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Meeting Report

Diversities of allergic pathologies and their modifiers: Report from the second DGAKI-JSA meeting

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ABPA/ABPM, Allergic bronchopulmonary

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AD, Atopic dermatitis

agr, accessory gene regulatory

BDNF, Brain-derived neurotrophic factor

CRD, Component-resolved diagnosis

CSU, Chronic spontaneous urticaria

ABSTRACT

In October 2021, researchers from the German Society of Allergy and Clinical Immunology (DGAKI) and from the Japanese Society of Allergology (JSA) focused their attention on the pathological conditions and modifiers of various allergic diseases. Topics included 1) the pathophysiology of IgE/mast cell-mediated allergic diseases; 2) the diagnosis and prevention of IgE/mast cell-mediated diseases; 3) the pathophysiology, diagnosis, and treatment of eosinophilic airway diseases; and 4) host–pathogen interaction and allergic diseases. This report summarizes the panel discussions, which highlighted the importance of recognizing the diversity of genetics, immunological mechanisms, and modifying factors underlying allergic diseases.

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DGAKI, German Society of Allergy and Clinical Immunology
 ECRS, Eosinophilic chronic rhinosinusitis
 EH, Eczema herpeticum
 ESS, Endoscopic sinus surgery
 GWAS, Genome-wide association study
 HSV, Herpes simplex virus
 HWP, Hydrolyzed wheat protein
 JSA, Japanese Society of Allergology
 MRGPRX2, Mastocyte-related G-protein coupled receptor X2
 PSM, Phenol-soluble modulin

Introduction

In November 2019, a group of key opinion leaders from Germany and Japan met in Frankfurt, Germany to discuss novel precision-medicine approaches to the treatment of allergic diseases. In the meeting summary, the researchers concluded that a key element in achieving precision-medicine is “individual phenotyping followed by a patient-centered and -stratified individualized treatment regime”.¹

The classic pathology of allergic diseases is IgE-mediated type I allergy, which manifests diseases such as anaphylaxis and urticaria through mast cell activation. These IgE-mediated allergic reactions are closely related to eczema and food allergy early in life, followed by asthma and allergic rhinitis, presenting with atopic march.^{2,3} To prevent such serial IgE-mediated allergic diseases, skin care in high-risk infants to correct skin barrier dysfunction has been demonstrated to be effective in some studies,⁴ while other studies have failed to show preventive effects.

However, similar phenotypes that result from mast cell activation are also caused by an IgE-independent or non-immunologic mechanism (phenocopy). The mechanism, namely mast cell-related G-protein coupled receptor X2 (MRGPRX2) expressed on mast cells, is becoming clear.⁵ Furthermore, various modifiers such as drugs can change the phenotype and its severity, even in IgE-dependent conditions. In particular, immune responses to microorganisms such as bacteria and viruses strongly modify the phenotype of allergic diseases. On the other hand, asthma and eosinophilic chronic rhinosinusitis that develop in adulthood demonstrate type 2 inflammation similar to early-onset allergic diseases, but they are not mediated by IgE or mast cells; their phenotype is characterized by eosinophilia in peripheral blood.⁶

Understanding the diversity of allergic conditions and their modifiers is essential for achieving precision medicine. Therefore, in October 2021, researchers from Germany and Japan gathered again, this time on the web, to discuss the pathological conditions and modifiers of various allergic diseases. The following report summarizes this discussion in four main sections – pathophysiology, diagnosis, treatments, and prevention of allergic diseases – all aimed at promoting precision medicine.

Background

The workshop was originally scheduled in September 2020 in Japan; however, the COVID-19 pandemic forced us to postpone the meeting. It took place in October 10, 2021 on the web with 15 panel members from the German Society of Allergy and Clinical Immunology (DGAKI) and the Japanese Society of Allergy (JSA) joining the discussions, based on 12 presentations on various topics related to allergic diseases. The workshop was also broadcast for the members of DGAKI and JSA on YouTube.

After the meeting, panel members wrote abstracts on the discussion topics and sent them to the corresponding author (KA),

who merged them. An initial draft of this report was then circulated via email to all coauthors for their comments. Finally, all coauthors and delegates gave formal approval for submission and publication.

