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# Regulation of oral antigen delivery early in life: Implications for oral tolerance and food allergy

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## Abstract

The increasing incidence of food allergy remains a significant public health concern. Food allergy is partially due to a lack, or loss of tolerance to food allergens. Clinical outcomes surrounding early life practices, such as breastfeeding, antibiotic use, and food allergen exposure, indicate the first year of life in children represents a unique time for shaping the immune system to reduce allergic outcomes. Animal models have identified distinctive aspects of when and where dietary antigens are delivered within the intestinal tract to promote oral tolerance prior to weaning. Additionally, animal models have identified contributions from maternal proteins from breastmilk and bacterial products from the gut microbiota in regulating dietary antigen exposure and promoting oral tolerance, thus connecting decades of clinical observations on the benefits of breastfeeding, early food allergen introduction, and antibiotic avoidance in the first year of life in reducing allergic outcomes. Here we discuss how exposure to gut luminal antigens, including food allergens, is regulated in early life to generate protective tolerance and the implications of this process for preventing and treating food allergies.

### Keywords

Regulatory T cells; oral tolerance; allergy; early life

## Introduction:

Allergic diseases are a heterogeneous set of disorders characterized by T helper type 2 (Th2) immune responses to harmless environmental antigens, also known as allergens. Food allergy affects 8% of young children and 10% of adults in the United States, numbers that represent a significant increase over the past forty years[1–3]. Polymorphisms in genes related to the generation of Th2 responses are known risk factors for the development of allergy[4],

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but changes in genetics alone is insufficient to explain this rapid increase. Allergic disorders are increased when individuals migrate from countries with a low prevalence of allergies to one with a high prevalence of allergy[5], providing strong support for environmental contributors to the risk of allergic outcomes. However, identifying and defining the role of these environmental contributors has been difficult in part due to the time-limited nature of some of the risks or benefits conferred by these environmental exposures.

There is a growing appreciation that allergies may in part be due to loss, or lack, of tolerance to allergens. Food allergies in particular remain a significant public health concern, with exposure to allergens in affected individuals resulting in clinical symptoms ranging from mild urticaria to severe anaphylaxis. Although allergy to any type of food is possible, the most common food allergies in the United States are to peanut, fish, egg, wheat, milk, tree nuts, and soy[1,2]. In the healthy individual, the immune system develops tolerance to dietary antigens to blunt potential inflammatory responses. This process, termed oral tolerance, is largely mediated via the development of dietary antigen specific Foxp3+ T regulatory cells (Tregs). Treg dysfunction contributes to allergic disorders, as children with allergy have deficiencies in Tregs[6,7] and Treg deficiency in mice results in immune skewing reminiscent of an allergic phenotype[8]. The majority of food allergies are acquired during the first few years of life[9], drawing significant interest in how early life events, including antibiotic use and breastfeeding, impact the development of tolerance and allergy later in life. Recent human and animal studies support that there is a critical window of time in early life for the introduction of food allergens to promote tolerance and to decrease the risk of food allergy. Here we will review these observations supporting the existence of this period in early life.

## The case for early life food allergen exposure

In sensitized individuals, food allergy manifests as dietary antigen specific IgE response leading to mast cell degranulation, Th2 responses, and clinical symptoms. Due to the fact that exposure to and introduction of food allergens can be controlled, food allergy is potentially the allergic disorder most amenable to dissecting environmental contributors to allergic outcomes. Despite this advantage, it is has taken decades to determine if and when food allergen introduction is beneficial. The current standard of care for food allergy is avoidance of food allergens, and because food allergy more commonly affects children, childhood feeding recommendations included food allergen avoidance in at risk children until recently. In the 1970s more than 70% of American babies were formula-fed, a practice that remained popular until the turn of the century. During this time allergic disorders, including food allergy continued to rise, suggesting that formula-feeding may be contributing to food allergy risk. This, as well as other potential benefits of breastfeeding, and the lack of suitable refrigeration of formulas in third world countries, prompted the resurgence of breastfeeding and the 2001 World Health Organizations recommendation for exclusive breastfeeding for the first six months of life. However, a 2011 retrospective analysis of children whose mothers followed this recommendation found that food allergies actually increased in exclusively breastfed children[10]. Concurrent with this, observational studies found that children consuming peanuts early in life had reduced peanut allergy[11], prompting trials that demonstrated that early introduction of peanut into the diets of susceptible children between the age of 4 and 11 months decreased the rates of allergy

