



Host–microbiome intestinal interactions during early life: considerations for atopy and asthma development

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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 coevolution between the microbes and human physiology. Examples of coadaptation 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 portrayal 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.

Keywords

atopic asthma, early-life gut microbiome, HPA axis, innate lymphoid cells, Treg/Th17/Th2 balance

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. Apart from 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 animals were first to show that the absence of commensal microbes profoundly alters the immune system's structural and functional development [2,3]. Apart from defects in lymphoid tissue within the spleen, thymus and lymph nodes, the GALT of germ-free animals displays 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 are 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

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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.

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 [10,11,12[•],13[•]]. Infants at increased risk of childhood atopy and/or asthma have characteristic gut microbiome that exhibits the depletion of specific bacterial genera, fungal expansion and altered microbial metabolic function (Table 1) [10,11,12[•],13[•],14^{••},15^{••},16[•],17[•]]. In this review, we outline the current ecological understanding of early-life interactions between the host and 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 (ILCs). Finally, we review the 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 cause (Fig. 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 [18,19]. 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 [20]. In the case of vaginal birth, the infant microbiota composition is initially driven by selective seeding with maternal gut strains [21,22] 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 [23,24]. 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 [25]. 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 [23]. 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 [26], 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 [27^{••}]. 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

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

Authors and years	Main objectives(s)	Birth cohort acronym	Study Population ^a	Samples collected	Techniques to assign bacterial and fungal taxa, and for metabolite detection	Key findings	Reference
Kirjavainen <i>et al.</i> 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 nonfarm homes of Finnish families, the authors showed that in children growing up in nonfarm homes, asthma risk decreases when their home bacterial composition is more similar to farm homes	[14 [■]]
Levan <i>et al.</i> 2019	To determine whether elevated fecal 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	[15 [■]]
Arrieta <i>et al.</i> 2018	To explore 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 month-old Ecuadorian infants was associated with later development of atopic wheeze. The dysbiosis was characterized by abundance changes in several bacterial taxa (<i>Streptococcus</i> sp., <i>Bacteroides</i> sp., <i>Ruminococcus gnavus</i> and <i>Bifidobacterium</i>) and increase in relative abundance of fungi <i>Pichia kudriavzevii</i> . 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 <i>et al.</i> 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 <i>Lactobacillus rhamnosus</i> supplementation. However, this effect was lost after cessation of the supplementation	[13 [■]]

Table 1 (Continued)

Authors and years	Main objectives(s)	Birth cohort acronym	Study Population ^a	Samples collected	Techniques to assign bacterial and fungal taxa, and for metabolite detection	Key findings	Reference
Stokholm <i>et al.</i> 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	[16]
Wopereis <i>et al.</i> 2018	To investigate the effects of interventions and breastfeeding 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 <i>Enterobacteriaceae</i> and <i>Parabacteroides</i> species in the first 26 weeks, as well as decreased acquisition of lactate-utilizing bacteria producing butyrate	[17]
Fujimura <i>et al.</i> 2016	To investigate whether compositionally distinct human neonatal gut microbiota exists 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 (<i>Bifidobacterium</i> , <i>Akkermansia</i> and <i>Faecalibacterium</i>), higher relative abundance of particular fungi (<i>Candida</i> and <i>Rhodotorula</i>) and a distinct fecal metabolome enriched for proinflammatory 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 <i>et al.</i> 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 <i>Lachnospira</i> , <i>Veillonella</i> , <i>Faecalibacterium</i> and <i>Rothia</i> . The reduction in bacterial taxa was accompanied by reduced levels of fecal acetate and dysregulation of enterohepatic metabolites	[10]

^aMultiple numbers refer to the listed birth cohorts, respectively. 12,13-diHOME, 12,13-dihydroxy-9Z-octadecenoic acid; DCs, dendritic cells; ITS, internal transcribed spacer; LC-MS, liquid chromatography mass spectrometry.