Pathophysiology of IgE/mast cell-mediated allergic diseases

Genetics of allergic diseases

Genome-wide association studies (GWAS) as well as sequencing studies have identified more than 60,000 genetic associations among thousands of human diseases and traits.⁷ The advent of technologies such as high-throughput sequencing and the availability of reference genomes from various populations have accelerated this progress. Functional genomics is helpful to understand how regulatory genetic variation influences pathophysiological phenotypes.

A recent review of atopic dermatitis (AD) indicated that GWASs have identified 34 loci containing multiple genes with roles in immune responses and skin barrier functions.⁸ The first GWAS of AD was conducted in European populations, where two loci were identified, including the filaggrin locus.⁹ A GWAS of AD was conducted in the Japanese population, finding a total of eight susceptibility loci.¹⁰ A multi-ancestry GWAS for AD was performed by the EAGLE eczema consortium, identifying a total of 11 new loci and revealing several ethnic-specific loci.¹¹ Candidate genes that may help regulate T cell function and innate host defenses were noted in the novel loci.

In 2021, a Japanese research group reported eight new AD susceptibility loci.¹² They performed a GWAS using BioBank Japan data and also conducted trans-ethnic meta-analysis using UK Biobank data. They found a strong enrichment of heritability in immune-related pathways and relevant cell types, which was shared across populations. They used a machine-learning model that predicts a mutation effect to alter the expression of transcribed promoter/enhancer as defined in FANTOM5. They identified two plausible causal variants at the *CCDC80* and *NLRP10* loci in the nine Japanese-specific loci.

A GWAS of immediate-type wheat allergy caused by hydrolyzed wheat protein-containing facial soap (Cha no shizuku) was conducted, and two susceptibility loci were identified on chromosomes 6 and 16.¹³ The soap, very popular in Japan, contained the allergen hydrolyzed wheat protein (HWP). The disease is caused by skin or mucosal sensitization, and symptoms occur after wheat consumption. The top locus was observed in the HLA region. The properties of the P1, P4, P6, and P9 pockets mainly characterize the binding grooves of HLA class II isotypes. Two amino acid variants, located in the P4 binding pockets, reached the level of genome-wide significance. The properties of the P4 binding pocket of the DQ molecule are likely involved in the allergenicity of HWP. The *RBFOX1* gene is located in the second locus on chromosome 16.

In 2021, a Japanese research group constructed an eQTL database of 28 distinct immune cells, using whole genome sequencing

and RNA sequencing.¹⁴ These datasets used immune cells from 79 healthy volunteers and 337 patients diagnosed with 10 immune-mediated diseases. The researchers combined these datasets with GWASs and found significant enrichment in immune-disease-relevant SNPs. The atlas implicated the disease-relevant genes, cell types, and environment.

Combining genetic data – such as GWASs and whole-genome sequencing, eQTL databases, and epigenetic data such as ENCODE – would improve our understanding of the functions of associated variants in allergic diseases. A good resource would be essential in improving the functional annotation of genomic variations.

Elicitors, mechanisms, and risk profile in anaphylaxis

Anaphylaxis is the most severe manifestation of immediate mast cell dependent systemic reactions. It is rapid in onset and potentially life threatening.¹⁵ Analysis of data from the European anaphylaxis registry revealed that the skin is the most frequently affected organ system (84%), followed by symptoms in the respiratory tract (66%) and in the cardiovascular system (63%). Gastrointestinal symptoms have been observed in 39% of affected individuals in this registry. The main elicitors of anaphylaxis are age dependent. In children, food followed by venom and drugs are among the most frequent elicitors, whereas in adults, this ranking is different, with venom, drugs, and food being the most frequent causes of anaphylaxis. Moreover, food-induced anaphylaxis consists of a wide range of elicitors, including peanuts, cow's milk, and hen's egg in children and adolescents, whereas in adults, wheat, shrimp, and soy are the most frequent elicitors.¹⁶

