



Microbes and asthma: the missing cellular and molecular links

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Purpose of review

In this review, we describe the 'state-of-the-art' in our knowledge of asthma and what gaps exist, which can be exploited in the future for effective translation of our knowledge from the bench or population studies to diagnosis and therapy.

Recent findings

The advent of microbiome research has expanded the potential role of microbes in asthma. There has been a significant increase in our understanding of the pathologic, genetic, cellular and molecular mechanisms of asthma. Nonetheless, the contribution of microbes to the genesis, exacerbation and treatment of asthma are poorly understood.

Summary

Asthma is a complex chronic disease of the lung whose incidence is growing at all ages despite the progress that has been made in the areas of diagnosis and treatment of asthma. The complexity is partly due to the environmental insults such as allergens and microbial infections that play differential roles in the pathogenesis of childhood vis-à-vis elderly asthma. Microbes may play important roles in the exacerbation of asthma and hence in the comorbidities due to asthma, and also in the causation of asthma.

Keywords

asthma, elderly, eosinophil, microbe, microbiota

INTRODUCTION

Asthma is a multifaceted disorder, which over the past few decades has increased noticeably in prevalence [1[•]]. It was seen that occurrence was highest among Puerto Rican Hispanics (14.6%) and non-Hispanic blacks (10.2%) as compared with the US average (7.9%) [2]. In 2007, it was estimated that for asthma treatment, the direct medical expenditure was approximately US\$ 37.2 billion [3]. Outcomes could be improved via promotion of suitable medical care as well as adequate self-management instruction [2].

There is a significant discrepancy in asthma prevalence in different age groups. For example, currently the prevalence of asthma in patients older than 60 years of age is more than 10%. In contrast to the general population, elderly asthmatic patients have an increased mortality from lung diseases, most likely respiratory tract infections [4]. About 40% of nonpneumonic lower respiratory illnesses have been due to viral infection [5[•]]. In the elderly, asthma is commonly incorrectly diagnosed or even missed due to an uncharacteristic appearance,

underestimation of their shortness of breath, and accompanying comorbidities such as chronic obstructive pulmonary disease (COPD) [4].

In this article, we intend to review the diversity of microbes affecting asthma and examine the correlation between infection and pathogenesis of asthma and the role of microbial infection in exacerbation of asthma. Also, it is intended to identify cellular and molecular links between microbes and asthma and discuss the potential mechanisms that are under investigation and those that remain to be explored and elucidated.

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KEY POINTS

- Bacteria have now been recognized as a possible cause of asthma, whereas fungal microbes have been identified in exacerbation cases.
- Asthmatic patients were noted to have more proteobacteria in their respiratory system, whereas nonasthmatic individuals were seen to have more bacteroidetes.
- The potential link between microbial infections and asthma is now thought to be innate immune cells such as eosinophils, neutrophils and the myeloid-derived suppressor cells.
- Cytokines and chemokines elaborated by infections constitute the molecular mechanisms linking microbial infections to asthma.

ASTHMA PATHOGENESIS

It has been suggested that most allergen-driven asthma in genetically predisposed children or adults is typically Th2 and eosinophil-dominant. In contrast, it has been suggested that asthma in older patients may be under epigenetic control and may be exacerbated by viral and bacterial pathogens instead of allergens, and may involve Th1 and/or Th2 cells and exhibit neutrophil dominance. A Venn diagram comparing asthma in children versus that in the elderly is depicted in Fig. 1 [6–9].

The pathogenesis of childhood asthma consists not only of genetic tendencies and environmental effects but also developmental influences, as this is a period of rapid growth not only for the lung but also for the immune system [6]. It is strongly connected to atopy, which is a genetic tendency to produce immunoglobulin E antibodies as a reaction to everyday exposures that is associated with Th2 responses, characterized by increased levels of Th2 cytokines such as interleukin (IL)-4, IL-5, IL-6 and IL-13 and increased levels of total and allergen-specific antibodies [10].

