The role of environmental factors in allergy: A critical reappraisal

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Abstract

Allergies are usually referred to as type I hypersensitivity reactions against innocuous environmental antigens, characterized by a Th2/IgE-dominated inflammation. They can manifest themselves in various organs, such as skin, gastrointestinal and respiratory tract, and comprise diseases as diverse as allergic rhinitis and conjunctivitis, bronchial asthma, oral allergy syndrome, food allergy, urticaria and atopic eczema, but also anaphylactic shock. Within the last decades, there was a significant global increase in allergy prevalence, which has been mostly attributed to changes in environment and lifestyle. But which, among all factors discussed, are the most relevant, and what are the mechanisms by which these factors promote or prevent the development of allergic diseases? To answer this, it is necessary to go back to the two key questions that have occupied allergy researchers for the last decades: Firstly, what makes an allergen an allergen? Secondly, why are more and more individuals affected? Within the last decade, we have made considerable progress in answering these questions. This review gives an overview over scientific progress in the field, summarizes latest findings and points out future prospective and research needs.

KEYWORDS
air pollution, allergy, environment, farming effect, psychosocial factors

1 | INTRODUCTION

The tremendous success story of modern medicine is mostly a history of success in fighting infections. At the same time, however, noncommunicable diseases like cancer, metabolic and neurodegenerative diseases, psychological disorders, autoimmune diseases and allergies, have risen. Allergies have become downright endemic in industrialized parts of the world, and incidences are still increasing in developing countries. The rise in prevalence of allergy spectrum diseases (allergic rhinitis, asthma, food allergies, urticaria, atopic eczema and anaphylaxis) has been attributed to a so-called westernized life style. This has spawned the original hygiene hypothesis and the concept of allergies as not only genetic, but also environmental diseases. The impact that environment and life style have on allergies is illustrated by the finding that immediately after the German reunification, lifetime prevalence of allergic diseases differed significantly in eastern and western federal countries of Germany[1] but progressively evened out within only 30 years.[2] Today, allergic sensitizations are almost equally frequent in both parts of Germany. According to a nationwide survey from 2008-2011, nearly half of the German population is sensitized against at least one allergen, ca. 30% to at least one inhalant allergen,[3] and ca. 20% of adults suffer from at least one allergy.[4] This dramatic short-term development cannot be attributed to a drift in gene pool of the population. It has to be due to changes in the people's environment in the broader sense.

Two master questions have dominated allergy research within the last decade. The first question is: what makes an allergen an allergen? And the second question: what makes more and more people become allergic? Have the allergens become more abundant or more "aggressive" due to environmental cofactors? Or is the rise in prevalence rather due to changes in host factors, such as altered life style, nutritional habits, medication use or higher psychological stress?

2 | ATOPY: THE ROLE OF GENETIC PREDISPOSITION

Before discussing the role of environmental factors in allergy, it is necessary to first consider the host that these factors act on. It has long been known that the predisposition to develop an allergic disease is to some extent an inheritable trait. Early linkage analyses identified loci on chromosomes 5 and 11, containing the IL9 and FCERB genes and the IL4 gene cluster, as relevant to atopy and asthma.[5] With the rising of the era of genomics, knowledge of the genetics behind allergic diseases advanced a great deal. Especially, genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in a large number of genes associated with an elevated risk to develop allergies. The picture as a whole, however, is difficult to catch. This is explained by the fact that allergy spectrum diseases are complex, often heterogeneous and always multifactorial. Moreover, they manifest themselves in different organs, which explains that some genetic markers associated with asthma are also found associated with nonallergic chronic lung diseases like COPD,[6,7] whereas other markers associated with atopic eczema are associated with chronic inflammatory skin diseases.[8,9] The typical "allergic triad",[10] consisting of atopic eczema, allergic rhinitis and asthma, is observed in many but not all patients. Those patients typically present with food allergy and atopic eczema in early childhood and progress to respiratory allergy and asthma in later life. This shows on the one hand that a high degree of relatedness exists between allergy spectrum diseases. On the other hand, asthma and atopic eczema are each by themselves highly heterogeneous diseases, different clinical phenotypes of which are commonly referred to as "endotypes".[11–13] The exact definition of endotypes, and the role of allergic sensitization in defining these endotypes, remains a matter of scientific debate. At least for asthma, several intermediate phenotypes exist, all of which could be linked with a different set of genetic markers.[14] Nevertheless, meta-analyses have identified a number of genes that have been reproduced in several independent cohorts as being associated with atopy, sensitization and allergy spectrum diseases. Among the top hits are genes for Th2/ILC2-associated and proinflammatory cytokines and chemokines (IL4, IL4RA, IL13, IL6, IL10, TNFA, IL33, TSLP and RANTES) and their receptors (IL4RA, IL1R1), transcription factors (STAT6), subunits of the high-affinity IgE receptor (FCER1A, FCER1B), genes of the MHC II gene cluster (HLA-DRB1, HLA-DQB1), genes of the epidermal differentiation complex (FLG, SPINK5) and innate pattern recognition receptor genes (CD14, TLR7, TLR9 and S100A7).[14–16] The complexity of the picture ensues from the fact that some of these genetic markers are linked with atopy in general, others with elevated serum IgE levels, allergic rhinitis, asthma of various types, atopic eczema, or with combinations. Since "allergy" is a trait governed by multiple genes, a combination of different genetic markers gives rise to different degrees of predisposition, or predisposes to develop certain types of allergies but not others. Given the heterogeneity in allergen sources and the fact that different sensitization profiles to inhalative allergens exist, it is well conceivable that we will come up with different endotypes of allergic rhinitis in the future, defined not so much by clinical phenotype but rather by different aetiology, and associated with different susceptibility genes.

3 | INNATE IMMUNE STIMULATION AS KEY TO ALLERGENICITY

When assessing environmental factors in allergy, we next have to continue by considering the obvious: the allergens. Allergens are the crucial environmental factors—without them, there is no allergy.

