife.10640

17 Crottet P, Corthésy B. Secretory component delays the conversion of secretory IgA into antigen-binding competent F(ab')2: a possible implication for mucosal defense. J Immunol. 1998 Nov;161(10):5445–53.

18 Duc M, Johansen F-E, Corthésy B. Antigen Binding to Secretory Immunoglobulin A Results in Decreased Sensitivity to Intestinal Proteases and Increased Binding to Cellular Fc Receptors. J Biol Chem. 2010 Aug;285(2):953–60.

19 Brandtzaeg P. Secretory IgA: Designed for Anti-Microbial Defense. Front Immunol. 2013;4:222.

20 Mostov KE, Friedlander M, Blobel G. The receptor for transepithelial transport of IgA and IgM contains multiple immunoglobulin-like domains. Nature. 1984 Mar;308(5954):37–43.

21 Moura IC, Centelles MN, Arcos-Fajardo M, Malheiros DM, Collawn JF, Cooper MD, et al. Identification of the transferrin receptor as a novel immunoglobulin (Ig)A1 receptor and its enhanced expression on mesangial cells in IgA nephropathy. J Exp Med. 2001 Aug;194(4):417–25.

22 Stockert RJ, Kressner MS, Collins JC, Sternlieb I, Morell AG. IgA interaction with the asialoglycoprotein receptor. Proc Natl Acad Sci USA. 1982 Oct;79(20):6229–31.

23 Rochereau N, Drocourt D, Perouzel E, Pavot V, Redelinghuys P, Brown GD, et al. Dectin-1 is essential for reverse transcytosis of glycosylated SIgA-antigen complexes by intestinal M cells. PLoS Biol. 2013 Sep;11(9):e1001658.

24 Shibuya A, Sakamoto N, Shimizu Y, Shibuya K, Osawa M, Hiroyama T, et al. Fc alpha/mu receptor mediates endocytosis of IgM-coated microbes. Nat Immunol. 2000 Nov;1(5):441–6.

25 Honda S, Kurita N, Miyamoto A, Cho Y, Usui K, Takeshita K, et al. Enhanced

humoral immune responses against T-independent antigens in Fc alpha/muR-deficient mice. Proc Natl Acad Sci USA. 2009 Jul;106(27):11230–5.

26 Baumann J, Park CG, Mantis NJ. Recognition of secretory IgA by DC-SIGN: implications for immune surveillance in the intestine. Immunol Lett. 2010 Jun;131(1):59–66.

27 Diana J, Moura IC, Vaugier C, Gestin A, Tissandie E, Beaudoin L, et al. Secretory IgA induces tolerogenic dendritic cells through SIGNR1 dampening autoimmunity in mice. J Immunol. 2013 Sep;191(5):2335–43.

28 Monteiro RC, Kubagawa H, Cooper MD. Cellular distribution, regulation, and biochemical nature of an Fc alpha receptor in humans. J Exp Med. 1990 Mar;171(3):597–613.

29 Kazeeva TN, Shevelev AB. IgA-specific proteins of pathogenic bacteria. Biochemistry Mosc. 2009 Jan;74(1):12–21.

30 Caparrós E, Munoz P, Sierra-Filardi E, Serrano-Gómez D, Puig-Kröger A, Rodríguez-Fernández JL, et al. DC-SIGN ligation on dendritic cells results in ERK and PI3K activation and modulates cytokine production. Blood. 2006 May;107(10):3950–8.

31 Daëron M. Fc receptor biology. Annu Rev Immunol. 1997;15:203–34.

32 Kremer EJ, Kalatzis V, Baker E, Callen DF, Sutherland GR, Maliszewski CR. The gene for the human IgA Fc receptor maps to 19q13.4. Hum Genet. 1992 Apr;89(1):107–8.

33 Patry C, Sibille Y, Lehuen A, Monteiro RC. Identification of Fc alpha receptor (CD89) isoforms generated by alternative splicing that are differentially expressed between blood monocytes and alveolar macrophages. J Immunol. 1996 Jun;156(11):4442–8.

34 Monteiro RC, Hostoffer RW, Cooper MD, Bonner JR, Gartland GL, Kubagawa H.

Definition of immunoglobulin A receptors on eosinophils and their enhanced expression in allergic individuals. J Clin Invest. 1993 Oct;92(4):1681–5.

35 van Egmond M, van Garderen E, van Spriel AB, Damen CA, van Amersfoort ES, van Zandbergen G, et al. FcalphaRI-positive liver Kupffer cells: reappraisal of the function of immunoglobulin A in immunity. Nat Med. 2000 Jun;6(6):680–5.