The pathogenesis of the asthma phenotype in elderly asthmatic patients is still poorly understood [11]. The function of eosinophils remains the same, but the amount of neutrophils goes up [12]. Immunosenescence, which is the enhanced vulnerability to begin or aggravate airway inflammation, has been recognized to shape the innate and adaptive immune systems with age [4,11]. For example, studies in older asthmatic patients have presented changes in the innate immune system via senescence of epithelial cells of the lung, augmented neutrophils in the airway, reduced function of eosinophils and a decline in the number of macrophages

and cytotoxic natural killer cells. Adaptive immune system modifications presented were the reduction in the performance of dendritic cells and a persistent proinflammatory condition illustrated by high quantities of tumor necrosis factor α (TNF- α), IL-1 and IL-6 [4].

CD4⁺ regulatory T (Treg) cells repress the effector performance of T-cell subsets such as Th1, Th2 and Th17. Natural Treg cells express the transcription factor forkhead box protein 3 (FoxP3) and facilitate suppression principally via cell-to-cell interaction. Various studies of asthma with aging have proposed a protective role of Treg cells. Furthermore, this study by Vale-Pereira *et al.* [11] determined that aging asthmatics had decreased FoxP3 mRNA expression in peripheral blood mononuclear cells. This maintains the notion of reduced immune tolerance by Treg cells in elderly asthmatic patients and therefore favors a persistent inflammatory process. Another study involving mouse models stated that initial infection of the mice with the gastric pathogen *Helicobacter pylori* increases the number of Treg cells in the airways and may therefore protect against the formation of asthma. As it was seen that the number of immature dendritic cells increased along with the number of Treg cells in the lungs of neonatally-infected mice, this study hypothesized that *H. pylori*-induced Treg cells could provide protection against airway inflammation by blocking the growth of dendritic cells in the lung [13].

DIVERSITY OF MICROBES

A general presumption is that the human microbiome is favorable to the host because of the stimulation and development of immune systems, maturation of mucosal structure and function as well as delivering actual 'colonization resistance' against pathogen attack [14]. Typically, the lung has been understood to be sterile with little to no specific microbiome in a normal person. Instead, the lung holds quantities of bacterial communities comparable to the upper respiratory tract, which may be steady or transient [15].

Frequent causes of acute wheezing and exacerbations of asthma are due to both respiratory infections and allergen exposure [16]. Potential pathogens include respiratory syncytial virus (RSV), human rhinovirus (HRV), human metapneumovirus, human parainfluenza virus (HPIV), human bocavirus, influenza viruses, adenoviruses and enterovirus. Both RSV and HRV have been most commonly linked to the exacerbation of asthma as well as its pathogenesis [7]. Low levels of parainfluenza and influenza viruses have generally been detected in asthma exacerbations [17].

