

The Role of IgA and IgA Fc Receptors as Anti-Inflammatory Agents

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Abstract

Materials and methods Serum monomeric immunoglobulin A (IgA) has powerful immunomodulatory roles in its ability to suppress immune responses. Monomeric IgA acts through Fc α RI, which plays a significant role in vivo in maintaining the integrity of immune responses by an inhibitory immunoreceptor tyrosine-based activation motif-mediated process and powerful inhibitory cellular effector mechanisms elicited by the IgA system.

Results Triggering of Fc α RI-mediated inhibitory function by Fab anti-Fc α RI-mediated inhibitory function is able to inhibit several inflammatory and autoimmune diseases including asthma and glomerulonephritis.

Conclusion The use of monomeric IgA as a therapeutic tool in human inflammatory diseases may offer much potential.

Keywords IgA · Fc receptor · inflammation · autoimmunity

Introduction

Immunoglobulin A (IgA) is by far the most abundantly produced isotype in humans and is differentially distributed

between the systemic and mucosal immune system. More IgA is produced per day (66 mg/kg/d) than all other classes combined [1, 2], notably at epithelial sites where most is lost daily within exocrine secretions as mucosal surfaces encompass more than 400 m². Serum IgA, the second most abundant isotype in the circulation, occurs mainly in a monomeric form (about 85% to 90% of total serum IgA) derived from bone marrow plasma cells [1], whereas secretory IgA (SIgA) is synthesized as a dimer by local plasma cells before being transported to mucosal surfaces through epithelial cells by the polymeric Ig receptor [3]. IgA displays a T-shaped structure, which differs from the common Y-shape of other immunoglobulins [4]. IgA is divided into closely related subclasses, IgA1 and IgA2, which basically differ by the absence of a 13-amino acid sequence in the hinge region of the IgA2 molecule [5].

Whereas SIgA antibodies are crucial for immune responses in the mucosal sites through a process known as immune exclusion, serum monomeric IgA (mIgA) is a poor player in systemic immune responses [6] and instead fulfills an anti-inflammatory role with its involvement in immune inhibition. Indeed, it has been demonstrated by several groups for more than two decades that in the absence of antigen serum, mIgA down-regulates IgG-mediated phagocytosis, chemotaxis, bactericidal activity, oxidative burst activity, and cytokine release [7–13]. The most striking supporting evidence for the inhibitory role of serum mIgA comes from patients with selective IgA deficiency [14]. In these patients, both IgA1 and IgA2 are usually markedly reduced or absent, although their levels of IgG and IgM may be normal or reduced. These patients show increased susceptibility to autoimmune and allergic disorders including arthritis, autoimmune endocrinopathies, chronic active hepatitis, ulcerative colitis, Crohn's disease, and autoimmune hematologic disorders.

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Role of Fc α RI in Immune Protection

The anti-inflammatory action of serum mIgA has been enigmatic until the discovery of the IgA Fc receptor type 1, Fc α RI. Fc α RI (CD89) is the only IgA Fc receptor expressed on blood myeloid cells including monocyte/macrophages, dendritic cells, Kupffer cells, neutrophils, and eosinophils [6]. Fc α RI plays a dual role in immunity (Fig. 1). Under physiologic conditions, it plays an essential anti-inflammatory role in immunity by allowing transmission of inhibitory signals following binding of serum mIgA [15]. By contrast, under pathologic conditions or during exacerbated immune responses, Fc α RI is aggregated by IgA-immune complexes. This leads to its activating state, where it performs several functions such as phagocytosis, cytokine release, antibody-dependent cellular cytotoxicity, superoxide release, and antigen presentation [6]. Fc α RI can bind IgA1 and IgA2 with moderate affinity ($K_a \sim 10^6 \text{ M}^{-1}$) in the boundaries of CH α 2 and CH α 3 domains. Whereas polymeric IgA and IgA immune complexes bind with a greater avidity [16], mIgA binding to Fc α RI was found to be transient *in vitro* using surface plasmon resonance approaches. It seems reasonable, however, to assume that in the presence of high concentrations of circulating mIgA ($\sim 2 \text{ mg/mL}$), Fc α RI may be constantly occupied. Indeed, there is some evidence in the literature that IgA can be detected on the surface of monocytes and neutrophils, which was initially described as cytophilic IgA [17, 18].

