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REVIEW

IgA and FcαRI: Versatile Players in Homeostasis, Infection, and Autoimmunity

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Abstract: Mucosal surfaces constitute the frontiers of the body and are the biggest barriers of our body for the outside world. Immunoglobulin A (IgA) is the most abundant antibody class present at these sites. It passively contributes to mucosal homeostasis via immune exclusion maintaining a tight balance between tolerating commensals and providing protection against pathogens. Once pathogens have succeeded in invading the epithelial barriers, IgA has an active role in host-pathogen defense by activating myeloid cells through divers receptors, including its Fc receptor, FcαRI (CD89). To evade elimination, several pathogens secrete proteins that interfere with either IgA neutralization or FcαRI-mediated immune responses, emphasizing the importance of IgA-FcαRI interactions in preventing infection. Depending on the IgA form, either anti- or pro-inflammatory responses can be induced. Moreover, the presence of excessive IgA immune complexes can result in continuous FcαRI-mediated activation of myeloid cells, potentially leading to severe tissue damage. On the one hand, enhancing pathogen-specific mucosal and systemic IgA by vaccination may increase protective immunity against infectious diseases. On the other hand, interfering with the IgA-FcαRI axis by monovalent targeting or blocking FcαRI may resolve IgA-induced inflammation and tissue damage. This review describes the multifaceted role of FcαRI as immune regulator between anti- and pro-inflammatory responses of IgA, and addresses potential novel therapeutic strategies that target FcαRI in disease.

Keywords: neutrophil, CD89, mucosa, infection, inflammation, autoimmunity

Introduction

The immune system is a central player in protecting the host against infectious diseases. Synergy between both innate and adaptive immunity is essential to induce effective immune responses against invading microbes. Immunoglobulins are major players of the adaptive immune response, and contribute to both immune defense and maintaining homeostasis.[1] Based on structure and effector functions, five major immunoglobulin isotypes can be distinguished, ie, IgM, IgD, IgG, IgA, and IgE that differ in the Fc tail. Immunoglobulins can mediate neutralization, thereby preventing invasion of pathogens or toxins. Additionally, immunoglobulins constitute a bridge between pathogens and the innate immune system facilitating complement activation as well as inducing effector cell functions by immune cells.[2,3] Binding of the immunoglobulin Fc tail to their cognate Fc receptor, which can be distinguished in receptors for IgG (FcγRs), IgE (FcεRI), IgA (FcαRI), IgM (FcμR), and IgA/IgM (Fcα/μR), induces cellular activation.[4]

Mucosal surfaces like the respiratory-, urogenital- and gastrointestinal tracts are continuously exposed to environmental factors and therefore considered as the

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frontiers of the body. Tolerating harmless antigens while providing protection against pathogens is a challenging feature of mucosal immunity. IgA is the predominant immunoglobulin at mucosal surfaces and in external secretions. It contributes to mucosal homeostasis by neutralizing toxins and viruses, preventing colonization and invasion of pathogenic bacteria, clearing unwanted particles, and promoting sampling of luminal antigens.[5,6] In serum, IgA is the second most abundant antibody after IgG. Nonetheless, the exact functions of serum IgA are relatively unexplored and ill understood.[7]

Binding of IgA to its Fc receptor, FcαRI, can initiate either pro- or anti-inflammatory responses. It was demonstrated that interaction of monomeric serum IgA with FcαRI induces inhibitory signals (Figure 1A).[8] As such, it is suggested that IgA and FcαRI contribute to homeostatic conditions.[9] By contrast, IgA immune complexes (eg, IgA-opsonized bacteria) induce pro-inflammatory responses by cross-linking of FcαRI, which is important in controlling infections (Figure 1B).[10,11] The presence of excessive IgA immune complexes or IgA-opsonized bacteria can however lead to uncontrolled and disproportionate FcαRI-mediated immune cell activation, resulting into severe tissue damage as observed during chronic inflammation and autoimmunity.[12] Increased serum IgA levels or IgA autoantibodies have been reported in multiple diseases including rheumatoid arthritis, IgA nephropathy, IgA vasculitis, dermatitis herpetiformis, celiac disease, inflammatory bowel disease, Sjögren's syndrome, ankylosing spondylitis, alcoholic liver cirrhosis, and acquired immunodeficiency syndrome.[13–20] The role of FcαRI-mediated inflammation in pathology is still poorly understood. This review summarizes the different functions of FcαRI and its ligand IgA during homeostasis, infection, chronic inflammation, or autoimmunity, and addresses the possibilities of targeting FcαRI for therapeutic strategies.

FcαRI and IgA: The Basics

FcαRI Structure and Expression

Human FcαRI is a member of the Fc receptor immunoglobulin superfamily. Nevertheless, FcαRI has some distinct features compared to other Fc receptors. The FcαRI gene

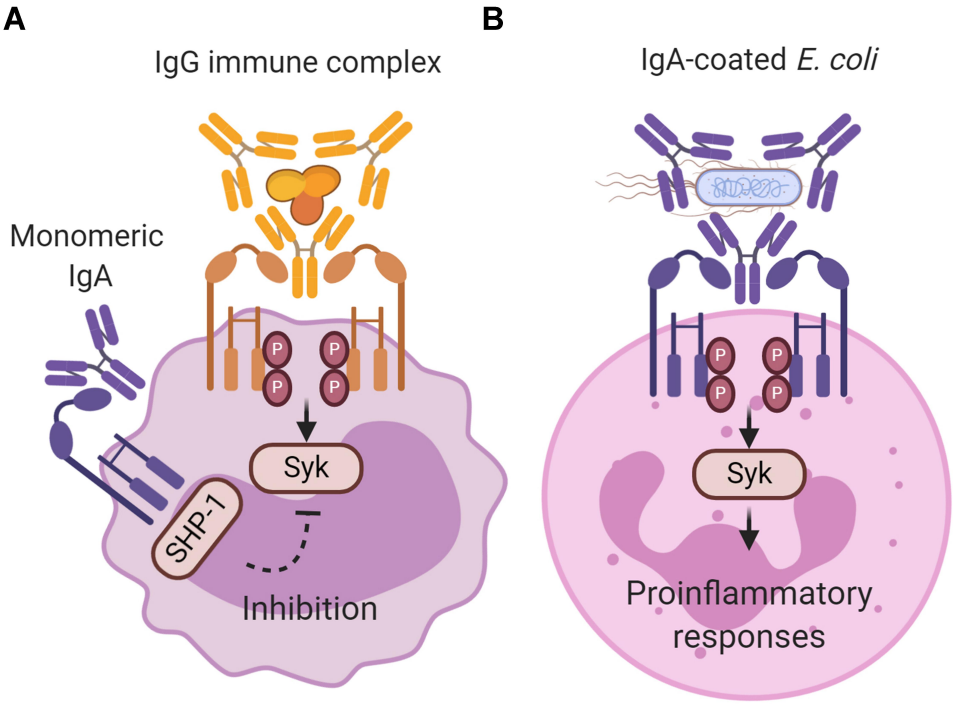

Figure 1 Inhibitory and activating signaling via FcαRI after ligand binding. (**A**) Monomeric IgA (not complexed to an antigen) does not induce FcαRI cross-linking resulting in partial phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) and recruitment of Src homology region 2 domain-containing phosphatase-1 (SHP-1). This results in inhibition of ITAM signaling, and impairs phosphorylation of spleen tyrosine kinase (Syk), LAT and ERK, which is initiated through signaling via other activating Fc receptors (like IgG-mediated Fcγ receptor activation). The exact binding of free dIgA to FcαRI, and concomitant signaling, has not yet been resolved. (**B**) IgA immune complexes (eg IgA-coated *Escherichia coli*) induce cross-linking of FcαRI, resulting in ITAM phosphorylation of the associated FcR γ-chain. Phosphorylated ITAMs subsequently function as a docking site for signaling molecules such as Syk. Syk plays an essential role in initiating signaling pathways, including the Ras/Raf/MEK/MAPK pathway. Activation of signaling pathways results in pro-inflammatory cellular functions such as phagocytosis, antibody-dependent cellular cytotoxicity, respiratory burst, degranulation, antigen presentation, and release of NETS, cytokines and inflammatory mediators. Created with BioRender.com.

