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Host-Microbiome Intestinal Interactions during Early Life: Considerations for Atopy and Asthma Development

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Abstract

Purpose of review: The body's largest microbial community, the gut microbiome, is in contact with mucosal surfaces populated with epithelial, immune, endocrine and nerve cells, all of which sense and respond to microbial signals. These mutual interactions have led to a functional co-evolution between the microbes and human physiology. Examples of co-adaptation are anaerobes *Bifidobacteria* and *Bacteroides*, which have adjusted their metabolism to dietary components of human milk, and infant immune development, which has evolved to become reliant on the presence of beneficial microbes. Current research suggests that specific composition of the early-life gut microbiome aligns with the maturation of host immunity. Disruptions of natural microbial succession patterns during gut colonization are a consistent feature of immune-mediated diseases, including atopy and asthma.

Recent findings: Here we catalog recent birth cohorts documenting associations between immune dysregulation and microbial alterations, and summarize the evidence supporting the role of the gut microbiome as an etiological determinant of immune-mediated allergic diseases.

Summary: Ecological concepts that describe microbial dynamics in the context of the host environment, and a portray of immune and neuroendocrine signaling induced by host-microbiome interactions, have become indispensable in describing the molecular role of early-life microbiome in atopy and asthma susceptibility.

Introduction

The human gastrointestinal tract hosts the most abundant and diverse community of microorganisms in the body, the gut microbiome (1). Many of these microbial species interact with the intestinal mucosa that includes the gut-associated lymphoid tissue (GALT), composed of more than 70% of all host immune cells. Besides local interactions, microbes modulate cells in more distant tissues and organs through their metabolites and other bioactive molecules that enter the bloodstream. Pioneering studies with germ-free (GF) animals were first to show that the absence of commensal microbes profoundly alters the immune system's structural and functional development (2, 3). Besides defects in lymphoid tissue within the spleen, thymus, and lymph nodes, the GALT of GF animals display structural abnormalities near the mucosal interface (4, 5) and an immune phenotype with a distorted ratio of different T cell types (6). These deficits can be fully corrected by introducing commensal microbiota exclusively during early life (7, 8), firmly establishing that postnatal microbial colonization modulates the immune system development.

An increasing number of studies is drawing attention to the microbiome as an essential element determining the transition from health to disease and *vice versa* (9). Epidemiological research on the effects of prenatal and postnatal exposures has pointed out the association between perturbations of the gut microbiome composition early in life and immunological dysregulation affecting the risk of allergic diseases such as atopy and asthma (10-13). Infants at increased risk of childhood atopy and/or asthma have characteristic gut microbiome that exhibits depletion of specific bacterial genera, fungal expansion and altered microbial metabolic function (**Table 1**). In this review, we outline the current ecological understanding of early-life interactions between the host and the gut microbiome that modulate immune responses relevant to the development of atopy and asthma. We discuss how microbiota sets the tone of allergen-specific responses as an immunological priming event, as well as the roles of specific type 2 T helper cells (Th2) and innate lymphoid cells. Lastly, we review recently revealed microbiome-derived signals that impact the neuroendocrine system, which is capable of modulating immune mechanisms in allergic responses, further underscoring the overall complexity of allergic diseases etiology (**Figure 1**).

Gut microbiome maturation and adaptation during early life

The human host and its microbiome have coevolved in a complex relationship that combines the host control of the microbial growth and microbial competition for resources in the host environment (14, 15). This process has led to a mutualistic symbiosis in which the microbiome augments host physiological processes, and the host provides a nutritious and hospitable environment for the microbes. The gut microbiome develops with age and reflects the history of exposures to external factors, beginning with those encountered during pregnancy (16). In the case of vaginal birth, the infant microbiota composition is initially driven by selective seeding with maternal gut strains (17, 18) and becomes gradually dominated by anaerobic species of the *Bifidobacteria* and *Bacteroides* genera. The maturation of the gut microbiome appears to happen in an orchestrated manner, and the timing of microbial succession may be biologically determined (19, 20). Integrative analyses of metagenomic data from 34 longitudinal studies worldwide revealed common patterns in the relative abundance of the five most abundant bacterial taxa in vaginally born infants. The same bacteria displayed delayed colonization in infants born by caesarian section (C-section), as reported previously (21). By the age of 12 months, major differences in the gut microbiota composition caused by the mode of birth seem to disappear, and this is also true for microbiomes affected by early-life antibiotic use (19).