36 Qian K, Xie F, Gibson AW, Edberg JC, Kimberly RP, Wu J. Functional expression of IgA receptor FcalphaRI on human platelets. J Leukoc Biol. 2008 Dec;84(6):1492–500.

37 Nikolova EB, Russell MW. Dual function of human IgA antibodies: inhibition of phagocytosis in circulating neutrophils and enhancement of responses in IL-8-stimulated cells. J Leukoc Biol. 1995 Jun;57(6):875–82.

38 Wehrli M, Cortinas-Elizondo F, Hlushchuk R, Daudel F, Villiger PM, Miescher S, et al. Human IgA Fc receptor FcαRI (CD89) triggers different forms of neutrophil death depending on the inflammatory microenvironment. J Immunol. 2014 Dec;193(11):5649–59.

39 Weisbart RH, Kacena A, Schuh A, Golde DW. GM-CSF induces human neutrophil IgA-mediated phagocytosis by an IgA Fc receptor activation mechanism. Nature. 1988 Apr;332(6165):647–8.

40 Geissmann F, Launay P, Pasquier B, Lepelletier Y, Leborgne M, Lehuen A, et al. A subset of human dendritic cells expresses IgA Fc receptor (CD89), which mediates internalization and activation upon cross-linking by IgA complexes. J Immunol. 2001 Jan;166(1):346–52.

41 Grossetête B, Launay P, Lehuen A, Jungers P, Bach JF, Monteiro RC. Down-regulation of Fc alpha receptors on blood cells of IgA nephropathy patients: evidence for a negative regulatory role of serum IgA. Kidney Int. 1998 May;53(5):1321–35.

42 Montenegro V, Chiamolera M, Launay P, Gonçalves CR, Monteiro RC. Impaired

expression of IgA Fc receptors (CD89) by blood phagocytic cells in ankylosing spondylitis. J Rheumatol. 2000 Feb;27(2):411–7.

43 Chiamolera M, Launay P, Montenegro V, Rivero MC, Velasco IT, Monteiro RC. Enhanced expression of Fc alpha receptor I on blood phagocytes of patients with gram-negative bacteremia is associated with tyrosine phosphorylation of the FcR-gamma subunit. Shock. 2001 Nov;16(5):344–8.

44 Oortwijn BD, Roos A, van der Boog PJM, Klar-Mohamad N, van Remoortere A, Deelder AM, et al. Monomeric and polymeric IgA show a similar association with the myeloid FcalphaRI/CD89. Mol Immunol. 2007 Feb;44(5):966–73.

45 Wines BD, Hulett MD, Jamieson GP, Trist HM, Spratt JM, Hogarth PM. Identification of residues in the first domain of human Fc alpha receptor essential for interaction with IgA. J Immunol. 1999 Feb;162(4):2146–53.

46 Wines BD, Sardjono CT, Trist HH, Lay CS, Hogarth PM. The interaction of Fc alpha RI with IgA and its implications for ligand binding by immunoreceptors of the leukocyte receptor cluster. J Immunol. 2001 Feb;166(3):1781–9.

47 Kumar N, Arthur CP, Ciferri C, Matsumoto ML. Structure of the secretory immunoglobulin A core. Science. 2020 Feb DOI: 10.1126/science.aaz5807

48 Herr AB, Ballister ER, Bjorkman PJ. Insights into IgA-mediated immune responses from the crystal structures of human FcalphaRI and its complex with IgA1-Fc. Nature. 2003 Jun;423(6940):614–20.

49 van Spriel AB, Leusen JH, van Egmond M, Dijkman HB, Assmann KJ, Mayadas TN, et al. Mac-1 (CD11b/CD18) is essential for Fc receptor-mediated neutrophil cytotoxicity and immunologic synapse formation. Blood. 2001 Apr;97(8):2478–86.

50 Woof JM, Burton DR. Human antibody-Fc receptor interactions illuminated by crystal structures. Nat Rev Immunol. 2004 Feb;4(2):89–99.

51 Xue J, Zhao Q, Zhu L, Zhang W. Deglycosylation of FcalphaR at N58 increases its binding to IgA. Glycobiology. 2010 Jul;20(7):905–15.

52 Gomes MM, Wall SB, Takahashi K, Novak J, Renfrow MB, Herr AB. Analysis of IgA1 N-glycosylation and its contribution to FcalphaRI binding. Biochemistry. 2008 Oct;47(43):11285–99.