From the immunological point of view, anaphylaxis is induced by rapid-release mast cell mediators. This can be caused by IgE-dependent, IgE-independent, or non-immunologic mechanisms. The IgE-dependent mechanism is well known and well understood whereas IgE-independent mechanisms via FcγRIII and/or complement have been less well characterized. Relatively new is the pathway via the mastocyte-related G-protein coupled receptor X2 (MRGPRX2), which has been recently described as the target for, e.g., drug-induced anaphylaxis (due to muscle relaxants or certain antibiotics). A given allergen can bind to an IgE receptor, resulting in degranulation of several mediators, which are in turn responsible for clinical symptoms. In addition to this interaction, many factors have been described that can either contribute to the elicitation or to the severity of an IgE-dependent, food-induced anaphylaxis. Such factors include allergen-related presentation (e.g., food matrix, dose, route of exposure), host behaviors (medication, exercise), other intrinsic and extrinsic factors (co-diseases, sex, and age) and mechanisms related to host compensation (endocrine, hormone).¹⁷

Regarding drugs and specifically non-steroidal antiphlogistics in drugs, it is well known that these can elicit but also potentiate the outcome of an allergic reaction. Here, the interference of these cyclooxygenase 1 and/or 2 inhibitors with the prostaglandin metabolism is mechanistically important. Recent findings from our group have shown that anaphylaxis in mice depends on the mouse strain used to induce anaphylaxis and that this is related to prostaglandin PGE₂ levels. BL6 mice display more severe anaphylaxis than by Balb/c mice, as demonstrated by passive systemic anaphylaxis, which is correlated with significantly decreased PGE₂ levels.¹⁸ Furthermore, in BL6 mice, the stabilization of PGE₂ reduces the severity of anaphylaxis, supporting the idea that systemic PGE₂ levels are relevant for the outcome of anaphylaxis in a given individual. These data from mice were confirmed in serum samples from anaphylaxis patients, whereas decreased levels of PGE₂ were observed in patients with severe anaphylactic reactions. In summary, all data indicate that PGE₂ has an important role in anaphylaxis

susceptibility as the relative lack of PGE₂ is associated with anaphylaxis severity in mice and human. These data suggest the potential therapeutic role of substances that can stabilize PGE₂ systemically.

MRGPRX2-triggered activation of human skin mast cells and the role of pseudoallergic reactions in urticaria

Mast cells are the most important cells in the pathogenesis of urticaria. The best-known activation of mast cells is IgE mediated, resulting in intracellular signaling cascades and histamine release as well as other pro-inflammatory mast cell mediators. However in urticaria, a true type I allergic pathogenesis is extremely rare. Still, IgE receptor-mediated activation of mast cells is important in the sense of Type I and II autoimmunity (i.e., IgE to autoallergens and IgG autoantibodies to IgE or its receptor, respectively). This activation has recently been implicated in the etiology and pathogenesis of chronic spontaneous urticaria (CSU).¹⁹ In addition, the G protein coupled receptor, Mas-related gene X2 (MrgX2) is elevated in patients with CSU on human MCTC and has been shown to bind basic proteins, including substance P and vasoactive intestinal polypeptide, suggesting another possible activation pathway. It can now be shown *in vitro* that in highly purified skin mast cells, simultaneous activation of FcεRI and MRGPRX2 results in cumulative histamine release.

This finding may be highly relevant in chronic spontaneous urticaria. In up to 30% of patients, pseudoallergic reactions to drugs are observed, especially NSAIDs as well as to food ingredients, mainly aromatic components in fresh food and preservatives.²⁰ On the other hand, an autoimmune IgE receptor mediated activation of mast cells has been described.

Diagnosis and prevention of IgE/mast cell-mediated diseases

Molecular-based approach to the diagnosis of tree nut allergy

Tree nut allergy is one of the most common food allergies in Western countries and is associated with severe allergic reactions that persist into adulthood. In Japan, a recent nationwide survey of immediate-type food allergies showed a dramatic increase in tree nut allergies, where it was ranked fourth among allergy-causative foods, suggesting that it has become a serious health concern.²¹

One characteristic of tree nut allergy is co-allergy and/or co-sensitization to different tree nuts. A recent study in Europe showed that the rate of coexistent peanut, tree nut, and sesame seed allergies was 60.7%, based on food challenge tests.²² This suggests that the high rate of co-allergy and/or co-sensitization among tree nuts makes it quite difficult to diagnose a specific tree nut allergy with skin prick tests or specific IgE (sIgE) tests to the whole nut extracts, due to cross-reactivity.