Considering that the factors that drastically alter the gut microbiota composition, including C-section, formula feeding, and antibiotic use, are also well-established risk factors for asthma (22), it is likely that even transient differences in the microbiota succession pattern may have long-term effects on the immunological development of the host.

Applying the theoretical framework of microbial and community ecology can help explain the connection between early life microbiome composition and later health outcomes. An experimental study that compared sequential order of microbial colonization in mice showed that the timing of bacterial arrival in the gut has lasting effects on the overall composition of the microbiota (23). This phenomenon, also known as priority effects, influenced how the bacterial community assembled and how ecologically successful the individual colonizers were. Human longitudinal studies provide additional evidence that discernible early life microbiomes associate with different microbial successional trajectories and health outcomes (**Table 1**). For example, infants at high risk of asthma differ from low-risk babies by a distinct meconium microbiota and a delay in the gut microbiota diversification over the first year of life (13). Pioneer microbial species that initially populate the infant gut might, therefore, not only impact the ecological succession of microbes, and the resulting microbiome functional traits but very likely also have a strong influence on immune tolerance and inflammation (1, 24, 25).

Another characteristic of infant gut microbiome is its low resilience, *i.e.*, a reduced capacity of the microbial ecosystem to maintain and return to a steady state in response to an external perturbation (1). The gut microbiome during early life displays a lower species richness and overall microbial diversity in contrast to the adult gut microbiome (26), in which a large number of bacterial strains perform similar functions (27). Compared to the substantial functional redundancy observed in adults, infant microbial communities do not have the same functional overlap and are more prone to loss of composition and functional traits upon external disturbances. This aspect makes the infant gut microbiome highly unstable during the first year of life.

One of the first colonizers of the human intestine that commonly dominate the gut during breastfeeding and dissipate through life are *Bifidobacteria*. Normal immune maturation appears to be dependent on this bacterial genus, since atopic infants display reduced bifidobacterial levels in their stool (28), and airway inflammation in murine model of asthma can be reduced by gut colonization with a *B. breve* strain (29). From an evolutionary perspective, increased abundance of maternal gut bifidobacteria during pregnancy facilitates their vertical transmission from mother to newborn (30). The species colonization success is further enhanced by their unique ability to metabolize human milk oligosaccharides (31). A current study by Duranti *et al.* looked into genetic adaptations that promote bifidobacteria-dominant microbiome during infancy, and illustrated how different bifidobacterial taxa have co-evolved to maximize their colonization capabilities through efficient resource sharing (32).

Adaptation of immune system to intestinal microbes in the context of atopic asthma etiology

Vaginal delivery and subsequent breastfeeding period reinforces *Bifidobacterium* as a keystone species of the infant microbiome (33). High bifidobacterial levels, which can reach up to 80% of the total gut microbiota (34), temporally correlate with critical stages of immune cell maturation (35, 36). Along with other prominent human commensals such as *Bacteroides fragilis* (37), *Lactobacillus reuteri* (38), and *Clostridium* spp. (39, 40), *B. bifidum* can induce $Foxp3^+$ regulatory T cells (Tregs) (41), a subpopulation of

T cells fundamental in promoting and maintaining mucosal tolerance to allergens (42). Mediating mechanisms of Tregs induction differ among species, either via cell surface polysaccharides (*B. bifidum, L. reuteri*, and *B. fragilis*) or through the production of short-chain fatty acids (SCFA) (*Clostridium* sp.), resulting in the release of anti-inflammatory interleukin (IL)-10. The signaling pathways of this interaction involve Toll-like receptors and MyD88 signal transducer and favor the production of immunoglobulin (Ig) A, which is essential to mucosal immunity and balanced gut microbiota (43). Tregs specific for luminal antigens are the primary negative regulators of inflammatory responses, maintaining responses of other immune cells, such as Th2, within a normal range. Failure to suppress an excessive Th2 response has been considered a hallmark of asthma and other allergic diseases.

