Recent Advances in Experimental Allergy

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Abstract

Atopic disorders are on the rise and pose a great burden on society. A better understanding of the underlying mechanisms is required for the development of improved or novel therapeutic strategies. Here we aim to highlight recent advances in experimental allergy, with a particular focus on proposed treatment alternatives for airway disorders, atopic dermatitis, and food allergy. Furthermore, we discuss recent work focusing on molecular and cellular mechanisms that might offer candidates for future preventive or therapeutic intervention.

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Introduction

Atopy refers to the tendency to develop allergic symptoms that are characterized by or associated with heightened immune responses, eventually associated with the production of immunoglobulin E (IgE) antibodies in response to common environmental allergens [1]. Atopic diseases include the clinical entities of asthma, dermatitis, and rhinitis as well as food allergy. In all cases, the preva-

lence of these diseases is on the increase. While during the last decades this was typically observed in developed countries, numbers are also increasing in the developing world [2–5].

Allergic dermatitis, asthma, and rhinitis are sequentially and causally related via a phenomenon described as the “atopic march” [1, 6]. The progression of the atopic march starts with the development of atopic dermatitis (AD), and subsequently allergic asthma and allergic rhinitis (AR) manifest. Frequently, sensitization and food allergy, mostly against cow’s milk and eggs, also run concurrently with early childhood AD. However, the role that food allergy plays in the atopic march remains poorly understood, as instances of food intake containing the relevant allergens do not exacerbate AD. Furthermore, the progression and sequence of events of the atopic march are highly variable between individuals and populations groups. For example, one of the three pathologies may not present at all, or allergic asthma may present before AD or at the same time [1, 6].

A significant source of allergens for the sensitization of atopic diseases are house dust mites (HDM), which are small arthropods that can be ubiquitously found in residences [7, 8]. HDM are therefore carefully considered with respect to the management and treatment of atopic

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diseases [9, 10]. Moreover, HDM extracts are frequently used in experimental models in research focused on allergy and atopy [11, 12].

Worldwide, the prevalence of AD has been reported to be as high as 20% in children and 3% in adults [3]. AR can be subdivided into seasonal AR (SAR) and perennial AR (PAR), depending on the length and distribution of symptoms throughout the year. In the USA, AR affects between 20 and 40 million people, of which approximately 20% are SAR, 40% PAR, and the remaining 40% reporting mix symptoms [5]. Backman et al. [2] report that in Europe allergic asthma increased from 5% in 1996 to 6% in 2006 and further to 7.3% in 2016. The food allergy statistics are in similar ranges, with global prevalence being estimated as high as 10% in some countries [13].

Given that increasing prevalence of atopic diseases, as well as food allergy, are on the increase, present a major societal burden, and negatively affect life quality of patients, it is vital that alternative treatment options be developed. The underlying mechanisms also remain to be elucidated. Therefore, continued scientific investigation is of utmost importance. Here we highlight recent advances in experimental allergy pertaining to novel therapeutic options and cellular and molecular mechanisms.

Asthma

Asthma is a complex disease in which both environmental (allergens) and genetic factors play a role in predisposition and causality. The most common long-term treatment for asthma is inhaled corticosteroids [14]. Depending on the dose and duration of use, corticosteroids can result in mild to severe side effects. In recent years, alternative therapies have come under the spotlight [15].

Investigation into the molecular mechanisms underlying allergic asthma is an ongoing endeavor of the research community. Kim et al. [16] investigated the activation mechanism of nuclear factor (NF)- κ B in allergic airway inflammation in two (active and passive) ovalbumin (OVA)-induced asthma mouse models. Several players were scrutinized in the study. Reactive oxygen species (ROS), known to be involved in an activation loop of NF- κ B, were investigated using NADPH oxidase (NOX) 2 and NOX4 knockout (KO) mice as these enzymes are required for ROS production [17]. CK2 α is a serine/threonine kinase that is upstream of NF- κ B [18], which was also assessed in this study. The CK2 α inhibitor 4,5,6,7-tetrabromobenzotriazole and the antioxidant N-acetyl-L-cysteine decreased CK2 α phosphorylation and overall

protein expression in airway epithelium. Nuclear translocation of NF- κ B subunits p50 and p65 was also inhibited upon these interventions. In line with these results, the authors report that CK2 α phosphorylation and protein expression were significantly decreased in the NOX2 KO mice. In the passive OVA-induced model, anti-OVA IgG activated NF- κ B and CK2 α , while sensitization with anti-OVA IgE did not. This suggests that signaling via the Fc γ receptor, ROS, and CK2 α play critical roles in the induction of NF- κ B activation in airway epithelium in asthma [16].