Component-resolved diagnosis (CRD) or molecular-based allergy diagnostics, which identify specific IgE responses to molecularly defined allergenic components, has improved diagnostic accuracy by minimizing the diagnostic cross-reactivity associated with conventional tests. In particular, the majority of allergens in tree nuts are seed storage proteins, including vicilins (7S globulins), 2S albumins, and legumins (11S globulins), which all contribute to allergenicity. Recent studies have demonstrated the diagnostic superiority of the IgE tests specific to tree nut components over the IgE tests specific to crude tree, as shown in the case of the Ana o 3 sIgE test for cashew nut allergy.^{23,24}

In addition, a recent study highlighting the clinical utility of recently identified macadamia nut 7S globulin sIgE tests for the diagnosis of macadamia nut allergy in Japanese children was presented.

Therapeutic potential of anti-IgE for prevention of allergic diseases

Atopic march is a well-known concept for describing the natural history of allergic diseases.^{2,3} In brief, atopic march refers to the progression from inflammatory skin manifestation in early life, usually diagnosed as atopic dermatitis, to subsequent food allergy, asthma, and allergic rhinitis. Therefore, preventive strategies targeting early life are attracting enormous attention.^{4,25,26} Several studies demonstrated that atopic dermatitis during early infancy, especially before the age of 5 months, but not at later ages, was a risk factor for sensitization to food antigens.²⁷ This indicates that early infancy is a critical time for induction of sensitization to foods. In addition, sensitization to hen's egg at one year of age was shown to be strongly associated with sensitization to house dust mites at three years of age.²⁸ Cumulatively, these findings suggest that early infancy, especially before the age of 5 months, could be the critical period for the initial development of allergic diseases and for intervention aimed at prevention. Therefore, early aggressive intervention for infantile atopic dermatitis may be a reasonable approach⁴ to preventing food allergies and other allergic diseases in later life.

Recently, another interesting approach, that is, administration of anti-IgE antibody during pregnancy to prevent allergic sensitization in early life, was proposed based on evidence from animal models.²⁹ This concept began with the late Professor Kimishige Ishizaka, who identified IgE antibody for the first time in 1966. In brief, the administration of anti-IgE antibody to pregnant mice suppressed IgE antibody production in offspring. On the other hand, administering anti-IgE antibody to pregnant mice did not suppress IgG antibody production or antigen-specific T cell responses. Surprisingly, the suppressive effect of maternal anti-IgE antibody injection persisted, even in offspring sensitized at six weeks of age.²⁹ Considering the difference in the serum half-life of antibodies between mice and humans, six weeks in mice is equivalent to 4 months in humans, covering the critical period for allergic sensitization. Although the mechanisms remain unclear, as the levels of IgE in serum are extremely low during infancy, anti-IgE antibody may reach membrane-bound IgE on B cells, resulting in apoptosis of IgE-producing B cells.

An anti-IgE antibody, omalizumab, has been used to treat allergic diseases, including in pregnant women, with no evidence of an increased risk of major congenital anomalies.³⁰ In addition, a case report of a patient who had anti-IgE treatment during pregnancy showed that the level of anti-IgE antibody in serum was higher in the cord blood of the neonate than in the maternal peripheral blood.³¹ These findings suggest that maternal injection efficiently delivers anti-IgE to neonates.

Although this strategy needs to be verified in human studies, it may lead to the primary prevention of allergic diseases.

Primary prevention of allergy and asthma

Primary prevention of allergic diseases including asthma is the golden goal for pediatric allergology.³² In order to stop the epidemiological trend of very high prevalence of allergic diseases starting in very young children and infants, we need active treatment protocols and effective management plans instead of only avoidance strategies.³³ Especially for young patients at high risk, early intervention and prevention of allergic sensitization or atopic dermatitis may prevent or reduce the development of respiratory allergies and asthma. To update the German guidelines for allergy prevention,³⁴ the current evidence (5,681 hits in databases between June 2013 and November 2020, 286 eligible papers) was evaluated for interventional studies on primary prevention and recommended preventive strategies for six

domains: nutrition, supplements, allergens/allergen immunotherapy, biodiversity, potential harmful substances, and psychosocial aspects. Recommendations were graded from strong (A) to moderate (B), weak (C), or missing (D), and consensus was obtained from the guideline group (S3 level). New recommendations were formulated, e.g., for nutrition (no evidence for a preventive effect of a dietary restriction by avoidance of potential food allergens in the first year (A); no evidence for the use of prebiotics/probiotics or vitamin D for primary prevention (A)), pet keeping (no restriction for pet keeping for families with normal risk (A); no acquisition of a new cat in families with increased risk (B)); or barrier defect (no recommendation for daily creaming for primary prevention of atopic dermatitis). The new guidelines will be published in the first half of 2022.

