



# IgA and Fc $\alpha$ RI: Pathological Roles and Therapeutic Opportunities

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Immunoglobulin A (IgA) is the most abundant antibody class present at mucosal surfaces. The production of IgA exceeds the production of all other antibodies combined, supporting its prominent role in host-pathogen defense. IgA closely interacts with the intestinal microbiota to enhance its diversity, and IgA has a passive protective role via immune exclusion. Additionally, inhibitory ITAMi signaling via the IgA Fc receptor (Fc $\alpha$ RI; CD89) by monomeric IgA may play a role in maintaining homeostatic conditions. By contrast, IgA immune complexes (e.g., opsonized pathogens) potently activate immune cells via cross-linking Fc $\alpha$ RI, thereby inducing pro-inflammatory responses resulting in elimination of pathogens. The importance of IgA in removal of pathogens is emphasized by the fact that several pathogens developed mechanisms to break down IgA or evade Fc $\alpha$ RI-mediated activation of immune cells. Augmented or aberrant presence of IgA immune complexes can result in excessive neutrophil activation, potentially leading to severe tissue damage in multiple inflammatory, or autoimmune diseases. Influencing IgA or Fc $\alpha$ RI-mediated functions therefore provides several therapeutic possibilities. On the one hand (passive) IgA vaccination strategies can be developed for protection against infections. Furthermore, IgA monoclonal antibodies that are directed against tumor antigens may be effective as cancer treatment. On the other hand, induction of ITAMi signaling via Fc $\alpha$ RI may reduce allergy or inflammation, whereas blocking Fc $\alpha$ RI with monoclonal antibodies, or peptides may resolve IgA-induced tissue damage. In this review both (patho)physiological roles as well as therapeutic possibilities of the IgA-Fc $\alpha$ RI axis are addressed.

**Keywords:** IgA, CD89, mucosa, autoimmunity, IgA deficiency, microbiome, vaccination, therapy

## INTRODUCTION

Immunoglobulins have important functions in immunity (1, 2). In mucosal areas like the gastrointestinal, genitourinary, and respiratory tracts, IgA is the predominant antibody present (3). It plays a key role at these surfaces, which are continuously exposed to antigens, food, and (commensal) microorganisms. Keeping a tight balance by tolerating commensals and harmless (food) antigens on the one hand and providing protection against harmful pathogens on the other hand is a challenging role of mucosal immunity. Mucosal IgA protects the host by diversifying the microbiota, neutralizing toxins and viruses, blocking colonization and penetration of pathogenic bacteria, clearing unwanted particles, and promoting sampling of antigens (4). Mucosal IgA is generally considered as a neutralizing, non-activating antibody. In serum, IgA is the second most

abundant antibody after IgG. In contrast to mucosal IgA, the roles of serum IgA are relatively unexplored (5).

IgA deficiency is a relatively common disease with limited effects on human health (6), which supported the notion of IgA as a non-inflammatory antibody. By contrast, increased serum IgA levels or IgA autoantibodies have been reported in multiple (inflammatory) diseases including IgA nephropathy (IgAN), IgA vasculitis, dermatitis herpetiformis, celiac disease, inflammatory bowel disease (IBD), Sjögren's syndrome, ankylosing spondylitis, alcoholic liver cirrhosis, and Acquired immunodeficiency syndrome (7–9), although the role of IgA in pathology is still ill-understood.

IgA can interact with several receptors that are present on a variety of (immune) cells. The polymeric immunoglobulin receptor (pIgR) is present on the basolateral side of epithelial cells and mediates transport of dimeric IgA (dIgA) to the mucosal lumen, where it is released as secretory IgA (SIgA) (10). Retrograde transport of SIgA immune complexes back into the lamina propria can occur via the transferrin receptor (Tfr or CD71) on epithelial cells or through microfold cells (M cells), possible via interaction with Dectin-1 (11, 12). It has been reported that SIgA immune complexes in the lamina propria can be taken up by sub-epithelial dendritic cells (DCs) through interaction with Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) (13). B cells were shown to express the inhibitory IgA receptor Fc receptor-like 4 (FcRL4), which was suggested to contribute to the regulation of mucosal IgA responses (14). In the liver, hepatocytes express the asialoglycoprotein receptor (ASGPR) that is involved in clearance of IgA from the circulation (15). Mesangial cells in the glomeruli of the kidneys express CD71 and the recently identified  $\beta$ -1,4-galactosyltransferase as potential receptors to clear IgA (16). Furthermore, an Fc alpha/mu receptor is expressed in gut, spleen and lymph nodes, although its functions remain to be elucidated (17). Finally, the IgA Fc receptor Fc $\alpha$ RI (CD89) is expressed by myeloid cells (18). It was demonstrated that interaction of monomeric serum IgA with Fc $\alpha$ RI induces inhibitory signals (19, 20). As such, it is thought that IgA has an anti-inflammatory role during homeostatic conditions. By contrast, IgA immune complexes bind avidly to Fc $\alpha$ RI, resulting in cross-linking and induction of pro-inflammatory responses, which may play an important role in resolving (mucosal) infections. Additionally, it was suggested that the presence of excessive IgA immune complexes can lead to uncontrolled and

disproportionate immune cell activation, which leads to severe tissue damage in autoimmune diseases, such as IgA blistering diseases and rheumatoid arthritis (RA) (18). The number of diverse IgA receptors, their differential expression on cells and the distinct IgA-induced effector functions support the complex roles of this antibody in maintaining homeostatic conditions, which go beyond the dogma of IgA as a non-inflammatory regulator of mucosal immunity. This is further supported by the fact that several bacteria have evolved to escape IgA-mediated functions by for instance producing IgA1 proteases or expressing molecules that hamper interaction with IgA receptors (21–23).

This review addresses the different functions of IgA, its interaction with Fc $\alpha$ RI,—as the best characterized IgA receptor—, in health and disease and the possibilities to target either molecule for therapeutic strategies.

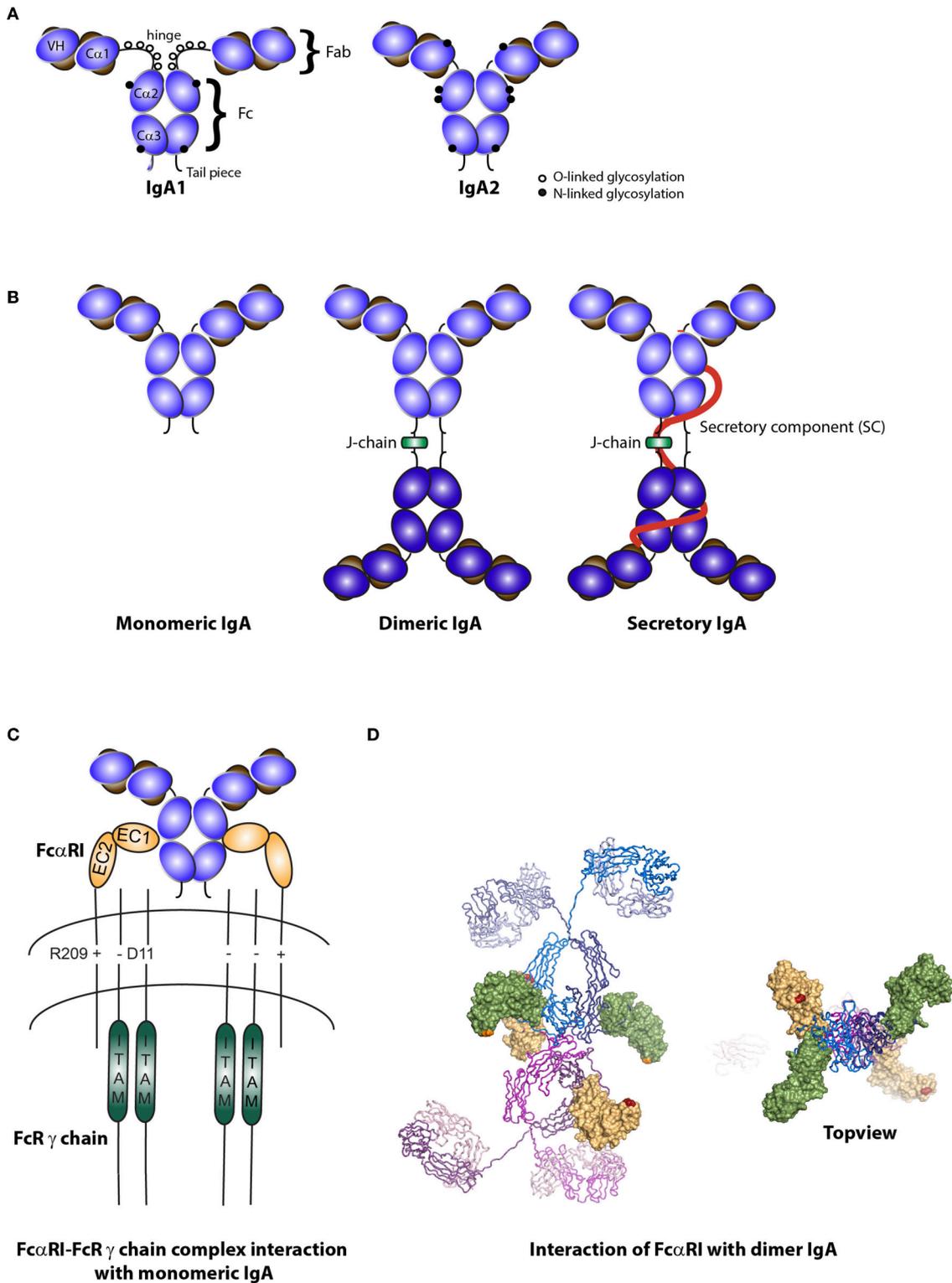
## STRUCTURE OF IgA

IgA is the most predominant antibody produced by humans with a synthesis rate of 66 mg/kg each day. IgA can be subdivided into IgA1 and IgA2 (**Figure 1A**). The IgA1 hinge region contains multiple O-linked glycans and two N-linked glycosylation sites per heavy chain. The truncated hinge of IgA2 lacks O-glycans and each heavy chain contains two additional N-glycans (25).

