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Microbes and Asthma in the Elderly: The Missing Cellular and Molecular Links

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Abstract

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 expounded the potential role of microbes in asthma. There has been significant increase in our understanding 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 co-morbidities due to asthma, and also in the causation of asthma.

Keywords

asthma; eosinophil; microbe; elderly; microbiota

1. 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 amongst Puerto Rican Hispanics (14.6%) and Non-Hispanic Blacks (10.2%) as compared to the US average (7.9%). [2] In 2007, it was estimated that for asthma treatment, the direct medical expenditure was approximately \$37.2 billion US dollars. [3] Outcomes could be improved via promotion of suitable medical care as well as adequate self-management instruction. [2]

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Conflicts of interest

Authors have no conflicts of interest to declare.

There is significant discrepancy in asthma prevalence in different age groups. For example, currently the prevalence of asthma in patients >60 years of age is more than ten percent. In contrast to the general population, elderly asthmatics have an increased mortality from lung diseases, most likely respiratory tract infections. [4] About 40% of non-pneumonic 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 report, we intend to review the diversity of microbes affecting asthma, 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, which are under investigation and those that remain to be explored and elucidated.

2. Asthma Pathogenesis

It has been suggested that mostly 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 Figure 1.

The pathogenesis of childhood asthma consists not only of genetic tendency and environmental effects but also developmental influences since this is a period of rapid growth for not only the lung but also 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 IL-4, IL-5, IL-6 and IL-13 and increased levels of total and allergen specific antibodies. [7]

The pathogenesis of the asthma phenotype in elderly asthmatics is still poorly understood. [8] The function of eosinophil remains, but the amount of neutrophils goes up. [9] 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. [4,8] For example, studies in older asthmatics 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 amount 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 TNF- α , IL-1 and IL-6. [4]

CD 4+ regulatory T (Treg) cells repress the effector performance of T cell subsets, such as Th1, Th2 and Th17. Natural Treg cells depict the transcription factor forkhead box protein 3 (FoxP3) and facilitate suppression principally via cell-to-cell interaction. Various data of asthma with aging have proposed a protective role of Treg cells. Furthermore, this study determined that ageing asthmatics had decreased FoxP3 mRNA expression in peripheral blood mononuclear cells. This maintains the notion of reduced immune tolerance by Treg cells in the elderly asthmatics and therefore favors a persistent inflammatory process. [8] Another study involving mouse models stated that initial infection of the mice with the gastric pathogen *Helicobacter pylori* improves the amount of Treg cells in the airways and may therefore protect against the formation of asthma. Since it was seen that the amount of immature dendritic cells went up along with the amount 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. [10]

3. Diversity of Microbes

A general presumption is that the human microbiome is favorable to the host because of stimulation and development of immune systems, maturation of mucosal structure and function as well as delivering actual ‘colonization resistance’ against pathogen attack. [11] Typically the lung has been understood to be sterile with little to no specific microbiome in a normal person. Instead, the lung holds low quantities of bacterial communities comparable to the upper respiratory tract, which may be steady or transient. [12]

Frequent causes of acute wheezing and exacerbations of asthma are due to both respiratory infections as well as allergen exposure. [13] 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 the pathogenesis. [14] Low levels of parainfluenza and influenza viruses have generally been detected in asthma exacerbations. [15]

Newer studies have begun to introduce 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. [16] *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 construction. [17] Table 1 lists all the different microbes involved in the possible causation and/or exacerbation of asthma.