Are there "typical" allergens? Allergenic proteins are highly heterogeneous. In the past, considerable effort has been put in the identification of common structural features of allergens. Mast cells are activated if membrane-bound high-affinity IgE receptors spiked with IgE molecules are cross-linked by allergens. This process is facilitated when allergens contain repetitive or linear epitopes for IgE antibodies.[17] Repetitive linear IgE epitopes are a structural feature of some but not of all allergens. Others, like the major dog allergen Can f 1 bind to IgE via conformational epitopes.[18] Without activation of FceRI, there is not mast cell activation and thus no allergy. This simple notion gave rise to the idea of designing hypoallergenic proteins that bind to but do not cross-link the high-affinity FceRI. Other groups used bioinformatics approaches to identify common structural features of allergenic proteins. Such a study revealed that only 5% of all protein families grouped by structural features contain allergens.[19] However, it remained impossible to predict the allergenic potential of a given protein based alone on its structural determinants.

What is it then that makes an allergen an allergen? This question is especially relevant when considering the potential of a given protein to elicit a Th2-skewed T cell response, which is prerequisite to an IgE-dominated antibody response. Factors discussed to confer allergenic potential to a protein are as unspecific as low molecular weight, stability against proteolytic degradation, dosage and route of exposure.[20] That antigens entering the body via the oral route tend to be tolerated has been known for long. The phenomenon is used in murine models of induced peripheral tolerance[21] and in oral immunotherapy (sublingual immunotherapy; SLIT). A straightforward explanation is the fact that the oral mucosa is populated by oral Langerhans cells (oLCs).[22,23] These epithelial dendritic cells are highly tolerogenic due to their dense expression of inhibitory

costimulatory B7 family proteins (B7-H1, B7-DC). Upon ligation of toll-like receptor 4 (TLR-4), oLCs tend to differentiate naïve $CD4^+$ T cells into regulatory T cells (Treg).[24] This feature is exploited in new generation immunotherapy preparations, which contain the small molecule adjuvant monophosphoryl-lipid A (MPLA), a TLR-4 ligand derived from *Staphylococcus minnesota* that inhibits lower cytotoxicity than LPS.[25]

This brings us to the key role of the innate immune system in allergenicity. Pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) are critical in the decision-making process of whether a given antigen is tolerated or whether it sensitizes the individual, that is elicits a Th2-dominated immune response. A seminal finding pointing towards that direction was that Der p 2, a major allergen of house dust mite, acts as a molecular mimic of MD-2, which, together with LPS, makes up the ligand for TLR-4.[26] Likewise, Fel d 2, a major allergen from cat saliva, has been shown to bind to LPS, and enhanced binding of the complex to TLR-4 has been suggested.[27] Finally, a minor allergen of house dust mite, Der p 13, was recently demonstrated to induce TLR-2 signalling, which could contribute to the strong sensitizing potential of dust mite particles.[28]

4 | MATRIX MATTERS: LESSONS TO BE LEARNED FROM POLLEN

For major pollen proteins, such intrinsic adjuvant activity is rare. Instead, pollen releases other cofactors that are not allergenic by themselves but are encountered by the immune system of the respiratory tract together with the allergens. These molecules are thought to facilitate allergic sensitization towards pollen proteins. Such cofactors include proteases, NADPH oxidases and lipid mediators.[29] We recently demonstrated that pollen extracts are inducers of the NLRP3 inflammasome in UV-B-primed human primary keratinocytes.[30] Activation of MD2 was shown to be involved in allergic sensitization towards ragweed pollen extract in a murine allergy model involving repeated intranasal instillations.[31] In this study, a pollen extract prepared from lyophilized pollen of a commercial source was used and was tested free of LPS by LAL-assay. However, purified ragweed pollen allergen was not tested in the mouse model. To our own experience, a general feature of highly purified recombinant pollen proteins, such as rBet v 1 and rAmb a 1, is that they have virtually no sensitizing potential in murine models.[32] In contrast, if the same proteins are applied within their natural "matrix," that is within an aqueous pollen extract, allergic sensitization results even in the absence of external adjuvants such as alum. Recently, however, a highly immunogenic Amb a 1 isoform was described to potently sensitize mice in the absence of adjuvant, presumably due to its stability to endolysosomal degradation in dendritic cells.[33]

The near future is likely to reveal many more mechanisms how single allergens induce innate immune signalling. The challenge in understanding the puzzle of allergic sensitization will be to integrate existing information about allergens from diverse sources, to exactly determine which pathways have necessarily to be involved, and in what target cells.

5 | ENVIRONMENT AND LIFE STYLE: THE HYGIENE HYPOTHESIS REVISITED

We have learned that among the top susceptibility genes for allergy are genes involved in innate immune signalling, such as CD14 and TLRs. Furthermore, the quest of defining a "typical allergen" has led to the key finding that activation of innate immune signalling, for example via TLRs or the inflammasome, is prerequisite to allergic sensitization. It now becomes clear how the "westernized life style" could impact on the predisposition to develop allergic diseases. Epidemiological studies suggest that there are harmful as well as protective environmental and life style factors that act mainly in early childhood and adolescence, sometimes in utero. Beneficial factors include growing up in a rural environment with contact to farm animals ("farming effect"),[34,35] nutrition rich in dietary fibres and a high food diversity,[36–39] and early contact with siblings or peers.[40] A feature common to all these environmental factors is that they favour the formation of a highly diverse microbiota on the bodies′ barrier organs that is of the skin and the mucosa of the respiratory, urogenital and gastrointestinal tract.[41,42] The early interaction of commensal and environmental microbiota, the so-called old friends,[43] with the host′s developing immune system, including epithelial pattern recognition receptors, seems to be instrumental to the adjustment of the innate immune system. This interaction likely establishes a "set point" for the activation of pattern recognition receptors and downstream signalling pathways, which influences immune homoeostasis and reaction capacity later in life. Harmful environmental and life style factors, in contrast, include obesity and lack of physical exercise,[44–46] a diet rich in industrially processed foods, growing up as singlet in an urban home with an overall reduced microbial diversity and possibly exposure to antibiotics.[41,43,47] All these factors are associated with a decreased diversity of environmental microbes and a more or less pronounced dysbiosis on the barrier organs of the body.[48] This, in turn, leads to an altered set point of the innate immune system in early childhood, which facilitates loss of peripheral tolerance and the development of hypersensitivity later in life.[49]