IgA1 comprises 80–85% of total human serum IgA (1–3 mg/ml) and is prevalent on many mucosal surfaces including the nasal, bronchial, gastric, and small intestinal mucosa. IgA2 is predominantly present in the colon (26). This division of IgA1 and IgA2 between the small and large intestine may reflect the luminal distribution of food proteins and gram-negative bacteria, which is supported by findings that bacterial overgrowth in the small intestine shifts production toward IgA2 (27). Whereas, IgA1 is susceptible to proteolytic cleavage due to a longer hinge region, IgA2 is resistant to bacterial proteases that are present in the lumen of mucosal areas (6, 21).

Serum IgA is predominantly monomeric in humans and primates (while dimeric in other animals) and is produced by local plasma cells in the bone marrow, spleen, and lymph nodes. IgA at mucosal surfaces is produced by local plasma cells as dimeric molecules, although small amounts of monomers, trimers and tetramers or polymers can also be present (1, 3). Dimeric IgA is composed of two monomers, which are linked with a J-chain (**Figure 1B**). It associates with the pIgR present at the basolateral side of epithelial cells in mucosal surfaces, after which dIgA is transported across the epithelium and released into the lumen. For every molecule of dIgA that is transported across the epithelium, one pIgR is needed (10, 28, 29). At the luminal side, pIgR is cleaved and a part, referred to as secretory component (SC), remains attached thereby forming SIgA (**Figure 1B**). Secretory component is a hydrophilic and highly (N- and O-linked) glycosylated negatively charged molecule, which protects SIgA from degradation when present in luminal secretions (30). Glycan removal led to reduced binding capacity of SIgA to gram-positive bacteria, indicating the essential role of carbohydrate structures in efficient IgA coating of (mainly commensal) bacteria (31).

**Abbreviations:** ASGPR, Asialoglycoprotein receptor; BsAb, Bispecific antibodies; DC-SIGN, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; DCs, Dendritic cells; dIgA, Dimeric IgA; Fc $\alpha$ RI, Fc alpha receptor; FcRL4, Fc receptor-like 4; fMLP, N-formylmethionyl-leucyl-phenylalanine; GF, Germ free; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IBD, Inflammatory bowel disease; IFN- $\gamma$ , Interferon-gamma; IgA, Immunoglobulin A; IgAN, IgA nephropathy; IL, Interleukin; ITAM, Immunoreceptor tyrosine-based activation motif; ITAMi, Inhibitory immunoreceptor tyrosine-based activation motif; kDa, Kilodalton; LABD, Linear IgA Bullous disease; LPS, Lipopolysaccharide; LTB4, Leukotriene B4; M cells, Microfold cells; pIgR, Polymeric immunoglobulin receptor; RF, Rheumatoid factor; SC, Secretory component; SIgA, Secretory IgA; SIgM, Secretory IgM; Tfr, Transferrin receptor; TGF- $\beta$ , Transforming growth factor-beta; TLR, Toll like receptor; TNF- $\alpha$ , Tumor necrosis factor-alpha.



**FIGURE 1 |** Structure of IgA isotypes and the IgA Fc receptor (FcαRI). **(A)** IgA1 vs. IgA2. IgA consists of two heavy chains (blue), each composed of three constant regions and one variable region, and two light chains (brown) that consist of one constant and one variable region. IgA1 contains a hinge region with O-linked glycosylation. **(B)** Monomeric, dimeric IgA, and secretory IgA. Dimeric IgA consist of two IgA molecules that are linked with a J-chain (green). Secretory IgA contains an additional molecule, the secretory component (SC; red). **(C)** Structure of FcαRI. FcαRI consist of a transmembrane domain, a short cytoplasmic tail and two

*(Continued)*

**FIGURE 1** | extracellular domains (EC1 & EC2). It is associated with the signaling FcR  $\gamma$  chain via an electrostatic interaction. The IgA heavy chain junction of C $\alpha$ 2 and C $\alpha$ 3 binds to the EC1 domain of Fc $\alpha$ RI in a 2:1 stoichiometry. **(D)** A model of dIgA1 bound to four Fc $\alpha$ RI molecules. The Fc $\alpha$ RI:IgA1-Fc complex (PDB 1OW0) was superimposed onto the solution structure of dIgA1 published by Bonner et al. (24) (PDB 2QTJ). Fc $\alpha$ RI molecules bound to the top or bottom IgA1 antibodies are colored green or yellow, respectively. The C-terminal residue of each receptor is shown in orange or red to illustrate the membrane-proximal region. Kindly provided by Andrew B. Herr, PhD (Cincinnati Children's Hospital).

## STRUCTURE AND EXPRESSION OF FC $\alpha$ RI

Fc $\alpha$ RI is a member of the Fc receptor immunoglobulin superfamily (32). It is expressed on cells of the myeloid lineage, including neutrophils, eosinophils, monocytes, macrophages, Kupffer cells, and certain DC subsets (18, 33, 34). Additionally, Fc $\alpha$ RI expression on human platelets was described (35). Unlike for other Fc receptors, the Fc $\alpha$ RI gene is located on chromosome 19 (19q13.4) within the leukocyte receptor cluster (LRC). This region also encodes natural killer cell inhibitory/activatory receptors and leukocyte Ig-like receptors. The Fc $\alpha$ RI amino acid sequence has therefore more similarity with these receptors than with other Fc receptors (19, 36). The EC1 and EC2 exons each encode an extracellular Ig-like domain. These domains are folded in an angle of  $\sim 90^\circ$ . The TM/C exon encodes both the transmembrane domain and a short cytoplasmic tail (**Figure 1C**) (36).

Surface expression of two isoforms of Fc $\alpha$ RI has been described on human phagocytes. The a.1 isoform is a 32 kDa single pass transmembrane receptor, which can be extensively glycosylated (six N-linked sites and seven O-linked sites) (37). The molecular weight of the a.1 isoform varies between 55 and 75 kDa on neutrophils and monocytes, while the molecule is heavier (70–100 kDa) on eosinophils due to more extensive glycosylation (21, 37). The a.2 isoform misses 66 nucleotides in the EC2 exon resulting in loss of one O-linked glycosylation site and has a weight of 28 kDa (without glycosylation) (38). The a.2 isoform is solely expressed on alveolar macrophages (38).

The expression of Fc $\alpha$ RI was estimated to represent 66,000 and 57,000 molecules on neutrophils and monocytes, respectively (33). Expression level can be modulated by several mediators. On neutrophils, N-formylmethionyl-leucyl-phenylalanine (fMLP), interleukin (IL)-8, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), lipopolysaccharide (LPS), and granulocyte-macrophage colony-stimulating factor (GM-CSF) enhanced the expression of Fc $\alpha$ RI (39–41). GM-CSF has also an important role in mobilizing neutrophils from the bone marrow (42) and was shown to induce high affinity binding of IgA by human neutrophils (43). Neutrophil Fc $\alpha$ RI upregulation was rapid and either induced by *de novo* synthesis or via transport from an intracellular pool to the cell surface (44). On monocytes and monocyte-like cell lines Fc $\alpha$ RI expression was enhanced by calcitriol, LPS, TNF- $\alpha$ , GM-CSF, and IL-1 $\beta$ , while downregulation was observed in response to transforming growth factor-beta (TGF- $\beta$ ) or interferon-gamma (IFN- $\gamma$ ) (45, 46). Both monomeric and, to a greater extent, polymeric IgA were able to downregulate Fc $\alpha$ RI, possibly due to receptor aggregation, resulting in internalization (47–49).

## IgA AND FC $\alpha$ RI

### Binding of IgA to Fc $\alpha$ RI

Fc $\alpha$ RI is a low affinity Fc receptor for monomeric IgA and dIgA ( $K_a = 10^6 \text{ M}^{-1}$ ), while IgA immune complexes bind with high avidity and cross-link Fc $\alpha$ RI (50). Monomeric IgA binds to the EC1 domain of Fc $\alpha$ RI via its C $\alpha$ 2 and C $\alpha$ 3 domains in a 2:1 stoichiometry (i.e., one IgA molecule binds two Fc $\alpha$ RI molecules) (**Figure 1C**) (51, 52). Presence of residues Pro440-Phe443 and Leu257-Leu258 in these domains is essential for IgA binding to Fc $\alpha$ RI (53).

Dimeric IgA contains four Fc $\alpha$ RI binding sites and can therefore theoretically bind four Fc $\alpha$ RI, although this is presumably not possible due to steric hindrance (**Figure 1D**) (24). It remains to be elucidated how dIgA exactly interacts with the Fc $\alpha$ RI. Binding of SIgA to Fc $\alpha$ RI is hampered because of steric hindrance by SC. In order for SIgA to activate cells, co-stimulation of Fc $\alpha$ RI, and the lectin Mac-1 (CD11b/CD18) was necessary (54).