53 Bakema JE, van Egmond M. The human immunoglobulin A Fc receptor FcαRI: a multifaceted regulator of mucosal immunity. Mucosal Immunol. 2011 Nov;4(6):612–24.

54 Morton HC, van den Herik-Oudijk IE, Vossebeld P, Snijders A, Verhoeven AJ, Capel PJ, et al. Functional association between the human myeloid immunoglobulin A Fc receptor (CD89) and FcR gamma chain. Molecular basis for CD89/FcR gamma chain association. J Biol Chem. 1995 Dec;270(50):29781–7.

55 Mkaddem SB, Murua A, Flament H, Titeca-Beauport D, Bounaix C, Danelli L, et al. Lyn and Fyn function as molecular switches that control immunoreceptors to direct homeostasis or inflammation. Nat Commun. 2017 15;8(1):246.

56 Park RK, Izadi KD, Deo YM, Durden DL. Role of Src in the modulation of multiple adaptor proteins in FcalphaRI oxidant signaling. Blood. 1999 Sep;94(6):2112–20.

57 Chen Y-W, Lang ML, Wade WF. Protein kinase C-alpha and -delta are required for FcalphaR (CD89) trafficking to MHC class II compartments and FcalphaR-mediated antigen presentation. Traffic. 2004 Aug;5(8):577–94.

58 Otten MA, Rudolph E, Dechant M, Tuk CW, Reijmers RM, Beelen RHJ, et al. Immature neutrophils mediate tumor cell killing via IgA but not IgG Fc receptors. J Immunol. 2005 May;174(9):5472–80.

59 Ouadrhiri Y, Pilette C, Monteiro RC, Vaerman J-P, Sibille Y. Effect of IgA on respiratory burst and cytokine release by human alveolar macrophages: role of ERK1/2 mitogen-activated protein kinases and NF-kappaB. Am J Respir Cell Mol Biol. 2002

Mar;26(3):315–32.

60 van der Steen L, Tuk CW, Bakema JE, Kooij G, Reijerkerk A, Vidarsson G, et al. Immunoglobulin A: Fc(alpha)RI interactions induce neutrophil migration through release of leukotriene B4. Gastroenterology. 2009 Dec;137(6):2018-2029.e1-3.

61 Aleyd E, van Hout MWM, Ganzevles SH, Hoeben KA, Everts V, Bakema JE, et al. IgA enhances NETosis and release of neutrophil extracellular traps by polymorphonuclear cells via Fcα receptor I. J Immunol. 2014 Mar;192(5):2374–83.

62 Pfirsch-Maisonnas S, Aloulou M, Xu T, Claver J, Kanamaru Y, Tiwari M, et al. Inhibitory ITAM signaling traps activating receptors with the phosphatase SHP-1 to form polarized “inhibisome” clusters. Sci Signal. 2011 Apr;4(169):ra24.

63 Van Epps DE, Brown SL. Inhibition of formylmethionyl-leucyl-phenylalanine-stimulated neutrophil chemiluminescence by human immunoglobulin A paraproteins. Infect Immun. 1981 Dec;34(3):864–70.

64 Van Epps DE, Williams RC. Suppression of leukocyte chemotaxis by human IgA myeloma components. J Exp Med. 1976 Nov;144(5):1227–42.

65 Van Epps DE, Reed K, Williams RC. Suppression of human PMN bactericidal activity by human IgA paraproteins. Cell Immunol. 1978 Mar;36(2):363–76.

66 Wilton JM. Suppression by IgA of IgG-mediated phagocytosis by human polymorphonuclear leucocytes. Clin Exp Immunol. 1978 Dec;34(3):423–8.

67 Blank U, Launay P, Benhamou M, Monteiro RC. Inhibitory ITAMs as novel regulators of immunity. Immunol Rev. 2009 Nov;232(1):59–71.

68 Moor K, Diard M, Sellin ME, Felmy B, Wotzka SY, Toska A, et al. High-avidity IgA protects the intestine by enchaining growing bacteria. Nature. 2017 Apr DOI: 10.1038/nature22058

69 Stubbe H, Berdoz J, Kraehenbuhl JP, Corthésy B. Polymeric IgA is superior to

monomeric IgA and IgG carrying the same variable domain in preventing Clostridium difficile toxin A damaging of T84 monolayers. J Immunol. 2000 Feb;164(4):1952–60.

70 Mazanec MB, Coudret CL, Fletcher DR. Intracellular neutralization of influenza virus by immunoglobulin A anti-hemagglutinin monoclonal antibodies. J Virol. 1995 Feb;69(2):1339–43.