development by 5 years of age[11–15]. Other studies showed similar associations of early introduction of solid food, including allergens other than peanuts, with reduced risk of food allergies[16–19]. Thus, decades of studies finally arrived at the recommendations of early food allergen consumption as protective for food allergy, yet why these benefits were restricted to this time in life remained unclear.

## Early life factors promoting tolerance and avoiding allergy

Insights into why early introduction of food allergens is protective come from observations that the benefits of early exposure to allergens are not restricted to the child's consumption of allergens. Recently, the role of maternal peanut consumption during breastfeeding and the early introduction of peanut allergen were examined more closely. This study revealed that the lowest incidence of peanut allergy by seven years of age occurred if the mothers both 1) consumed peanuts while breastfeeding and 2) introduced peanuts into the diet of their children before 12 months of age[20]. Of note, the rates of sensitization to peanut by seven years of age was increased if breastfeeding mothers did not introduce peanut into the diets of their children by this 12 month time point, yet again suggesting a critical role for the early introduction of antigen for the best development of oral tolerance to foods such as peanuts. Other studies found that the benefit of early introduction of a food allergen was most apparent in children who were breastfed[21]. Thus, complimentary breastfeeding and dietary antigen introduction provided the maximal benefit of early food allergen introduction in decreasing food allergy[20,21], even without continual exposure to the food allergen[12].

### Breastfeeding

Additional insights into the benefits of breastfeeding come from mouse models which have shown complexes of maternal IgG antibodies and dietary antigens in the breastmilk are potent inducers oral tolerance and help prevent future allergic disorders[22,23]. Free antigens not bound in maternal IgG complexes were also able to induce tolerance in the presence of TGF-β, a cytokine present in the breastmilk with potent tolerogenic properties[22,24]. Further, breastfeeding is associated with significantly reduced risk of other atopic conditions in children, including asthma, eczema, and allergic rhinitis[25]. As children with food allergy are significantly more likely to have other atopic conditions[26], breastfeeding may confer similar protective effect to the reduced risk of multiple types of allergic disorders regardless of the environmental antigen.

### Microbial exposure

Multiple observations indicate that exposure to microbes, and in particular gut microbes, is protective of allergy. Decreased exposure to microbes is associated with increased allergic outcomes in humans[27–29], and germ free mice are Th2 skewed[30,31]. This protective role does not extend to all microbes. Dysbiosis of the gut microbiota is associated with allergy and only specific bacterial taxa from the gut microbiota protect against an allergic phenotype in mice[32,33]. Interestingly the protective effects of specific gut bacteria on the allergic phenotype may be most pronounced in early life. A recent systematic review pinpointed the association of antibiotic use and development of childhood allergy to the first 6–12 months of life[34]. Cephalosporin use was associated with an increased risk of cow's milk