6 | GOOD DUST AND BAD DUST: NATURAL BIOAEROSOLS VERSUS ANTHROPOGENIC AIR POLLUTION

Anthropogenic air pollution and the composition of inhaled bioaerosols can influence the risk for developing allergic diseases, mainly of the airways. Traffic-related air pollution, such as diesel exhaust particles, NOx and ozone, but also indoor pollutants such as cigarette smoke and volatile organic compounds of other sources, have direct adverse effects on the airways of exposed individuals. By priming airway inflammation, for example via inflammasome pathway

activation, anthropogenic air pollutants aggravate pulmonary inflammation to allergen challenge.[50] Epidemiological studies reveal a correlation between living near to high-traffic roads and increased odds for developing asthma.[51] Prenatal exposure to maternal smoking seems to predispose for the development of allergic asthma.[52] On the other hand, there are also beneficial aerosols. The beneficial farming effect has mostly been attributed to raw cow milk consumption,[53] but also the inhalation of immune modulatory plant-derived compounds from cowshed dust could be protective.[54] A recent study that compared different farming and nonfarming homes in the German state of Bavaria pointed out the possible importance of environmental microbes. In this study, dust samples were collected from children's bed mattresses, and 16S sequencing was performed. Proximity to the nearest farm as well as a broader bacterial diversity in the dust samples was linked to a higher degree of protection against asthma and atopy in the children.[55] This is in line with the intriguing findings of a seminal study in which two different northern American cohorts from Hutterite and Amish people, both practicing a farming life style, were compared in terms of asthma and allergy prevalence, peripheral blood eosinophil counts and house dust composition.[56] Amish people, who live in close proximity to their animals and practice a traditional way of farming, had low prevalence of atopy and low blood eosinophil counts. The dust samples collected in their homes were rich in bacterial LPS and were found to be protective in a mouse model of asthma. Hutterites, in contrast, who practiced industrial farming, had comparably high allergic sensitization rates as a northern American control cohort. Dust samples collected from Hutterite homes contained low levels of bacterial LPS and failed to confer protection against asthma in the mouse model.

Stays in alpine environments have historically been applied to support recovery of patients from chronic lung conditions in Europe. The famous lung sanatorium in Davos, Switzerland, setting of Thomas Mann's novel The Magic Mountain, is still in use as a rehabilitation hospital mainly for asthmatics but also for patients suffering from atopic eczema. Moderate altitude seems to be a mediating factor of this environmental regime, possibly due to an overall reduced airborne allergen burden.[57] Recent clinical evidence gathered from two trials on adolescents staying in the Davos rehabilitation hospital points out a beneficial effect of short-term stays in moderate altitude on asthma[58] and difficult-to-treat atopic eczema. The latter specifically points out a role of the alpine environment, since the short-term outcome in the Davos group was superior to that of a control group who stayed in a hospital in the Netherlands. The beneficial effect on disease activity and quality of life was detectable for up to 6 weeks after discharge.[59]

7 | ANTHROPOGENIC AND BIOGENIC MODIFIERS OF PLANT ALLERGENICITY: MICROBES, POLLUTANTS AND CLIMATE CHANGE

Allergens are environmental antigens and are as such subject to modification by environmental factors. Pollen-producing plants, in specific, react to biotic and abiotic stressors by inducing secondary metabolites, such as lipid mediators, and host-defense proteins, some of which are allergenic. Birch trees growing at sites with chronically elevated ambient ozone levels induced the major allergen Bet v 1 and chemotactic lipid mediators in pollen, which resulted in increased allergenic potency. Furthermore, pollen grains might not be sterile but carry microbes that elicit, in vitro, T cell responses via activation of dendritic cells.[60] Indeed, pollen of birch trees and grasses harbours specific microbial communities, a pollen-specific "microbiome".[61] Intriguingly, the diversity of pollen-associated microbiota was found reduced in pollen from birch trees located at sites with elevated ambient NO_2 levels. This implies that anthropogenic environmental stressors, such as air pollutants, negatively affect human health by more than one mechanism: either directly, by priming airway inflammation, or indirectly, by enhancing the immune-stimulatory or allergenic potential of plant pollen. Finally, also climate change has to be considered as an influence factor for the allergenicity of plant pollen and fungal allergens. Heavy rainfalls, high humidity episodes and thunderstorms might occur more frequently in parts of the world due to local climate change. Especially, thunderstorms have been shown to go along with atmospheric peaks in highly respirable subpollen particles[62] and fungal spores,[63] which are discussed as causatives of thunderstorm asthma. Earlier onset of plant flowering and higher pollen peaks have already been observed in some regions of Europe.[64,65] Additionally, changes in local climate favour the spreading of a highly allergenic neophyte, *Ambrosia artemisiifolia* (ragweed), in parts of Europe. Ragweed pollen is small and upon inhalation is deposited in the lower airways. They are highly cross-allergenic to the native weed *Artemisia vulgaris* (mugwort)[66,67] and have shown to induce symptoms in conjunctival challenges of patients sensitized to *Artemisia* pollen.[68] This means that even without relevant numbers of genuine sensitizations to ragweed, as presently found for Southern Germany,[69] we have to face the occurrence of "new," potentially severe respiratory allergies to ragweed pollen in large parts of Europe.[70] Under climate change scenarios, progressive spreading of stable ragweed plant populations and concomitant increases in pollen burden across large parts of Europe is predicted even for the near future.[71] In a recently published survey in patients with chronic lung diseases and a tourist cohort, both staying in an alpine Bavarian region, the overall propensity to perceive the risk of climate change-related adverse health effects was positively correlated with symptom severity in both, allergic patients and tourists.[72] Apart from stressing the importance of psychological modifiers in allergy, this shows that measures to limit adverse health effects of climate change should be taken and awareness should be raised.