71 Mazanec MB, Kaetzel CS, Lamm ME, Fletcher D, Peterra J, Nedrud JG. Intracellular neutralization of Sendai and influenza viruses by IgA monoclonal antibodies. Adv Exp Med Biol. 1995;371A:651–4.

72 Planque S, Salas M, Mitsuda Y, Sienczyk M, Escobar MA, Mooney JP, et al. Neutralization of genetically diverse HIV-1 strains by IgA antibodies to the gp120-CD4-binding site from long-term survivors of HIV infection. AIDS. 2010 Mar;24(6):875–84.

73 Devito C, Hinkula J, Kaul R, Lopalco L, Bwayo JJ, Plummer F, et al. Mucosal and plasma IgA from HIV-exposed seronegative individuals neutralize a primary HIV-1 isolate. AIDS. 2000 Sep;14(13):1917–20.

74 Wills S, Hwang K-K, Liu P, Dennison SM, Tay MZ, Shen X, et al. HIV-1-Specific IgA Monoclonal Antibodies from an HIV-1 Vaccinee Mediate Galactosylceramide Blocking and Phagocytosis. J Virol. 2018 01;92(7). DOI: 10.1128/JVI.01552-17

75 Sterlin D, Mathian A, Miyara M, Mohr A, Anna F, Claer L, et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. medRxiv. 2020 Jan;2020.06.10.20126532.

76 Mallery DL, McEwan WA, Bidgood SR, Towers GJ, Johnson CM, James LC. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). Proc Natl Acad Sci USA. 2010 Nov;107(46):19985–90.

77 McEwan WA, Tam JCH, Watkinson RE, Bidgood SR, Mallery DL, James LC. Intracellular antibody-bound pathogens stimulate immune signaling via the Fc receptor

TRIM21. Nat Immunol. 2013 Apr;14(4):327–36.

78 Bidgood SR, Tam JCH, McEwan WA, Mallery DL, James LC. Translocalized IgA mediates neutralization and stimulates innate immunity inside infected cells. Proc Natl Acad Sci USA. 2014 Sep;111(37):13463–8.

79 Balu S, Reljic R, Lewis MJ, Pleass RJ, McIntosh R, van Kooten C, et al. A novel human IgA monoclonal antibody protects against tuberculosis. J Immunol. 2011 Mar;186(5):3113–9.

80 Hellwig SM, van Spriel AB, Schellekens JF, Mooi FR, van de Winkel JG. Immunoglobulin A-mediated protection against Bordetella pertussis infection. Infect Immun. 2001 Aug;69(8):4846–50.

81 Matson DO, O'Ryan ML, Herrera I, Pickering LK, Estes MK. Fecal antibody responses to symptomatic and asymptomatic rotavirus infections. J Infect Dis. 1993 Mar;167(3):577–83.

82 O'Ryan ML, Matson DO, Estes MK, Pickering LK. Acquisition of serum isotype-specific and G type-specific antirotavirus antibodies among children in day care centers. Pediatr Infect Dis J. 1994 Oct;13(10):890–5.

83 Saif L, Yuan L, Ward L, To T. Comparative studies of the pathogenesis, antibody immune responses, and homologous protection to porcine and human rotaviruses in gnotobiotic piglets. Adv Exp Med Biol. 1997;412:397–403.

84 Tô TL, Ward LA, Yuan L, Saif LJ. Serum and intestinal isotype antibody responses and correlates of protective immunity to human rotavirus in a gnotobiotic pig model of disease. J Gen Virol. 1998 Nov;79 (Pt 11):2661–72.

85 Feng N, Burns JW, Bracy L, Greenberg HB. Comparison of mucosal and systemic humoral immune responses and subsequent protection in mice orally inoculated with a homologous or a heterologous rotavirus. J Virol. 1994 Dec;68(12):7766–73.

86 Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006 Jan;354(1):11–22.

87 Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006 Jan;354(1):23–33.

88 Vesikari T. Rotavirus vaccination: a concise review. Clin Microbiol Infect. 2012 Oct;18 Suppl 5:57–63.

89 Patel M, Glass RI, Jiang B, Santosham M, Lopman B, Parashar U. A systematic review of anti-rotavirus serum IgA antibody titer as a potential correlate of rotavirus vaccine efficacy. J Infect Dis. 2013 Jul;208(2):284–94.

90 Ogra PL, Karzon DT, Righthand F, MacGillivray M. Immunoglobulin response in serum and secretions after immunization with live and inactivated poliovaccine and natural infection. N Engl J Med. 1968 Oct;279(17):893–900.

