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Microbiome-Immune Interactions in Allergy and Asthma

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Abstract

The human microbiota has been established as a key regulator of host health, in large part due to its constant interaction with, and impact on, host immunity. A range of environmental exposures, spanning from the prenatal period through adulthood are now known to impact the composition and molecular productivity of microbiomes across mucosal and dermal tissues with short- and long-term consequences for host immune function. Here we review the more recent findings in the field that provide insights into how microbial-immune interactions promote and sustain immune dysfunction associated with allergy and asthma. We consider both early life microbiome perturbation and the molecular underpinnings of immune dysfunction associated with subsequent allergy and asthma development in childhood, as well as microbiome features that relate to phenotypic attributes of allergy and asthma in older patients with established disease.

Keywords

Microbiota; Airway; Gut; Immunology; Immunometabolism

Introduction

The prevalence of allergy and asthma has increased significantly over the past several generations; data from national and state surveillance systems administered by the Centers for Disease Control and Prevention indicate that the burden of asthma in the United States population in 2019 was 7.8%. Recent meta-analyses in US populations showed that childhood asthma incidence rates vary by age, sex, parental asthma history, race/ethnicity, and calendar year with higher rates observed in younger children, particularly African American and Caribbean American populations (1, 2). Changes in disease incidence rates over time and with demographic factors (1) indicate that complex interactions between the human host and time-dependent variation in environmental and social factors underlie disease development and expression. Efforts to treat established disease have been met

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with some success but indicate that early intervention is key. For example, peanut oral immunotherapy is effective but age-dependent, with older children less likely to be successfully desensitized and tolerized (3), suggesting that very early-life priming of immunity is key to allergic disease development and that interventions for disease prevention should target this window of development.

These observations have led to increased interest in the developmental origins of allergy and asthma as well as the dynamic interactions with host immunity that promote pathogenesis in later life. Consistently, allergy and asthma-associated immune dysfunction is coincident with perturbation to airway, skin and gut microbiomes (4–8). That perturbed microbiomes are drivers of disease and not simply a bystander effect of disease processes comes from elegant germ-free mouse experiments (9). Transfer of feces from an infant with cow's milk allergy to previously germ-free mice promoted an anaphylactic response to sensitization with cow's milk allergen β-lactoglobulin (BLG) and increased BLG-specific IgE (9), indicating a functional contribution to allergic sensitization by the gut microbiome. In the airways, a relatively small number of distinct age-related airway microbiota colonization patterns are evident, that relate to risk of asthma development in later childhood (10–12), or to risk of exacerbation or loss of asthma control in older patients with diagnosed disease (13, 14). More recently it has become evident that the airway bacterial and viral microbiota exhibit seasonal dynamics, and that in the Fall, networks of upper airway bacteria interact with epithelial response to viral infection events to significantly increase asthma exacerbation risk (15). These findings underscore the complexity of the disease and highlights the temporal and dynamic nature of microbial-host interactions at the two largest mucosal surfaces that shape allergy and asthma development and disease expression.

Since immune function serves as the rheostat for human health, the capacity to sense, respond and clear noxious environmental or pathogenic microbial exposures is fundamental to host immunoprotection and relatively well understood (16). However, the ability to tolerate antigenic stimuli or, indeed, the burden and diversity of microbes that exist in human microbiomes is somewhat enigmatic. In humans, immune cell populations with the capacity for inflammatory cytokine production and established memory responses to microbes are evident in the fetal intestine as early as the second trimester of pregnancy (17, 18). In parallel, sparse colonies of viable bacteria with the capacity to induce memory T cell activation, expand fetal lymph node T cells or reduce inflammatory cytokine production by fetal-specific T cell populations are also detectable in the human fetal intestine by mid-gestation (17, 19). These data indicate that immune priming events relevant to allergy and asthma commence *in utero* and are dependent, in part, on maternal microbiomes. Evidence that prenatal microbial-immune priming events have long-lasting effects on immune function comes from mouse studies; prebiotic supplementation of pregnant dams promoted short chain fatty acid production by the maternal gut microbiome and increased the abundance of regulatory B and T cells in the fetus, tolerogenic effects that were sustained in the postnatal period (20). Independently, mouse models of prenatal infection indicate that maternal prenatal microbial-immune interactions shape fetal and early life immune function in part, via epigenetic imprinting (21). These processes are reliant on substrate availability and the activity of metabolic pathways which are intimately related to microbial activities. In post-natal life microbiome perturbation coupled with metabolic

