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Aging and the microbiome: implications for asthma in the elderly?

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Abstract

Asthma in the elderly remains a clinical challenge. Recognition, diagnosis and treatment are all complex. Influenced by processes such as aging, the identification of an ‘asthma microbiome’ presents a further challenge. This editorial discusses aging and the ‘asthma microbiome’ separately and then evaluates their potential relationship. Current evidence suggests that differences in the airway microbiome are associated with asthma however whether such associations are comparable or different for late-onset disease is yet to be established. Microbes are now linked to fundamental physiological processes such as aging based on data from invertebrate systems. This will likely confer implications for asthma in the elderly and it is crucial that such emerging scientific data is considered in the context of aging, asthma and late-onset disease.

Introduction

Asthma in the older population remains challenging. Its recognition, diagnosis and treatment are complex and challenges exist in performing and interpreting pulmonary function testing. Combined with specific therapeutic issues, asthma in the elderly represents a disease entity further impacted by the physiological aging process that we review elsewhere [1,2].

Our emerging understanding of the human airway ‘microbiome’ has presented new challenges particularly for chronic inflammatory diseases such as asthma. Interestingly, the number of organisms outweighs number of host cells and microbial genes encode antigens that can interact with the host immune system [3].

While our fledgling understanding of these immunological interactions between host and microbiome grows, data continues to emerge in pulmonary disease such as asthma. The microbiome is thus far largely bacterial and, *in-vivo* maintains immune homeostasis. In this context, renewed focus is necessary particularly in the way aberrant responses contribute to airway inflammation in disease such as asthma.

Asthma may be diagnosed at any age and various clinical or molecular phenotypes are described. Critically, aging influences the dynamic between immune function, environment and microbe to affect clinical outcome. Attention to date has focused on early life and hence this editorial aims to draw attention to asthma in the elderly and the impact of emerging asthma microbiome data on the aging process, immunosenescence and our understanding of this disease subtype.

Immunosenescence and Inflamm-aging

Immunosenescence reflects age-related declines in immune function at cellular and serological levels [2,4]. Specific responses to foreign and self-antigens ensue with an increased susceptibility of the elderly to infectious disease, poorer vaccine response and

increased prevalence of cancer, autoimmune and other chronic disease. Innate and especially adaptive responses are both weakened [5]. Three theories are proposed to account for immunosenescence: autoimmunity, immunodeficiency and immune-dysregulation. It is most likely that a combination of these occurs.

A chronic state of low grade inflammation also accompanies physiological aging [6]. This is characterized by increased levels of pro-inflammatory cytokines including TNF- α , IL-1 and IL-6. This 'inflamm-aging' state is implicated in the pathogenesis of several inflammatory diseases including atherosclerosis, diabetes and Alzheimer's [7]. However, some individuals advance in age without health problems, so called 'healthy aging' in which this pro-inflammatory state is somewhat inhibited by cytokines such as IL-10 [5]. Undoubtedly, genetic and environmental factors may also play key roles. The effects of immunosenescence and inflamm-aging on asthma in the elderly have been recognized but remain underexplored however association with a changing (and aging) microbiome are yet to be considered [2,8].

The airway microbiome and asthma

Microbes influence both health and disease making their interaction critical for therapeutics [9]. Advancing molecular based techniques including 16S rRNA sequencing, whole microbe genomic sequencing and meta-genomics have revolutionized our practice of microbiology [10]. Microbial species richness, community evenness and diversity have been associated with variations in both normal and diseased states however direct causality is yet to be established.

Work on the gastrointestinal (GI) microbiome led the field and has progressed beyond broad associations [11]. Our understanding of the airway microbiome lagged behind because of pre-conceived notions of a 'sterile airway' but also challenges with sampling lower

airways and avoiding oropharyngeal contamination. It has however become clear that abnormalities in bacterial load, composition and structure occur in airway diseases such as cystic fibrosis (CF), chronic obstructive airway disease (COPD) and asthma [12].

Initial work on asthma microbiology, both acute infection and chronic colonization focused on single causative agents such as *M.* or *C. pneumonia* however we know that a far more complex microbial community exists. Hilty *et al* produced the seminal study identifying disordered bacterial airway communities in asthma and COPD illustrating members of the *Proteobacteria* phylum (in particular *Haemophilus*) at higher prevalence in patients with COPD and asthma. Members of the *Bacteriodes* phylum (such as *Prevotella*) were predominant in healthy subjects [13]. The study assessed upper and lower airway specimens separately and illustrated that airways were not sterile and that a particular microbiome was characteristic of airway disease.

A larger study utilizing bronchial brushings subsequently found consistent phyla but further correlated the severity of airway hyper-responsiveness with bacterial diversity in asthmatic airways. Certain taxa related to this clinical finding included *Proteobacteria*, *Pseudomonadaceae*, *Enterobacteriaceae*, *Burkholderiaceae* and *Neisseriaceae* [14]. Subsequent analysis of induced sputum from steroid naïve asthmatics compared to healthy subjects further confirmed greater bacterial diversity and higher proportions of *Proteobacteria* [15]. Several identified genera demonstrate functional relevance to asthma including *Sphingomonadaceae* which incite natural killer cell responses, *Nitrosomonas* possessing NO reductases, macrolide-susceptible *Oxalobacter* and *Comamonadaceae* capable of steroid metabolism [14]. This latter group has been further evaluated in corticosteroid resistant asthma suggestive of a potential relationship between therapy, infection and disease within certain asthmatic phenotypes [16]. In severe asthma, asthma control and sputum

neutrophilia are associated with *Proteobacteria* while elevated BMI is linked to *Bacteriodes* [17].

