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YEAR IN REVIEW

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Developments in the field of allergy in 2017 through the eyes of Clinical and Experimental Allergy

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Summary

In this article, we described the development in the field of allergy as described by Clinical and Experimental Allergy in 2017. Experimental models of allergic disease, basic mechanisms, clinical mechanisms, allergens, asthma and rhinitis and clinical allergy are all covered.

1 | ASTHMA AND RHINITIS

1.1 | Underlying mechanisms of asthma

Although novel technologies that allow unbiased detection of biomarkers for diseases are being used increasingly their clinical application remains uncertain.[1] Omics approaches are high-throughput technologies that provide a cross-sectional analysis of biological systems including genomics (measure of DNA variation), transcriptomics (assessment of RNA expression), epigenomics (DNA alterations that influence RNA expression), proteomics (protein expression) and most recently metabolomics (metabolite levels). These analyses help to generate hypotheses about disease mechanisms. In the context of asthma, however, they have also been used to identify biomarkers that identify specific disease phenotypes especially if current diagnostic techniques are not very helpful. One such phenotype includes aspirin-induced respiratory disease which has featured in one Clinical and Experimental Allergy paper. Ban and colleagues have used metabolomics profiling in both serum and urine to assess differences between patients who have aspirin-tolerant asthma compared to those with aspirin-exacerbated respiratory disease.[2] They found that serum levels of leukotrienes (LTE4) and the ratio of LTE4/prostaglandin (PGF2a) before and after an aspirin bronchoprovocation test were significantly higher in patients with aspirin-exacerbated respiratory disease.

An advantage of metabolic profiling is the ability to give signals in non-invasive samples, such as urine and breathe. Metabolic profiles are being increasingly assessed in exhaled breath to find biomarker signatures that may identify clinical phenotypes and predict of loss of asthma control. Exhaled breath volatile organic compounds (VOCs) were measured in patients with partly controlled asthma as part of a steroid withdrawal study.[3] Two techniques were used,

eNose and gas chromatography/mass spectrometry (GC/MS). Unbiased analyses were applied to assess ability to predict loss of asthma control. Breath profiles analysed by eNose predicted loss of control in 95% of cases while GC/MS was accurate in prediction in between 68% and 77% of cases. Prediction of exacerbations and loss of control are a key component of asthma management, and these data suggest exhaled breath compounds should be pursued in future interventional studies to validate utility in a clinical setting.

The utility of an unbiased pathway-based association study was applied from a previous genomewide association study (GWAS) of asthma to identify novel asthma susceptibility genes by Barreto-Luis et al.[4] Significant biological pathways using a gene-set enrichment analysis from the GWAS were identified, and all tested SNPs on significant gene pathways were identified and those with a disproportionate number of nominal significant associations were prioritized. Analyses revealed two biological processes that were significantly enriched including a known asthma susceptibility locus (encoding SMAD family member 3), but also a novel susceptibility locus near Wnt signalling genes, which may be associated with fibrosis and airway remodelling, thus highlighting a potential novel mechanistic avenue and pathway to be interrogated in asthma.

One of the key components of asthma pathophysiology, in addition to airway inflammation,[5,6] is airway structural change, or remodelling. Increasingly mechanistic studies show structural airway cells are immunologically active and contribute to disease manifestation. A group of manuscripts in Clinical and Experimental Allergy over the last year have shown the importance of investigating the interactions between airway structural and immune cells to find novel therapeutic avenues. The bronchial epithelium is undoubtedly central to asthma pathogenesis with multiple functions. Winnica and colleagues have demonstrated reduced nitric oxide (NO) formation and increased oxidative and nitrosative stress in primary bronchial epithelial cells from asthmatics.[7] This was restored towards normal NO formation following L-citrulline supplementation. This shows mechanistic differences in epithelial cell function and also proposes the utility of L-citrulline as a potential therapeutic to restore function. An important phenotypic change in the bronchial epithelium in asthma includes goblet cell metaplasia and associated functional increased mucus production. The impact of corticosteroids alone or in combination with long-acting beta agonists on goblet cell metaplasia and the mechanisms involved was investigated by Lachowicz-Scroggins and colleagues.[8] Corticosteroids alone inhibited IL-13-induced goblet cell metaplasia, and the addition of long-acting beta agonists had an additive effect of reduced goblet cell metaplasia and mucus secretion. Given that mucous production is an important feature of obstructive airway disease, this may be an important therapeutic mechanism.

Another structural cell that is significantly altered in asthma is airway smooth muscle. The role of the inflammatory cytokine calpain (a family of calcium-dependent endopeptidases), which are important role in extra-cellular matrix remodelling, was investigated in airway smooth muscle remodelling by Rao et al.[9] Calpain was shown to mediate cytokine-induced collagen-I synthesis and proliferation of airway smooth muscle cells via the mTORC2/Akt signalling pathway in a murine model and thus shown to play a role in regulating airway smooth muscle remodelling in asthma.

The range of mechanistic studies undertaken and published in the journal is highlighted by the data from the manuscript by Low et al.[10] The difficulty of disentangling vocal cord dysfunction from true wheeze in patients with asthma remains a significant clinical challenge. However, it is likely that in many patients, they are not completely distinct but overlap. The presence of paradoxical vocal cord movement (PVCM) and whether it is associated with airflow limitation or other disease characteristics of asthma were investigated. PVCM was quantified using dynamic 320-slice computerized tomography of the larynx. Approximately a quarter of all patients with asthma had evidence of PVCM, and this was more frequently associated with airflow limitation. This unexpected relationship highlights the relatively high prevalence of PVCM in asthma and the need to investigate mechanistic interactions between extrathoracic airway obstruction and lower airway obstruction in asthma.

Finally, Davies and colleagues have published some interesting data showing a clear inverse association between hospitalization rates for children with asthma and total hours of sunshine in England.[11] Is this related to vitamin D or socioeconomic factors?

1.2 | Asthma clinical phenotypes

We are increasingly understanding asthma phenotypes as reviewed by Just and colleagues.[12] An asthma phenotype, in which both diagnosis and management are challenging, is fungal sensitization. Immunological and inflammatory diagnostic biomarkers were related to clinical features including lung function and CT scan structural pathology in adults with fungal allergy and asthma by Woolnough et al.[13] Unbiased cluster analyses revealed specific IgE sensitization to fungi, specifically thermotolerant fungi including *Aspergillus fumigatus* was associated with fixed airflow limitation; no relationship was seen with total serum IgE. This highlights the risk of lung damage from fungal allergy in all asthmatic patients with positive-specific IgE to filamentous fungi, not just those who meet the criteria for allergic bronchopulmonary aspergillosis (ABPA).

Disentangling asthma and chronic obstructive pulmonary disease (COPD) have increased in complexity with development of greater insights into the immunology. Cluster analysis in the hunt for more precise phenotypes has become more sophisticated in terms of factors used as discriminators for both asthma and COPD and for overlaps between them. In a study, Hiriai and colleagues looked at the usual factors plus mRNA for a variety of transcription factors; they found four clusters, COPD, asthma-COPD overlap, late-onset non-atopic asthma and early-onset atopic asthma.[14] Perhaps reassuringly the asthma-COPD overlap cluster showed an overlapping of asthma and COPD features with atopy, eosinophilia and raised IgE but with worse lung function and a history of smoking. Presumably the "acid" test of this sort of increasingly sophisticated phenotype development will be treatments that target the appropriate immunological features.