dysfunction precedes allergy and asthma development in childhood (22–25), relationships that remain evident in preschool aged children (26). The human microbiome develops across body sites and with advancing age (27, 28), and is influenced by a large number of exposures known to be risk factors for allergy and asthma development. This fact coupled with the knowledge that microbes tune immune function indicate that temporal and dynamic microbial-immune interactions are paramount to allergy and asthma development and chronicity. Here we provide an overview of the most recent developments implicating successional microbial mechanisms of immune dysfunction across life stages that promote allergy and asthma (Figure 1) and propose a framework for the developmental origins and temporal disease dynamics observed in patient populations.

Early life development relates to childhood allergy and asthma outcomes.

Dermal, intestinal and respiratory microbiomes develop over the first several years of life, with body habitat-specific microbial colonization patterns in infancy associated with increased risk of atopy and asthma development in later childhood (10, 23, 25, 30–34). In infancy, upper airway colonization by respiratory pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae* is associated with early life wheeze, febrile respiratory illness and asthma in later childhood (10–12). These particular species also thrive in chronically inflamed airways and are also associated with respiratory diseases like pneumonia and chronic obstructive pulmonary disease (35–37). Therefore, these microbes may be more broadly indicative of pathogenic microbial activity and dysregulation of conserved immune pathways related to these events. More recently, in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) birth cohort, upper airway microbial composition in infants was associated with allergic rhinitis development 6 years of age, mediated in part by differentially methylated CpGs in upper airway epithelial cells (38). Studies of neonatal murine skin have determined that commensal *Staphylococcus epidermidis* colonization is required to promote regulatory T cell accumulation in hair follicles – a key site of bacterial colonization (39). In humans at 3 months of age, skin colonization by pathogenic *Staphylococcus aureus* is more prevalent in infants who develop atopic dermatitis (40). In the gut, early life microbiota perturbation and metabolic dysfunction precedes atopy and asthma development in childhood (23, 24). A number of studies to date have focused on the gut microbiota which houses the largest burden and diversity of microbes in the human body and produces a diverse repertoire of bioactive molecules. These studies provide insights into how early life microbial encounters prime immune function and offer a framework for improved understanding of the developmental origins of allergy and asthma across other body sites. Gut microbiome composition is dynamic, particularly in early life when it rapidly diversifies over the first years of life before stabilizing, with respect to dominant bacterial phylum distribution, by age 3 years (27). Despite phylum-level stability, microbial species, strains and their encoded genes continue to evolve throughout life course, in part shaped by extrinsic exposures such as pharmaceuticals, diet and antimicrobial exposures (40–43), but also by intrinsic factors such as epigenetic modifications (44). Despite these influences, recent data has indicated that bacterial strains that initially colonize the human intestine in very early life are detectable in adulthood (45), suggesting that pioneer microbial colonizers may represent sustained and

contributing members to the overall function of the microbiome and its interactions with host immunity throughout an individual's lifetime.

Early life is a pivotal time for the establishment and development of both the gut microbiome and immune system. Human fetal dendritic cells, which are crucial for effective immunity and tolerance, can migrate to lymph nodes and respond to toll-like receptor ligation (canonical receptor for microbial ligands) to induce regulatory T-cells that reduce inflammation *in utero* (46). Recent evidence suggests that initial intestinal encounters with viable bacteria commences *in utero*. Human fetal intestinal colonization by sparse colonies of a limited number of bacterial species including *Lactobacillus*, *Staphylococcus* and *Micrococcus* is evident as early as the second trimester of pregnancy (17, 19). The presence of these fetal bacteria corresponds with distinct programs of innate and adaptive immunity. For example, *Micrococcus luteus*, detected in human fetal intestinal samples, associated with increased expression of intestinal epithelial genes involved in host response to microbes, e.g. NFκB, BCL6 (modulates transcription of STAT-dependent B cell IL-4 responses), and with accumulation of fetal specific T-cells (19). Moreover, a fetal isolate of *M. luteus* exhibited the capacity to survive in fetal antigen presenting cells, metabolize progesterone and estradiol and reduce interferon gamma expression by T-cells, indicating strategies by which specific bacteria may survive the hostile environment of the fetal gut. These and more recent findings from independent studies suggest that the fetal intestine can support a very limited number of bacterial species, and that those species identified and isolated from this unique niche contribute to immune cell priming and development of bacterial antigen experienced memory T cell populations *in utero* (17, 19). These data suggest that the origins of tolerance priming can occur *in utero* and is, in part, dependent on translocation of maternal prenatal microbes to the developing fetus.

