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The quest for bacterial allergens

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ABSTRACT

Allergies are complex diseases featuring local tissue inflammation, which is characterized by an exaggerated type 2 immune response to environmental compounds known as allergens. Pollens, environmental fungi, and house dust mites are examples of common allergens. Bacteria have a dual role in allergy. Usually, they are associated with protection, however, certain bacterial species promote the development and exacerbation of allergic inflammation. Notably, IgE antibodies specific for bacterial antigens are found in the sera of allergic individuals. This implies that some bacterial factors are allergens, eliciting a specific type 2 immune response. However, to date, only a few of these are molecularly defined. This review summarizes the current knowledge about known bacterial allergens, and it provides an overview of the available techniques for the discovery of new allergens as well as for measuring the immune responses directed against them.

1. Introduction

The prevalence of allergic diseases is very high and still increasing globally, particularly in low- and middle-income countries. Moreover, the complexity and severity of allergic diseases, including asthma, continue to increase, particularly in children and young adults (Masoli et al., 2004; Pawankar, 2014). To address these challenges and to fight these diseases, which place a huge burden on patients and health care systems worldwide, the molecular identification of allergens and their functional characterization is required. After briefly summarizing current knowledge about the role of bacteria in allergy, this review will focus on the nature and functions of bacterial allergens as well as on methods for their discovery and characterization.

1.1. The pathophysiology of allergy

Allergies are chronic inflammatory diseases caused by dysregulated immune responses to certain environmental substances, called allergens. Allergens are molecules that typically elicit IgE responses in the host. Besides, they have to meet additional criteria of the WHO/IUIS allergen nomenclature sub-committee, encompassing molecular and structural properties, that qualify them as allergens (Breiteneder and Chapman, 2014).

The most common allergens are found in pollens, environmental fungi, dust mites, and animal dander as well as in some foods and drugs (Ipci et al., 2016). A central feature of allergies is type 2 inflammation, characterized by increased numbers of Th2 cells, which release IL-4, IL-5, IL-9 and IL-13 upon allergen exposure, as well as by allergen-specific IgE, mast cell activation and tissue infiltration by eosinophils (Barnes, 2009; Wills-Karp et al., 2012). However, other types of helper T cells and their cytokines may also be involved (Farahani et al., 2014). Th17 cells, for example, can produce Th2-type cytokines (Cosmi et al., 2010; Raymond et al., 2011), and the Th9 subset releases large amounts of IL-9 (Koch et al., 2017). Moreover, Th22 cells, which secrete IL22 and IL-13, and Th25 cells, which secrete IL-25, are believed to be important in allergic reactions and airway inflammation (Angkasekwinai et al., 2007).

During airway inflammation, epithelial cells respond to allergens by producing potent mediators such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). These mediators promote the recruitment and activation of specialized immune cells and affect their differentiation towards a type 2 immune response profile (Golebski et al., 2013). IL-33 enhances allergic inflammation through induction of other pro-allergenic cytokines and chemokines, such as IL-4, IL-5, and IL-13. Notably, ST2, an IL-33 receptor component, is primarily expressed by Th2 cells, mast cells, eosinophils and basophils (Borish and Steinke, 2011; Oboki et al., 2011).

Innate lymphoid cells (ILCs), which are related to natural killer cells, are emerging as important effectors in innate immunity because they are involved in protection against pathogens and associated with lymphoid tissue formation and tissue remodelling. There are three types of ILCs, which are differentiated based on their similarities to helper T

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cells. Among them, ILC2s have the ability to secrete type 2 cytokines such as IL-4, IL-5, IL-9 and IL-13. High levels of ILC2 cells have been observed in the tissues of patients with asthma or atopic dermatitis (AD). Thus, this subset of cells contributes to the immunopathology of chronic airway inflammation and to inflammation in other barrier organs (Bal et al., 2016; Mjosberg et al., 2012).