Zhou et al. [19] investigated the role of mouse Fc γ RIIIA and Fc γ RIIB in an OVA-induced mouse asthma model. Allergic asthma was induced using OVA in wild-type, Fc γ RIIIA, and Fc γ RIIB KO mice, respectively. An increase in serum OVA-specific IgG and IgE was observed in the Fc γ RIIIA KO animals, while no evidence of aggravated lung inflammation and associated pathology was detected. All local and systemic parameters of asthma pathology assessed in the Fc γ RIIB KO animals confirmed the previously reported immune inhibitory role of Fc γ RIIB in mice. In an ex vivo arm of the study, the expression levels of Fc γ RIIIA, Fc γ RIIB, and IgE were measured in human asthma patients. It was found that Fc γ RIIB negatively correlated with serum IgE; however, this was not the case for Fc γ RIIIA [19]. Interestingly, unlike previously published work [20–22], the work of Zhou et al. [19] did not support the positive immune regulatory roles of mouse Fc γ RIIIA.

Initially, the anti-inflammatory properties of secretoglobulin (SCGB) 3A2 was discovered in an OVA-induced allergic airway inflammation mouse model. SCGB 3A2 is a small molecular weight cytokine-like, secreted protein, which was recently shown to be enriched in the murine lung and possessing a variety of pharmacological activities [23]. Yoneda et al. [24] sought to validate the previously published anti-inflammatory actions of SCGB 3A2 in an HDM-induced allergic airway inflammation model using Scgb3a2 KO mice. More severe airway inflammation was observed in Scgb3a2 KO mice sensitized/challenged with HDM allergens. For molecular and cellular inflammatory mechanisms, endpoints measured were significantly higher in the HDM-induced Scgb3a2 KO mice when compared to the saline-treated control group. Of particular interest is that the mRNA levels of Ccr4 and Ccl17 levels were higher in HDM-treated lungs of Scgb3a2 KO animals when compared to saline-treated KO animals. This suggests a regulatory role of SCGB 3A2 in the CCR4-CCL17 pathway and confirms its anti-inflammatory mode of action [24].

Hagner et al. [25] assessed the efficacy of HDM-specific sublingual immunotherapy (SLIT) in an experimental mouse model of asthma, sensitized with HDM *Derma-tophagoides farinae* extract (DFE). SLIT was tested in both prophylactic and treatment settings. As a prophylaxis, SLIT reduced the number of eosinophils, which characterized the lung inflammation. Amelioration of airway hyperresponsiveness was also noted. In addition, significantly lower levels of IL-5 and IL-13 in restimulated mediastinal lymph node cells, indicative of prevention of local T-helper cell 2 (Th2) responses, were observed in SLIT-treated animals when compared to untreated controls. Interestingly, reduced numbers of CD4⁺CD8⁺ $\gamma\delta$ cells and an increase in CD8⁺CD25⁺IFN γ ⁺ T cells in the lungs of treated animals were also observed. In a treatment setting, similar attenuations of lung inflammatory responses were seen upon SLIT [25].

Hu et al. [26] investigated the role of Notch1 signaling as well as therapeutic capabilities of a γ -secretase inhibitor (GSI), which inhibits Notch 1. Notch 1 is thought to contribute to the development of asthma by contributing to the Th1/Th2 disbalance [27]. Given that glucocorticoids are the standard of care for allergic asthma, the effect of glucocorticoids on the Notch 1 pathway was also investigated in parallel. An OVA-induced asthma mouse model was used in this study and the animals were treated with either dexamethasone (DEX) or GSI alone, or in combination. Both monotreatment and double treatment significantly reduced asthmatic symptoms, such as airway inflammation infiltration, goblet cell metaplasia, and airway hyperresponsiveness, in OVA-sensitized mice. Expression levels of proinflammatory cytokines (IL-4 and IL-13) in the bronchoalveolar lavage fluid (BALF) of DEX- and GSI-treated animals were significantly decreased, while in contrast anti-inflammatory cytokines (IFN- γ and IL-2) were decreased. Decreased eosinophil and lymphocyte counts were also observed. DEX and/or GSI treatment reduced the expression of the Notch1/NICD1 pathway in the lung, particularly in CD4⁺ T cells. Evidence of the upregulation of Th1/Th2 ratios in lung tissues, via a reduction in GATA3 and an increase in T-bet, was observed [26].