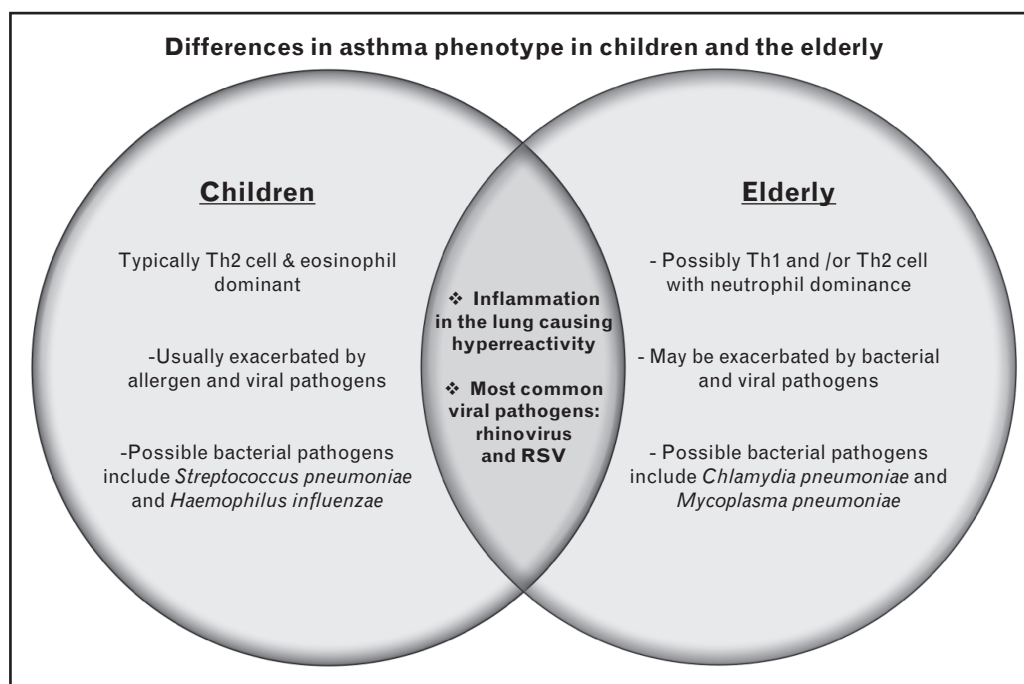


FIGURE 1. Comparison of asthma in children and the elderly. Asthma in children is more Th2 type and eosinophilic in nature as opposed to the elderly, in whom asthma is more infectious and neutrophilic [6–9]. RSV, respiratory syncytial virus.

Newer studies have begun to implicate typical bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, as well as atypical bacteria such as *Chlamydia pneumoniae*, as being responsible for acute wheezing in children [18]. *Chlamydia* appears to promote innate immunity via pro-inflammatory cytokines and allergic reactions by a Th2 cellular pathway as well as adaptive immunity via antibody production [8]. Table 1 [5,12,13,19–24] lists the possible different microbes involved in the causation and/or exacerbation of asthma.

Fungal infections have developed into a considerable healthcare problem in recent years and there has been a remarkable increase in the incidence of fungal respiratory tract illnesses over the past few decades [23]. Indoor fungal exposure showed an elevation in asthma exacerbations, whereas outdoor contact was more clearly linked to symptom impairment. In a two-year prospective analysis, the most frequently retrieved outdoor fungi included the *Aspergillus*, *Cladosporium*, *Penicillium* and *Alternaria* genera [24].

MICROBIOME AND ASTHMA

The outermost sections of the nose, the nostrils, assist in filtering inhaled air and are dominated by bacteria from the classes *Staphylococcus*, *Corynebacterium* and *Propionibacterium*. Studies using 16S rRNA gene clone libraries found that actinobacteria were the most common species from this site. On the

contrary, the oropharynx harbors bacteria from the classes *Streptococcus*, *Haemophilus* and *Neisseria*, with minor amounts of *Staphylococcus* and assorted anaerobic bacteria [20]. It has been noted that children with asthma had more proteobacteria in their respiratory system, including pathogens such as influenza, whereas those without asthma were seen to have more bacteroidetes, bacteria that are found in the environment such as seawater and soil [21].

Huang *et al.* [22], in a first of its kind study, postulated that the airway maintains a multifarious group of bacteria that may add to clinical aspects of asthma among asthmatic patients who use inhaled corticosteroids. Also noted was that the amount of hyperresponsiveness in the bronchi demonstrated by participants was associated with community organization and the amount of particular bacterial families encompassing the microbiota in the airway. It was suggested that occupation by certain bacteria could promote inflammation, disease production and, possibly, even disease heterogeneity (Table 2) [25–35]. For example, bacteria in the family Comamonadaceae, which have the ability to break down steroids, can potentially be a factor in steroid resilient asthma pathology [22].