1.2. Bacteria counteract allergy development – the hygiene hypothesis

It is well documented that exposure to bacteria is associated with protection against allergy. Mycobacteria, for example, are potent inducers of Th1 responses including the release of IFN-γ, which counteract type 2 inflammation (Yoshida et al., 2002), and they elicit regulatory T cell (Treg) responses, which likely represent the main anti-allergic immune mechanism. Infection with *Mycobacterium tuberculosis* as well as vaccination with *Bacillus Calmette-Guérin* or other mycobacteria reduce the prevalence of allergy, both in humans and animals (Choi, 2014; Choi and Koh, 2002, 2003; Kim et al., 2014; Shirakawa et al., 1997; Umetsu et al., 2002). Moreover, there is a wealth of information available in the literature showing that bacterial products modulate the innate immune system. Innate pattern recognition receptors, e.g., the toll-like receptor (TLR) family including TLR4 mediate important anti-allergenic effects. Among these are antimicrobial responses such as phagocytosis, the induction of nitrogen oxide as well as the stimulation of the maturation of antigen-presenting cells (APCs). The latter increase the secretion of the type 1 cytokines, IL-6, TNF-α, IL-1, IFN-γ, and IL-12, and have a prominent role in B cell and T cell activation and differentiation (Chandler and Ernst, 2017; Freyne et al., 2018; Nagai et al., 2018; Shibata et al., 2018; Vandepapelière et al., 2008).

The observation of a sharp decline in infectious diseases accompanied by the steep rise in the incidence of allergy in recent decades has prompted the hygiene hypothesis: “The main factor in the increased prevalence of these allergic diseases in industrialized countries is the reduction in the incidence of infectious diseases in those countries over the past three decades” (Bach, 2002). This hypothesis was later modified, because the role of the commensal microflora in inflammatory homeostasis and immune regulation is being increasingly appreciated. Exposure to innocuous exogenous and endogenous microorganisms early in life protects against allergy. Generally, variations in the microbiome, both in terms of the number and diversity of bacteria, may significantly affect the incidence of allergic manifestations (Atkinson, 2013; Edwards et al., 2012; Hilty et al., 2010; Ipci et al., 2016; Medina et al., 2012; Ramsey and Celedon, 2005; Ribet and Cossart, 2015; Schaub et al., 2006). Because of these findings the capacity of certain species of the commensal gut microflora (probiotic strains), such as lactic acid bacteria including Lactobacillus or Bifidobacteria species, of enhancing immune tolerance is now being tested. Several excellent texts reporting the beneficial role of these strains in the primary prevention of allergic diseases are available (Chua et al., 2017; Chung, 2017; West et al., 2017).

1.3. Bacteria can promote allergy – epidemiological evidence

Conversely, there is increasing epidemiological evidence that colonization or infection with certain bacterial species can trigger or exacerbate allergies (Edwards et al., 2012; Emre et al., 1995; Seggev et al., 1996; Welliver and Duffy, 1993). In asthma, for example, bacteria may exacerbate disease symptoms alone or in conjunction with viruses such as human rhinovirus or respiratory syncytial virus (Barnes, 2009; Darveaux and Lemanske et al., 2014).