allergy (CMA) development[35], and cohort studies revealed patients with CMA were found to have significant intestinal microbial dysbiosis compared to healthy controls, with healthy children having increased levels of *Clostridial* species, which were critical for the protection against an allergic response to food[33]. Further supporting the importance of this period in life for protective effects of the gut microbiota on allergic outcomes, children with allergic outcomes later in life had a transient dysbiosis of the gut microbiota in the first 100 days of life[36]. Other environmental factors that correlate with reduced risk of allergic disorders include exposure to a domesticated pet, such as a dog or cat[37,38], which could impact the development of the gut microbiota in early life[39]. During early life, the pioneering microbiota in the neonate develops and matures into the microbiota found after weaning[9,40]. Breastfeeding, aside from having direct beneficial effects on protection from allergy, also contributes to early microbial colonization by providing a number of nutrients such as maternal IgA, human milk oligosaccharides (HMOs), and lactoferrin which help shape microbial communities in the neonate[41–44]. The combination of environmental factors such as breastfeeding, domestic pets, and avoidance of antibiotics all converge to facilitate the development of a healthy intestinal microbiota that is protective of allergic outcomes.

## Establishing Oral Tolerance:

Over the past decade, multiple lines of work have converged to connect mechanisms regulating exposure to antigens and the necessity of the commensal microbiota in establishing oral tolerance. Tregs expressing the transcription factor Foxp3, have been shown as indispensable players in oral tolerance by suppressing subsequent immune responses[45]. Tregs that are raised against dietary or microbial antigens are peripherally derived Tregs (pTregs) that differentiate extrathymically in the lymph nodes draining the gut[45,46]. During their generation in the gut draining lymph nodes, these pTregs become preferentially imprinted with gut homing molecules allowing them to localize in the intestinal lamina propria[47]. The intestinal lamina propria contains a large population of Tregs, including pTregs induced in the gut draining lymph nodes, due in part to the favorable environment for inducing pTregs[48]. Notably, TGF-β present in the intestine, as well as retinoic acid (RA) from the diet, and microbial metabolites such as butyrate and other short-chain fatty acids are critical factors in the induction of Foxp3+ Tregs[49–52]. Tregs present in the intestine are potent suppressors of future inflammatory responses including food allergies and colitis driven responses against commensals[53].

### M cells and Peyer’s patches

Importantly, the induction of pTregs requires the acquisition, processing, and presentation of the cognate antigen by antigen presenting cells, indicating that the development of dietary antigen, or microbial antigen, specific pTregs is dependent upon these antigens traversing the epithelial barrier. Paracellular transport, or leak, is a well-known and studied pathway by which substances cross the epithelium by passing through the space between intestinal epithelial cells[54]. However, the size of peptides or amino acids delivered by paracellular leak are generally too small to generate antigen specific T cell responses[55]. One route to traverse the epithelial barrier to generate antigen specific T cell responses is through microfold cells (M cells), a specialized subset of intestinal epithelial cells found in the

follicle-associated epithelium of Peyer's patches, cecal patches, and isolated lymphoid follicles[56]. Through a variety of cellular transport mechanisms, including pinocytosis, macrocytosis, receptor-mediated endocytosis, luminal antigens transverse M cells and are delivered to underlying mononuclear phagocytic cells or antigen presenting cells, including macrophages and dendritic cells[57]. Whether the Peyer's patch antigen presenting cells migrate to the MLN and are significant contributors to the induction of dietary and microbial antigen specific pTregs in the MLN is unclear, however Peyer's patches have been observed to be dispensable for oral tolerance[58,59]. The primary immunological outcome for most luminal antigens delivered via M cells to Peyer's patch follicles is induction of IgA secreting plasma cells[60]. Selective IgA deficiency has been associated with an increased risk of food allergy[61,62], and presence of high levels of luminal IgA in early life has been associated with reduced risk of IgE-mediated diseases including food allergy[63,64]. M cells are present on the follicle associated epithelium overlying Peyer's patches beginning in utero, and have not been shown to change in density or transport capacity during early life. In aged mice, the density and function of M cells decreases[65,66], though this suggests M cell mediated transport represents a consistent pathway for antigen delivery from early life through most of adulthood.