The gastrointestinal tract of a human is considered sterile prior to birth, with establishment of microbes directly after birth and completion by the age of two years. Throughout life, populations of intestinal flora are fairly steady and hard to alter permanently [36]. Also, diet was reported to have a

Table 1. The microbes involved in causation and exacerbation of asthma

	Genome	Causation/exacerbation	References
Bacteria			
<i>Streptococcus pneumoniae</i>	Gram positive, α-hemolytic	++/-	[12,19]
<i>Haemophilus influenzae</i>	Gram negative, rod shaped	++/-	[12,19]
<i>Moraxella catarrhalis</i>	Gram negative, oxidase positive	++/-	[12,19]
<i>Staphylococcus aureus</i>	Gram positive	++/-	[12,19]
<i>Ureaplasma urealyticum</i>	Lack a cell wall	++/-	[12,19]
<i>Chlamydia pneumoniae</i>	Obligate intracellular pathogen	++/++	[12,19]
<i>Mycoplasma pneumoniae</i>	Lack a cell wall	-/++	[12,19]
Virus			
RNA			
Picornaviruses	ss positive		
Human rhinovirus		-/+++ (20–80%)	[12,13,20–22]
Paramyxovirus	ss negative		
Respiratory syncytial virus		++/+++ (5–50%)	[5 ^a ,12,13,20–22]
Human metapneumovirus		-/++ (2–13%)	[12,13,20–22]
Human parainfluenzavirus		-/+ (1–8%)	[12,13,20–22]
Orthomyxovirus	ss negative		
Human influenza A, B, C virus		-/+ (1–9%)	[12,13,20–22]
Coronavirus		ss +ve	
HCoV-229E			
HCoV-NL63			
HCoV-OC43			
HCoV-HKU1		-/+ (1–4%)	[12,13,20–22]
DNA			
Adenovirus	ds linear	-/+ (<7%)	[12,13,20–22]
Bocavirus	ss circular	-/+ (6–13%)	[12,13,20–22]
Fungus			
Aspergillus	Thermotolerant, ubiquitous	-/++	[23,24]
Cladosporium		-/++	[23,24]

+, ++, +++ represents degree of evidence showing causation; – depicts no evidence.

substantial influence on the configuration of the gut microbiota [37^a]. Several studies have determined that the microbiota of allergic and nonallergic infants are distinct even before the progression of symptoms, with the most critical period being the first 6 months [38]. At one time, the gut microbiota was believed to be only destructive, but now it is clear that commensal bacteria perform many favorable tasks as well, such as organizing the inflammatory reactions [37^a]. Findings have shown that *Staphylococcus*, Enterobacteriaceae, *Bacteroides* and *Clostridium* are linked to an increased chance for atopic disease while *Bifidobacterium* and *Lactobacillus* presented a more shielding outcome [38]. For instance, children from urban cities of Sweden harbored less *Bifidobacterium* and *Lactobacillus* and more *Staphylococcus* and *Clostridium* in their bowels compared with children from Estonia, where asthma is

not prevalent. Nondigestible nutrients called probiotics have been used to selectively promote an increase of bifidobacteria and lactobacilli [39].

As an increasing trend in various parts of the world, probiotics have been encouraged as a way to control allergic diseases. It has been recognized since the beginning of the 20th century that lactic acid bacilli in fermented milk can produce advantages in health [36]. Theoretically, probiotics could regulate Toll-like receptors (TLRs) leading to a Th1 response [39]. However, currently, there is no hard evidence based on human studies to support an advantageous role of probiotics in the management of asthma [36]. It may be necessary to include dietary concerns in future studies, because probiotics need fiber for their metabolism. It is also unclear in these prior studies whether the probiotics were able to persist during their passage through the stomach [37^a].