Pathophysiology, diagnosis, and treatment of eosinophil-associated allergic diseases*Neuroimmune interaction mechanisms in atopic dermatitis: a novel role for itch mediators*

Atopic dermatitis is a chronic inflammatory skin disease characterized by intense itch. During the last decade, it has become evident that neuroimmune interaction mechanisms between the cutaneous immune and peripheral nervous system play a pivotal role in the mechanism of itch in atopic dermatitis.³⁵ In this regard, recent evidence suggests that specific cytokines including IL-31 and neurotrophins such as brain-derived neurotrophic factor (BDNF) are crucial in peripheral nerve activation but also in immune cell stimulation leading to itch.^{36–38}

In atopic dermatitis, IL-31 serum levels are increased³⁹ and correlate with disease severity and pruritus.⁴⁰ Of note, key target effector cells, including eosinophil granulocytes, that are in close proximity to peripheral nerves are capable of IL-31 production and are functionally activated by IL-31 with induction of chemotaxis, release of superoxide anions, and Ca²⁺ flux.⁴¹ Most strikingly, IL-31 induces nerve sprouting of peripheral nerves that express IL-31 receptor A.⁴² Thus, IL-31 is pivotal in neuroimmune interaction mechanisms for the transmission of itch. Pharmacological therapy using anti-IL-31RA is currently under development.

Further prime candidates for the interaction between immune and neuronal cells are presented by neurotrophins, which have initially been described for their neurotrophic function. In atopic dermatitis, neurotrophin brain-derived neurotrophic factor (BDNF) is increased in the serum of patients compared to healthy controls and also correlates with disease severity and eosinophilic cationic protein.⁴³ Indeed, eosinophils are a source of BDNF, as shown in patients with atopic dermatitis, and vice versa are functionally activated by BDNF with induction of chemotaxis.⁴⁴ Interestingly, as shown recently, atopic dermatitis eosinophils release biologically active BDNF with induction of neuronal sprouting,³⁶ thus underlining its role in the neuroimmune interaction mechanism in atopic dermatitis.

To summarize, cytokines including IL-31 as well as neurotrophins including BDNF are crucial in neuroimmune interaction mechanisms in atopic dermatitis, playing a role in the mechanism of itch. Further research will highlight whether these mediators can be used in clinical therapy. The use of IL-31 in atopic dermatitis is already under development.

Late-onset severe eosinophilic asthma

Phenotyping of severe asthma with cluster analyses has identified later-onset eosinophilic asthma, part of a group of adult-onset eosinophilic airway diseases that includes eosinophilic chronic

rhinosinusitis (ECRS). NSAID-exacerbated respiratory disease, eosinophilic granulomatosis with polyangiitis, and allergic bronchopulmonary aspergillosis/mycosis (ABPA/ABPM).⁶

Later-onset eosinophilic asthma, which begins in patients in their 30s and 40s, has been identified by clinical as well as molecular phenotyping using transcriptomic analysis in sputum cells. This type of asthma is characterized by rapid decline of pulmonary function, increased eosinophils in sputum and peripheral blood, high levels of FeNO and serum periostin, and co-morbidities such as ECRS.^{45–47} Eosinophils and the IL-5 pathway are indispensable for the pathophysiology of later-onset eosinophilic severe asthma, as the super-responders to anti-IL-5 treatments such as mepolizumab and benralizumab share three characteristics: adult-onset asthma, peripheral blood eosinophilia, and the presence of nasal polyps.^{48,49}

However, not all types of asthma with peripheral blood eosinophilia are either adult-onset or severe. Eosinophilia is more common in patients with childhood asthma, but peripheral blood eosinophilia is associated with severe asthma only in the adult population,⁵⁰ suggesting that some additional factors make eosinophils and eosinophilia more harmful for asthmatics. High periostin, high eosinophil populations demonstrated the clinical characteristics compatible with later-onset eosinophilic asthma.⁵¹ In animal models, a combination of IL-5 and IL-13 in the airways, but not just a single cytokine, was necessary to induce blood and tissue eosinophilia.⁵²