Li et al. [28] developed a new antibody reactive against an epitope of the extracellular domain of Toll-like receptor 2 (TLR2), called TSP-2. Previously, therapies blocking TLR2 have been shown to be effective against allergies by modulating the immune system [29]. Li et al. [28] tested their newly developed anti-TLR2 antibody TSP-2 in the setting of allergic asthma using an OVA-induced mouse model. Upon TSP-2 treatment both dendritic cell (DC)

Fig. 1. The reported potential of an anti-TLR2 antibody, TSP-2, to influence T-helper cell 1 (Th1)/Th2 cytokine secretion. Similar to a TLR-2 ligand, this antibody favored the secretion of IFN- γ and IL-12 and reduced levels of IL-4 and IL-13 in an in vivo model of asthma [28]. Illustration by Aldona von Gunten.

maturation and lymphocyte proliferation were observed. Furthermore, TSP-2 influenced Th1/Th2 cytokine secretion. Similar to a TLR-2 ligand, this antibody favored the secretion of IFN- γ and IL-12, and reduced levels of IL-4 and IL-13 (Fig. 1). Cytokines were measured in both BALF and lung tissue of mice. In addition, airway hyperresponsiveness, lung inflammation, and OVA-specific

IgE levels were reduced in TSP-2 treated animals when compared to controls. The TSP-2 antibody also increased OVA-stimulated I-A, CD80, CD86, and MHC-II levels on bone marrow-derived DCs [28].

Sappanone A (SA) was also investigated as a novel/alternative treatment for allergic asthma in an OVA-induced asthma mouse model [30]. SA is an extract of *Caesalpinia sappan*, a flowering tree species of the legume family, which has been reported to have diverging pharmacological applications [31]. Liu et al. [30] observed that SA treatment significantly reduced the cell counts of inflammation-associated eosinophils, macrophages, neutrophils, and lymphocytes in BALF in a dose-dependent manner. Reduced levels IL-4, IL-5, and IL-13, as well as OVA-specific IgE, were also observed in SA-treated animals when compared to the sham-treated control group. Suppression of IFN- γ by OVA was reversed upon SA treatment, and airway inflammation and mucus hypersecretion were reduced. SA was also shown to positively regulate the expression of nuclear factor erythroid 2-related factor (Nrf2) and heme oxygenase-1 (HO-1), both of which play pivotal roles in antioxidant, anti-inflammatory, and cytoprotective pathways [32]. This highlights a possible mechanism for the therapeutic benefits observed of SA [30].

Atopic Dermatitis

AD is a disease characterized by inflammation of the skin that results in itchiness, redness, swelling, and thickening [1, 3]. The exact cause of AD is poorly understood, with both genetic and environmental factors being described as contributing factors. The conventional treatment is topical corticosteroids, which eventually may be ineffective or cause side effects [33].

Skin barrier dysfunction and pruritus (itchiness) are major characteristics of AD, and HDM allergens are thought to be major contributing factors [34]. HDM can also be a source of cysteine and serine proteases, which is thought to stimulate cytokine production in keratinocytes leading to pruritus and other AD-related symptoms [35]. Yamada and Matsumoto [36] investigated whether DFE can stimulate endothelin-1 (ET-1), matrix metalloproteinase (MMP)-2, and MMP-9 in primary human epidermal keratinocytes. Additionally, they assessed the effect of the pretreatment with protease inhibitors or proteinase-activated receptor-2 (PAR-2) on keratinocytes. DFE, as well as mite-derived serine proteases, stimulated ET-1 and MMP-9 (but not MMP-2) production in hu-

man epidermal keratinocytes in a dose- and time-dependent fashion. In line with these results, production of ET-1 and MMP-9 was suppressed by pretreatment of DFE with the serine protease inhibitor (which was not the case for the cysteine protease inhibitor) and the PAR-2 antagonist. This study suggests that HDM-derived serine proteases induce ET-1 and MMP-9 production in keratinocytes via PAR-2 activation [36].