Table 2. List of bacteria from the proteobacteria phylum involved in bronchial hyperresponsiveness^a

Family/taxon representative species	Clinical manifestations	References
Bartonellaceae/ <i>Bartonella quintana</i>	Trench fever, chronic bacteremia, endocarditis, bacillary angiomatosis, lymphadenopathy and recently correlated with bronchial hyperresponsiveness	[25]
Caulobacteraceae/ <i>Brevundimonas diminuta</i>	Undetermined clinical significance, possible nosocomial infections and recently correlated with bronchial hyperresponsiveness	[26,27]
Comamonadaceae/ <i>Comamonas testosteroni</i>	Rarely been implicated in human infections of the abdomen, bloodstream, central nervous system, and urinary tract. Recently correlated with bronchial hyperresponsiveness	[28]
Enterobacteriaceae/ <i>Serratia fonticola</i>	Possible respiratory tract infections and recently correlated with bronchial hyperresponsiveness	[29,30]
Nitrosomonadaceae/ <i>Nitrosomonas eutropha</i>	Recently correlated with bronchial hyperresponsiveness	[31]
Nitrosomonadaceae/ <i>Nitrosomonas europaea</i>	Recently correlated with bronchial hyperresponsiveness	[32]
Ralstoniaceae/ <i>Wautersia paucula</i>	Strains have sporadically been isolated from blood, wounds, sputum, urine, eye, throat and peritoneal fluid. Recently correlated with bronchial hyperresponsiveness	[33]
Shewanellaceae/ <i>Shewanella</i> sp.	Rarely implicated in cellulitis, bacteremia, otitis infections, respiratory distress, intra-abdominal infection, pneumonia, and empyema. Recently correlated with bronchial hyperresponsiveness	[34]
Sphingomonadaceae/ <i>Sphingomonas paucimobilis</i>	Nosocomial infections, rarely been isolated from blood, sputum, urine, wound, bile, cerebrospinal fluid, vagina and cervix. Recently correlated with bronchial hyperresponsiveness	[35]

^aCompiled based on the report by Stein *et al.* [31].

It has been recognized for many years now that children raised on farms are less likely to develop asthma and allergies than others. This is the essence of the 'hygiene hypothesis', which is the notion that the comparatively germ-free lifestyle most of us now live can disturb the maturation of the immune system [21]. These ideas presumably led to the 'diet hypothesis', which suggests a different idea, in which the children living on farms have a vastly different diet from those in urban environments. A noteworthy challenge to the hygiene hypothesis is the case of Japan, where there is a great amount of hygiene and development but fewer cases of asthma than in the United States. Another example is that of the American urban lower class, which have a greater number of asthma cases as well as infectious diseases suggesting that diet has more of a correlation than originally believed [37^{*}].

LINKS BETWEEN MICROBES AND ASTHMA: WHAT ARE THE MECHANISMS?

Asthma is a chronic inflammatory disorder of the airways comprising several cells and mediators [17]. It is a type 1 hypersensitivity reaction characterized by inflammation, recurrent bronchial obstruction, mucus hypersecretion and bronchial hyperreactivity.

The principal cells involved are eosinophils, CD4⁺ T cells and mast cells [40]. Studies show that Th2 cells, which are part of the adaptive immune response, predominate in asthma [17]. Mast cells are chief cells in the immediate reaction in asthma. After an initial exposure, allergens or pathogenic antigens may trigger mast cells to begin their IgE-mediated degranulation within minutes following their next contact. Granules from mast cells contain proinflammatory molecules such as heparin, proteases, TNF and histamine. Leukotrienes and prostaglandins are also secreted from these cells, which begin the activation of basophils, eosinophils, T cells, macrophages, neutrophils and other immune cells in the lung, which further cause an immediate reaction with symptoms such as bronchial spasms, edema and smooth muscle contraction [40].