Additional evidence for the role of IL-5 combined with IL-13 is their contribution to mucus plug formation in the bronchi, of major importance in the pathophysiology of airway obstruction unresponsive to bronchodilators in later-onset severe asthma.⁵³ There are three eosinophil-related mechanisms for the mucus plug formation. The first is the crosslinking of mucin. IL-13 induces the bronchial epithelial cell expression of MUC5AC and pendrin, an anion transporter that translocates SCN[−] from blood to the airway lumen. Then eosinophil peroxidase converts SCN[−] to hypothiocyanous acid, promoting mucus crosslinking in the airway lumen.⁵³ The second mechanism is the formation of fibrin mesh in the mucus with activated eosinophils that express tissue factor on the cellular surface, activating the coagulation pathway.⁵⁴ The third is the release of extracellular traps, chromatin containing DNA and histone, from eosinophils.⁵⁵ These extracellular traps, which can be found in the airways of ABPA patients, are denser and stickier than those released from neutrophils.⁵⁶ Bacteria such as *Staphylococcus aureus*, fungi, virus, and autoantibodies to eosinophil peroxidase are implicated as the potential triggers for eosinophil extracellular trap cell death.

Eosinophilic mucus plugs in the bronchi are the major pathophysiology of later-onset eosinophilic asthma and other adult-onset eosinophilic airway diseases, and IL-5, IL-13, and microbiome are all important in their formation.⁶ Biologics targeting these molecules are effective in controlling these diseases.

Eosinophilic chronic rhinosinusitis

ECRS is a subgroup of chronic rhinosinusitis with nasal polyps (CRSwNP), which is associated with severe eosinophilic infiltration and is intractable. Its symptoms include loss of smell, nasal obstruction, and viscous nasal discharge. Retrospective studies were carried out in twelve universities in Japan. In all, 3241 patients with chronic rhinosinusitis who had undergone endoscopic sinus surgery (ESS) during the previous three years were enrolled in this study. Clinical data included relapse and prognosis of nasal polyps. Kaplan–Meier analysis showed that half of the patients had a recurrence of nasal polyps at 72 months after ESS. Bronchial asthma and NSAID-exacerbated respiratory disease are very important

comorbidities of ECRS. CT shadows indicating dominant ethmoid cells and more than 10% of eosinophils in peripheral blood are also risk factors for recurrence of nasal polyps. CRS patients with nasal polyps containing more than 70 eosinophils/HPF had significantly higher rates of recurrence as well as a poorer prognosis than those with <70 eosinophils/HPF.

A JESREC score was established to diagnose ECRS using four clinical factors (both sides, nasal polyp, ethmoid cells-dominant shadow in CT, and % of eosinophils in blood). ECRS were classified into three groups (mild, moderate, and severe).⁵⁷

The pathogenesis of ECRS has not been clear. Microorganisms might be involved in stimulating type 2 inflammation to promote IgE production and eosinophil infiltration through various pathways. RNAseq and proteomics of nasal polyps of ECRS patients were carried out to find the specific cellular and molecular factors contributing to pathogenesis. The coagulation system is activated and the fibrinolytic system is suppressed, leading to deposition of fibrinous networks in nasal polyps. A fibrin-degrading agent could be a candidate for a new treatment for ECRS.⁵⁸

Treatment options for nasal polyps of ECRS are to target the type 2 inflammation, which is characterized by cytokines — such as IL-4, IL-5, IL-13, and IgE — playing a prominent role. Clinical studies of these biologics, anti-IL-4R α chain Ab (dupilumab), have been performed for large nasal polyps of CRSwNP (nasal polyp score ≥ 5). Dupilumab improved the nasal polyp score, the CT score as calculated by the Lund–Mackay score, QOL scores, and the olfactory test score.^{6,59,60} These effects of dupilumab were examined according to the algorithm used by the Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis. Dupilumab consistently improved the symptoms of severe CRSwNP, irrespective of ECRS status. Therefore, blood eosinophil level may not be a suitable biomarker for dupilumab efficacy in CRSwNP.⁶¹

Host–pathogen interaction and allergic diseases

The role of Staphylococcal quorum sensing in the pathogenesis of atopic dermatitis

AD is commonly associated with colonization by *S. aureus* in the affected skin. *S. aureus* colonizes the epidermis, but it remains unclear how the host detects virulent but not commensal *S. aureus*, triggering skin inflammation.