After birth, mode of delivery, antimicrobial exposure and early life nutrition represent some of the key exposures that influence the pace of early life gut microbiome establishment (27, 47–50), which has now been linked to asthma risk in later childhood (25, 32). Independent human birth cohorts in the United States and Europe have shown that delayed gut microbiota development is characteristic of infants at significantly higher risk of asthma in later childhood (25, 32). Appropriately paced infant gut microbial development with key bacteria including *Lactobacillus*, *Bifidobacterium* and *Faecalibacterium*, is associated with protection against atopy and asthma development in later childhood (24). These microbes thrive on human milk oligosaccharides and produce bioactive metabolites that influence brain, adipose tissue, and immune cell functional development (51–53). Breastmilk, a complex and dynamic living liquid, supports the growth and activities of lactic acid bacteria and *Bifidobacteria* in the gut (54), which prevent enteric pathogen invasion and inflammation (55, 56). Breastmilk also contains microbes, immune cells and their products, e.g. immunoglobulin A and anti-microbial products such as lactoferrin which further regulate early life gut microbiome species accumulation and prevent pathogenic microbial activity and associated inflammation (57–63). These data indicate that failure to regulate early-life microbial development particularly in the gastrointestinal tract, contributes to risk of atopic disease and asthma development in later childhood. Though parallel longitudinal skin microbiome studies are currently lacking, the existing cross-sectional evidence (61) and longitudinal early life airway studies (10, 30, 31) suggest that early life microbial

colonization status at these sites also contributes to local immune tuning and to childhood allergy and asthma risk.

Microbial-derived metabolites shape immune function.

Numerous clinical and preclinical studies have demonstrated that early life microbial perturbation and metabolic dysfunction associates with heightened risk of allergic and asthmatic phenotypes in later childhood (23, 24). Murine studies have shown that even transient microbiome perturbation in early life is sufficient to promote long-term effects on host metabolism (64). This suggests that microbe-host metabolic interactions in infancy may have lasting consequences for host health. Indeed, a number of birth cohort studies have now shown that early life gut microbiome metabolic dysfunction is a recurring characteristic of childhood atopy and asthma development and have highlighted suites of microbial metabolites that co-vary with risk of atopy or asthma development in later childhood (23–26). Data from multiple fields now indicates that gut microbial-derived metabolites influence remote tissues and organs (65, 66). Encouragingly, a relatively consistent metabolic signature dominated by lipid metabolites (depletion of polyunsaturated fatty acids, PUFAs, and enrichment of mono-hydroxy fatty acids), is consistently observed at various stages of early life development (1 month and 3 years) in those at heightened risk of developing childhood disease (23, 24, 26). Several studies have provided evidence for the immunomodulatory effect of microbial derived metabolites (Table 1). The anti-inflammatory effects of microbial-derived short chain fatty acids are well described. We refer readers to an excellent recent review article detailing these activities (74). More recent studies have identified bacterial-derived metabolites that protect against allergic airway inflammation, including p-cresol sulfate, an L-tyrosine derivative that reduces CCL20 (a lymphocyte chemoattractant) production by airway epithelial cells (67). Bacterial-derived inflammatory mediators have also been associated with increased risk of atopy and asthma. For example, elevated fecal concentrations of 12,13-diHOME in infancy increases risk of atopy and asthma in childhood. Mechanistically, this gut bacterial-derived oxylipin promotes allergic inflammation by decreasing the frequency and IL-10 productivity of lung Treg populations (24, 68). Gamma-Tocopherol, a vitamin E metabolite, has also been implicated in increased risk of asthma in human cohorts, and has been shown to increase the inflammatory response to aeroallergens in mouse models of asthma (26, 69). Skin associated microbes and their metabolites can contribute to the development of atopic dermatitis (75). Most notably ceramides which are important for maintaining healthy skin, decrease in concentration in the context of atopic dermatitis (70). Murine models have demonstrated that decreasing *Pseudomonas* ceramidase activity alleviates skin inflammation, implicating microbial metabolic activity as a driver of atopic disease in this case (71). Additionally, in the colon commensal gut bacteria such as *Bacteroides fragilis*, produce anti-inflammatory products like polysaccharide A which decreased IL-17 production and colonic inflammation in mouse models, further identifying bacterial products of key regulators of immune cell function (73).