(FCAR) is located on chromosome 19 (19q13.4) within the leukocyte receptor cluster (LRC), whereas other human FcR genes are located on chromosome 1.[21,22] LRC also encodes leukocyte Ig-like receptors and natural killer cell immunoglobulin-like receptors. The amino acid (aa) sequence of FcαRI resembles LRC encoded receptors more closely than other Fc receptors.[23] FCAR consists of five exons that encode for the leader peptide (S1; 34 base pairs (bp), and S2; 36 bp), two extracellular Ig-like domains (EC1 and EC2; 291 bp and 288 bp) and a combined transmembrane and cytoplasmic region (TM/C; 215 bp).[24] FCAR encodes a transmembrane receptor, which consists of two extracellular domains (EC1 and EC2; each 206 aa) that are folded with an angle of approximately 90° to each other.[25] The transmembrane region (19 aa) is crucial for association with FcR γ-chain,[26] and FcαRI has a short cytoplasmic tail (41 aa). FcαRI is expressed on the surface of myeloid cells, including neutrophils, eosinophils, monocytes, macrophages, Kupffer cells, and human platelets.[12,27,28] Additionally, low FcαRI levels were observed on in vitro cultured immature monocyte-derived dendritic cells (DCs) as well as on monocyte-derived $CD103^+$ DCs, which resemble human epithelial interstitial-type DCs.[29,30] The molecular weight of FcαRI ranges between 50 and 75 kilodalton (kDa) due to differences in N glycosylation, with the exception of FcαRI on eosinophils, which is between 70 and 100 kDa.[31] Orthologues of human FcαRI have been identified in several monkey species, horses, cattle, hamsters, gerbils, and rats, but not in mice due to a gene translocation.[32,33]

FcαRI is constitutively expressed and independent of its ligand. Expression can be modulated by several mediators, such as lipopolysaccharide (LPS), chemoattractants, cytokines, or adapter protein binding to the intracellular domain of FcαRI.[33,34] Upregulation of FcαRI on neutrophils occurs rapidly by either transport from an intracellular pool to the cell surface or via de novo synthesis and is induced by N-formylmethionyl-leucyl-phenylalanine (fMLP), interleukin (IL)-8, tumor necrosis factor-alpha (TNF-α), LPS, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[35–38] On monocytes and monocyte-like cell lines FcαRI expression was enhanced by calcitriol, LPS, TNF-α, GM-CSF, and IL-1β.[39,40] Downregulation occurs in the presence of transforming growth factor-β (TGF-β), interferon-γ (IFN-γ), or by ligand binding due to FcαRI aggregation and internalization.[41,42]

IgA Binding to FcαRI

Humans express two closely related IgA subclasses, ie, IgA1 and IgA2, whereas most mammals, except for rabbits and certain primates, express only a single IgA subclass that resembles IgA2.[43–45] In serum, IgA1 is the predominant subclass with an IgA1:IgA2 ratio of 9:1, while IgA2 is mainly found in the colon. In other mucosal tissues, IgA1 and IgA2 are more evenly distributed. IgA1 and IgA2 differ in their hinge region and number of glycosylation sites.[46] IgA1 contains a hinge region that is 13 amino acids longer compared to IgA2, which results in enhanced antigen recognition capacity but also in increased susceptibility for proteolytic cleavage by bacterial proteases.[47] Furthermore, IgA1 contains three to six O-linked glycans in the hinge region, while IgA2 is devoid of O-linked glycosylation.[48] O-linked glycans of IgA1 in external secretions can interact with bacterial adhesion molecules, contributing to mucosal homeostasis.[49] Altered O-linked glycosylation can cause IgA1 conformational changes resulting in increased immune complex formation, which is a key pathogenic factor in diseases like IgA nephropathy.[50]

In humans, IgA is expressed in three different forms: ie, monomeric IgA, dimeric IgA (dIgA), and secretory IgA (SIgA). Serum IgA is mostly monomeric and produced by plasma cells in the bone marrow, spleen, and lymph nodes. By contrast, IgA at mucosal sites is predominantly dimeric and produced by local plasma cells in the lamina propria.[51,52] Dimeric IgA (dIgA) is composed of two monomers that are linked tail-to-tail with a joining (J-) chain via Cys471-mediated disulfide bonds forming a boomerang-like structure.[53] It is transported across the epithelium by binding to the polymeric Ig receptor (pIgR), which is expressed on the basolateral membrane of epithelial cells.[53,54] At the luminal side, pIgR is cleaved and a part of this receptor, referred to as secretory component (SC), remains attached to dIgA by binding both Fc-tails and J-chain across the ~50° gap between the two monomers, thereby forming SIgA (Figure 2A).[55,56]

All (iso)forms of IgA are ligands for FcαRI, although binding of SIgA to FcαRI is (partially) hampered due to steric hindrance of SC.[57] Furthermore, binding of SIgA requires the presence of macrophage-1 antigen (Mac-1, CD11b/CD18).[58] Monomeric IgA and dIgA bind with moderate affinity (K_a = 10^6 M^{-1}), whereas IgA immune complexes bind with higher avidity and induce crosslinking of FcαRI.[33] Optimal binding of IgA immune complexes occurs with five to six molecules of IgA per complex.[59] In particular residues Pro440-Phe443 and