## Dendritic cell-mediated antigen acquisition

Dendritic cells in the lamina propria have the capacity to extend dendrites between epithelial cells into the gut lumen in response to bacterial metabolites as a potential mechanism to directly sample luminal contents[67–69]. Mice deficient in the chemokine receptor $CX_3CR1$ lack these trans-epithelial dendrites and are deficient in oral tolerance, yet can still generate antigen specific T cell responses to dietary antigens in the gut draining lymph nodes[68,70,71]. This indicates that delivery of dietary antigen to the gut draining lymph nodes is not impaired in the absence of trans-epithelial dendrite extension, and suggests that the loss of oral tolerance may be due to other effects of the absence of $CX_3CR1$. Further the extension of trans-epithelial dendrites is lacking in mouse strains which are not impaired in oral tolerance[72], suggesting the presence of other pathways of antigen delivery supporting oral tolerance.

## Goblet cell-associated antigen passages

Goblet cells are the second most abundant intestinal epithelial cell lineage and play a crucial role in maintaining the epithelial barrier by secreting mucins and anti-microbial peptides[73]. Similar to M cells, goblet cells have also been shown as capable of translocating luminal antigens to underlying immune cells through the formation of goblet cell-associated antigen passages (GAPs)[74,75]. Goblet cells are located on non-follicle bearing epithelium overlaying lamina propria, which represents the vast expanse of the intestinal landscape where a majority of the immune cells reside. The lamina propria has been shown to be a major site for antigen acquisition by antigen presenting cells for the induction of tolerance. Thus, GAPs are potentially a major pathway for antigens to cross the epithelium to be acquired by antigen presenting cells in the lamina propria and generate T cell responses. Compared to M cells, GAP formation by goblet cells is a dynamic process with multiple regulatory mechanisms to control when antigen exposure occurs. Just prior to the time of weaning (21 days old in most standard specific pathogen free mouse facilities) GAPs form in the

small intestine in the healthy state and presumably persist throughout life[7475,76]. Antigen delivered via small intestinal GAPs induce and maintain pTregs within the small intestinal environment[77]. Small intestinal Tregs developing in adult life require frequent dietary antigen exposure[53], delivered via GAPs[77], to be maintained, revealing a limitation of oral tolerance generated during adult life. Cessation of antigen exposure either through lack of ingestion or inhibition of delivery via GAPs resulted in a fairly rapid decrease in pTregs[53,77]. There are times in life when tolerance is not the desired outcome of immune responses to luminal antigens, and indeed during times of infection, GAP formation, and therefore antigen exposure is inhibited by inflammatory cytokines present as part of the immune response to the pathogen[78]. Ignorance of luminal antigens through temporarily halting luminal delivery would prevent the development of undesired inflammatory responses to innocuous antigens[79–81]. This apparent plasticity in the adult pTreg response subject to disruption during infection or cessation of antigen delivery suggests functional, though potentially transient, oral tolerance induction occurs during adulthood and could underlie why later introduction of food allergens is less effective at reducing food allergy (Figure 1).

## Defining antigen delivery and oral tolerance in early life:

While tolerance to dietary antigens can be induced both in early life and adulthood, observations in humans and animals indicate there are differences in the outcomes of dietary antigen introduction at these times in life. Breastfeeding is unique to early life and contributes to these differences by controlling when and where dietary antigens are encountered by the gut immune system. Breastmilk contains high levels of epidermal growth factor receptor (EGFR) ligands including EGF, amphiregulin, HB-EGF, and TGFα which promote intestinal barrier function by supporting intestinal epithelial cell development[82] and IgA development[83]. EGF levels in breastmilk are highest immediately after parturition and decrease through lactation until weaning[84]. Activation of EGFR on goblet cells in the intestine inhibits delivery of luminal antigens by inhibiting GAP formation[75]. In nursing mice EGF levels in the gut lumen have a proximal to distal gradient and a temporal decrease throughout nursing reflective of the origin of EGF, the breastmilk. High levels of EGFR ligands in the gut lumen in the first week of life result in no GAP formation and limited antigen delivery across the intestine[76,85], a time when oral tolerance is difficult to induce, which is reversed after the first week of life[86,87] (Figure 1). Around day of life 10 in nursing mice, the EGF levels decrease in the colonic lumen to allow colonic GAPs to form, but remain higher in the small intestinal lumen and inhibits small intestinal GAPs, directing antigen delivery to the colonic immune system resulting in tolerance to dietary and commensal antigens[76,85]. That tolerance to dietary antigens introduced pre-weaning would be induced in the colon, as opposed to the small intestine, is a surprising and unique feature of this time in life.

