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Allergy Prevention and Exacerbation

The Paradox of Microbial Impact on the Immune System

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Overview: The Paradox of Microbial Impact on the Immune System in Allergy Prevention and Exacerbation

Carsten B. Schmidt-Weber

Abstract Allergy prevalence has been increasing to epidemic proportions. The term "allergy tsunami" was even coined after the prevalence of allergen sensitization in school-aged children jumped to more than 40%. Because of the huge economic impact on the health care system and the dramatic impact on quality of life, allergy prevention has become very relevant. In this context, it is interesting that infectious diseases are becoming less prevalent and increasingly under control, while noncommunicable diseases (including, but not limited to, allergy) increase. This also applies to autoimmune diseases, which are characterized by an overactive immune response.

The immune system's response to antigens and the microbiome is critical for the outcome of infections and allergies. Paradoxically, the microbiome can play a protective role in allergies, but it is also known to be the driver of exacerbations. The current chapter focuses on this paradox and therefore starts with the topic of autoallergy, in which microbial antigens are considered to be potential pathogens and disease initiators. Bacterial allergens are generally thought of as potential "virulence factors" and exacerbation factors in allergy. In contrast, the allergy-protective microbiome, which was discovered in protective agricultural environments, is the second key aspect of this chapter. Additional environmental elements that were lost due to lifestyle changes are also highlighted. Both farm and lifestyle effects contributed to the hygiene hypothesis, which is challenged by the author to show that "dirt" is not at all protective against allergies. Determinants and metabolites of bacteria and molds that co-evolutionized with man have been identified in rural environments, with stunning effects on our immune systems.

Allergy prevention at least partially develops in our gut through a complex interplay of microbiota with our immune system. Here, the persistence of type-2 allergen memory, such as interleukin-4 and immunoglobulin E–producing cells, is particularly important and relevant for food allergies. This chapter also describes a recently discovered mechanism that links the gut microbiome with pro-allergic

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type-2 immunity. The mechanism of environmental sensing is discussed, using the example of the aryl hydrocarbon receptor to demonstrate the link between microbiota, their metabolites, and their recognition at cellular and molecular levels. For the prevention of microbiome-driven exacerbations, the chapter also discusses therapeutic options with novel diagnostics and biologics that are likely to influence the future management of allergies. (For a graphical chapter overview, see Fig. 1.)

1 Introduction: Allergy Exacerbation Triggers Are Also the Prevention Factors

Initial allergic sensitization is thought to originate as a loss of tolerance against otherwise harmless antigens, such as that contained in pollen. Signals that convey a danger signal, such as bacterial wall components, are thought to promote inflammation and downregulate inhibitory immune mechanisms. The result of this accidental co-recognition of harmless and potentially dangerous antigens is an unwanted immune response against the harmless antigen. This mechanism may not only apply to exogenous antigens from pollen, but also to autologous molecules of the organism and thus may cause autoimmune reactions (Fig. 1).

However, it is currently unclear why the allergen drives immunoglobulin (Ig) E/type-2 responses when autoimmunity is usually characterized by IgG/type-1 or 17 responses. Type-2 responses are characterized by interleukin (IL)-4, IL-5, and IL-13; here, IL-4 drives Th2 cells and the IgM to IgE switch of B cells, IL-5 promotes eosinophilic inflammation, and IL-4 and IL-13 promote epithelial and

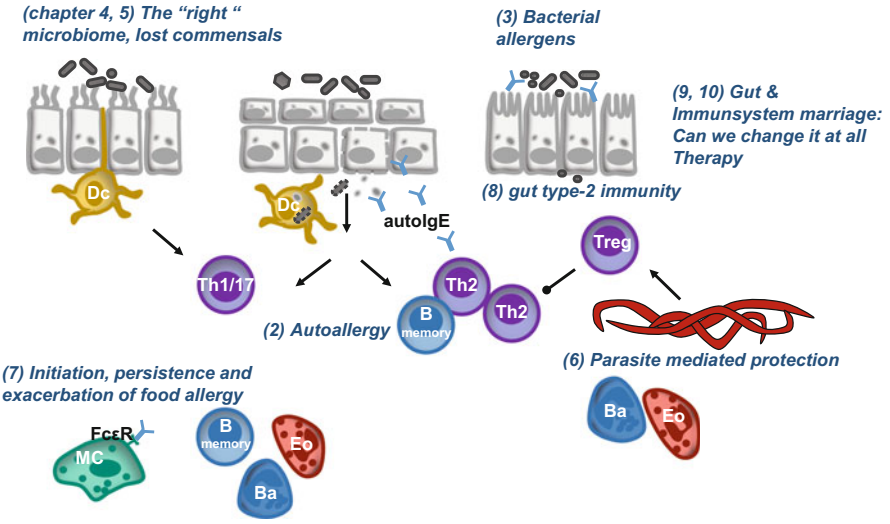

Fig. 1 Environmental challenges and in particular the microbiome can interact with the immune system on different levels. The paradox of triggering disease on one hand and promoting protection against allergies is illustrated and related book chapters indicated in brackets

