Editorial

Dysbiosis of the respiratory tract mucosa—how microbial imbalances lead to asthma

Andrew B. Peebles[1], R. Stokes Peebles Jr[1,2,3]

[1]Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [2]Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, TN, USA; [3]United States Department of Veterans Affairs, Nashville, TN, USA

Correspondence to: R. Stokes Peebles Jr. T-1218 MCN, Vanderbilt University Medical Center, 1161 21st Avenue South, Nashville, TN 37232-2650, USA. Email: stokes.peebles@vanderbilt.edu.

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Introduction

From birth, the body's environmental interfaces adapt, mature, and interact with a dynamic community of microorganisms. These bacterial, viral, and fungal microorganisms form the microbiome, which is one part of an ecosystem that lives amongst the body's cellular infrastructure. Microbiomes play essential roles in maintaining homeostasis. Each biome influences its respective anatomical home by modulating the activity of its eukaryotic constituents. The evolving microbiomes residing in the respiratory tract can modulate immune system activity. This modulation is especially relevant from birth to age 3 years when the microbiome is most impressionable to its host environment and the immune system is most responsive to the changing microbiome (1). In recent years, increasing numbers of studies show that certain microbiome profiles influence future immune reactions implicated in respiratory illnesses such as asthma (2). Asthma is of particular importance due to its already high global prevalence, large economic burden, and increasing pervasiveness (3). In their review paper "*Respiratory tract mucous membrane microecology and asthma*", the subject of this editorial, Chen and Qiu discuss interactions between the dynamic microbiome and immune system that may lead to asthma (4). Specifically, a lack of host exposure to specific symbiotic microbiota early in life may result in immune deviation and a dysbiotic respiratory mucosal membrane. Symbiotic bacteria promote balanced immune activity by inhibiting pro-inflammatory cytokines [interleukin (IL)-4, IL-5, and IL-9], decreasing IgE production, downregulating infiltration of white blood cells, and reducing colonization of pathogens. A lower abundance of symbiotic bacteria can lead to increased pathogenic adhesion to the epithelial barrier which is the initiation site of inflammatory immune activity. Prolonged interactions between an immune system and an imbalanced microbial community can lead to diseases such as asthma. However, the mechanisms underlying microbiome-driven alterations in immune activity are still not fully understood. Understanding these mechanisms may aid in the early intervention and prevention of asthma. This editorial will analyze and supplement findings provided by Chen and Qiu's review in order to further elucidate the way in which an imbalanced microbiome contributes to a dysbiotic mucosal barrier and asthma.

The microbiome—friend or foe?

The respiratory tract microbiome consists of interconnected airways lined by epithelial cells and the microorganisms that live within these structures. It is generally accepted that the airways are populated from birth onwards by millions of different unicellular organisms of varying abundances falling predominantly under the genera *Firmicutes*, *Actinobacteria*, *Bacteriodetes*, *Proteobacteria*, or *Fusobacteria* (5,6). By the age of 3, the complexion of the microbiome is relatively stable

