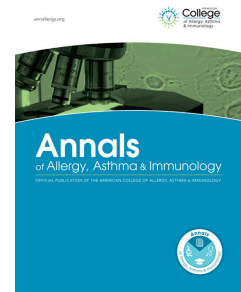


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## The Role of Immunoglobulin A in Oral Tolerance and Food Allergy

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### Abbreviations:

GI – gastrointestinal tract  
IgA – Immunoglobulin A  
GALT - Gut-associated lymphoid tissue  
M Cells - Microfold cells  
TGF- $\beta$  - transforming growth factor beta  
BLG -  $\beta$ -lactoglobulin  
DC - Dendritic cell  
CM – Cow's milk  
IL-10 - Interleukin 10  
PP – Peyer's patches  
Naïve T - naïve T cell  
Treg- regulatory T cell  
Tfh - T follicular helper cell  
Mast- mast cell.

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Tables: None

1 Mucosal surfaces, which are frequently exposed to external antigens, are a major part of the  
2 immune system. The development of oral tolerance is a result of a complex interplay between a  
3 variety of innate and adaptive immune functions; deficiencies in these mechanisms may  
4 contribute to the development of allergic disorders. Although regulatory T cells have a clear role  
5 in enforcing oral tolerance, the role of the dominant immunoglobulin in the gut, immunoglobulin  
6 A (IgA), is less clear. This perspective will focus on IgA and its role in tolerance to oral antigens  
7 and development of food allergies.

8  
9 IgA is the most abundantly produced antibody isotype and has two subsets, IgA<sub>1</sub> and IgA<sub>2</sub>, of  
10 which IgA<sub>2</sub> predominates in colonic secretions.<sup>1</sup> It exists primarily in two forms: monomeric IgA  
11 in the serum and polymeric IgA in the mucosal surface. Secretory IgA is predominantly dimeric,  
12 with two monomers, of the same subsets, connected via a J chain and associated with secretory  
13 component. Gut-associated lymphoid tissue (GALT), composed of Peyer's patches (PP) and  
14 other aggregates of lymphoid tissue, located throughout the intestine, are composed primarily of  
15 B lymphocytes, with a lesser amount of T lymphocytes, myeloid cells and innate lymphoid cells.  
16 Antigen is sampled via transcytosis through microfold cells (M cells), goblet cells, and  
17 macrophages and dendritic cells (DC); DCs in PPs and mesenteric lymph nodes (MLNs) present  
18 antigen and guide antigen-specific IgA development, which is promoted by transforming growth  
19 factor beta (TGF- $\beta$ ), retinoic acid, and interleukin 10 (IL-10).<sup>1</sup> Polymeric IgA, as well as IgM, is  
20 excreted into the gastrointestinal lumen and other mucosal surfaces via transcytosis through the  
21 polymeric immunoglobulin receptor.<sup>1</sup>

IgA is thought to have a variety of functions to maintain the epithelial barrier and promote intestinal homeostasis. One of the main forms of mucosal defense is immune exclusion, which limits bacterial colonization and penetration of antigen through the epithelial surface.<sup>1</sup> Immune exclusion is accomplished primarily through secretory IgA, which can trap antigen. This, along with intestinal peristalsis, defensins, and mucin, results in removal of antigen from the epithelial surface and hindrance of potential immune responses. IgA also allows for intestinal homeostasis by shaping the composition of commensal micro-organisms.<sup>1</sup> Given these demonstrated roles of IgA in the gut to microbes and toxins, it is presumed that IgA might also promote oral tolerance to food antigens.

The role of IgA in the development of atopic disorders has been investigated by examining patients with selective IgA deficiency. Results have been mixed but overall show that those with IgA deficiency or a delay in IgA production (due to immune system immaturity) are at an increased risk of atopic disorders, but there is limited data for food allergy. Systemic versus mucosal IgA production have different dynamics, with IgA production initiating in the first weeks of life in the gut after exposure to foreign antigens such as the commensals, but serum IgA responses mature slowly in the first 2 years and then more rapidly. Clinical studies have examined the association between mucosal IgA, measured as fecal or salivary IgA responses, and development of atopy, with conflicting results. Limited data suggest that in immune competent hosts (in whom IgA responses are intact), mucosal IgA was associated with tolerance to foods whereas elevated systemic IgA indicated increased level of sensitization. Clinical discoveries suggest that IgA may be involved in the development of tolerance overtime. IgA<sub>2</sub> may counteract IgE responses in egg allergy in children who naturally “outgrew” their allergy

46 compared to those who did not<sup>2</sup>, although more recent findings are conflicting. Upregulation of  
47 specific IgA (along with IgG) has been seen in those with clinical response to oral and sublingual  
48 food immunotherapy. It is not known whether mucosal IgA is an epiphenomenon (i.e. secondary  
49 effect) seen in development or loss of oral tolerance due to antigen exposure (resulting in  
50 specific IgA) or inflammation (resulting in non-specific IgA), or whether IgA plays a causal role  
51 in food allergy. While IgA can play a role in immune exclusion, other mechanisms may be  
52 involved, such as IgA control of gut microbiota and homeostasis or a modified response elicited  
53 by targeted antigen uptake as immune complexes<sup>1</sup> (**Figure 1**). Mechanistic work on the role of  
54 mucosal IgA in food allergy and oral tolerance is needed, but studies in humans are challenging.  
55 In our work, we found little induction of food-specific IgA in the gut through oral exposure  
56 unless an adjuvant is co-administered with the food<sup>3</sup>, which is consistent with a number of  
57 published mouse models using different food antigens. This suggests that IgA is not a part of  
58 steady state oral tolerance in mice and highlights that a better mechanistic understanding of IgA-  
59 inducing factors in the gut is needed.

60  
61 Limited human data into the potential role for IgA as an active component promoting oral  
62 tolerance come from studies assessing the association of human milk IgA to food allergy.  
63 Antibodies in breast milk are the result of exposure to antigens in the maternal gut, as B cells in  
64 the mammary gland migrate from the intestine (via “enteromammary link”) and other mucosal  
65 surfaces. Those studies found that maternal cow’s milk (CM) avoidance resulted in lower levels  
66 of CM-specific IgA in human milk and lower CM-specific IgA was associated with the  
67 development of CM allergy<sup>4</sup>. In this report we showed that human milk IgA may decrease  
68 transcytosis of CM antigens in a gut epithelial cell model enhancing immune exclusion. In an

animal model, we showed that breast milk IgA may contribute to targeted peanut antigen uptake to the Peyer's patches.<sup>5</sup>

The maintenance of oral tolerance is an important and necessary function of the immune system and disruption is thought to play a role in the development of allergic hypersensitivities, such as food allergies. How exactly systemic and mucosal IgA responses contribute to development of oral tolerance versus sensitization to foods is unknown and an area of active investigation. A deeper understanding of these mechanisms would not only provide a better understanding of the gut immune system but may ultimately lead to advancements in allergy prevention and treatment.

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**Figure 1. Mechanisms by which IgA may ameliorate the risk of food allergy.**

Left: Food-specific IgA may lead to immune exclusion, targeted uptake by PP, and shape microbiome, promoting tolerance. Right: Without food-specific IgA, food antigen may be taken up and presented under conditions that promote IgE sensitization.

## With IgA

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## Without IgA