Fungal infections have developed into a considerable health care problem in recent years and there has been a remarkable increase in the incidence of fungal respiratory tract illnesses over the past few decades. [20] Indoor fungal exposure showed an elevation in asthma exacerbations, whereas outdoor contact was more clearly linked to symptom impairment. A two-year prospective analysis, the most frequently retrieved outdoor fungi included the *Aspergillus*, *Cladosporium*, *Penicillium* and *Alternaria* genera. [21]

4. 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 sequences from this site. On the other hand, the oropharynx harbors bacteria from the classes *Streptococcus*, *Haemophilus*, *Neisseria* with minor amounts of *Staphylococcus* and assorted anaerobic bacteria. [22] It has been noted that children with asthma had more proteobacteria in their respiratory system, including pathogens such as influenza while non-asthmatics were seen to have more bacteroidetes, which is bacteria found in the environment such as seawater and soil. [23]

Huang et al. postulated, in a first of its kind study, that the airway maintains a multifarious group of bacteria that may add to clinical aspects of asthma among asthmatics that use inhaled corticosteroids. Also noted was that the amount of hyperresponsiveness in the bronchi demonstrated by participants was associated to 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 (see Table 2). For example, bacteria in

the family Comamonadaceae, which are recognized to have the ability to break down steroids, can potentially be a factor to steroid resilient asthma pathology. [24]

The gastrointestinal tract of a human is considered sterile prior to birth with establishment of microbes directly after and completion by about the age of 2 years and throughout life, intestinal flora are fairly steady and hard to alter permanently. [36] Also, diet was reported to have a substantial influence on the configuration of the gut microbiota. [37*] Several studies have determined that the microbiota of allergic and non-allergic 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 produce many favorable tasks as well, such as organizing the inflammatory reactions. [37*] Findings depicted 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 to children from Estonia, where asthma is not prevalent. Non-digestible 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 TLRs leading to a Th1 response. [39] However, currently there is no hard evidence based on conducted 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 since probiotics need fiber for their metabolism. It is also unclear in these prior studies if the probiotics were able to persist during their passage through the stomach. [37*]

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. [23] These ideas presumably led to the 'diet hypothesis' that suggests a different idea, in which the children living on farms have a vastly different diet from those in urban environments. A noteworthy challenge is that 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 that suggests diet has more of a correlation than originally believed. [37*]

5. Links between Microbes & Asthma: What are the mechanisms?

Asthma is a chronic inflammatory disorder of the airways comprising of several cells and mediators. [15] It is a type-1 hypersensitivity reaction characterized by inflammation, recurrent bronchial obstruction, mucus hypersecretion and bronchial hyper-reactivity. The principal cells involved are eosinophils, CD4+ T cells and mast cells. [40] Studies show that Th2 cells, which are part of the innate immune response, predominate in asthma. [15] Mast cells are chief cells in the immediate reaction in asthma. After an initial exposure, that allergen or offending pathogenic antigen may trigger these cells to begin their IgE-mediated degranulation within minutes following their next contact. Granules from mast cells include proinflammatory molecules such as heparin, proteases, tumor necrosis factor 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 of symptoms such as bronchial spasms, edema and smooth muscle contraction. [40]

Pathogenic Link

A dynamic relationship occurs amongst the respiratory host defenses and the microbial flora, which inhabits the airway mucosal surfaces or enters 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 of mucociliary performance due to a delayed clearance time and a decrease in the rate of ciliary beating. [17] The inhaled air then travels down the trachea towards 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, while the macrophages and dendritic cells take up the other items. 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 immunity response. When a bacteria 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. [17]

Cellular Links

Despite extensive studies, notably the questions still remain as to the patho-physiologic link concerning infection and long-term allergic disease. [41**] Numerous studies have begun to display 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 alongside allergy to generate the essential immune and physiologic conditions. [41**]