Moreover, gut microbial manipulation resulting in reprogramming of metabolism has beneficial effects on airway inflammatory responses. Oral supplementation of the gut microbiome with *Lactobacillus johnsonii* protects mice from airway allergic inflammatory

response to allergen exposure or viral respiratory infection (76). Introduction of this single microbial species into the gut microbiome of animals subjected to airway infection with respiratory syncytial virus resulted in significant changes in the serum metabolome 48 hours post infection, including increased concentrations of circulating PUFAs and depletion of monohydroxy fatty acids, including 12,13 DiHOME (76, 77), suggesting that gut microbiome-produced or induced metabolites that shape airway response to inhaled insults. A more recent study indicates that maternal pre-natal and pup post-natal supplementation with *L. johnsonii* affords the greatest protection against airway inflammatory response to viral infection (78), implicating microbial-influenced pre- and post-natal immune training and function as key to protection against early life airway insults.

The mechanisms by which microbiota-derived metabolites shape immune function are well described for some classes of molecules. For example, short chain fatty acids signal through activation of G-protein coupled receptors that regulate immune function as well as by inhibition of histone deacetylase which removes acetyl groups from histones rendering DNA less accessible to transcription factors. Tryptophan metabolites which include immunomodulatory microbial-derived indoxyl metabolites, signal via the aryl hydrocarbon receptor, a transcription factor that has emerged as an important player in asthma control [Reviewed in (72)]. Beyond interactions between microbial-derived metabolites and their cognate receptors, the emerging field of immunometabolism has demonstrated that immune cell phenotypes are intimately linked to their metabolic state (79–81). Microbes, particularly those in the intestine, play a key role in defining the availability of glucose, fatty acids and amino acids which are crucial to defining the immunometabolic state of immune cells. Thus, it is unsurprising that emerging data implicates the microbiome as a regulator of immune cell function via immunometabolism (82). The importance of metabolism in the function of antigen-presenting, T and B cells that are instrumental in allergic inflammation has been demonstrated (83). Naïve T cells largely rely on OXPHOS for energy biogenesis, while activated T cells derive energy primarily through glycolysis to serve as helpers to initiate B cell activation, cytotoxic effects, and cytokine production (82, 83). Recently, studies have shown that microbial metabolites such as short-chain fatty acids and tryptophan metabolites are also essential in shaping the function of a range of immune cells including epithelial, innate, and adaptive immune cells (84).

In addition to microbial metabolites being utilized as substrates by immune cells and altering their potential function, new concepts for microbial influence over immunity are arising. One important emerging idea is that microbial metabolites can influence the long-term functioning of innate immune cells through “trained immunity”. This concept describes functional reprogramming of innate immune cells via changes to their epigenetic landscape (85). These epigenetic changes re-tune responses of innate immune cells to secondary inflammatory insults, such as bacterial lipopolysaccharide, to either decrease or increase functional responses including cytokine secretion or phagocytosis. These newer data offer insights into the molecular mechanisms by which the microbiome, particularly as it develops in early life, shape immune function. Although trained immunity in the context of allergy and asthma is a relatively new field, several potential mechanisms by which trained immunity may contribute to asthma development have recently been reviewed (86). The observations provide a framework for understanding the developmental origins

of allergy and asthma in which prenatal and early life extrinsic exposures and intrinsic factors shape microbial and immune development *in utero*, setting the stage for post-natal microbial colonization trajectories that shape emerging immune function. With this in mind, a focus on maternal prenatal health and diet, in addition to reducing early life exposure to microbiome-perturbing factors such as stress, antimicrobials, formula feeding and processed foods, seem key and imminently implementable approaches to reduce disease burden. While the impact of reducing formula feeding and processed foods on allergy and asthma incidence has not yet been directly tested, they are both associated with perturbed microbiomes and are known to shape the early life microbiome (28, 87). However, a large population-based Canadian study demonstrated that the recent reduction in pediatric asthma incidence was attributable in part to improved antimicrobial stewardship in infancy and preservation of the gut microbiome (88), offering reason for optimism that reducing microbiome perturbing exposures, particularly in early life could significantly reduce disease burden.

