Developments allergy in 2019 through the eyes of Clinical and Experimental Allergy, Part I mechanisms

Authors

Graham Roberts[1,2,3] C. Almqvist[4,5], R. Boyle[6], J. Crane[7], S. P. Hogan[8], B. Marsland[9], S. Saglani[10], J. A. Woodfolk[11]

Affiliations

1. Clinical and Experimental Sciences and Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK
2. NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
3. The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK
4. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
5. Pediatric Allergy and Pulmonology Unit at Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
6. Department of Paediatrics, Imperial College London, London, UK
7. Department of Medicine, University of Otago Wellington, Wellington, New Zealand
8. Mary H Weiser Food Allergy Center, Department of Pathology, Michigan Medicine, University of Michigan, Ann Arbor, MI, USA
9. Department of Immunology and Pathology, Monash University, Melbourne, Vic., Australia
10. National Heart & Lung Institute, Imperial College London, London, UK
11. Division of Asthma, Allergy and Immunology, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA

Correspondence

Graham Roberts, Paediatric Allergy and Respiratory Medicine (MP803), Clinical and Experimental Sciences and Human Development in Health, Faculty of Medicine & University Hospital Southampton, University of Southampton, Southampton, UK. Email: g.c.roberts@soton.ac.uk

Short title

Year in review: mechanisms

Key words

Experimental models, basic mechanisms, clinical mechanisms, allergens

Word count

4050

Abstract

In the first of two linked articles, we describe the development in the mechanisms underlying allergy as described by Clinical & Experimental Allergy and other journals in 2019. Experimental models of allergic disease, basic mechanisms, clinical mechanisms and allergens are all covered. In this article, we described the development in the field of allergy as described by Clinical and Experimental Allergy and other journals in 2019. Experimental models of allergic disease, basic mechanisms, clinical mechanisms and allergens are all covered

Experimental models of allergic disease

Development of oral tolerance

To prevent the development of systemic immune responsiveness to dietary protein antigens, the immune system has developed mechanisms of local and systemic immune unresponsiveness termed “oral tolerance” [1-3]. Soluble dietary protein antigens within the gastrointestinal tract are acquired by small intestine (SI) lamina propria (LP) antigen presenting cells [$CX3CR1^+$ macrophages and $CD103^+$ migratory dendritic cells (DCs)] and are presented via cognate interaction to naive $CD4^+$ T cells [4-6]. $CD103^+$ DC-derived retinoic acid, indoleamine 2,3-dioxygenase and transforming growth factor (TGF-β promote *de novo* Foxp3 expression and generation of peripheral Regulatory T cells (Tregs) [5-8]. These newly derived $CD4^+$ Treg cells traffic back to the SI LP where they maintain a tolerant homeostatic environment through secretion of the cytokines, TGF-β and IL-10 [9]. The $FoxP3^+$ $CD4^+$ Treg cells are maintained and supported by additional regulatory cells positioned within the SI mucosa, including $MHCII^+$ $CX3CR1^{Hi}$ IL-10 producing macrophages, gut resident ILC3s, and B regulatory cells [9-12].

Development of food allergy

In food allergic individuals, food allergen exposure leads to the production of the pro-type 2 epithelial derived cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP)13 which drive

a $CD4^+$ Th2 response and food sensitization [14]. The pro-type-2 cytokines are thought to act on $CD103^+$ DC cells to promote OX40L expression which drives the IL-4-dependent $CD4^+$ Th2 cells. The $CD4^+$ Th2 cells stimulate $CD4^+$ Th9 cells [15-17]; ILC2-derived cytokines (IL-5 and IL-13), isotype switching and induction of IgE^+ plasma cells in the GI compartment and expansion of basophils, mast cells and suppresses Treg function [18, 19].

Targeted immunotherapy

Recently there has been significant interest in developing immunotherapy approaches targeting DCs, B and $CD4^+$ T cells to efforts switch the pro-Type-2 allergic response to promote immune regulatory function and suppress allergic disease phenotype. In particular, DC vaccine approaches to stimulate TGFβ1 and IL-10 producing immune regulatory DCs to facilitate induction of $FoxP3^+$ $CD4^+$ Treg cells [20]. DEC-205 (CD205) is a 205 kDa endocytotic receptor predominantly expressed by DCs and thymic epithelial cells and is thought to act as a cell surface receptor for CpG oligonucleotides and promote DC immunoregulatory activity [21-23]. Xu and colleagues constructed a fusion protein consisting of an epitope of the ovalbumin (OVA) molecule and a segment of the anti-DEC205 antibody, scFv [24]. The fusion protein termed chimeric Ag peptide (CAP), specifically binds DEC205 and present on the surface of DCs. The authors show that exposure of bone marrow-derived DCs to scFv-IC fusion protein led to DC uptake of scFv-IC and also surface expression. Presentation of the scFv-IC on surface DCs was associated with immune regulatory phenotype including expression of CD80 and CD86 as well as the regulatory cytokines, IL-6, IL-23 and TGFβ. In vivo studies revealed that transfer of CAP-DCs or injection of scFv-IC induced antigen (Ag)-specific IL-17^+ $FoxP3^+$ iTreg response in gastrointestinal tract of food allergic mice. Notably, the iTregs showed immune suppressive activity, suppressing Ag-specific CD4+ Th2 response and ameliorating food allergy via an IL-17-dependent mechanism. These studies show that scFv-IC chimeric DC technology can ameliorate FA response by inducing Ag-specific IL-17^+ $FoxP3^+$ iTregs and maybe a therapeutic technology to treat allergic diseases.