8 | STRESS—THE MISSING LINK IN ALLERGY

Clinical studies on allergy are amongst the studies with the most pronounced placebo effects. The extent to which psychological factors, such as general well-being or perceived stress level, influence allergic

symptom perception is indication for a largely unappreciated pathophysiological component in allergy: neuroendocrine and neuroimmunological mechanisms. A lot of detail knowledge on cellular and molecular level exists, for instance on how hormones of the HPA axis, neurotransmitters and neuropeptides impact on T cells,[73] specifically on cytokine production and T helper cell differentiation.[74–77] In atopic eczema patients, numbers of physical interactions between cutaneous mast cells and neuronal fibres were increased in lesional as compared to nonlesional skin and correlated with itch and SCORAD.[78] Still, today's knowledge on the neuroimmunology in allergy is mostly sporadic. Insight from in vivo allergy models is very limited. One mouse model combined social disruption stress with allergic sensitization to *Aspergillus fumigatus*.[79] In this model, social disruption increased the allergic airway inflammation induced by allergen challenge. This was paralleled by reduced glucocorticoid sensitivity and by impaired function of the glucocorticoid receptor in splenocytes and lung tissue. Another model combining social disruption with OVA sensitization also found aggravating effects of social stress on allergic inflammation, which was attributed to an over-activation of the HPA axis and reduced glucocorticoid sensitivity.[80] Data from epidemiological and (sporadic) human clinical studies, however, indicate that psychosocial factors are indeed relevant. The strongest evidence so far comes from studies on atopic eczema. In a German mother-child cohort, maternal levels of perceived chronic stress, anxiety and depression during pregnancy correlated with prevalence of atopic eczema symptoms in the offspring at 2 years of age.[81] A recent study from China on two large mother-baby dyads found that maternal depression and anxiety during pregnancy increased the odds for atopic eczema in the offspring at 1 year of age.[82] In a Danish prospective cohort, self-reported job strain of mothers during pregnancy increased the risk for atopic eczema in their 7-year old children.[83] Authors of a smaller mother-child birth panel study based in Taiwan even suggest that levels of nerve growth factor (NGF) in chord plasma and maternal plasma might be a better predictor of paediatric atopic eczema than IgE levels.[84] Finally, hyporesponsiveness of the HPA axis to stress appears to be associated with atopy in humans.[85,86]

Taken together, both epidemiology and clinical practice point out the need to better understand neuroimmunological mechanisms involved in the pathophysiology of allergic diseases. What is missing so far is the big picture. A concerted research approach, applying combinations of epidemiology, clinical trials, mouse models and primary human cell culture systems will be needed. Due to their strong psychological component, allergic diseases have the potential to become model disease in the field and to shed light into the blurry semi-darkness of neuroimmunology.

9 | A COMPLEX INTERPLAY OF GENETIC AND ENVIRONMENTAL FACTORS DETERMINES THE INDIVIDUAL ALLERGY RISK

The human host is more or less susceptible to allergic diseases by means of individual genetic background. This genetic background consists in several tens to several hundreds of more or less relevant genes, each present in two specific allelic variants, and is subject to modification by both, beneficial and harmful environmental and life style factors. Chronic exposure to inhalant pollutants, psychosocial stress, an unhealthy diet or a lack of physical exercise induce epigenetic changes in some of the many susceptibility genes for allergy. This altered expression pattern is then transmitted to the next generation (for overview, see Figure 1). Such complex gene-gene and gene-environment interactions have been extensively described for other frequent noncommunicable diseases, such as cardiovascular, metabolic and neurodegenerative diseases or cancer. The logic of the interplay between genetic background and environmental influence factor becomes evident by previous studies on effects of environmental exposure in populations that were stratified by genetic background. Such studies revealed single alleles of the genes for CD14,[87] TLR2, TLR-4 and TLR6[88] that rendered their carriers susceptible to the beneficial effect of growing up on a farm and consuming raw cow's milk. Such interactions typically showed a clear dose effect of the protective allele, with homozygous allele carriers profiting more than heterozygous carriers.

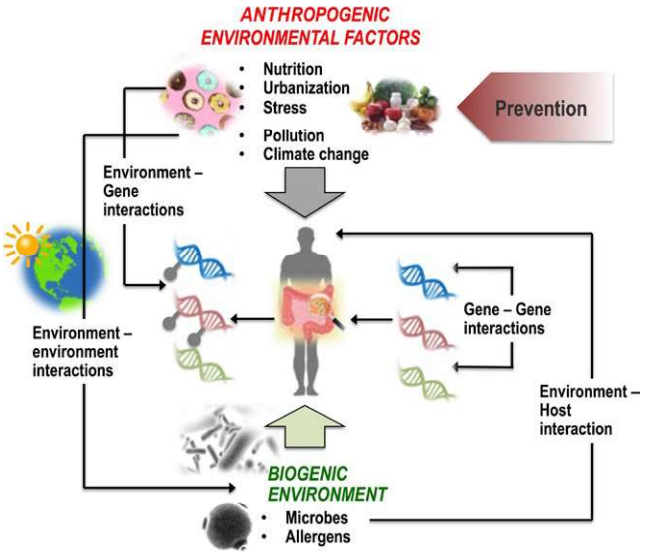

FIGURE 1 Allergies are complex diseases, influenced by genetic, environmental and life style factors. Many genes can confer susceptibility to allergic diseases. Typically, the contribution of each single gene is small, and several genes contribute to the disease phenotype (gene-gene interactions). Environmental and life style factors modify the expression of genes via epigenetic mechanisms, which means these modifiers can affect subsequent generations (environment-gene interactions). Priming of the innate immune system occurs by shaping the composition of the body's microbiota. This, in turn, affects immune homoeostasis and predisposition to hypersensitivity in the adult (environment-host interaction). Finally, anthropogenic pollutants and climate change-related factors exert their negative effects on human health either directly, by enhancing tissue inflammation and increasing comorbidities (environment-host interactions), or indirectly, by modifying allergen carriers, as shown for pollen-producing plants (environment-environment interactions)

10 | CONCLUSIONS

Allergies are among the most frequent of noncommunicable diseases. Because they are not considered classical "killers" like cancer or cardiovascular diseases, their clinical and societal relevance is high. Also, mortality due to fatal asthma attacks and anaphylaxis remains underestimated risks. From a scientist's point of view, allergy research has advanced considerably within the last two decades. The most challenging puzzles in basic allergy research, what makes an allergen an allergen, and what makes people increasingly allergic, are on the verge of being solved. Allergy spectrum diseases have served as important models for uncovering the role of early life innate immune priming by environmental and host microbiota and understanding the interplay between genetic susceptibility and environmental factors. Lessons learned from allergy research will help to better understand the pathobiology of other complex, chronic noncommunicable diseases, such as diabetes, autoimmunity, neurodegenerative diseases, and even cancer. The understanding of how harmful and beneficial environmental factors impact on the overall risk for allergic diseases will motivate people to adjust their life style in order to minimize individual risks. Integrated information from GWAS, combined with data from gene-environment interaction studies, will advance precision medicine to predict whether and how a given individual will benefit from an environmental regime or medication and to tailor adjuvants for enhanced allergen-specific immunotherapy regimes. Finally, the strong psychological component of allergies should be regarded as unique chance for clinical and laboratory researchers to study psycho-/neuro-immunological pathomechanisms that, if understood thoroughly on the cellular and molecular level, could be exploited as adjuvant therapy in the symptomatic and causal treatment of various diseases.

