Paediatric Respiratory Reviews 19 (2016) 69–74

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Review

A bug's view of allergic airways disease

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EDUCATIONAL AIMS THE READER WILL BE ABLE:

- To explore the relationship between the microbiome and allergic airways disease
- To understand the factors that predispose to dysbiosis and allergic airways disease
- To discuss the potential roles of interventions that may correct dysbiosis and therefore prevent or treat allergic airways disease

ARTICLE INFO

Keywords:
Microbiome
Allergic airways disease
Dysbiosis
Prebiotic
Probiotic

SUMMARY

The increase in allergic airways disease has been linked to modern urbanization and lifestyle. Recent evidence suggests that the associated reduction in microbial exposure, reduction in dietary fibre intake and increased antibiotic use may cause early dysbiosis in infancy, which predisposes to immune dysregulation and allergic airways disease later in life. This implies that there may be a window of opportunity for primary prevention strategies aimed to protect or restore the microbiome early in life and thereby decrease the risk of developing allergic airways disease. Alternatively, strategies that correct dysbiosis may aid in the treatment of established allergic airways disease.

INTRODUCTION

Allergy is a clinical manifestation of an inappropriate immune response to common harmless environmental antigens, which under normal circumstances would be tolerated. Atopic diseases including allergic airways disease represent a significant health burden, both in developed and developing regions. Over the last decade, rates of asthma appear to have plateaued in the developed world, albeit at high levels, whereas allergic rhinitis and aeroallergen sensitization continue to rise in prevalence [1]. However exactly how and why some children are susceptible to and suffer from allergic airways disease is not well understood. One of the main hypotheses regarding the increasing incidence of atopy is the "hygiene hypothesis", which, in its most commonly propagated form, proposed that the excessive "cleanliness" of modern living conditions leads to inadequate exposure to microbes, both environmental and symbiotic, and subsequent lack of immune stimulation early in life, with consequent dysregulation of the immune system leading to atopy [2]. The original hygiene hypothesis, proposed by Strachan in 1989, related to his observation of the protective effect of increasing birth order and household size on the incidence of allergic rhinitis [3]. In a broader and contemporary view, the hygiene hypothesis now might be more aptly termed microbiome depletion or deprivation syndrome. It acknowledges that we live generally in equilibrium, in the presence of a great host of microbial agents, both in the environment and as non-pathogenic colonizers of almost every nook and cranny of the human body. Although the medical community is well aware of the threats posed by microbes related to infections, we are only beginning to understand the important role the microbiome plays in regulating our immune system, with mounting evidence that disturbances in the "normal" microbiome significantly contribute to the development of atopy and other inflammatory and immune mediated diseases.

In this review, we will summarize recent evidence of the associations between the microbiome and the development of allergic airways disease. In doing so, we aim to also highlight potential future strategies in the prevention and treatment of allergic airways disease.

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http://dx.doi.org/10.1016/j.prrv.2016.02.002
1526-0542/

IMMUNO-PATHOLOGY OF ALLERGIC AIRWAYS DISEASE

Allergic asthma is a complex disease characterized phenotypically by reversible airflow obstruction and immunologically by increased T-helper 2 (Th2) response to common aeroallergens and dysregulation of T-helper immune responses [4]. Inflammation is central to the pathogenesis of asthma, with involvement of the conducting airways subsequently spreading to the smaller airways with disease progression [5]. This inflammation is characterized early on by a predominance of Th2 lymphocytes bearing the CCR4 chemokine receptor, with the production of a large range of cytokines such as IL-4, IL-5 and IL-13 [6], which is associated with eosinophil recruitment and IgE production. Allergen induced, IgE mediated activation of mast cells, basophils and dendritic cells is also an important aspect of asthma pathogenesis, as clearly demonstrated by the efficacy of the anti-IgE monoclonal antibody, omalizumab, in the management of severe asthma [7]. However, as the disease progresses in severity and chronicity, T-helper 1 (Th1) type T cells are recruited and produce interferon-gamma and tumor necrosis factor alpha [8], mediating further tissue damage. Evidence also suggests impaired numbers and function of immune-modulatory regulatory T cells (Tregs) may contribute to airway inflammation as reflected in the bronchial alveolar lavage of asthmatic children [9]. In addition to immune dysregulation and inflammation, abnormal signaling between the epithelium and mesenchyme also contributes to the epithelial damage with poor repair, as well as airway and vascular remodeling in asthma [4].