### Peripherally derived RORγt Tregs

Tregs developing early in life have been shown to have distinct roles in restraining inflammatory responses[88], and much attention has been focused on a specialized subset of RORγt expressing Foxp3+ Tregs arising in the colon and driven by the microbiota[89–91]. Indeed early life antibiotics been shown to reduce the development of Tregs[92,93]. RORγt+

Foxp3+ Tregs have been shown to control a variety of immune responses[89,90] and support the development of future tolerogenic responses against dietary antigens[85]. Clinical data has found a reduction of RORγt+ Foxp3+ Tregs in individuals with food allergy[7] revealing the importance of RORγt+ Foxp3+ Tregs in humans. Intriguingly expansion of RORγt+ Foxp3+ Tregs appears to be maternally regulated with a setpoint determined in early life[94] and peripherally derived Tregs may have age-dependent fates[95] further implicating the importance of early life in the induction of oral tolerance. While pediatricians recommend exposing infants to a wide variety of dietary proteins starting at 6 months old, early life exposure to every food product one would ever encounter to develop dietary antigen specific pTregs to all possible components of the diet is simply unachievable. Given the potent suppressive nature of these RORγt+ Foxp3+ Tregs, their expansion during early life in response to the microbiota may help explain why this phase in life is so critical to lifelong immune balance and tolerance. The multifaceted nature of this population of Tregs in suppressing inflammatory responses suggest presence of these Tregs sets the stage for tolerance[96] and disruption of this “window of tolerance” can result in allergy.

Distinct T cell responses induced in various periods of life suggest T cells have the capacity for differential phenotypes depending on the phase of life in which the response is initiated. One potential difference between the colon lamina propria prior to and following weaning still to be explored is the antigen presenting cell population. Dendritic cells necessary for oral tolerance are imprinted by the microbiota in early life[97,98], and may have reduced capacity to induce effector T cell responses[99,100]. Prior to weaning, resident colonic macrophages are derived from yolk sac macrophages, and are replaced by bone-marrow derived macrophages which respond to antigens differently[101,102]. Thus unique components of the developing immune system might also define this ‘window of tolerance’.

## Disrupting the “window of tolerance”

The fine control of the “window of tolerance” relies on input from maternal ligands from the breastmilk and bacterial products from the commensal microbiota to define this phase (Figure 2). Disruption of synchronous breastfeeding by cross-fostering newborn pups to dams delivering litters two weeks prior, resulted in reduced EGF concentrations in the pups’ lumen, reflecting the reduced concentrations of EGF found in formula-fed children’s stool. Asynchronously cross-fostered offspring had significantly reduced RORγt+ Foxp3+ pTregs, and lacked the ability to induce oral tolerance to dietary antigens[85]. Furthermore, pups asynchronously cross-fostered in the reversed combination, older pups to dams having recently delivered, had a profound inability to induce oral tolerance following exposure to antigens both in prior to weaning, and as adults. Following immunization against antigens that had first been introduced orally, asynchronously cross-fostered mice developed strong Th2 immune responses and became lethargic and hypothermic resembling anaphylaxis[85]. The increased EGF concentrations in these mice resulted in significantly reduced antigen delivery via GAPs, highlighting the importance of early life exposure to antigens. Thus, the combination of multiple breastmilk proteins with oral antigens support oral tolerance by opening the “window of tolerance” at the proper time and regulating antigen delivery to the colon lamina propria for the induction of long-lived pTregs prior to weaning[85].