with only minor adaptations occurring throughout the rest of the lifespan (7). Therefore, the early years in the development of the microbiome exert the greatest intensity of growth and adaptation (7). Specifically, alterations in the relative abundance of commensal and pathogenic bacteria either confer health benefits or risk factors in asthma development. Further, certain viral exposures promote a dysbiotic airway microbiome associated with asthma phenotypes (3). Tracking human infant microbiome profiles in response to respiratory syncytial virus (RSV) infection (before 6 months) revealed a microbiome favoring pathogenic bacteria (8). For instance, the microbiome of RSV-infected infants was dominated by pathogens *Moraxella*, *Streptococcus*, *Corynebacterium*, *Dolosigranulum*, and *Haemophilus* (9). Conversely, the bacterial profile in healthy infants displayed a significantly lower abundance of *Haemophilus* and pathogenic bacteria in general, and a much higher abundance of commensals such as *Staphylococcus* (9). A similar pathogenic microbiome profile appeared in human rhinovirus (HRV)-infected infants. Compared to viral negative samples, HRV-infected infants had significantly higher relative abundance of *Moraxella*, and significantly lower abundance of *Staphylococcus* and *Bacillus* (10). *Streptococcus* became the dominant cluster following HRV infection along with changes in enhanced microbial diversity, increased bacterial load, and bacterial richness (6). These were not minor changes but profound alterations in the bacterial hierarchy of the microbiome. These maladaptive alterations of the microbiome early in its development are associated with the development of asthma. A related study showed that relative higher abundance of certain pathogenic bacteria such as *Moraxella* and *Haemophilus* were associated with wheezing episodes and developing asthma symptoms (11). Additionally, the diversity of the RSV-infected microbiome was positively associated with not only severity of viral symptoms but also a higher number of wheezing episodes at age 4 (8). However, a microbiome reflecting a greater exposure to symbiotic bacteria seems to protect against asthma. When the relative abundance of *Lactobacillus* was greater than ~0.001, none of the infants developed subsequent wheezing episodes (10). Additionally, the detection of *Lactobacillus* in infants decreased the odds of subsequent wheeze by 70% and recurrent wheeze by 80% (11). However, when the relative abundance of *Lactobacillus* was lower, infants were more at risk for future wheezing episodes (10). These findings illustrate the consequences of microbe-specific domination, as well as the fine balance between commensal and pathogenic bacteria. A study examining viral-induced cluster switching showed just how delicate this balance is. Cluster switching in infants following RSV infection from commensal bacteria such as *Corynebacterium* and *Dolosigranulum* to pathogenic dominated clusters of *Streptococcus* and *Moraxella* confer the greatest risk of asthma exacerbation (6). A study examining human microbiome profiles of asthmatics show these same themes in microbial alterations. During acute exacerbation of asthmatic patients, microbiomes of the nasal airway displayed changing compositions, suggesting an unstable nasal microbiota. During acute asthma exacerbations in young children, pathogenic microbial populations were significantly associated with allergic asthma. In these children, abundance of *Streptococcus* was significantly higher while *Corynebacterium* and *Dolosigranulum* were depleted. Again, these studies show that microbiome profiles that display intense changes, specifically changes from commensal dominating bacteria to pathogenic domination confer the greatest asthma risk (6,9-11). However, the question remains, how do these microbial alterations in the early life microbiome modulate response patterns of the immune system? The next section will suggest how certain microbiome profiles modulate immune activity in relationship to asthma.

Immunological conversations with the microbiome

The microbial species of the mucosal membranes are in constant conversation with their immunological neighbors. In their paper, Chen and Qiu discuss toll-like receptors (TLRs) as a critical method of communication between the microbiota and immune cells. TLRs recognize a wide variety of microbial products and the array of responses TLRs induce are in part responsible for the maturation and activation of immune cells. Due to the response of TLRs reflecting the microbial environment in which they reside, TLRs may play a role in mediating microbiome modulation of the immune system. In mice and humans, activation of TLR2 and TLR4 pathways upregulated Treg development and activation (12), suggesting a protective role of certain TLRs in immune development. However, not all TLR activation confers protective benefits, rather the microbiome composition determines the response TLRs induce. For instance, children exposed to high levels of lipopolysaccharides (LPS) in early life had decreased production of regulatory cytokines such as IL-10 compared

to children exposed to low levels of endotoxin (13). Further, LPS of pathogenic bacteria *Haemophilus* and *Moraxella* elicited 10-fold higher TLR4 signaling *in vitro* compared to the LPS of commensal bacteria (14). TLR4 signaling has also been implicated in inducing a Th1 response (15). In humans, the penta-acylated lipid A isoform induced substantial TLR4 inhibition, whereas the hepta-acylated lipid A variants are considered a potent stimulator of TLR4 signaling which led to a Th1 response (16). Thus, TLR activation by pathogenic-dominated microbiomes may be a critical mediator in the mechanisms underlying immunomodulation leading to asthma.

Chen and Qiu discuss other ways in which an imbalanced microbial environment can modulate immune activity. In their review, they reveal the protective role of symbiotic bacteria in the setting of asthma via their ability to inhibit Th2 pro-inflammatory cytokines (IL-4, IL-5, IL-9), IgE production, decrease in white blood cell infiltration, and increase in numbers of $CD4^+$ and $CD8^+$ T cells. Studies of infants infected by RSV show dampened and impaired $CD4^+$ and $CD8^+$ T cell responses likely due to RSV's ability to drastically alter the microbiome composition (17). An RSV-altered microbiome also displayed higher overall levels of Th2 and Th17 cytokines (IL-4, IL-5, IL-6, IL-13) while at the same time decreasing immunoregulatory and non-interferon (IFN) mediators (18). In another infant-RSV study, there was a positive association between infection, pathogenic-driven bacteria (*Moraxella* and *Klebseilla*), and increased in Th2 and Th17 pro-inflammatory cytokines (9). Lastly, there is an association of serum IgE with severity of asthma (19). Further, higher levels of pathogenic bacteria such as *Haemophilus* have also been positively correlated with higher IgE levels (20).