Pathogenic link

A dynamic relationship occurs between the respiratory host defenses and the microbial flora which inhabit the airway mucosal surfaces or enter via inhaled air. Each segment of the respiratory tract is predisposed to disease. The respiratory epithelium is an important barricade which includes a coating of mucus secretions, immunoglobulins and cilia

that generate mucociliary clearance. It has been noted that with age, there is a decrease in mucociliary performance due to a delayed clearance time and a decrease in the rate of ciliary beating [8]. The inhaled air then travels down the trachea toward the alveolar space while the bronchial mucosa entraps microbes, allergens and debris to either remove or react to them. The mucus and goblet cell secretions capture these particles to be driven back up the airway, whereas the macrophages and dendritic cells take up various molecules. The host must be able to authorize discriminatory antigen tolerance, otherwise it would react to every environmental antigen that was inhaled. Once the air makes its way to the respiratory bronchioles, the surfactant proteins assist in controlling inflammation via the innate immune response. When a bacterium presents to the alveolus, it becomes opsonized and phagocytized by a macrophage possibly requiring a C3b fragment. If necessary, macrophages discharge chemokines that create inflammation and draw neutrophils [8].

Cellular links

Despite extensive studies, questions still remain as to the pathophysiological link between infection and long-term allergic disease [41^{***}]. Numerous studies have demonstrated the consequence of wheezing due to lower respiratory viral infections and the subsequent risk of asthma [42^{*}]. The latest theory for the development of asthma is that viral infections function along with allergy to generate the essential immune and physiologic conditions for asthma pathogenesis [41^{***}].

Eosinophils, usually thought to be key effector cells in asthma, are also considered as a potential link between viral infections and asthma. Recruitment of eosinophils is considered to be a key trigger of the inflammation, which leads to bronchoconstriction, destruction of tissue and ultimately respiratory dysfunction. Lately, studies have demonstrated eosinophils stimulating the removal of viruses and antiviral host immunity and, more specifically, decreasing the infection of RSV in epithelial cells *in vitro*. Although no direct research has established a causal correlation, an extended study involving the viruses occurring during the winter and the timing of birth independently predicted the incidence of asthma [41^{***}].

Acute viral and bacterial infections of the lung also cause neutrophil infiltration to the lungs as part of the innate immune response. This is particularly true for nonallergic individuals, who have fewer circulating eosinophils [43]. There is increasing evidence showing that significant numbers of neutrophils are present in the lungs of some patients with

chronic asthma as well as in some patients whose death has been connected to exacerbations of asthma. One study suggested that intratracheal antigen challenge-induced late asthmatic response (LAR) is partially facilitated by the invasion of neutrophils but not eosinophils. This antigen-stimulated neutrophilia was reliant on activated CD4⁺ cells that participated in the production of IL-17A, keratinocyte-derived chemokine and macrophage inflammatory protein 2 [43]. Further, during an inflammatory response, circulating neutrophils must cross the blood vessel endothelium in a luminal-to-abluminal direction to gain access to injured lung tissue. A recent report has shown that trans-endothelial migration does not always proceed in one direction only; neutrophils can undergo 'reverse transendothelial migration' and potentially spread the inflammatory response to other tissues [44].

Moreover, a heterogeneous group of myeloid cells, termed myeloid-derived suppressor cells (MDSCs), is known to accumulate in almost all known inflammatory conditions. MDSCs comprise pathologically-activated precursors of granulocytes, macrophages and dendritic cells. They are characterized by a potent ability to inhibit T-cell functions. Our unpublished studies in mice, which involved injection of low doses of bacterial lipopolysaccharide or RSV infection showed a significant expansion and accumulation of the MDSC population. The increase was associated with proinflammatory factors such as IL-7 and IL-17. Thus, MDSCs might be involved as a regulatory component of the immune system and protect tissue from immune-mediated damage. Under physiological conditions, these cells are absent and exist as immature myeloid cells. In conditions of chronic infection or inflammation as seen in asthma, there is a marked expansion of and activation of a large population of myeloid cells with immunosuppressive abilities. These MDSCs accumulate in peripheral lymphoid organs and home to sites of inflammation, where they contribute to immunosuppression and are particularly relevant to elderly asthmatic patients. A schematic illustration of the role of MDSCs in asthmatic patients is shown in Fig. 2. Furthermore, some evidence suggests that MDSCs can also induce the expansion of Treg cells. Future studies will reveal the biology of these cells in asthma and whether they can be considered part of a natural immune regulatory network.

