

Active control of mucosal tolerance and inflammation by human IgA and IgG antibodies



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Key words: *Fc receptor, antibodies, inflammation, tolerance, allergy, inflammatory bowel disease, chronic rhinosinusitis, dendritic cells, epithelial cells*

The antibody repertoire at mucosal sites consists mostly of IgA and IgG and is tailored to the individual's microbiome.¹ Recently, a series of findings uncovered new functions of antibodies that demonstrate that antibodies actively control human mucosal immunity. Both human IgA and IgG (and their different subclasses) are able to suppress or amplify the production of proinflammatory and anti-inflammatory cytokines and chemokines in a wide range of mucosal cell types, including immune cells and epithelial cells.^{2–5} This antibody-induced control of cytokine production is predominantly mediated by the antibody receptors FcαRI (recognizing IgA) and FcγRs (recognizing IgG). Antibody control of mucosal tolerance or inflammation is dependent on intricate compartment-specific activation (schematically summarized in Fig 1, A and B).

IgA and IgG antibodies are thought to provide environmental cues, which appear to depend on 3 conditions, that is: (1) the presence of soluble antibodies versus immune complexes (ICs); (2) the absence or presence of a “second signal” (mostly from microorganisms); and (3) the location/compartment of the antibodies. The first environmental cue is the presence of either soluble (unbound) antibodies or ICs, of which the latter are formed when microorganisms or other antigens are bound by antibodies. Under homeostatic conditions, immune cells located in the lamina propria are mainly surrounded by unbound soluble IgA and IgG that bind to FcRs with relatively low affinity. This low-affinity binding induces an inhibitory signaling pathway known as inhibitory immunotyrosine-based activation motif signaling, which provides immune suppression and/or tolerance by promoting anti-inflammatory and suppressing proinflammatory cytokine production⁶ (Fig 1, A). Alternatively, the binding of antibodies to their antigen leads to the formation of ICs. Whether these ICs induce tolerance or inflammation depends on the second

condition, that is, the absence or presence of a second signal. In the absence of additional signals, for example, in the case of antibody-opsonized food antigens, the recognition of antibody ICs by FcRs facilitates the uptake of antigens, but does not evoke any proinflammatory responses (Fig 1, C). This is instrumental in the induction of immune tolerance, for example, by providing tolerance to food antigens (such as egg and peanut) by intestinal dendritic cells.⁷

In stark contrast, during infection, antibody-opsonized microorganisms invade the lamina propria (Fig 1, B). This will not only activate FcRs on immune cells but will simultaneously also trigger pathogen-sensing receptors such as Toll-like receptors (TLRs), thereby providing a second signal to the same cell. Consequently, FcRs and TLRs engage in cross-talk that is dependent on the kinase Syk, which breaks the otherwise tolerogenic response of immune cells and epithelial cells by eliciting large amounts of proinflammatory cytokines and chemokines.^{3,4} This appears to serve a physiological function by enabling the mucosal immune system to discriminate between harmless commensals and invading pathogens. Because of the high load of TLR-activating microbial structures from commensal bacteria that reach the lamina propria under steady-state conditions, mucosal immune cells are generally tolerogenic to these structures. Because both commensals and invading pathogens often express similar antigens, the recognition of microbial structures by TLRs and other pathogen-sensing receptors falls short to explain how the mucosal immune system can discriminate commensal from invading bacteria. An IgA/IgG antibody-dependent mechanism may fill this void, by providing an environmental cue that indicates infection. However, this also depends on a third condition, that is, the compartment-specific presence of antibody ICs. IgA and IgG isotypes are differently compartmentalized under homeostatic conditions compared with infection. Under steady-state conditions, IgA-ICs (ie, IgA-opsonized microorganisms) are scarce in the lamina propria, but become very high on invasion by microorganisms. Inversely, under steady-state conditions, IgG is mostly found in the lamina propria, but breaching of the epithelial layer will strongly increase IgG concentrations in the lumen, leading to IgG opsonization of luminal microorganisms. Ultimately, the combination of complex formation, cross-talk with other receptors, and the change in compartmentalization induces a vigorous immune response that (temporarily) breaks mucosal tolerance to counteract infections (schematically summarized in Fig 1, A and B). For example, the recognition of IgA-ICs in the intestinal lamina propria by FcαRI drastically converts the tolerogenic phenotype of human intestinal dendritic cells into a proinflammatory phenotype, which induces protective immunity by activating antibacterial TH17 and type 3 innate lymphoid cell responses⁴ (Fig 1, B). A similar phenomenon occurs in nasal and lung epithelial cells, where activation of FcγRIII by IgG-ICs in

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 20, 2020; revised April 24, 2020; accepted for publication April 28, 2020.

Available online May 5, 2020.