Little is known about the difference between IgA1 and IgA2 binding to Fc $\alpha$ RI (if any) or the influence of glycosylation on binding capacity. It was however shown that a specific mutation (Asn58 to Glu58) resulted in an altered glycosylation pattern of Fc $\alpha$ RI, which increased the binding capacity of IgA nearly 2-fold (55). Removal of sialic acids led to a nearly 4-fold increase of IgA binding. This demonstrates the importance of glycosylation at position 58 of Fc $\alpha$ RI in binding affinity for IgA (55). N-glycans located at the external surface of the IgA heavy chain were important for interaction with Fc $\alpha$ RI as well (56). Furthermore, it was demonstrated that alterations in IgA1 glycosylation and impaired sialylation of Fc $\alpha$ RI were linked to increased binding of IgA1 to Fc $\alpha$ RI on neutrophils of patients with IgA nephropathy, which may influence pro-inflammatory functions (47). In transfectants, eosinophils, and monocytes Fc $\alpha$ RI binding capacity for IgA immune complexes was enhanced by incubation with several cytokines like GM-CSF, IL-4, and IL-5, without affecting the expression level of the Fc $\alpha$ RI on the cell surface (43, 57).

Competitive binding for Fc $\alpha$ RI has been described for pentraxins, including the acute phase C reactive protein and serum amyloid P component, resulting in cell activation (58). These proteins are characterized by a pentameric ring-like structure containing five subunits, which recognize a similar site on Fc $\alpha$ RI as IgA. However, mutations in Fc $\alpha$ RI outside the IgA binding site did not affect IgA binding, but enhanced pentraxin binding 2-fold, suggesting that pentraxins bind to a broader region on Fc $\alpha$ RI than IgA (58).

Importantly, *Staphylococcus aureus* and group A and B streptococci developed evasion strategies for IgA-mediated elimination by Fc $\alpha$ RI-expressing immune cells by producing

several decoy proteins that obstruct binding of IgA to Fc $\alpha$ RI (22, 23). Anti-IgA proteins from group B streptococci include Sir22, Arp4 and an unrelated  $\beta$  protein, whereas *Staphylococcus aureus* produces staphylococcal superantigen-like protein seven. These proteins bind to specific Fc residues (amino acids Pro440-Phe443; i.e. PLAF) in the C $\alpha$ 2 and C $\alpha$ 3 domains of IgA (22, 23, 59). The fact that pathogens evolved and developed mechanisms to evade IgA-mediated elimination by Fc $\alpha$ RI-expressing immune cells (60), challenges the dogma of IgA as a non-inflammatory and possibly redundant antibody.

### Cell Activation After Fc $\alpha$ RI Cross-Linking

Cross-linking of Fc $\alpha$ RI by IgA immune complexes (or IgA-opsonized pathogens) induces a variety of processes, including phagocytosis, antibody-dependent cellular cytotoxicity, superoxide generation, release of inflammatory mediators, and cytokines as well as antigen presentation (61–65). Due to hampered binding of SIgA to Fc $\alpha$ RI, SIgA does not induce efficient uptake of pathogens by neutrophils or Kupffer cells. However, respiratory burst in neutrophils can be triggered by SIgA, although less efficiently compared to serum IgA (54). Phagocytosis of IgA-coated bacteria or yeast particles by neutrophils was enhanced after priming with GM-CSF or IL-8 (43, 66). Uptake of IgA-coated particles induces increased reactive oxygen species production, subsequently resulting in the release of neutrophil extracellular traps (NETs), which are web-like structures consisting of DNA and proteins (e.g., elastase and myeloperoxidase) able to catch pathogens (61). Fc $\alpha$ RI cross-linking furthermore induces release of the neutrophil chemoattractant leukotriene B4 (LTB4) by neutrophils, thereby generating a positive migration feedback loop (64). LTB4 was also shown to mediate migration of monocyte derived DCs (67). As such, in case of mucosal infection neutrophils can function as potent phagocytes, which eliminate invading IgA-coated pathogens, and attract DCs that present antigens to T cells. It was recently shown that *in vitro* generated human mucosal CD103<sup>+</sup> DCs (cultured with retinoic acid) express Fc $\alpha$ RI. After stimulation with IgA-coated *Staphylococcus aureus* in the presence of Pam3CSK4 CD103<sup>+</sup> DCs produced pro-inflammatory cytokines including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-23, which was dependent on Fc $\alpha$ RI (68). Furthermore, IgA-stimulated CD103<sup>+</sup> DCs enhanced IL-17 production by allogeneic T cells and IL-22 production by intestinal type three innate lymphoid cells, respectively. This suggests that Fc $\alpha$ RI crosslinking by IgA induces a pro-inflammatory T helper 17 response accompanied with IL-22 induced activation of epithelial cells, which might contribute to tissue repair (68).

### Signaling via Fc $\alpha$ RI

In order to initiate optimal effector functions after Fc $\alpha$ RI cross-linking, Fc $\alpha$ RI needs association with the FcR  $\gamma$ -chain, which contains an immunoreceptor tyrosine-based activation motif (ITAM) in its intracellular domain (69–72). After cross-linking of Fc $\alpha$ RI, the src family kinase Fyn aggregates with the receptor complex and phosphorylates the tyrosines in the ITAM in order to act as docking sites for signaling molecules (69, 73, 74). Recruited Syk associates with the phosphorylated

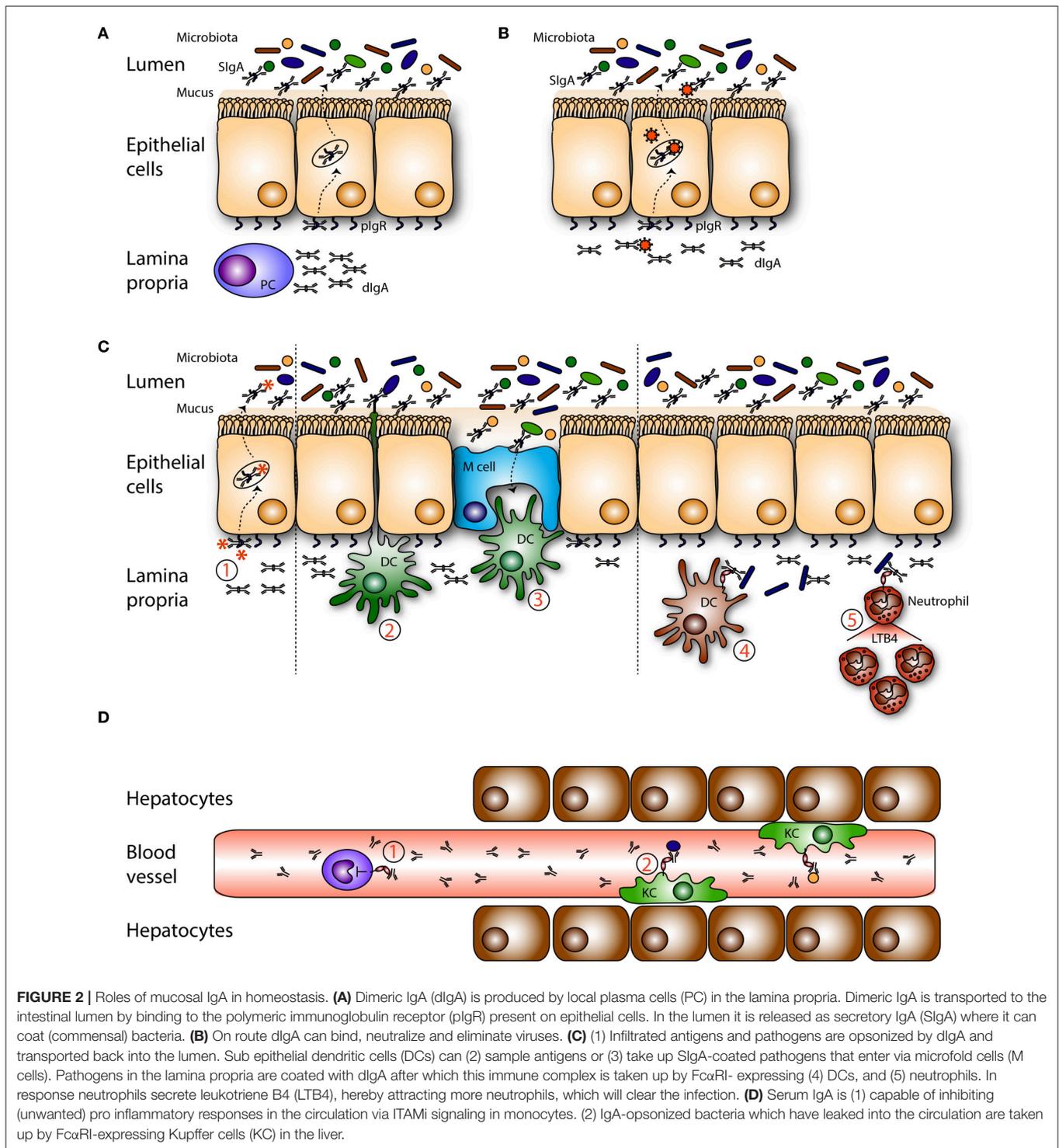
ITAM and plays an essential role in the signaling cascade. It directly activates phosphoinositide 3-kinase and phospholipase C $\gamma$ , which are involved in two separate signaling routes. These pathways are interconnected and can therefore modulate each other (69, 72, 75). Eventually the signaling pathways will activate the cell, resulting in pro-inflammatory functions (18, 66). Alternatively, it was demonstrated that inhibitory signals can also be transduced via the Fc $\alpha$ RI-FcR  $\gamma$ -chain complex. Monomeric targeting of Fc $\alpha$ RI (not leading to cross-linking) results in an inhibitory signal and is dependent on Lyn instead of Fyn kinase (74). Phosphorylation of Syk, LAT, and ERK is hampered by “inhibisomes” that contain signaling molecules and both inhibitory and activating receptors (20, 76). Inhibisomes impair activating Fc receptor functioning via a process referred to as inhibitory ITAM (ITAMi) receptor signaling that initiates anti-inflammatory responses to dampen pro-inflammatory responses induced by other Fc receptors (77). Thus, Lyn and Fyn are essential molecules controlling ITAM inhibition and activation, respectively (74). Signaling via Fc $\alpha$ RI was recently described in more detail in Aleyd et al. (18).