Induced Tregs are derived from the interaction of naïve T cells with antigen-presenting dendritic cells (DCs) (44), which are critical regulators of T cell responses and interact closely with the gut microbiome. A recent animal study demonstrated that DCs produce a cytokine milieu that promotes Tregs differentiation, as intraperitoneal administration of DCs reduced airway inflammation in a model of allergic inflammation triggered by dust mite (45). Conversely, a pro-inflammatory lipid commonly found in feces of infants at risk of atopy and asthma (12,13-diHOME) reduced *in vitro* anti-inflammatory cytokine secretion in human DCs (46).

In line with the view of commensal-induced antigen tolerance, GF mice cannot be tolerized to oral antigens, have reduced levels of IL-10-producing Tregs and IgA antibodies, abnormally high serum levels of the allergic marker IgE, and overall phenotype characterized by a Th2 cell–biased immune response (47-50). Although the susceptibility of the Th2 responses can be restored in GF animals by introducing commensal bacteria, this strategy is only effective when done within a narrow early life window, emphasizing the essential role of microbes in immune system priming. In addition to these mechanistic studies in mice, a recent study in two European longitudinal infant cohorts revealed that microbiome features linked with asthma protection were associated with increased tolerance to bacterial lipopolysaccharide (LPS)(51), suggesting that microbiome-induced mucosal tolerance is a critical mechanism of preventing allergic responses.

Among the molecular mechanisms that promote and maintain mucosal tolerance to luminal antigens is the differentiation of induced Tregs expressing the transcription factor RORγt in the draining lymph nodes of the small intestine (52). The gut microbiota, and bacterial commensals of the order *Clostridiales* and *Bacteroidales* in particular, has been reported to elicit the RORγt$^+$ Tregs induction (53, 54). Abdel-Gadir *et al.* recently showed that infants with food allergy display dysbiotic fecal microbiota accompanied by decreased IgA and increased IgE levels, and deficiency of RORγt$^+$ Tregs (55). In mouse models, the absence of RORγt$^+$ Tregs results in dysregulated Th2 (53) and Th17 cell responses (54). In addition, mice genetically engineered to be prone to food allergy have altered gut microbiota (56) and impaired generation of allergen-specific Tregs, whose function was marked by Th2-like reprogramming (57).

Microbiota-induced Tregs RORγt$^+$ differentiate along a pathway that also promotes Th17 immune responses (53). Several studies demonstrated that Th17 cells co-exist in a well-regulated balance with Foxp3$^+$ Tregs, which is dependent on the composition of the intestinal microbiota (58). Details of how the intestinal microbiota controls the Th17 development remain unclear but may involve the understudied fungal microbiota, or mycobiota (59, 60). Th17 cells are abundantly present under a steady-state condition in the small intestinal lamina propria where they act protectively during extracellular bacterial and fungal invasion by producing pro-inflammatory cytokines IL-17 and IL-22. At the same time, excessive Th17 responses have been implicated in lung pathogenesis in response to exogenous stimuli (61, 62).

In addition to modulating dendritic and T cells responses to reduce inflammation and promote commensal immune reactions, the gut microbiome acts on other cell types, including epithelial cells (63), basophils (64), macrophages (65, 66) and innate lymphoid cells (ILC) (67). The past decade has witnessed the discovery of ILC, the innate counterparts of T cells that play essential roles during early life when the adaptive immunity has not been fully developed (68). It is important to note that composition, development, and function of ILC is regulated by the gut microbiome (69).

