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

0952-7915/© 2017 Published by Elsevier Ltd.

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

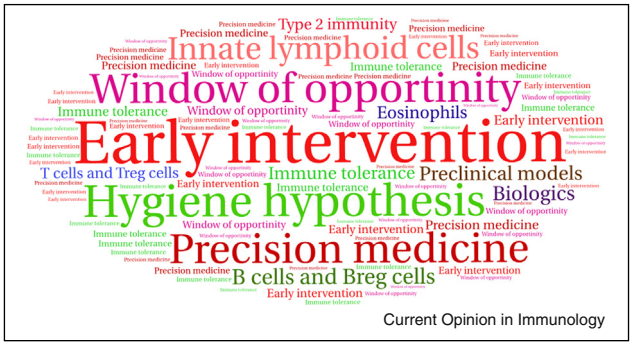
Digestive system is a place where the majority of microbiota resides, but it can also be a place of tissue-specific allergic inflammation called eosinophilic esophagitis (EoE) [29]. As extensively reviewed by Paul and colleagues [30], EoE is a type 2 immunity disease, developed as an abnormal response 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,

IL-5 and IL-13 contribute to EoE pathology [34,35]. Eosinophils, CRTH2+ Th2 cells, iNKT cells, ILC2s basophils and mast cells are involved in on-going type 2 inflammation [36–38]. Interestingly, IgG4-positive plasma cells are present in the inflamed tissue and the disease in experimental settings seems not be exclusively IgE-mediated according to findings based on the experimental EoE models and lack of patient's response to anti-IgE therapies [39,40]. Therefore, further studies are needed to uncover the complexity and reasons for the anatomic location of EoE within the spectrum of other type 2 immunity diseases.

Immune correlates and biologics in atopic dermatitis and psoriasis in humans and mouse models

As a major barrier tissue, skin is often involved in a diverse spectrum of T-cell mediated inflammation in atopic dermatitis (AD) and psoriasis. It can also be an entry site for the sensitization against food and aeroallergens, especially in the inflamed state [41]. Guttman-Yassky and Krueger [42] review here the immunopathogenic features of these two clinically separate diseases, with subtypes in Asian-origin, western-origin, intrinsic and pediatric AD. Thus, some immunological and molecular mechanisms overlap and as such, some of the developing therapeutic options might be of benefit for both of them. Psoriasis is a unique example of an inflammatory skin disease in which highly-successful therapy with IL-17 antagonists confirmed the major role of Type 17 (Th17, Tc17) T cells in its pathogenesis, with subsequent activation of Th1 and Th22 and neutrophil influx to the epidermis [43,44]. Additionally, IL-17 axis in psoriasis depends on IL-23 and the novel treatment options with specific anti-IL-23 gives the next, highly effective therapeutic approach [44]. In contrast, AD is a multi-factorial disease with several disease subtypes. Th2 and Th22 cells together with their signature cytokines IL-4, IL-5, IL-13 and IL-22, respectively, are often present and activated in majority of the AD subtypes [45,46]. Also, DCs of the AD dermis have high expression of TSLP receptor and OX40L, which lead to Th2 polarization [47]. AD is often associated with the presence of increased IgE and coexists with allergies and asthma. However, in Asian AD, pediatric AD and intrinsic AD there is a substantial component of Th17 and Th1 pathways, with normal IgE levels, together with clinical overlap with characteristics of psoriasis [48,49]. Beside cyclosporine, which is effective at suppressing AD, but has substantial side effects, the usage of dupilumab, an antibody blocking IL-4/IL-13 signalling has been recently approved after successful clinical trials [50,51]. The efficacy of dupilumab in AD is lower compared to the treatment effect of blocking of IL-17/IL-23 pathways in psoriasis, probably due to a wide spectrum of AD, existing in several endotypes. Thus, it remains to be determined if a fraction of patients with AD could benefit from psoriasis-based treatments.

Figure 1



Immune mechanisms of allergic disease and their clinical usage are linked to type 2 immunity, immune tolerance, hygiene hypothesis, early intervention, window of opportunity, precision medicine, T cells and Treg cells, B cells and Breg cells, Innate lymphoid cells, eosinophils, biologics and preclinical models.