91 Onorato IM, Modlin JF, McBean AM, Thoms ML, Losonsky GA, Bernier RH. Mucosal immunity induced by enhance-potency inactivated and oral polio vaccines. J Infect Dis. 1991 Jan;163(1):1–6.

92 Resik S, Tejeda A, Sutter RW, Diaz M, Sarmiento L, Alemañi N, et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med. 2013 Jan;368(5):416–24.

93 Hird TR, Grassly NC. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. PLoS Pathog. 2012;8(4):e1002599.

94 Boyaka PN. Inducing Mucosal IgA: A Challenge for Vaccine Adjuvants and Delivery Systems. J Immunol. 2017 01;199(1):9–16.

95 Fukuiwa T, Sekine S, Kobayashi R, Suzuki H, Kataoka K, Gilbert RS, et al. A combination of Flt3 ligand cDNA and CpG ODN as nasal adjuvant elicits NALT dendritic cells for prolonged mucosal immunity. Vaccine. 2008 Sep;26(37):4849–59.

96 Kim E-D, Han SJ, Byun Y-H, Yoon SC, Choi KS, Seong BL, et al. Inactivated Eyedrop Influenza Vaccine Adjuvanted with Poly(I:C) Is Safe and Effective for Inducing Protective Systemic and Mucosal Immunity. PLoS ONE. 2015;10(9):e0137608.

97 Ebensen T, Libanova R, Schulze K, Yevsa T, Morr M, Guzmán CA. Bis-(3',5')-cyclic dimeric adenosine monophosphate: strong Th1/Th2/Th17 promoting mucosal adjuvant. Vaccine. 2011 Jul;29(32):5210–20.

98 Sanchez MV, Ebensen T, Schulze K, Cargnelutti D, Blazejewska P, Scodeller EA, et al. Intranasal delivery of influenza rNP adjuvanted with c-di-AMP induces strong humoral and cellular immune responses and provides protection against virus challenge. PLoS ONE. 2014;9(8):e104824.

99 Eriksson AM, Schön KM, Lycke NY. The cholera toxin-derived CTA1-DD vaccine adjuvant administered intranasally does not cause inflammation or accumulate in the nervous tissues. J Immunol. 2004 Sep;173(5):3310–9.

100 Hagiwara Y, Kawamura YI, Kataoka K, Rahima B, Jackson RJ, Komase K, et al. A second generation of double mutant cholera toxin adjuvants: enhanced immunity without intracellular trafficking. J Immunol. 2006 Sep;177(5):3045–54.

101 Rochereau N, Pavot V, Verrier B, Jospin F, Ensinas A, Genin C, et al. Delivery of antigen to nasal-associated lymphoid tissue microfold cells through secretory IgA targeting local dendritic cells confers protective immunity. J Allergy Clin Immunol. 2016 Jan;137(1):214-222.e2.

102 Nichol KL, Mendelman PM, Mallon KP, Jackson LA, Gorse GJ, Belshe RB, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working

adults: a randomized controlled trial. JAMA. 1999 Jul;282(2):137–44.

103 Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007 Feb;356(7):685–96.

104 Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012 Jan;12(1):36–44.

105 Asahi-Ozaki Y, Yoshikawa T, Iwakura Y, Suzuki Y, Tamura S-I, Kurata T, et al. Secretory IgA antibodies provide cross-protection against infection with different strains of influenza B virus. J Med Virol. 2004 Oct;74(2):328–35.

106 Ainai A, Tamura S-I, Suzuki T, van Riet E, Ito R, Odagiri T, et al. Intranasal vaccination with an inactivated whole influenza virus vaccine induces strong antibody responses in serum and nasal mucus of healthy adults. Hum Vaccin Immunother. 2013 Sep;9(9):1962–70.

107 Sano K, Ainai A, Suzuki T, Hasegawa H. The road to a more effective influenza vaccine: Up to date studies and future prospects. Vaccine. 2017 25;35(40):5388–95.

108 Suzuki T, Kawaguchi A, Ainai A, Tamura S, Ito R, Multihartina P, et al. Relationship of the quaternary structure of human secretory IgA to neutralization of influenza virus. Proc Natl Acad Sci USA. 2015 Jun;112(25):7809–14.

109 Jhaveri R, Allyne K. A Feasibility Trial of Home Administration of Intranasal Vaccine by Parents to Eligible Children. Clin Ther. 2017 Jan;39(1):204-211.e4.

110 Blutt SE, Conner ME. The gastrointestinal frontier: IgA and viruses. Front Immunol. 2013 Nov;4:402.

111 Breedveld A, van Egmond M. IgA and FcαRI: Pathological Roles and Therapeutic Opportunities. Front Immunol. 2019;10:553.