From three distinct ILC types (ILC1, ILC2, ILC3), ILC2 promote type 2 immunity in an antigen-independent manner and secrete IL-5 and IL-13 cytokines that induce eosinophilic inflammation, mucin overproduction, and tissue remodeling. Experiments in mice and human cohort studies identified the role of ILC2 in causing airway hyperreactivity and eosinophilic inflammation and suggested that ILC2 are involved in allergic asthma development and exacerbation (70-74). ILC2 have been found in intestinal lamina propria as well as in circulating blood and lungs of both healthy and asthmatic subjects (73), and ILC2 accumulation in airways appears to be driven by cytokine IL-33 and chemokine CXCL16 in murine models of asthma (75). However, parabiosis studies in which mice are surgically joined, and thus develop a shared blood circulation, showed that ILC2 cells found in lungs did not circulate in either steady-state conditions or inflammatory conditions (76, 77), suggesting that the ILC2 accumulation in lungs mostly results from the proliferation of a tissue resident ILC2 population. Still, there appears to be a crosstalk between cells responsible for gut and pulmonary immune homeostasis that might determine respiratory immune responses to airborne allergens, irritants and respiratory viruses (78). In relation to the latter, early-life respiratory viral infections are well-known factor associated with an increased risk of developing childhood asthma (79). The bi-directional relationship between lungs and gut is evident from studies describing, for example, intestinal complications following viral respiratory infection (80), oral antibiotic treatment impairing pulmonary host defense (81), and commensal fungus gut colonization modulating invasive fungal lung infection (60). The lung microbiome plays a vital role in promoting airway tolerance (82), and alterations of lower airway microbiota has been linked to the severity of airway obstruction (83). Moreover, a recent study showed that microbial diversity and the relative abundances of Gram-negative bacteria *Veillonella* and *Prevotella* in the airways at age one month are associated with asthma by age 6 years (84). However, it remains to be elucidated whether lung microbial dysbiosis drives or reflects immune hyperreactivity.

Emerging role of the neuroendocrine system as a key player tuning the balance between immune system and intestinal microbiota

Besides the crosstalk between ILCs and intestinal microbiome, ILCs co-localize and functionally interact with cells of the enteric nervous system (ENS) and neuroendocrine cells. Contained within the lamina propria, these cells share a common biochemical language, consisting of cytokines, chemokines, neuropeptides, neurotransmitters, hormones, and related receptors, which enable them to respond to the same signals and interact with each other (85). Analogous to the GALT, the ENS is the largest and most complex part of the peripheral nervous system, and, unsurprisingly, the gut microbiota regulates the postnatal maturation of ENS (86). Enteric glial cells, the supportive cells for enteric neurons located in the lamina propria, can directly modulate ILC3 cytokine release (84), sense the microbiota as well as tissue damage, and respond to host-derived alarmin cytokines IL-1β and IL-33 (87). It is noteworthy that the IL-1β and IL-33 have been recently shown to differentially regulate the functional adaptation of $Foxp3^+$ Tregs during mucosal inflammation (88).

In the context of asthma and other allergic diseases, neuronal regulation of ILC2 can modulate the induction of type 2 inflammation. As first evidenced in a murine model (89), ILC2 colocalize with adrenergic neurons in the intestine and express the β2-adrenergic receptor (β2AR), which interacts with the neurotransmitter epinephrine (adrenaline), a representative of catecholamines. The same study demonstrated that β2AR signaling suppresses ILC2 proliferation, while β2AR-deficient mice exhibited exaggerated ILC2-mediated type 2 inflammation in the intestine and lungs. Thus, catecholamines such as adrenaline, noradrenaline, and dopamine may have the capacity to suppress ILC2 and regulate type 2 inflammation. Other β2AR agonists, such as Ventolin, have been commonly used in pulmonology as bronchodilators, the first line inhaled medications used to treat asthma. From the microbiota perspective, catecholamines act as signals in the gut lumen (90), and noradrenaline levels in the cecal and colonic contents of specific-pathogen-free mice are substantially higher than those in GF mice. Although the gut microbiota can produce or stimulate the production of neurotransmitters such as serotonin (91), GABA and dopamine (92), their exact contribution to the levels of the neuroactive compounds remains to be determined (93). Finally, catecholamines and other biogenic amine neurotransmitters are potent hormones primarily released during the body’s stress response (89), which has a strong effect on the gut microbiome composition (94).