macrophage differentiation of epithelial cells and macrophages. Type-1/17 responses promote a lytic immunity and are characterized by interferon (IFN)-γ and IL-17 expression, which promotes the antigen presentation of dendritic cells and the recruitment of neutrophils to the site of inflammation. An interesting exception to this distinction between types 1 and 2 is the phenomenon of autoantigens being recognized by IgE.

In the chapter titled "Microbial Triggers in Autoimmunity, Severe Allergy, and Autoallergy," the nature of autoallergy is described in detail; in particular, auto-IgE appears to recognize antigens with structures that are very similar between human and bacterial organisms because they are highly conserved evolutionarily. This "molecular mimicry" is one way that self-tolerance may be overcome accidentally (Virtanen et al. 1999). It is also speculated that this autoallergy against tissue antigens may drive transient allergies to become chronic allergies. However, it remains unclear why IgE is raised against these autoantigens, rather than IgG and type-1/17 responses as is normally observed for autoantigens.

A possible explanation is that epithelial cells provide this type-2 bias from the epithelial mediators IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which are also called "alarmins" (Bianchi 2007). These cytokines can activate a recently discovered group of cells called innate lymphoid cells (ILCs). As the name indicates, these cells cannot recognize antigens, but they release cytokines themselves, including IL-4 (Licona-Limon et al. 2013). The IL-4-secreting ILCs are called ILC2s; it was hoped that the initial source of IL-4 at the beginning of allergic sensitization was discovered in this group of cells. However, mice lacking a key ILC2 transcription factor have normal levels of Th2 cells (Verhoef et al. 2016); thus, ILC2s are currently thought to contribute as amplifiers to Th2 cell activity but not account for the root of type-2 immune responses. It was also shown that Th2-derived IL-4, but not ILC2-derived IL-4 and IL-13, were correlated with lung pathology in an experimental asthma model (Oeser et al. 2015). Other initial sources of IL-4 are still the subject of intensive research.

The question remained on how uncommitted, naive T cells can be driven or differentiated into cell that produce IL-4. Certain transcription factors, such as GATA3 and STAT5, were found to be important. However, weak T-cell receptor stimulations also favor Th2 commitment (for an overview, see Paul and Zhu 2010). Generally speaking, it seems that a unique Th2 path has not been discovered; possibly, multiple factors need to come together to generate type-2 immunity, break tolerance, and induce sensitization. Of note, an already committed Th2 cell may still be counteracted by regulatory immune responses and prevent greater support of B cells and IgE production. However, regulatory responses are diminished under conditions of inflammation, including type-2 cytokines (Mantel et al. 2006). Similarly type-1 and/or type-17 responses compete with and antagonize Th2 responses. These dynamics underlie the complex role of microbiota, which can trigger inflammation, exacerbation, tolerance, sensitization, and allergy. The spectrum of bacterial allergens is described in the chapter titled "Bacterial Allergens," which illustrates the importance of the *Staphylococcus* species and the specific virulence factors in allergy, while also highlighting protective factors such as *Staphylococcal pneumonia* PspC and PspA.

The identification of microbiotic factors that prevent allergies has been challenging and their nature is only partially understood. Early epidemiologic research suggested that agricultural environments may have a protective effect for hay fever; this was extrapolated in the "hygiene hypothesis". The history and recently identified key factors are presented in the chapter titled, "Good and Bad Farming: The Right Microbiome Protects from Allergy." A clear conclusion of the author is that the farm effect is far more specific than one would think in the context of the hygiene hypothesis. Farms keeping sheep only or those using pressed hay do not show equal levels of allergy protection; furthermore, allergies other than those directed against grass allergens are affected to a much lower degree.