1.3 | Asthma clinical management

The importance of stepping down inhaled corticosteroid (ICS) treatment in asthma has long been recognized. The criteria and factors that might inform this process are less clear than have those for stepping up ICS treatment. Saito and colleagues have looked at some of these factors using a factor analysis approach.[15] Upper airway complications, psychiatric morbidity and poor adherence to ICS were examined for their effects on a step down programme. Perhaps unsurprisingly, poor adherence to ICS was the most strongly predictive of failure to step down followed by upper airway complications. Interestingly, psychiatric factors did not lead to significant step down failure on its own but it did increase problems in conjunction with the other two factors. This study suggests that factors other than just the state of a patient's asthma should be considered and remedied before a ICS reduction is considered.

Bjerregaard and colleagues have studied stable adult asthmatics from a specialist outpatient clinic.[16] Participants with elevated sputum eosinophils or elevated FeNO were found to be at greater risk of future viral-induced asthma exacerbations. It is not clear if this is an interaction between virus and type 2 inflammatory markers or simply that any exacerbation will tend to be more severe in those with elevated markers. The authors argue that understanding these interactions will be important in personalizing future antibody treatments.

There has long been an interest in the question of corticosteroid resistance amongst patients with severe asthma. Sousa and colleagues have explored this amongst a group of moderate and severe asthmatics.[17] Following a two-week course of oral prednisolone, both groups experienced a similar degree of suppression of blood and airway eosinophilia and serum cytokines. Even in patients on high doses of inhaled steroids, many showed a suppressive eosinophil response. As would be expected oral corticosteroids increased airway and blood neutrophils but interestingly airway neutrophilia was greater amongst the more severe asthmatics suggesting that neutrophils in severe asthma are related to corticosteroids therapy.

Electronic medical records from 1.4-m adult patients in primary care have been analysed to compare co-morbidities in patients with active asthma defined by read code and recent prescribed therapy and those without.[18] Almost all of the 39 co-morbidities were significantly more common amongst those with active asthma. Many are not surprising, COPD, bronchiectasis, eczema, other are less easily explained, chronic pain, hypertension, irritable bowel syndrome. Depression and anxiety were both more common as has been shown in many studies. Some of the co-morbidity may be related to more frequent primary care contact but, as the authors point out, it has implications for studies of new asthma treatments where many comorbidities are excluded and for patient management where some of these, especially depression and anxiety, may need to be managed.

In this clinical study, Jabbal and colleagues explore one possible mechanism by which tiotropium added to ICS/LABA combinations might reduce asthma exacerbations.[19] They explore the idea that LAMA's might reduce LABA-induced beta2 receptor down regulation by receptor cross-talk thereby reducing airway hyperresponsiveness. This turned out not to be the case, at least for mannitol airway hyper-responsiveness amongst mild/moderate asthmatics, suggesting that other mechanisms such as remodelling or anti-inflammatory effect of tiotropium may be responsible. However, tiotropium is currently considered as an option for steps 4 and 5 of the Global Initiative for Asthma in poorly controlled asthma.

Asthma and psychological disorders seem to be closely associated. Chang and colleagues published data demonstrating an independent association among suicidal ideation, asthma and bronchial hyperresponsiveness in adolescents.[20]

It is getting increasingly difficult to know which biological to use in severe asthma. Cabon and colleagues have undertaken a systematic review and indirect meta-analysis of anti-interleukin-5 (IL-5) therapies for severe asthma.[21] They found that all the IL-5 blockades have similar efficacies and similar adverse effects.

1.4 | Rhinitis

Many cross-sectional studies have found associations between reported damp mouldy environments and a variety of self-reported respiratory symptoms. In a study taken from the Swedish Galen study amongst 26 000 adults, these self-reported associations are again confirmed.[22] In addition, there were similar associations between dampness and chronic rhinosinusitis. Also, they reported some evidence for a dose-response relationship in terms of the number of positive dampness measures. The key question in these studies is the potential mechanism for these associations, assuming of course that they are indeed causal.

Many patients with chronic upper airway disease complain that alcohol worsens their symptoms. Derycke and colleagues surveyed 1281 subjects and then looked at inflammatory markers in a subset.[23] Alcohol-related problems were commonest with NSAID exacerbated respiratory disease then chronic rhinosinusitis with nasal polyps and less so with chronic rhinosinusitis patients without nasal polyps and allergic rhinitis. This was associated with significantly higher nasal levels of the eosinophilic biomarker ECP.

Pfaar and colleagues described the dose-response characteristics of a new Timothy grass pollen allergoid immunotherapy product in comparison with a 6-grass pollen allergoid.[24] Both had similar efficacies. There has been discussion about the appropriate end-point for trials. Vicaut and colleagues use data from five previous trials to compare end-points.[25] In each study, the Combined Score or Adjusted Symptom Score gave similar results.

Some novel interventions for allergic rhinitis have also been described in Clinical and Experimental Allergy. Ellis and colleagues described a beneficial effect of an intranasal TLR7 agonist (GSK2245035).[26] Meanwhile, Berrings and colleagues describe how probiotics-impregnated bedding covers reduced house dust mite allergic rhinitis symptoms although allergens levels were not altered.[27]

2 | CLINICAL ALLERGY

2.1 | Anaphylaxis

The Royal College of Anaesthetists 6th National Audit Project examined perioperative anaphylaxis over one year in the UK.[28] A total of 266 cases met the inclusion criteria, three-quarters with an identified trigger. Egner and colleagues call for a harmonization of approach to testing, access to services and MHRA reporting. They also emphasized the need to involve expert anaesthetists in managing these cases.

Motomura and colleagues have examined the effect of aspirin on challenge tests for food-dependent exercise induced anaphylaxis.[29] Twenty-six children had positive challenges. In half the combination of food and exercise induced allergic symptoms. Aspirin induced a positive reaction in 14 patients who had no or mild symptoms just with food and exercise. So we now need to think about combinations of three factors when understanding the precipitants of anaphylaxis.

Low-osmolar non-ionic radiocontrast media are in common use in clinical practice. Kim and colleagues have looked at the rate of adverse reactions to these in one hospital.[30] Iopromide was associated with most immediate reactions (1.03%) followed by iopamidol (0.67%), iohexol (0.64%) and iobitridol (0.34%).

Mastocytosis is associated with a high prevalence of anaphylaxis. Zanoni and colleagues have looked at rates of vaccine reactions in their mastocytosis clinic.[31]They saw very few reactions and only recommend extending the normal 15-minute observation period to 30 minutes along with training for parents in how to recognize and manage allergic reactions.

Finally, Stretz and colleagues looked at whether temporary omalizumab co-treatment with high maintenance venom dose can prevent recurrent systemic allergic reactions with venom immunotherapy.[32] Their retrospective, observational case series with 10 patients on combination therapy and five just on immunotherapy suggested that a short course of omalizumab is very helpful in this group.

2.2 | Food allergy

We now have a much better understanding about how childhood food allergy develops. The review by Foong and Brough nicely summarizes this.[33] We also have an improving understanding of the allergens that induce allergy reactions to foods as exemplified by Sharp and colleagues review on fish allergens.[34] It also seems that there are specific patterns or phenotypes of food allergy.[35] Finally, Stensgaard and colleague have demonstrated the major impact that food allergy has on the whole family.[36]

Diagnosing food allergy remains a challenge with food provocation challenges frequently being required. van der Valk and colleagues have described, in a prospective study, how specific IgE to components Ana o 1, 2 and 3 can be used to diagnosis children with suspected cashew nut allergy.[37] Another approach, which is become more established, is the basophil activation test which Santos and Shreffler reviewed.[38] There are some novel approaches, and Lindvik and colleague published data from 81 children demonstrating that conjunctival provocation testing has a sensitivity and the specificity of 0.96 and 0.83, respectively, for peanut allergy.[39] None had a severe adverse reaction with this approach where as a quarter had an anaphylactic reaction with the food challenge.