Pre-clinical animal models are used to study the disease pathogenesis and evaluate potential treatment options. Recent transcriptomic analyses of human AD skin and several mouse models of AD revealed surprisingly that none of the currently used mouse models of AD could fully represent all aspects of human AD profile, whereas IL-23-injected mice, considered previously as psoriasis model, represented best the human AD transcriptomic profile, yet still with only 37% similarity in gene expression [52]. Accordingly, Kabashima and Nomura [53] present here the detailed description of several current AD and psoriasis models in mice in an effort to provide clearer understanding of their relevance to human diseases. It needs to be considered that since human AD is not a homogenous disease and several endotypes and phenotypes occur [54], more than one pre-clinical model should often be studied to recapitulate the whole spectrum.

Figure 1

Immunology of multiple omics in precision/personalized medicine

In quest to understand the early pathogenesis of asthma and allergic diseases, their clinical immunological and molecular subtypes, as well as their course and response to treatment, several modern scientific tools have been applied. Scott Boyd and colleagues [55] describe here recent advances in the field of immune monitoring tools and propose the strategy of big data integration to create useful instruments for precision allergy and immunology. The authors suggested that allergy diagnosis can use recombinant allergens, allergen-microarray technologies, basophil activation tests, cytometry by time-of flight mass spectrometry (CyTOF) [56–58]. Novel asthma and allergy monitoring approaches may include in the future several – omics techniques such as genomics, epigenomics, transcriptomics, proteomics, metabolomics,

lipidomics, microbiome sequencing and detailed exposome characterisation, together with deeper immunophenotyping of cells of innate immunity and allergen-specific T and B cells [2–4,59]. All of these tools, first require to overcome their level of complexity, and difficulty to perform at the point of care, but they are expected to help to decipher patient's endotype (molecular mechanisms related to pathophysiology) and teratype (response to treatment) [60,61].

In conclusion, modern science and medicine, including allergy and immunology is at the early stage of beginning to understand the complexity of diseases and the models to study them, seems to leave its comfort zone and admits that it needs to broaden the must-have focus both in basic and clinical research. Bigger studies in diverse populations, with real hypothesis-free approaches and thoughtful involvement of novel methodology, are needed to enable understanding of the disease. We are also humbly coming back to the origins. Precision medicine of today repeats after Hippocrates and his followers what we all might have forgotten: "It is more important to know what sort of person has a disease than to know what sort of disease a person has" [62,63].