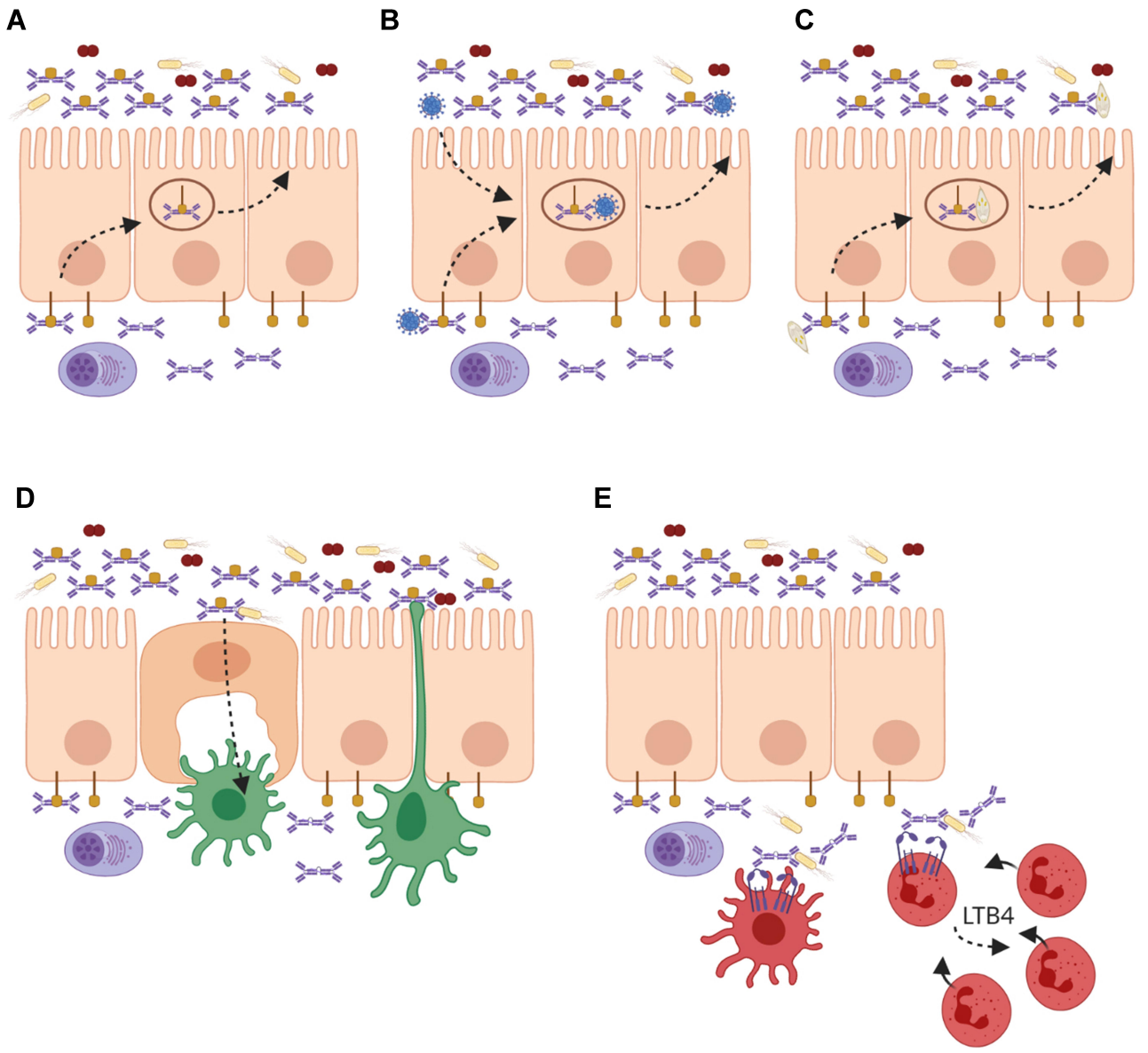

Figure 2 Roles of IgA and FcαRI in homeostasis and infection at mucosal sites. (**A**) Local plasma cells in the lamina propria produce dimeric IgA (dIgA), which is transported across the epithelium into luminal secretions by binding to the polymeric Ig receptor (pIgR). At the luminal side it is released as secretory IgA (SIgA) where it can neutralize pathogens and toxins. (**B**) On route of being secreted, dIgA can intercept viruses, which have infected epithelial cells and redirect them into the lumen. (**C**) Invading pathogens and antigens in the lamina propria are opsonized by dIgA and transported back into the lumen. (**D**) Microbes that are opsonized with SIgA are shuttled via microfold (M) cells to dendritic cells (DCs) in Peyer's patches for sampling. Additionally, DCs can extend dendrites through the epithelial layer for sampling of the luminal content. (**E**) During infection, dIgA-opsonized pathogens are taken up by FcαRI-expressing DCs, and presented to T cells. Additionally, phagocytosis of dIgA-opsonized pathogens by neutrophils results in the release of leukotriene B4 (LTB4), which mediates the chemotaxis of more neutrophils to the site of infection, thereby functioning as a self-contained positive feedback loop of immune cell recruitment to clear invading pathogens. Created with BioRender.com.

Leu257-Leu258 in the FcαRI EC1 are essential for IgA binding.[60] Monomeric IgA binds to FcαRI via its Cα2 and Cα3 domains in a 2:1 stoichiometry (one IgA molecule binds simultaneously two FcαRI molecules).[25,61] This is in contrast with other Fc receptors since FcεRI and FcγRIII bind their ligands in EC2 in a 1:1 stoichiometry.[62–65] In theory, dIgA can bind four FcαRI due to its multiplied binding sites, although this may not be possible due to steric hindrance. As such, it still remains unclear how dIgA exactly binds to FcαRI.[66] It has been described that pentraxins, including acute phase C reactive protein (CRP) and serum amyloid P (SAP), compete for FcαRI binding since these proteins recognize a similar binding site on FcαRI as IgA.[67] Mutations in FcαRI outside the IgA-binding site enhanced pentraxin binding to FcαRI with 2-fold whereas IgA binding was unaffected, suggesting additional binding sites for pentraxins.[67]

FcαRI harbors six N-glycosylation sites which affect the binding affinity of IgA to FcαRI. Altered glycosylation of FcαRI due to a specific mutation (Asn58 to Glu58) resulted in a nearly 2-fold increased binding of IgA. Furthermore, removal of sialic acids increased IgA binding with nearly 4-fold.[68] IgA binding to FcαRI can also be regulated by intracellular signals that are modulated by cytokine stimulation of cells (also referred to as inside-out signaling), independently of FcαRI expression levels.[69] Increased binding of IgA to FcαRI in transfected cells, eosinophils, and monocytes was reported in the presence of cytokines like GM-CSF, IL-4, and IL-5 without increasing FcαRI expression levels on the cell surface.[70,71]

FcαRI Signaling and Cellular Activation

FcαRI does not contain any known signaling motifs. In order to initiate effector functions, FcαRI associates with the FcR γ-chain subunit, which contains an immunoreceptor tyrosine-based activation motif (ITAM) in its intracellular domain.[26] In the transmembrane regions, the positively charged arginine on position 209 (R209) in FcαRI associates with the negatively charged aspartic acid 11 (D11) in FcR γ-chain.[72] The FcR γ-chain ITAMs contain conserved paired tyrosines and leucines in a consensus sequence (YxxL-x_{7-12}-YxxL). Binding of monomeric serum IgA (not complexed with an antigen) leads to partial phosphorylation of FcR γ-chain and involves extracellular signal-related kinases (ERK)-dependent recruitment of tyrosine phosphatase Src homology region 2 domain-containing phosphatase-1 (SHP-1) to sphingolipid–cholesterol-rich membrane domains.[8] Cytoplasmic clusters referred to as inhibisomes hamper spleen tyrosine kinase (Syk), linker for activation of T cells (LAT), and ERK phosphorylation, thereby inhibiting pro-inflammatory responses that are induced by other activating Fc receptors.[73] This process is referred to as inhibitory ITAM (ITAMi) signaling (Figure 1A), which may represent an anti-inflammatory mechanism to prevent uncontrolled release of inflammatory responses (see also below).

By contrast, binding of IgA immune complexes to FcαRI induces cross-linking of FcαRI, resulting in pro-inflammatory responses (Figure 1B). After crosslinking, tyrosines in ITAMs are phosphorylated by the Src kinase Fyn, forming docking sites for other tyrosine kinases, including Syk.[74–76] Syk plays an essential role in the activation of several proteins, including phosphoinositide 3-kinase (PI3-K), phospholipase Cγ (PLCγ), and Src homology and collagen adaptor protein (Shc). These proteins initiate multiple signaling pathways, including the Ras/Raf/MEK/MAPK pathway and the Rho family GTPase pathway. These pathways are also interconnected and can therefore modulate each other.[74–76] Syk additionally induces the release of second messengers such as calcium and diacylglycerol.[77] Activation of signaling pathways results in remodeling of the actin cytoskeleton and activation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb), ultimately leading to cellular activation (for detailed description of FcαRI signaling, see Aleyd et al).[10]

Depending on the cell type, FcαRI activation can result in phagocytosis, degranulation, superoxide generation, release of neutrophil extracellular traps (NETs), antibody-dependent cellular cytotoxicity (ADCC), release of cytokines and chemokines, or antigen presentation.[12] It has been shown that phagocytosis of IgA-coated particles by neutrophils induces increased reactive oxygen species (ROS) production and NET release, which can contribute to pathogen elimination.[78] Additionally, cross-linking of FcαRI by serum or dIgA initiates the release of the chemoattractant leukotriene B4 (LTB4) with concomitant neutrophil recruitment.[79] SIgA was able to induce respiratory burst in neutrophils, although less efficiently compared to serum IgA. It did not induce efficient uptake of pathogens by either neutrophils or Kupffer cells.[27,80] Cross-linking of FcαRI by IgA immune complexes on immature DCs resulted in antigen presentation through the major histocompatibility complex class II pathway, DC maturation, and production of IL-10.[81–83] Since IL-10, together with TGF-β, mediates IgA isotype switching in B cells, FcαRI-positive DCs are described to be important for the induction of IgA by B cells in secondary lymphoid organs.[84] Additionally, cross-linking of FcαRI on in vitro generated human $CD103^+$ DCs (resembling human epithelial interstitial-type DCs) resulted in the release of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-23.[29] SIgA was internalized by DCs as well, albeit through carbohydrate-recognizing receptors instead of FcαRI, which did not result in DC maturation.[85]

FcαRI and IgA: Homeostasis

Immune Exclusion and Immune Regulation

In mucosal areas like the respiratory-, urogenital-, and gastrointestinal tracts, SIgA plays a key role in keeping a tight balance between tolerating commensals and harmless antigens while providing protection against harmful pathogens.[86]