Other hygiene effects, such as the presence of *Heliobacter pylori* (see the chapter titled, "The Lost Friend: *H. pylori*") are more controversially discussed and may explain the increase of allergies. In the 1950s, *H. pylori* colonization reached 80–90%; however, it has dropped to 2% in the population born after 2000 due to sanitary improvements. With these improvements, many parasites also disappeared as pathogens in developed countries (see the chapter titled, "Parasite-Mediated Protection Against Allergy"). Many parasites such as helminths elicit a type-2 nonlytic response, which allows the organism to survive and protects the host from major tissue damage. Particularly interesting for allergy is that helminths also developed immunosuppressive mechanisms that support their lifecycles, which are attenuated with deworming of the host. The immunoregulatory mechanisms of parasites are very specific: helminths, for example, induce both exacerbation and tolerance, whereas the whipworm *Trichuris suis* failed to improve allergic rhinitis. The developmental stage of the worm is relevant for these effects. In addition, the allergy-affected organ seems to be important: for example, worm-mediated protection works in the lung but not in the skin. The chapter titled "Parasite-Mediated Protection Against Allergy" provides a very specific and molecularly defined avenue for how parasites influence allergy.

2 Cellular Player: From Genetics to the Immune System

Some simple considerations that identify critical cellular mechanisms of allergy are likely to be important in the context of prevention and exacerbation. First, the fact that allergies occur every year and specifically for selected allergens highlights immune cells that mediate long-lived antigen-specific immunologic memory, such as T- and B-cells. Furthermore, as also discussed in the chapter titled, "Initiation, Persistence, and Exacerbation of Food Allergy," the IgE memory cell produces large amounts of the Ig (plasma cell), but these IgE-producing cells were found to be surprisingly short lived. Therefore, a reservoir of IgE plasma cells may reside in the IgG^+ memory B-cell compartment, which undergoes sequential class switching (from IgG to IgE).

T-cells require phagocytic antigen-presenting cells for their activation, multiple types and variants of which are present in different tissues. The induction of

unresponsiveness (tolerance) is particularly well documented for antigens that are taken up orally. Specialized mechanisms mediate this tolerance, such as the transepithelial transport of antigens via microfold (M) cells (Suzuki et al. 2008) or other yet undiscovered mechanisms (Kraus et al. 2005). Novel mechanisms mediating tolerance, including specialized Tregs, are presented in the chapter titled, "The Role of the Gut in Type 2 Immunity."

Another important cellular player are epithelial cells because they directly face the environment and microbiota (e.g. skin, lung, gut). These cells are also home to genes such as *IL33* and *Filaggrin* mutations, which were discovered to be genetically associated with allergy (Campbell et al. 2015; Barnes 2006; Holgate 1999). Epithelial cells are in contact with multiple resident (dendritic cells, mast cells) and infiltrating immune competent cells (neutrophils, eosinophils, innate lymphoid cells) that interact closely upon microbial or parasite impact; therefore, they have different protective effects on allergy, as discussed in the chapter titled "Parasite Mediated Protection Against Allergy." These protective effects arise from species-specific evasion strategies. An example are *Schistosoma* components, which promote dendritic cells to a Th2-stimulating ability, and the nematode*Acanthocheilonema viteae*, which promotes anti-inflammatory IL-10 secretion by macrophages.

Common among T cells, innate lymphocytes, macrophages, and epithelial cells (Zissler et al. 2016) is that these cells can differentiate into a type-2 phenotype. This differentiation is usually initiated by IL-4 and antagonized by IFN-γ. This differentiation changes the functional profile of these cells, which is already well described for T cells; however, the meaning for tissue cells, such as epithelial cells, is yet unclear.

3 Protection Against Allergy

A key motivation for the concept of allergy protection comes from farm studies, where therapeutic vaccinations with allergens have been performed for more than 100 years. Immunological findings indicate that the immune system can actively and antigen-specifically suppress immune responses. In this situation, tolerogenic vaccination generates nonresponsiveness against allergens, which in turn generates allergen-specific IgG4 that competes and therefore neutralizes the inflammation caused by allergen-specific IgE. Furthermore, regulatory responses such as allergen-specific regulatory T cells and B cells are induced. However, can this approach also be used prior to an outbreak of allergy symptoms? This question was positively answered for peanuts through feeding studies of young subjects, with allergy prevalence shown to be lower than in the avoidance group (Du Toit et al. 2008). The risk of inducing an allergy rather than protecting against it is obviously the key obstacle; it currently prevents substantial engagement in this direction, although allergen avoidance at least is not recommended anymore.