We are still working on effective therapies for food allergies. A popular approach is to initiate patients with cow's milk or egg allergy on baked milk or baked egg, respectively.[40] Unfortunately, there seems to be limit evidence to suggest that this approach speeds up outgrowth although it may simplify meals times for families.[41] A potential treatment strategy is omalizumab, and Vetander and colleagues publish data to suggest that an individualized dosing can prevent reactions in patients with food allergy.[42] Specific immunotherapy is another option although serious adverse events are not infrequent.[43] An alternative route is to utilize an allergen that has been processed to reduce its allergenicity without reducing its immunogenicity. Tao has described how boiled peanuts are associated with less reactions than expected in an observational cases series of children undergoing peanut oral allergen immunotherapy (OIT).[44] Promising but needs to be tested against conventional OIT protocols. Finally, the psychological issues associated with food allergy need to be addressed. Boyle and colleagues have published a randomized controlled trial looking at a brief psychological intervention for food allergy.[45] They found that anxiety could be reduced in mother with moderate/high anxiety at enrolment.

2.3 | Eczema

Perhaps the most convincing evidence for the preventative impact of probiotics is for eczema. Peldan and colleagues have followed their randomized control trial participants to 10 years of age. Perinatal probiotics were still associated with reduced eczema at 10 years.[46] However, they were also associated with increased allergic rhinoconjunctivitis as defined by the ISAC questions (130/337 [38.6%] vs 84/325 [25.8%]). While they suggest that it is likely to be a false positive, long-term follow-up of other studies is obviously required.

Also, Wang and colleagues have looked at the proteomic signature associated with eczema.[47] They found unique proteomic signatures in the serum which appear to potential distinguish different inflammatory skin diseases. The authors suggest that this approach might provide an insight into disease pathogenesis, diagnosis and novel therapies.

3 | EPIDEMIOLOGY

3.1 | Early risk factor for atopic disease

The interest in early risk factors for subsequent asthma, rhinitis and eczema with a special focus towards the hygiene hypothesis and microbiota has been displayed in several publications in 2017. In a Finnish study, significant differences were found in allergy prevalence between young people from Finnish and Russian Karelia.[48] Skin microbiota, as well as bacterial and fungal communities in nasal

mucosa, was also contrastingly different between the populations, and diversity of Actinobacteria was clearly associated with reduced allergy in Russia. Early exposure to dogs has been reported to decreases the risk of asthma,[49,50] and Wegienka et al have now proposed that there are subgroup differences (race, gender and delivery mode) in the association.[51] Laboratory animals do not offer a similar protection towards asthma and allergic disease. Simoneti and colleagues have reported in Clinical and Experimental Allergy that allergic sensitization to laboratory animals is more associated with asthma, rhinitis and skin symptoms than sensitization to common allergens.[52] Exposure to antibiotics in fetal life does not seem to increase the risk of asthma after taking family confounding such as genes and shared environmental factors into account[53] or using paternal exposure as negative control.[54] Timm and colleagues though report an association between prenatal exposure to antibiotics and increased risk of atopic dermatitis (AD) in the first 18 months of life among children born to atopic mothers.[55] Travelling is another risk factor that may be associated with microbiota and also with socioeconomic status. Results from GINIplus and LISAplus show that early life travelling does not increase the risk of atopic outcomes until 15 years of age.[56] Nevertheless, there is a need to carefully interpret potential causal effects and to take genetic and environmental confounding as well as residual confounding into account. We look forward to future studies using family design and other innovative methods.[57,58]

3.2 | Nutritional influences

Infant feeding patterns[59] as well as dietary antioxidant[60,61] and subsequent allergic disease have also been in focus in 2017 Clinical and Experimental Allergy, along with risks of asthma in overweight children.[62] Two interesting articles have focused on maternal distress or psychiatric symptoms before and during pregnancy, and later risk of childhood eczema or atopic disease.[63,64] In the Southampton Women's Survey, an association was found between maternal stress *before* pregnancy and offspring risk of eczema at 12 months. There was also somewhat increased risk of offspring eczema among mothers with symptoms postnatally but not after taking account of preconception stress.[65] These findings confirm the importance to address critical exposure periods or cumulative exposure to maternal distress over pregnancy[66] and also point to potentially modifiable influences. The other study, from the Generation R, found that maternal psychiatric symptoms during pregnancy were associated with increased risks of childhood inhalant allergy and eczema, independent of symptoms after delivery.[64] They also adjusted their finding for *paternal* psychiatric symptoms which highlights the importance of using fathers as negative control.[66]

3.3 | Other epidemiological highlights

Finally, Clinical and Experimental Allergy has also included reports on sensitization patterns for rhinitis and asthma multimorbidity from the EGEA study,[67] an association between DNA methylation of Th2 lineage determinants of genes at birth and later allergic outcomes in the EpiGene consortium[68] and expression of the filaggrin gene in cord blood as predictor of eczema risk in infancy from the Isle of Wight study.[69]

4 | EXPERIMENTAL MODELS OF ALLERGIC DISEASE

4.1 | Mechanisms of allergic disease

4.1.1 | Immune mechanisms of allergic airway disease

Allergen exposure of the pulmonary epithelium results in epithelial cell-derived production of cytokines such as TSLP, IL-25 and IL-33, which are thought to launch the pro-allergic type 2 cytokine response through activation of innate lymphoid type 2 cells (ILC2) and antigen-specific CD4+ Th2 T cell response.[70,71] The ILC2- and CD4+ Th2 cell-derived type 2 cytokines IL-4, IL-5, IL-9 and IL-13 promote IgE production and engagement of IgE-FcεRI-basophils and MCs; tissue eosinophilia and MC hyperplasia; mucus production by goblet cells and AHR, which are hallmark clinical manifestations of allergic asthma.[72]

The antigen-specific CD4+ Th2 T cell response is thought to be mediated by DC presentation of pollen allergens to naïve CD4+ T cells in the draining lymph nodes.[70, 73] Critical steps for the DC-CD4+ type 2 cell polarization is the interaction of co-stimulatory molecules (CD28 and CD80/CD86; OX40L and OX40) between antigen-presenting cells (APCs) and T cells.[74] A recent study by Moe and colleagues demonstrated that the dust mite allergen Dermatophagoides farina 8 (Der f8), a glutathione S-transferase, induces the expression of T cell immunoglobulin mucin domain 4 (TIM4) on DC cells and provided evidence to support a role for TIM4 in the expansion of CD4+ Th2 cells in the mouse allergic lung.[75] Interestingly, the authors show that direct stimulation of DCs with Derf8 induced TIM4 expression and that the induction of TIM4 on DC cells was specific to Der f8 as stimulation of DCs with a Derf8-deficient dust mite extract (DME) did not stimulate TIM4 expression in BMDCs. Employing an in vivo model, the authors show that exposure of mice to Derf8 or DME and not Der f8-deficient DME led to the induction of allergic airway disease (AAD) in mice including expansion of CD4+ cells, increased systemic Th2 cytokines, Derf8-specific IgE and pulmonary inflammation (eosinophils, neutrophils and macrophages). Notably, the pulmonary allergic response was inhibited by anti-TIM4 mAb treatment suggesting that Derf8-driven allergic inflammatory phenotype was dependent on TIM4 activity. Intriguingly, treatment of DME-allergic mice with Derf8-deficient DME-specific immunotherapy (SIT) reduced the pulmonary allergic response and that this was associated with the development of antigen-specific CD4+ CD25+ FoxP3+ T regulatory (Treg) cells in the lung. In support of an important role for TIM4 in the development of CD4+ Th2 cell differentiation, previous studies by Lee et al have demonstrated using a DC: CD4 T cell co-culture system that

blockade of TIM4 on DC's significantly inhibits Th2 cell differentiation and facilitated the induction of CD4+ T reg cell expansion.[76] The molecular action of how glutathione S transferases (GST) provoke TIM4 expression on DC cells is not yet clear. The authors provided data showing that Der f8 induced the TIM4 gene transcription through direct chromatin remodelling of the TIM4 gene locus.[75]