Similar to the first week of murine life being a poor time for the induction of oral tolerance[86,87], a defect in induction of oral tolerance was noted at the time of weaning[103]. This time in life has been associated with a brief inflammatory state coined as a "weaning reaction"[93]. This inflammatory state requires the developing microbiota and potentially imprints the pTregs to protect from intestinal inflammation later in life[93]. The presence of the microbiota at the time of weaning also is required to inhibit GAP formation and antigen delivery to the colon following weaning[75,76]. Extension of antigen exposure past weaning by allowing colonic GAP formation resulted in reduced development of antigen specific Tregs in favor of an expanded effector response specific to commensal bacterial antigens[76]. Together these data suggest the closing of the "window of tolerance" is equally as important for the stable development of long lived Tregs.

## Future Directions: Prevention and Treatment of Food Allergies

Risk factors for food allergy can be described by alterations in this window of tolerance: missing this window, as in the case of delayed allergen exposure, disrupting this window, as in the case of formula-feeding[9,104,105], or dysbiosis of the microbiota during this window, as in the case of oral antibiotics, all can contribute to improper development of Tregs and oral tolerance. The necessity of antibiotics to treat bacterial infections and formula for parents unable to breastfeed stresses the need for future work focusing on optimizing these therapies and diets for minimal disruption to oral tolerance. Clinically used antibiotics should be vetted for those that are least disruptive to microbiota, the development of RORγt+ Foxp3+ Tregs, and the induction of tolerance during early life. Additionally, work has long been underway to modulate infant formula through the inclusion of tolerogenic factors found in breastmilk[24]. With the improvement of these practices, prevention of food sensitization could be simpler than treatment of existing food allergies.

### Oral Immunotherapy

Strategies to relieve food allergy symptoms concentrate on oral tolerance, similar to strategies to prevent food allergies. Much attention has been paid to oral immunotherapy, where patients ingest small doses of allergens, particularly peanuts, in an attempt to reduce adverse reactions by modifying allergen specific IgE concentrations[106–108]. Such trials have shown moderate success and have resulted in "sustained unresponsiveness" or a lack of an allergic reaction towards the allergen in about 1/3–1/2 of the treated group[106,109]. Patients receiving oral immunotherapy (OIT) treatment for peanut allergy had increased antigen-specific Treg induction, with increased Foxp3 transcripts, along with decreased methylation of the Foxp3 locus consistent with an increased production of Tregs[110]. Importantly, successful OIT marked by "sustained unresponsiveness" appears to require "maintenance" doses of allergens to prevent regaining reactivity to peanut[107]. Intriguingly these data parallel the requirement for continued dietary antigen in mice for the maintenance of RORγt+ Foxp3+ Tregs developing in the small intestine after weaning[53]. Thus, the limitations how oral tolerance is induced and maintained after the "window of tolerance" has important ramifications into how difficult it may be to shift an allergic response towards a tolerant one later in life.

### Targeting early life for prevention

Attempting to utilize the potent Treg-inducing nature of some bacterial species, groups have turned to bacteriotherapy to relieve food allergy symptoms, with some modest success in animal models[7]. General probiotic administration in early life has shown some improvement in allergic diseases, such as eczema and wheeze[111,112], but appear to have limited to no effect in food sensitization[113]. Probiotic bacteria, such as *Lactobacillus rhamnosus*, has been included along with peanut allergens during oral immunotherapy in clinical trials, again with modest success[114,115]. However, more research is needed to understand how to utilize the microbiota both to prevent and treat food allergies, to understand how the microbiota is disrupted in allergic individuals, and to understand how reversing dysbiosis may affect allergic outcomes[116,117].