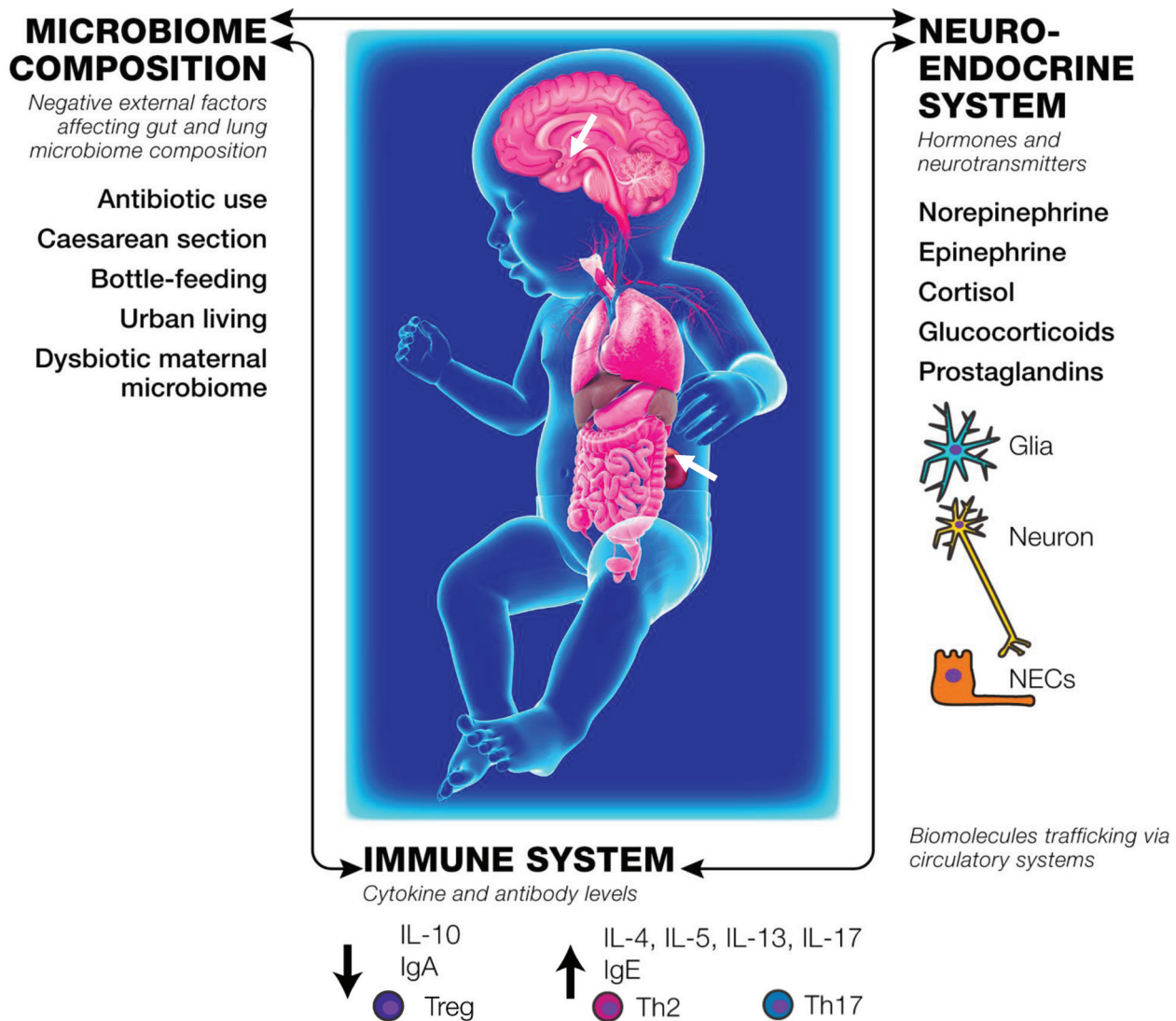


FIGURE 1. Early-life host–microbiome interactions influencing atopy and asthma development. External environmental factors shape the gut and lung microbiome in early life and can cause perturbations that lead to immune-mediated allergic diseases, such as atopy and asthma. Gut microbiome composition can 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.

microbes, and the resulting microbiome functional traits but very likely also have a strong influence on immune tolerance and inflammation [1,28,29].

Another characteristic of infant gut microbiome is its low resilience, that is, 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 [30], in which a large number of bacterial strains perform similar functions [31]. 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, as atopic infants display reduced bifidobacterial levels in their stool [32], and airway inflammation in murine model of asthma can be reduced by gut colonization with a *Bifidobacterium breve* strain [33[¶]]. From an evolutionary perspective, increased abundance of maternal gut bifidobacteria during pregnancy facilitates their vertical transmission from mother to newborn [34]. The species colonization success is further enhanced by their unique ability to metabolize human milk oligosaccharides [35]. A current study by Duranti *et al.* [36] looked into genetic adaptations that promote bifidobacteria-dominant microbiome during infancy, and illustrated how different bifidobacterial taxa have coevolved to maximize their colonization capabilities through efficient resource sharing.

ADAPTATION OF IMMUNE SYSTEM TO INTESTINAL MICROBES IN THE CONTEXT OF ATOPIC ASTHMA CAUSE

Vaginal delivery and subsequent breastfeeding period reinforces *Bifidobacterium* as a keystone species of the infant microbiome [37]. High bifidobacterial levels, which can reach up to 80% of the total gut microbiota [38], temporally correlate with critical stages of immune cell maturation [39,40]. Along with other prominent human commensals, such as *Bacteroides fragilis* [41], *Lactobacillus reuteri* [42] and *Clostridium* spp. [43,44], *Bifidobacterium bifidum* can induce Foxp3⁺ regulatory T cells (Tregs) [45^{¶¶}], a subpopulation of T cells fundamental in promoting and maintaining mucosal tolerance to allergens [46]. Mediating mechanisms of Tregs induction differs among species, either via cell surface polysaccharides (*B. bifidum*, *L. reuteri* and *B. fragilis*) or through the production of short-chain fatty acids (SCFAs) (*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 [47]. 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 naive T cells with antigen-presenting dendritic cells [48], which are critical regulators of T-cell responses and interact closely with the gut microbiome. A recent animal study demonstrated that dendritic cells produce a cytokine milieu that promotes Tregs differentiation, as intraperitoneal administration of dendritic cells reduced airway inflammation in a model of allergic inflammation triggered by dust mite [49[¶]]. Conversely, a proinflammatory 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 dendritic cells [15^{¶¶}].