Prenatal and neonatal stress is yet another strong risk factor for asthma (95). Among the biological pathways by which stress amplifies the immune responses in asthma is cortisol metabolism and the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1), which is essential for normal neuroendocrine adaptation to stress. Inflammatory mediators, including cytokines and prostaglandins, are potent activators of the HPA axis (96), leading to the release of glucocorticoids that have inhibitory effects on a broad range of immune responses. The HPA axis dysfunction in asthma has been suggested by an animal model of bronchial asthma in which exposure to early life stress increased the number of eosinophils and total mononuclear cells (97). Early life events program the sensitivity of the HPA axis to stress (98), and multiple evidence supports the role of the gut microbiota in this process. An early groundbreaking study showed that when neonatal rats are exposed to bacterial LPS (endotoxin), they exhibit significantly greater hormonal responses to stress, a decreased glucocorticoid feedback inhibition of the HPA axis in adulthood, and reduced glucocorticoid receptor density in the brain (99). Further, SCFA produced by the gut microbiota influence the maturation of intestinal enteroendocrine cells and microglia, the latter being cytokines releasing neuro-immune cells that activate the HPA axis. In a series of animal experiments, Erny and colleagues showed that GF mice or antibiotic-treated animals displayed global defects in microglia, leading to impaired innate immune responses (100). The gut microbiome thus profoundly impacts the normal functioning of the HPA axis that is necessary for diminishing ongoing allergic reactions.

The gut microbiome as a therapeutic target for atopy and asthma prevention strategies

Given the documented link between alterations of the early life gut microbiome and the risk of atopy and asthma, there has been rising interest in the role of probiotics, including bacterial strains of the *Lactobacillus* and *Bifidobacterium* genera, for the prevention and treatment of the immune-mediated disorders. However, an extensive body of research on probiotics has not yet been translated into clearly defined health benefits or clinical recommendations (101-103). Part of the issue is the substantial heterogeneity in the strains used, their dosage, use of different prebiotics, as well as in the timing and duration of the interventions among various studies. Although several systematic reviews and meta-analyses showed a benefit in some probiotic administrations to both mothers during pregnancy and infants in their first month of life for the prevention of atopic dermatitis (104-106), currently, there is not enough scientific evidence that would support a general use of probiotics in the prevention of atopy and asthma.

Similarly, the role of breastfeeding in preventing allergic diseases has gained significant attention. Breastmilk shapes the infant's gut microbiota by delivering live microorganisms present in the milk and maternal skin, as well as active immune factors and prebiotic oligosaccharides that affect bacterial growth and metabolism. Even though there is significant discrepancy regarding the effect of breastmilk on allergic diseases development (107), both rodent and human studies suggest that breastmilk factors modulate essential aspects of infant gut physiology, such as gut barrier function, gut microbiota composition and associated metabolites production, and oral tolerance induction (108-111). Variations in breastmilk immune and microbial composition (112, 113), together with differences in the infant gut microbiota response, can in part explain why breastfeeding seems to have an inconsistent relationship with allergy and asthma prevention. For example, a study of 40 mother-child dyad identified that breastmilk from mothers whose children developed allergic symptoms during early childhood had lower bacterial richness when compared to milk that was consumed by children without the symptoms (114). Maternal lifestyle, including dietary habits and physical activity, have a considerable influence on breastmilk composition, as well as pre- and post-natal probiotic supplementations that can alter the breastmilk microbiota composition and subsequently the infant's gut microbial colonization (114, 115). A number of longitudinal birth-cohort studies currently seeks to determine the effects of probiotic use on later health outcomes (116, 117), still, more hypothesis-driven research is needed before commencing with intervention trials in large populations. Nonetheless, current findings emphasize that the immunological and microbial interactions between mother and infant are critical factors in the child immune development and indicate the possibility of modulating microbiota of pregnant and breastfeeding women as a strategy to promote healthy gut microbial colonization and normal immune maturation (111).

Conclusions and future directions

The balance between effector, tolerogenic, and regulatory immune mechanisms relies on continuous microbial signals, especially during early life. Emerging evidence suggests that infant’s immune maturation is synchronized with specific microbial molecules that match gradual gut colonization by microbes adapted to the early life diet. Our modern lifestyle has been remodeling the early life microbiome, and human birth cohort studies are increasingly connecting individual microbial species with the risk of immune-mediated diseases. Animal studies studying perturbations of the early-life microbiome in the context of whole-body physiology will expand the mechanistic understanding of the strains function and interactions with host cells. Ultimately, the findings from *in vivo* models need to be translated back into human trials that can inform the development of future microbiome-based health interventions, for example, for asthma prevention.