Eosinophils, usually thought to be key effector cells in asthma, are also considered to 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 depicted eosinophils stimulating the removal of viruses and antiviral host immunity and more specifically, decreasing the contamination 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 estimated 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 non-allergic subjects, who have less circulating eosinophils. [43] There is increasing evidence showing that neutrophils are significant 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 intra-tracheal 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 development of IL-17A, keratinocyte-derived chemokine (KC) and macrophage inflammatory protein (MIP)-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 transendothelial migration

does not always proceed down in one direction; 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 (MDSC) is known to accumulate in almost all known inflammatory conditions. MDSC is comprised of pathologically activated precursors of granulocytes, macrophages and dendritic cells. They are characterized by the potent ability to inhibit T cell functions. Our unpublished studies in mice, which involved low doses of bacterial lipopolysaccharide injection or Respiratory Syncytial Virus infection showed a significant expansion and accumulation of the MDSC population. The increase was associated with proinflammatory factors like 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 cells termed MDSC accumulate in peripheral lymphoid organs and home into sites of inflammation, where they contribute to immunosuppression and are particularly relevant to the elderly asthmatics. A schematic illustration of the role of MDSCs in asthmatics is shown in Figure 2. Furthermore, some evidence suggests that MDSCs can also induce the expansion of CD 4+ regulatory T (Treg) cells. Future studies will reveal the biology of these cells in asthma and if can be considered part of a natural immune regulatory network.

Molecular Links

The major molecular links between microbial infection and asthma comprise (i) activation of innate immune system of the host via a combination of innate immune cells and molecules that are necessary for the detection and removal of pathogens via activation of a number of signaling pathways that initiate antimicrobial response, (ii) a cascading inflammatory response associated with innate immune activation, and (iii) the production of cytokines and chemokines that play a role also in asthma pathogenesis. In order to invade the host cell, intracellular microbe 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 anti-viral responses. Once the virus inhabits its host, infected non-immune cells identify it, and with the help of innate immune cells they promptly induce a response by the assembly of type I interferons (IFN) and proinflammatory cytokines. Intracellular signaling cascades monitor the expressions of these genes, which are triggered by germline-encoded pattern recognition receptors (PRRs). Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) proteins, which exist in 'inflammasomes,' toll-like receptors (TLRs), and retinoic acid-inducible gene I (RIG-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 (PAMPs) and 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 surrounding 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 toxins distributed by pathogens, while 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 naïve 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 assist delayed type hypersensitivity reactions and specifically makes 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]

8. Concluding Remarks

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 remains is the impact of external microbial population in a specific geographic location on local and systemic immunity of humans, who live in this environment, which also may be referred to as “ecological immunity”. The microbial infections may produce differential responses based on ecological immunity. What is still unanswered about the epigenetics of asthma in the elderly and how do they contrast from those of younger adults and children? Where and how does fungus play a role in asthma? A better understanding of the qualities of a host’s genome and microbiota, and their interactions, will lead to more individualized methodologies to the prevention and management of asthma.

Further, there has been advance in understanding the link between viral infections and the development or exacerbation of asthma, but less is known on the role of bacterial infections and for both the molecular mechanism underlying the causal nature of the relationship remains to be elucidated. From the presented data, the development of asthma arises from a multifaceted communication of genetic susceptibility and environmental aspects with viral and bacterial infection likely playing a meaningful role in the effect of asthma inception. Moreover, the role of local microbiota in the nasal cavity or in the lung may significantly affect 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 investigate the immunologic, cellular and molecular effects of an incipient microbe. Future studies involving appropriate population and laboratory investigations, animal models and in vitro studies are necessary to achieve elucidate the links between microbial infections and either pathogenesis or protection of asthma.

Key Points

- Bacteria have now been recognized as a possible causation of asthma while fungal microbes have been identified in exacerbation cases.
- Asthmatics were noted to have more proteobacteria in their respiratory system while non-asthmatics 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 he myeloid-derived suppressor cells.
- Cytokines and chemokines elaborated by infections constitute the molecular mechanisms linking microbial infections to asthma.