Phenol-soluble modulins (PSM) peptides from *S. aureus* form amphipathic α -helical structures capable of forming pores in artificial membranes. The expression of PSMs is regulated by accessory gene regulatory (agr) quorum-sensing, a two-component system that responds to bacterial density. Expression of agr-regulated virulence factors, including RNIII, were reportedly associated with community-associated-MRSA skin and soft tissue infections. Previously, we found that δ -toxin, a PSM peptide, promotes Th2 type skin inflammation by inducing mast cell degranulation in a mouse epicutaneous model of *S. aureus* infection.⁶² We also found that PSM α induces keratinocyte damage and the release of the alarmins IL-1 α and IL-36 α . Alarmin release elicits the induction of IL-17–producing $\gamma\delta$ T cells and ILC3 via Myd88 signaling, which is critical for skin inflammation in response to epicutaneous *S. aureus*.⁶³ Recently, whole genome sequencing of *S. aureus* strains isolated from the cheek skin of 270 Japanese infants was performed. The finding was that the cutaneous acquisition of loss-of-function mutations in *S. aureus* agr virulence loci reduces skin colonization and protects against the development of AD.⁶⁴ These studies indicate that agr-dependent virulence is critical for induction of cutaneous inflammation with features of new-onset pediatric AD in which colonized *S. aureus* retains agr gene expression.

Recent studies also demonstrated that commensal bacteria or autoinducing peptide-derived commensal staphylococci has been reported to suppress *S. aureus* quorum sensing and reduce its pathogenicity in an animal AD model and in skin disease found in AD patients.^{65,66} Further investigations are needed, but these studies indicate that utilizing commensal microbes may be a new therapeutic approach for AD.

Atopic dermatitis in Germany and disturbed viral immune response

German dermatologists treat around 200 AD patients per year, of whom one in four suffers from a moderate to severe form.⁶⁷ Of note, viral infections are more prevalent in AD patients, especially in those who are severely affected. A generalized infection with herpes simplex virus (HSV), also known as eczema herpeticum (EH), is present in one in five patients in the AD registry TREATgermany. As EH can be life-threatening and often needs intravenous acyclovir therapy, it is imperative to identify at-risk patients. Additionally, with the growing armamentarium of systemic treatments for moderate to severe AD that influence the immune system, understanding the pathomechanisms of viral defense in AD is even more important.⁶⁸ Different predisposing factors, especially aberrations in the interferon pathway, have been identified as contributing to viral susceptibility in AD patients.^{69,70} Furthermore, it was shown that the disturbed skin barrier supports viral skin infection with HSV.⁷¹ Assessing the role of the virus-specific immune response, T cell lines from AD patients reactive to HSV antigens showed elevated IL-4 secretion and reduced IFN- γ . Analyzing HSV-specific T cells in patients with and without a history of EH via antigen-reactive T cell enrichment, a type 2 skewing of the immune profile of HSV-specific T helper cells was seen.⁷² In epitope-specific cytotoxic T cells, identified with MHC class I tetramers bearing an epitope of HSV1 UL25, elevated IL-4 and reduced IFN- γ expression was seen. Further “multi-omics” studies are planned to identify additional risk factors for viral infections in AD. In addition, the impact of novel targeted treatments on viral susceptibility in AD will be investigated.

SARS-CoV2/Covid-19 and asthma: A complex relationship

Covid-19, the disease caused by the SARS-Cov-2 virus, typically originates in the upper airways, followed by the development of systemic disease affecting many organs including lung, heart, liver, kidney, brain, and blood vessels, as well as the immune clotting system.⁷³

In countries with a robust healthcare system, about 1% of infected individuals require intensive care treatment (including patients infected with the Delta variant). The course of the disease is mainly determined by the presence of co-morbidities including diabetes, hypertension, coronary heart disease, chronic liver disease, and chronic obstructive pulmonary disease. Together with colleagues in Wuhan, the striking observation was made early on in the pandemic that, in contrast to these and other co-morbidities, hospitalized Covid-19 patients show fewer asthma/co-morbidities than would be expected based on the regional prevalence data.⁷⁴

Further assessment of the available global data revealed two distinct disease patterns. In one pattern, some countries had a clear underrepresentation of asthma among hospitalized Covid-19 patients (Central Europe, Brazil, Russia, China, India among others). In the second pattern, an over-representation of asthmatics was noted in countries including the US, Australia, Great Britain, and Spain.⁷⁵ Further *in vitro* data revealed that type-2 inflammation with development of TH2-T-Cells; increased IL-13, IL-5 and IL-4 production; eosinophili; and mast cell activation can reduce the risk for SARS-CoV-2 infection in the airways. This is due to downregulation of ACE-2 receptor expression and anti-

viral activities of eosinophils and mast cells, among other mechanisms (reviewed in Ref.⁷⁵).