References

1. van de Veen W, Wirz OF, Globinska A, Akdis M: **Novel Mechanisms in Immune Tolerance to Allergens during Natural Allergen Exposure and Allergen-Specific Immunotherapy**. *Curr Opin Immunol* 2017, **48**:74-81.
2. Ryan JF, Hovde R, Glanville J, Lyu SC, Ji X, Gupta S, Tibshirani RJ, Jay DC, Boyd SD, Chinthrajah RS *et al.*: **Successful immunotherapy induces previously unidentified allergen-specific CD4+ T-cell subsets**. *Proc Natl Acad Sci U S A* 2016, **113**:E1286-E1295.
3. Wambre E, Bajzik V, DeLong JH, O'Brien K, Nguyen QA, Speake C, Gersuk VH, DeBerg HA, Whalen E, Ni C *et al.*: **A phenotypically and functionally distinct human TH2 cell subpopulation is associated with allergic disorders**. *Sci Transl Med* 2017:9.
4. Hoh RA, Joshi SA, Liu Y, Wang C, Roskin KM, Lee JY, Pham T, Looney TJ, Jackson KJ, Dixit VP *et al.*: **Single B-cell deconvolution of peanut-specific antibody responses in allergic patients**. *J Allergy Clin Immunol* 2016, **137**:157-167.
5. Boonpiyathad T, Meyer N, Moniuszko M, Sokolowska M, Eljaszewicz A, Wirz OF, Tomasiak-Lozowska MM, Bodzenta-Lukaszyk A, Ruxrungtham K, van de Veen W: **High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers**. *Allergy* 2017, **72**:407-415.
6. Mascarell L, Airouche S, Berjont N, Gary C, Gueguen C, Fourcade G, Bellier B, Togbe D, Ryffel B, Klatzmann D *et al.*: **The regulatory dendritic cell marker C1q is a potent inhibitor of allergic inflammation**. *Mucosal Immunol* 2017, **10**:695-704.
7. Palomares O, Akdis M, Martin-Fontecha M, Akdis CA: **Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells**. *Immunol Rev* 2017, **278**:219-236.
8. Bach JF: **The effect of infections on susceptibility to autoimmune and allergic diseases**. *N Engl J Med* 2002, **347**: 911-920.
9. Schaub B, Vercelli D: **Environmental protection from allergic diseases: From humans to mice and back**. *Curr Opin Immunol* 2015, **36**:88-93.
10. von Mutius E, Vercelli D: **Farm living: effects on childhood asthma and allergy**. *Nat Rev Immunol* 2010, **10**:861-868.
11. Ober C, Sperling A, von Mutius E, Vercelli D: **Immune Development and Environment: Lessons from Amish and Hutterite Children**. *Curr Opin Immunol* 2017, **48**:51-60.
12. Frei R, Roduit C, Bieli C, Loeliger S, Waser M, Scheynius A, van Hage M, Pershagen G, Doekes G, Riedler J *et al.*: **Expression of genes related to anti-inflammatory pathways are modified among farmers' children**. *PLoS One* 2014, **9**:e91097.
13. Frei R, Ferstl R, Roduit C, Ziegler M, Schiavi E, Barcik W, Rodriguez-Perez N, Wirz OF, Wawrzyniak M, Pugin B *et al.*: **Exposure to nonmicrobial N-glycolylneuraminic acid protects farmers' children against airway inflammation and colitis**. *J Allergy Clin Immunol* 2017.
14. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, Ledford JG, Marques Dos Santos M, Anderson RL, Metwali N *et al.*: **Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children**. *N Engl J Med* 2016, **375**:411-421.
15. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, Blanchard C, Junt T, Nicod LP, Harris NL *et al.*: **Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis**. *Nat Med* 2014, **20**:159-166.
16. Gollwitzer ES, Saglani S, Trompette A, Yadava K, Sherburn R, McCoy KD, Nicod LP, Lloyd CM, Marsland BJ: **Lung microbiota promotes tolerance to allergens in neonates via PD-L1**. *Nat Med* 2014, **20**:642-647.
17. Man WH, de Steenhuijsen Piters WA, Bogaert D: **The microbiota of the respiratory tract: gatekeeper to respiratory health**. *Nat Rev Microbiol* 2017, **15**:259-270.
18. Smits HH, Hiemstra PS, Prazeres da Costa C, Ege M, Edwards M, Garn H, Howarth PH, Jartti T, de Jong EC, Maizels RM *et al.*: **Microbes and asthma: Opportunities for intervention**. *J Allergy Clin Immunol* 2016, **137**:690-697.
19. Barcik W, Wawrzyniak M, Akdis CA, O'Mahony L: **Immune Regulation by Histamine and Histamine-Secreting Bacteria**. *Curr Opin Immunol* 2017, **48**:108-113.
20. Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OA, Malolepszy J, Zak-Nejmark T, Koga R, Kobayashi T, Blaser K *et al.*: **Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors**. *Nature* 2001, **413**:420-425.
21. O'Mahony L, Akdis M, Akdis CA: **Regulation of the immune response and inflammation by histamine and histamine receptors**. *J Allergy Clin Immunol* 2011, **128**:1153-1162.
22. Barcik W, Pugin B, Westermann P, Perez NR, Ferstl R, Wawrzyniak M, Smolinska S, Jutel M, Hessel EM, Michalovich D *et al.*: **Histamine-secreting microbes are increased in the gut of adult asthma patients**. *J Allergy Clin Immunol* 2016, **138**:1491-1494 e1497.
23. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, Robinson Z, Geoghegan N, Jarrold K, Reeves T *et al.*: **Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis**. *JAMA* 2016, **316**:1181-1192.
24. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, Halken S, Katz Y, Ebisawa M, Eichenfield L *et al.*: **Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants**. *J Allergy Clin Immunol* 2015, **136**:258-261.
25. Turcanu V, Brough H, du Toit G, Foong R-X, Marrs T, Santos A, Lack G: **Immune Mechanisms of Food Allergy and its Prevention by Early Intervention**. *Curr Opin Immunol* 2017, **48**:92-98.
26. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M *et al.*: **Randomized trial of peanut consumption in infants at risk for peanut allergy**. *N Engl J Med* 2015, **372**:803-813.
27. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, Brough HA, Santos AF, Harris KM, Radulovic S *et al.*:

Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. *N Engl J Med* 2016, **374**:1435-1443.