Molecular links

The major molecular links between microbial infection and asthma comprise activation of the innate

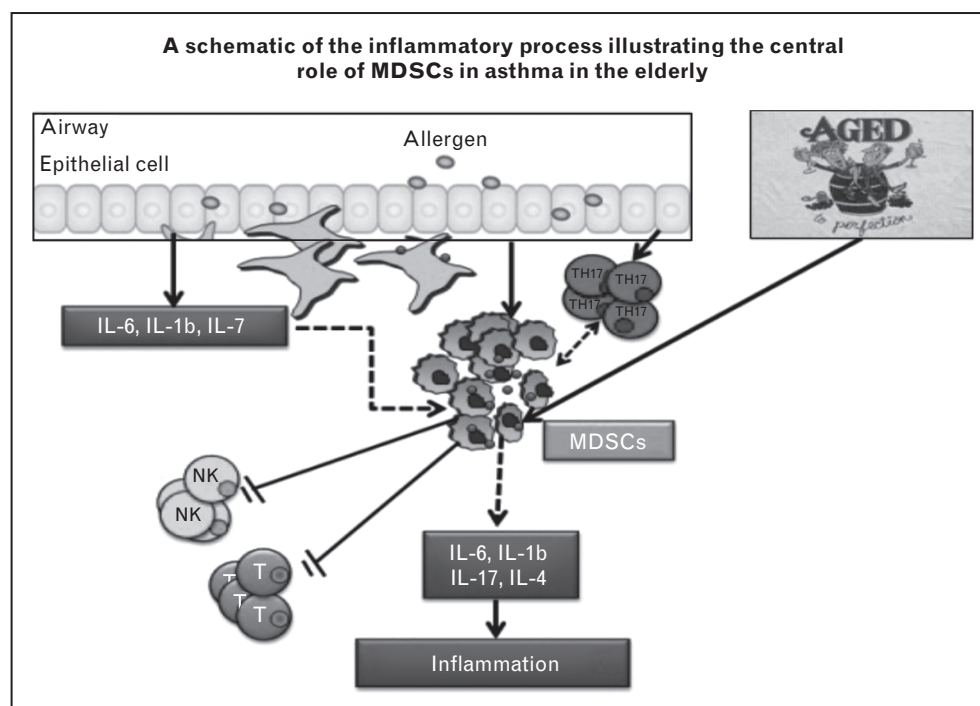


FIGURE 2. The respiratory system in older adults is continuously exposed to a barrage of potentially harmful external factors, leading to systemic inflammation. Inflammation involves a well orchestrated group of cytokines and cellular events from an acute to a chronic stage. Acute inflammation begins with the exposure of airway epithelium to environmental factors such as allergens, viral and bacterial infections, which produce a number of cytokines and chemokines including IL-6, IL-1 β , IL-17 and tumor necrosis factor α . These cytokines then act on monocytes and activate both the innate and adaptive immunity in the lung. The myeloid-derived suppressor cells (MDSCs) play a central role in the process.

immune system of the host via a combination of innate immune cells and molecules necessary for the detection and removal of pathogens via activation of a number of signaling pathways that initiate antimicrobial response, a cascading inflammatory response associated with innate immune activation, and the production of cytokines and chemokines that also play a role in asthma pathogenesis. In order to invade host cells, intracellular microbes must regulate both the innate and adaptive immune systems [45].