Metainflammation and eosinophilic oesophagitis

Emerging clinical studies have revealed that lifestyle factors such as sedentary lifestyle and diet high in fat and simple sugars can promote chronic metabolic inflammation termed metainflammation [25-27] which modulate immune mediated disease processes including allergic diseases [28-30]. The metabolic overload as a consequence of excess nutrients and their metabolites leads to the release of metabolism-associated molecular patterns (MAMPs) such as

oxidized low-density lipoproteins (OxLDLs), free fatty acids (FFAs), glucose, advanced glycation end products (AGEs), and cholesterol [31]. These danger signals activate pattern recognition receptors (PRRs) downstream NFkB, MAPK and NLRP3-inflammaosme pathways in macrophages (IL-6, TNFα and IL-1β), $CD4^+$ Th1 cells (IFNγ) and $CD4^+$ Th17 cells (IL-17) leading to chronic low-grade inflammation [31, 32]. The molecular basis of how chronic low grade inflammation alters the allergic phenotypes is not yet fully elucidated [30].

Silva and colleagues utilizing a murine model of eosinophilic oesophagitis (EoE) examined the effect of obesity on EoE in mice [33]. The authors induced obesity and associated increase in body mass index (BMI), greater perigonadal fat accumulation and serum total cholesterol, LDL cholesterol and triglycerides in BALB/c male mice by feeding the mice high fat diet (HFD). Increased levels of these MAMPS was associated with metainflammation as evidenced by heightened systemic leptin and TNFα levels. The authors show that HFD alone was sufficient to promote a systemic allergic phenotype characterized by a significant mast cell and eosinophil accumulation in the oesophagus, trachea, gut and lung. Induction of the EoE phenotype in lean and obese mice revealed that obesity aggravated the histopathological characteristics EoE including increased eosinophils and mast cells, Th2 cytokines (Il5 and TSLP) and systemic $CD4^+$ Th2 response [33]. Clinical studies have revealed that the presence of eosinophils and eosinophil granule proteins correlates with histologic features of EoE including intercellular oedema, basal zone hyperplasia, lamina propria elongation and lamina propria fibrosis [34]. Given the exaggerated inflammatory cell infiltrate in obese-mice, one would predict increased oesophageal epithelial remodelling and disease severity, however this was not examined. Despite these limitations, the study demonstrates that obesity can exacerbate allergic inflammatory responses and be an important risk and aggravating factor for EoE.

Metainflammation and asthma

Schroder and colleagues examined the effect of short-term HFD, mild weight gain on the induction of the asthma phenotype in mice [35]. In these studies, the author show that female (C57BL6JRJ) mice feed HFD to induce mild increase in body weight accompanied by mild metabolic alterations develop a less severe asthma phenotype. Moreover, the asthma phenotype in chow diet fed mice was associated with more severe airway inflammation and AHR response compared to HFD-fed mice. Analyses of the immune phenotype revealed the reduced asthma phenotype was associated with decreased OVA-induced DC and $CD4^+$ T-cell recruitment. Mechanistic analyses revealed that the pulmonary $CD11b^+$ DCs phenotype from the HFD-fed mice was markedly

different with reduced MHC-II and CD40 expression. These findings suggest that short-term HFD feeding attenuates the development of AHR, airway inflammation, pulmonary DC recruitment and MHC-II/CD40 expression leading to diminished Th1/17 but unchanged Th2 differentiation. Thus, short-term HFD feeding and associated metabolic alterations may have protective effects in allergic asthma development.

The two studies clearly show that metainflammation can alter allergic disease susceptibility and severity and that further in-depth studies will be required to fully decipher the mechanism of action.

Sex switching in asthma risk at puberty

Another factor that has been recently shown to be linked with allergic phenotypes, particularly asthma is sex hormones [36]. The prevalence of asthma in prepubescent boys is higher than that observed in girls, with boys having increased wheeze, serum IgE levels, and use of asthma medications [37]. During puberty, the sex disparity is switched with girls having increased asthma incidence which is maintained in adulthood [38, 39]. This has led to the concept that female sex hormones such as oestrogen (E2) plays a role in immune regulation and susceptibility to allergic disease phenotypes. Experimental studies have shown that female sex hormones modulate multiple immune cell populations including DC, B cells and alter balance in Th1/Th2 immunity [36, 40, 41]. However, the contribution of E2 to development of the asthma phenotype (eosinophilic inflammation, airway remodelling and AHR) is not fully elucidated.

Lauzon-Joset and colleagues employed a rat model of experimental atopic asthma to gain insight into the role of E2 in experimental atopic asthma [42]. The authors use two rat strains, which express highly dichotomous $Th2^{high}$ (Brown Norway, BN) versus $Th2^{low}$ (Piebald Virol Glaxo, PVG) immunophenotypes that model the human IgE responsiveness spectrum. The authors show that the male and female rats of the pro-allergic BN rat strain demonstrate different immune cell composition phenotype at baseline. Moreover, BN females displayed increased number of BAL cells including macrophages, neutrophils, lymphocytes and a marked increase in eosinophils. Furthermore, female BN rats displayed significantly higher peripheral blood eosinophil levels and total IgE titres compared to their male counterparts. Implantation of male BN rats with E2-releasing pellets which induced serum E2 concentrations that were comparable to female levels induced a heightened baseline $CD4^+$ Th2 phenotype characterized by increased pulmonary neutrophils and eosinophils and total serum IgE titres suggesting that E2 may contribute to driving the elevated systemic Th2 response observed in female BN rats. Employing an antigen model

system in BN female and male rats transplanted with E2 releasing pellets the authors show that E2 perpetuates the activation of the $CD4^+$ Th2 response in the pulmonary compartment. Importantly, these effects of E2 were not replicated in the $Th2^{low}$ PVG rat strain, suggesting the involvement of Th2-promoting cofactors within the $Th2^{high}$ background in the potentiation of the E2-dependent effects. Collectively these studies show that E2 can alter the eosinophilic component of pre-existing Th2-high immunophenotype, and modulate the asthma phenotype. These findings suggest E2 may contribute to increasing the risk of asthma development in females.