Recently, we demonstrated for the first time that monovalent targeting of Fc α RI, either by mIgA or by anti-Fc α RI Fab, inhibits IgG-mediated phagocytosis in human monocytes [15]; this explains previous inhibitory

functions of serum IgA [7–13]. More importantly, we have been able to show that Fc α RI-mediated inhibition was not mediated by conventional inhibitory motifs such as the immunoreceptor tyrosine-based inhibition motif (ITIM). Indeed, Fc α RI does not contain any ITIM in its cytoplasmic tail but can be expressed with or without physical association to the Fc receptors (FcR) γ adaptor [19]. Whereas γ -less Fc α RI recycles monomeric IgA and plays an essential role in mIgA homeostasis, FcR γ -associated Fc α RI mediates either activating or inhibitory responses [15]. This dual-function receptor operates based on the type of ligand, multimer, or monomer. Both opposite functions were mediated by the FcR γ adaptor, which contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic tail. These data might explain why Fc α RI has been found to be a unique member of the FcR family.

Analysis of the three-dimensional structure of Fc α RI reveals that it binds IgA in a manner different from other Ig isotypes. Its two Ig-like domains are oriented at right angles, and two Fc α RI molecules can bind 1 IgA molecule within the EC1 domain, at a site completely different from the other FcRs. This yields a 2:1 stoichiometry compared with the 1:1 stoichiometry of IgE and IgG to their FcRs [20]. The Fc α RI gene is not located in the FcR gene cluster but in chromosome 19, inside the leukocyte receptor cluster (LRC). Fc α RI is distantly related to other FcRs, being more homologous to LRC-encoded activating and inhibitory receptors [21]. Taken together, our findings allow the definition of a new inhibitory motif: the inhibitory ITAM or ITAMi [22]. ITAMi signaling results from an inhibitory configuration of the ITAM present within an activating receptor [22]. These configurations (activating vs. inhibitory)

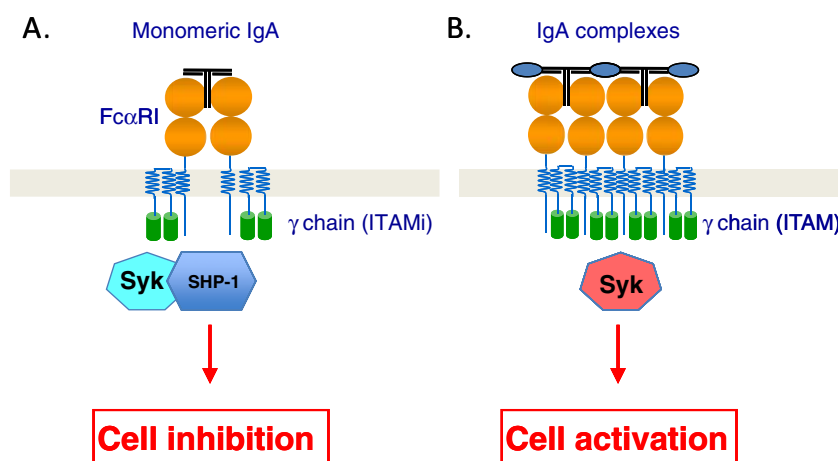


Fig. 1 Dual role of Fc α RI in the immune system. **a** Monomeric IgA binds to FcR γ -associated Fc α RI and promotes partial phosphorylation of the FcR γ . This induces an inhibitory ITAM (ITAMi) configuration, which results in sequential recruitment of Syk (partial activation) followed by recruitment of SHP-1 phosphatase. This process allows

for cell inhibition such as inhibition of heterologous receptor activation by external agents. **b** IgA-immune complexes lead to enhanced IgA binding to Fc α RI on blood myeloid cells. Cell activation then occurs through crosslinking of transmembrane FcR γ -associated Fc α RI and recruitment of Syk and other activating effectors

were dependent on the way the ITAM-containing receptor interacted with its ligand. In the case of Fc α RI, although highly multimeric interaction induced an activating signal, interactions of the receptor with ligands binding at low valency such as mIgA or anti-Fc α RI Fab fragments produced an inhibitory response. Indeed, the 2:1 stoichiometry of Fc α RI/mIgA interaction can lead to receptor dimerization. This dimeric interaction generates an inhibitory signal, in contrast to the signal induced by multimeric receptor aggregation. The inhibitory signal was also generated with anti-Fc α RI Fab fragments, which in principle should target the receptor in a monomeric fashion. Thus, the inhibitory signal may also be generated by a conformational change upon Fab binding.