## IgA AND FC $\alpha$ RI MEDIATED FUNCTIONS AT DIFFERENT LOCATIONS

### In the Lumen of Mucosal Sites

The functions of SIgA in the intestinal lumen have been well-characterized (Figure 2A). SIgA and commensal microbes have important roles in maintaining balance between tolerance toward non-harmful commensals and food compounds vs. immunity against pathogens (78, 79). When SIgA is released from the epithelial layer into the lumen, it remains attached to the outer mucus layer (80). This close localization to bacteria enables SIgA to disturb bacterial motility and to surround pathogens that have a hydrophilic shell. SIgA coating blocks entrance of pathogens into the intestinal epithelium (a process called immune exclusion). This coating leads to agglutination, because antibody-mediated crosslinking of surface antigens will lead to formation of bacterial clumps. Peristaltic bowel movements ensure removal of bacterial aggregates. Bacterial products like enzymes and toxins can be neutralized by SIgA and adherence to host cells, including epithelial cells, is prevented (78). Thus, together with the mucus layer, SIgA forms a barrier against pathogens, and commensals by preventing colonization and penetration of the mucosal epithelium, thereby avoiding infection and antigen leakage into the systemic circulation (81).

Recently the interplay between luminal microbiota and SIgA was investigated in more detail (4, 82) (Figure 2A). It is still unclear how SIgA and the microbiota exactly relate to each other, but it was described that SIgA shapes and diversifies the gut microflora on the one hand, while the microbiota on the other hand has an important role in regulating IgA levels (82–84). During weaning up to 70% of intestinal commensals are coated with SIgA in mice and the majority of human fecal bacteria in healthy donors are opsonized with IgA, emphasizing the importance of this association in maintaining homeostasis (31, 85). A wide variety of commensals can be opsonized with



polyreactive IgA, although it remains unclear how these IgA antibodies are generated, what the relevant targets are and how binding affects the fitness and physiology of commensals (86). In contrast to commensals, pathogens elicit highly specific T-cell dependent IgA responses (86, 87). Genetic background was shown to influence the repertoire diversity and abundance

of innate IgA as germ free (GF) naïve BALB/c mice already had substantial innate IgA levels, independent of microbiota colonization, while this was not the case for C57BL/6 mice (83).

Furthermore, highly glycosylated IgA was able to bind to several gram negative bacteria, which modulated their gene expression, leading to enhanced processing of fibers and

production of butyrate as well as a diversified microbiota composition (82). Moreover, it was shown that the disbalanced microbiota of colitogenic mice became more balanced and diversified after oral administration of the monoclonal IgA W27, which is a high-affinity polyreactive antibody (84). Importantly, mice lacking IgA, J-chain or pIgR were unable to efficiently protect themselves against mucosal infections. These mice have an altered gut microbiota as well as increased mucosal permeability, which renders them more susceptible to develop colitis (80, 88–94). Of note, lack of J-chain or pIgR also led to absence of SIgM which may have contributed to altered microbiota and compromised immunity (88, 91, 94). A diversified microbiota can regulate the amount of SIgA present in luminal secretions by enhancing the level of pIgR on epithelial cells (1, 31, 95), illustrating the complex interrelationship between IgA (and IgM) and the microbiota in maintaining homeostatic conditions.

### In Epithelial Layers

It was described that SIgA can be translocated back into the lamina propria (retrograde transport). SIgA and SIgA immune complexes can be transported across specialized epithelial cells, referred to as M cells, which are located in the Peyer's patches of the intestine. Dectin-1 that is expressed by M cells may facilitate transepithelial transport (11, 96). Additionally, a role for Tfr1 on epithelial cells in retrotransport of SIgA-coated gliadin was reported in studies investigating celiac disease (12). Retrotransported SIgA immune complexes can be taken up by DCs that are present in the subepithelial dome. *In vitro* models support an essential role for DC-SIGN in recognizing SIgA immune complexes (13). The retrograde transport mechanism and recognition of SIgA by DCs is thought to be essential in monitoring the antigenic status of the intestinal lumen.

On route through epithelial cells, dIgA has the ability to intercept and disarm viruses and redirect them into the lumen, after which they are removed with the feces (**Figure 2B**). Neutralization of several viruses by IgA including sendai, influenza, rota, measles, and human immunodeficiency virus (HIV), as well as bacterial LPS was demonstrated *in vitro* (97–104). IgA has enhanced neutralizing capacity compared to other Ig isotypes due to the N-linked glycosylation of position N459D in the heavy chain C $\alpha$ 3 (105). This effect is independent of the antigen binding site as glycosylated non-specific IgA neutralized the virus as well.

IgA deficient mice, J-chain deficient mice (lacking dIgA, SIgA, and SIgM) and pIgR deficient mice (lacking SIgA and SIgM) have defects in clearing viruses, are more susceptible to reinfection and lack protective immunity (106–108), which emphasizes the important role of IgA in anti-viral immune responses. By contrast, in a recent study pIgR knock-out mice showed a reduced acute norovirus infection rate, suggesting that pIgR and natural polymeric immunoglobulins may promote viral infections. It was suggested that the less diversified intestinal microbiota present in pIgR deficient mice was responsible for reduced infection. pIgR deficient mice had enhanced levels of the anti-viral cytokine IFN- $\gamma$ , which might explain the reduced infection rates (109).

### In the Lamina Propria

Food particles and commensal microbiota are abundantly present in the lumen and can continuously reach the lamina propria through diffusion (via epithelial tight junctions) or transcytosis (**Figure 2C**). These non-harmful components need to be tolerated and they need to be cleared from the mucosa to avoid the formation of immune complexes, which may trigger undesired immune responses. In the lamina propria dIgA can eliminate both non-harmful and harmful components from the tissue by transporting immune complexes back into the lumen through association with the pIgR (97, 101). Additionally, Fc $\alpha$ RI<sup>+</sup> residing immune cells may help to clear IgA-opsonized pathogens. Under homeostatic conditions, only few Fc $\alpha$ RI<sup>+</sup> cells are found in mucosal areas (own unpublished data). However, as dIgA-opsonized complexes have the ability to cross-link Fc $\alpha$ RI, leading to release of LTB<sub>4</sub>, neutrophils can be rapidly recruited (64) (**Figure 2C**). Furthermore, *in vitro* generated Fc $\alpha$ RI<sup>+</sup> CD103<sup>+</sup> DCs were shown to produce pro-inflammatory cytokines after stimulation with IgA-coated *Staphylococcus aureus* in the presence of Pam3CSK4, suggesting that a protective adaptive immune response is initiated during mucosal infections (68).

### Systemic Protection

It was demonstrated that a variety of commensal microbes in the gut influenced serum IgA levels, which protected mice against lethal sepsis when the intestinal barrier was damaged (110). Serum IgA was shown to target the same epitopes and used the same V-gene segments as plasma cells in the gut (111), suggesting that systemic and mucosal plasma cells originated from the same B cell clone. Diminished serum IgA titers were found in GF mice compared to specific pathogen free mice, supporting the essential role for microbiota diversity in IgA production (110, 112). Mice lacking pIgR and SIgA have epithelial barrier disruption, enhanced numbers of IgA-secreting plasma cells and systemic immune activation indicated by increased levels of serum IgG and IgA (113, 114). Higher levels of albumin were found in the feces, suggesting leakage of serum proteins across the epithelium (113). At the same time intestinal proteins and microorganisms can leak into the tissue and enter the bloodstream. After entering the portal circulation they will encounter Kupffer cells in the liver, which are specialized Fc $\alpha$ RI<sup>+</sup> macrophages that can eliminate IgA-coated bacteria from the bloodstream (**Figure 2D**) (34). Kupffer cells, macrophages, and monocytes produced increased levels of pro-inflammatory cytokines (e.g., TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) after cross-linking of Fc $\alpha$ RI in the presence of pathogen recognition receptor ligands (such as Pam3CSK4, LPS, flagellin) (reflecting IgA-opsonized pathogens) (115).

In contrast to the activating properties of complexed serum IgA, monomeric serum IgA was capable of downregulating cell responses and promoted powerful anti-inflammatory effects (**Figure 2D**). This is referred to as ITAMi signaling (see above) (19). Monomeric targeting of the Fc $\alpha$ RI with serum IgA may protect against enhanced receptor activation, which is beneficial in inflammatory diseases characterized by the presence of IgG immune complexes or enhanced Fc $\epsilon$ RI signaling.

## IgA-ASSOCIATED DISEASES

In babies circulating IgA levels are physiologically low because IgA cannot be transported across the placenta. Colostrum and breast milk are important sources of SIgA antibodies to provide local protection against infections. As soon as exposure to microbiota takes place, the SIgA immune system is rapidly maturing. Nonetheless, adult serum IgA levels are not reached before puberty as the systemic IgA compartment develops very slowly. The daily production rate of IgA exceeds that of all other combined antibody classes (66 mg/kg/day), suggesting that the role of IgA in immune defense must be considerable for the body to spend high energy levels (30). Abnormal IgA levels in serum and external secretions (either higher or lower) have been described in numerous pathologies. Very low or absent IgA is referred to as IgA deficiency (116). High levels of (aberrantly glycosylated) IgA are present in multiple diseases including IgA nephropathy, dermatitis herpetiformis, IgA vasculitis, and rheumatoid arthritis.

