Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Highlights in immune response, microbiome and precision medicine in allergic disease and asthma☆

Milena Sokolowska and Cezmi A. Akdis

Current Opinion in Immunology 2017, **48**:iv–ix

For a complete overview see the Issue

http://dx.doi.org/10.1016/j.coi.2017.10.009

Milena Sokolowska

Cezmi A Akdis*

Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland, Christine Kühne - Center for Allergy Research and Education (CK-CARE), Davos, Switzerland
e-mail: akdisac@siaf.uzh.ch

*Corresponding author at: Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland. Tel.: +41 81 4100848; fax: +41 81 4100840.

Cezmi Akdis, MD is the Director of the Swiss Institute of Allergy and Asthma Research (SIAF), Davos and Professor in Zurich University Medical Faculty. He was president of the European Academy of Allergy & Clinical Immunology (11'000 members) between 2011-2013. He is the Editor-in-Chief of Journal of Allergy & Clinical Immunology and founder and organizer of World Immune Regulation Meetings, Davos. Prof. Akdis is a Senate Member of the Swiss Academy of Medical Sciences and an honorary member of the Swiss Society of Allergy Immunology (SGAI-SSAI). He was honoured with 13 international awards.

Outside the comfort zone in modern immunology and allergology: revised and broadened spectrum of focus

The scientific world is now slowly realizing that seemingly endless omics technologies are bringing us immense amounts of new perspectives on revisiting past, performing current and planning future research. It is now quite challenging to ask simple scientific questions. Instead though, we are in the era of extensive opportunities to verify and revise previous findings, as well as to plan new studies that are aiming for even more unknown variables. Recent findings in allergy/immunology, presented in this series of reviews highlight these opportunities and challenges. They also led to our deeper understanding of the role of microbiome and other environmental factors, innate immunity, barriers in the tissues and interplay of innate and adaptive immunity in the development of allergy or immune tolerance in asthma, food allergy, eosinophilic esophagitis, atopic dermatitis as well as in allergen-specific immunotherapy and healthy immune response to allergens.

Immune tolerance to allergens

Specific immune response to allergens is decisive in the development of clinically healthy or allergic states. Peripheral immune tolerance to allergens is essential in this decision and functions in parallel to clinical tolerance. van de Veen and colleagues provide here an overview of the current advances on the allergen-specific immune tolerance mechanisms [1]. Healthy bee keepers, who receive multiple bee stings and do not develop allergy and allergen-specific immunotherapy (AIT) of allergic patients represent two relevant human *in vivo* models to investigate immunological correlates with the clinical immune tolerance. New methodology such as next generation sequencing or sequencing of the receptor repertoire enables to describe novel cell subsets, uncover their heterogeneity and link their phenotype with immunoregulatory function [2–4]. In addition, several studies are currently being performed because of an urgent need to understand the main mechanisms in detail and uncover good biomarkers of the effective AIT in the face of its cost-effectiveness. Among others, novel subsets of allergen-specific regulatory and effector T cells, detailed phenotype of allergen-specific Breg cells, interactions between regulatory DCs and T cells, as well as a novel role of ILCs in the development of Breg cells have been recently described [2–7].

Further on with hygiene hypothesis and immune correlates

Allergic diseases and asthma have been on the rapid rise worldwide over the last decades, which indicates a strong environmental component [8]. This relationship has been studied for a while in the context of "hygiene

☆ **The authors' laboratory is supported by** Swiss National Science Foundation grant 310030-156823 and Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland.

hypothesis" with important clinical and immunological findings suggesting the protective effect of traditional farming, rapidly declining all over the world, being replaced by industrialized food production [9,10]. Ober and colleagues [11] describe here in detail how the protective effect of traditional farms has been linked to the broad exposure to animal barns, higher endotoxin level and consumption of raw milk, resulting in greater diversity of microbiota and specific modifications in innate and adaptive immune profiles [12,13]. These findings have been eloquently supported in a recent study analysing Amish farm children, with low prevalence of asthma and allergic sensitization in comparison to Hutterite children raised in the industrialised farms, who have high rates of both diseases [14]. These children having similar genetic background, however living in different microbiota and endotoxin levels, presented significant changes in the frequencies and in the gene expression profiles of circulating innate immune cells. Amish children had higher proportions of less mature neutrophils and lower proportions of eosinophils. Their monocytes presented a more suppressive phenotype, and the gene expression networks of their PBMCs were concentrated around key proteins in the innate immune response to microbial stimuli. Supporting these findings, house dust extract from Amish houses was able to inhibit allergic inflammation in mouse model of allergic airway diseases. Interestingly, this effect disappeared in the *MyD88*- and *Trif*-deficient mice, indicating a critical role of innate immunity in providing traditional farm-based protection [14].