Key points:

- Host-microbiome interactions in early life play a central role in intestinal and pulmonary immune maturation and development, however, only few functional analyses of these interactions have been described.

- Birth cohort longitudinal studies that explore details of early life exposures have become instrumental in describing the bidirectional relationship between the gut microbiome and the onset of allergic diseases, including asthma.
- The alliance of translational microbiology, gnotobiotic animal models, and high-throughput molecular approaches has become essential to describe properties of individual gut microbes that might impact host physiological systems and allergic diseases susceptibility.
- The use of probiotics as a prevention strategy for immune-mediated diseases is currently under question and not yet fully supported by scientific evidence, as the most favorable strains and their dosages, together with timing and duration of the probiotic administration still need to be ascertained.

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* Infants with eczema by 18 months showed discordant development of intestinal bacterial families *Enterobacteriaceae* and *Porphyromonadaceae* in the first 26 weeks, as well as decreased acquisition of lactate-utilizing and butyrate-producing bacteria.

Figure 1. Early life host-microbiome interactions influencing atopy and asthma development. External environmental factors shape the gut and lung microbiome in early life and can cause perturbations that lead to immune-mediated allergic diseases such as atopy and asthma. Gut microbiome composition can dictate susceptibility to allergen-specific responses, which are a result of interactions between microbial molecules and immune cells. Perturbations of the early life microbiome might mediate alterations in the number of regulatory T cells (Tregs), type 2 helper (Th2) and Th17 cells, as well as in the cytokine and antibody milieu. Changes that have been associated with asthmatic immune phenotype are indicated, including increase/decrease of specific interleukins (IL) and immunoglobulins (Ig). Microbiome-derived signals also impact the neuroendocrine system, which is capable of modulating immune mechanisms in allergic responses via the hypothalamic-pituitary-adrenal (HPA) axis and dysregulation of cortisol release. White arrows indicate adrenal gland on top of the kidney and hypothalamus located in the brain above the pituitary gland. Microbiome composition can also influence the activities of microglia (Glia), neurons and neuroendocrine cells (NECs), which are known to interact with immune cells relevant in the pathogenesis of asthma.

Table 1 Prospective birth cohort studies combining microbiome analysis and determination of atopy and asthma risk [1].