### IgA Deficiency

Selective IgA deficiency is the most common human immunodeficiency and is characterized by a serum IgA concentration of <7 mg/dL. Both serum IgA and mucosal IgA are very low or absent in selective IgA deficient patients (6, 117). Defects in B cell isotype switching, terminal differentiation of IgA<sup>+</sup> plasma cells into secretory cells or long-term survival of IgA-secreting plasma cells can result in IgA deficiency (118, 119). Unbalanced cytokine production (including IL-4, IL-6, IL-7, IL-10, and IL-21) has been reported with a key role for TGF- $\beta$ , as it induces isotype switching and differentiation of antigen-stimulated B cells into IgA-secreting plasma cells (120, 121). The initial defect may lie in the stem cell compartment as IgA deficiency can be transferred by bone marrow transplantation (122).

A significant heterogeneity exists among IgA deficient patients. Many patients are asymptomatic and only few show minor clinical symptoms. This may in part be due to better hygiene, vaccination, and antibiotic use in modern Western society. Furthermore, it was shown that increased production of IgM and/or IgG can partially compensate for the lack of IgA (**Figure 3A**) (123, 124). IgA deficient patients can develop severe pathology when IgG and/or IgM does not compensate for IgA loss (117, 125). Conflicting reports on the influence of IgA deficiency on fecal microbiota in patients have been reported. One study showed a significantly less diverse fecal microbiota of IgA deficient patients compared to healthy controls, and specific taxa were lost in IgA deficient patients (124). Another study reported a mild loss in microbial diversity in IgA deficient patients (117). SIgM could partially rescue the microbiota composition in IgA deficient patients (117). However, SIgM targeted a broader range of microbes and showed less specificity for microbes compared to SIgA (124). Patients can have increased C reactive protein levels, which is indicative for enhanced inflammation, along with an increased risk of death 10–15 years after initial diagnosis (126, 127). In a recent study no risk association was found between

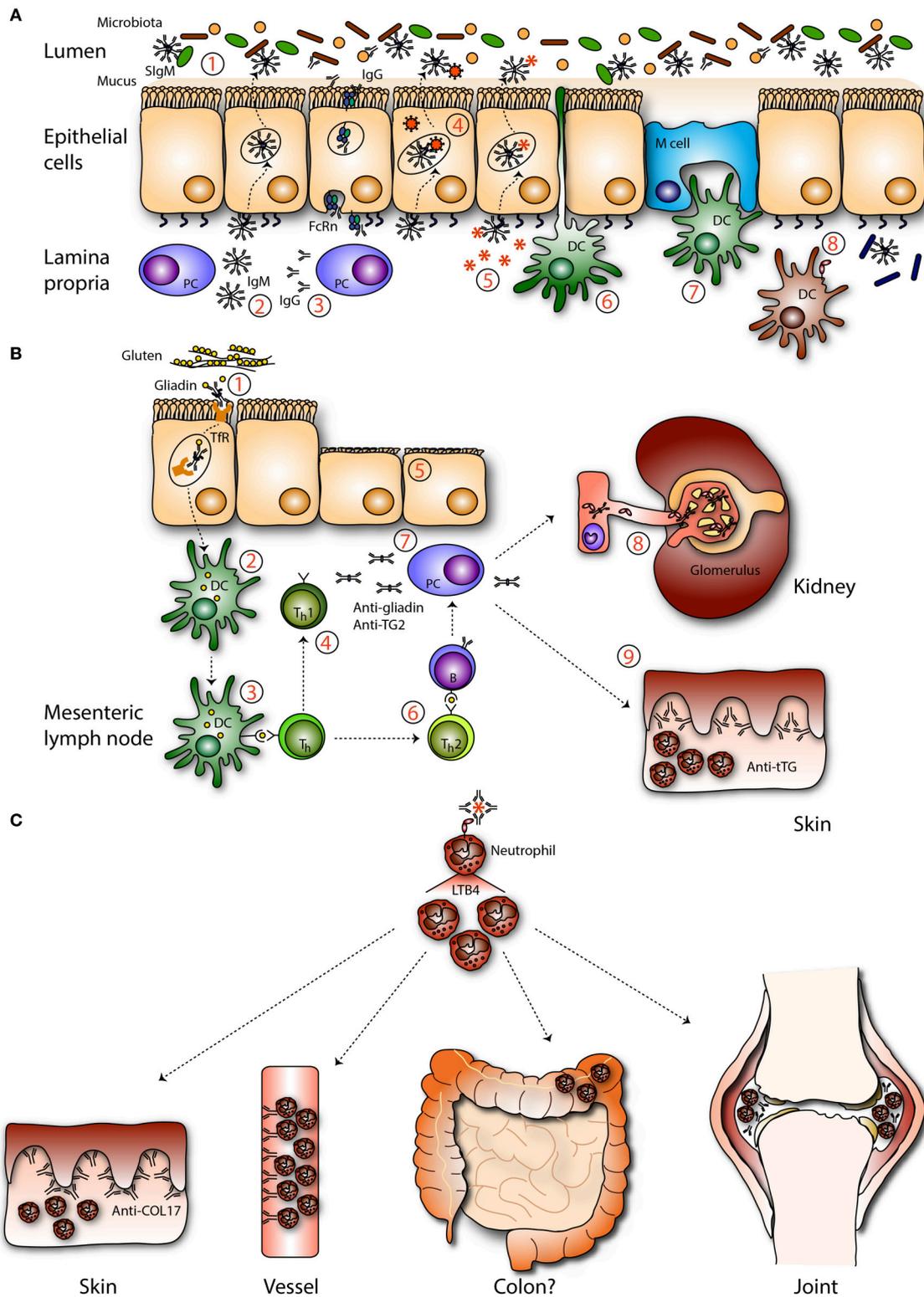
IgA deficiency and hospital infections (127). IgA deficiency was also not more common among hospitalized individuals compared to healthy blood donors (123). However, patients have moderate enhanced susceptibility to gastrointestinal, urinary, and recurrent respiratory infections, allergies, celiac disease, and autoimmune diseases (6, 128, 129). Forty-five percent of IgA deficient patients have the 8.1 haplotype (HLA-A1, B8, DR3, DQ2 haplotype) compared to 16% in the general population (123, 130). The 8.1 haplotype is also commonly found in patients with autoimmune diseases (including rheumatoid arthritis and systemic lupus erythematosus), which are strongly associated with IgA deficiency (123). These findings suggest that patients share predisposing genes, which may explain the increased prevalence of selective IgA deficiency in certain autoimmune disorders.

Eighty-four percent of IgA deficient patients were positive for a wide variety of allergens in skin prick tests (131). The link between IgA deficiency and allergies may be explained by higher levels of circulating antigens due to increased permeability at mucosal surfaces. Alternatively Fc $\alpha$ RI may not be able to induce ITAMi signaling in the absence of monomeric serum IgA, possibly resulting in overactivation of immune cells that can lead to development of allergies and autoimmune diseases (132).

Anti-IgA antibodies, usually of the IgG subclass, are commonly found in IgA deficient patients (40%), although their etiology remains unknown. Transfusing IgA-containing blood products to treat IgA deficiency is therefore complicated, as IgA-anti-IgA immune complexes can induce severe reactions, especially when anti-IgA antibodies of the IgE subclass are present (133, 134).

### Allergic Diseases

Allergic diseases are inflammatory conditions of which the majority are characterized by high specific IgE levels and activated mast cells (135). Alterations in microbiota diversity reduced immunological tolerance, potentially resulting in food allergies, allergic rhinitis, and asthma (136). It was suggested that the current hygienic life style in the western world altered normal microbiota colonization in infants thereby contributing to the enhanced prevalence of allergies (“hygiene hypothesis”) (137). A less diverse composition of the microbiota was associated with lower IgA levels, suggesting that IgA can be involved in the development of allergic diseases as well. Studies investigating the link between IgA levels and allergy and asthma have however been conflicting. In children, serum IgA levels correlated negatively with asthma severity (138). Moreover, it was shown that lower levels of intestinal bacteria were coated with IgA in infants with asthma (139). In adults, both house dust mite sensitization and airway hyper-responsiveness correlated negatively with serum IgA (140). Furthermore, asthma symptoms like shortness of breath and sputum production inversely correlated with, respectively mucosal SIgA and serum IgA levels (141). These results suggest a potential link between low IgA levels and the risk and severity of allergic asthma, which supports a protective role for IgA in allergy. However, data has also been reported showing enhanced specific IgA levels in patients with allergic rhinitis and atopic asthma



**FIGURE 3 |** Mucosal IgA in pathogenesis. **(A)** IgA deficiency. In absence of IgA the intestinal microbiota is (1) less diverse and unbalanced. (2) IgM, and (3) IgG can be transported across the epithelium by associating with the pIgR or the neonatal Fc receptor (FcRn), respectively, to compensate IgA loss. Theoretically, IgM may be able to (4) neutralize viruses and (5) exclude infiltrated antigens. Sub epithelial DCs are not described to (6) sample IgM coated bacteria. (7)

(Continued)

**FIGURE 3** | IgM-coated bacteria are not described to enter M cells. (B) Invaded IgM-coated pathogens are not recognized by FcαRI-expressing immune cells, resulting in less efficient pathogen elimination. (B) Celiac disease and gluten-associated diseases. (1) IgA-gliadin complexes bind to the transferrin receptor (TfR) and are retrotransported across the epithelium. (2) In the lamina propria deamidated gliadin is taken up by DCs and after processing (3) presented to T helper (Th) cells. (4) Th1 cell activation leads to the release of pro-inflammatory mediators (5) causing tissue damage. (6) Activated Th2 cells stimulate autoantibody production directed against gliadin and tissue transglutaminase by B cells. (7) Plasma cells produce autoantibodies which (8) can be detected in the circulation and form deposits with soluble FcαRI in the kidney resulting in damage (IgA nephropathy). (9) IgA anti-tissue transglutaminase forms complexes in the dermis, resulting in neutrophil activation and concomitant tissue damage (dermatitis herpetiformis). (C) IgA-FcαRI induced pathology. IgA immune complexes activate neutrophils by cross-linking FcαRI, resulting in release of LTB4 and enhanced neutrophil influx, which induces tissue damage as seen in the skin (LABD), vessels (IgA vasculitis), joints (RA), and potentially in colon (IBD).