112 Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med. 2012 Apr;366(14):1275–86.

113 Tomaras GD, Ferrari G, Shen X, Alam SM, Liao H-X, Pollara J, et al. Vaccine-induced plasma IgA specific for the C1 region of the HIV-1 envelope blocks binding and effector function of IgG. Proc Natl Acad Sci USA. 2013 May;110(22):9019–24.

114 Ruiz MJ, Ghiglione Y, Falivene J, Laufer N, Holgado MP, Socías ME, et al. Env-Specific IgA from Viremic HIV-Infected Subjects Compromises Antibody-Dependent Cellular Cytotoxicity. J Virol. 2016 15;90(2):670–81.

115 Neidich SD, Fong Y, Li SS, Geraghty DE, Williamson BD, Young WC, et al. Antibody Fc effector functions and IgG3 associate with decreased HIV-1 risk. J Clin Invest. 2019 Nov;129(11):4838–49.

116 Liadaki K, Sun J, Hammarström L, Pan-Hammarström Q. New facets of antibody deficiencies. Curr Opin Immunol. 2013 Oct;25(5):629–38.

117 Favre O, Leimgruber A, Nicole A, Spertini F. Intravenous immunoglobulin replacement prevents severe and lower respiratory tract infections, but not upper respiratory tract and non-respiratory infections in common variable immune deficiency. Allergy. 2005 Mar;60(3):385–90.

118 Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol. 2011 Jun;31(3):315–22.

119 Hodkinson JP, Bangs C, Wartenberg-Demand A, Bauhofer A, Langohr P, Buckland MS, et al. Low IgA and IgM Is Associated with a Higher Prevalence of Bronchiectasis in Primary Antibody Deficiency. J Clin Immunol. 2017;37(4):329–31.

120 Langereis JD, van der Flier M, de Jonge MI. Limited Innovations After More Than 65 Years of Immunoglobulin Replacement Therapy: Potential of IgA- and IgM-Enriched Formulations to Prevent Bacterial Respiratory Tract Infections. Front Immunol. 2018;9:1925.

121 Rachid R, Bonilla FA. The role of anti-IgA antibodies in causing adverse reactions to gamma globulin infusion in immunodeficient patients: a comprehensive review of the literature. J Allergy Clin Immunol. 2012 Mar;129(3):628–34.

122 Kerstens PJ, Endtz HP, Meis JF, Oyen WJ, Koopman RJ, van den Broek PJ, et al. Erysipelas-like skin lesions associated with Campylobacter jejuni septicemia in patients with hypogammaglobulinemia. Eur J Clin Microbiol Infect Dis. 1992 Sep;11(9):842–7.

123 Borleffs JC, Schellekens JF, Brouwer E, Rozenberg-Arska M. Use of an immunoglobulin M containing preparation for treatment of two hypogammaglobulinemic patients with persistent Campylobacter jejuni infection. Eur J Clin Microbiol Infect Dis. 1993 Oct;12(10):772–5.

124 Welte T, Dellinger RP, Ebelt H, Ferrer M, Opal SM, Singer M, et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). Intensive Care Med. 2018;44(4):438–48.

125 Pan-Hammarström Q, Hammarström L. Antibody deficiency diseases. Eur J Immunol. 2008 Feb;38(2):327–33.

126 Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer. Nat Rev Cancer. 2012 Mar;12(4):278–87.

127 Boross P, Lohse S, Nederend M, Jansen JHM, van Tetering G, Dechant M, et al. IgA EGFR antibodies mediate tumour killing in vivo. EMBO Mol Med. 2013 Aug;5(8):1213–26.

128 Borrok MJ, Luheshi NM, Beyaz N, Davies GC, Legg JW, Wu H, et al. Enhancement of antibody-dependent cell-mediated cytotoxicity by endowing IgG with FcαRI (CD89) binding. MAbs. 2015;7(4):743–51.

129 Lohse S, Loew S, Kretschmer A, Jansen JHM, Meyer S, Ten Broeke T, et al. Effector mechanisms of IgA antibodies against CD20 include recruitment of myeloid cells for antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. Br J Haematol. 2018;181(3):413–7.

130 Brandsma AM, Bondza S, Evers M, Koutstaal R, Nederend M, Jansen JHM, et al. Potent Fc Receptor Signaling by IgA Leads to Superior Killing of Cancer Cells by Neutrophils Compared to IgG. Front Immunol. 2019;10:704.