28. Santos AF, James LK, Bahnson HT, Shamji MH, Couto-Francisco NC, Islam S, Houghton S, Clark AT, Stephens A, Turcanu V *et al.*: **IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens**. *J Allergy Clin Immunol* 2015, **135**: 1249-1256.

29. Guagnozzi D, Arias A, Lucendo AJ: **Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders**. *Aliment Pharmacol Ther* 2016, **43**:851-862.

30. Paul M, Caldwell J, Rothenberg M: **Novel Immunologic Mechanisms in Eosinophilic Esophagitis**. *Curr Opin Immunol* 2017, **48**:114-121.

31. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, Mukkada VA, Succop PA, Abonia JP, Foote H *et al.*: **Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis**. *J Allergy Clin Immunol* 2014, **134**:1084-1092 e1081.

32. Rochman M, Travers J, Miracle CE, Bedard MC, Wen T, Azouz NP, Caldwell JM, Kc K, Sherrill JD, Davis BP *et al.*: **Profound loss of esophageal tissue differentiation in patients with eosinophilic esophagitis**. *J Allergy Clin Immunol* 2017, **140**:738-749.e3.

33. Litosh VA, Rochman M, Rymer JK, Porollo A, Kottyan LC, Rothenberg ME: **Calpain-14 and its association with eosinophilic esophagitis**. *J Allergy Clin Immunol* 2017, **139**:1762-1771 e1767.

34. Paul WE, Zhu J: **How are T(H)2-type immune responses initiated and amplified?** *Nat Rev Immunol* 2010, **10**:225-235.

35. Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomin PR, Nair MG, Benitez AJ, Ruymann KR, Muir AB, Hill DA *et al.*: **Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis**. *Nat Med* 2013, **19**:1005-1013.

36. Mitson-Salazar A, Yin Y, Wansley DL, Young M, Bolan H, Arceo S, Ho N, Koh C, Milner JD, Stone KD *et al.*: **Hematopoietic prostaglandin D synthase defines a proeosinophilic pathogenic effector human T(H)2 cell subpopulation with enhanced function**. *J Allergy Clin Immunol* 2016, **137**:907-918 e909.

37. Rayapudi M, Rajavelu P, Zhu X, Kaul A, Niranjan R, Dynda S, Mishra A, Mattner J, Zaidi A, Dutt P *et al.*: **Invariant natural killer T-cell neutralization is a possible novel therapy for human eosinophilic esophagitis**. *Clin Transl Immunology* 2014, **3**:e9.

38. Doherty TA, Baum R, Newbury RO, Yang T, Dohil R, Aquino M, Doshi A, Walford HH, Kurten RC, Broide DH *et al.*: **Group 2 innate lymphocytes (ILC2) are enriched in active eosinophilic esophagitis**. *J Allergy Clin Immunol* 2015, **136**:792-794 e793.

39. Rocha R, Vitor AB, Trindade E, Lima R, Tavares M, Lopes J, Dias JA: **Omalizumab in the treatment of eosinophilic esophagitis and food allergy**. *Eur J Pediatr* 2011, **170**:1471-1474.

40. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, Lowichik A, Chen X, Emerson L, Cox K *et al.*: **Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE**. *Gastroenterology* 2014, **147**:602-609.

41. Noti M, Kim BS, Siracusa MC, Rak GD, Kubo M, Moghaddam AE, Sattentau QA, Comeau MR, Spergel JM, Artis D: **Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis**. *J Allergy Clin Immunol* 2014, **133**:1390-1399 1399 e1391-1396.

42. Guttman-Yassky E, Krueger JG: **Atopic Dermatitis and Psoriasis: Two different immune diseases or one spectrum?** *Curr Opin Immunol* 2017, **48**:68-73.

43. Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, Menter A, Philipp S, Sofen H, Tyring S *et al.*: **Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis**. *N Engl J Med* 2017, **376**:1551-1560.

44. Kim J, Krueger JG: **Highly Effective New Treatments for Psoriasis Target the IL-23/Type 17 T Cell Autoimmune Axis**. *Annu Rev Med* 2017, **68**:255-269.

45. Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, Whynot J, Novitskaya I, Cardinale I, Haider A, Khatcherian A, Carucci JA, Bergman R *et al.*: **Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis**. *J Allergy Clin Immunol* 2007, **119**:1210-1217.

46. Guttman-Yassky E, Nograles KE, Krueger JG: **Contrasting pathogenesis of atopic dermatitis and psoriasis–part II: immune cell subsets and therapeutic concepts**. *J Allergy Clin Immunol* 2011, **127**:1420-1432.