Weight gain and asthma risk

The reported association between weight gain and asthma in females, but not in males suggests that there may also be interaction between metabolic syndromes and sex hormones that exacerbates allergic disease phenotypes [43].

To test this concept of interaction between weight gain and sex in allergic disease phenotypes, e-Lacerda and colleagues examined allergic pulmonary inflammatory responses in female and male mice independently on a HFD regime [44]. The authors show that HFD led to 36% and 27% increase in body weight and elevated levels of metabolic parameters, glucose, triglycerides and total cholesterol in male and females respectively, in comparison to their standard chow fed counterparts. Notably, HFD alone was sufficient to increase total BAL leukocyte levels in both males and females. Induction of allergic pulmonary inflammatory response revealed that HFD enhanced antigen-induced accumulation of leukocytes in BAL of males which was a predominantly caused by increased eosinophil numbers. In contrast, antigen challenge did not increase BAL leukocyte levels in HFD-fed female mice. However, examination of leukocyte infiltrate in lung tissue demonstrated a completely different picture. HFD alone did not alter total BAL leukocyte levels in both males and females. Furthermore, HFD had no impact on antigen-induced lung tissue leukocyte counts in male mice. However, HFD alone was sufficient to enhance lung tissue leukocyte counts in female mice with macrophage, neutrophil and eosinophil counts significantly higher than the control chow diet feed female mice. HFD did not alter antigen-induced pulmonary inflammation of the lung tissue in female mice. With respect to pulmonary tissue remodelling, HFD did not impact antigen-induced collagen deposition or presence of pro-fibrotic BAL TGFβ1 levels in male mice; however, HFD exacerbated antigen-induced collagen deposition and pro-fibrotic BAL TGFβ1 levels in female mice.

Collectively these studies identify a complex interaction between sex and weight gain in the progression of allergic asthma in mice with females developing airway remodelling at a much earlier stage than males. Additional studies will be required to tease apart the individual contribution and the complex interaction between these pathways in the exacerbation of the allergic phenotypes and how life events, (e.g. pregnancy) can alter disease phenotypes. Despite this, these studies contribute to a better understanding of the clinical differences in the development and severity of allergic asthma observed between men and women of reproductive age.

New model of eosinophilic oesophagitis

While there has been increased understanding of the underlying immunological processes that drive the immunopathophysiology of EoE [45], a limitation has been the lack of suitable models of EoE. With a vast array of readily available immunological tools coupled with excellent understanding of immunological systems, the mouse has been the standard model of investigation for immunopathology of disease processes. However, the oesophagus of the mouse is anatomically different to human (keratinized versus non-keratinized) which greatly limits interpretation and translatability of studies derived from using this animal model system [46]. Plundrich and colleagues examined whether food (hen egg white protein) induced allergy in young pigs induced an EoE like phenotype [47]. The advantage of the pig system is that pig oesophagus is anatomically similar to humans, non-keratinized and display oesophageal submucosal glands and is similar in size to the human oesophagus allowing for the use of endoscopy [48]. The authors showed that challenge of hen egg white protein (HEWP)-sensitized pigs by gavage with HEWP induced clinical signs of food allergy including diarrhoea, emesis, and skin rash. Endoscopic analyses revealed clinical signs of oesophagitis including oedema, granularity, furrowing, while histological assessment showed evidence of oedema, immune cell infiltration including a dominant eosinophilic infiltrate, and oesophageal epithelial remodelling including basal zone hyperplasia, dilated intercellular spaces. Limitations of this model was the authors did not observe large numbers of eosinophils in the intraepithelial region nor layering of eosinophils which is often used observed in humans.

Collectively these studies suggest that the pig may be an effective model to study immunological processes that drive some EoE-associated oesophageal epithelia remodelling features and to study the role of the underlying oesophageal inflammatory component in EoE with endoscopic features.

Basic mechanisms underpinning allergy

Mast cells

Tissue resident mast cells are key mediators of inflammation, with their rapid degranulation and release of proinflammatory molecules upon activation being central to many of the hallmark pathological features of allergic diseases [49,50]. Recent studies have described populations of mast cell precursors in the circulation [51], which are recruited to the airways upon allergen challenge [52]. Salomonsson and colleagues, have now investigated whether these circulating mast cell progenitors are linked with the severity of atopic asthma [53]. Studying 38 asthmatics and 29 controls, the authors found that increased circulating mast cell progenitors were associated with reduced lung function, indicating these cells might play an active role in the severity of asthma and strengthening their potential use as biomarkers of disease [53].

The impact of mast cells certainly goes beyond asthma, with medication allergies, for example against antibiotics or chemotherapies, posing threats to both appropriate clinical treatment and inducing severe adverse reactions.