Immunoregulatory role of bioamines secreted by commensal bacteria

Farm effect and hygiene hypothesis strongly suggest that microbiota, metabolites from bacteria and food-microbiota interactions influence the susceptibility to allergy and asthma development, as well as the course and severity of the diseases and their response to treatment [15–17]. The direct role of specific bacteria, fungi and/or archea or their metabolites such as short chain fatty acids or biogenic amines, which may play a role in their protective or deleterious effects are slowly starting to be recognized [13,15,18]. Barcik and colleagues [19] review in the journal recent evidence on histamine, one of the most often studied immune modulatory biogenic amines. Known for long time in immediate type allergic reactions, histamine is a multi-faced immune regulatory molecule, whose effects depend on the engaged receptor [20,21]. The authors discuss here their recent exciting findings that biologically active histamine is produced by certain bacteria in the human gut microbiome in large quantities, comparable to activated mast cells [22]. *Escherichia coli*, *Morganella morgani and Lactobacillus vaginalis* isolated from human fecal samples produced the largest amounts of histamine. Interestingly, histamine-producing bacteria were more abundant in patients with asthma compared to controls, as well as they were increased in patients with severe asthma [22]. These recent findings suggest that high biodiversity in commensals has a good reason to dilute out potent bioamines and abundance of such bioamine producing bacteria might play a role in the course of allergic diseases. Other bioamines and their link with chronic diseases remain to be investigated.

The immunological window-of-opportunity for early intervention

Probably human microbiome and its further influence on the changes in immune system is shaped by the food, its dose, the routes of exposure and the age of the child in which the food is introduced [18]. For many years, in accordance with the allergen avoidance theory, parents were advised not to give certain foods to infants until their immune system is mature enough. However, latest data, build on previous observations, probably make us to revisit this guideline [23,24]. According to the recent findings of LEAP (Learning Early About Peanut), EAT and LEAP-On studies, described in this issue of the journal in detail by their investigators. Turcanu and colleagues [25] describe that early introduction of peanuts - one of the most potent food allergens - in the diet of the infants at risk result in significant protection against peanut allergy [26,27]. In contrast, children who are exposed to allergen at homes, probably due to skin exposure to food antigens in the house dust, but do not eat peanut have higher risk of developing allergy to peanut. Children who consumed peanuts developed an earlier increase in serum peanut-specific IgG4, and specific IgG4 levels stayed higher up to 6 years compared to children avoiding peanut consumption. Interestingly, there was no difference in peanut-specific IgE between those groups also up to 6 years of age. Plasma from children having peanut-specific IgE, but clinically tolerating peanut consumption was shown to have the ability to block activation of mast cells, partially due to the presence of peanut-specific IgG4 [28]. Further immunological mechanisms at the foundations of this early intervention at the immunologic window-of-opportunity still await to be discovered.

Eosinophilic esophagitis, a type 2 immunity disease

Digestive system is a place where the majority of microbiota resides, but it can also be a place of tissue-specific allergic inflammation called eosinophilic esophagitis (EoE) [29]. As extensively reviewed by Paul and colleagues [30], EoE is a type 2 immunity disease, developed as an abnormal response to several food-derived or aeroallergens, with a substantial component of epithelial barrier impairment and dysregulation of epithelial differentiation [31]. Genetic loci associated with the increased risk of EoE include genes important in several epithelial barriers such as fillagrin (*FLG*), as well as esophagus-specific genes such as cysteine protease *CAPN14* [32,33]. Type 2 cytokines, such as TSLP, IL-33, IL-25,