Alterations in the microbiome have significant impact on many different aspects of immune functioning, but as Chen and Qiu report, the most impactful change a microbiome may have on the immune system is inducing a dysbiotic epithelial-mucosal barrier. The epithelial mucosal barrier is the first line of defense, initiates subsequent immunological responses, and, during asthma exacerbations, is also the immunological endpoint of activity (21). In other words, a hyperreactive epithelial barrier, after being activated, will significantly increase mucus production, bronchial constriction, and vascular permeability, allowing white blood cells to infiltrate the airways (21). These phenomena are the pathological hallmarks of asthma, making it difficult to breathe. As discussed in their review, pathogenic-driven alterations in the microbiome can promote a dysregulated epithelial barrier. Alterations in microbial species and their relative abundance reflect changes in host environment and lifestyle. How the microbiome changes in response to environment is addressed next.

Environment, the microbiome, and asthma

Ultimately, cross talk does not only occur on a micro scale between bacteria and immune cells in the airway, but also occurs on a larger scale where environmental and lifestyle factors shape the microbiome profile, and this profile then shapes the body's response to future environmental encounters and lifestyle habits. As seen with birth delivery method, infants delivered by C-section have a larger relative proportion of Firmicutes and lower relative abundance of Actinobacteria compared to vaginally-delivered infants (22). Within the heightened Firmicutes, *Staphylococcus* was found at a higher relative abundance in C-section-delivered infants (22). On the other hand, commensal bacteria, such as *Corynebacterium*, were at a higher relative abundance in vaginally-delivered infants. Overall, these studies show that the taxonomic profile of airway microbiomes in vaginally-delivered infants more closely matched the previously observed nasal microbiome profile of adults than those delivered by C-section. This supports the idea that the nasal microbiome of vaginally-delivered infants may be more representative of an environment successfully colonized by stable commensal bacteria. It also shows that certain environmental interactions alter microbiome profiles and confer protection, in the case of commensal colonization, or asthma risk, in the case of pathogenic colonization. Diet also influences the development of the microbiome. Infants who were exclusively breastfed display microbiome profiles with higher abundances of commensal bacteria such as *Dolosigranulum* and *Corynebacterium* and lower abundances of pathogenic bacteria like *Streptococcus*, *Prevotella*, and *Veillonella* (23). Diet changes substantially from birth until the age of 2. Initially, infants are usually restrained to a limited diet, with solid and a more diverse range of food introduced around 6 months. Changes in diet are significant markers in the development of the microbiome and more studies examining the changing gut microbiome across these critical developmental years are needed in order to fully understand the effect diet has on the dynamic microbiome profile. Lastly, antibiotic use has a robust effect on the microbiome profile. Early life and prenatal exposure to antibiotics increased the risk for allergic asthma (24). Following maternal antibiotic use, infants had relative

higher abundance of pathogenic *Moraxella* than those who had antibiotic-free maternal environments. Further, neonatal treatment with vancomycin increased eosinophil infiltration and allergen-specific IgE as found in broncoalveolar lavage (24). In summary, environmental and lifestyle factors, especially early in life, are the source of the microbiomes' organisms, and significant changes in the microbiome reflect changes in the host's environment and lifestyle. The developing microbiome, depending on its commensal or pathogenic profile in conjunction with the immune system can either confer protection or increase the risk of asthma.

Conclusions

After analyzing Chen and Qiu's review of the respiratory tract mucosal membrane and supplementing with related literature, it is evident the microbiome has immunomodulatory abilities. Maladaptive modulatory effects are induced by alterations in the composition of the microbiome. Specifically, pathogenic bacteria and their interaction with several immunological cells and mechanisms such as T cells, toll-like receptors, IgE producing B cells, pro-inflammatory cytokine production, and cell recruitment promote a dysbiotic epithelial barrier. The dysbiotic epithelial barrier may create hyperactive epithelial responses to allergens and airway stressors, thus driving hyperinflammatory immune cascades that may lead to asthma. Changes in microbiomes are a result of host environment and lifestyle. Thus, exposure to symbiotic microbial communities early in life is of critical importance in respiratory health. Additionally, a further understanding of the wide ranges of immunological responses to altered microbiomes is needed.