In a study by Killoran and colleagues, the authors used a mouse model to investigate the potential of rush desensitization, a process where short-term exposure to an allergen can provide a window of tolerance, to protect against diverse allergens. Although rush desensitization with a single model allergen resulted in sustained subclinical degranulation of mast cells, mice were then also protected against a second, unrelated, model allergen [54]. These data, although needing further investigation, highlight a potentially valuable future intervention approach whereby poly-sensitized allergic individuals might be afforded a window of tolerance against multiple allergens.

Airway remodelling in asthma

Airway remodelling in asthma is aligned with disease severity, and in part, is linked with the responsiveness of airway epithelial cells to allergen exposure [55]. Through the use of both an *in vitro* human epithelial cell culture system and a mouse model, Labram and colleagues reported that *Aspergillus fumigatus* antigens led to endothelin-1 production, which was associated with extensive inflammation and tissue remodelling [56]. Administration of an endothelin-1 antagonist protected against airway wall remodelling [56], highlighting endothelin-1 as a key player in this disease process, and potentially, an excellent therapeutic target.

Preventing the development of asthma and airway remodelling would ultimately be the most impactful approach. The cytokine, IL-17, is a potent driver of neutrophil recruitment and plays a complex role in both initiation and suppressing type 2 inflammatory responses, such as those seen in allergic asthma [57]. A study by de-Oliverira and colleagues investigated the rules governing the localisation of IL-17-producing gamma-delta T cells in the airways of mice [58]. Specifically, the authors found that offspring of mice that had been immunized with an antigen, and subsequently developed a specific IgG response, exhibited a reduced number of IL-17 producing gamma-delta cells in the airways [58]. The mechanism was linked to the maternal IgG binding the gamma-delta T cells, and the phenomenon was evident in both mice and human cells [58]. This previously unrecognized role of IgG in modulating gamma-delta cell IL-17-producing cells could lead to both preventative strategies (via maternal tolerance) and new IgG-based therapeutics.

Clinical Mechanisms

Mediators driving granulocytes function in inflamed airways

Several articles published on clinical mechanisms emphasized the cellular mechanisms of disease. Two of these focused on mediators that may impact the recruitment or function of granulocytes in the inflamed airways. In addition to basophils, both neutrophils and eosinophils are implicated in the pathogenesis of chronic inflammatory processes in the upper and lower airways. Cao et al presented evidence to support a role for LL-37, in promoting the formation of neutrophil extracellular traps (NETs) in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) [59]. LL37, a cathelicidin-derived anti-microbial peptide, is produced by NETs and was already known to aid in NET formation as an innate defence mechanism. The present report advances knowledge, by linking LL-37 to NET formation in CRSwNP, and supporting a pathogenic role for extracellular traps beyond asthma, possibly influenced by the airway microbiome or else microbial exposures.

Other work in the journal added another mediator to the list of those implicated in eosinophil recruitment to the airways. This area of study continues to be a major focus in the field, since it may inform targeted interventions in a variety of eosinophilic diseases [60].

In their report, Kobayashi and colleagues found that the chemokine macrophage inflammatory protein 1β/CCL4 was chemotactic for eosinophils *in vitro*, and that neutralization of CCL4 attenuated infiltration of eosinophils into the airways in an OVA challenge mouse model [61].

Other work examined eosinophils in order to address mechanisms of glucocorticoid (GC) resistance in non-myeloid hypereosinophilic syndromes (HES). That report found no differences in GC receptor isoforms that might explain GC resistance based on a comparison of mRNA expression levels in eosinophils from GC-resistant versus GC-sensitive patients with HES [62]. However, elevated levels of serum IL-5 in a subset of patients who were GC-resistant raised an alternative theory wherein the actions of IL-5 on eosinophils may serve to counter GC-mediated eosinophil apoptosis. Such variability in IL-5 levels across patients warrants further work to identify additional mechanisms of GC resistance.

Single cell approaches to understanding allergy

The variability in cellular responses in allergic patients poses challenges to understanding immune mechanisms of disease. With this in mind, there has been a shift towards experimental platforms that enable the discovery of new immunophenotypes based on the ability to collect large amounts of data at the single-cell level.

One such method, high-dimensional mass cytometry, was used to identify B cell signatures linked to red meat allergy [63]. The hallmark of this increasingly recognized disease is the production of IgE to an oligosaccharide ("alpha-gal") found in the tissues of all non-primate animals [64]. In their work in the journal, Cox and colleagues identified atypical B cell types in meat allergic patients that were present in the naïve B cell population, as opposed to the isotype-switched memory subset. These B cells secreted IgE specific for alpha-gal when activated *in vitro* and displayed the chemokine receptors CXCR4 and CCR6 on their surface, which might indicate gut-homing. Further work is needed to understand the mode of differentiation of these B cells into IgE-secreting cells, and whether or not the production of IgE to alpha-gal requires T cell help, as is the case for protein allergens.

Advances in food allergy

Three opinion articles were also published related to food allergy. These focused on the need for psychological services for food allergy in the UK [65]; identifying and managing patients at risk of severe allergic reactions to food [66]; and evidenced-based approaches to the application of

precautionary allergen labelling [67]. The latter two papers were the result of reports from workshops related to the Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM) held in 2016 and 2018. These reports outlined the work the iFAAM project has done in each area, including the development of a Food Allergy Severity Score and a tiered risk approach for allergen labelling designed to better inform the allergic consumer.