CONFLICT OF INTEREST

The authors have declared no conflicting interests.

AUTHOR'S CONTRIBUTIONS

Stefanie Gilles wrote the manuscript. Cezmi Akdis, Roger Lauener, Peter Schmid-Grendelmeier, Thomas Bieber, Georg Schäppi and Claudia Traidl-Hoffmann discussed the content and critically reviewed the text and figures.

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REFERENCES

[1] E. Hermann-Kunz, *Gesundheitswesen*, **1999**, *61*, S100.
[2] K. C. Bergmann, J. Heinrich, H. Niemann, *Allergo J. Int.* **2016**, *25*, 6.
[3] M. Haftenberger, D. Laußmann, U. Ellert, M. Kalcklösch, U. Langen, M. Schlaud, R. Schmitz, M. Thamm, *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **2013**, *56*, 687.
[4] U. Langen, R. Schmitz, H. Steppuhn, *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **2013**, *56*, 698.
[5] I. J. Doull, S. Lawrence, M. Watson, T. Begishvili, R. W. Beasley, F. Lampe, T. Holgate, N. E. Morton, *Am. J. Respir. Crit. Care Med.* **1996**, *153*, 1280.
[6] D. S. Postma, M. Kerkhof, H. M. Boezen, G. H. Koppelman, *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 1588.
[7] J. Smolonska, G. H. Koppelman, C. Wijmenga, J. M. Vonk, P. Zanen, M. Bruinenberg, I. Curjuric, M. Imboden, G. A. Thun, L. Franke, N. M. Probst-Hensch, P. Nürnberg, R. A. Riemersma, C. P. van Schayck, D. W. Loth, G. G. Brusselle, B. H. Stricker, A. Hofman, A. G. Uitterlinden, L. Lahousse, S. J. London, L. R. Loehr, A. Manichaikul, R. G. Barr, K. M. Donohue, S. S. Rich, P. Pare, Y. Bossé, K. Hao, M. van den Berge, H. J. Groen, J. W. Lammers, W. Mali, H. M. Boezen, D. S. Postma, *Eur. Respir. J.* **2014**, *44*, 860.
[8] A. M. Bowcock, W. O. Cookson, *Hum. Mol. Genet.*, **2004**, *13*, R43.
[9] M. Quaranta, B. Knapp, N. Garzorz, M. Mattii, V. Pullabhatla, D. Pennino, C. Andres, C. Traidl-Hoffmann, A. Cavani, F. J. Theis, J. Ring, C. B. Schmidt-Weber, S. Eyerich, K. Eyerich, *Sci. Transl. Med.* **2014**, *6*, 244ra90.
[10] K. D. Stone, *Curr. Opin. Pediatr.* **2002**, *14*, 634.
[11] T. Bieber, C. Akdis, R. Lauener, C. Traidl-Hoffmann, P. Schmid-Grendelmeier, G. Schäppi, J. P. Allam, C. Apfelbacher, M. Augustin, L. Beck, T. Biedermann, C. Braun-Fahrländer, F. T. Chew, T. Clavel, R. Crameri, U. Darsow, M. Deleuran, D. Dittlein, H. W. Duchna, L. Eichenfeld, K. Eyerich, R. Frei, C. Gelmetti, U. Gieler, S. Gilles, M. Glatz, K. Grando, J. Green, J. Gutermuth, E. Guttman-Yassky, J. Hanifin, D. Hijnen, W. Hoetzenecker, A. Irvine, A. Kalweit, N. Katoh, E. Knol, H. Koren, M. Möhrenschlager, D. Münch, N. Novak, L. O'Mahony, A. S. Paller, C. Rhyner, C. Roduit, K. Schiesser, J. Schröder, D. Simon, H. U. Simon, M. Sokolowska, P. Spuls, J. F. Stalder, D. Straub, Z. Szalai, A. Taieb, R. Takaoka, G. Todd, A. Todorova, C. Vestergaard, T. Werfel, A. Wollenberg, J. Ring, *Allergy* **2016**, *71*, 588.
[12] A. Muraro, R. F. Lemanske Jr, P. W. Hellings, C. A. Akdis, T. Bieber, T. B. Casale, M. Jutel, P. Y. Ong, L. K. Poulsen, P. Schmid-Grendelmeier, H. U. Simon, S. F. Seys, I. Agache, *J. Allergy Clin. Immunol.* **2016**, *137*, 1347.
[13] T. Bieber, A. M. D'Erme, C. A. Akdis, C. Traidl-Hoffmann, R. Lauener, G. Schäppi, P. Schmid-Grendelmeier, *J. Allergy Clin. Immunol.* **2017**, *139*(4S), S58.
[14] C. Ober, T. C. Yao, *Immunol. Rev.* **2011**, *242*(1), 10.
[15] K. Bønnelykke, M. C. Matheson, T. H. Pers, R. Granell, D. P. Strachan, A. C. Alves, A. Linneberg, J. A. Curtin, N. M. Warrington, M. Standl, M. Kerkhof, I. Jonsdottir, B. K. Bukvic, M. Kaakinen, P. Sleiman, G. Thorleifsson, U. Thorsteinsdottir, K. Schramm, S. Baltic, E. Kreiner-Møller, A. Simpson, B. St Pourcain, L. Coin, J. Hui, E. H. Walters, C. M. T. Tiesler, D. L. Duffy, G. Jones, AAGC, S. M. Ring, W. L. McArdle, L. Price, C. F. Robertson, J. Pekkanen, C. S. Tang, E. Thiering, G. W. Montgomery, A. L. Hartikainen, S. C. Dharmage, L. L. Husemoen, C. Herder, J. P. Kemp, P. Elliot, A. James, M. Waldenberger, M. J. Abramson, B. P. Fairfax, J. C. Knight, R. Gupta, P. J. Thompson, P. Holt, P. Sly, J. N. Hirschhorn, M. Blekic, S. Weidinger, H. Hakonarsson, K. Stefansson, J. Heinrich, D. S. Postma, A. Custovic, C. E. Pennell, M. R. Jarvelin, G. H. Koppelman, N. Timpson, M. A. Ferreira, H. Bisgaard, A. J. Henderson, *Nat. Genet.* **2013**, *45*, 902.
[16] M. A. Portelli, E. Hodge, I. Sayers, *Clin. Exp. Allergy* **2015**, *45*(1), 21.
[17] M. Focke-Tejkl, R. Campana, R. Reininger, C. Lupinek, K. Blatt, P. Valent, T. Pavkov-Keller, W. Keller, R. Valenta, *J. Allergy Clin. Immunol.* **2014**, *133*, 836.