In line with the view of commensal-induced antigen tolerance, germ-free mice cannot be tolerated 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 [50–53]. Although the susceptibility of the Th2 responses can be restored in germ-free 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) [14^{¶¶}], 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 ROR γ t in the draining lymph nodes of the small intestine [54]. The gut microbiota, and bacterial commensals of the order *Clostridiales* and *Bacteroidales* in particular, has been reported to elicit the ROR γ t⁺ Tregs induction [55,56]. Abdel-Gadir *et al.* [57[¶]] recently showed that infants with food allergy display dysbiotic fecal microbiota accompanied by decreased IgA and increased IgE levels, and deficiency of ROR γ t⁺ Tregs. In mouse models, the absence of ROR γ t⁺ Tregs results in dysregulated Th2 [55] and Th17 cell responses [56]. In addition, mice genetically engineered to be prone to food allergy have altered gut microbiota [58] and impaired generation of allergen-specific Tregs, whose function is marked by Th2-like reprogramming [59].

Microbiota-induced Tregs ROR γ t⁺ differentiate along a pathway that also promotes Th17 immune responses [55]. Several studies demonstrated that

Th17 cells coexist in a well-regulated balance with Foxp3⁺ Tregs, which is dependent on the composition of the intestinal microbiota [60]. Details of how the intestinal microbiota controls the Th17 development remain unclear but may involve the understudied fungal microbiota, or mycobiota [61,62^{***}]. 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 proinflammatory cytokines IL-17 and IL-22. At the same time, excessive Th17 responses have been implicated in lung pathogenesis in response to exogenous stimuli [63,64].

In addition to modulating dendritic and T-cell responses to reduce inflammation and promote commensal immune reactions, the gut microbiome acts on other cell types, including epithelial cells [65], basophils [66], macrophages [67,68] and ILCs [69]. The past decade has witnessed the discovery of ILCs, the innate counterparts of T cells that play essential roles during early life when the adaptive immunity has not been fully developed [70]. It is important to note that composition, development and function of ILCs are regulated by the gut microbiome [71].

From three distinct ILC types (ILC1, ILC2 and 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 [72–76]. ILC2 have been found in intestinal lamina propria as well as in circulating blood and lungs of both healthy and asthmatic individuals [75], and ILC2 accumulation in airways appears to be driven by cytokine IL-33 and chemokine CXCL16 in murine models of asthma [77]. 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 [78,79], 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 [80]. In relation to the latter, early-life respiratory viral infections are well-known factor associated with an increased risk of developing childhood asthma [81]. The bidirectional relationship between lungs and gut is evident from

studies describing, for example, intestinal complications following viral respiratory infection [82], oral antibiotic treatment impairing pulmonary host defense [83] and commensal fungus gut colonization modulating invasive fungal lung infection [62^{***}]. The lung microbiome plays a vital role in promoting airway tolerance [84], and alterations of lower airway microbiota have been linked to the severity of airway obstruction [85]. Moreover, a recent study showed that microbial diversity and the relative abundances of Gram-negative bacteria *Veillonella* and *Prevotella* in the airways at age 1 month are associated with asthma by age 6 years [86]. 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

Apart from the crosstalk between ILCs and intestinal microbiome, ILCs colocalize 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 [87]. 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 post-natal maturation of ENS [88]. Enteric glial cells, the supportive cells for enteric neurons located in the lamina propria, can directly modulate ILC3 cytokine release [86], sense the microbiota as well as tissue damage and respond to host-derived alarmin cytokines IL-1 β and IL-33 [89]. It is noteworthy that the IL-1 β and IL-33 have been recently shown to differentially regulate the functional adaptation of Foxp3⁺ Tregs during mucosal inflammation [90].

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 [91^{***}], ILC2 colocalize with adrenergic neurons in the intestine and express the β 2-adrenergic receptor (β 2AR), which interacts with the neurotransmitter epinephrine (adrenaline), a representative of catecholamines. The same study demonstrated that β 2AR signaling suppresses ILC2 proliferation, whereas β 2AR-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 β 2AR 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 [92], and noradrenaline levels in the cecal and colonic contents of specific-pathogen-free mice are substantially higher than those in germ-free mice. Although the gut microbiota can produce or stimulate the production of neurotransmitters, such as serotonin [93], GABA and dopamine [94], their exact contribution to the levels of the neuroactive compounds remains to be determined [95]. Finally, catecholamines and other biogenic amine neurotransmitters are potent hormones primarily released during the body's stress response [91¹¹], which has a strong effect on the gut microbiome composition [96].