Mechanisms underlying hereditary angioedema and atopic dermatitis

Finally, two articles focused on mechanisms of diseases with skin manifestations. The first one probed the genetic basis of hereditary angioedema (HAE) arising from mutation of the angiopoietin-1 gene (*ANGPT1*), a phenomenon that was only recently described [68]. The authors presented evidence to support the view that heterozygous forms of the A119S mutation impact the endothelial barrier through loss of function of angiopoietin arising from haploinsufficiency [69]. Using *in vitro* assays, data was presented to support the inability for the heterozygous state to counteract the damaging effects of critical mediators of HAE, bradykinin and VEGF, on integrity of the epithelial barrier.

The other paper related to skin explored how the skin microbiome is influenced by the alpine climate in patients with atopic dermatitis (AD) [70]. This paper built on earlier reports describing the benefits of an alpine climate on skin condition. Notable findings included increased microbial diversity in both lesional and non-lesional skin, and a decrease in the load of *S. aureus* in lesional skin of patients in an alpine climate versus a moderate maritime climate. Whether such differences reflect the presence of decreased environmental triggers, changes in the immune response, or both, remain important questions.

Allergens

The increasing number of peanut and tree nut allergen components

A number of articles in 2019 focused on peanut allergen components. Hazebrouck and colleagues looked at the cross reactivity between peanut 2S-albumins Ara h2 and Ara h 6 [71]. They identified low rates of cross-reactivity but, importantly, low affinity cross-reactivity appeared to be leading to diagnostic inaccuracy due to these antibodies being unable to trigger mast cell degranulation. They suggested that testing IgE binding to a mixture of 2S-albumins might be a more efficient diagnostic approach. The storage 2S albumins are also important allergens in the tree nuts that may be responsible for allergic symptoms to more than one type. For example, Bueno-Diaz and colleagues demonstrated that allergic sensitisation to the 2S albumins (Pis v 1 and Ana o 3)

results in allergy to pistachio and/or cashew but hot the other nuts [72]. Finally back to peanut with Ara h 7 isoforms. Three have been identified with differing potential to degranulate basophils in an *ex vivo* system. Ehlers and colleagues found that they have similar linear epitopes and so they must therefore differ in terms of their conformational epitopes [73].

Tree pollen allergens

There are a number of variants of the birch pollen Bet v 1 component which may have therapeutic implications. Von Loetzen and colleagues compared the serum IgE and IgG binding to these variants [74]. They found eight recombinant Bet v 1 variants that showed similar specific IgE binding to Bet v 1. A number of papers focused on Pru p 7 sensitisation. Klingebiel and colleagues found a Pru p 7 related pollen protein in three Cupressaceae species [75]. They presented data suggesting that primary sensitisation to the tree pollen was leading to symptoms of allergy in 51 peach allergy individuals. Their paper lead to some interesting correspondence [76,77].

Other aeroallergens and food allergens

Allergy healthcare professionals are often asked whether there are “hypoallergenic” animals. Victor and colleagues looked at levels of horse allergen in the dander and saliva of 10 different breeds [78]. There was a lot of variability but both between and within breeds. Much higher levels were found in stallions than mares and geldings, independent of breed. So there is not a “hypoallergenic” horse.

In other papers from 2019, Pulsawat and colleagues demonstrated that the house dust mite Der p5 allergen can trigger an allergic reaction via a TLR-2 dependent mechanism [79], Yang and colleagues identified crab IgE epitopes [80], Safi and colleagues demonstrated that non-specific lipid-transfer protein Tri tu 14 is a risk factor for wheat exercise dependent allergy [80] and Kern and colleagues mapped the soy bean IgE epitopes [81].

Conclusions

The year 2019 provided further advances in the mechanism underlying allergy. In the related paper we look at more clinical aspects [82]. We look forward to publishing more interesting observations in 2021.

References

1. Pabst O, Mowat AM. Oral tolerance to food protein. Mucosal Immunol 2012; 5:232-9.
2. Commins SP. Mechanisms of Oral Tolerance. Pediatr Clin North Am 2015; 62:1523-9.
3. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol 2016; 16:751-65.
4. Esterhazy D, Canesso MCC, Mesin L, Muller PA, de Castro TBR, Lockhart A, et al. Compartmentalized gut lymph node drainage dictates adaptive immune responses. Nature 2019; 569:126-30.
5. Coombes JL, Maloy KJ. Control of intestinal homeostasis by regulatory T cells and dendritic cells. Semin Immunol 2007; 19:116-26.
6. Sun CM, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. J Exp Med 2007; 204:1775-85.
7. Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. J Allergy Clin Immunol 2016; 137:984-97.
8. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun CM, Belkaid Y, et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. J Exp Med 2007; 204:1757-64.
9. Hadis U, Wahl B, Schulz O, Hardtke-Wolenski M, Schippers A, Wagner N, et al. Intestinal tolerance requires gut homing and expansion of FoxP3+ regulatory T cells in the lamina propria. Immunity 2011; 34:237-46.
10. Mortha A, Chudnovskiy A, Hashimoto D, Bogunovic M, Spencer SP, Belkaid Y, et al. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. Science 2014; 343:1249288.
11. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, et al. Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A 2014; 111:13145-50.
12. Satitsuksanoa P, Jansen K, Globinska A, van de Veen W, Akdis M. Regulatory Immune Mechanisms in Tolerance to Food Allergy. Front Immunol 2018; 9:2939.