[18] M. Curin, M. Weber, G. Hofer, D. Apostolovic, W. Keller, R. Reininger, I. Swoboda, S. Spitzauer, M. Focke-Tejkl, M. van Hage, R. Valenta, *Sci. Rep.* **2017**, *7*(1), 12135.

[19] C. Radauer, M. Bublin, S. Wagner, A. Mari, H. Breiteneder, *J. Allergy Clin. Immunol.* **2008**, *121*, 847.

[20] C. Traidl-Hoffmann, T. Jakob, H. Behrendt, *J. Allergy Clin. Immunol.* **2009**, *123*, 558.

[21] J. H. Shin, J. M. Kang, S. W. Kim, J. H. Cho, Y. J. Park, S. W. Kim, *Otolaryngol. Head Neck Surg.* **2010**, *142*, 370.

[22] J. P. Allam, G. Stojanovski, N. Friedrichs, W. Peng, T. Bieber, J. Wenzel, N. Novak, *Allergy* **2008**, *63*, 720.

[23] Y. Tanaka, H. Nagashima, K. Bando, L. Lu, A. Ozaki, Y. Morita, S. Fukumoto, N. Ishii, S. Sugawara, *Mucosal Immunol.* **2017**, *10*(1), 79.

[24] J. P. Allam, W. M. Peng, T. Appel, M. Wenghoefer, B. Niederhagen, T. Bieber, S. Bergé, N. Novak, *J. Allergy Clin. Immunol.* **2008**, *121*, 368.

[25] S. Schülke, A. Flaczyk, L. Vogel, N. Gaudenzio, I. Angers, B. Löschner, S. Wolfheimer, I. Spreitzer, S. Qureshi, M. Tsai, S. Galli, S. Vieths, S. Scheurer, *Allergy* **2015**, *70*, 1259.

[26] A. Trompette, S. Divanovic, A. Visintin, C. Blanchard, R. S. Hegde, R. Madan, P. S. Thorne, M. Wills-Karp, T. L. Gioannini, J. P. Weiss, C. L. Karp, *Nature* **2009**, *457*, 585.

[27] J. Herre, H. Grönlund, H. Brooks, L. Hopkins, L. Waggoner, B. Murton, M. Gangloff, O. Opaleye, E. R. Chilvers, K. Fitzgerald, N. Gay, T. Monie, C. Bryant, *J. Immunol.* **2013**, *191*, 1529.

[28] P. Satitsuksanoa, M. Kennedy, D. Gilis, M. Le Mignon, N. Suratannon, W. T. Soh, J. Wongpiyabovorn, P. Chatchatee, M. Vangveravong, T. Rerkpattanapipat, A. Sangasapaviliya, S. Piboonpocanun, E. Nony, K. Ruxrungtham, A. Jacquet, Mite Allergy Research Cohort (MARC) study team, *Allergy* **2016**, *71*, 1425.

[29] S. Gilles, H. Behrendt, J. Ring, C. Traidl-Hoffmann, *Curr. Pharm. Des.* **2012**, *18*, 2314.

[30] D. C. Dittlein, S. Gilles-Stein, J. Hiller, I. Beck, S. A. Overbeek, J. Durner, D. Ernst, U. Frank, O. Groß, C. Traidl-Hoffmann, *Exp. Dermatol.* **2016**, *25*, 991.

[31] K. Hosoki, I. Boldogh, L. Aguilera-Aguirre, Q. Sun, T. Itazawa, T. Hazra, A. R. Brasier, A. Kurosky, S. Sur, *J. Allergy Clin. Immunol.* **2016**, *137*, 1506.

[32] M. Wimmer, F. Alessandrini, S. Gilles, U. Frank, S. Oeder, M. Hauser, J. Ring, F. Ferreira, D. Ernst, J. B. Winkler, P. Schmitt-Kopplin, C. Ohnmacht, H. Behrendt, C. Schmidt-Weber, C. Traidl-Hoffmann, J. Gutermuth, *Allergy* **2015**, *70*, 944.

[33] M. Wolf, L. Aglas, T. E. Twaroch, M. Steiner, S. Huber, M. Hauser, H. Hofer, M. A. Parigiani, C. Ebner, B. Bohle, P. Briza, A. Neubauer, F. Stolz, M. Wallner, F. Ferreira, *J. Allergy Clin. Immunol.* **2018**, *141*, 1488.

[34] C. Ober, A. I. Sperling, E. von Mutius, D. Vercelli, *Curr. Opin. Immunol.* **2017**, *48*, 51.

[35] D. A. Marfortt, D. Josviack, A. Lozano, E. Cuestas, L. Agüero, J. A. Castro-Rodriguez, *J. Asthma* **2018**, *55*, 470.

[36] S. Arslanoglu, G. E. Moro, G. Boehm, F. Wienz, B. Stahl, E. Bertino, *J. Biol. Regul. Homeost. Agents* **2012**, *26*(3 Suppl), 49.

[37] C. Grüber, M. van Stuijvenberg, F. Mosca, G. Moro, G. Chirico, C. P. Braegger, J. Riedler, G. Boehm, U. Wahn, MIPS 1 Working Group, *J. Allergy Clin. Immunol.* **2010**, *126*, 791.

[38] C. Grüber, M. van Stuivenberg, F. Mosca, G. Moro, G. Chirico, C. P. Braegger, J. Riedler, Y. Yavuz, G. Boehm, U. Wahn, MIPS II Working Group, *J. Allergy Clin. Immunol.* **2015**, *136*, 1696.