Microbiome-immune interactions and asthma outcomes/endotype.

Over the last decade it has become clear from studies in adults that the airway microbiome in particular is altered in chronic asthma. Recent investigations have also shown that airway microbiota characteristics differ in relation to immune response patterns, especially level of type 2 (T2) inflammation (5, 89, 90). Far fewer studies have demonstrated clear relationships between the gut microbiome and adult asthma phenotype (89, 90), which is challenging for a number of reasons including failure to account for variance in the gut microbiome attributable to factors such as age, sex, diet and body mass index, as well as medications and age-related co-morbidities. In this section we briefly summarize and highlight key findings from studies in these areas.

First, we note that findings from most studies of the airway microbiome to date have analyzed sputum, which is easier to obtain, but analyses of samples collected directly by bronchoscopy also have been performed (5, 91–94). Secondly, many investigations have examined cohorts that focus on severe asthma, the latter representing a minority of the patient population but who experience disproportionate morbidity and healthcare utilization. With these potential caveats in mind, existing evidence from well-conducted studies has converged on the following observations. Airway microbiome characteristics differ across the spectrum of asthma severity and associate with clinical measures and immune biomarkers (5, 91–102). In addition, these associations may be further influenced by additional clinical factors such as treatments and co-morbidities (5, 92, 94).

Studies have shown that the composition of airway microbiota, in general, is shifted in severe asthma compared to milder asthma. In some severe asthma subjects, this is reflected by an enrichment in specific bacterial groups, such as members of the *Proteobacteria*, a large phylum that includes representative species that are potential respiratory pathogens (87, 89, 96). Far fewer studies of the microbiome have been conducted in subjects with mild asthma. However, carefully conducted comparisons have shown that even in those with mild atopic asthma, the configuration of the airway microbiome differs from both non-atopic healthy individuals and atopic individuals without asthma (5, 92, 98).

These observations, in concert with the known immunological complexity of asthma, have led investigators to further interrogate microbiome-immune relationships in chronic asthma. Studies pursuing this have generally made use of accessible biomarkers of T2 inflammation (e.g., eosinophils), with some studies further defining T2 status by airway epithelial gene expression signatures (5, 91, 92, 97). While underlying molecular mechanisms and treatment options are best understood for the T2-high endotype, this is less true for non-T2 (T2-low) asthma which represents a multitude of phenotypes. The latter may include overlapping evidence of concurrent T2 pathway activation, as seen in some severe asthma patients with increased blood eosinophils but also increased sputum neutrophils. The pathobiological drivers of such differences and variation in immune responses in chronic asthma remain incompletely understood.

Recent studies have offered clues into how airway microbiome-immune interactions may impact asthma phenotype. Investigations in severe asthma cohorts have reported differences in sputum bacterial diversity associated with airway inflammatory phenotypes, indicative that microbiome alterations in severe asthma are not uniform across patients. Taylor et al. (91), found that neutrophilic severe asthma patients harbored a significantly less diverse sputum bacterial community than those with eosinophilic airway inflammation. The difference was reflected by greater prevalence in the neutrophilic group of potentially pathogenic organisms (e.g. *Haemophilus*) coupled with a reduction in *Streptococcus, Gemella*, and other bacteria traditionally viewed as respiratory tract commensals (Table 2). Similar findings were noted from another severe asthma cohort in which two sputum microbiome clusters were identified (93). The smaller cluster of subjects had neutrophil-predominant sputum, comparatively reduced diversity, and increased representation of potential pathogens. Of note subjects in this cluster also had elevated sputum or blood eosinophils, suggestive of concurrently activated T2 pathways. Lastly, an earlier study examined microbiome-immune relationships in severe asthma using bronchial epithelial brushings to characterize and compare microbial relationships to gene expression signatures (97). No specific bacteria from the brushings associated with the T2-high signature, and in congruence, bronchial biopsy eosinophil numbers inversely correlated with brush bacterial burden. In contrast, a Th17 gene expression signature correlated with multiple *Proteobacteria* members, whose increased relative abundance also correlated with less stable asthma control.