Intentional exposure to a food allergen was shown to mediate allergen tolerance in children, although not without risks. Primary interventions and food tolerance are driven by the allergen itself, but the protection of farm effects as well as the parasite-mediated effects are not necessarily driven by the allergen itself. Thus, it is hoped that microbial- or parasite- derived factors can be identified, which could be used for therapeutic interventions (see the chapters titled "Bacterial Allergens" and "The Lost Friend: *H. pylori*"). An example of an allergen-independent mechanism is the route of the so-called aryl hydrocarbon receptor (AhR), which is present in many tissue and immune cells and is able to respond to microbial tryptophan metabolites. The AhR can induce immune mediators such as IL-22, which in turn act on epithelial cells to close or reinforce the epithelial barrier. Because the AhR can bind multiple ligands and also interacts with several adaptor proteins, both ligand specificity and function are still subject to intense research (see the chapter titled "The Role of the Gut in Type 2 Immunity").

4 Chronification and Exacerbation of Allergies

The cause of chronic disease progression is largely unknown, although it is important to note that allergen-specific immunotherapy can prevent the progression of allergic rhinitis into asthma. Viral exacerbations of airway diseases are well documented; they activate the innate immune system (e.g. the TLR3 receptor) and allow direct interventions (Silkoff et al. 2017). The previously mentioned autoallergery could be an explanation; at least for asthma, it has been observed that an exacerbation leads to another, more escalated disease severity level.

For both airway and skin manifestation, *Staphylococci* can cause exacerbations or predispose children to asthma if they are colonized in the hypopharyngeal region (Bisgaard et al. 2007). They are a source of enterotoxins (A, B, C, D), superantigens, and can even produce toxins that degranulate mast cells independently of IgE. *Staphylococci* antigens are targets of IgE (see the chapter titled "Bacterial Allergens") and can identify patients with chronic sinusitis and nasal polyposis (Tripathi et al. 2004; Van Zele et al. 2004). In atopic dermatitis, *Staphylococcus aureus* can cause a superinfection at sites of inflammation; this is thought to be supported by type-2 immunity, which inhibits the type-1 lytic immune response and would be more appropriate to defend the pathogen (Eyerich et al. 2009a). Therefore, *Staphylococci* may use type-2 immunity as an evasion strategy.

Another observation of T cells isolated from the airway and skin biopsies of patients with chronic allergies (Pennino et al. 2013; Eyerich et al. 2009b) is that these tissue-derived T cells show a very broad T-cell subset and uncharacteristic cytokine profile. For example, there is an unusual co-expression of IL-4 and IFN-γ that is not observed in the periphery, where IL-4 and IFN-γ fall into discrete and antagonistically regulated Th1- and Th2-subset phenotypes. Similar observations were reported for Th17 cells (Gelfand et al. 2017), which are activated in asthma exacerbation along with the inflammasome (Lee et al. 2014). The plasticity of

tissue-derived T cells was proposed to be the result of repetitive or chronic stimulation of the T cells because it may occur under the crossfire of allergens and superantigens. This increased plasticity has become a major research focus because it is anticipated that these cells have a high potential to cause damage and worsen pathology of the disease. For example, the plastic Th17 cells switch to IFN-γ production and form the majority of cells found in synovial fluids of patients with rheumatoid arthritis (Nistala et al. 2010; Cosmi et al. 2011), the guts of patients with Crohn disease (Kleinschek et al. 2009), and cerebrospinal fluid (Kebir et al. 2009). It also appears that these cells are resistant to the suppression of regulatory T cells (Basdeo et al. 2017).

5 Concluding Remarks and Therapeutic Relevance

Vitamins B and K are well-known symbiotic elements of bacteria in our gut from which we benefit. These vitamins highlight the complex synthetic machinery of the 1.5 kg of bacteria carried by each person. Approximately 2–3 years after birth, an individual is living with a stable microbiota composition. Therefore, a question is raised: can the microbiome be manipulated to confer protection against allergy without creating other problems in the symbiotic relationship or turning symbionts into pathogens? This issue is currently being explored with some interesting therapeutic options arising, although it has been noted that frequent antibiotic intake can increase allergic sensitization (see the chapter titled "Aryl Hydrocarbon Receptor: An Environmental Sensor in Control of Allergy Outcomes").

The authors of this book draw a differentiated picture of the role of the microbiota and their impact on the exacerbation and prevention of allergies. Consequences for therapy will therefore only develop out of profound knowledge that considers the elements of the microbiota (ranging from superantigens to Ahr ligands) and cellular recipients (ranging from dendritic cells and epithelial cells to several lymphocyte populations). Equally important is the recipient, his or her genetic predisposition, and the diverse disease endotypes that are subject to current research. Biomarkers described in chapter titled "Specific Therapies for Asthma Endotypes: A New Twist in Drug Development" may support the endotype diagnosis so that appropriate therapies can be used to control disease along with the resulting microbiota (see the chapter titled "The Gut Microbiome and Its Marriage to the Immune System: Can We Change It All?").

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