As early as the 1970s and 1980s, studies demonstrated a correlation between bacterial colonization and allergic diseases. Atypical bacteria such as *Chlamydia trachomatis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are associated with an increased incidence of asthma, wheezing episodes and asthma exacerbations, as well as with lung remodelling. Similarly, these pathogens have been frequently identified in bronchoalveolar lavage fluid (BAL), nasal washes and sera from asthmatic patients (Emre et al., 1995; Hahn et al., 1991; Hahn and Peeling, 2008; Hahn et al., 2012; Huhti et al., 1974; Ikezawa, 2001; Johnston and Martin, 2005; Patel et al., 2012; Seggev et al., 1996; Tang et al., 2009; Wark et al., 2002; Webley et al., 2009; Yano et al., 1994; Ye et al., 2014). Regarding the common bacterial inhabitants of the human respiratory tract, colonization or infection with *Haemophilus influenzae*, *Streptococcus pneumoniae, Moraxella catharralis* and *Staphylococcus aureus* have been associated with the induction and exacerbation of asthma, chronic obstructive pulmonary diseases and recurrent wheezing early in life (Bachert et al., 2003; Barnes, 2009; Bisgaard et al., 2010; Bisgaard et al., 2007; Brarda et al., 1996; Darveaux and Lemanske et al., 2014; Davis et al., 2015; Hales et al., 2012; Hilty et al., 2010; Kjaergard et al., 1996; Pauwels et al., 1980). Moreover, in patients suffering from allergic disorders such as asthma, AD or nasal polyposis, *S. aureus* colonization appears to occur much more frequently (87%, 90%, 87%, respectively), in contrast to 20%–50% colonization of healthy adults (Holtfreter et al., 2016; Krismer et al., 2017; Mulcahy and McLoughlin, 2016; Ryu et al., 2014; Weidenmaier et al., 2012). In addition, asymptomatic colonization of neonates with *S. pneumoniae* or *M. catarrhalis* is associated with later development of recurrent wheezing and asthma (Bisgaard et al., 2007).

1.4. Bacterial mechanisms of allergy induction and exacerbation

Numerous pro-allergenic functions, both antigen-specific and non-antigen-specific, have been ascribed to bacteria. Bacteria have the ability to infect airway epithelial cells, thereby inducing inflammation, cell death and epithelial barrier failure. Moreover, pore-forming toxins, e.g., *S. aureus* α-toxin (Hla), and bacterial proteases contribute to epithelial barrier failure (Inoshima et al., 2011). Increased epithelial permeability facilitates microbial invasion and exposes the immune system to environmental pollutants and allergens.

On the other hand, antibacterial immune defense systems appear to be impaired in allergy. In response to bacterial invasion the innate immune system of human skin elaborates large amounts of antimicrobial peptides (AMPs) known as cathelicidins and beta-defensins. This response is defective in AD patients. Moreover, Th2 cytokines such as IL-4, IL-10, and IL-13 act synergistically to down-regulate AMP expression in the skin of AD patients. This results in a higher susceptibility to *S. aureus* colonization in AD patients, which in turn promotes the exacerbation of AD symptoms (Howell et al., 2006; Ong et al., 2002; Ryu et al., 2014; Takahashi and Gallo, 2017).

Respiratory pathogens can induce an excess of mediators of airway repair, resulting in airway remodelling accompanied by thickening of the airway walls and impairment of lung function. Fibroblast growth factors and vascular endothelial growth factors are involved in angiogenesis, airway smooth muscle proliferation and hypertrophy, collagen and fibronectin deposition as well as in the generation of new lymphatic vessels (Edwards et al., 2012; Smith-Norowitz et al., 2016). For example, in a murine asthma model, *M. pneumoniae* infection increases airway collagen deposition (Chu et al., 2003, 2005). In mice with chronic and recurrent *C. pneumoniae* infection, an increase in the thickness of the subepithelial basement membrane suggestive of airway remodelling was observed (Chen et al., 2009).

Some bacteria are able to elicit histamine release from human basophil leukocytes and mast cells via IgE-dependent or -independent mechanisms (Ahren et al., 2003; Clementsen et al., 1990; Emre et al., 1995; Kjaergard et al., 1996; Larsen et al., 1998; Nakamura et al., 2013; Pauwels et al., 1980; Seggev et al., 1996; Tee and Pepys, 1982; Welliver and Duffy, 1993; Ye et al., 2014). In asthmatic children infected with *M. pneumoniae*, elevated numbers of basophils are present in the peripheral blood and eosinophilia is observed in the BAL, suggestive of exacerbations of bronchial asthma (Tang et al., 2009). *H. influenzae* and *S. pneumoniae* activate eosinophils and potentiate the release of