13. Khodoun MV, Tomar S, Tocker JE, Wang YH, Finkelman FD. Prevention of food allergy development and suppression of established food allergy by neutralization of thymic stromal lymphopoietin, IL-25, and IL-33. J Allergy Clin Immunol 2018; 141:171-9 e1.
14. Li J, Wang Y, Tang L, de Villiers WJ, Cohen D, Woodward J, et al. Dietary medium-chain triglycerides promote oral allergic sensitization and orally induced anaphylaxis to peanut protein in mice. J Allergy Clin Immunol 2013; 131:442-50.
15. Xie J, Lotoski LC, Chooniedass R, Su RC, Simons FE, Liem J, et al. Elevated antigen-driven IL-9 responses are prominent in peanut allergic humans. PLoS One 2012; 7:e45377.
16. Brough HA, Cousins DJ, Munteanu A, Wong YF, Sudra A, Makinson K, et al. IL-9 is a key component of memory TH cell peanut-specific responses from children with peanut allergy. J Allergy Clin Immunol 2014; 134:1329-38.e10.
17. Blazquez AB, Berin MC. Gastrointestinal dendritic cells promote Th2 skewing via OX40L. J Immunol 2008; 180:4441-50.
18. He SH, Liu ZQ, Chen X, Song CH, Zhou LF, Ma WJ, et al. IL-9(+) IL-10(+) T cells link immediate allergic response to late phase reaction. Clin Exp Immunol 2011; 165:29-37.
19. Hoh RA, Joshi SA, Lee JY, Martin BA, Varma S, Kwok S, et al. Origins and clonal convergence of gastrointestinal IgE(+) B cells in human peanut allergy. Sci Immunol 2020; 5.
20. Gornati L, Zanoni I, Granucci F. Dendritic Cells in the Cross Hair for the Generation of Tailored Vaccines. Front Immunol 2018; 9:1484.
21. Lahoud MH, Ahmet F, Zhang JG, Meuter S, Policheni AN, Kitsoulis S, et al. DEC-205 is a cell surface receptor for CpG oligonucleotides. Proc Natl Acad Sci U S A 2012; 109:16270-5.
22. Jiang W, Swiggard WJ, Heufler C, Peng M, Mirza A, Steinman RM, et al. The receptor DEC-205 expressed by dendritic cells and thymic epithelial cells is involved in antigen processing. Nature 1995; 375:151-5.
23. Spiering R, Margry B, Keijzer C, Petzold C, Hoek A, Wagenaar-Hilbers J, et al. DEC205+ Dendritic Cell-Targeted Tolerogenic Vaccination Promotes Immune Tolerance in Experimental Autoimmune Arthritis. J Immunol 2015; 194:4804-13.
24. Xu LZ, Xie RD, Xie H, Ju JY, Fu XY, Di DL, et al. Chimeric specific antigen epitope-carrying dendritic cells induce interleukin-17(+) regulatory T cells to suppress food allergy. Clin Exp Allergy 2020; 50:231-43.
25. Charles-Messance H, Mitchelson KAJ, De Marco Castro E, Sheedy FJ, Roche HM. Regulating metabolic inflammation by nutritional modulation. J Allergy Clin Immunol 2020.

26. Christ A, Latz E. The Western lifestyle has lasting effects on metaflammation. Nat Rev Immunol 2019; 19:267-8.
27. Christ A, Lauterbach M, Latz E. Western Diet and the Immune System: An Inflammatory Connection. Immunity 2019; 51:794-811.
28. Brumpton BM, Camargo CA, Jr., Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. Eur Respir J 2013; 42:1495-502.
29. Pite H, Aguiar L, Morello J, Monteiro EC, Alves AC, Bourbon M, et al. Metabolic Dysfunction and Asthma: Current Perspectives. J Asthma Allergy 2020; 13:237-47.
30. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol 2018; 141:1169-79.
31. Wang X, Wang Y, Antony V, Sun H, Liang G. Metabolism-Associated Molecular Patterns (MAMPs). Trends Endocrinol Metab 2020.
32. McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. Immunity 2014; 41:36-48.
33. Silva F, Oliveira EE, Ambrósio MGE, Ayupe MC, Souza VP, Gameiro J, et al. High-fat diet-induced obesity worsens TH2 immune response and immunopathologic characteristics in murine model of eosinophilic oesophagitis. Clin Exp Allergy 2020; 50:244-55.
34. Protheroe C, Woodruff SA, de Petris G, Mukkada V, Ochkur SI, Janarthanan S, et al. A novel histologic scoring system to evaluate mucosal biopsies from patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2009; 7:749-55 e11.
35. Schröder T, Wiese AV, Ender F, Quell KM, Vollbrandt T, Duhn J, et al. Short-term high-fat diet feeding protects from the development of experimental allergic asthma in mice. Clin Exp Allergy 2019; 49:1245-57.
36. Yung JA, Fuseini H, Newcomb DC. Hormones, sex, and asthma. Ann Allergy Asthma Immunol 2018; 120:488-94.
37. Wijga A, Tabak C, Postma DS, Kerkhof M, Wieringa MH, Hoekstra MO, et al. Sex differences in asthma during the first 8 years of life: the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. J Allergy Clin Immunol 2011; 127:275-7.
38. Vink NM, Postma DS, Schouten JP, Rosmalen JG, Boezen HM. Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. J Allergy Clin Immunol 2010; 126:498-504.e1-6.