Another molecule recently linked with the exacerbation of the allergic pulmonary inflammation and the asthma phenotype is the Duffy antigen receptor for chemokines (DARC).[77] DARC is membrane-bound atypical promiscuous chemokine receptor that binds immunomodulatory ligands including CXC and CC chemokines and cytokines.[78] DARC is thought to act as chemokine Rheostat as it lacks the characteristic Asp-Arg-Tyr (DRY) motif within the second cytoplasmic loop characteristic of G-protein coupled receptors and therefore lacks classical GPCR signalling.[79,80] Clinical studies have reported an association between SNPs in DARC and asthma prevalence in African descendants[81]; however, the immunological basis by which DARC contributes to the pro-asthmatic phenotype is not fully delineated. Chapman and colleagues employed DARC knockout ($DARC^{\Delta E2}$) mice to examine the contribution this molecule to the development of AAD.[77] The authors show that house dust mite (HDM) challenge of WT mice increased DARC expression in alveolar airway epithelial cells and that HDM challenge of WT and $DARC^{\Delta E2}$ mice induced a comparable pulmonary cellular infiltrate and immune phenotype (Th1 Th2 and Th17 associated cytokines). The only notable differences between WT and $DARC^{\Delta E2}$ mice were increased pulmonary neutrophils in $DARC^{\Delta E2}$ mice suggesting that DARC contributes to the resolution of neutrophil leak information. Chemokine analyses of the BALF did reveal altered level of DARC-binding chemokine CXCL2 in $DARC^{\Delta E2}$ mice compared with WT mice. While the authors did not observe a major impact of ablation of DARC on the exacerbation of the allergic airway inflammatory phenotype, DARC did appear to regulate the severity and resolution of HDM-induced airway hyper-responsiveness (AHR). AHR measured by both tissue resistance and elastance was significantly reduced in the $DARC^{\Delta E2}$ compared to WT mice. Interestingly, ablation of DARC did not alter HDM-induced airway remodelling as the level of mucus hyperplasia and collagen deposition was comparable between HDM-challenged WT and $DARC^{\Delta E2}$ mice. These observations in animal systems prompted the investigators to examine for associations between DARC SNPs and symptoms in healthcare utilization in an asthma cohort. The authors identified a SNP in DARC (rs12042349) that was associated with worse asthma control in a poorly controlled white asthmatic cohort. Collectively, these experimental-based and clinical observations suggest that DARC may contribute to altered severity and resolution of AHR.

The functional role for B cells in allergic asthma phenotype has been controversial. Previous reports employing B cell deficient mice have shown the B cells are not required for eosinophilic inflammation and induction of the asthma phenotype.[82-84] However, there is emerging evidence to suggest that B cells may interact with DC cells to promote the differentiation of IL-4 committed follicular T helper (Tfh) cells into memory CD4+ Th2 cells.[85] Vroman and colleagues employing a chronic HDM provocation mouse asthma model revealed that the absence of B cells or lack of CD40L signalling (B-T cell interaction) does not impact pulmonary eosinophilic inflammation.[86] The authors further demonstrated that loss of B cells or B-T cell interaction impacted the frequency of T follicular helper (Tfh) and CD4+ Th2 cells, however, had no impact on the type II innate lymphoid cell (ILC2) frequency. Notably, the loss of B cells and B-T cell interaction did not impact pulmonary eosinophilic inflammation but led to reduced pulmonary remodelling as the HDM treated Mb1−/− and CD40l−/− mice had reduced airway remodelling and AHR. The pulmonary eosinophilic inflammation in the presence of reduced CD4+ Th2 immunity is likely to be attributed to normal ILC2 functionality as ILC2s are a prodigious source of the cytokines IL-5 and IL-13 which orchestrate eosinophil differentiation and maturation recruitment and effector function.[87-89] The authors speculate that divergence between these data sets and previous studies employing HDM-driven asthma models with a short challenge phase may relate to the formation of iBALTs (inducible bronchus-associated lymphoid tissue). Short allergen challenge protocols do not promote the formation of iBALTs, whereas Chronic HDM exposure as used by Vroman and colleagues promotes the development of iBALTs which possess IgE-expressing GC B cells, plasma cells as well as Tfh Th2 cells. Loss of B-T cell interaction and iBALT structures in the lung of chronically HDM exposed Mb1−/− and CD40l−/− mice led to reduced Tfh and CD4+ Th2 cell numbers in the presence of normal ILC2s. The authors conclude that B-T cell interaction is required for robust Tfh and Th2 cell induction but not essential for eosinophilic airway inflammation during a chronic HDM-driven asthma model.

4.1.2 | Molecular mechanisms of allergic airway remodelling

Kondo and colleagues examined the involvement of Tmem16A [Anoctamin 1 (Ano1)] a Ca^{2+}-activated chloride (Cl^-) channel in goblet cell (GC) metaplasia in a guinea-pig asthma model.[90] Previous studies have reported that Ano1 modulates mucus secretion and airway smooth muscle contraction in experimental asthma.[91,92] The authors show that in vitro antigen (ovalbumin [OVA]) challenge of the trachea from OVA-sensitized guinea-pigs and not non-sensitized guinea-pigs induced a rapid chloride (Cl^-) ion secretion that was dependent on TMEM16A activity. Notably the sensitized airway epithelium demonstrated increased frequency of GCs and that in vitro OVA-challenge stimulated GC secretion that was dependent Tmem16A activity. Immunofluorescence analyses revealed that TMEM16A was predominantly localized to the apical membrane of the sensitized epithelium and mucus granules in GC and basal cells. Employing an in vitro airway epithelial culture system the authors show that IL-13 treatment of airway epithelial cells led to MUC5AC-positive GC metaplasia that was strongly associated with increased TMEM16A expression and enhanced Ca^{2+}-activated TMEM16A-dependent Cl^- secretion. Collectively these studies suggest that ANO1 may contribute to GC metaplasia and mucus secretion during pulmonary allergic inflammation.