131 van Egmond M, van Vuuren AJ, Morton HC, van Spriel AB, Shen L, Hofhuis FM, et al. Human immunoglobulin A receptor (FcalphaRI, CD89) function in transgenic mice requires both FcR gamma chain and CR3 (CD11b/CD18). Blood. 1999 Jun;93(12):4387–94.

132 Launay P, Grossetête B, Arcos-Fajardo M, Gaudin E, Torres SP, Beaudoin L, et al. Fcalpha receptor (CD89) mediates the development of immunoglobulin A (IgA) nephropathy (Berger's disease). Evidence for pathogenic soluble receptor-Iga complexes in patients and CD89 transgenic mice. J Exp Med. 2000 Jun;191(11):1999–2009.

133 Pascal V, Laffleur B, Debin A, Cuvillier A, van Egmond M, Drocourt D, et al. Anti-CD20 IgA can protect mice against lymphoma development: evaluation of the direct impact of IgA and cytotoxic effector recruitment on CD20 target cells. Haematologica. 2012 Nov;97(11):1686–94.

134 Roopenian DC, Christianson GJ, Sproule TJ, Brown AC, Akilesh S, Jung N, et al. The MHC Class I-Like IgG Receptor Controls Perinatal IgG Transport, IgG Homeostasis, and Fate of IgG-Fc-Coupled Drugs. The Journal of Immunology. 2003 Apr;170(7):3528–33.

135 Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007 Sep;7(9):715–25.

136 Rouwendal GJ, van der Lee MM, Meyer S, Reiding KR, Schouten J, de Roo G, et al. A comparison of anti-HER2 IgA and IgG1 in vivo efficacy is facilitated by high N-glycan sialylation of the IgA. MAbs. 2016;8(1):74–86.

137 Lohse S, Meyer S, Meulenbroek LAPM, Jansen JHM, Nederend M, Kretschmer A, et al. An Anti-EGFR IgA That Displays Improved Pharmacokinetics and Myeloid Effector Cell Engagement In Vivo. Cancer Res. 2016 Jan;76(2):403–17.

138 Meyer S, Nederend M, Jansen JHM, Reiding KR, Jacobino SR, Meeldijk J, et al. Improved in vivo anti-tumor effects of IgA-Her2 antibodies through half-life extension and serum exposure enhancement by FcRn targeting. MAbs. 2016;8(1):87–98.

139 Peters T. Serum albumin. Adv Protein Chem. 1985;37:161–245.

140 Treffers LW, Ten Broeke T, Rösner T, Jansen JHM, van Houdt M, Kahle S, et al. IgA-Mediated Killing of Tumor Cells by Neutrophils Is Enhanced by CD47-SIRPα Checkpoint Inhibition. Cancer Immunol Res. 2020 Jan;8(1):120–30.

141 Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. N Engl J Med. 2018 Nov;379(18):1711–21.

142 Mkaddem SB, Christou I, Rossato E, Berthelot L, Lehuen A, Monteiro RC. IgA, IgA receptors, and their anti-inflammatory properties. Curr Top Microbiol Immunol. 2014;382:221–35.

143 Kanamaru Y, Pfirsch S, Aloulou M, Vrtovsnik F, Essig M, Loirat C, et al. Inhibitory ITAM signaling by Fc alpha RI-FcR gamma chain controls multiple activating responses and prevents renal inflammation. J Immunol. 2008 Feb;180(4):2669–78.

144 Watanabe T, Kanamaru Y, Liu C, Suzuki Y, Tada N, Okumura K, et al. Negative

regulation of inflammatory responses by immunoglobulin A receptor (FcαRI) inhibits the development of Toll-like receptor-9 signalling-accelerated glomerulonephritis. Clin Exp Immunol. 2011 Nov;166(2):235–50.

145 Lombana TN, Rajan S, Zorn JA, Mandikian D, Chen EC, Estevez A, et al. Production, characterization, and in vivo half-life extension of polymeric IgA molecules in mice. MAbs. 2019 Sep;11(6):1122–38.

146 Virdi V, Juarez P, Boudolf V, Depicker A. Recombinant IgA production for mucosal passive immunization, advancing beyond the hurdles. Cell Mol Life Sci. 2016 Feb;73(3):535–45.

147 Nakanishi K, Matsuda M, Ida R, Hosokawa N, Kurohane K, Niwa Y, et al. Lettuce-derived secretory IgA specifically neutralizes the Shiga toxin 1 activity. Planta. 2019 Oct;250(4):1255–64.

