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The relationships between environmental bacterial exposure, airway bacterial colonization and asthma

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Abstract

Purpose of this review—Recent application of advanced culture-independent molecular techniques for identification of microorganisms has contributed to our knowledge on the role of early life microbial exposure and colonization in health and disease. The purpose of this review is to present the current perspectives regarding the role of microbial exposure and airway bacterial colonization on the development and the activity of asthma.

Recent findings—Recent findings continue to support the protective role of early life diverse microbial exposure against the development of atopic disease. However, airway bacterial colonization early in life serves as a risk factor for the development of asthma. Culture-independent molecular techniques for identification of microorganisms have challenged the traditional paradigm that the lower airway is a sterile compartment. Asthmatics, compared to non-asthmatics appear to have a different lung microbiome composition and some of these differences might contribute to asthma activity, severity, and corticosteroid response.

Summary—Bacterial presence in the airway appears to influence the inception and may affect the activity of asthma. Complex interactions between different types and routes of bacterial exposures, the airway and the immune system early in life may determine whether these exposures augment or reduce the risk of asthma development.

Keywords

Bacteria; Microbiome; Asthma; Atopy

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Introduction

The increase in prevalence of asthma and other allergic diseases over the past decades has been postulated to be related to a more "westernized" life style that results in a cleaner environment and a reduced environmental bacterial exposure[1]. This "hygiene hypothesis" was proposed more than 20 years ago based on the observation that household size was inversely related to the prevalence of childhood hay fever[2]. Since then, multiple epidemiological studies have provided support to this theory, including the protective effects of the farming environments against the development of atopy[3], while delivery by cesarean section, which presumably prevents an infant's early exposure to maternal gut and vaginal flora, is associated with an increased risk of childhood asthma[4].

Exposure to a diverse microbial environment could affect the development and activity of childhood asthma either directly by establishing a "normal" pattern of airway microbial colonization that might protect from colonization with bacteria that have been shown to be related to asthma development[5], or indirectly by affecting the composition of the gut microbiome. In the normal state, complex interactions between the gut microbiome and the host's innate and adaptive intestinal mucosal immune system result in differentiation of regulatory T-cells in the gut that can then be recruited to the periphery (including the lungs) and induce tolerance. In addition, a balanced composition of the gut microbiome has an important role in shifting TH2 immune skewing toward TH1 cell differentiation[6–8]. Alteration of the composition of the gut microbiome can affect these immunoregulatory processes and is a risk factor for the development of inflammatory, autoimmune, and allergic diseases[9]. Detailed reviews of the effects of the gut microbiome on the development of allergy and asthma are described elsewhere[6–8]. This review will examine the recent reports regarding the effects of environmental microbial exposure and the airway microbiome on asthma and atopy. Since the advanced knowledge that has been accumulated over the past few years is related to genetic methods for microorganism identification, we will start with a brief review of these new microbiome research tools.

Culture-independent techniques for identification of microorganisms

The field of microbiology began in the mid-17th century with the invention of the microscope, allowing for direct visualization of bacteria[10]. However, the advancement of genomic technologies allows for microbe identification while avoiding the reliance on traditional culture methods. Using these techniques, we have learned that the human body harbors 10 to 100 trillion microbes, greatly outnumbering human cells[10]. Most of these microbes were not detected previously since 70% of the bacterial species on human surfaces could not be isolated using traditional culture methods, and some of the remaining 20–30% of species could not be easily cultured[11]. Most recent microbiome studies have utilized PCR amplification of the bacterial 16S ribosomal RNA (rRNA) gene, a highly conserved locus of the bacterial genome. DNA sequence differences within the hypervariable regions of the 16S rRNA gene allow identification of bacterial species by reference to existing 16S rRNA gene sequence databases. In addition to taking the bacterial census of sample by 16S rRNA gene sequencing, microbial community profiling can be performed by next-generation sequencing approaches that analyze the total genomic content of samples. The latter method has the

advantages of more precise identification of bacteria, up to the sub-species level through identification of mutations, plasmids, or other horizontally transferred genes within a bacteria's genome, identification of specific metabolic pathways and their abundance, and identification of other classes of microorganisms such as viruses and fungi. A detailed description of these culture independent techniques is provided elsewhere[11–14].