(142, 143). Moreover, allergen specific IgA in combination with eosinophilia were common characteristics of asthma and allergic rhinitis (142), possibly because IgA can induce eosinophil survival, thereby contributing to disease severity (144). These results demonstrate a dual role of IgA in allergies, which is currently ill-understood.

### Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic and chronic autoimmune disorder characterized by infiltration of inflammatory immune cells in the joints, resulting in swelling and pain. Presence of autoantibodies including rheumatoid factor (RF) and anti-citrullinated protein antibodies are commonly present, which can be of the IgM, IgG or IgA isotype. High IgA anti-citrullinated protein antibodies and IgA RF titers correlate with worse disease prognosis and severity, and have been used as predictive value for disease progression (145–147). This suggests that IgA contributes to disease pathology. It was demonstrated that blocking the interaction between IgA RF and macrophage FcαRI resulted in reduced levels of TNF-α (148). Additionally, neutrophils stimulated with plasma of RA patients, containing IgA RF, induced NET release, which was inhibited by blocking FcαRI (149). Thus, IgA-immune complexes in patients can induce pro-inflammatory functions of neutrophils and macrophages, which are prominently present in inflamed joints (150), and as such contribute to inflammation in RA.

### IgA Nephropathy

IgA nephropathy (IgAN) is the most common form of glomerulonephritis and progresses to end-stage kidney failure in 50% of patients. IgA levels are increased in both serum and urine of IgAN patients. A link with RA was suggested, as patients can also have enhanced IgA RF in their serum. This condition is referred to as rheumatoid nephropathy (151). It was hypothesized that galactose-deficient O-glycans in IgA1, produced by plasma cells in the gut, can trigger the production of anti-glycan IgG/IgA antibodies, after which formed immune complexes deposit in the glomeruli where renal injury is initiated (152, 153). The enzymes responsible for production of O-linked glycans are glycosyltransferases, which expression are amongst others regulated by bacterial products, suggesting that the microbiome regulates the specific glycosylation pattern of IgA1 during the initial phase of IgAN (154, 155). In mice, galactose-deficient IgA1 was not cleared from the murine circulation and deposited in the kidney (15). FcαRI<sup>+</sup> Kupffer cells were unable to clear circulating IgA of IgAN patients *in vivo* (156). In transgenic mice expressing

the human FcαRI on monocytes and macrophages, soluble FcαRI-IgA complexes that were deposited in the mesangium, induced glomerular and interstitial macrophage infiltration, hematuria, mesangial matrix expansion, and mild proteinuria (157, 158). Moreover, in FcαRI transgenic and human IgA knock-in mice soluble FcαRI-IgA complexes induced kidney inflammation by interacting with TfR1 on mesangial cells, which induced the release of pro-inflammatory mediators. Additionally, the expression of transglutaminase 2 was induced, which subsequently enhanced the expression of TfR1, thereby inducing a pathogenic amplification loop (157). Of note, shedding of FcαRI from macrophages of transgenic mice may have aggravated disease, which will likely not occur in patients as human macrophages express lower FcαRI levels. Nonetheless, IgA-soluble FcαRI complexes have been found in patients with IgAN, and serum IgA immune complexes bound more avidly to TfR1 *in vitro* compared to those from healthy controls (158, 159). It was demonstrated that IgAN and Henoch-Schönlein purpura nephritis patients had reduced levels of soluble FcαRI and transglutaminase 2 in their urine (160), which makes it plausible that soluble FcαRI immune complexes deposit in the human kidney.

### IgA Vasculitis

IgA vasculitis, also known as Henoch-Schönlein purpura, is the most common form of vasculitis. The condition is characterized by IgA1 immune deposits and neutrophil infiltrates affecting the small vessels. As a result, red blood cells can leak into the skin leading to typical cutaneous hemorrhages, which leads to diagnosing the disease (161, 162). The pathology of IgA vasculitis remains unclear. However, it is suggested to represent a systemic equivalent of IgAN, as IgA vasculitis can be accompanied with nephropathy, resembling IgAN (163). Unlike IgAN, which is characterized by deposits of galactose-deficient IgA1, it is unknown which type of IgA accumulates in IgA vasculitis (152, 164).

Increased levels of soluble FcαRI-IgA complexes were found in sera of adult and pediatric vasculitis patients with or without co-existing nephritis, which was associated with decreased FcαRI expression on monocytes (165, 166). Furthermore, it was proposed that IgA1 anti-endothelial cell antibodies might play a role. Serum IgA from IgA vasculitis patients was shown to bind *in vitro* to human but not bovine glomerular endothelial cells (167). IgA anti-endothelial cell antibodies induced the production of IL-8 by endothelial cells, thereby contributing to an inflammatory environment and neutrophil recruitment

(168, 169). In addition to enhanced levels of serum TNF- $\alpha$ , which promoted anti-endothelial cell antibody binding to endothelial cells, IL-8 production increased inflammation in IgA vasculitis patients (167, 169, 170). It was hypothesized that neutrophils become activated by IgA-Fc $\alpha$ RI mediated cross-linking, resulting in inflammatory processes like reactive oxygen species production and NET formation. Moreover, IgA-activated neutrophils release LTB<sub>4</sub>, inducing neutrophil migration, thereby enhancing a positive feedback loop, which may result in pathogenesis observed in IgA vasculitis (162).

## Inflammatory Bowel Disease

Inflammatory bowel disease is characterized by chronic inflammation in the intestinal tract and is subdivided into ulcerative colitis and Crohn's disease (171). The barrier function in these patients is disrupted allowing bacteria to invade the subepithelial lamina propria (171). Downregulation of pIgR on intestinal epithelial cells and a disturbed microbiota were observed in IBD patients (172). It was proposed that intracellular signaling pathways and protein trafficking was altered due to damage caused by the inflammatory environment resulting in pIgR regulation defects (10). Mice lacking pIgR have enhanced numbers of IgA-secreting plasma cells, possibly as compensation. Increased production, combined with diminished transcytosis of dIgA into the lumen may potentially result in accumulation of dIgA in the lamina propria. Invading bacteria can become opsonized with dIgA, potentially resulting in activation of neutrophils by cross-linking of Fc $\alpha$ RI, leading to tissue damage. Neutrophils that had taken up IgA were observed in the mucosa of ulcerative colitis patients (64). Cross-talk between Fc receptors and TLRs was induced by antibody-coated bacteria, resulting in release of pro-inflammatory mediators (e.g., LTB<sub>4</sub>) by DCs, which may also contribute to inflammation in IBD. LTB<sub>4</sub> induces recruitment of neutrophils and monocytes. Additionally, simultaneous triggering of Fc $\alpha$ RI and TLR4 on neutrophils resulted in enhanced release of pro-inflammatory TNF- $\alpha$  (173). Furthermore, due to diminished SIgA levels in the lumen, neutralization, and immune exclusion of microbes is decreased, which may worsen disease in patients (10). Patients have increased levels of specific IgA against microbiota in their serum (174). Highly IgA-coated bacteria obtained from IBD patients induced colitis in GF mice (175). The extent to which IgA responses against microbiota differ in homeostatic conditions vs. IBD, remain unclear (86).

Surprisingly, an increased amount of fecal bacteria of IBD patients was opsonized with IgA compared to those obtained from healthy control feces (85, 175, 176). It was suggested that leakage of serum IgA or dIgA due to a disrupted epithelial layer contributed to enhanced fecal bacteria coating (176, 177). The exact role of IgA and Fc $\alpha$ RI in inflammatory bowel disease however remains to be elucidated.

## Celiac Disease and Dermatitis Herpetiformis

Celiac disease is a multifactorial autoimmune disease characterized by a damaged small intestinal mucosa and nutrient malabsorption following gluten ingestion. Individuals carrying the DQ2 and DQ8 HLA haplotypes have an increased

risk to develop celiac disease (178). Gliadin, a glycoprotein of gluten, can complex with specific IgA, after which it can be retrotransported across the epithelium via the TfR (Figure 3B). Celiac disease patients have increased expression of TfR on their epithelial cells, allowing increased retrotransport (12). Intracellular degradation of these peptides is disturbed in patients and after entrance in the lamina propria gliadin peptides are deamidated by tissue transglutaminase after which they are presented to HLA-DQ2 or HLA-DQ8 expressing CD4<sup>+</sup> T cells. This results in the release of pro-inflammatory mediators, concomitant tissue damage and production of autoantibodies (179). IgA anti-tissue transglutaminase antibodies play a key role in disease pathogenesis (180). Presence of these antibodies serve to diagnose the disease and are furthermore linked to other IgA-related diseases like dermatitis herpetiformis and IgA nephropathy (Figure 3B). In dermatitis herpetiformis aberrant IgA antibodies are directed against structural proteins maintaining cell-cell adhesion in the epidermis leading to skin tissue damage (181). It is hypothesized that celiac disease patients can develop dermatitis herpetiformis as high avidity IgA anti-tissue transglutaminase antibodies form immune complexes and deposit in the dermis of these patients, although it is ill understood why some patients develop dermatitis herpetiformis, and others do not. Furthermore, small bowel inflammation in celiac disease is mostly the result of mononuclear cell infiltration, whereas neutrophils accumulate in the skin of dermatitis herpetiformis patients (181). Patient neutrophils have increased ability to bind IgA without Fc $\alpha$ RI expression alteration, supporting that Fc $\alpha$ RI is primed (e.g., by cytokines or differential glycosylation) (182).