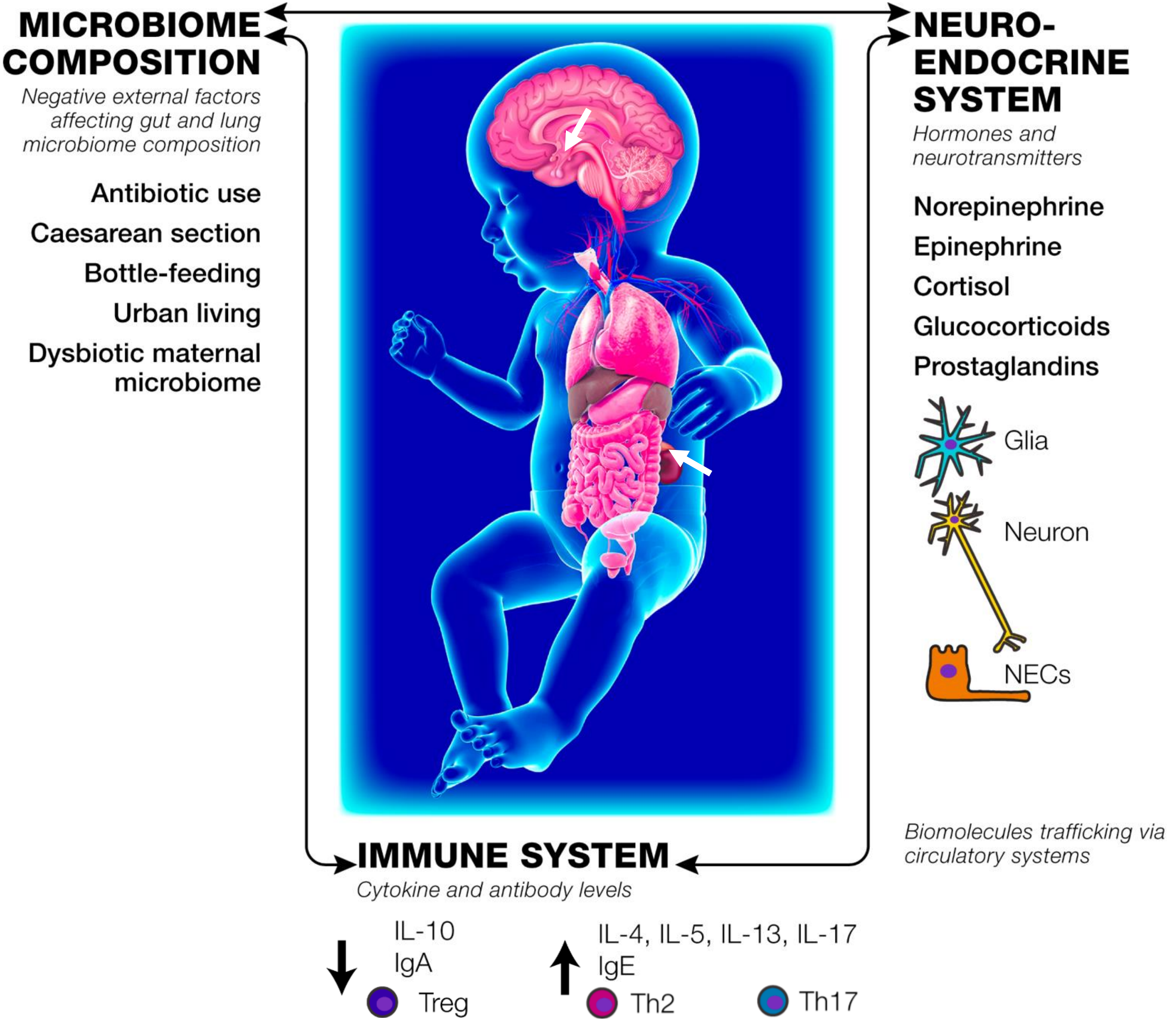
Authors & Years	Main objectives(s)	Birth Cohort Acronym	Study Population[2]	Samples Collected	Techniques to assign bacterial and fungal taxa, and for metabolite detection	Key findings	Reference
Kirjavainen et al. 2019	To identify microbial exposures that could be exploited for preventive interventions of asthma.	LUKAS1&2, GABRIELA	Children ≤ 6 years, N=395+1031	Living room floor dust samples	16S rRNA gene and ITS region amplicon sequencing	By modeling differences in house dust microbiota between farm and non-farm homes of Finnish families, the authors showed that in children growing up in non-farm homes, asthma risk decreases when their home bacterial composition is more similar to farm homes.	(51)
Levan et al. 2019	To determine whether elevated faecal concentrations of 12,13-diHOME promote allergic inflammation by inducing DCs dysfunction, resulting in a subsequent reduction in the number of anti-inflammatory Treg cells.	Subsets of the WHEALS and TIPS cohorts	Infants 1 month old, N=41+50	Stool	Shotgun metagenomic sequencing, LC-MS metabolomic analyses	Increase in the copy number of bacterial epoxide hydrolase genes among the gut microbiota or the concentration of 12,13-diHOME in infants feces, was associated with an increased probability of developing atopy, eczema or asthma during childhood.	(46)
Arrieta et. al. 2018	To explored whether similar microbiome patterns (as observed in Canada) can be observed in a geographically distinct population with similar reported rates of asthma prevalence to Canada.	ECUAVIDA	Infants 3 months old N=97	Stool	16S rRNA gene and 18S region amplicon sequencing, LC/MS metabolomic analyses	Microbial dysbiosis in 3 months-old Ecuadorian infants was associated with later development of atopic wheeze. The dysbiosis was characterized by abundance changes in several bacterial taxa (*Streptococcus* sp., *Bacteroides* sp., *Ruminococcus gnavus*, *Bifidobacterium*) and increase in relative abundance of fungi *Pichia kudriavzevii*. Levels of the fecal short-chain fatty acids acetate and caproate were reduced and increased, respectively, in the stool samples of children who went on to have atopic wheeze.	(12)
Durack et al. 2018	To determine whether neonates at high risk for asthma exhibit meconium gut microbiota dysbiosis and a reduced rate of gut bacterial diversification over the first year of life.	Subset of TIPS and DIMES cohorts	Infants ≤ 12 months old, N=25+29	Stool	16S rRNA gene amplicon sequencing, LC/MS metabolomic analyses	Children at high risk for asthma, exhibited a distinct meconium microbiota, delayed gut microbial diversification and were depleted for a range of anti-inflammatory fecal lipids in infancy. These deficits were partly rescued by *Lactobacillus rhamnosus* supplementation. However, this effect was lost after cessation of the supplementation.	(13)
Stokholm et al. 2018	To analyze the nature of gut colonization patterns during the first year of life, and the associations of these patterns with the later risk of asthma.	COPSAC$_{2010}$	Children ≤ 5 years, N=690	Stool	16S rRNA gene amplicon sequencing	One-year-old children with an immature gut microbiota composition had an increased risk of asthma at age 5 years. This effect was only apparent in children born to asthmatic mothers, and especially characterized an asthma phenotype also comprising allergic sensitization.	(118)