During a pulmonary allergic response aeroallergens are thought to lead to the release of mast cell-derived mediators including histamine and leukotrienes which can act as secretagogues and activate Ca^{2+} signalling cascades[93,94] making it tempting to speculate that mediators such as histamine and leukotrienes stimulate GC ANO1-dependent Cl^- activity and promote airway mucus secretion. The molecular basis of how a Ca^{2+} signal activates ANO1 activity remains unclear.[95] Experimental evidence suggests that Ca^{2+} directly binds to ANO1 protein and activates Cl^- ion transport. However, there is emerging data of the interaction of other proteins including calmodulin (CaM) and annexin A1 that may regulate the Ca^{2+}-activated Cl^- channel activity.[96-98] The authors' demonstration that the Cl^- transport response was dependent on TMEM16A clearly indicates that respiratory allergen induces a Ca^{2+}-dependent Cl^- ion transport via TMEM16A and not by cAMP-dependent Cftr-mediated Cl^- ion transport. Intriguingly, the authors revealed ANO1 expression in the proliferative basal cells within the airway epithelium. In recent years, there has been emerging interest in the role of bioelectric circuits in the regulation of cellular proliferation.[99] These studies have revealed a roles for bioelectric regulation and activation of Cl^- currents by Ca^{2+}-activated Cl^- channels (ClC3) and chloride intracellular channels (CLIC5) in cellular proliferation.[99] Consistent with this argument, AN01 gene is overexpressed in oral head and neck squamous cell carcinomas and level of expression correlates with cell proliferation.[100] With respect to the role for Ca^{2+}-dependent Cl^- ion transport in mucus secretion, it is postulated that the influx of Cl^- ions into the granule GC granule is important in the disruption of cationic shielding which leads to rapid swelling exocytosis and hydration of the mucus.[101,102] Additionally, ANO1-dependent Cl^- transport activity may also contribute to Cl^-/bicarbonate exchange through SLC26A4 which is also important in supporting mucin release.[103] Given the demonstration that ANO1 may be a key regulator for hypersecretory diseases such as asthma and GC hyperplasia and mucus secretion, this would make them an attractive candidate for asthma therapeutics.

4.1.3 | The impact of allergic comorbidities on allergic phenotypes

Epidemiological reports indicate an association between food sensitization and increased risk for the development of allergic diseases, in particular asthma.[104-107] Furthermore, it is well-established that asthma is a comorbidity for the development of severe food anaphylactic reactions.[108-110] Utsch and colleagues employing an experimental model to peanut (PN)-induced food allergy examined the impact of food sensitization on aeroallergen (HDM) sensitization and the development of asthmatic phenotype.[111] The authors show that prior sensitization to PN enhanced HDM-induced Th2 responses in the lung. Surprisingly, the increased CD4+ Th2 cytokine response was not associated with enhancement of HDM-induced asthma manifestations such as pulmonary eosinophilic inflammation, mucus hypersecretion and AHR. Given the previous demonstrations that CD4+ Th2 cells and ILC2 cells are important in the augmentation of the food allergic response, it would suggest that the pre-existing peanut food allergic response provides an unspecific bystander activation for the HDM-sensitization leading to increased Type II cytokine production.[112] Intriguingly, the HDM-induced airway inflammation while enhancing the mast cell response did not seem to impact the anaphylactic response to PN. However, the lack of effect of HDM-sensitization on exacerbation of the PN-induced anaphylactic reaction may relate to the induction of both a IgG1-basophil/macrophage and IgE-MC-dependent responses[113] following systemic antigen challenge and potential masking of any differences in the IgE-mediated induced clinical symptoms.

4.1.4 | Inhibiting airway inflammation and remodelling

A major histopathologic manifestation of asthma is the onset of airway remodelling, which is thought to contribute to the irreversible, or partially reversible, airflow obstruction and ultimately unresponsiveness to asthma therapies such as corticosteroids.[114-116] Recently, there has been advancement in the utilization of mesenchymal stem cells (MSCs) in the treatment of pulmonary disease phenotypes.[117] Human mesenchymal stem cells (huMSCs) are non-hematopoietic multipotent stromal cells that have regenerative properties and significant immunosuppressive potential and are well tolerated following allo- and xeno-transplantation.[118-121] Given this potential immunomodulatory capacity, Kang and colleagues investigated the immunomodulatory impact of huMSCs on the development of the asthma phenotype in mice. The authors show that human umbilical cord blood derived MSCs administered to antigen-sensitized mice suppressed the development of antigen-induced AHR. The reduction in AHR was importantly associated with a significant reduction in pulmonary inflammation including Th2 cytokine production, eosinophilic infiltration and airway remodelling (smooth muscle hypertrophy and mucus hypersecretion). Notably the protective effects of the huMSCs were associated with an increase in the frequency of CD4+ CD25+ FoxP3+ TR cells and production of the pro-inflammatory cytokines IL-10 and TGFβ1. The molecular mechanisms by which MSCs induce T regulatory expansion are not yet fully delineated. Experimental evidence suggests that MSCs can induce TR cells responses via contact-dependent mechanisms through inducible T cell co-stimulator (ICOS)—ICOSL and potentially through contact-independent mechanisms involving indolamine 2,3-dioxygenase (IDO).[122,123] These studies are the first demonstration of xenogenic huMSC-mediated suppression of the allergic asthma phenotype. While further studies are required to delineate the molecular basis of huMSC-mediated up regulation of TR cells and the protective effects against allergen-induced asthma phenotype, this shows great promise in the utilization of these cells for the prevention or treatment of allergic disease.

4.2 | Food allergy and anaphylaxis

4.2.1 | Oral tolerance

As food allergy has become a major public health concern, there has been increasing interest in the understanding of the immunological

processes that regulate oral tolerance versus sensitization.[124] In non-food allergic individuals, food antigens promote immune tolerance associated with the expansion of FoxP3+ TR cells and also IL-10 or IFNγ-secreting TR1 cells.[125] In food allergic individuals, exposure to innocuous dietary antigens leads to an inappropriate CD4+ Th2 response associated with pro-Type II cytokine production (IL-4, IL-5, IL-9, IL-13) ILC2 response which leads to priming of the basophils and mast cells and development of food-specific IgE.[124,125] Currently, the behavioural and environmental determinants that favour oral immune tolerance vs sensitization to foods are not fully understood. Recent clinical evidence suggests that early introduction of solid foods in the diet such as egg and peanut can be beneficial and promote food tolerance.[126-129] Furthermore, introduction of solid foods while continuing breastfeeding is also thought to enhance tolerance induction and prevention of food allergy possibly through the presence of immunomodulatory factors such as TGFβ in breastmilk.[130] Rekima and colleagues examined a birth cohort that consisted of mother-child pairs from the French EDEN birth study and surprisingly detected egg antigen (OVA)-specific IgG and IgA in breastmilk from allergic and not allergic mothers.[131] While OVA-specific IgA levels in mother milk from allergic and non-allergic mothers were similar, the level of OVA-specific IgG was found to be significantly higher in milk from allergic mothers compared with non-allergic mothers. These clinical observations prompted the question of whether oral antigen exposure through breastmilk could prevent food allergy in young offspring the investigators employed a mouse model of food allergy.[99]

The author shows that mice breastfed from OVA-sensitized mothers who were exposed to OVA during lactation had decreased food allergy susceptibility at 6 weeks of age. Notably the protective effects were temporary as food allergen exposure to breastfed pups at 13 weeks of age-induced food allergy. In efforts to prolong the breastfeeding-mediated suppressive effects, the authors administered a TGFβ-enriched formula to mice post weaning. The authors show that post weaning oral supplementation with TGFβ prolonged the beneficial effects of breastfeeding as breastfed pups at 13 weeks of age was protected from the development of food allergy. Interestingly, the TGFβ-enriched formula protective effects were not associated with enhanced FoxP3+ TR populations but rather improved gastrointestinal (GI) epithelial barrier function in the mice suggesting that TGFβ-enriched formula significantly improved GI barrier function. Previous experimental studies have demonstrated that TGFβ stimulation of intestinal epithelial cells enhances epithelial barrier function via increased expression of tight junction proteins claudin-1 and claudin-4 via the SMAD-signalling axis.[132,133]