However, asthmatics with the non-type 2 endotype seem to be at higher risk for a more severe Covid-19 course. This might be related to the presence of additional metabolic co-morbidities such as obesity or diabetes. These patients demonstrate a sub-clinical chronic inflammatory response that is in part characterized by elevated levels of IL-6 and TNF 2.⁷⁶

Furthermore, it is striking that SARS-CoV-2 does not trigger severe asthma exacerbations to the extent observed with other respiratory viruses including influenza, RSV, and rhinoviruses. Bioinformatics analysis of available SARS-CoV-2 and allergen protein sequences revealed that MHC class-I and MHC class-II restricted homologies on the level of T-cell epitope mapping. Whether this is of functional relevance in terms of developing cross-reactivities in previously allergic individuals, leading to cross-protection against SARS-CoV-2 viruses, is currently under investigation.⁷⁷

These findings taken together constitute evidence that asthma is not a co-morbidity of severe Covid-19 in many countries, and that type-2 inflammation favors a mild course of the disease. The SARS-CoV-2 virus is not a respiratory virus causing severe asthma exacerbations, and the virus shows homologies to food and aero-allergen proteins. In summary, the SARS-CoV-2 virus shows a unique pattern of host-virus interaction in allergic and asthmatic individuals. Further mechanistic research would help to develop novel strategies against this pandemic virus.

Conclusion

In the second DGAKI-JSA joint meeting, as in the first meeting in 2019, high-quality scientific presentations were again provided by expert researchers. Although each presentation dealt with a specific topic, the entire meeting and this summary emphasize the importance of recognizing the diversity of genetics, immunological mechanisms, and modifying factors underlying allergic diseases.

The international discussions in 2019 and 2021 by German and Japanese experts has made clear that there are some differences in research interests, diagnoses, treatment preferences, and recommendations for allergic diseases. Recognizing these differences may lead to elucidating important basic and clinical questions. Continuous close cooperation between the two scientific communities will pave the way for a deeper understanding of the mechanisms of allergic diseases, thereby optimizing both diagnosis and treatment.

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Conflict of interest

KA received lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis Pharma, and Sanofi. MT received lecture fees from Kyorin Pharmaceutical, AstraZeneca and Sanofi. HM received Grants-in-Aid for Scientific Research (B) (20H01622) and Scientific Research Fund of the Ministry of Health, Labour and Welfare, Japan (21FE2001). SF received consulting fees from AstraZeneca, GlaxoSmithKline, Kyowa Hakko Kirin, and Sanofi, and honoraria from Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, and Taiho Pharma. YN received support from AMED-PRIME (JP18gm6010016h002) and 2020 LEO Foundation Award – Region Asia-Pacific. MB received consulting fees from Health Advances, Escient, and

honoraria from Escient. MO received honoraria from Sanofi. NK has received honoraria as a speaker/consultant for Sanofi, Maruho, Abbvie, Eli Lilly Japan, and Leo Pharma, and has received grants as an investigator from Maruho, Eli Lilly Japan, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, Boehringer Ingelheim Japan and Leo Pharma. ME received honoraria for lectures from Mylan. MW received consulting fees from ALK-Abelló Arzneimittel, Mylan Germany, honoraria from ALK-Abelló Arzneimittel, Mylan Germany. MW is a Board member of DBV Technologies, Stallergenes, HAL Allergopharma (Oxford). MW received grants from DFG (WO541/16-2). The rest of the authors have no conflict of interest.

Authors' contributions

KA, HR, KI, MW organized the meeting. KA, MT, TZ, HY, HM, SF, YN, ST, EH, UR, HR, MW wrote the first draft, and all authors contributed to the critical revision of the manuscript and approved the final version of the manuscript.

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