Jin et al. [37] used an HDM-induced AD mouse model, in which DFE is used to induce AD on exposed skin of mouse ears by repeated applications, to investigate the anti-allergic effects of 1,2,4,5-tetramethoxybenzene (TMB). TMB can be isolated from the plant extract of the *Amomum xanthioides* species [38, 39]. A relative decrease of ear thickness in TMB-treated HDM-induced AD mice was observed when compared to the sham-treated control group. Histopathological analysis also showed less severe inflammation, with decreased infiltration of eosinophils and mast cells. Furthermore, lower serum levels of DFE-specific IgE, IgG2a, and histamine were observed in TMB-treated animals. Inhibition of the expansion of CD4⁺IFN- γ ⁺, CD4⁺IL-4⁺, and CD4⁺IL-17A⁺ lymphocytes in draining lymph nodes upon TMB treatment was also observed, as well as attenuation of Th2 cytokine expression in ear tissue. The authors also used the TNF- α - and IFN- γ -activated human keratinocyte cell line, HaCaT, in their study and found that TMB significantly reduced the expression of cytokines and chemokines. Furthermore, the authors proposed the mitogen-activated protein kinase (MAPK)-mediated mechanism for this observation. The in vitro results further highlight the potential of TMB as a therapeutic agent in AD [37].

Verbascoside, which naturally occurs in some flowering astrids, is also reported to have antimicrobial effects [40]. The potential therapeutic effect of verbascoside was assessed in a 2,4-dinitrochlorobenzene (DNCB) AD-like mouse model [41]. Skin lesion severity and scratching were decreased in the group receiving verbascoside treatment. In addition, decreased levels of DNCB-induced IgE and Th2 cytokines were observed systemically in verbascoside-treated animals. Furthermore, verbascoside decreased the mRNA expression levels of proinflammatory cytokines TNF- α , IL-6, and IL-4. Li et al. [41] also tested verbascoside using a human monocyte THP-1 cell line model and found that DNCB-induced upregulation of surface CD86 and CD54 was reduced, as well as TNF- α and IL-6 secretion. The activation of the NF- κ B pathway was also observed upon verbascoside treatment in vitro.

In recent years, alternative treatments for AD have been investigated. Two promising agents, used in tradi-

tional Chinese medicine (TCM), have shown interesting results. Kim et al. [42] investigated the potential of *Canavalia gladiata*, commonly known as sword bean, in treating AD. *C. gladiata* is commonly used in TCM as an anti-inflammatory agent; however, its use is limited by the fact that it contains potentially allergenic substances [43, 44]. Kim et al. [42] used the strategy of fermenting *C. gladiata* with the fungus *Aspergillus oryzae* in an attempt to mitigate potential adverse effects. An AD NC/Nga mouse model was used. It was reported that mice that received fermented *C. gladiata* as a dietary supplement exhibited alleviated macroscopic AD symptoms and scratching, when compared to the untreated control group. Treatment with fermented *C. gladiata* increased AD-specific IgE and histamine via a mechanism which improved the balance of Th1/Th2 cytokine and chemokine production.

Indigo naturalis, also used in TCM, was shown to have beneficial effects in an oxazolone-induced AD mouse model [45]. Adachi et al. [45] observed that AD symptoms, assessed via ear thickness and histology, decreased in severity upon treatment with indigo naturalis. Reduced IL-4 and eosinophil recruitment was also observed.

Some of these recent publications highlight the potential of naturally occurring/herbal therapeutics in the treatment of AD, as well as the significance of HDM as a contributing factor in pathogenesis. Improved and novel models to study the disease will also contribute to further developing alternative treatment [46].

Allergic Rhinitis

AR is an atopic disease characterized by inflammation and irritation in the mucous membranes of the nasal passages. The chief allergens are pollen and dander and the main treatment options are intranasal corticosteroids and antihistamines, depending on severity [5]. As with other atopic diseases, AR is a complex disease for which the underlying molecular and cellular mechanisms still require further elucidation.

Murakami et al. [47] investigated the role of DC subsets in an OVA-induced AR mouse model. Specifically, they assessed the effect DEC-205⁺ DCs, which drive Th1 polarization, and 33D1⁺ DCs, which establish Th2 dominance. To this end, they drove Th1 polarization in their AR mouse model by either depleting 33D1⁺ DCs with a 33D1-specific monoclonal antibody or by activating DEC-205⁺ DCs via intraperitoneal injection of α -galactosylceramide. Allergic symptoms, such as sneezing

Fig. 2. Putative potential of microRNA R30a-5p (miR30a-5p) to target suppressor of cytokine signaling 3 (SOCS3) and to reduce IgE levels in allergic rhinitis. SOCS3 protein was found to be over-expressed in human allergic rhinitis [51]. Treatment with an agomir of miR30a-5p downregulated SOCS3 expression and allergen-specific IgE levels in an experimental in vivo model of allergic rhinitis [51]. Illustration by Aldona von Gunten.