39. Castro-Rodriguez JA. A new childhood asthma phenotype: obese with early menarche. Paediatr Respir Rev 2016; 18:85-9.
40. Kovats S. Estrogen receptors regulate an inflammatory pathway of dendritic cell differentiation: mechanisms and implications for immunity. Horm Behav 2012; 62:254-62.
41. Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest 2002; 109:1625-33.
42. Lauzon-Joset JF, Mincham KT, Abad AP, Short BP, Holt PG, Strickland DH, et al. Oestrogen amplifies pre-existing atopy-associated Th2 bias in an experimental asthma model. Clin Exp Allergy 2020; 50:391-400.
43. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007; 175:661-6.
44. e-Lacerda RR, Anhê GF, Page CP, Riffo-Vasquez Y. Sex differences in the influence of obesity on a murine model of allergic lung inflammation. Clin Exp Allergy 2020; 50:256-66.
45. Davis BP. Pathophysiology of Eosinophilic Esophagitis. Clin Rev Allergy Immunol 2018.
46. Wang DH. The Esophageal Squamous Epithelial Cell-Still a Reasonable Candidate for the Barrett's Esophagus Cell of Origin? Cell Mol Gastroenterol Hepatol 2017; 4:157-60.
47. Plundrich NJ, Smith AR, Borst LB, Snider DB, Käser T, Dellon ES, et al. Oesophageal eosinophilia accompanies food allergy to hen egg white protein in young pigs. Clin Exp Allergy 2020; 50:95-104.
48. Krüger L, Gonzalez LM, Pridgen TA, McCall SJ, von Furstenberg RJ, Harnden I, et al. Ductular and proliferative response of esophageal submucosal glands in a porcine model of esophageal injury and repair. Am J Physiol Gastrointest Liver Physiol 2017; 313:G180-g91.
49. Bradding P, Walls AF, Holgate ST. The role of the mast cell in the pathophysiology of asthma. Journal of Allergy and Clinical Immunology. 2006;117(6):1277-84.
50. Reber LL, Sibilano R, Mukai K, Galli SJ. Potential effector and immunoregulatory functions of mast cells in mucosal immunity. Mucosal immunology. 2015 May;8(3):444-63.
51. Dahlin JS, Malinovschi A, Öhrvik H, Sandelin M, Janson C, Alving K, Hallgren J. Lin− CD34hi CD117int/hi FcεRI+ cells in human blood constitute a rare population of mast cell progenitors. Blood, The Journal of the American Society of Hematology. 2016;127(4):383-91.
52. Hallgren J, Jones TG, Abonia JP, Xing W, Humbles A, Austen KF, Gurish MF. Pulmonary CXCR2 regulates VCAM-1 and antigen-induced recruitment of mast cell progenitors. Proceedings of the National Academy of Sciences. 2007;104(51):20478-83.

53. Salomonsson M, Malinovschi A, Kalm-Stephens P, Dahlin JS, Janson C, Alving K, Hallgren J. Circulating mast cell progenitors correlate with reduced lung function in allergic asthma. Clinical & Experimental Allergy. 2019;49(6):874-82.
54. Killoran KE, Kropp LE, Lindrose AR, Curtis HE, Cook D, Mitre E. Rush desensitization with a single antigen induces subclinical activation of mast cells and protects against bystander challenge in dually sensitized mice. Clinical & Experimental Allergy. 2019;49(4):484-94.
55. Saglani S, Lloyd CM. Novel concepts in airway inflammation and remodelling in asthma. European Respiratory Journal. 2015;46(6):1796-804.
56. Labram B, Namvar S, Hussell T, Herrick SE. Endothelin-1 mediates Aspergillus fumigatus-induced airway inflammation and remodelling. Clinical & Experimental Allergy. 2019 Jun;49(6):861-73.
57. Ajendra J, Chenery AL, Parkinson JE, Chan BH, Pearson S, Colombo SA, Boon L, Grencis RK, Sutherland TE, Allen JE. IL-17A both initiates, via IFNγ suppression, and limits the pulmonary type-2 immune response to nematode infection. Mucosal Immunology. 2020; 13: 958–968.
58. de-Oliveira MG, Lira AA, Sgnotto FR, Inoue AH, Santos LS, Nakamatsu BY, Duarte AJ, Leite-de-Moraes M, Victor JR. Maternal IgG impairs the maturation of offspring intrathymic IL-17-producing γδT cells: Implications for murine and human allergies. Clinical & Experimental Allergy. 2019;49(7):1000-12.
59. Cao Y, Chen F, Sun Y, et al. LL-37 promotes neutrophil extracellular trap formation in chronic rhinosinusitis with nasal polyps. *Clin Exp Allergy*. 2019;49(7):990-999.
60. Klion AD, Rothenberg ME. Advances in eosinophilic diseases in 2018. *J Allergy Clin Immunol*. 2019;144(6):1490-1494.
61. Kobayashi Y, Konno Y, Kanda A, et al. Critical role of CCL4 in eosinophil recruitment into the airway. *Clin Exp Allergy*. 2019;49(6):853-860.
62. Stokes K, Yoon P, Makiya M, et al. Mechanisms of glucocorticoid resistance in hypereosinophilic syndromes. *Clin Exp Allergy*. 2019;49(12):1598-1604.
63. Cox KM, Commins SP, Capaldo BJ, et al. An integrated framework using high-dimensional mass cytometry and fluorescent flow cytometry identifies discrete B cell subsets in patients with red meat allergy. *Clin Exp Allergy*. 2019;49(5):615-625.
64. Platts-Mills TAE, Commins SP, Biedermann T, et al. On the cause and consequences of IgE to galactose-α-1,3-galactose: A report from the National Institute of Allergy and Infectious Diseases Workshop on Understanding IgE-Mediated Mammalian Meat Allergy. *J Allergy Clin Immunol*. 2020;145(4):1061-1071.