To further improve oral tolerance-based therapies to treat food allergies, attention should be given to the components driving the long-lasting oral tolerance initiated during early life. If the desired goal is to recapitulate the RORγt+ Foxp3+ Tregs developing prior to weaning, understanding what drives expansion of this specialized population during early life may be the pathway forward. The concerted effort undertaken to deliver antigens to the colonic lamina propria prior to weaning suggests unique factors present within the colonic environment. As described above, antigens introduced through the small intestine following weaning induce tolerance, but in a manner that requires frequent antigen exposure to maintain these Tregs[53]. Delivering dietary antigens to the colon following weaning to induce T cell responses may have minimal effect as antigen delivery across the colonic epithelium following weaning in minimized[75] and limited to the distal colon[77]. Allowing GAPs to form in the proximal colon in adults resulted in inflammatory responses toward the commensal microbiota[118], possibly due to the complexity and immunogenicity of the adult microbiota. Therefore, directing antigens to the colon following weaning without the context of the infant microbiota and/or other unique factors to this time of life could have deleterious consequences. These observations suggest that recapitulating the unique events surrounding oral tolerance induction to develop therapies for treatment of allergies may be complicated.

In conclusion, the benefit of early introduction of allergens in protection from food allergies later in life, may be due to multiple contributions that regulate oral tolerance in early life. Within the intestinal lumen proteins from the maternal breastmilk and the microbiota synergize to direct dietary antigens and food allergens to the colon prior to weaning. These proteins may also contribute to the immune environment in the infant colon lamina propria which, along with include factors yet unknown, to induce long-lasting Tregs that provide suppression of allergic responses throughout life. Such concepts help clarify what is unique about early life oral tolerance, why complimentary early introduction of food allergens with breastfeeding is protective of food allergy, and what factors may define potential therapeutics for future food allergies treatments.

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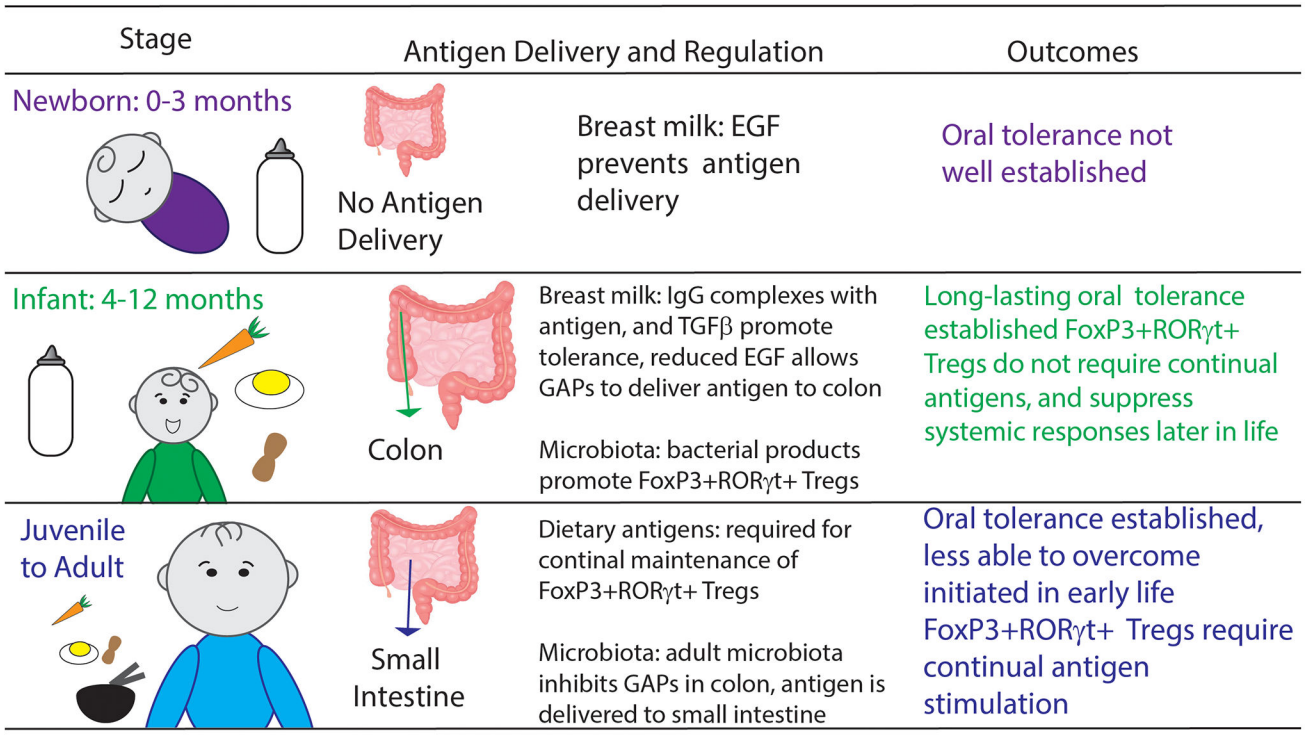