Besides bacteria, other members of the airway microbiome with potentially greater allergenic potential such as fungi are yet to be comprehensively examined. This is due to a lack of fungal reference sequence databases however increased fungal abundance is described in asthma and mechanisms other than persistent allergen are touted including the expression of fungal lipoxygenases with homology to human 5-lipoxygenase [18-20].

It is likely that microbes influence asthma in particular phenotypes including neutrophil predominant and treatment resistant asthma, both sharing characteristics of asthma in the elderly [14,17].

The association between aging and the microbiome

Evidence presented thus far illustrates key roles for the microbiome in asthma however emerging data illustrates that microbes even influence central physiological processes such as aging. This may have implications for asthma in the elderly. Key experiments originate in invertebrate systems such as *Drosophila melanogaster* and *Caenorhabditis elegans*. Despite their limitations, such models determine causality from microbe exposure which otherwise are expensive and technically challenging in mammalian settings [21]. Genes modulating the ‘healthy aging’ process have been uncovered and include the IGF-1 signalling pathway, target of rapamycin (TOR) and AMP-activated protein kinase (AMPK). Major mechanisms to explain how the microbiome influences these pathways and affects aging includes direct interspecies signalling, manipulation of microbial metabolites, deprived nutrient conditions and re-modelling of host metabolic networks. These effects occur through influences on host transcriptional pathways and cross-species regulation of RNA and microRNAs [8]. While it is premature to suggest how such invertebrate derived results will influence our

understanding of mammalian aging, it is fair to speculate the impact it will have on age-related disease phenomena such as late-onset asthma. Coupled with effects of immunosenescence and inflamm-aging, the microbiome in late-onset disease is likely to influence the clinical phenotype observed in practice. Factors associated with aging such as immune and inflammatory change combined with the lifelong effects of anti-microbial, allergic and infective exposures places the microbiome found in the elderly asthmatic likely unique when compared to other asthma phenotypes.

“Microbiomic” implications for asthma in the elderly?

As we age, our microbial composition changes and effects on immunity vary. From infancy decreased microbiome diversity increases allergic tendencies compared to an increased burden of *Proteobacteria* in adult asthma [22]. No information however is currently accessible addressing the microbiome of elderly asthmatics (>65 years). This is imperative because increases of knowledge in this field will influence future treatment approaches. Key mechanisms by which the asthmatic microbiome, particularly in the elderly are likely affected include lifelong antibiotic use, a relative state of immunodeficiency, airway neutrophilia and interactions with the gut microbiome. Manipulation of microbial composition and functional derivatives with antibiotics or vaccines may represent novel approaches to asthma care. Asthma remains a heterogeneous disease with many phenotypes all with likely influences from the microbiome that are potentially different.

While the microbiome has been investigated in neutrophil-dominant and treatment-resistant asthma, it is similarly likely to be important in elderly asthma which share some of the characteristics of the prior studied populations. The airway microbiome is likely further influenced by immunosenescence, inflamm-aging and medication in the older patient which contributes to misdiagnosis and the lack of classical asthmatic features.

Animal models, *in-vitro* data and epidemiological studies suggest relationships between the microbiome and development of allergic disease however transferring such findings to interventions are difficult. Despite this, attempts at interventions targeting initial childhood colonization are unproven and consequently a lack of incentive exists for similar approaches in later life. Asthma in the elderly is likely less allergic however and perhaps provides a better model to understand relationships between immune crosstalk, the host and microbe.

Age-related changes to the GI microbiome influence childhood asthma. As one ages, however eating habits and cultural differences add complexity [23]. The largest elderly microbiome study to date originates from Ireland [24]. The frailest older people harbour similar intestinal microbial communities driven by diets high in fat and lacking fibre. Declines in microbial make-up subsequently underlie ill health as one ages, however this relationship may be applicable conversely: an individual's health and immune state affects the microbiome. If this mutually interdependent relationship is true and the microbiome is driven by eating habits, what are the pulmonary consequences? Could this promote asthma in the elderly? What influence do medications have? What are the impacts of living environments or infections in older individuals? Most importantly is the undetermined effect of immunosenescence on inter-individual airway microbiome variability as one ages and its relationship with onset of airway hyper-reactivity. The impact of age-related changes in gut microbiota promotes imbalance that in turn impacts immunosenescence and inflamm-aging, two concepts that have implications for asthma in the elderly.

What remains unclear is whether inter-individual microbiome variation mediates inflammation and pathologic airway changes directly or indirectly through underlying systemic differences in immune function. The concept of a 'common mucosal system' has therefore been proposed because variations in gut microbiome development during early life

may drive systemic immune differences. Could the airway and gut both be part of the same continual mucosal spectrum? Additional considerations important for the older asthmatic include immunological and infective effects and the role of co-morbidities/polypharmacy complicating the inflammatory milieu. What does remain clear however is that there much to be learned about the asthma microbiome and its association to the physiological process of aging.

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