Environmental microorganism exposure, asthma and atopy

One of the initial studies that investigated the association between environmental bacterial exposure and the development of atopic diseases included 812 children in rural areas of Europe, some of them living on farms[15]. The investigators demonstrated an inverse association between the levels of bedding dust endotoxin, a cell wall component of gram negative bacteria, and the occurrence of hay fever, atopic asthma, and atopic sensitization. Exposure to farming in the first year of life showed a strong inverse association with all clinical outcomes, suggesting that the farming environment has protective effects against the development of allergy and asthma. The inverse association between endotoxin levels and atopic outcomes were valid even in a subset of participants who did not have farming exposure, suggesting that certain types of bacterial exposure can be protective regardless of its source. Furthermore, *in vitro* cytokine production was also inversely related to the endotoxin level in the bedding, leading the authors to speculate that environmental bacteria interacts with the innate immune system and results in immune tolerance[15].

A recent study confirmed the previous finding by showing that among two cohorts of children living in rural central Europe, children living on farms had lower prevalence of asthma and atopy (defined by allergic sensitization to aeroallergens)[16]. Children living on farms were exposed to a higher diversity of environmental fungi and bacteria, and this greater diversity of exposure was inversely related to asthma prevalence independent of the farming environment, suggesting that the diverse microbial exposure is the important element for asthma prevention. The authors suggested that exposure to a diverse microbial environment might prevent asthma either by interaction of these microorganisms with the GI innate immune system that result in the induction of regulatory T-cell, and/or with a direct effect on the airway that may prevent colonization of the lower airways with harmful bacteria. Although diverse microbial exposure was important, some microorganisms exerted greater influence, as the protective effects were largely related to one group of bacterial species, and one mold (the fungal taxon eurotium)[16].

The potential effects of diverse microbial exposure on the gut microbiome, and as a result the development of atopic diseases, occurs early in life. Lower diversity of stool bacteria at the age of one month, prior to development of atopic features, was a predictor of eczema at the age of 2 years[17] and of allergic sensitization and allergic rhinitis at the age of 6 years[18]. These observations support the hypothesis that a diverse bacterial exposure very early in life may create a milieu which is less likely to support the development of atopy.

Airway bacterial presence and asthma: are the lower airways a sterile compartment?

For many years, the traditional paradigm was that the lower airways represented a sterile compartment. Recent findings using modern methodologies for identification of microorganisms challenge this paradigm, which now appears to have been a reflection of the limitations in traditional culture-dependent techniques to detect most of these microorganisms. Recent studies in healthy adults have indicated that the lower airways are not sterile[19, 20]. Interpretation of these findings is complicated by potential contamination of lower airway samples as a result of passage of a bronchoscope through the oropharynx. A study of 6 healthy adults took special efforts to avoid upper airway contamination, and revealed that bacteria found in the lower airway represented a diluted reflection of the bacteria found in the in the upper airways, suggesting that the presence of lower airway bacteria is related to micro-aspiration[20]. However, a recent study, which is the largest to date on this topic (64 healthy adults), revealed that that lung microbiota is in part similar to the oral cavity microbiota, but specific bacteria were detected in significantly higher abundance in the lungs than would be expected if they originated from the upper airway. These results suggest that at least part of the lung microbiome is unique, and some bacteria have adapted toward proliferation in the lung environment rather than being just a reflection of diluted upper airway microbiota. Moreover, the results of this study imply that lung microbiome might have a role in lung pathology as some of the bacterial communities that were overrepresented in the lungs included common causes of pneumonia, the members of the family *Enterobacteriaceae sp*. and *Haemophilus sp*.[21].

Does the composition of the lung microbiome differ between asthmatics and non-asthmatics?

Hilty et al[19] compared lower airway samples from 11 asthmatic and 8 healthy adults, and from 13 asthmatic and 7 non-asthmatic children. The lung microbiome composition among asthmatics included a greater abundance of members of the *Proteobacteria phylum*, mainly *Haemophilus* species, and lesser abundance of members of the *Bacteroidetes phylum*, mainly *Prevotella* species than non-asthmatics[19]. Huang and colleagues compared lower airway bacterial content between 42 asthmatic adults and 5 healthy adults and showed greater bacterial burden and diversity in the asthmatic subjects. Specifically, greater representation of the *Proteobacteria*[22] *phylum* was found to be overrepresented among asthmatics including many pathogenic species that might cause acute respiratory illnesses, including *H. influenzae, Pseudomonas, Neisseria*, and *Burkholderia* species, as well as members of the *Enterobacteriaceae* family[23]. Generalizability of these 2 studies is limited by the inclusion of asthmatics treated with inhaled corticosteroids (ICS), introducing uncertainty as to whether the observed differences are related to the asthma, or are at least partially related to changes in the lung microbiome induced by ICS treatment.