Prenatal and neonatal stress is yet another strong risk factor for asthma [97]. Among the biological pathways by which stress amplifies the immune responses in asthma are cortisol metabolism and the hypothalamic–pituitary–adrenal (HPA) axis (Fig. 1), which is essential for normal neuroendocrine adaptation to stress. Inflammatory mediators, including cytokines and prostaglandins, are potent activators of the HPA axis [98], 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 [99]. Early-life events program the sensitivity of the HPA axis to stress [100], and multiple evidence support 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 [101]. Further, SCFAs produced by the gut microbiota influence the maturation of intestinal enteroendocrine cells and microglia, the latter being cytokines releasing neuroimmune cells that activate the HPA axis. In a series of animal experiments, Erny *et al.* [102] showed that germ-free mice or antibiotic-treated animals displayed global defects in microglia, leading to impaired innate immune responses. 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 [103–105]. 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 [106–108], 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 [109], 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 [110–113]. Variations in breastmilk immune and microbial composition [114,115], 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 [116]. Maternal lifestyle, including dietary habits and physical activity, have a considerable influence on breastmilk composition, as well as pre and postnatal probiotic

supplementations that can alter the breastmilk microbiota composition and subsequently the infant's gut microbial colonization [116,117]. A number of longitudinal birth-cohort studies currently seek to determine the effects of probiotic use on later health outcomes [118,119], 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 [113].

CONCLUSION

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.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Gilbert JA, Lynch SV. Community ecology as a framework for human microbiome research. *Nat Med* 2019; 25:884–889.
2. Bauer H, Horowitz RE, Levenson SM, Popper H. The response of the lymphatic tissue to the microbial flora. Studies on germfree mice. *Am J Pathol* 1963; 42:471–483.
3. Gordon HA, Bruckner-Kardoss E, Staley TE, *et al.* Characteristics of the germfree rat. *Cells Tissues Organs* 1966; 64:367–389.
4. Mosconi I, Geuking MB, Zaiss MM, *et al.* Intestinal bacteria induce TSLP to promote mutualistic T-cell responses. *Mucosal Immunol* 2013; 6:1157.
5. Baptista AP, Olivier BJ, Goverse G, *et al.* Colonic patch and colonic SILT development are independent and differentially regulated events. *Mucosal Immunol* 2012; 6:511.
6. Kennedy EA, King KY, Baldridge MT. Mouse microbiota models: comparing germ-free mice and antibiotics treatment as tools for modifying gut bacteria. *Front Physiol* 2018; 9:1534.
7. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005; 122:107–118.
8. Al Nabhani Z, Dulauroy S, Marques R, *et al.* A weaning reaction to microbiota ■ is required for resistance to immunopathologies in the adult. *Immunity* 2019; 50:1276–1288.e5.
9. Sonnenburg ED, Sonnenburg JL. The ancestral and industrialized gut microbiota and implications for human health. *Nat Rev Microbiol* 2019; 17:383–390.
10. Arrieta M-C, Stiemsma LT, Dimitriu PA, *et al.* Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015; 7:307ra152.
11. Fujimura KE, Sitarik AR, Havstad S, *et al.* Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med* 2016; 22:1187.
12. Arrieta M-C, Arévalo A, Stiemsma L, *et al.* Associations between infant fungal ■ and bacterial dysbiosis and childhood atopic wheeze in a nonindustrialized setting. *J Allergy Clin Immunol* 2018; 142:424–L434.e10.

Similarly to observations from previous US and Canadian cohorts, the authors showed that gut microbial dysbiosis of 3-month old Ecuadorian infants was associated with later development of atopic wheeze. Additionally, the risk of asthma was associated with early-life antibiotic use and increased relative abundance of certain gut fungi.

13. Durack J, Kimes NE, Lin DL, *et al.* Delayed gut microbiota development in ■ high-risk for asthma infants is temporarily modifiable by *Lactobacillus* supplementation. *Nat Commun* 2018; 9:707.

The study showed that infants at high risk for asthma exhibit a distinct meconium microbiota, delayed gut microbial diversification and depletion of a range of anti-inflammatory fecal lipids. These deficits could be partly rescued following *Lactobacillus rhamnosus* supplementation.

14. Kirjavainen PV, Karvonen AM, Adams RI, *et al.* Farm-like indoor microbiota in ■ nonfarm homes protects children from asthma development. *Nat Med* 2019; 25:1089–1095.

The study investigated the well-known asthma-protective effect of farming. The authors showed that the microbial composition in farm homes is distinct from that in nonfarm homes. Indoor dust bacterial/archaeal microbiota with similarities to farm homes appeared to be protective in nonfarm environments, as asthma risk decreased for children growing up in nonfarm homes when their home bacterial composition was more similar to farm homes. The protective effect was associated with reduced proinflammatory cytokine responses against bacterial cell wall components *ex vivo*.

15. Levan SR, Stamnes KA, Lin DL, *et al.* Elevated faecal 12,13-diHOME concentration in neonates at high risk for asthma is produced by gut bacteria and impedes immune tolerance. *Nat Microbiol* 2019; 4:2020.

The authors showed that treatment with 12,13-diHOME decreased the number of regulatory T cells in mice lungs and altered PPAR γ -regulated genes expression of human dendritic cells leading to reduced anti-inflammatory cytokine secretion. Further, an 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 a higher risk of developing atopy, eczema or asthma during childhood.

16. Stokholm J, Blaser MJ, Thorsen J, *et al.* Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun* 2018; 9:141.

As a part of investigations of the COPSAC2010, a population-based birth cohort of 700 children, the study showed that 1-year-old children with an immature gut microbiota composition have 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.

17. Wopereis H, Sim K, Shaw A, *et al.* Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. *J Allergy Clin Immunol* 2018; 141:1334–1342.e5.