Recently, there has been increasing reports of food allergic reactions to food additives.[134,135] In Denmark, it is reported that a prevalence of 1%-2% of children and about 1% of adults have had an adverse reaction to food additives.[135] Food additives are defined as substances added to food at any stage of production, processing, treatment packaging or storage, and there are currently greater than 3000 substances approved for use as food additives by the US Food Drug Administration. Yamashita and colleagues evaluated the ability of artificial sweeteners and mixtures of food additives to break oral tolerance and induce food allergy in mice.[136] The authors assessed a number of sweeteners (acesulfame potassium, aspartame, xylitol and meso-erythritol), moisture absorber (silicon dioxide), natural sugars (glucose and sucrose) and other additives such as benzoic acid, sweetener saccharin sodium and annatto pigment. The authors show that co-administration of food additives including acesulfame, erythritol, glucose and sucrose and egg antigen (OVA)-specific IgE, however, saccharin induced a robust OVA-specific IgE suggesting that saccharin could break tolerance and promote sensitization. The authors further demonstrated that administration of OVA with saccharin could prevent the acquisition of oral tolerance and promote food sensitization and food allergy. The authors show that saccharin-induced sensitization was associated with altered migration of classical antigen-presenting cell APCs.

Intriguingly, the authors assessed the risk of pleural food additives in the induction of food sensitization and development of food allergy.[136] The authors show that exposure of mice to a mixture of pleural food additives that were at a concentration equivalent to the average daily intake (ADI) of the Food Safety Commission in Japan/the joint FAO/WHO expert committee on food allergy additives in the presence of OVA promoted OVA sensitization and food allergy. Importantly, exposure to single food additives while promoting OVA-specific IgE did not predispose to OVA-induced food allergy. However, exposure to a mixture of food additives or saccharin not only promoted OVA-specific igE but also predisposed to the induction of food allergy following subsequent exposure to the allergen OVA. Food additive treatment of saccharin or mixture led to altered migration of APCs reducing proportions of MHCII+ CD11b+ CD103+ APCs and augmented MHCII+ CD11b+ CD103− APCs. While the dose of saccharin sodium used per mouse (100 mg) corresponded to 100 times the ADI dosage of additives, the mixture of food additives was only approximately 10 times the ADI dose and was sufficient to break immune tolerance and promote food allergy. These results suggest that intake of pleural additives amplifies the risk of developing food allergies. The breaking of oral tolerance appeared to be associated with altered balance of tolerogenic CD11b+ CX3CR1+ CD103+ DCs and allergic resident CD11b+ CD103− DCs which is consistent with previous investigations demonstrating that CD11c+ positive CX3CR1+ DCs drive immune tolerance where is the CD11b+ DCs are associated with the induction of allergic responses.[137]

Lozano-Ojalvo and colleagues utilized a different approach and examined whether a hydrolysate of the egg antigen (OVA) could prevent and/or possibly treat egg allergy.[138] The investigators demonstrated that the hydrolysate of ovalbumin (OVA-H) lacked sensitizing eliciting potential in an in vivo mouse model. Moreover, administration of the OVA-H and not egg white (EW) in the presence of cholera toxin (CT) did not induce OVA-specific IgE and IgG1. Consistent with this observation, subsequent exposure to OVA-H did not promote the development of CD4+ Th2 response and development of anaphylactic symptoms in the mice. These studies suggest that OVA-H was weakly immunogenic and hypoallergenic. The authors next assessed the prophylactic potential of OVA hydrolysate in the development of allergy to EW in mice. The authors show that pre-treatment of mice with

OVA-H prior to EW plus CT prevented sensitization and the development of anaphylaxis following oral challenge with EW. The pre-treatment of mice with OVA-H was associated with an increased FoxP3+ TR phenotype expression of regulatory cytokines IL-10 and TGFβ. These results indicate that pre-treatment with a hydrolysed form of antigen (OVA-H) can more effective in the inhibition of EW allergy in mice than the intact antigen (OVA). Notably, the OVA-H induced sustained desensitization to EW in mice suggesting that OVA-H may provide effective immunotherapy with durable effects.

Antidotal clinical data suggest that the gastric pathobiont *Helicobacter pylori* (*H. pylori*) may confer protection against oesophageal disorders as well as asthma, allergy and IBD.[139] Further support of this concept is large epidemiological studies revealing an inverse association with *H. pylori* and development of allergic diseases such as allergic asthma.[140] Kyburz and colleagues investigated whether experimental infection with *H. pylori* or prophylactic treatment with the *H. pylori*-derived immunomodulatory vacuolating cytotoxin A (VacA) molecule can impact the onset and severity of food allergy and anaphylaxis.[141] The investigators show that infection of neonatal mice with *H. pylori* or treatment of animals with *H. pylori* VacA reduced the rate of allergen sensitization and subsequent development of anaphylaxis following allergen challenge. The authors showed that the protective effect in mice was associated with a stable TR response associated with demethylation of the TR-specific demethylated region (TSDR) within the FoxP3 locus. These studies suggest that *H. pylori* possesses strong immunomodulatory properties mediated at least in part by the VacA protein that leads to enhanced T regulatory response and protection from food allergy.

Clinical study performed in rural alpine area of Switzerland has revealed that children raised on farms have less allergies than children living in the same area but not on a farm.[142] This was supported by a cross-sectional study including farmers and non-farmers children from Austria, Germany and Switzerland that revealed the protective farming effect where the presence of cattle and other animals provided a strongly protective environment against atopy in young children.[143] A limitation to our understanding of the molecular mechanisms involved in the driving the protective farming effect is the lack of appropriate animal model systems. To begin to address, Frossard and colleagues developed a mouse model system that mimics the farm versus non-farm (University animal facility) environments to assess the influence of microbial environment on allergy susceptibility.[144] The authors stratified Balb/c mouse breeding colonies into two different environments (a) cattle barn of a typical Alpine farm in rural western Switzerland, where the mice are located in the same area as the cows and naturally exposed to cows and hay dust and (b) controlled environment where mice are bred in a conventional animal facility at the University of Geneva school of medicine under SPF conditions (AF). The investigators took the F2 generation mice and showed that mice from both locations were in good health and demonstrated comparable weight gain. Examination of the susceptibility to allergen-induced contact hypersensitivity revealed that the farm environment protected mice from skin allergy. The farm mice had reduced levels of antigen-specific IgE and IgG3 compared to the AF mice. Analysis of the peripheral blood revealed that the farm mice displayed less B (CD19+) cells and heightened level of CD3+ CD4+ T cells suggesting CD4+ T cell activation by the farm environment. Analyses of gut microbiome revealed significant microbiome differences between farm and AF mice. Interestingly, the proportion of several bacterial genera (*Lactobacillus*, *Alistipes*, *Roseburia*, *Adlercreutzia* and *Clostridium*) which are known to have immunomodulatory properties was significantly different between farm and AF mice making it tempting to speculate that the commensal microbiota may potentially regulate the innate and adaptive immune compartment and alter susceptibility to allergic conditions. While the contribution of the altered peripheral blood T cell phenotype and cytokine production or microbiota to the allergen-induced contact hypersensitivity responses was not ascertained, this study sets an excellent platform to begin to distinguish the molecular pathways that may contribute to the environmental factor modulation of allergy susceptibility outcomes.