Airway microbiome differences by T2 status have also been observed in mild asthma. Measures of bronchial bacterial burden are higher in T2-low compared to T2-high mild asthma (5, 92). However, airway bacteria differentially associated with T2-low mild asthma differ from those noted above to be associated with neutrophilic severe asthma. While criteria used to define T2 status have varied between studies (e.g., airway vs. blood eosinophils vs. epithelial gene expression), additional factors likely contribute to differences in the airway microbiome between severe and mild asthma. One hypothesized factor is effects of cumulative exposure to inhaled corticosteroids (ICS). While difficult to adjust for this in cross-sectional studies of severe asthma due to high prevalence of ICS use, results of a recent randomized, placebo-controlled trial of inhaled fluticasone in subjects with mild asthma demonstrated changes in the airway microbiome (5, 92). In particular, the overall composition of airway bacteria shifted with fluticasone intervention, particularly

in non-responders, and responsiveness to fluticasone was related to differences in the baseline (pre-intervention) microbiome. Additional possible factors are other treatments not yet studied for their impact on the airway microbiome, as well as co-morbidities such as obesity. Current evidence suggests that obesity, as defined by body-mass index, is associated with differences in the airway microbiome of severe asthma patients, in addition to differences in gut microbiota (90, 97). This implicates obese state as potentially shaping the airway microbiome via mechanisms not yet defined. Lastly, many other cell types (e.g., mast cells, ILCs) and cytokines (e.g., IL-17, IL-6, IL-1b) contribute to T2 and non-T2 mechanisms in asthma (103–105). Given asthma's clinical heterogeneity, more detailed study of microbiome relationships, both in the airways and gut, to other components of the immune response could reveal additional insights that clarify opportunities for more precise therapeutic targeting.

A recent study of upper airway samples from school-aged children with asthma in the Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) trial identified six distinct airway microbiota compositions which significantly differed with respect to asthma features (14). Nasal microbiotas dominated by *Moraxella* were associated with increased exacerbation risk and eosinophil activation. Children with airway microbiota dominated by *Staphylococcus* or *Corynebacterium* were associated with reduced respiratory illness and exacerbation events, whereas *Streptococcus*-dominated assemblages increased the risk of rhinovirus infection. Only DNA was available for study, precluding the possibility of examining microbial activities that may underlie these relationships. However, a more recent study of children with severe asthma in the Mechanisms Underlying Asthma Exacerbations Prevented and Persistent With Immune-Based Therapy trial found that interactions between discrete networks of bacteria with specific epithelial transcriptional modules increase asthma exacerbation risk following respiratory viral infection (15). Specifically, discrete networks of upper airway bacteria comprising either *Streptococcus* or *Staphylococcus* exhibited opposing interactions with an exacerbation-associated SMAD3 nasal epithelial transcriptional module to significantly increase odds of subsequent exacerbation. Of note the airway microbiota exhibited temporal, seasonal dynamics and these relationships predominated in the fall (14).

Conclusions and Future Directions

The future for asthma and allergy research depends upon deeper understanding of molecular mechanisms that underlie both the trajectory to disease development and endotypes once established. This will be facilitated through the application of high-resolution immune and microbial cellular and molecular profiling approaches to samples collected longitudinally from multiple diverse and well-characterized human cohorts. Given the numerous factors that shape microbiomes which in turn tune immune function, we envision a future where cost-effective metabolomic pre- and/or postnatal screening can be utilized both as a prognostic tool to determine disease risk and as a monitor for microbial-immune status throughout development to identify those at risk and determine efficacy of interventions to alter disease course.