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Differences in asthma phenotype in children and elderly

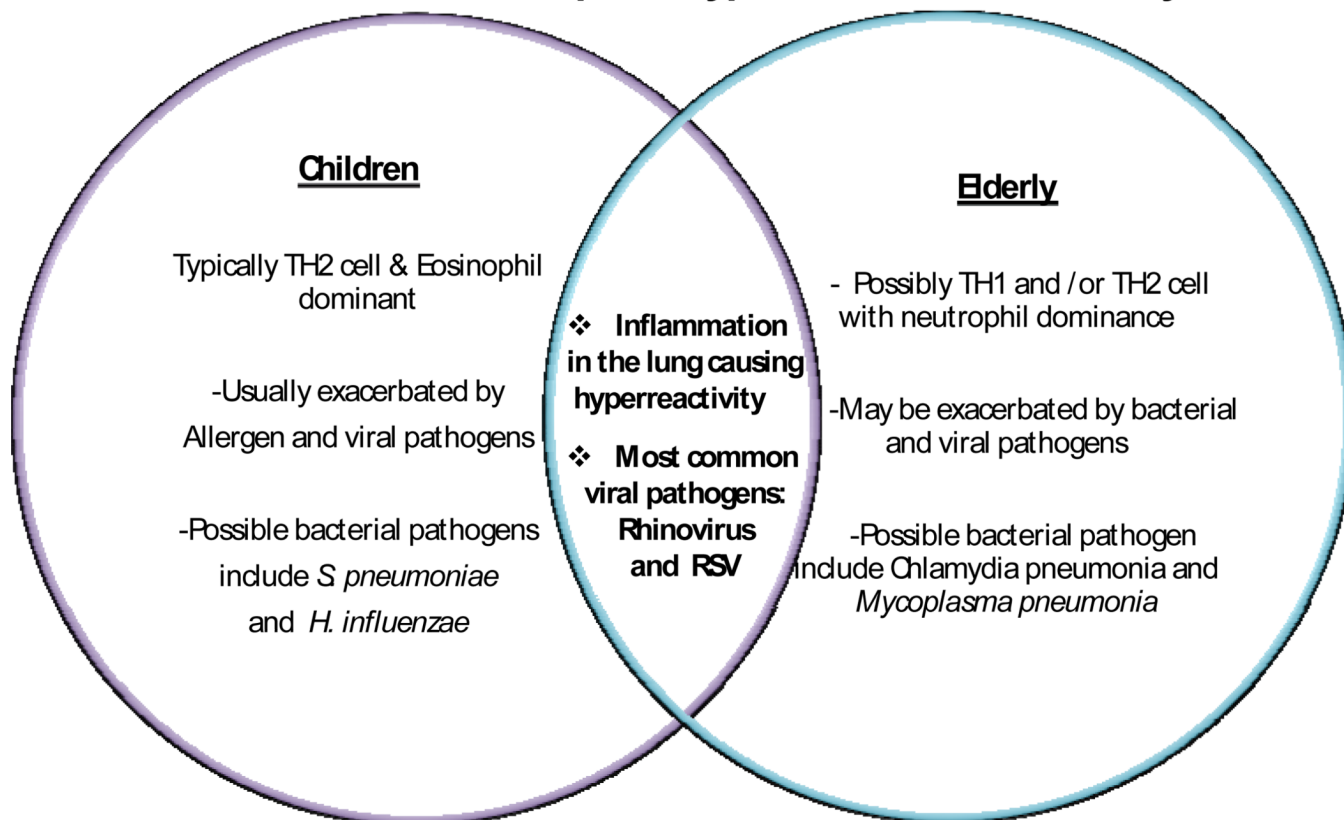


Figure 1. Comparison of asthma in children and the elderly. Asthma in children is more TH2 type and eosinophilic in nature as opposed to elderly, in whom asthma is more infectious and neutrophilic [4,6,8,9]

A schematic of inflammatory process illustrating the central role of MDSCs in asthma in elderly