A study by Malik and colleagues performed genomic and immunohistochemistry analysis on positive house dust mite (HDM) atopy patch test (APT) from patients with and without AD and healthy controls.[145] The investigators performed HDM patch test on normal appearing back of 30 individuals of which 15/30 responded positively to HDM. Of the 15 individuals who responded positively four had coexisting AD and four others had elevated IgE. The positive HDM lesions contained higher T cell, eosinophil and DC cell infiltrates versus controls. Microarray analysis revealed that HDM-positive skin reactions versus control skin induced an increase of 743 and decrease of 326 differentially expressed genes. The upregulated genes included inflammation/immune activation phenotype (Th2 and Th17, Th22/Th17 and Th9), and down regulated genes included selective barrier and lipid genes. Notably, the terminal differentiation, tight junction and lipid genes characteristically down regulated and AD were not decreased in HDM. Analyses revealed that HDM responses in individuals with concomitant AD displayed a more robust inflammatory response to HDM than non-AD individuals. Pathway enrichment analysis of the HDM transcriptome revealed many significant upregulated pathways in the HDM signature including T cell receptor, NOD, Toll-like receptor signalling, JAK-STAT signalling, interferon gamma signalling and Th22. This was the first comprehensive molecular profiling of positive HDM APT responses of human skin. While the HDM APT demonstrated a strong Th2 response, HDM lesions illustrated some qualitative differences in Th2 induction and epidermal abnormalities as compared to AD.

Another entity of food hypersensitivities is eosinophilic gastrointestinal disorders (EGIDs). Eosinophilic esophagitis (EoE) is the most common form of EGIDSs in humans with symptoms related to eosinophil predominate mucosal inflammation and oesophageal dysfunction.[146,147] Patients with EoE have a high rate of concurrent IgE-mediated food allergy and food elimination diet, and amino acid feeding is one of the mainstay therapies for young children with EoE.[148,149] Recent clinical studies have revealed efficacy of epicutaneous immunotherapy (EPIT) in peanut allergic children.[150] To examine the potential impact of EPIT on EGIDs, Mondoulet and colleagues developed a model of gastric eosinophilia in peanut-

sensitized piglets.[151] The authors show that intraperitoneal sensitization to peanut protein extract (PPE) and subsequent oral exposure led to a gastric eosinophilia. Treatment of piglets with active EPIT by using the VIASKIN loaded with PPE applied daily to the ear induced a significant reduction in median antigen-specific IgE, number of gastric mucosal lesions and histological improvement including reduced gastric mucosal eosinophil numbers. The reduction in the gastric eosinophil phenotype was associated with reduced GATA-3, IL-5 and CCL11m RNA expression in splenocytes. These studies suggest EPIT may be an efficacious approach to treat peanut-induced EGIDs.

Metal allergies are generally classified as a Th1-dependent hypersensitivity response. Nickel (Ni) is the most frequent metal allergen among various metals, and the mechanism by which small metal antigens induce specific immune responses is currently unclear. Sato and colleagues recently developed a mouse model of Ni allergy utilizing lipopolysaccharide (LPS) as an adjuvant[152] and revealed an interaction between TLR signalling and Ni in the development of nickel allergy. In their recent study, Kuroishi and colleagues perform a series of elegant studies to show that LPS stimulates the production of the chemokine, CXCL4 which acts as a Ni-binding protein and exacerbates Ni allergy. Performing a series of in vivo mouse experiments in combination with tandem mass spectrometry and surface plasmon resonance analyses, the authors show that (a) LPS stimulates CXCL4; (b) CXCL4 binds Ni and (c) that co-administration of CXCL4 and Ni augmented Ni allergy at both the elicitation and sensitization phase. Flow cytometric analysis suggests that CXCL4 chemotactic activity is not responsible for the augmenting effects. These studies clearly identified CXCL4 as a novel Ni-binding protein and demonstrate a role for this chemokine in augmentation of nickel allergy. While further studies are required to delineate the mechanism by which CXCL4 augments nickel allergy and or whether interactions between CXCL4 and other metal antigens such as cobalt or palladium occur in metal allergies, this information will be useful in the development of effective methods to prevent and treat metal allergy.

5 | BASIC MECHANISMS IN ALLERGIC DISEASE

The nature of a cell's energy metabolism is closely tied to its function, and recent research has started to shed light on how targeting cell metabolism could be a novel avenue for therapeutic interventions in respiratory diseases. In particular, reports have shown that in some chronic inflammatory settings, myeloid cells undergo metabolic reprogramming from oxidative phosphorylation of glucose to the oxidation of fatty acids. Al-Khami and colleagues investigated the impact of the fatty acid oxidation pathway on the magnitude of a mouse model of asthma by pharmacologically blocking it with Etomoxir.[153] The result was a clear reduction in the overall inflammatory response. The lack of cell specificity inherent to this type of approach clearly has its caveats, but given there is existing medication which can block fatty acid oxidation, there is potential for rapidly harnessing this novel therapeutic approach should further research support its application.

Cell-to-cell communication occurs through the release of soluble mediators such as cytokines and chemokines, and then their recognition by cognate receptors on responding cells. Alternatively, direct cell-to-cell contact via receptor-ligand pairs is a fundamental mechanism of cellular communication. Another mechanism, as investigated by Gon and colleagues, is through extracellular vesicles, which are cell-derived membranous structures that are shed from the cell surface.[154] These extracellular vesicles can contain cellular components such as microRNA's, and the nature of their content differs depending on the activation and differentiation state of the cells. Gon and colleagues reported that during house dust mite induced allergic airway inflammation in mice, there is an 8.9-fold increase in extracellular vesicles that are secreted into the airways. Importantly, the microRNA constituents of these vesicles were different between sham-control and house dust mite exposed animals, with the vesicles from house dust mite exposed airways having diminished microRNAs targeting Th2 transcripts such as IL-13 and IL-5R. Overall, these data highlight the likely role of vesicles and their microRNA constituents in regulating the magnitude of allergic responses in the airways.

The pathological role of mast cells in allergic diseases, often instigated following cross-linking of IgE on their surface, is well established. Clinical desensitization with specific allergens is a common and effective means to induce tolerance; however, this tolerance is not long-lasting and can recur following allergen withdrawal. Lewis and colleagues used an in vitro culture to assess whether human mast cells recover from IgE-mediated desensitization.[155] Following removal of the allergen, the mast cells recovered their effector function within days, suggesting this process of sensitization might be mediated by the temporary accumulation of intracellular inhibitors, as opposed to a fundamental change in the cellular programme, for example, by epigenetic modifications.

Are mast cells always bad? Salamon and colleagues provided data which suggest we might need to rethink the role of mast cells in allergic dermatitis.[156] Using in vitro cultures and a mouse model, the authors showed that following stimulation with IL-33 and IgE, mast cells produced IL-2 that could promote the expansion of regulatory T cells. This pathway of pro-inflammatory signals eventually leading to a regulatory pathway might represent a key mechanism through which allergic inflammation is resolved.

6 | CLINICAL MECHANISMS IN ALLERGIC DISEASE

6.1 | Probiotic supplementation

Several reports in 2017 focused on immune changes in children and adults following various interventions. Ro and colleagues examined the effects of maternal probiotic supplementation on discrete T helper (Th) subsets in relation to the development of AD in offspring during the first 2 years of life.[157] Analysis of 5 discrete Th subsets in the peripheral blood revealed that those children in the probiotic group had a reduced proportion of Th22 cells, vs the placebo group

at age 3 months, regardless of whether AD was present at aged 2. Moreover, increased Th22 cells were evident in those children who developed AD. Statistical modelling indicated a partial role for the reduction of Th22 cells by probiotics in preventing AD. Th22 cells, which secrete IL-22, IL-13 and TNF-alpha, act directly on keratinocytes via IL-22. As such, they are candidates for promoting inflammatory processes in the skin that lead to AD, despite their low numbers relative to other Th types.