Gluten exposure can also lead to glomerular IgA deposition and IgAN (183). Transgenic human IgA and Fc $\alpha$ RI knock-in mice developed severe pathology when gluten were present in their diet, including intestinal injury, increased IgA1-soluble Fc $\alpha$ RI complexes, mesangial IgA1 deposition, and elevated serum IgA1 anti-gliadin antibodies. IgAN patients also have increased IgA1 anti-gliadin antibodies in their serum, suggesting that entrance of gluten can potentially result in loss of oral tolerance thereby contributing to IgAN (184). Consumption of a gluten-free diet can resolve manifestations of celiac disease, dermatitis herpetiformis, and IgAN.

## Linear IgA Bullous Disease

Linear IgA Bullous Disease (LABD) patients suffer from extensive skin damage and blister formation caused by the presence of IgA autoantibodies against collagen XVII, and concomitant neutrophil accumulation (Figure 3C). Collagen XVII plays a critical role in maintaining adhesion between dermis and epidermis in the skin (185). Neutrophil activation is likely the direct result of Fc $\alpha$ RI triggering by IgA autoantibodies (186). Tissue damage was induced in the presence of neutrophils and serum of LABD patients (containing IgA anti-collagen XVII autoantibodies) in an *ex vivo* skin model, as presence of activated neutrophils led to separation of the dermis from the epidermis (reflecting blister formation) (186). Eosinophil influx has been observed in the skin of LABD patients as well, suggesting that these cells might also contribute to disease pathology through Fc $\alpha$ RI mediated respiratory burst activity (185).

## IGA AND FC $\alpha$ RI AS THERAPY

IgA plays an important role in dampening mucosal infections, but can also have detrimental effects in inflammatory or autoimmune diseases. Lack of IgA may increase susceptibility to infection, whereas overabundant IgA complexes or autoantibodies can be harmful as enhanced activation of the Fc $\alpha$ RI may lead to various pathologies. Several therapeutic strategies have been proposed that influence the IgA-Fc $\alpha$ RI axis (Figure 4). For instance, in order to benefit from increased IgA levels during infections it was proposed to increase pathogen-specific IgA levels through passive or active vaccination thereby resulting in efficient clearance of pathogens. Furthermore, IgA might be used as a therapeutic antibody to mediate efficient tumor cell killing. Additionally, two different strategies of targeting Fc $\alpha$ RI have been proposed. First, the induction of ITAMi signaling via Fc $\alpha$ RI may dampen inflammation that is caused by other pro-inflammatory receptors (e.g., Fc $\epsilon$ RI). Second, blocking Fc $\alpha$ RI may reduce activation of immune cells in IgA-mediated inflammation.

### IgA in Vaccination Strategies

Administration of specific IgA (passive immunization) or enhancing IgA production through active immunization might be effective strategies to combat viral and bacterial infections (104). Intranasal passive administration of either specific monomeric or polymeric IgA against a mycobacterium tuberculosis antigen led to short, but effective protection against infection in mice (187). The short protection duration was probably due to degradation of IgA by bacterial proteases present in the respiratory tract fluid. Furthermore, mice expressing human Fc $\alpha$ RI on blood neutrophils and monocytes had a lower mycobacterium tuberculosis infection rate compared to control mice after inoculation of human IgA mAb, supporting an additive beneficial role for Fc $\alpha$ RI in clearing the infection (188). Wild type (WT) mice which orally received *Salmonella typhimurium* that had been complexed with human plasma-derived IgA and IgM had reduced intestinal infection rates compared to mice exposed to *Salmonella typhimurium* only. Enhanced bacterial clearance was observed when SC was coupled to plasma-derived IgA and IgM (189). Polymeric IgA against influenza virus reached the nasal mucosa after intravenous administration and protected WT mice against infection, and was 10 times more effective than IgG in reducing viral shedding (190, 191). Passive immunization with recombinant dIgA showed better prevention against intra-rectal simian HIV transmission in rhesus macaques. Dimeric IgA could either directly neutralize simian HIV or the virus was trapped by large immune complexes preventing entrance in the epithelial barrier (103). It was demonstrated that IgA isolated from serum of HIV survivors and vaccinated HIV patients neutralized HIV through occupying the CD4 binding site of the virus (192, 193). By contrast, in another study, HIV specific IgA levels in plasma interfered with IgG effector functions *in vitro*, thereby increasing HIV infection risk (194). Recently, it was reported that oral and nasal administrated HIV antigens bound to SIgA were retro transported through M cells and reached sub-epithelial

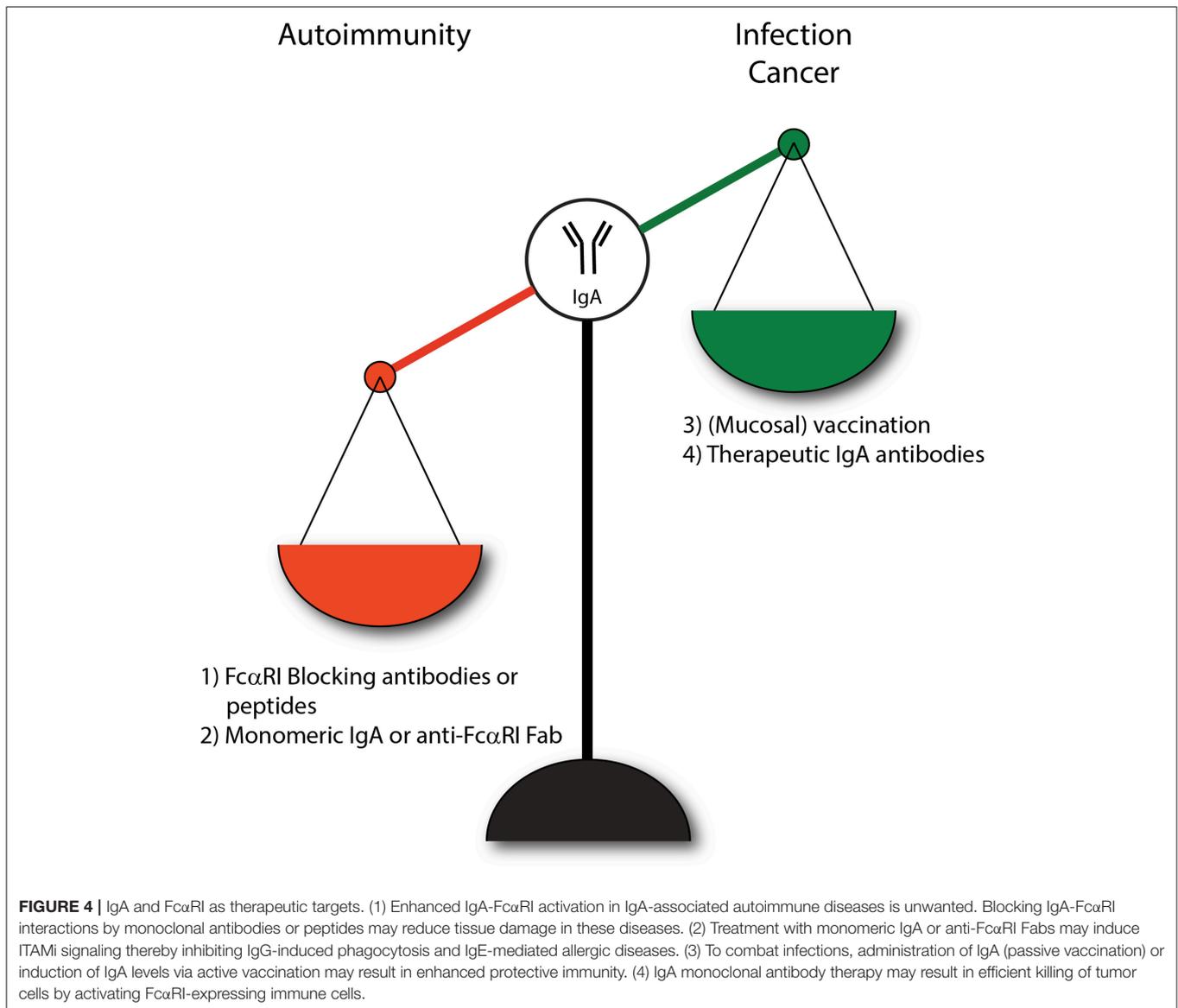
DCs, thereby inducing both mucosal and systemic humoral and cellular immune responses in CX3CR1/GFP transgenic mice (195). Vaccination with SIgA-HIV antigen protected these mice from infection after challenge with a recombinant vaccinia virus expressing the HIV antigen (195, 196). This demonstrates the potential of SIgA to serve as a vaccine carrier for HIV via mucosal administration.

Vaccination with live attenuated polio induced intestinal IgA production and induced long-lived memory immune responses in elderly who still had detectable serum and salivary IgA levels (197–199), which suggested that priming with live virus is needed to obtain IgA responses after booster vaccination with inactivated polio virus. Furthermore, WT mice that were immunized and re-challenged with reovirus had enhanced serum and intestinal IgA levels and were protected from infection (108, 200). IgA<sup>-/-</sup> mice were unable to clear reovirus infection (108). Mice immunized with hemagglutinin (surface protein on influenza virus) produced anti-influenza specific SIgA, which protected mice from infection after intranasal administration (201). Mice deficient of IgA, J-chain or pIgR showed compromised immune protection (106–108), supporting that IgA enhances protective immunity against viral and bacterial infections.