47. Fujita H, Shemer A, Suarez-Farinas M, Johnson-Huang LM, Tintle S, Cardinale I, Fuentes-Duculan J, Novitskaya I, Carucci JA, Krueger JG *et al.*: **Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets**. *J Allergy Clin Immunol* 2011, **128**:574-582 e571-512.

48. Noda S, Suarez-Farinas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, Peng X, Estrada YD, Nakajima S, Honda T *et al.*: **The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization**. *J Allergy Clin Immunol* 2015, **136**:1254-1264.

49. Suarez-Farinas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C, Krueger JG, Guttman-Yassky E: **Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis**. *J Allergy Clin Immunol* 2013, **132**:361-370.

50. Khattri S, Shemer A, Rozenblit M, Dhingra N, Czarnowicki T, Finney R, Gilleaudeau P, Sullivan-Whalen M, Zheng X, Xu H *et al.*: **Cyclosporine in patients with atopic dermatitis modulates activated inflammatory pathways and reverses epidermal pathology**. *J Allergy Clin Immunol* 2014, **133**:1626-1634.

51. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP *et al.*: **Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis**. *N Engl J Med* 2016, **375**:2335-2348.

52. Ewald DA, Noda S, Oliva M, Litman T, Nakajima S, Li X, Xu H, Workman CT, Scheipers P, Svitacheva N *et al.*: **Major differences between human atopic dermatitis and murine models, as determined by using global transcriptomic profiling**. *J Allergy Clin Immunol* 2017, **139**:562-571.

53. Kabashima K, Nomura T: **Revisiting murine models for atopic dermatitis and psoriasis with multipolar cytokine axes**. *Curr Opin Immunol* 2017, **48**:99-107.

54. Muraro A, Lemanske RF Jr, Hellings PW, Akdis CA, Bieber T, Casale TB, Jutel M, Ong PY, Poulsen LK, Schmid-Grendelmeier P *et al.*: **Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology**. *J Allergy Clin Immunol* 2016, **137**:1347-1358.

55. Boyd S, Hoh R, Nadeau K, Galli S: **Immune monitoring for precision medicine in allergy and asthma**. *Curr Opin Immunol* 2017, **48**:82-91.

56. Cabauatan CR, Lupinek C, Scheiblhofer S, Weiss R, Focke-Tejkl M, Bhalla PL, Singh MB, Knight PA, van Hage M, Ramos JD *et al.*: **Allergen microarray detects high prevalence of asymptomatic IgE sensitizations to tropical pollen-derived carbohydrates**. *J Allergy Clin Immunol* 2014, **133**:910-914 e915.

57. Mukai K, Gaudenzio N, Gupta S, Vivanco N, Bendall SC, Maecker HT, Chinthrajah RS, Tsai M, Nadeau KC, Galli SJ: **Assessing basophil activation by using flow cytometry and mass cytometry in blood stored 24 hours before analysis**. *J Allergy Clin Immunol* 2017, **139**:889-899 e811.

58. Bendall SC, Simonds EF, Qiu P, Amir el AD, Krutzik PO, Finck R, Bruggner RV, Melamed R, Trejo A, Ornatsky OI *et al.*: **Single-cell mass cytometry of differential immune and drug responses across a human hematopoietic continuum**. *Science* 2011, **332**:687-696.

59. Sokolowska M, Chen LY, Liu Y, Martinez-Anton A, Logun C, Alsaaty S, Cuento RA, Cai R, Sun J, Quehenberger O *et al.*: **Dysregulation of lipidomic profile and antiviral immunity in response to hyaluronan in patients with severe asthma**. *J Allergy Clin Immunol* 2017, **139**:1379-1383.

60. Galli SJ: **Toward precision medicine and health: Opportunities and challenges in allergic diseases**. *J Allergy Clin Immunol* 2016, **137**:1289-1300.

61. Galli SJ: **Mast Cells and KIT as Potential Therapeutic Targets in Severe Asthma**. *N Engl J Med* 2017, **376**:1983-1984.

62. Abrahams ESM: *The history of personalized medicine; in Integrative neuroscience and personalized medicine:* New York: Oxford University Press; 2010, 3-16:. 2010.

63. John M: **From Osler to the cone technique**. *HSR Proc Intensive Care Cardiovasc Anesth* 2013, **5**:57-58.