**Figure 1:**

Oral antigens are encountered through distinct routes throughout life. How these delivery pathways are regulated and the outcomes following antigen delivery are unique to each phase of life.

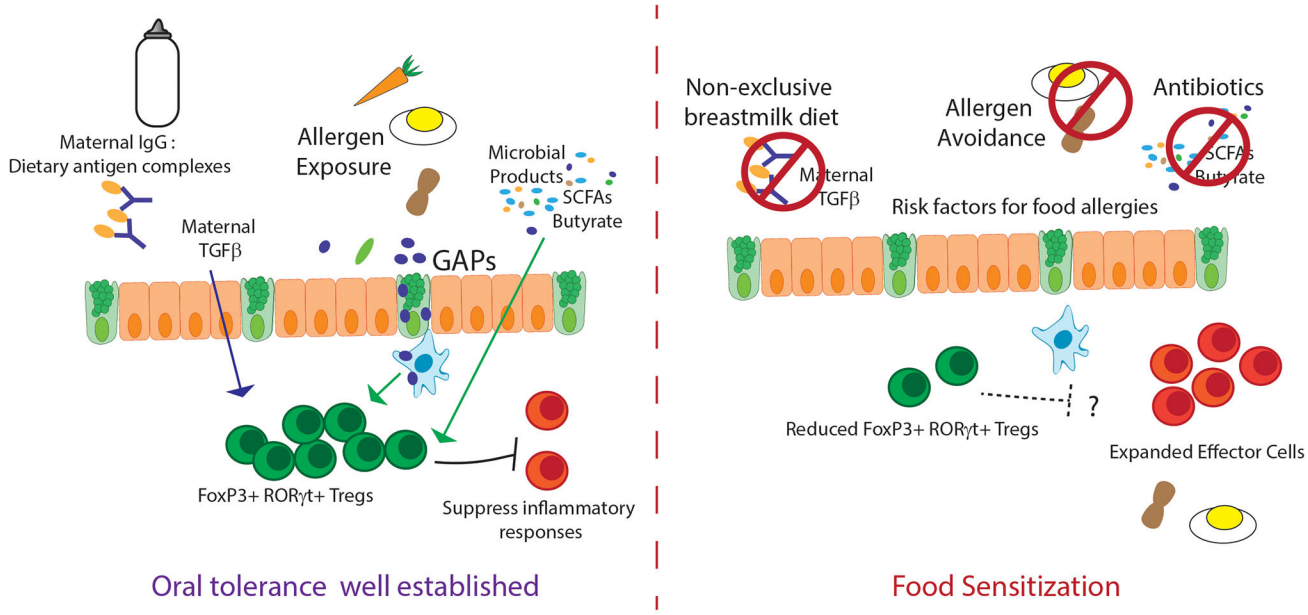


**Figure 2:**

Multiple factors contribute to establishing oral tolerance during early life. Absence of any one of these factors increases the risk of food sensitization and food allergies later in life.