### Fc $\alpha$ RI as Therapeutic Target in Cancer Antibody Therapy

Antibodies targeting specific tumor-associated antigens like epidermal growth factor receptor (EGFR) and human epidermal growth factor two (HER2) are increasingly used to treat solid tumors (respectively colorectal cancer and breast cancer) (202). These therapeutic antibodies are often of the IgG isotype and have long half-life, can activate complement, and recruit natural killer cells as well as macrophages as cytotoxic effector cells (202, 203). Alternatively, IgA or Fc $\alpha$ RI bispecific antibodies (BsAb) may represent promising novel drugs to treat cancer by enhancing activation of Fc $\alpha$ RI-expressing immune cells (204). For instance, BsAb targeting both tumor antigens and Fc $\alpha$ RI efficiently recruited neutrophils *in vitro*, which was not observed after targeting Fc $\gamma$  receptors (205–207). Moreover, (immature) neutrophils were able to kill tumor cells more efficiently due to Fc $\alpha$ RI-induced antibody dependent cellular cytotoxicity (62, 203, 208). Similarly, IgA anti-tumor mAbs mediated tumor killing more efficient compared to IgG mAbs. *In vitro* studies demonstrated the superior ability of Fc $\alpha$ RI to induce neutrophil-mediated tumor cell killing for multiple tumor antigens, including EGFR, HER2, EpCAM, HLA-II, CD20, CD30, and carcinoembryonic antigen (203, 205, 209).

Unfortunately, *in vivo* tumor targeting using IgA anti-tumor mAbs has been difficult as mice do not express a homolog of the human Fc $\alpha$ RI, and human IgA has a short half-life in mice (158). The generation and utilization of Fc $\alpha$ RI transgenic mice (71, 158) can contribute to study IgA as therapeutic antibody *in vivo*. Treatment with IgA anti-HER2 or IgA anti-EGFR anti-tumor mAbs resulted in significantly enhanced anti-tumor cytotoxicity in Fc $\alpha$ RI transgenic mice compared to WT littermates, which was mediated by Fc $\alpha$ RI-expressing macrophages (210, 211). Furthermore, IgA anti-CD20



mAbs inhibited B cell lymphoma cell proliferation *in vitro* and recruited Fc $\alpha$ RI-expressing immune cells *in vivo* in Fc $\alpha$ RI transgenic mice (212, 213).

Thus, IgA antibodies have been shown to recruit neutrophils and macrophages as effector cells, but the short half-life of IgA in serum is a major drawback for use of IgA as therapeutic antibody. Compared to IgG, the glycosylation sites of therapeutic IgA mAbs that are produced in non-human systems (like rodent cells) have higher immunogenic potential (high glycosylation) and therapeutic IgA will be likely cleared efficiently from the human (or murine) circulation. Increasing the sialylation of glycans on IgA mAbs enhanced their serum half-life due to decreased clearance by the ASGPR in the liver (210). Inducing sialylation of IgA mAbs was done by using fully human systems thereby augmenting their *in vivo* therapeutic potential (211, 214–216). Increased sialylation of the N-glycans in IgA anti-HER2

mAbs resulted in significantly reduced tumor growth in Fc $\alpha$ RI-transgenic SCID mice bearing BT-474 tumors (214). Addition of an albumin-binding domain to IgA1 (IgA1-albumin) enhanced interaction of the antibody with the FcRn, which extended the half-life of IgA1 *in vivo*. Although *ex vivo* studies showed that IgA1-albumin induced lower maximal tumor cell lysis, enhanced tumor cell killing was observed *in vivo* (211). Another modified IgA molecule against EGFR lacking glycosylation and free cysteine's, and with a stabilized heavy and light chain linkage, showed increased efficacy by interacting with Fc $\alpha$ RI-expressing myeloid cells *in vivo*. Some therapeutic activity was observed in non-Fc $\alpha$ RI transgenic mice demonstrating contribution of Fab-mediated effector functions as well (216). Although IgA antibodies are not used in clinical studies yet, engineering IgA with increased half-life represents a promising strategy for targeting tumors in patients.

## Induction of ITAMi Signaling

Enhancing ITAMi signaling by monomeric targeting of the Fc $\alpha$ RI may be a promising strategy to inhibit IgG-induced phagocytosis and IgE-mediated allergic diseases (20). Monovalent targeting of Fc $\alpha$ RI with the anti-Fc $\alpha$ RI mAb A77 inhibited degranulation of RBL-2H3 transfected cells and reduced airway inflammation in Fc $\alpha$ RI transgenic mice after crosslinking Fc $\epsilon$ RI with IgE immune complexes in an allergic asthma model (20, 217). Furthermore, naturally occurring serum IgA dampened immune responses by inducing ITAMi signaling via Fc $\alpha$ RI (19). Fc $\alpha$ RI transgenic mice (expression on monocytes/macrophages), which developed RA after injection with IgG anti-collagen had reduced manifestations or even complete resolution of arthritis after treatment with monomeric IgA. IgG-induced ITAM signaling was blocked efficiently, implicating a potential role of monomeric IgA in treatment of autoimmune diseases with IgG autoantibodies (218). Moreover, prior targeting of Fc $\alpha$ RI by Fab A77 suppressed inflammation in transgenic mice with Fc $\alpha$ RI-expressing monocytes and macrophages that suffered from IgG immune complex glomerulonephritis and obstructive nephropathy (219). Renal inflammation induced by pristane was characterized by enhanced serum IgG levels, pro-inflammatory cytokines and immune infiltration in Fc $\alpha$ RI transgenic mice with receptor expression on monocytes and macrophages. Blocking Fc $\alpha$ RI with Fab MIP8a inhibited cytokine production, leukocyte recruitment and inflammation (77). Furthermore, renal inflammation induced by CpG (TLR9 agonist) in these Fc $\alpha$ RI transgenic mice was downregulated by monomeric occupancy of Fc $\alpha$ RI (220). Thus, monomeric targeting of Fc $\alpha$ RI is suggested to induce anti-inflammatory properties, which could be useful in treatment of inflammatory diseases with involvement of myeloid cells.

## Fc $\alpha$ RI Blocking

Blocking Fc $\alpha$ RI might be effective in IgA-mediated inflammation. *In vitro* it was shown that neutrophils stimulated with IgA immune complexes obtained from RA patients released neutrophil extracellular traps. Fc $\alpha$ RI blocking on neutrophils with the anti-Fc $\alpha$ RI mAb MIP8a reduced NET formation and might alleviate neutrophil induced tissue damage in RA patients (149). IgA autoantibodies in serum of LABD patients induced neutrophil-mediated tissue damage in an *ex vivo* human skin model. Fc $\alpha$ RI blocking with MIP8a prevented IgA induced tissue damage (186). Similarly, peptides targeting the interaction sites of IgA and Fc $\alpha$ RI showed effective blocking of IgA binding to Fc $\alpha$ RI, and reduced IgA-induced neutrophil migration *in vitro*. These peptides were able to penetrate into human skin, supporting that they might function as novel therapy in skin autoimmune diseases (221). As such, blocking Fc $\alpha$ RI might serve as therapeutic strategy for IgA-associated inflammatory diseases.

## CONCLUSION

IgA is important in maintaining balance of mucosal immunity. SIgA regulates immune exclusion by neutralizing pathogens

and more recently the role of SIgA in diversifying the intestinal microbiota has become clear. The mechanisms involved in IgA-mediated regulation of microbiota diversity and reciprocal regulation of IgA levels by microbes are incompletely understood. Moreover, it remains unclear why certain SIgA coated antigens associate with the epithelial layer while others are eliminated via immune exclusion. In addition to the traditional role of IgA as non-inflammatory regulator of homeostasis, several pro-inflammatory functions have been described, which need to be clarified in more detail.

After binding to Fc $\alpha$ RI, IgA plays important roles in pathogen elimination. It can also have detrimental effects on human health when aberrant IgA is present. Perpetual IgA-Fc $\alpha$ RI interaction results in enhanced activation of immune cells with concomitant tissue damage as seen in autoimmune diseases like LABD (64). It is yet undefined why neutrophil influx is observed in some IgA-Fc $\alpha$ RI mediated diseases, including LABD and dermatitis herpetiformis, but not others. For instance, Crohn's disease is generally less characterized by neutrophil influx in the intestinal mucosa, while in patients with ulcerative colitis massive neutrophil infiltration is present (171). Similarly, and maybe even more confusing, is the fact that celiac disease patients develop IgA anti-tissue transglutaminase antibodies resulting in infiltration of mainly mononuclear cells in the intestinal tract, while in dermatitis herpetiformis (skin manifestation of celiac disease) binding of IgA autoantibodies to epidermal transglutaminase results in neutrophil recruitment (181).

Targeting the IgA-Fc $\alpha$ RI axis with blocking monoclonal antibodies or peptides may alleviate inflammation and concomitant tissue damage. Moreover, inhibitory ITAMi signaling induced by monomeric targeting of Fc $\alpha$ RI has been suggested to represent a promising strategy in allergies or IgG immune complex-mediated diseases. By contrast, in infectious diseases and cancer enhancing pro-inflammatory effects of IgA-Fc $\alpha$ RI interaction might be very beneficial.

Lack of an Fc $\alpha$ RI equivalent in mice has hampered our understanding of the functions and therapeutic applications of IgA and Fc $\alpha$ RI. Future research will be facilitated by the use of several human Fc $\alpha$ RI transgenic and human IgA knock-in models (71, 158, 222). This will help to increase our knowledge on the complex roles of IgA and Fc $\alpha$ RI in (patho)physiology as well as the therapeutic possibilities for targeting these multifaceted molecules.

## AUTHOR CONTRIBUTIONS

AB wrote the paper and designed the figures. MvE designed and illustrated the figures, supervised, and revised the paper.

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