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References

1. Laue HE, Coker MO, Madan JC. The Developing Microbiome From Birth to 3 Years: The Gut-Brain Axis and Neurodevelopmental Outcomes. Front Pediatr 2022;10:815885.
2. Hufnagl K, Pali-Schöll I, Roth-Walter F, et al. Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol 2020;42:75-93.
3. Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. Front Pediatr 2019;7:246.
4. Chen X, Qiu C. Respiratory tract mucous membrane microecology and asthma. Ann Transl Med 2019;7:495.
5. Moore RE, Townsend SD. Temporal development of the infant gut microbiome. Open Biol 2019;9:190128.
6. Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms 2019;7:14.
7. Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. Allergol Int 2017;66:515-22.
8. Rosas-Salazar C, Tang ZZ, Shilts MH, et al. Upper

respiratory tract bacterial-immune interactions during respiratory syncytial virus infection in infancy. J Allergy Clin Immunol 2022;149:966-76.
9. Rosas-Salazar C, Shilts MH, Tovchigrechko A, et al. Differences in the Nasopharyngeal Microbiome During Acute Respiratory Tract Infection With Human Rhinovirus and Respiratory Syncytial Virus in Infancy. J Infect Dis 2016;214:1924-8.
10. Rosas-Salazar C, Shilts MH, Tovchigrechko A, et al. Nasopharyngeal Lactobacillus is associated with a reduced risk of childhood wheezing illnesses following acute respiratory syncytial virus infection in infancy. J Allergy Clin Immunol 2018;142:1447-1456.e9.
11. Zhou Y, Jackson D, Bacharier LB, et al. The upper-airway microbiota and loss of asthma control among asthmatic children. Nat Commun 2019;10:5714.
12. Dai J, Liu B, Li Z. Regulatory T cells and Toll-like receptors: what is the missing link? Int Immunopharmacol 2009;9:528-33.
13. Braun-Fahrländer C, Riedler J, Herz U, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med 2002;347:869-77.
14. Bernasconi E, Pattaroni C, Koutsokera A, et al. Airway Microbiota Determines Innate Cell Inflammatory or Tissue Remodeling Profiles in Lung Transplantation. Am J Respir Crit Care Med 2016;194:1252-63.
15. Vuillermin PJ, Macia L, Nanan R, et al. The maternal microbiome during pregnancy and allergic disease in the offspring. Semin Immunopathol 2017;39:669-75.
16. Park BS, Song DH, Kim HM, et al. The structural basis of lipopolysaccharide recognition by the TLR4-MD-2 complex. Nature 2009;458:1191-5.
17. Chirkova T, Rosas-Salazar C, Gebretsadik T, et al. Effect of Infant RSV Infection on Memory T Cell Responses at Age 2-3 Years. Front Immunol 2022;13:826666.
18. Turi KN, Shankar J, Anderson LJ, et al. Infant Viral Respiratory Infection Nasal Immune-Response Patterns and Their Association with Subsequent Childhood Recurrent Wheeze. Am J Respir Crit Care Med 2018;198:1064-73.
19. Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320:271-7.
20. Chiu CY, Chan YL, Tsai MH, et al. Cross-talk between airway and gut microbiome links to IgE responses to house dust mites in childhood airway allergies. Sci Rep 2020;10:13449.
21. Heijink IH, Kuchibhotla VNS, Roffel MP, et al. Epithelial cell dysfunction, a major driver of asthma development. Allergy 2020;75:1902-17.
22. Shilts MH, Rosas-Salazar C, Tovchigrechko A, et al. Minimally Invasive Sampling Method Identifies Differences in Taxonomic Richness of Nasal Microbiomes in Young Infants Associated with Mode of Delivery. Microb Ecol 2016;71:233-42.
23. Rosas-Salazar C, Shilts MH, Tang ZZ, et al. Exclusive breast-feeding, the early-life microbiome and immune response, and common childhood respiratory illnesses. J Allergy Clin Immunol 2022;150:612-21.
24. Russell SL, Gold MJ, Hartmann M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep 2012;13:440-7.

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