THE MICROBIOME AND IMMUNE OUTCOMES

We have known for a long time that our bodies are colonized by a host of microbial agents which are labeled as "normal flora". In fact, the human microbial community is thought to outnumber human cells by about tenfold [10]. However, the details and function of this flora, now known as the microbiome, remained elusive. With the advent of new technologies such as high-throughput DNA sequencing and enhanced bioinformatics, researchers have been able to examine the microbiome in much greater detail. In doing so, we are beginning to discover that the microbiome has significant influences on many aspects of health and disease, from metabolic processes to epigenetics, oncogenesis and immune outcomes [11]. Indeed, our immune system operates in a delicate balance with the microbiome, in which there is an essential requirement for one another [12]. Proof of concept of the critical importance of the microbiome is demonstrated in early studies in the murine model, where the germ free (GF) mice were found to have an underdeveloped immune system, which was largely corrected by re-colonization of the germ free mice with "normal flora" [13]. Further murine studies have shown that a host specific microbiome is required to generate a mature immune system [14], indicating that the immune system has adapted to a specific composition and diversity of microbiome.

Another important factor to consider is the location of microbiome relative to the disease. Whilst the gut harbors the highest concentration of microbial community, which can affect immune outcomes at a distant site [15], recent studies have shown that site-specific microbiome is important for inducing local immunity [16]. Therefore it is important to consider both the gut and respiratory microbiome in the context of allergic airways disease.

Finally, the microbiome may play quite different roles in immune induction, tolerance and inflammation depending upon the stage of disease process. For example in early life, evidence suggests that microbial diversity may induce stronger regulatory immune responses, and protect against the development of allergic disease, in genetically susceptible individuals [17]. Once airways disease is established, and mucosal and epithelial integrity compromised, microbial colonization with "unfriendly" microbes may play a role in perpetuating inflammation and airway hyperresponsiveness [18].

EARLY LIFE GUT MICROBIAL COLONIZATION AND SUSCEPTIBILITY TO ALLERGIC AIRWAYS DISEASE

A growing body of evidence supports the concept that the gut microbiome can affect immune outcomes at a distant site. This is perhaps not surprising since the gut harbors both the largest microbial reservoir and the greatest mass of lymphoid tissue in the human body. In addition to its influence on local gut immunity, disturbance of the gut microbiome (dysbiosis) has been associated with obesity and type 2 diabetes [19], rheumatoid arthritis [20] and allergic diseases in general [21].

In the Copenhagen Prospective Study on Asthma in Childhood, Bisgaard et al showed that reduced diversity of intestinal microbiota in infancy was associated with atopic sensitization and allergic rhinitis but not asthma in the first 6 years of life [22]. In a smaller study, Abrahamsson et al [23] showed that reduced diversity of gut microbiome at 1 week and 1 month of age, but not 12 months, was associated with development of asthma at 7 years of age. No relationship was found between the gut microbiome and allergic rhinitis, eczema or atopic sensitization, however the power of the study was undermined by the small number of subjects [23]. In the KOALA birth cohort, the presence of Clostridium difficile at 1 month of age was associated with recurrent wheeze and eczema at 2 years of age, although here the investigators did not examine microbial diversity [24]. Collectively, these human studies suggest that early and appropriate gut microbial colonization may be important for airway immune outcomes.

Potential mechanistic insights have been revealed through animal studies. Trompette et al showed that gut microbial colonization and fermentation of dietary fermentable fibres in mice led to production of short chain fatty acids (SCFA), which protected against development of allergic airways disease [25]. This was due to enhanced bone marrow generation of antigen presenting cells, which seeded the lung and inhibited Th2 responses. Whilst SCFA have been shown to induce Treg cells locally in the gut [26], in this particular instance, the protection against allergic airways disease was not due to Treg cell enumeration. However, in an earlier study, Atarashi et al showed that early (but not adult) colonization of germ free mice with Clostridium IV and XIV species not only resulted in colonic induction of Treg cells and reduction of IgE responses, but also led to a systemic (including the lung) increase in IL-10 secreting CD4+ T cells, though it was unclear whether these included Foxp3+ Treg cells [27]. A more recent murine study showed that SCFA (particularly acetate) did protect against allergic airways disease by enhancing Treg numbers and function, and that this protective effect was extended to the fetus [28]. Despite minor differences, collectively these animal studies do suggest that early gut microbial colonization and production of metabolites significantly impacts on airway immune outcomes.

THE ENVIRONMENTAL INFLUENCE ON THE MICROBIOME AND ALLERGIC AIRWAYS DISEASE

Perhaps the largest body of evidence for the influence of microbiome on allergic airways disease comes from cohort and cross sectional studies examining the impact of environmental exposures. In the KOALA cohort, antibiotic exposure in the first 2 years of life (whether directly or through breast milk) was associated with increased risk of recurrent wheeze [29], which