65. Knibb R, Halsey M, James P, du Toit G, Young J. Psychological services for food allergy: The unmet need for patients and families in the United Kingdom. *Clin Exp Allergy*. 2019;49(11):1390-1394.
66. Roberts G, Allen K, Ballmer-Weber B, et al. Identifying and managing patients at risk of severe allergic reactions to food: Report from two iFAAM workshops. *Clin Exp Allergy*. 2019;49(12):1558-1566.
67. DunnGalvin A, Roberts G, Schnadt S, et al. Evidence-based approaches to the application of precautionary allergen labelling: Report from two iFAAM workshops. *Clin Exp Allergy*. 2019;49(9):1191-1200.
68. Bafunno V, Firinu D, D'Apolito M, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol*. 2018;141(3):1009-1017.
69. d'Apolito M, Santacroce R, Colia AL, Cordisco G, Maffione AB, Margaglione M. Angiopoietin-1 haploinsufficiency affects the endothelial barrier and causes hereditary angioedema. *Clin Exp Allergy*. 2019;49(5):626-635.
70. van Mierlo MMF, Totté JEE, Fieten KB, et al. The influence of treatment in alpine and moderate maritime climate on the composition of the skin microbiome in patients with difficult to treat atopic dermatitis. *Clin Exp Allergy*. 2019;49(11):1437-1445.
71. Hazebrouck S, Guillon B, Paty E, Dreskin SC, Adel-Patient K, Bernard H. Variable IgE cross-reactivity between peanut 2S-albumins: The case for measuring IgE to both Ara h 2 and Ara h 6. Clinical & Experimental Allergy. 2019;49(8):1107-15.
72. Bueno-Díaz C, Martín-Pedraza L, Benedé S, Haroun-Díaz E, de Las Heras M, Batanero E, Cuesta-Herranz J, Villalba M. Seed storage 2S albumins are predictive indicators of exclusive Anacardiaceae cross-reactivity. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2019;49(4):545.
73. Ehlers AM, Klinge M, Suer W, Weimann Y, Knulst AC, Besa F, Le TM, Otten HG. Ara h 7 isoforms share many linear epitopes: Are 3D epitopes crucial to elucidate divergent abilities?. Clinical & Experimental Allergy. 2019;49(11):1512-9.
74. Seutter von Loetzen C, Reuter A, Spiric J, Schulenborg T, Bellinghausen I, Völker E, Vogel L, Rösch P, Schiller D. Quality and potency profile of eight recombinant isoallergens, largely mimicking total Bet v 1-specific IgE binding of birch pollen. Clinical & Experimental Allergy. 2019;49(5):712-23.

75. Klingebiel C, Chantran Y, Arif-Lusson R, Ehrenberg AE, Östling J, Poisson A, Liabeuf V, Agabriel C, Birnbaum J, Porri F, Sarrat A. Pru p 7 sensitization is a predominant cause of severe, cypress pollen-associated peach allergy. Clinical & Experimental Allergy. 2019;49(4):526-36.
76. Poncet P, Aizawa T, Sénéchal H. The subtype of Cupressaceae pollinosis associated with Pru p 7 sensitization is characterized by a sensitization to a cross-reactive gibberellin-regulated protein in cypress pollen: BP 14. Clinical & Experimental Allergy. 2019;49(8):1163-6.
77. Klingebiel C, Chantran Y, Demoly P, Caimmi D, Birnbaum J, Apoil PA, Caimmi DP, Gouitaa M, Cabon-boudard I, Guez S, Bourrain JL. Response to commentary by Drs. Poncet and Sénéchal. Clinical & Experimental Allergy. 2019;49(8): 1167-1168.
78. Victor S, Binnmyr J, Lampa E, Rask-Andersen A, Elfman L. Levels of horse allergen Equ c 4 in dander and saliva from ten horse breeds. Clinical & Experimental Allergy. 2019;49(5):701-11.
79. Pulsawat P, Soongrung T, Satitsuksanoa P, Le Mignon M, Khemili S, Gilis D, Nony E, Kennedy MW, Jacquet A. The house dust mite allergen Der p 5 binds lipid ligands and stimulates airway epithelial cells through a TLR2-dependent pathway. Clinical & Experimental Allergy. 2019;49(3):378-90.
80. Yang Y, Hu MJ, Jin TC, Zhang YX, Liu GY, Li YB, Zhang ML, Cao MJ, Su WJ, Liu GM. A comprehensive analysis of the allergenicity and IgE epitopes of myosinogen allergens in Scylla paramamosain. Clinical & Experimental Allergy. 2019;49(1):108-19.
80. Safi H, Wangorsch A, Lidholm J, Brini F, Spiric J, Rihs HP, et al. Identification and molecular characterization of allergenic non-specific lipid-transfer protein from durum wheat (Triticum turgidum). Clinical & Experimental Allergy. 2019;49(1):120-9.
81. Kern K, Havenith H, Delaroque N, Rautenberger P, Lehmann J, Fischer M, et al. The immunome of soy bean allergy: Comprehensive identification and characterization of epitopes. Clinical & Experimental Allergy. 2019;49(2):239-51.
82. Roberts G, Almqvist C, Boyle R, Crane J, Hogan S, Marsland B et al. Developments allergy in 2019 through the eyes of Clinical and Experimental Allergy, Part II clinical allergy. Clinical and Experimental Allergy 2020; 50(12): XXX-XXX.