and nasal rubbing, were significantly decreased in OVA-challenged mice receiving the 33D1-specific monoclonal antibody or α -galactosylceramide. Furthermore, OVA-specific IgG1, IgG2a, and IgE nasal lavage fluid levels were decreased in AR mice with depleted 33D1⁺ DCs or activated DEC-205⁺ DCs, respectively; this was, however, not observed in the BALF. Activated DEC-205⁺ DCs were shown to suppress the release of histamine from IgE-sensitized mast cells, presumably via an IL-12 dependent

mechanism. This work highlights the role of innate DC subsets that may be exploited for therapeutic benefit in the context of AR and other atopic diseases [48].

T-helper cell differentiation is an important aspect of the pathogenesis of AR [49], while suppressor of cytokine signaling 3 (SOCS3) in turn plays an important role in T-helper cell differentiation [50]. Zhao et al. [51] identified a possible regulatory link between SOCS3, overexpressed in human AR, and microRNA R30a-5p (miR30a-5p). This relationship was validated in vitro, using luciferase reporter assays, and in vivo, using an OVA-induced AR mouse model. Mice treated with an agomir of miR30a-5p down-regulated SOCS3 expression and allergen-specific IgE levels (Fig. 2). Ultimately, they demonstrated that SOCS3 is upregulated in AR and targeted by miR30a-5p [51]. This work adds to emerging evidence that miRNAs play an important role in the orchestration of allergic disorders [52].

Food Allergy

In vivo Ovalbumin Food Allergy Models and Novel Therapeutics

Egg food allergy remains a major public health concern, without any satisfactory treatment available [53]. Consequently, egg food allergy is a relevant area of allergy research and egg food allergy experimental models often serve as tools in the field. Maeta et al. [54] published a study that aimed to determine the dosing of dietary egg white supplementation required for an oral immunotherapy regimen in an egg white allergic mouse model. The findings showed that 1% egg white resulted in desensitization and immune tolerance with lower incidences of diarrhea, lower ovomucoid-specific IgE, IgA, and IgG2a, lower percentages of CD4⁺Foxp3⁺ cells, and higher IFN- γ and IL-10 spleen lymphocyte secretions. Alternative therapies are also under investigation. For example, two recent publications highlight the potential of traditional Japanese Kampo Medicines (TJKMs). Yamamoto et al. [55] published that the TJKM Kakkonto attenuated the allergic responses in an OVA food allergy mouse model via a regulatory T cell (Tregs)-mediated mechanism. They found that Kakkonto significantly induced Foxp3⁺CD4⁺CD25⁻ Tregs in the colon of OVA allergic mice, highlighting it as a potential novel treatment for egg food allergy, as well as for other food allergies. Eppikajutsuto (EJT), another TJKM, was also recently identified as a novel treatment for food allergy in an OVA allergic mouse model. Matsui et al. [56] described EJT's anti-allergic effect as likely being mediated via the suppression

of IL-4 and degranulation of mucosal mast cells. Fructooligosaccharides (FOS), a prebiotic, has also been investigated for its anti-allergic properties in the context of egg food allergy. A recent report describes that the dietary intake of FOS provided moderate protection against allergy-induced inflammatory responses in an ovalbumin food allergy mouse model. The beneficial effect was attributed to a reduction in intestinal Th2 cytokine responses; however, this phenomenon was not observed systemically. Evidence of the attenuation of the activation of naïve CD4⁺ T cells by FOS was also found [57]. While the ovalbumin mouse models are useful tools for experimental work on food allergy in general, research focusing specifically on egg allergy is still underway.

Peanut Allergy

Peanut allergy is a widespread phenomenon and potentially life-threatening [58]. As with most food allergies, adequate molecular characterization and treatment are still lacking.

How peanut allergens are taken up by the intestine remains poorly elucidated. Recent work by Price et al. [59] described a novel mechanism by which peanut allergens Ara h 1 and Ara h 2 traverse the intestinal epithelial layer by early endosomes and eventually end up in the lysosomal compartment. Targeting endosomal pathways may therefore be a viable option for the development of new therapeutics for peanut allergy. Recent technical advances in detecting Ara h 2 and Ara h 6 in human breast milk has also been made, which would facilitate the study of how breastfeeding plays a role in the development or prevention of peanut allergy [60].