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.

18. Foster KR, Schluter J, Coyte KZ, Rakoff-Nahoum S. The evolution of the host microbiome as an ecosystem on a leash. *Nature* 2017; 548:43.
19. Moeller AH, Caro-Quintero A, Mjunga D, *et al.* Cospeciation of gut microbiota with hominids. *Science* 2016; 353:380–382.
20. Pärnänen K, Karkman A, Hultman J, *et al.* Maternal gut and breast milk microbiota affect infant gut antibiotic resistome and mobile genetic elements. *Nat Commun* 2018; 9:3891.
21. Ferretti P, Pasoli E, Tett A, *et al.* Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host Microbe* 2018; 24:133–145.e5.
22. Korpela K, Costea P, Coelho LP, *et al.* Selective maternal seeding and environment shape the human gut microbiome. *Genome Res* 2018; 28:561–568.
23. Korpela K, de Vos WM. Early life colonization of the human gut: microbes matter everywhere. *Curr Opin Microbiol* 2018; 44:70–78.
24. Korpela K, Blakstad EW, Moltu SJ, *et al.* Intestinal microbiota development and gestational age in preterm neonates. *Sci Rep* 2018; 8:2453.
25. Jakobsson HE, Abrahamsson TR, Jenmalm MC, *et al.* Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by Caesarean section. *Gut* 2014; 63:559.
26. Gensollen T, Blumberg RS. Correlation between early-life regulation of the immune system by microbiota and allergy development. *J Allergy Clin Immunol* 2017; 139:1084–1091.
27. Martinez I, Maldonado-Gomez MX, Gomes-Neto JC, *et al.* Experimental evaluation of the importance of colonization history in early-life gut microbiota assembly. *eLife* 2018; 7:e36521.

This experimental animal study showed that the order of species arrival and timing by which host surfaces are colonized early in life has a lasting impact on the microbiome. The colonization order influenced both the outcome of community assembly and the ecological success of individual colonizers.

28. Sprockett D, Fukami T, Relman DA. Role of priority effects in the early-life assembly of the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2018; 15:197.
29. Litvak Y, Bäumlér AJ. The founder hypothesis: a basis for microbiota resistance, diversity in taxa carriage, and colonization resistance against pathogens. *PLoS Path* 2019; 15:e1007563.
30. Yatsunenkov T, Rey FE, Manary MJ, *et al.* Human gut microbiome viewed across age and geography. *Nature* 2012; 486:222.
31. Heintz-Buschart A, Wilmes P. Human gut microbiome: function matters. *Trends Microbiol* 2018; 26:563–574.
32. Kalliomäki M, Kirjavainen P, Eerola E, *et al.* Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* 2001; 107:129–134.
33. Raftis EJ, Delday MI, Cowie P, *et al.* Bifidobacterium breve MRx0004 protects against airway inflammation in a severe asthma model by suppressing both neutrophil and eosinophil lung infiltration. *Sci Rep* 2018; 8:12024.

A strain of *B. breve*, MRx0004, isolated from feces of healthy humans, possessed a protective action in a house dust mite mouse model of severe asthma.

34. Nuriel-Ohayon M, Neuman H, Ziv O, *et al.* Progesterone increases Bifidobacterium relative abundance during late pregnancy. *Cell Rep* 2019; 27:730–736.e3.
35. Duranti S, Milani C, Lugli GA, *et al.* Insights from genomes of representatives of the human gut commensal Bifidobacterium bifidum. *Environ Microbiol* 2015; 17:2515–2531.
36. Duranti S, Lugli GA, Milani C, *et al.* Bifidobacterium bifidum and the infant gut microbiota: an intriguing case of microbe-host co-evolution. *Environ Microbiol* 2019; 21:3683–3695.
37. Laforest-Lapointe I, Arieta M-C. Patterns of early-life gut microbial colonization during human immune development: an ecological perspective. *Front Immunol* 2017; 8:788.
38. Pannaraj PS, Li F, Cerini C, *et al.* Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. *JAMA Pediatr* 2017; 171:647–654.
39. Neill I, Schofield Z, Hall LJ. Exploring the role of the microbiota member Bifidobacterium in modulating immune-linked diseases. *Emerg Top Life Sci* 2017; 1:333.
40. Ruiz L, Delgado S, Ruas-Madiedo P, *et al.* Bifidobacteria and their molecular communication with the immune system. *Front Microbiol* 2017; 8:2345.
41. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci U S A* 2010; 107:12204–12209.
42. Mu Q, Tavella VJ, Luo XM. Role of Lactobacillus reuteri in human health and diseases. *Front Microbiol* 2018; 9:757.
43. Atarashi K, Tanoue T, Shima T, *et al.* Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* 2011; 331:337.
44. Furusawa Y, Obata Y, Fukuda S, *et al.* Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013; 504:446.
45. Verma R, Lee C, Jeun E-J, *et al.* Cell surface polysaccharides of Bifidobacterium bifidum induce the generation of Foxp3+ regulatory T cells. *Sci Immunol* 2018; 3:eaat6975.