The innate immune system has a crucial part in identifying viral infections and inducing primary antiviral responses. Once the virus inhabits its host, infected nonimmune cells identify it and, with the help of innate immune cells, they promptly induce a response by the assembly of type I interferons (IFNs) and proinflammatory cytokines. Intracellular signaling cascades monitor the expressions of these genes, which are triggered by germline-encoded pattern recognition receptors. Nucleotide-binding oligomerization domain-like receptor (NLR) proteins, which exist in 'inflammasomes', TLRs and retinoic acid-inducible gene I-like receptors (RLRs) are groups of innate pattern recognition receptors that recognize viral RNAs or DNAs. TLRs

mainly distinguish viruses within the endosomal compartments, whereas RLRs are important in the recognition of cytosolic pathogens [46].

Bacteria may be divided into two major classes depending upon different staining characteristics of their cell walls, specifically Gram-positive and Gram-negative. The distinctive cell wall components stimulate the immune cells and serve as pathogen-associated molecular patterns that are recognized by specific TLRs [47]. TLRs can detect several constituents of the bacterial cell wall, such as peptidoglycan from Gram-positive bacteria and lipopolysaccharides from Gram-negative bacteria [48]. Recent studies show that intracellular bacteria infect the host cells and flourish inside the cell, thus avoiding luminal defenses, and therefore depend upon NLRs for detection [47]. These signals then instigate an inflammatory cascade, which assists in fighting the infection as well as activating the adaptive immune system [49].

The ultimate molecular mechanisms that link microbial infections to asthma include a plethora of cytokines and chemokines, which are produced in response to infection and innate and adaptive immune activation, but are also relevant to modulating asthma. Cytokines and chemokines attach to

cells and conduct cell-to-cell communications among dendritic cells and lymphocytes [47,50]. The adaptive immune system is made up of B and T cells that impart pathogen-specific immunity to the host via reordering of antigen receptor genes [48]. B cells generate pathogen-specific antibodies to counteract pathogens, whereas T cells deliver cytokines to eliminate pathogen-infected cells via their cytotoxic effects or from signals to B cells [47]. A key feature of the adaptive immune system is memory [50]. Once an antigen is presented to a naive T cell, that CD4⁺ cell will further differentiate into a T helper type 1 cell (Th1) or T helper type 2 cell (Th2). Th1 cells cause delayed type hypersensitivity reactions and specifically make IL-2 and IFN- γ . The Th2 cells produce cytokines such as IL-4, IL-5 and IL-13, which stimulate B lymphocytes to produce IgE [40].

CONCLUSION

There has been substantial progress in our understanding of the relationship between different infections and asthma. However, several significant questions remain unanswered. A major question still remaining is the impact of external microbial populations in a specific geographic location on local and systemic immunity of the humans who live in this environment, which may also be referred to as 'ecological immunity'. The microbial infections may produce differential responses based on ecological immunity. What is the role of epigenetics in asthma in the elderly and how does it differ from that in young adults and children? Where and how does fungus play a role in asthma? A better understanding of the host's genome and microbiota, and their interactions, will lead to more individualized methodologies for the prevention and management of asthma.

There has been progress in understanding the link between viral infections and the development or exacerbation of asthma, but less is known about the role of bacterial infections, and the molecular mechanism underlying the nature of the relationship remains to be elucidated for both. From the data accumulated in the literature, the development of asthma appears to arise from a multifaceted interaction between gene susceptibility and environmental aspects with viral and bacterial infection likely playing a meaningful role in asthma inception. Moreover, the local microbiota in the nasal cavity or in the lung may significantly alter the effects of exogenous infectious agent(s). An integration of ecological immunity (combines host genetics and environmental microbial burden) and local microbiota will be required to understand

the immunologic, cellular and molecular effects of microbial infection. Future studies involving appropriate populations and laboratory investigations, animal models and in-vitro studies are necessary to elucidate the links between microbial infection and either the pathogenesis of asthma or protection from the disease.

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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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 90–91).

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