6.2 | Immunotherapy

In other work, circulating invariant natural killer T cells (iNKTs) were assessed in the blood of children who received oral immunotherapy (OIT) for cow milk allergy (CMA).[158] These cells, which respond to lipid antigens, had previously been shown by the investigators to be lower in CMA. In the present study, increased numbers of iNKTs were associated with OIT, along with a switch in cytokine profile from Th2 to Th1. Notably, children were able to reintroduce milk in their diet after OIT and increased iNKTs persisted for several months after completion of the OIT regimen. These results warrant further examination of iNKTs in allergen desensitization to foods.

Sensitization to multiple foods is common in patients with food allergy. With this in mind, Gomez and colleagues tested whether sublingual immunotherapy targeting a peach protein (Pru p 3) altered the response to a peanut protein (Ara h 9) belonging to the same family of highly stable non-specific lipid transfer proteins.[159] Such "pan-allergens," which can induce severe reactions, are widely distributed across plant food species. Among peach allergic adults, 1 year of Pru p 3 sublingual immunotherapy resulted in decreased weal size by skin prick test, along with increased threshold upon food challenge, for both peach and peanut. Similarly, a rise in specific IgG4 and in the IgG4/IgE ratio was observed for both allergens.

6.3 | Asthma mechanisms

Several papers in 2017 focused on cellular and biologic mechanisms of asthma. Neutrophils have been widely implicated in the pathogenesis of severe asthma. While their anti-microbial function is generally well understood, their role in asthma pathogenesis remains enigmatic. In addition to their phagocytic and cytokine-secreting abilities, neutrophils emanate DNA structures that arise from decondensation and spreading of chromatin in response to a variety of activating triggers. While such DNA traps (NETs) can capture microbes, work by Pham and colleagues in the journal points to a pro-inflammatory role in asthma.[160] Peripheral blood neutrophils from patients with severe asthma that were stimulated with IL-8 displayed enhanced autophagy and NET levels compared with cells from patients with less severe disease. Notably, higher NET levels were linked to worse lung function, and the ability to mediate epithelial damage and mediator release from eosinophils in functional assays, thereby supporting a pathogenic role.

Two papers focused on metabolites in exhaled breath as markers of disease processes in the asthmatic airways. Kowal et al reported increased levels of a variety of arachidonic acid metabolites in patients experiencing bronchoconstriction after bronchial challenge with dust mite extract.[161] These included the potent eosinophil chemoattractant 5-oxo-eicosatetraenoic acid (5-oxo-ETE), which is a product of the 5-lipoxygenase pathway that also results in leukotriene synthesis. Levels of 5-oxo-ETE were markedly higher than other 5-lipoxygenase metabolites, including leukotriene D4, suggesting an important role in asthma pathogenesis. The second paper conducted a systematic review of 27 studies to assess the diagnostic accuracy of the fraction of NO in exhaled breath.[162] This test, which can be performed using a hand-held monitor, may provide an indicator of eosinophilic inflammation of the airways. Diagnostic accuracy was found to be highly variable, and the results imply that more work is needed using well-designed studies to determine the suitability of this test within the asthma diagnosis pathway.

6.4 | Rhinitis allergic mechanisms

Other work pointed to an adverse effect of seasonal allergic rhinitis on cognitive functions related to memory and multitasking.[163] This study highlighted the knowledge gap regarding the actions of various inflammatory mediators of allergic disease on the central nervous system.

6.5 | Systemic mastocytosis

Gulen et al addressed whether elevated levels of mast cell mediators in systemic mastocytosis derive from increased numbers of tissue mast cells or their increased activation status at the single-cell level.[164] Assessment of the responsiveness of skin and airway mast cells both in vitro and in vivo was found to be similar in the face of increased numbers in blood and urine. The authors proposed that leakage of mediators from cells explains the high levels of mast cell mediators in systemic mastocytosis, but acknowledged that more work is needed to understand the episodic symptoms in this disease.

7 | ALLERGENS

7.1 | House dust mite

In Clinical and Experimental Allergy in 2017, Oseroff and colleagues have analysed the house dust mite (HDM)-derived protein targets of T cell responses in individuals with HDM allergy.[165] They used a mass spectrometry proteomic approach finding 29 known allergens and 61 novel proteins. T cell reactivity was seen to a large number of T cell epitopes—15 antigens dominated the response with most being novel. Most of the known allergens were also IgE reactive but few of the novel ones were IgE reactive. This will provide lots of new targets for diagnostics and immunotherapeutics for HDM allergy.

7.2 | Pollens

The current European Union regulatory framework controlling allergen products distinguishes between relevant and non-relevant

allergens. Minor allergens are usually not controlled by these regulations. Zimmer and colleagues have looked at three minor birch pollen allergens (Bet v 4, Bet v 6, Bet v 7) in 70 different products using an ELIZA system.[166] They found large differences within and between products in minor allergen content with no relationship with major allergen content. Does this variability impact on characteristics as diagnostic tools or therapies?

Smiljanic and colleagues have looked at the allergome of the ragweed subpollen particles which can be inspired into the lower airway.[167] These are generated when ragweed is hydrated or exposed to a thunder storm. The subpollen particles contained large amounts of the minor Amb a 4 and major Amb a 1 allergens. This suggests that this is important in ragweed allergy.

Specific IgG4 levels increase with allergen immunotherapy, and this is thought to be one of mechanisms by which it minimizes clinical allergy. Groh and colleagues described how they assessed whether birch pollen immunotherapy generates Bet v 1a IgG4 that compete with IgE for identical epitopes or whether it has novel epitopes.[168] They concluded that patients receiving allergen immunotherapy develop Bet v 1a-specific IgG4 which competes with IgE for partly identical or largely overlapping epitopes.

7.3 | Cockroach

In 2017 Clinical and Experimental Allergy, Mindaye and colleagues described how liquid chromatography and multiple reaction monitoring mass spectrometry can be used to quantify five German cockroach allergens (Bla g 1, Bla g 2,Bla g 3, Bla g 4 and Bla g 5).[169] Meanwhile, Polley and colleagues described how they looked for trypsin-like proteinases in German cockroach allergen extracts.[170] Proteinases contribute to allergenicity and airway inflammation by activating proteinase-activated receptors. They used a trypsin-specific activity-based probe to detected proteins that were then isolated using ion-exchange chromatography. Three serine proteinases were isolated which showed some homology to Per a 10. The authors speculate that they may be important in allergen sensitization and may represent therapeutic targets.

7.4 | Jack Jumper ant venom

Allergy to Jack Jumper ant venom is important in some areas, such as Australia. Wanandy and colleagues described how they assessed the consistency of allergenic material and the impact of environmental factors.[171] They found good batch to batch consistency but degradation above 40°C. This is important to maintain the diagnostic utility of skin prick testing reagents and efficacy of immunotherapy product.

7.5 | Precautionary allergen labelling

Zurzolo and colleagues have looked at how widely the Australian food industry is using the VITAL approach to making rational decisions on precautionary allergen labelling.[172] A total of 59 manufacturers completed the questionnaire. They reported that a quarter of products had been through the VITAL risk assessment process but had no PAL statement on the label. They suggested that it might be helpful if such foods had a permissive "safe to eat" label.

8 | CONCLUSIONS

The year 2017 has provided further advances in the field of allergy. We look forward to publish more interesting observations in 2019.

CONFLICT OF INTEREST

The authors declare no conflict interest.

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