The authors showed that β -glucan/galactan polysaccharides derived from the cell wall of *B. bifidum* are responsible for promoting Treg cell induction in the intestine. Further, they reported that this process is dependent on intestinal dendritic cells that express Toll-like receptor 2.

46. Hadis U, Wahl B, Schulz O, *et al.* Intestinal tolerance requires gut homing and expansion of FoxP3+ regulatory T cells in the lamina propria. *Immunity* 2011; 34:237–246.
47. Catanzaro JR, Strauss JD, Bielecka A, *et al.* IgA-deficient humans exhibit gut microbiota dysbiosis despite secretion of compensatory IgM. *Sci Rep* 2019; 9:13574.
48. Esterházy D, Loschko J, London M, *et al.* Classical dendritic cells are required for dietary antigen-mediated induction of peripheral Treg cells and tolerance. *Nat Immunol* 2016; 17:545.
49. Aragão-França LS, Rocha VCJ, Cronemberger-Andrade A, *et al.* Tolerogenic dendritic cells reduce airway inflammation in a model of dust mite triggered allergic inflammation. *Allergy Asthma Immunol Res* 2018; 10:406–419.

This experimental animal study found that treatment with tolerogenic dendritic cells protects against dust mite-induced allergy in a mouse model.

50. Cahenzli J, Köller Y, Wyss M, *et al.* Intestinal microbial diversity during early-life colonization shapes long-term IgE levels. *Cell Host Microbe* 2013; 14:559–570.
51. Sudo N, Sawamura S, Tanaka K, *et al.* The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997; 159:1739.
52. Fritz JH, Rojas OL, Simard N, *et al.* Acquisition of a multifunctional IgA+ plasma cell phenotype in the gut. *Nature* 2012; 481:199–203.
53. Geuking Markus B, Cahenzli J, Lawson Melissa AE, *et al.* Intestinal bacterial colonization induces mutualistic regulatory T cell responses. *Immunity* 2011; 34:794–806.
54. Esterházy D, Canesso MCC, Mesin L, *et al.* Compartmentalized gut lymph node drainage dictates adaptive immune responses. *Nature* 2019; 569:126–130.
55. Ohnmacht C, Park J-H, Cording S, *et al.* The microbiota regulates type 2 immunity through ROR γ t+ T cells. *Science* 2015; 349:989–993.
56. Sefik E, Geva-Zatorsky N, Oh S, *et al.* Individual intestinal symbionts induce a distinct population of ROR γ t+ regulatory T cells. *Science* 2015; 349:993–997.
57. Abdel-Gadir A, Stephen-Victor E, Gerber GK, *et al.* Microbiota therapy acts via a regulatory T cell MyD88/ROR γ t pathway to suppress food allergy. *Nat Med* 2019; 25:1164–1174.

The authors demonstrated that gut dysbiosis promotes the breakdown of oral tolerance as a result of a failure to induce protective ROR γ t-dependent Treg responses in food allergic children and mice, allowing instead for the emergence of Th2 cells. Administering a human-origin *Clostridiales* cluster alone or together with *Subdoligranulum variabile* to mice suppressed Th2-cell activity and induced Tregs to express the transcription factor ROR γ t, and conferred protection to a common food allergy trigger, chicken egg ovalbumin.

58. Noval Rivas M, Burton OT, Wise P, *et al.* A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. *J Allergy Clin Immunol* 2013; 131:201–212.
59. Noval Rivas M, Burton Oliver T, Wise P, *et al.* Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. *Immunity* 2015; 42:512–523.
60. Omenetti S, Pizarro TT. The Treg/Th17 axis: a dynamic balance regulated by the gut microbiome. *Front Immunol* 2015; 6:639.
61. Bär E, Whitney Paul G, Moor K, *et al.* IL-17 regulates systemic fungal immunity by controlling the functional competence of NK cells. *Immunity* 2014; 40:117–127.
62. Bacher P, Hohnstein T, Beerbaum E, *et al.* Human antifungal Th17 immunity and pathology rely on cross-reactivity against Candida albicans. *Cell* 2019; 176:1340–1355.e15.

The authors demonstrated that among 30 described members of the human mycobiome, intestinal *Candida albicans* is the major inducer of Th17 cells in humans and that it can influence inflammation and antifungal responses at distal sites. By showing that the *C. albicans*-specific Th17 cells are cross-reactive to other fungal species, including the airborne fungus *Aspergillus fumigatus*, the study underlined the link between protective immunity in the gut and immune disease in the lung.