[39] C. Roduit, R. Frei, M. Depner, B. Schaub, G. Loss, J. Genuneit, P. Pfefferle, A. Hyvärinen, A. M. Karvonen, J. Riedler, J. C. Dalphin, J. Pekkanen, E. von Mutius, C. Braun-Fahrländer, R. Lauener, PASTURE study group, *J. Allergy Clin. Immunol.* **2014**, *133*, 1056.

[40] B. Campbell, C. Raherison, C. J. Lodge, A. J. Lowe, T. Gislason, J. Heinrich, J. Sunyer, F. Gómez Real, D. Norbäck, M. C. Matheson, M. Wjst, J. Dratva, R. de Marco, D. Jarvis, V. Schlünssen, C. Janson, B. Leynaert, C. Svanes, S. C. Dharmage, *Thorax* **2017**, *72*, 236.

[41] H. Okada, C. Kuhn, H. Feillet, J. F. Bach, *Clin. Exp. Immunol.* **2010**, *160*(1), 1.

[42] J. Penders, K. Gerhold, C. Thijs, K. Zimmermann, U. Wahn, S. Lau, E. Hamelmann, *Gut. Microbes* **2014**, *5*(2), 239.

[43] S. F. Bloomfield, G. A. Rook, E. A. Scott, F. Shanahan, R. Stanwell-Smith, P. Turner, *Perspect. Public Health* **2016**, *136*, 213.

[44] M. Kilpeläinen, E. O. Terho, H. Helenius, M. Koskenvuo, *Respir. Med.* **2006**, *100*, 1518.

[45] H. J. Tsai, A. C. Tsai, J. Nriagu, D. Ghosh, M. Gong, A. Sandretto, *J. Asthma* **2007**, *44*, 397.

[46] D. A. Beuther, E. R. Sutherland, *Am. J. Respir. Crit. Care Med.* **2007**, *175*, 661.

[47] C. H. Kuo, H. F. Kuo, C. H. Huang, S. N. Yang, M. S. Lee, C. H. Hung, *J. Microbiol. Immunol. Infect.* **2013**, *46*, 320.

[48] P. Vangay, T. Ward, J. S. Gerber, D. Knights, *Cell Host Microbe* **2015**, *17*, 553.

[49] M. J. Nash, D. N. Frank, J. E. Friedman, *Front. Endocrinol. (Lausanne)* **2017**, *8*, 349.

[50] R. A. Martin, J. L. Ather, L. K. Lundblad, B. T. Suratt, J. E. Boyson, R. C. Budd, J. F. Alcorn, R. A. Flavell, S. C. Eisenbarth, M. E. Poynter, *Am. J. Respir. Cell Mol. Biol.* **2013**, *48*, 655.

[51] D. I. Bernstein, *Allergy Asthma Immunol. Res.* **2012**, *4*, 178.

[52] E. Simons, T. To, R. Moineddin, D. Stieb, S. D. Dell, *J. Allergy Clin. Immunol. Pract.* **2014**, *2*(2), 201.

[53] J. S. House, A. B. Wyss, J. A. Hoppin, M. Richards, S. Long, D. M. Umbach, P. K. Henneberger, L. E. Beane Freeman, D. P. Sandler, E. Long O'Connell, C. Barker-Cummings, S. J. London, *J. Allergy Clin. Immunol.* **2017**, *140*(1), 249.

[54] M. Stiehm, A. Bufe, M. Peters, *Thorax* **2013**, *68*(1), 31.

[55] S. E. K. Müller-Rompa, I. Markevych, A. J. Hose, G. Loss, I. M. Wouters, J. Genuneit, C. Braun-Fahrländer, E. Horak, A. Boznanski, D. Heederik, E. von Mutius, J. Heinrich, M. J. Ege, GABRIELA Study Group, *Pediatr. Allergy Immunol.* **2018**, *29*, 275.

[56] M. M. Stein, C. L. Hrusch, J. Gozdz, C. Igartua, V. Pivniouk, S. E. Murray, J. G. Ledford, M. Marques Dos Santos, R. L. Anderson, N. Metwali, J. W. Neilson, R. M. Maier, J. A. Gilbert, M. Holbreich, P. S. Thorne, F. D. Martinez, E. von Mutius, D. Vercelli, C. Ober, A. I. Sperling, *N. Engl. J. Med.* **2016**, *375*, 411.

[57] A. Jung, I. Heinrichs, C. Geidel, R. Lauener, *Paediatr. Respir. Rev.* **2012**, *13*(2), 123.

[58] E. Bersuch, F. Gräf, E. D. Renner, A. Jung, C. Traidl-Hoffmann, R. Lauener, C. Roduit, *Pediatr. Allergy Immunol.* **2017**, *28*, 768.

[59] K. B. Fieten, R. Schappin, W. T. Zijlstra, L. Figee, J. Beutler, F. Raymakers, H. van Os-Medendorp, R. Stellato, M. Vandewall, J. Winkelhof, M. Uniken Venema, C. A. F. M. Bruijnzeel-Koomen, L. Rijssenbeek-Nouwens, C. K. van der Ent, E. van Hoffen, Y. Meijer, S. G. M. A. Pasmans, *Clin. Exp. Allergy* **2018**, *48*(2), 186.

[60] B. Heydenreich, I. Bellinghausen, B. König, W. M. Becker, S. Grabbe, A. Petersen, J. Saloga, *Clin. Exp. Allergy* **2012**, *42*(1), 76.

[61] A. Obersteiner, S. Gilles, U. Frank, I. Beck, F. Häring, D. Ernst, M. Rothballer, A. Hartmann, C. Traidl-Hoffmann, M. Schmid, *PLoS ONE* **2016**, *11*(2), e0149545.

[62] G. D'Amato, C. Vitale, M. D'Amato, L. Cecchi, G. Liccardi, A. Molino, A. Vatrella, A. Sanduzzi, C. Maesano, I. Annesi-Maesano, *Clin. Exp. Allergy* **2016**, *46*, 390.

[63] A. Grinn-Gofron, A. Strzelczak, *Int. J. Biometeorol.* **2013**, *57*, 759.

[64] C. Fotiou, A. Damialis, N. Krigas, J. M. Halley, D. Vokou, *Int. J. Biometeorol.* **2011**, *55*(1), 35.