In an effort to characterize airway microbiota among asthmatics while minimizing confounding by ICS treatment, Mari et al[24] compared the composition of the microbiota in induced sputum samples obtained from 10 non-asthmatic and 10 asthmatic adults, 8 of

which were not using ICS. The results confirmed previous reports, showing that *Proteobacteria* were present in higher proportions in asthmatic patients, and that samples from asthmatics had greater bacterial diversity compared with samples from non-asthmatic subjects. The investigators also reported a higher abundance of *Moraxellaceae* and *Pasteurellaceae families* (to which *Moraxella catarrhalis* and *Haemophilus influenza* belong, respectively) in samples from asthmatics, which support reports on the role of these bacteria in the inception of asthma[5].

Differences in lung microbiome characteristics among asthma patients may correlate with parameters of disease severity[25]. Microbiota composition in BAL samples obtained from 12 healthy control and 39 asthmatics, defined as either corticosteroid resistant or corticosteroid sensitive, did not differ between the groups in general parameters of microbiota communities such as richness, evenness, diversity and community composition at the phylum level. However, compared to corticosteroid sensitive asthmatics, approximately half of the corticosteroid resistant subjects had unique expansion of bacteria defined at the genera level[25].

While most studies of the microbiome and asthma to date have focused on the bacterial component of the microbiome, other elements of the microbiome, such as fungi, may have a role in asthma inception and activity. In support of this, a recent study reported on differences in the pattern of fungi present in induced sputum samples obtained from asthma patients and controls[26]. Ninety fungal species were more common in asthma patients, while 46 species were more common in control subjects[26]. The fungus *Malassezia pachydermatis* was found in patients with asthma but not the control group, which suggests importance of fungal elements of the microbiome in asthma, as this organism has been associated with atopic conditions including atopic dermatitis[27]. In summary, multiple recent studies have suggested that asthmatics and non-asthmatics have different lung microbiome compositions. However, further research is needed to determine if this is an aspect of disease pathogenesis, ICS treatment, or other factors, and whether the differences in microbiome composition are the cause of the asthma, or the asthma induces a lung microenvironment that supports the proliferation of certain bacteria.

The role of airway bacterial colonization in infancy and the inception asthma

It is well established that viral infections are closely associated with the inception of early childhood wheezing and asthma[28]. The immunologic interaction between host airway epithelial cells and respiratory viruses may be responsible for translating acute viral infections into chronic airway disease[29]. Viral infections are also a major “trigger” for acute exacerbations. Emerging data have implicated early life airway colonization with bacteria as a potentially important factor in the inception of asthma. Bisgaard and colleagues[5] provided one of the first reports on this topic while investigating the effects of bacterial colonization of the hypopharynx in asymptomatic neonates born to mothers with asthma. Using traditional culture-based techniques for identification of bacteria, they noted that asymptomatic colonization of the hypopharynx with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxella catarrhalis* was associated with the development

of the persistent wheezing phenotype during the first 5 years of life, asthma diagnosis, positive bronchodilator response, and with the development of atopic markers as an elevated peripheral eosinophil count and elevated total serum IgE. However, it is not possible to determine whether these bacteria actually promote the development of asthma, or whether bacterial colonization of the upper airway is a marker for immune dysregulation very early in life, which promotes the development of asthma. This asymptomatic colonization of the hypopharynx at the age of one month was also associated with increased risk of pneumonia and bronchiolitis in the first three years of life, and the effect was independent of future diagnosis of asthma, suggesting that the development of pneumonia and bronchiolitis are not just a reflection of respiratory morbidity associated with asthma. The authors proposed that bacterial colonization of upper airway may affect the immune maturation of the neonate and result in an increased risk of pneumonia and bronchiolitis[30]. Bacterial colonization of the airway was shown to be associated with a distinct immunophenotype evident by airway cytokine patterns (Th1, Th2, Th17) that were dependent on the type of the bacteria in the airway, suggesting that colonization with these organisms is not immunologically silent[31]. It is unknown if the specific airway cytokine milieu with the context of bacterial colonization is a marker of asthma predisposition or a causal effect of the colonization. All together, these findings suggest the potential role of bacterial airway colonization by itself or in conjunction with subsequent viral infections as antecedents to childhood airway disease, especially asthma.