63. De Luca A, Pariano M, Cellini B, *et al.* The IL-17F/IL-17RC axis promotes respiratory allergy in the proximal airways. *Cell Rep* 2017; 20:1667–1680.
64. Manni ML, Robinson KM, Alcorn JF. A tale of two cytokines: IL-17 and IL-22 in asthma and infection. *Expert Rev Respir Med* 2014; 8:25–42.
65. Allaire JM, Crowley SM, Law HT, *et al.* The intestinal epithelium: central coordinator of mucosal immunity. *Trends Immunol* 2018; 39:677–696.
66. Hill DA, Siracusa MC, Abt MC, *et al.* Commensal bacteria–derived signals regulate basophil hematopoiesis and allergic inflammation. *Nat Med* 2012; 18:538.
67. Scott NA, Andrusaitis A, Andersen P, *et al.* Antibiotics induce sustained dysregulation of intestinal T cell immunity by perturbing macrophage homeostasis. *Sci Transl Med* 2018; 10:eaa04755.
68. Mortha A, Chudnovskiy A, Hashimoto D, *et al.* Microbiota-dependent cross-talk between macrophages and ILC3 promotes intestinal homeostasis. *Science* 2014; 343:1249288.
69. Cording S, Medvedovic J, Lecuyer E, *et al.* Control of pathogens and microbiota by innate lymphoid cells. *Microb Infect* 2018; 20:317–322.
70. Eberl G, Colonna M, Di Santo JP, McKenzie ANJ. Innate lymphoid cells: a new paradigm in immunology. *Science* 2015; 348:aaa6566.
71. Gury-BenAri M, Thaïs CA, Serafini N, *et al.* The spectrum and regulatory landscape of intestinal innate lymphoid cells are shaped by the microbiome. *Cell* 2016; 166:1231–1246.e13.
72. Hong JY, Bentley JK, Chung Y, *et al.* Neonatal rhinovirus induces mucous metaplasia and airways hyperresponsiveness through IL-25 and type 2 innate lymphoid cells. *J Allergy Clin Immunol* 2014; 134:429–439.
73. Stier MT, Bloodworth MH, Toki S, *et al.* Respiratory syncytial virus infection activates IL-13-producing group 2 innate lymphoid cells through thymic stromal lymphopoietin. *J Allergy Clin Immunol* 2016; 138:814–824.e11.
74. Flayer CH, Ge MQ, Tompkins DG, *et al.* Group 2 innate lymphoid cells display ILC3-like functional plasticity in asthmatics and nonhuman primates. *J Allergy Clin Immunol* 2018; 141:AB1.
75. Barnig C, Cernadas M, Dutilleul S, *et al.* Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. *Sci Transl Med* 2013; 5:174ra26.
76. KleinJan A, Klein Wolterink RGJ, Levani Y, *et al.* Enforced expression of Gata3 in T cells and group 2 innate lymphoid cells increases susceptibility to allergic airway inflammation in mice. *J Immunol* 2014; 192:1385.
77. Li Y, Chen S, Chi Y, *et al.* Kinetics of the accumulation of group 2 innate lymphoid cells in IL-33-induced and IL-25-induced murine models of asthma: a potential role for the chemokine CXCL16. *Cell Mol Immunol* 2019; 16:75–86.
78. Moro K, Kabata H, Tanabe M, *et al.* Interferon and IL-27 antagonize the function of group 2 innate lymphoid cells and type 2 innate immune responses. *Nat Immunol* 2016; 17:76–86.
79. Gasteiger G, Fan X, Dikiy S, *et al.* Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. *Science* 2015; 350:981.
80. Borger JG, Lau M, Hibbs ML. The influence of innate lymphoid cells and unconventional T cells in chronic inflammatory lung disease. *Front Immunol* 2019; 10:1597.
81. Toivonen L, Forsström V, Waris M, Peltola V. Acute respiratory infections in early childhood and risk of asthma at age 70 years. *J Allergy Clin Immunol* 2019; 143:407–410.e6.
82. Wang J, Li F, Wei H, *et al.* Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell–dependent inflammation. *J Exp Med* 2014; 211:2397.
83. Schuijt TJ, Lankelma JM, Scicluna BP, *et al.* The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. *Gut* 2016; 65:575–583.
84. Gollwitzer ES, Saglani S, Trompette A, *et al.* Lung microbiota promotes tolerance to allergens in neonates via PD-L1. *Nat Med* 2014; 20:642.
85. Turturice BA, McGee HS, Oliver B, *et al.* Atopic asthmatic immune phenotypes associated with airway microbiota and airway obstruction. *PLoS One* 2017; 12:e0184566.
86. Thorsen J, Rasmussen MA, Waage J, *et al.* Infant airway microbiota and topical immune perturbations in the origins of childhood asthma. *Nat Commun* 2019; 10:5001.
87. Quatrini L, Vivier E, Ugolini S. Neuroendocrine regulation of innate lymphoid cells. *Immunol Rev* 2018; 286:120–136.
88. Kabouridis Panagiotis S, Lasrado R, McCallum S, *et al.* Microbiota controls the homeostasis of glial cells in the gut lamina propria. *Neuron* 2015; 85:289–295.
89. Ibiza S, Garcia-Cassani B, Ribeiro H, *et al.* Glial-cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence. *Nature* 2016; 535:440.
90. Alvarez F, Istomine R, Shourian M, *et al.* The alarmins IL-1 and IL-33 differentially regulate the functional specialisation of Foxp3+ regulatory T cells during mucosal inflammation. *Mucosal Immunol* 2019; 12:746–760.
91. Moriyama S, Brestoff JR, Flamar A-L, *et al.* β_2 -adrenergic receptor–mediated negative regulation of group 2 innate lymphoid cell responses. *Science* 2018; 359:1056–1061.