148 Hu Y, Kumru OS, Xiong J, Antunez LR, Hickey J, Wang Y, et al. Preformulation Characterization and Stability Assessments of Secretory IgA Monoclonal Antibodies as Potential Candidates for Passive Immunization by Oral Administration. J Pharm Sci. 2020;109(1):407–21.

149 Kelton W, Mehta N, Charab W, Lee J, Lee C, Kojima T, et al. IgGA: a “cross-isotype” engineered human Fc antibody domain that displays both IgG-like and IgA-like effector functions. Chem Biol. 2014 Dec;21(12):1603–9.

150 Bakema JE, Ganzevles SH, Fluitsma DM, Schilham MW, Beelen RHJ, Valerius T, et al. Targeting FcαRI on polymorphonuclear cells induces tumor cell killing through autophagy. J Immunol. 2011 Jul;187(2):726–32.

151 Guettinger Y, Barbin K, Peipp M, Bruenke J, Dechant M, Horner H, et al. A recombinant bispecific single-chain fragment variable specific for HLA class II and Fc alpha RI (CD89) recruits polymorphonuclear neutrophils for efficient lysis of malignant

B lymphoid cells. J Immunol. 2010 Feb;184(3):1210–7.

152 Saito S, Sano K, Suzuki T, Ainai A, Taga Y, Ueno T, et al. IgA tetramerization improves target breadth but not peak potency of functionality of anti-influenza virus broadly neutralizing antibody. PLoS Pathog. 2019;15(1):e1007427.

Figures

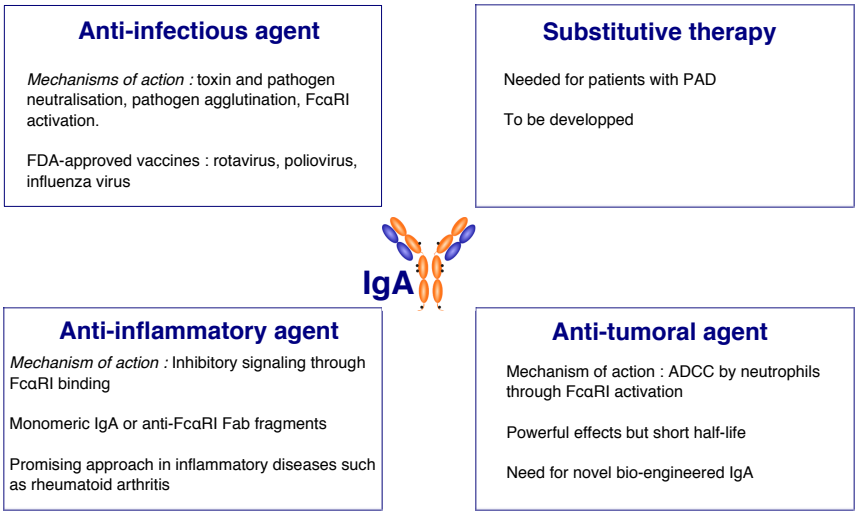

Figure 1 : Therapeutic potential of IgA.

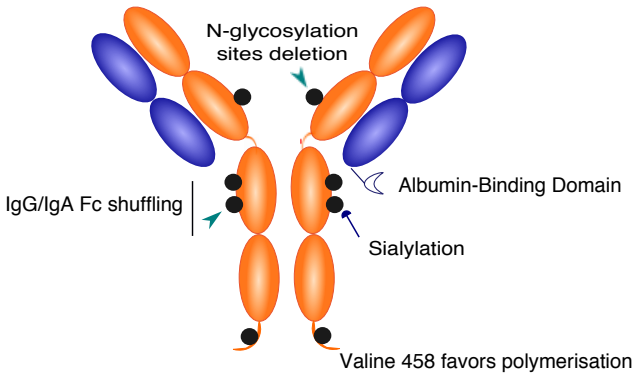

Figure 2 : Improving IgA therapeutic potential through engineering

IgA has a shorter half-life than IgG since it cannot bind to the FcRn. To facilitate binding to the latter, modified IgA with higher terminal sialylation of N-glycans [136] (blue round arrow), albumin-binding domain [138] or IgG Fc domains [145,149] have been generated. Removing of N-linked glycosylation sites (N166G and N337T) decrease IgA clearance by the asialoglycoprotein receptor and thereby increase serum half-life [137]. Valine introduction at position 458 improve IgA polymerisation [145], and as a result extends half-life and improves neutralizing capacities [145,152]. Heavy chain domains are depicted in orange while light chains are shown in dark blue. Black circles represent N-glycosylation sites. Orange lines indicate hinge regions and tailpieces. For clarity, IgA1 is omitted, only IgA2 is drawn.