Airway bacterial colonization and exacerbation of early childhood wheezing episodes

Airway infections are a frequent trigger of wheezing episodes, and recent evidence suggests that in addition to viral pathogens, bacteria are frequently recovered from the upper airway at the time of acute wheezing episodes during the first 3 years of life[32]. The presence of bacteria in upper airway samples was significantly associated with wheezing episodes independent from the effect of viral infection, suggesting that bacterial colonization of the airway might directly trigger wheezing, or influence whether a viral respiratory infection will progress to an acute wheezing episode. Bacterial colonization of the airway during acute viral induced wheezing could also affect short and long term outcome of viral induced wheezing episodes. A *post-hoc* analysis in a cohort of children younger than 3 years of age hospitalized for their first viral induced wheezing episode (viral swab positive in 93% of participants) showed that 60% of these children had positive NP culture for *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. In addition, children with bacterial colonization of the upper airway had longer durations of hospitalization and were more likely to develop recurrent wheezing in the year following the initial wheezing compared to children without evidence for bacterial colonization[33].

Bacterial airway colonization is associated with asthma activity and might affect corticosteroid response

Bacterial burden and diversity in the lower airway among adults with mild-moderate asthma were significantly greater than among healthy controls[22]. Furthermore, airway microbiota

diversity was significantly correlated with bronchial hyperresponsiveness. The investigators were able to identify approximately 100 bacterial taxa that were associated with the degree of bronchial hyperresponsiveness. Among the bacteria that were more common among asthmatics were members of the *Comamonadaceae*, which include members that have *in vitro* steroid-degrading capacities. The presence of such bacteria in asthmatic airways might be related to selective growth pressure exerted by ICS. Alternatively, the presence of steroid-degrading bacteria in the airway may impair ICS treatment response, and could explain the observation that some asthma patients do not respond well to ICS[22]. This concept is supported by findings that a bacteria detected in the BAL of some corticosteroid resistant asthmatics (*Haemophilus parainfluenzae*) can reduce *in vitro* steroid responsiveness in metabolic pathways induced by corticosteroids[25]. Taken together, these findings suggest that the airway microbiome might have a mechanistic role in asthma activity either by direct effect on physiologic characteristics of asthma as bronchial hyperresponsiveness, and /or by affecting steroid metabolism pathways that can affect response to endogenous corticosteroids and/or ICS treatment.

Summary

While acute airway infections have been associated with multiple aspects of asthma for decades, recent advances in pathogen detection methods have substantially broadened the recognition of the potential microbial contributions to airway disease causation and activity. The airways, once considered a sterile location, do indeed contain a wide variety of organisms that likely impact disease expression. Recent evidence has demonstrated potential influences of the respiratory tract microbiome on asthma inception and exacerbations, thereby opening new areas for potential interventions involving microbiome manipulation with the goals of asthma treatment and prevention.

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Abbreviations

HRV	human rhinovirus
ICS	Inhaled corticosteroids
rRNA	ribosomal RNA
RSV	Respiratory Syncytial Virus

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Key points

- Exposure to a diverse microbial environment early in life is associated with a reduced prevalence of childhood asthma
- A lower diversity of gut microbiota is detectable at a very young age among infants who subsequently develop atopic disease
- Recent studies utilizing culture-independent molecular methods for identification of microorganisms have revealed that the lower airway is not a sterile compartment, and that unique lung microbiome communities most probably exist
- Asthmatics have a different lung microbiome composition compared to non-asthmatics, which includes a greater bacterial burden and diversity along with an overrepresentation of some bacterial taxa
- Specific characteristics of the lung microbiome among asthmatics, such as increased bacterial diversity, were reported to correlate with disease activity and severity and the presence of specific bacteria might be related to corticosteroid response