92. Bäumler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 2016; 535:85.
93. Yano Jessica M, Yu K, Donaldson Gregory P, *et al.* Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015; 161:264–276.
94. Valles-Colomer M, Falony G, Darzi Y, *et al.* The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol* 2019; 4:623–632.
95. Asano Y, Hiramoto T, Nishino R, *et al.* Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. *Mucosal Biol* 2012; 303:G1288–G1295.
96. Karl JP, Hatch AM, Arcidiacono SM, *et al.* Effects of psychological, environmental and physical stressors on the gut microbiota. *Front Microbiol* 2018; 9:2013.
97. Dreger LC, Kozyrskyj AL, HayGlass KT, *et al.* Lower cortisol levels in children with asthma exposed to recurrent maternal distress from birth. *J Allergy Clin Immunol* 2010; 125:116–122.
98. Serrats J, Schiltz JC, Garcia-Bueno B, *et al.* Dual roles for perivascular macrophages in immune-to-brain signaling. *Neuron* 2010; 65:94–106.
99. Chida Y, Sudo N, Sonoda J, *et al.* Early-life psychological stress exacerbates adult mouse asthma via the hypothalamus-pituitary-adrenal axis. *Am J Respir Crit Care Med* 2007; 175:316–322.
100. van Bodegom M, Homberg JR, Henckens MJAG. Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. *Front Cell Neurosci* 2017; 11:87.
101. Shanks N, Larocque S, Meaney MJ. Neonatal endotoxin exposure alters the development of the hypothalamic-pituitary-adrenal axis: early illness and later responsiveness to stress. *J Neurosci* 1995; 15:376.
102. Erny D, Hrabě de Angelis AL, Jaitin D, *et al.* Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 2015; 18:965.
103. West CE, Jenmalm MC, Kozyrskyj AL, Prescott SL. Probiotics for treatment and primary prevention of allergic diseases and asthma: looking back and moving forward. *Expert Rev Clin Immunol* 2016; 12:625–639.
104. Wang HT, Anvari S, Anagnostou K. The role of probiotics in preventing allergic disease. *Children (Basel, Switzerland)* 2019; 6:24.
105. Day RLJ, Harper AJ, Woods RM, *et al.* Probiotics: current landscape and future horizons. *Future Sci OA* 2019; 5:FSO391.
106. Zuccotti G, Meneghin F, Aceti A, *et al.* Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. *Allergy* 2015; 70:1356–1371.
107. Cuello-Garcia CA, Brożek JL, Fiocchi A, *et al.* Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2015; 136:952–961.
108. Li L, Han Z, Niu X, *et al.* Probiotic supplementation for prevention of atopic dermatitis in infants and children: a systematic review and meta-analysis. *Am J Clin Dermatol* 2019; 20:367–377.
109. Kim JH. Role of breast-feeding in the development of atopic dermatitis in early childhood. *Allergy Asthma Immunol Res* 2017; 9:285–287.
110. Dogaru CM, Nyffenegger D, Pescatore AM, *et al.* Breastfeeding and childhood asthma: systematic review and meta-analysis. *Am J Epidemiol* 2014; 179:1153–1167.
111. Lodge CJ, Tan DJ, Lau MXZ, *et al.* Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* 2015; 104(S467): 38–53.
112. Munblit D, Verhasselt V. Allergy prevention by breastfeeding: possible mechanisms and evidence from human cohorts. *Curr Opin Allergy Clin Immunol* 2016; 16:427–433.
113. van den Elsen LWJ, Garssen J, Burcelin R, Verhasselt V. Shaping the gut microbiota by breastfeeding: the gateway to allergy prevention? *Front Pediatr* 2019; 7:47.
114. Moossavi S, Sepehri S, Robertson B, *et al.* Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. *Cell Host Microbe* 2019; 25:324–335.e4.
115. Boix-Amorós A, Collado MC, Van't Land B, *et al.* Reviewing the evidence on breast milk composition and immunological outcomes. *Nutr Rev* 2019; 77:541–556.
116. Dzidic M, Mira A, Artacho A, *et al.* Allergy development is associated with consumption of breastmilk with a reduced microbial richness in the first month of life. *Pediatr Allergy Immunol* 2019; doi: 10.1111/pai.13176. [Epub ahead of print]
117. Gueimonde M, Sakata S, Kalliomäki M, *et al.* Effect of maternal consumption of *Lactobacillus GG* on transfer and establishment of fecal *Bifidobacterium* microbiota in neonates. *J Pediatr Gastroenterol Nutr* 2006; 42:166–170.
118. Barthow C, Wickens K, Stanley T, *et al.* The Probiotics in Pregnancy Study (PiP Study): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy. *BMC Pregnancy Childbirth* 2016; 16:133.
119. Awasthi S, Wilken R, Patel F, *et al.* Dietary supplementation with *Bifidobacterium longum* subsp. *infantis* (B. *infantis*) in healthy breastfed infants: study protocol for a randomised controlled trial. *Trials* 2016; 17:340.

The study described the existence of a neuronal-derived regulatory circuit that limits ILC2s-dependent type 2 inflammation. This circuit includes the β 2AR that ILC2s express in the small intestine, and its ligand, the neurotransmitter epinephrine. The authors demonstrated that the β 2AR pathway is a cell-intrinsic negative regulator of ILC2 responses through inhibition of cell proliferation and effector function.