Wopereis et al. 2018	To investigate the effects of interventions and breast-feeding on fecal microbiota. Additionally, to identify microbial patterns associated with the onset of eczema.	PATCH	Infants in the first 26 weeks N=138	Stool	16S rRNA gene amplicon sequencing	Infants with eczema by 18 months showed discordant development of bacterial genera of *Enterobacteriaceae* and *Parabacteroides* species in the first 26 weeks, as well as decreased acquisition of lactate-utilizing bacteria producing butyrate.	(119)
Fujimura et al. 2016	To investigate whether compositionally distinct human neonatal gut microbiota exist and is differentially related to relative risk of childhood atopy and asthma.	Subset of WHEALS	Infants 1-11 months N=97	Stool	16S rRNA gene amplicon sequencing	American infants at risk of asthma showed lower relative abundance of certain bacteria (*Bifidobacterium*, *Akkermansia* and *Faecalibacterium*), higher relative abundance of particular fungi (*Candida* and *Rhodotorula*) and a distinct fecal metabolome enriched for pro-inflammatory metabolites. *Ex vivo* culture of human adult peripheral T cells with sterile fecal water from infants having a high risk of asthma increased the proportion of CD4+ cells producing interleukin (IL)-4 and reduced the relative abundance of CD4+CD25+FOXP3+ cells.	(11)
Arrieta et. al. 2015	To elucidate the factors involved in asthma and atopic disease development.	Subset of CHILD	Infants 3- and 12-months old N=312	Stool	16S rRNA gene amplicon sequencing	The study for the first time reported that infants at risk of asthma have transient gut microbial dysbiosis during the first 100 days of life with significantly decreased relative abundance of the bacterial genera *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*. The reduction in bacterial taxa was accompanied by reduced levels of fecal acetate and dysregulation of enterohepatic metabolites.	(10)

[1] Abbreviations used: ITS - internal transcribed spacer, LC-MS - liquid chromatography mass spectrometry, 12,13-diHOME – 12,13-dihydroxy-9Z-octadecenoic acid, DCs – Dendritic cells

[2] Multiple numbers refer to the listed birth cohorts respectively.

Figure


MICROBIOME COMPOSITION
Negative external factors affecting gut and lung microbiome composition
Antibiotic use
Caesarean section
Bottle-feeding
Urban living
Dysbiotic maternal microbiome
NEURO-ENDOCRINE SYSTEM
Hormones and neurotransmitters
Norepinephrine
Epinephrine
Cortisol
Glucocorticoids
Prostaglandins
Glia
Neuron
NECs
Biomolecules trafficking via circulatory systems
IMMUNE SYSTEM
Cytokine and antibody levels
IL-10
IgA
Treg
IL-4, IL-5, IL-13, IL-17
IgE
Th2
Th17