Due to its multiple binding sites, SIgA opsonizes bacteria with high avidity thereby interfering with bacterial motility and inducing bacterial agglutination. This can block the entrance of bacteria into the mucosal epithelium.[87] Additionally, bacterial products like enzymes and toxins are also neutralized by SIgA.[88] This process, referred to as immune exclusion, is the main described function of SIgA and prevents local and systemic infection (Figure 2A).[86] Not only bacteria but also viruses can be neutralized by mucosal IgA. On route to be secreted, dIgA has the ability to intercept and disarm viruses, which have infected epithelial cells and redirect them back into the lumen (Figure 2B).[12] Similarly, pathogens that have invaded the epithelial barrier into the lamina propria are likely opsonized by dIgA and transported back into the lumen (Figure 2C). It has been shown that IgA neutralized several viruses, including sendai, influenza, rota, measles, and human immunodeficiency virus 1 (HIV-1).[89–94] Additionally, SIgA plays an important role in shaping and diversifying the gut microbiome.[95] Mice lacking IgA showed reduced overall microbial diversity resulting in altered bacterial composition, increased bacterial translocation, and ultimately intestinal inflammation.[96–98] Similarly, humans with defective mucosal IgA responses, such as Selective IgA-deficiency (SIgAd), showed modest but significant changes in the gut microbiota composition.[99] High-microbiota binding as well as cross-species reactivity of IgA was shown to promote host-microbiota symbiosis, hereby maintaining intestinal mucosal integrity and homeostasis.[100–102] Yet, the functional effects of IgA binding to microbiota fitness or physiology remain unclear. IgA production is also microbiota-dependent, as germ-free showed diminished IgA titers compared to specific-pathogen-free mice.[103,104] IgA-producing plasma cells were absent in most tissues of germ-free mice and significantly reduced in the small intestine, reflecting the importance of microbiota in initiating humoral responses.[101]

SIgA immune complexes (eg, IgA-opsonized bacteria) can be transported from the lumen into the lamina propria via the transferrin receptor 1 (TfR1 or CD71) on epithelial cells or via Dectin-1 on microfold cells (M cells) (Figure 2D).[105,106] Reverse transcytosis of SIgA is important for the uptake and delivery of antigens from the intestinal lumen to gut-associated lymphoid tissues (GALTs) influencing immune responses.[106,107] SIgA immune complexes are taken up by DCs through interaction with Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN).[85]

In the circulation, serum IgA has likely an immunomodulatory role through inhibitory signals via ITAMi signaling (Figure 1A). It was shown that monovalent targeting of FcαRI resulted in the inhibition of oxidative burst activity, chemotaxis and IgG-mediated phagocytosis and cytokine production.[108–111] Furthermore, in transgenic mice that express human FcαRI on myeloid cells, IgE-mediated asthma was prevented by the binding of soluble IgA to FcαRI, which inhibited FcεRI-induced degranulation of mast cells.[8] ITAMi signaling by FcαRI is therefore suggested to play a role in maintaining homeostasis and protection against enhanced Fcγ receptor- or FcεRI-mediated activation during inflammatory diseases and allergies.[9]

Early-Life Immunity

SIgA is the predominant antibody in human colostrum and described to protect offspring from infection when the neonatal immune system is still immature.[112,113] IgA and IgM are not able to cross the placenta through the neonatal Fc receptor (FcRn) and can therefore only be provided through maternal milk.[114] Breastfeeding is important for the development of the neonatal intestinal microbiota and can protect infants from infectious diseases.[114–116] Studies in mice have shown that colostrum is the only source of SIgA in the first weeks of life since it takes up to approximately 4 weeks for the neonatal intestine to be populated by IgA-secreting B cells.[116,117] In humans, mucosal IgA in the fetal intestine is absent or rarely present until 10 days after birth.[118] IgA-producing B cells become pre-dominant 1–2 months after birth and increase in number until 6 to 11 months of age.[119] The highest concentration of SIgA is found in colostrum; however, prolonged breastfeeding resulted in increased IgA in maternal milk as well.[120,121] Although the opsonic activity of SIgA is poor, early studies demonstrated that SIgA initiated macrophage phagocytosis and neutrophil respiratory burst.[122] After antigen interaction, SIgA undergoes conformational changes, which enhanced the binding of SIgA immune complexes to FcαRI.[123] In addition to immunoglobulins, maternal milk also facilitates the transfer of leukocytes. IgA-induced cellular effector functions may therefore contribute to early immunity against pathogens in newborns. It has been demonstrated that the majority of leukocytes present in maternal milk have a similar phenotype to blood cells, although leukocyte subsets are present in different frequencies. Myeloid precursors, neutrophils, and immature granulocytes are the main identified cells

present in colostrum.[124] Colostral neutrophils were able to phagocytose IgA-opsonized bacteria although this did not result in significant bacterial-killing and release of superoxide anion. This is likely due to FcαRI expression without γ subunit association.[125] The exact contribution of FcαRI-mediated cellular responses initiated by SIgA or leukocytes in maternal milk remains incompletely understood.

FcαRI and IgA: Infection

The production of IgA, with a synthesis rate of 66mg/kg, exceeds that of all other antibodies combined supporting its importance in host-pathogen defense.[12] Pathogen-specific IgA is found at mucosal surfaces and in circulation during several infectious diseases, while the exact function of IgA remains unclear.[6,11] Passive immunity (via neutralization) as well as immune activating properties of IgA have been described for infections in the respiratory- and reproductive tracts such as *Mycobacterium tuberculosis* (*Mtb*), HIV-1, and more recently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.[126–128]

Passive Immunity

Respiratory infections often occur via inhalation of airborne droplets containing pathogens or via direct contact with respiratory secretions.[129,130] The nasopharyngeal mucosa is furthermore a natural reservoir for several pathogens like *Streptococcus pneumoniae (S. pneumoniae)* and *Neisseria meningitides (N. meningitides)*.[131] In individuals who lack protective antibody titers, infections can occur causing various pathologies like pneumonia, meningitis, bacteremia, and sepsis.[132,133] In mice, SIgA against *Mtb* or *S. pneumoniae* has been associated with protection against tuberculosis (TB) or pneumococcal disease respectively.[134,135] The neutralizing capacities of IgA are not only described for bacteria since IgA against HIV-1 or rotavirus was able to neutralize either virus. Monomeric IgA1 or dIgA2 against envelope proteins (Env) of HIV-1 showed neutralizing activity in vitro.[136] Moreover, mucosally applied Env-specific dIgA1 and dIgA2 protected rhesus macaques against an intrarectal challenge with simian-human immunodeficiency virus (SHIV).[137,138] IgA against rotavirus (RV-IgA) neutralized both virus in solution and virus that had bound to epithelial cells in vitro.[139] Furthermore, it was shown that RV-IgA was produced in all rotavirus animal models (horse, cow, sheep, gnotobiotic piglet, rat, rabbit, and mouse) which correlated with clearance of infection and protective immunity.[140–142] Generation of specific IgA in coronavirus disease 2019 (COVID-19) was described as well.[143–146] It was suggested that SIgA antibodies against SARS-CoV-2 were able to neutralize the spike protein or nucleocapsid protein thereby providing protective mucosal immunity.[147] It is unknown whether serum IgA anti-SARS-CoV-2 antibodies contribute to protection against COVID-19. On the one hand, it was demonstrated that severe COVID-19 illness was significantly associated with increased total serum IgA but not with total serum IgG levels.[148] Furthermore, IgA levels correlated with disease score in critically ill patients.[149] On the other hand, the presence of IgA and IgG antibodies against SARS-CoV-2 spike protein subunit 1 (S1) showed an inverse correlation with viral load. Additionally, enhanced titers of specific anti-S1 IgA in serum correlated with significant increased survival in COVID-19 patients 28 days post intensive care unit admission.[150] Passive antibody therapy using convalescent plasma from recovered COVID-19 patients resulted in a reduction in viral load and better disease outcomes, most notably in less severely ill COVID-19 patients.[151–153] Nonetheless, since IgA-specific SARS-CoV-2 neutralizing antibodies were not determined in convalescent plasma that was transferred to COVID-19 patients, the exact contribution of IgA neutralizing antibodies in COVID-19 remains unknown.[154–156] Longitudinal investigation of potentially protective functions of mucosal and systemic IgA is needed to determine their role in COVID-19.