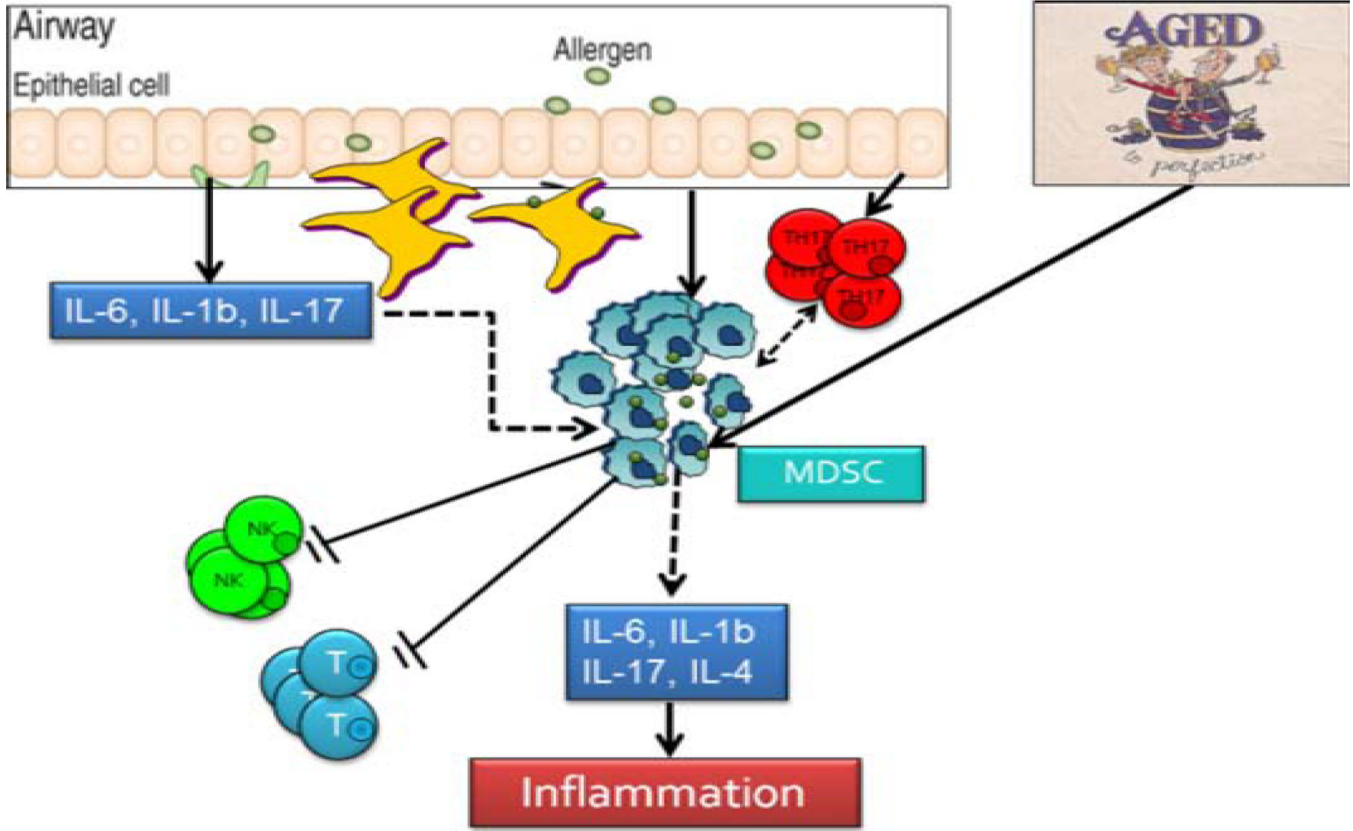


Figure 2. The respiratory system in older adults is continuously exposed to a barrage of potentially harmful external factors, leading to systemic inflammation. Inflammation involves a well-orchestrated group of cytokines and cellular events from an acute to a chronic stage. Acute inflammation, begins 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 TNF- α . These cytokines then act on monocytes and activate both the innate and adaptive immunity in the lung. The MDSCs play a central role in the process.