Specific targeting of the ITAM-containing receptor with a weakly binding ligand (low affinity, low avidity, low valency) favors the recruitment of a signaling effector such as the phosphatase SH2-homology-containing protein-tyrosine phosphatase (SHP)-1 that has inhibitory potential instead of activation signal-promoting kinases. The prototype receptor for such a mechanism is Fc α RI upon interaction with anti-Fc α RI Fab or mIgA. Indeed, in contrast to highly multimeric ligation, which leads to a strong src-kinase-mediated phosphorylation of FcR γ and recruitment of Syk [23], interaction with these low-valency ligands induces only scant ITAM phosphorylation, thereby favoring the recruitment of SHP-1 phosphatase instead of Syk [15, 24].

At present, the mechanism favoring phosphatase recruitment seems to depend on low-level recruitment of Syk and weak ITAM phosphorylation. Yet, they do not seem to depend on a particular tyrosine residue because mutation of either tyrosine residue in the FcR γ ITAM in a chimeric Fc α RI-FcR γ receptor did not support ITAMi signaling [15]. However, SHP-1 recruitment is further positively regulated by the MAPKinase extracellular signal-regulated kinase (ERK). ERK inhibitors abrogated ITAMi signaling and SHP-1 recruitment while only minimally affecting cell activation [15].

Monomeric IgA as a New Immunotherapeutic Tool

Despite considerable progress in research, the mechanisms of the beneficial action of intra venous immunoglobulin (IVIG) are still not completely understood. This is due likely to the involvement of multiple mechanisms [25]. Given the clear evidence for the participation of activating FcR, the mechanisms may also include ITAMi-initiated anti-inflammatory actions. To test the potential therapeutic actions of ITAMi signaling directly, we used several experimental inflammatory disease models and investigated whether ITAMi-induced signaling through Fc α RI could prevent disease development.

Such an inhibitory function was tested first in an asthma model using transgenic (Tg) mice expressing human Fc α RI on myeloid cells [15]. Following immunization with IgE immune complexes, Fc α RI⁺ Tg mice developed bronchial hyperreactivity after combined antigen/methacholine challenge. Symptoms were considerably reduced when mice had been pretreated with anti-Fc α RI Fab that initiate ITAMi signaling, but not after pretreatment with irrelevant control Fab antibodies. At the same time, the perivascular and peribronchial inflammatory infiltrate was significantly reduced in anti-Fc α RI Fab-treated mice as revealed by histology of lung tissue [15].

We also tested the therapeutic potential of anti-Fc α RI Fab treatment in kidney inflammation models such as immune-mediated glomerulonephritis and nonimmune obstructive nephropathy. Whereas receptor crosslinking aggravated these diseases, anti-Fc α RI Fab treatment was beneficial and reduced inflammatory cell infiltration and fibrosis development [24]. Interestingly, direct analysis of patient cells showed that this treatment can prevent the activation of monocytes from both healthy subjects and patients who were induced by several stimuli including lipopolysaccharide, tumor necrosis factor α , and Monocyte chemotactic protein-1 (MCP-1) [24].

These findings point to a crucial role of ITAMi signaling in the control of multiple heterologous or autologous inflammatory responses. They also identify anti-Fc α RI Fab as a new potential therapeutic tool to prevent the progression of renal inflammatory diseases. Further studies are required to determine whether, similar to IVIG, intravenous mIgA treatment may also be beneficial to prevent or reverse an established inflammatory disease.

Conclusions

IgA and Fc α RI play a significant role in vivo in maintaining the integrity of immune responses by an ITAMi-mediated process and powerful cellular-effector mechanisms elicited by the IgA system. The consequences of favoring a long-lasting dampening of immune responses support the potential of IgA and anti-Fc α RI Fab as therapeutic tools in human inflammatory diseases.

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