Active Immunity

Although few FcαRI-positive cells are observed in mucosal areas in homeostatic conditions, FcαRI-positive neutrophils are the first cells that are recruited after infection.[79,157] Once pathogens have successfully invaded the epithelial barrier, they can become opsonized by dIgA in the lamina propria. It was shown that dIgA induced efficient phagocytosis by neutrophils.[80] As such, a pro-inflammatory role for dIgA in eliminating infiltrating pathogens was proposed.[33] Enhanced phagocytosis of *Escherichia coli, Streptococcus pneumonia, Staphylococcus aureus, Porphyromonas gingivalis, Candida albicans, Bordetella pertussis,* and *Neisseria meningitides* by neutrophils after targeting FcαRI has been demonstrated in vitro.[27,79,80,158–161] Specific IgA antibodies against meningococcal capsular polysaccharides were shown to induce moderate phagocytosis by neutrophils but initiated respiratory burst more potently than IgG.[80] Cross-linking of FcαRI on neutrophils furthermore results in the release of LTB4, which is a potent neutrophil

chemoattractant, and additionally mediates the migration of monocytes and monocyte-derived DCs.[79,162,163] LTB4 release after neutrophil activation through FcαRI has therefore been proposed to function as a self-contained positive feedback loop of immune cell recruitment to clear invading pathogens and maintain homeostasis (Figure 2E).[33] Alveolar macrophages, which express an alternatively spliced variant of FcαRI, also contribute to host-pathogen defense by clearance of inhaled antigens that were opsonized by IgA.[164] A recent study showed that antibodies from patients with latent TB induced enhanced macrophage killing of intracellular *Mtb*.[165] Since IgA levels against TB antigens distinguished patients with pulmonary TB, patients with latent TB, and non-infected individuals, a role for FcαRI-mediated effector functions in *Mtb* control is predicted, although this is formally not yet established.[166] Interestingly, a recent study showed that FcαRI also acts as an innate receptor, by binding bacteria directly independent of its ligands IgA or CRP. Binding of bacteria to FcαRI induced phagocytosis by $CD11c^+$ DCs and monocytes/macrophages. Moreover, FcαRI transgenic mice were protected against two different sepsis-induced models, identifying FcαRI as a first-line innate receptor for bacterial clearance.[167]

The contribution of antibody-dependent cellular phagocytosis (ADCP) in protective immune responses against viruses remains debatable. Nonetheless, there is substantial evidence that supports the involvement of ADCP in protection against several types of viruses and reduction of disease.[168] It has been described that human NK cells and neutrophils perform ADCC and ADCP of HIV-1 gp120-pulsed target CEM-NKr cells or gp120-coated beads, respectively, in the presence of polyclonal antibodies from different HIV-positive subject groups.[169] Moreover, HIV-1 gp41 envelope-specific IgA induced FcαRI-mediated ADCC of HIV-1 Clade A- and B-infected target cells by monocytes.[170] HIV-1 gp41 envelope-specific IgA additionally triggered ADCP of HIV-1 infected $CD4^+$ T cells by monocytes and neutrophils more efficiently than anti-gp41 IgGs.[171] FcαRI-mediated neutrophil phagocytosis initiated by vaccine-induced IgA was associated with reduced risk of infection against simian immunodeficiency virus (SIV) after immunization via the nasal, but not the intramuscular route in non-human primates.[172] These studies may provide new insights into FcαRI-mediated immune responses against HIV-1 infected cells and address the potential functions of IgA during viral infections. By contrast, the RV144 HIV-1 vaccine trial showed that IgA interfered with IgG-mediated ADCC by NK cells of HIV-1 infected cells.[173] It was proposed that Env-specific IgA competed with IgG for NK cell-mediated ADCC of HIV-1 infected cells, while enhancing ADCP by FcαRI-expressing cells like neutrophils, which represent the dominant phagocyte population in tissues from the lower female reproductive tract.

The severity of infections increases when invading pathogens from the respiratory- or gastrointestinal tract enter the bloodstream. In mice it was shown that serum IgA directed against commensal bacteria protected mice against lethal sepsis when the intestinal barrier was damaged, suggesting that serum IgA provided protection against systemic infection.[103] Mice lacking pIgR and SIgA have epithelial barrier disruption, enhanced numbers of IgA-secreting plasma cells, and increased levels of serum IgG and IgA.[174] It was furthermore demonstrated that in human FcαRI-transgenic mice IgA-opsonized bacteria in the circulation were phagocytosed by Kupffer cells, which express FcαRI.[27] FcαRI cross-linking by serum IgA immune complexes and cross-talk with pathogen recognition receptors (PRRs) on Kupffer cells initiated the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[175,176] As such, clearance of serum IgA-coated bacteria by Kupffer cells may act as a systemic line of defense, through elimination of invasive bacteria that have escaped mucosal immune responses (Figure 3).

Bacterial Evasion Mechanisms

Pathogens have evolved and developed strategies to either disarm IgA or evade FcαRI-mediated activation of immune cells, emphasizing the importance of IgA-FcαRI interactions in the elimination of pathogens and prevention of infection.[177] Pathogens that colonize the oral and upper respiratory mucosa like *S. pneumoniae* and *N. meningitides* produce specific proteases cleaving both mucosal and serum IgA1 at the hinge region, which abrogates its protective effects and interferes with host antibacterial immunity.[178,179] Binding of pneumococcal surface protein (SpsA) to SIgA is suggested to recruit SIgA to the bacterial surface to promote its degradation by IgA proteases, hinder SIgA from clearing bacteria, or block the interaction between SIgA and FcαRI thereby preventing immune responses.[53] Additionally, IgA1 proteases were shown to degrade lysosomal-associated membrane protein 1 (LAMP-1) promoting intracellular bacterial survival in epithelial cells in vitro.[180] Furthermore, it was described that serine proteases do not only cleave IgA1, which prevents FcαRI-mediated immune responses but also reduce the binding

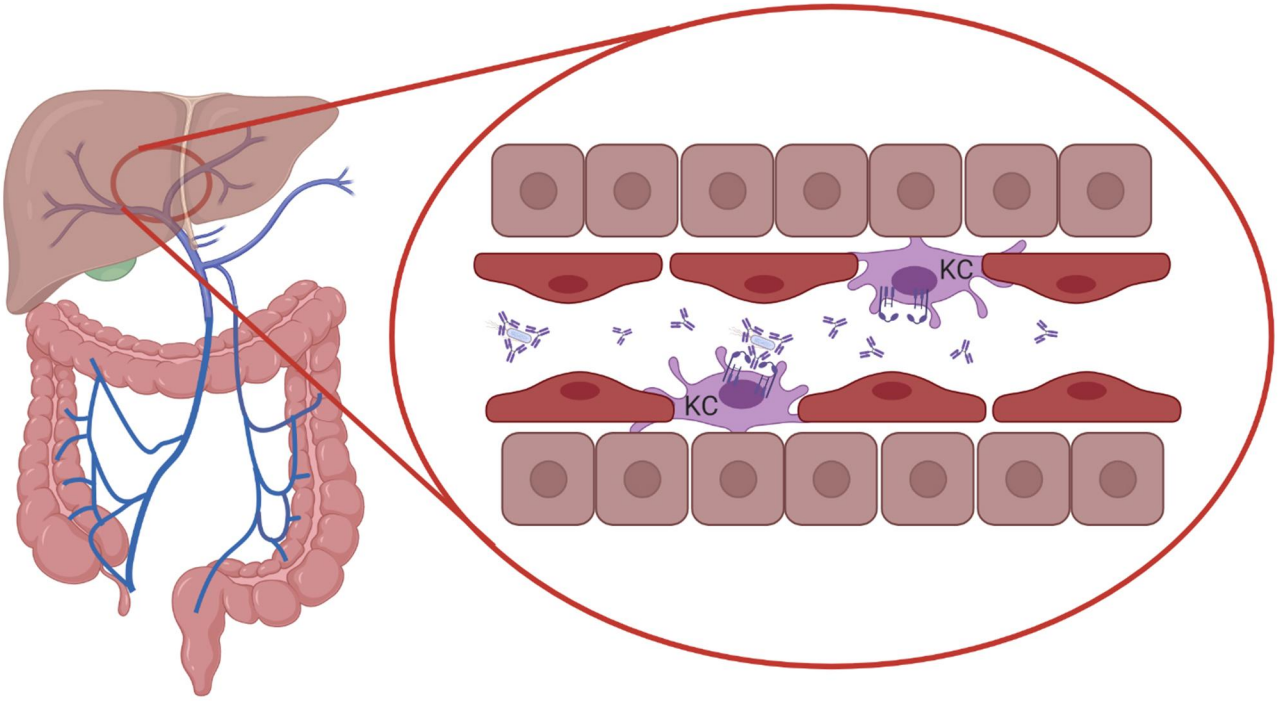

Figure 3 Systemic protection by serum IgA and FcαRI-expressing Kupffer cells. Serum IgA-opsonized bacteria in the circulation are transported to the liver through the portal vein and phagocytosed by Kupffer cells (KC), which express FcαRI, providing protection against systemic infection. Cross-talk between FcαRI and pathogen recognition receptors (PRRs) may break the tolerance of Kupffer cells to bacterial structures. Created with BioRender.com.