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J Allergy Clin Immunol 2020;146:273–5.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2020.04.032>

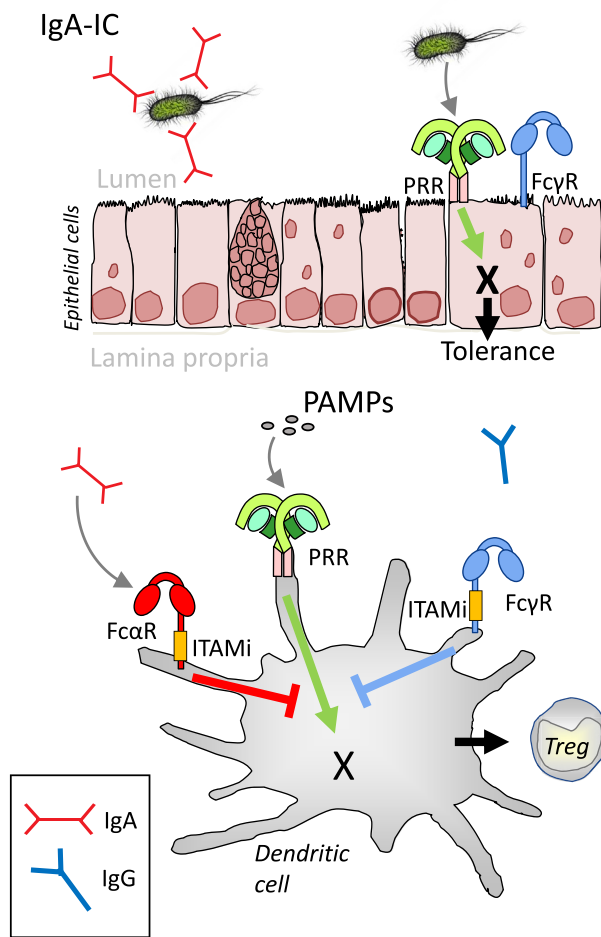
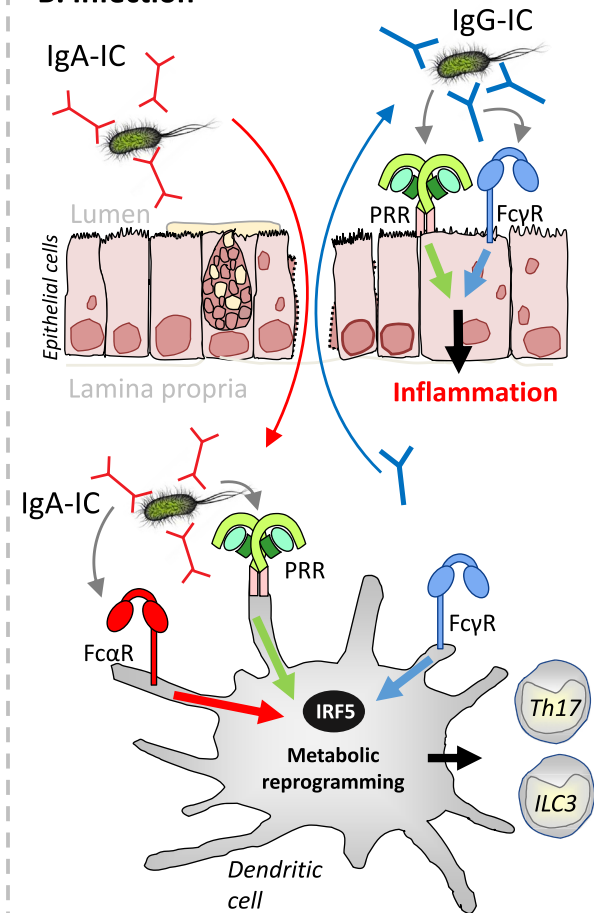
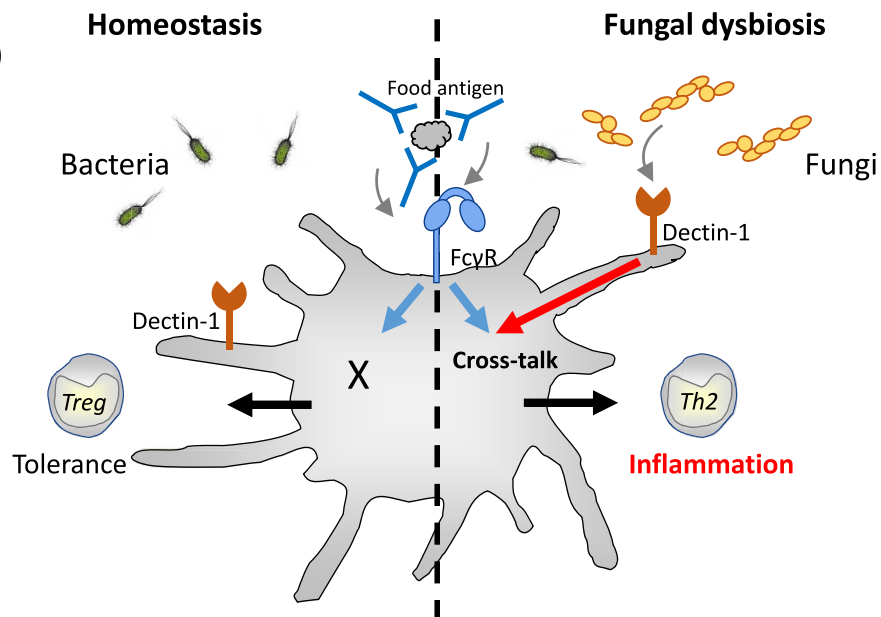
A. Homeostasis**B. Infection****C. Allergy (hypothesis)**