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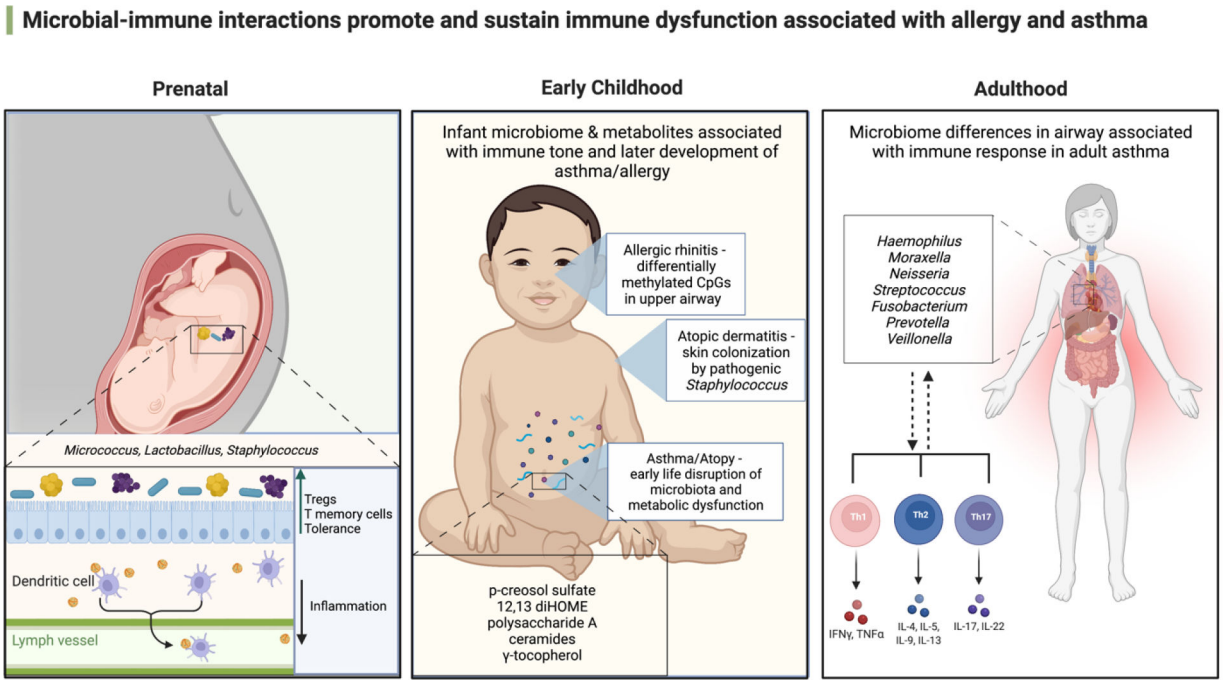

Figure 1.

Microbial immune interactions promote and sustain immune dysfunction associated with allergy and asthma. Adapted from BioRender.com. Lipid handling in the small intestine modulates immune system homeostasis. https://app.biorender.com/biorender-templates.[29]

Table 1.

Recently identified microbial metabolites that shape immune function in early life.

Bacterial derived metabolite	Molecule class	Influence on immunity	Allergic disease association	Reference
p-cresol sulfate	Amino acid derivative	Reduces CCL20 production	Atopy/asthma	67
12,13-diHOME	oxylipin	Decreases lung Tregs and IL-10 production	Atopy/asthma	24, 68
Gamma-Tocopherol	Vitamin E metabolite	Increases CCL11, amphiregulin, activin A, and IL-5	Atopy/asthma	69
ceramides	lipid	Reduce mast cell numbers	Atopic dermatitis	70,71
Tryptophan metabolites	Amino acids	Aryl hydrocarbon receptor ligation	asthma	72
Polysaccharide A	carbohydrate	Decreases Th17 inflammation	Colonic inflammation	73

Table 2.

Main respiratory bacteria (genus) and reported associations with asthma. Species-level differences likely exist but are not discernible by the 16S rRNA sequencing methods used in most studies.

Bacterial genus	Compartment	Outcome association(s)	References
Haemophilus	nasopharyngeal, lower respir tract	(+) asthma (T2-low in adults) (+) exacerbations in children	5,10–15,90,91,96
Moraxella	nasopharyngeal, lower respir tract	(+) asthma (T2-low in adults) (+) exacerbations in children	5,10–15,90,91,96
Streptococcus	nasopharyngeal, lower respir tract	(+) asthma (+) exacerbations in children	5,10–15,90,91
Corynebacterium Dolosigranulum,	nasopharyngeal	(—) asthma, (—) exacerbation in children	13,30
Neisseria	lower respir tract	(+) asthma status (T2-low in adults)	5,91
Fusobacterium	lower respir tract	(+) asthma status (T2-high in adults)	5,91
Veillonella	lower respir tract	(+) asthma in adults	5,91