avidity of IgA1 thereby reducing the neutralizing ability of IgA1.[181] Closely related strains of *N. meningitides*, as well as *S. pneumoniae* that lack IgA1 proteases are considered nonvirulent.[182] Furthermore, *Staphylococcus aureus* (*S. aureus*) and group A and B streptococci developed evasion mechanisms to circumvent FcαRI-mediated elimination by secreting decoy proteins that inhibit binding of IgA to FcαRI. Decoy proteins Sir22, Arp4, and an unrelated β protein from group B streptococci, as well as staphylococcal superantigen-like protein seven that is produced by *S. aureus*, bind to specific Fc residues in the Cα2 and Cα3 domains of IgA.[183,184] The ability of bacteria to escape FcαRI-mediated immunity enhances survival in mucosal environments and may contribute to systemic infections.

FcαRI and IgA: Chronic Inflammation and Autoimmunity

Because FcαRI potently activates immune cells, aberrant IgA responses may contribute to pathogenesis in inflammatory and/or autoimmune diseases. The presence of IgA autoantibodies, aberrant IgA glycosylation, or excessive IgA immune complexes can contribute to chronic inflammation and tissue damage. The detrimental role of IgA and FcαRI-mediated immune responses has been proposed in several inflammatory diseases like IgA nephropathy, rheumatoid arthritis, IgA vasculitis, dermatitis herpetiformis, linear IgA bullous disease, and inflammatory bowel disease.

IgA Nephropathy

IgA nephropathy (IgAN) is the most common IgA-mediated autoimmune disease. It is characterized by primary glomerulonephritis, resulting in chronic renal failure in 30% of the patients.[185,186] Infections or microbiome dysbiosis prior to IgAN have been suggested to initiate abnormal IgA1 glycosylation as glycosyltransferases are regulated by bacterial products.[187] Elevated synthesis of galactose-deficient IgA1 (gd-IgA1) triggers the production of anti-glycan antibodies. IgA immune complexes can deposit in the glomeruli inducing mesangial proliferation and matrix expansion, which eventually initiates renal injury.[188] The release of pro-inflammatory cytokines such as TNF-α, IL-6, and TGF-β by mesangial cells after IgA immune complex binding was suggested to induce inflammation and glomerulosclerosis.[187,189] In mice, gd-IgA1 immune complexes were not cleared from the circulation and deposited in the kidney. Shedding of FcαRI in transgenic mice however resulted in the deposition of soluble

FcαRI-IgA immune complexes in the mesangium, which induced glomerular and interstitial macrophage infiltration, hematuria, mesangial matrix expansion, and mild proteinuria.[190–192] Soluble FcαRI-IgA complexes additionally mediated kidney inflammation by interacting with TfR1 on mesangial cells, resulting in the release of pro-inflammatory mediators.[190] Human FcαRI transgenic mice developed IgAN after injection of serum IgA of IgAN patients. Furthermore, human IgA1 knock-in mice that had been crossed with FcαRI transgenic mice already developed IgAN in 6 weeks.[193] These data clearly support the contribution of IgA and FcαRI-mediated inflammation in IgAN.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic and chronic auto-immune disorder characterized by inflammation in the joints, which frequently leads to joint destruction and disability.[194] Although the etiology of RA is unknown, the presence of autoantibodies is a distinctive feature of RA. In particular, IgM rheumatoid factor (RF) and IgG anti-citrullinated protein antibodies (ACPA) are commonly used for diagnosing and classifying RA.[195] Interestingly, elevated levels of IgA RF, but not of IgM- or IgG RF, correlated with worse disease prognosis and extra-articular manifestations in RA.[196] Additionally, high levels of IgA RF were associated with a poor response rate to TNF-α blockers as therapeutic agents in advanced RA.[197] In IgM RF negative patients it was shown that IgA ACPA was associated with disease severity based on disease activity score.[15] RF or ACPA can be elevated in the serum years prior to the onset of clinical disease, referred to as pre-clinical RA.[198,199] An increased number of IgA^+ plasmablasts was identified in preclinical RA without a history of or current inflammatory arthritis.[200] In both clinical and preclinical RA, IgA ACPA was highly specific for RA.[201,202] IgA ACPA and RF immune complexes furthermore increased the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by myeloid cells via cross-linking of FcαRI, whereas blocking of FcαRI on macrophages resulted in reduced levels of TNF-α.[203] Additionally, increased NET release by neutrophils in the presence of plasma of RA patients containing IgA RF was demonstrated, which was dependent on FcαRI.[78] Altogether, this supports that IgA contributes to disease, as activation of FcαRI-expressing neutrophils and macrophages in the joint via IgA auto-immune complexes likely enhances inflammation and pathology of RA.

IgA Vasculitis

IgA vasculitis, formerly known as Henoch-Schönlein purpura, is the most common form of vasculitis involving the small vessels of the joints, kidneys, gastrointestinal tract, and the skin.[204] Although the etiology of IgA vasculitis remains unknown, the disease is characterized by IgA1 immune deposits and neutrophil infiltrates damaging the small vessels. Abnormal glycosylation of the hinge region of IgA1 is suggested to cause aggregation into macromolecular immune complexes.[204] FcαRI-mediated cross-linking of neutrophils induces inflammatory processes like ROS production, NET formation, and LTB4 release. As such, it is hypothesized that FcαRI-mediated activation of neutrophils results in vessel damage and leakage of red blood cells into the skin causing typical cutaneous hemorrhages.[14] Antigen recognition sites of accumulated IgA1 in IgA vasculitis have not yet been identified. However, it was proposed that these antibodies can recognize epitopes on endothelial cells as serum IgA from IgA vasculitis patients was shown to bind to human but not bovine glomerular endothelial cells in vitro.[205] Notably, sera of IgA vasculitis patients had increased levels of soluble FcαRI-IgA complexes, which was associated with decreased FcαRI expression on monocytes.[206] A positive feedback loop of inflammation in IgA vasculitis was proposed, since binding of IgA1 antibodies to endothelial cells induced the release of IL-8, thereby attracting more neutrophils that can be activated through FcαRI.[16]

Skin Blistering Diseases

Dermatitis herpetiformis (DH) is an autoimmune disease that often occurs in combination with gluten-sensitive enteropathy (celiac disease). Anti-transglutaminase IgA antibodies (mainly anti-epidermal transglutaminase 3; TGase3) play a key role in disease pathogenesis of DH as it was shown that serum anti-epidermal transglutaminase IgA positively correlated with disease activity.[207] IgA anti-tissue transglutaminase antibodies form immune complexes and deposit in the dermis of patients with DH.[12] In the skin, transglutaminase/IgA immune complexes induce fibrinolysis, which directly contributes to blister formation in DH, and results in chemotaxis of neutrophils and monocytes.[208,209] Accumulating FcαRI-positive neutrophils in the skin of DH had increased ability to bind IgA. As such, they presumably bind transglutaminase/IgA immune complexes and induce cellular activation contributing to tissue damage.[210,211] Released proteolytic enzymes by activated neutrophils can induce sub-epidermal split by cleaving adhesion molecules

such as collagen VII.[212] Circulating epidermal transglutaminase/IgA immune complexes have been detected in patients with DH which, together with disease manifestations, decrease over time after following a gluten-free diet.[213] Some DH patients also showed IgA immune complex deposition in the kidney, which ultimately can lead to IgA nephropathy (IgAN).[213]