FIG 1. Active control of mucosal tolerance and inflammation by IgA and IgG antibodies. Mucosal IgA and IgG antibodies shape immune responses during homeostasis, infection, and allergy. **A.** Mucosal surfaces are colonized by commensal bacteria. Epithelial cells can sense these bacteria through PRRs such as TLR4, but isolated TLR4 stimulation results in tolerance. DCs express various PRRs, and their binding by microbial components (PAMPs) promotes tolerance through activation of Treg cells. ITAMi signaling induced

the lumen breaks the tolerance of epithelium to commensal gram-negative bacteria³ (Fig 1, B).

Unfortunately, erroneous activation of this mechanism may lead to pathology by skewing the balance toward (chronic) inflammation. For example, increased anticomensal IgG contributes to intestinal inflammation in patients with ulcerative colitis.² In addition, in patients with chronic rhinosinusitis with nasal polyps, the IgG/FcγRIII-induced pathway is constitutively active in polyp epithelium, leading to breaking of tolerance to commensal bacteria.³ Interestingly, IgA subclasses have recently been identified to be associated with disease activity, with IgA₂ inducing more vigorous inflammatory responses than IgA₁, which is related to IgA glycosylation differences that may activate additional receptors.⁸ For future research, it would be valuable to assess whether these differences in inflammatory capacity also hold true for the 4 IgG subclasses, which also display extensive variability in glycosylation and FcR-binding affinity.

It is still a paradox how IgA/IgG antibodies promote inflammation in the context of allergy. For example, antifood antibodies would be expected to induce tolerance,⁷ because FcR activation in the absence of a second signal such as bacteria-sensing TLRs generally leads to immunosuppression (Fig 1, C). An explanation to this paradox may be provided by fungal dysbiosis, which can aggravate allergic airway disease.⁹ Overgrowth of fungal species such as *Candida albicans* leads to activation of receptors such as Dectin-1 on mucosal immune cells, which is known to promote T_H2 responses and consequent exacerbation of allergic airway inflammation.⁹ Therefore, fungi may provide an aberrant microbial second signal that, when combined with FcR activation, would lead to exacerbation of T_H2-dependent allergic responses (Fig 1, C). Intriguingly, similar to FcRs, most fungi-recognizing receptors signal through Syk, suggesting that the combination of IgA/G-ICs and fungal dysbiosis could amplify (excessive) activation of type 2 immunity in the lungs by overactivation of the Syk pathway or by lowering its threshold for activation.

The identified involvement of aberrant FcR responses in various chronic inflammatory disorders could provide new therapeutic opportunities by counteracting antibody-induced inflammation. One of the proteins that appears to play a crucial role in shifting the balance from tolerance to inflammation by FcRs is the transcription factor IRF5 regulatory factor 5 (IRF5). Interestingly, IRF5 genetic polymorphisms have long been known to be associated with inflammatory bowel disease.⁵ Recently, it

was identified that IgG-induced inflammation by FcγRIIIa critically depends on IRF5, which strongly amplifies gene transcription and gene translation of key proinflammatory cytokines.⁵ Interestingly, this depends not only on the function of IRF5 as a transcription factor but also on the additional function of IRF5 to induce metabolic reprogramming of immune cells.⁵ These findings suggest that IRF5 may be an interesting therapeutic target. However, although reducing IRF5 expression indeed attenuates colitis, it also impairs the clearance of intestinal pathogens,¹⁰ underlining its crucial role in balancing host defense and chronic inflammation. Therefore, further investigation and identification of the underlying molecular mechanisms of (aberrant) antibody-induced inflammation may be highly valuable to find new targets for treatment.

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by unbound IgA and IgG actively supports DCs tolerance. **B**, During infection, IgA and IgG promote a switch from tolerance to inflammation. A breach in the epithelial barrier translocates IgG to the lumen. IgG-ICs bind FcγRIII on epithelial cells, and with TLR costimulation activate inflammatory mechanisms. In the intestine, IgA-IC translocation to the lamina propria occurs. Both IgA-ICs and IgG-ICs help to switch the tolerogenic response of intestinal DCs to activation of T_H17 cells and ILC3. IRF5 is a key protein in DCs and macrophages for shifting from tolerance to inflammation. **C**, Hypothesized mechanism of the role of mucosal antibodies in allergy. Under homeostasis (left), allergen-specific antibodies bind FcRs in absence of other signals, resulting in Treg-cell activation and tolerance. Overgrowth with pathogens such as fungi could provide an aberrant second signal through costimulation of fungi-sensing receptors such as Dectin-1, converting the tolerogenic response into an inflammatory response. *FcαR*, Fc alpha receptor; *FcγR*, Fc gamma receptor; *ILC3*, type 3 innate lymphoid cell; *ITAMi*, inhibitory immunotyrosine-based activation motif; *PAMP*, pathogen-associated molecular pattern; *PRR*, pattern-recognition receptor; *Treg*, regulatory T cell.