Table 1

The Microbes involved in Causation and Exacerbation of Asthma

	Genome	Causation/Exacerbation	References
Bacteria			
Streptococcus pneumoniae	Gram +, α-hemolytic	++/-	[9,19]
Haemophilus influenza	Gram -, rod shaped	++/-	[9,19]
Moraxella Catarrhalis	Gram -, oxidase positive	++/-	[9,19]
Staphylococcus Aureus	Gram +	++/-	[9,19]
Ureaplasma Urealyticum	Lack a cell wall	++/-	[9,19]
Chlamydia pneumonia	Obligate intracellular pathogen	++/++	[9,19]
Mycoplasma pneumonia	Lack a cell wall	-/++	[9,19]
Virus			
RNA:			
<u>Picornaviruses-</u>			
Human Rhinovirus	ss +ve	-/+++ (20-80%)	[9,10,22,23,24]
<u>Paramyxovirus</u>			
Respiratory Syncytial Virus	ss -ve	++/+++ (5-50%)	[5,9,10,22,23,24]
Human Metapneumovirus		-/++(2-13%)	[9,10,22,23,24]
Human Parainfluenzavirus		-/(1-8%)	[9,10,22,23,24]
<u>Orthomyxovirus</u>			
Human Influenza A,B,C virus	ss -ve	-/(1-9%)	[9,10,22,23,24]
<u>Coronavirus-</u>			
HCoV-229E HCoV-NL63 HCoV-OC43 HCoV-HKU1	ss +ve	-/(1-4%)	[9,10,22,23,24]
DNA:			
Adenovirus	ds linear	-/(<7%)	[9,10,22,23,24]
Bocavirus	ss circular	-/(6-13%)	[9,10,22,23,24]
Fungus			
Aspergillus	Thermotolerant, ubiquitous	-/++	[26,27]
Cladosporium		-/++	[26,27]

Abbreviations: ++, +++ represent degree of evidence showing causation and -, means no evidence.

Table 2

List of Bacteria from the Proteobacteria Phylum involved in bronchial hyperresponsiveness*

Family/Taxon Representative Species	Clinical Manifestations	Reference
Bartonellaceae/Bartonella quintana	Trench fever, Chronic Bacteremia, Endocarditis, Bacillary Angiomatosis, Lymphadenopathy and recently correlated with bronchial hyperresponsiveness	[32]
Caulobacteraceae/Brevundimonas diminuta	Undetermined clinical significance, possible Nosocomial infections and recently correlated with bronchial hyperresponsiveness	[33, 34]
Comamonadaceae/Comamonas testosteroni	Rarely been implicated in human infections of the abdomen, bloodstream, central nervous system, and urinary tract. Recently correlated with bronchial hyperresponsiveness	[35]
Enterobacteriaceae/Serratia fonticola	Possible respiratory tract infections and recently correlated with bronchial hyperresponsiveness	[36, 37]
Nitrosomonadaceae/Nitrosomonas eutropha	Recently correlated with bronchial hyperresponsiveness	[38]
Nitrosomonadaceae/Nitrosomonas europaea	Recently correlated with bronchial hyperresponsiveness	[39]
Ralstoniaceae/Wautersia paucula	Strains have sporadically been isolated from blood, wounds, sputum, urine, eye, throat and peritoneal fluid. Recently correlated with bronchial hyperresponsiveness	[40]
Shewanellaceae/Shewanella sp.	Rarely implicated in cellulitis, bacteremia, otitis infections, respiratory distress, intra-abdominal infection, pneumonia, and empyema. Recently correlated with bronchial hyperresponsiveness	[41]
Sphingomonadaceae/Sphingomonas paucimobilis	Nosocomial infections, rarely been isolated from blood, sputum, urine, wound, bile, cerebrospinal fluid, vagina and cervix. Recently correlated with bronchial hyperresponsiveness.	[42]

* Compiled based on the report by [31]