Similar to DH, linear IgA bullous disease (LABD) is a skin blistering disease characterized by IgA autoantibodies against collagen XVII and FcαRI-mediated neutrophil activation.[214] It was shown in an ex vivo skin model that activated neutrophils in the presence of serum of LABD patients (containing anti-collagen XVII IgA) caused the separation of dermis from epidermis (Figure 4). This separation, reflecting blister formation in LABD patients, was prevented by blocking IgA-FcαRI interaction on neutrophils.[215] Additionally, eosinophil influx has also been observed in the skin of LABD, which may contribute to LABD pathology through FcαRI-mediated respiratory burst activity.[214,215]

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract and disruption of the epithelium. IBD can be subdivided into two major forms, ulcerative colitis (UC) and Crohn's disease (CD).[216] The etiology of IBD is ill-understood, but likely involves derailed immune responses against commensal bacteria. Fecal bacteria of patients with IBD, that were highly opsonized with IgA,induced colitis in germ-free mice.[217] Furthermore, fecal bacteria in IBD patients showed increased opsonization with IgA compared to healthy individuals, suggesting that leakage of serum IgA or dIgA through the disrupted epithelial layer contributes to enhanced opsonization.[217,218] In line with this, it was shown that IBD patients have increased levels of specific IgA against microbiota in their serum.[219] The percentage of IgA-opsonized bacteria in CD strongly correlated with multiple clinical indexes of disease activity and may therefore be useful for monitoring CD.[220] Due to the disruption of the intestinal epithelial barrier in these patients, bacteria are able to invade the sub-epithelial lamina propria and are likely opsonized with dIgA. This may subsequently induce neutrophil activation via FcαRI cross-linking, since uptake of IgA complexes by neutrophils was observed in the mucosa of patients with UC.[79] FcαRI-mediated neutrophil activation induces migration through the release of LTB4. It was therefore hypothesized that in UC patients a continuous neutrophil recruitment loop is initiated. Newly recruited neutrophils will be activated by IgA-opsonized bacteria and initiate a feedback loop of neutrophil chemotaxis, which eventually results in tissue damage.[79] Moreover, cross-talk of FcαRI and toll-like receptor 4 (TLR4) on neutrophils resulted in enhanced release of pro-inflammatory TNF-α, which plays a central role in IBD pathogenesis.[221,222] Excessive influx of neutrophils causing major tissue damage was demonstrated in UC patients.[222] As such, a role for IgA and FcαRI is proposed in especially UC, but their exact roles still need to be established.

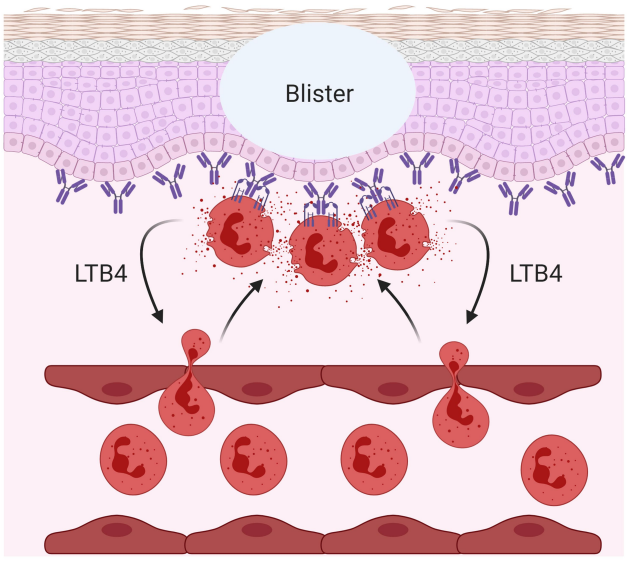

Figure 4 IgA-FcαRI induced pathology in skin blistering diseases. Cross-linking of FcαRI on neutrophils with IgA immune complexes results in the release of leukotriene B4 (LTB4) inducing enhanced neutrophil influx, causing tissue damage in a variety of inflammatory- and autoimmune diseases. An example is the blister formation in linear IgA bullous disease (LABD). Created with BioRender.com.

FcαRI and IgA: Therapeutic Opportunities

IgA Vaccination Strategies

Inducing pathogen-specific mucosal and systemic IgA through passive or active immunization may be an attractive strategy to combat bacterial and viral infections.[223] Licensed oral and nasal vaccines have demonstrated to induce mucosal SIgA responses as well as system responses contributing to protection.[223,224] Furthermore, mucosal application of the TB protein subunit vaccine H56/CAF01 followed by intramuscular priming induced high levels of antigen-specific lung mucosal and systemic IgA.[225] *Mtb*-specific IgA may contribute to prevention of TB, since

mucosally administered human IgA antibodies against *Mtb* in mice provided passive protection.[226] Additionally, vaccine-induced pulmonary SIgA in mice was associated with passive protection against TB.[134,227] Recombinant monoclonal antibodies (mAb), generated from single isolated B cells of untreated adult patients with acute pulmonary TB and from MTB-exposed healthcare workers, revealed that IgA against *Mtb* inhibited mycobacterial infection of human epithelial-like and macrophage-like cells, whereas IgG promoted infection.[126] Thus, it is suggested that IgA may be particularly important for protection against TB infection.[228] This is supported by experiments with human FcαRI transgenic mice, which had a lower *Mtb* infection rate compared to control WT mice after inoculation of human IgA mAbs, implicating an important role for FcαRI in clearing *Mtb* infection.[226] Nasal immunization with pneumococcal surface protein A (PspA) and cholera toxin as adjuvant elicited PspA-specific mucosal IgA and systemic IgG antibody responses, which provided protection against colonization of *S. pneumoniae* and pneumococcal infection in mice.[229] PspA-specific SIgA effectively neutralized colonized *S. pneumoniae*, diminished nasal carriage and prevented subsequent infection with *S. pneumoniae*. IgA-deficient mice failed to prevent nasal colonization by *S. pneumoniae*, in spite of having functional anti-PspA IgG antibodies in the nasal cavity, stating the necessity of specific IgA to prevent infection.[230]

Vaccine-induced IgA also provides effective protection against viral infections. Both the inactivated and the live-attenuated oral poliovirus vaccines, which played a tremendous role in the elimination of the poliovirus, induced potent-specific IgA responses.[231] Oral vaccines consisting of live attenuated rotavirus (RV) mediate significantly reduced disease. Serum rotavirus-specific IgA (RV-IgA) correlated with vaccine efficacy and protective immunity.[232] IgA knockout, as well as J-chain knockout mice, showed delayed viral clearance and absence of protective immunity, supporting the critical role of IgA in RV immunity.[233,234] Interestingly, in both humans and animals, RV-IgA can persist for a long time, suggesting the presence of long-lived IgA^+ plasma cells.[235] Similar to RV, it has been shown that vaccination with live attenuated poliovirus induced long-lived IgA memory immune responses in elderly.[236] Intravenous administration of polymeric IgA against influenza showed protection against infection in mice. Inhibition of influenza virus shedding by IgA was 10 times more effective than IgG.[237] Additionally, IgA antibodies against influenza A virus hemagglutinin, purified from respiratory tract washings of hemagglutinin immunized mice, were able to protect naïve mice from influenza infection.[238] Similar protective effects of IgA were shown in mice that received passive oral administration of IgA against reovirus-specific adhesion molecule sigma1, which prevented entry of reovirus into the Peyer's patches. Since IgG mAbs against sigma1 did not prevent Peyer's patch infection by reovirus, this effect was IgA specific.[239] Thus, inducing systemic and mucosal IgA responses through vaccination may play an important role in either passive or active protection against pathogens (Figure 5). Notably, the adjuvant alum, which is currently used in many injectable vaccines does not effectively induce IgA class-switching.[240] Newly developed mucosal adjuvants like TLR agonists and toxin derivatives (ADP-ribosyltransferase enterotoxins and adenylate cyclase toxins) are suggested to improve IgA responses in vaccination strategies.[241] Thus, inducing enhanced IgA responses through vaccination represents a promising therapeutic strategy for future vaccine development.