[65] C. Ziello, T. H. Sparks, N. Estrella, J. Belmonte, K. C. Bergmann, E. Bucher, M. A. Brighetti, A. Damialis, M. Detandt, C. Galán, R. Gehrig, L. Grewling, A. M. Gutiérrez Bustillo, M. Hallsdóttir, M. C. Kockhans-Bieda, C. De Linares, D. Myszkowska, A. Pàldy, A. Sánchez, M. Smith, M. Thibaudon, A. Travaglini, A. Uruska, R. M.

Valencia-Barrera, D. Vokou, R. Wachter, L. A. de Weger, A. Menzel, *PLoS ONE* **2012**, *7*, e34076.
[66] R. Asero, N. Wopfner, P. Gruber, G. Gadermaier, F. Ferreira, *Clin. Exp. Allergy* **2006**, *36*, 658.
[67] G. Gadermaier, N. Wopfner, M. Wallner, M. Egger, A. Didierlaurent, G. Regl, F. Aberger, R. Lang, F. Ferreira, T. Hawranek, *Allergy* **2008**, *63*, 1543.
[68] F. Ruëff, B. Przybilla, A. Walker, J. Gmeiner, M. Kramer, D. Sabanés-Bové, H. Küchenhoff, T. Herzinger, *Int. Arch. Allergy Immunol.* **2012**, *159*(1), 65.
[69] M. W. Boehme, I. Kompauer, U. Weidner, I. Piechotowski, T. Gabrio, H. Behrendt, *Dtsch. Med. Wochenschr.* **2013**, *138*, 1651.
[70] J. Buters, B. Alberternst, S. Nawrath, M. Wimmer, C. Traidl-Hoffmann, U. Starfinger, H. Behrendt, C. Schmidt-Weber, K. C. Bergmann, *Allergo J. Int.* **2015**, *24*, 108.
[71] J. Storkey, P. Stratonovitch, D. S. Chapman, F. Vidotto, M. A. Semenov, *PLoS ONE* **2014**, *9*(2), e88156.
[72] J. Götschke, P. Mertsch, M. Bischof, N. Kneidinger, S. Matthes, E. D. Renner, K. Schultz, C. Traidl-Hoffmann, H. W. Duchna, J. Behr, J. Schmude, R. M. Huber, K. Milger, *PLoS ONE* **2017**, *12*, e0186632.
[73] M. Levite, *Curr. Opin. Pharmacol.* **2008**, *8*, 460.
[74] I. J. Elenkov, *Neurochem. Int.* **2008**, *52*(1–2), 40.
[75] H. Kikuchi, J. Itoh, S. Fukuda, *Neurosci. Lett.* **2008**, *432*, 217.
[76] E. Kuhlwein, M. Irwin, *J. Neuroimmunol.* **2001**, *117*(1–2), 51.
[77] K. Nakano, T. Higashi, R. Takagi, K. Hashimoto, Y. Tanaka, S. Matsushita, *Int. Immunol.* **2009**, *21*, 645.
[78] E. M. Peters, A. Michenko, J. Kupfer, W. Kummer, S. Wiegand, V. Niemeier, N. Potekaev, A. Lvov, U. Gieler, *PLoS ONE* **2014**, *9*, e113552.
[79] M. T. Bailey, S. Kierstein, S. Sharma, M. Spaits, S. G. Kinsey, O. Tliba, Y. Amrani, J. F. Sheridan, R. A. Panettieri, A. Haczku, *J. Immunol.* **2009**, *182*, 7888.
[80] B. Li, X. H. Duan, J. F. Wu, B. J. Liu, Q. L. Luo, H. L. Jin, Y. J. Du, H. Y. Zhang, Y. X. Cao, J. C. Dong, *Chin. Med. J. (Engl)* **2013**, *126*(2), 325.
[81] S. Braig, J. M. Weiss, T. Stalder, C. Kirschbaum, D. Rothenbacher, J. Genuneit, *Pediatr. Allergy Immunol.* **2017**, *28*(2), 144.
[82] H. Y. Chang, D. I. Suh, S. I. Yang, M. J. Kang, S. Y. Lee, E. Lee, I. A. Choi, K. S. Lee, Y. J. Shin, Y. H. Shin, Y. H. Kim, K. W. Kim, K. Ahn, H. S. Won, S. J. Choi, S. Y. Oh, J. Y. Kwon, Y. H. Kim, H. J. Park, K. J. Lee, J. K. Jun, H. S. Yu, S. H. Lee, B. K. Jung, J. W. Kwon, Y. K. Choi, N. Do, Y. J. Bae, H. Kim, W. S. Chang, E. J. Kim, J. K. Lee, S. J. Hong, *J. Allergy Clin. Immunol.* **2016**, *138*(2), 468.
[83] A. D. Larsen, V. Schlünssen, B. H. Christensen, J. P. Bonde, C. Obel, A. M. Thulstrup, H. Hannerz, K. S. Hougaard, *Scand. J. Work Environ. Health* **2014**, *40*, 639.
[84] I. J. Wang, W. S. Hsieh, Y. L. Guo, S. H. Jee, C. J. Hsieh, Y. H. Hwang, P. C. Chen, *Clin. Exp. Allergy* **2008**, *38*, 1302.
[85] A. Buske-Kirschbaum, M. Ebrecht, D. H. Hellhammer, *Brain Behav. Immun.* **2010**, *24*, 1347.
[86] A. Buske-Kirschbaum, A. Geiben, H. Höllig, E. Morschhäuser, D. Hellhammer, *J. Clin. Endocrinol. Metab.* **2002**, *87*, 4245.
[87] C. Bieli, W. Eder, R. Frei, C. Braun-Fahrländer, W. Klimecki, M. Waser, J. Riedler, E. von Mutius, A. Scheynius, G. Pershagen, G. Doekes, R. Lauener, F. D. Martinez, PARSIFAL study group, *J. Allergy Clin. Immunol.* **2007**, *120*, 1308.
[88] M. Y. Lau, S. C. Dharmage, J. A. Burgess, A. K. Win, A. J. Lowe, C. Lodge, J. Perret, J. Hui, P. S. Thomas, S. Morrison, G. G. Giles, J. Hopper, M. J. Abramson, E. H. Walters, M. C. Matheson, *Sci. Rep.* **2017**, *7*, 43681.