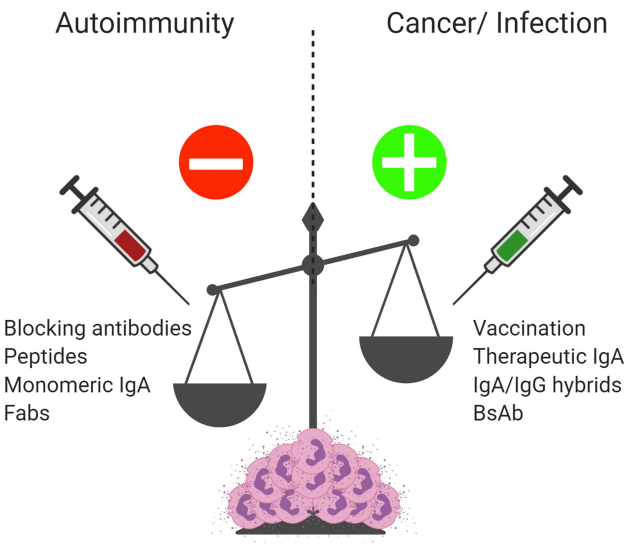

Figure 5 IgA and FcαRI as therapeutic targets. Enhanced IgA complexes or autoantibodies result in excessive activation of immune cells contributing to chronic inflammation and tissue damage in autoimmune diseases. Blocking IgA-FcαRI interactions by either monoclonal antibodies or peptides may reduce inflammation and tissue damage in these diseases. Treatment with monomeric IgA or anti-FcαRI Fabs may dampen immune responses by inducing inhibitory ITAM signaling and inhibiting IgG-induced phagocytosis and IgE-mediated allergic diseases. To combat bacterial and viral infections, inducing pathogen-specific IgA via passive or active vaccination may result in enhanced protective immunity. Enhancing pro-inflammatory responses by FcαRI-expressing immune cells via IgA monoclonal antibody therapy, bi-specific antibodies, or cross-isotype hybrid antibodies may result in efficient killing of tumor cells and represent a promising therapeutic opportunity for cancer patients. Created with BioRender.com.

Promoting FcαRI-Mediated Anti-Tumor Immunity

IgA or FcαRI bispecific antibodies have been proposed as novel drugs to treat cancer by enhancing activation of FcαRI-expressing immune cells.[242–245] Tumor cell killing by neutrophils was superior after targeting FcαRI, compared with targeting to IgG Fc receptors, which was demonstrated for several tumor antigens such as EGFR, HER2, EpCAM, HLA-II, CD20, CD30, and carcinoembryonic antigen.[242,245,246] Treatment of FcαRI transgenic mice with anti-tumor IgA mAbs against CD20, HER2, or EGFR resulted in enhanced migration of FcαRI-expressing immune cells and significantly increased anti-tumor cytotoxicity, which was mostly mediated by FcαRI-expressing macrophages.[243,247,248] However, in contrast to IgG, IgA mAbs cannot activate natural killer cells, which do not express FcαRI. Moreover, IgA is a poor complement activator and has a shorter half-life compared to IgG. IgA therapeutic antibodies that are produced in non-human systems contain different glycosylation profiles, which may also enhance immunogenicity and are likely to be cleared from the human circulation.[12] Alternatively, the efficacy of FcαRI bispecific antibodies targeting both tumor antigens and FcαRI has been investigated. FcαRI bispecific antibodies efficiently induced neutrophil migration in vitro, which was not observed after targeting Fcγ receptors.[249] Additionally, tumor cell killing was more effective.[250,251] Engineering of a cross-isotype antibody that contains merged Fc domain residues from IgG1 and IgA, combining the effector functions of both isotypes, mediated increased complement-dependent cytotoxicity and $Her2^+$ tumor cell killing by both neutrophils and macrophages.[252] Furthermore, it was shown that anti-epidermal growth factor receptor-2 IgG1/IgA2 cross-isotype antibodies induced increased recruitment of neutrophils, resulting in enhanced ADCC of human breast cancer cells by neutrophils.[253] Pharmacokinetics of IgG and IgA cross-isotype antibodies were similar to the parental IgG antibodies and may therefore augment IgG-based antibody therapies.[253] Thus, antibody-based strategies that target FcαRI represent a promising therapeutic opportunity for cancer patients (Figure 5).

Inhibiting FcαRI-Mediated Immunity

Naturally occurring serum IgA was shown to dampen immune responses by inducing ITAMi signaling via FcαRI (Figure 1A).[8] Enhancing ITAMi signaling by monovalent targeting of FcαRI has been proposed as a promising strategy to inhibit IgG-induced phagocytosis and IgE-mediated allergic diseases (Figure 5).[254] Monovalent targeting of FcαRI with the anti-FcαRI mAb A77 inhibited degranulation of RBL-2H3 transfected cells.[8] In in vivo models for allergic asthma and arthritis, FcαRI transgenic mice had reduced airway inflammation or resolution of arthritis after monovalent targeting of FcαRI.[254,255] Additionally, targeting of FcαRI by mAb A77 suppressed inflammation in transgenic mice with IgG immune complex-induced glomerulonephritis and obstructive nephropathy.[256] Renal inflammation induced by CpG dinucleotides (TLR9 agonist) in FcαRI transgenic mice was downregulated by monomeric targeting of FcαRI as well.[257] Thus, monomeric targeting of FcαRI was shown to induce anti-inflammatory properties, which could be used as treatment of inflammatory diseases with involvement of myeloid cells (Figure 5). Alternatively, blocking FcαRI with mAb MIP8a inhibited cytokine production, leukocyte recruitment, and inflammation in a lupus nephritis model.[258] FcαRI blocking also reduced NET release by neutrophils that had been stimulated with IgA immune complexes obtained from serum and synovial fluid of RA patients.[259] Similarly, in an ex vivo LABD skin model, FcαRI blocking with MIP8a prevented IgA-induced neutrophil-mediated blister formation.[215] In a recent study, peptides targeting the interaction sites of IgA and FcαRI were suggested as novel therapeutic strategy for IgA-mediated skin autoimmune diseases, as these peptides were able to penetrate into human skin ex vivo and reduced IgA-induced neutrophil migration.[260] As such, blocking FcαRI-IgA interactions represents a promising therapeutic strategy for IgA-associated inflammatory diseases and autoimmunity (Figure 5).

Concluding Remarks and Future Perspectives

IgA and FcαRI-mediated cell activation is important for maintaining homeostasis and preventing infections. SIgA contributes to passive immunity at mucosal surfaces by neutralizing pathogens, whereas active immunity is provided by dIgA and serum IgA through induction of FcαRI-mediated activation of myeloid cells. Future research regarding vaccination and infectious diseases should therefore also include serological and functional studies of IgA and FcαRI-mediated immune responses. It is becoming clear that the presence of overabundant IgA complexes or autoantibodies can result in excessive activation and recruitment of immune cells contributing to tissue damage and the development of

chronic inflammation in multiple diseases. A better understanding of the IgA-FcαRI axis in health and disease can provide multiple options for therapeutic interventions. On the one hand, immune responses against pathogens or cancer cells may be enhanced by vaccination or passive transfer of therapeutic IgA. On the other hand, initiating inhibitory ITAM signaling by monomeric targeting of FcαRI or blocking IgA-FcαRI interactions with mAbs or peptides can dampen inflammation and disease.

Highlights

- SIgA contributes to mucosal homeostasis and passive immunity through immune exclusion and by diversifying the gut microbiome
- Monomeric IgA induces inhibitory signaling, whereas active immunity is provided by complexed dIgA and serum IgA through cross-linking of FcαRI on myeloid cells
- Pathogen-specific IgA is associated with protection against infections
- Altered IgA glycosylation or excessive IgA immune complexes contribute to chronic inflammation and autoimmunity through FcαRI-mediated immune activation
- Understanding the IgA-FcαRI axis during infection and autoimmunity will provide new therapeutic opportunities.

Disclosure

The authors report no conflicts of interest for this work.

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