DNA vaccination as a possible treatment was assessed by Zhu et al. [61] in a preclinical setting. A DNA vaccine encoding peanut protein Ara h 2 (pAra h 2), was administered with or without poly-L-lysine (PLL) modification as either prophylaxis or therapy in a peanut allergic mouse model. In the prophylaxis setting the DNA vaccines resulted in lower levels of Ara h 2-specific IgG1, IgG2a, and IgE after pAra h2 sensitization. In the treatment arm of the study, significantly lower levels of Ara h 2-specific antibodies were observed in the vaccinated animals. Increased numbers of CD207⁺ DCs and Tregs, as well as increased IFN- γ and IL-10 secretion from splenocytes were found in the group which was administered with the PLL-pAra h 2 vaccine. In all aspects the PLL modified version of the DNA vaccine outperformed the unmodified version. This work highlights the potential of DNA vaccines as therapy for peanut allergy (and other food allergies) as both prophylaxis and treatment. Furthermore, pretreatment with PLL may

be a strategy to overcome low immunogenicity that has often proved a hurdle to DNA vaccine efficacy [61, 62].

Moutsoglou and Dreskin [63] investigated the role of long-lived antibody-secreting cells in peanut allergy and the potential of the proteasomal inhibitor bortezomib as a therapy in this context. While they found that bortezomib decreased long-lived anti-peanut IgE in mice, a correlative decrease in allergic symptoms was not observed. They speculate that prolonged depletion of specific serum IgE was not successful in decreasing disease severity as mast cell-bound IgE may act as a reservoir. This potential factor should be taken into consideration when the depletion of antibody-secreting cells by proteasomal inhibitors or other means is used as a treatment in food allergy as sensitization may persist in the absence of serum IgE.

Shellfish Allergy

Allergy to shellfish is one of the leading causes of death by anaphylaxis in humans [64]. Leung et al. [65] investigated the use of allergen-specific immunotherapy in the context of shrimp allergy in a mouse model. Recombinant shrimp allergen rMet e 1 was used to sensitize BALB/c mice, which was subsequently challenged. Three different doses of the allergen-specific immunotherapy were administered as treatment and the effects were found to be dose-dependent. While all the mice treated were desensitized, the group receiving the highest dose experienced adverse events systemically. Furthermore, the upregulation of Treg-associated genes was only observed in the low and moderately dosed groups and these groups exhibited higher numbers of Foxp3⁺ cells in the gut when compared to the high-dosage group. This work underlines the potential of allergen-specific immunotherapy as treatment for shrimp allergy and that dosage may play an important role in safety and efficacy [65]. Tools to study shellfish allergy are also continually being developed and refined. For example, an adjuvant-free mouse model for shellfish allergy was developed and clinical studies using the ImmunoCAP-FEIA technology highlighted the need for food challenge tests when diagnosing shrimp allergy [66, 67].

External Factors and Food Processing

Determining factors contributing to the pathogenesis of food allergy is a topic that requires further investigation. A common allergy amongst infants is that of cow's milk. An association between Caesarean births and instances of formula feeding in hospitals was recently reported to have a positive association with cow milk allergy [68]. This work highlights the importance of food intake during early life with respect to the development of food allergy.

Food processing is a potential strategy option to lessen the disease burden of food allergy and possibly elicit tolerance. Soybean products are a major source of food allergies. Cabanillas et al. [69] investigated the impact of thermal and pressure processing of soybeans on specific IgE binding capacity in a small cohort of sensitized individuals. They found that boiling for 60 min led to reduced IgE binding ex vivo. Pretreatment that combined both heat and pressure seemed to be more effective, exhibiting an even more pronounced reduction in IgE binding ex vivo, as well as reduced skin prick testing wheal size in patients ex vivo [69].

Concluding Remarks

Atopic diseases, as well as food allergy, are on the increase and exert a significant societal burden worldwide. Allergic asthma, AD, and AR are complex, intertwined diseases for which the relationship is described as the atopic march. The underlying mechanisms which drive these disorders require more investigation. Clues from cellular biology to the pharmacodynamics of traditional or alternative therapeutics may pave the way. Recently, we highlighted the potential of pleiotropic agents, such as glucocorticoids [70], vitamin D, or polyclonal intravenous immunoglobulin that target multiple molecular processes in inflammatory and allergic disorders [15]. Exploring the underlying mechanisms of pleiotropic agents may further lead to the identification of druggable pathways, for instance effects of specific antibodies within polyclonal [71] and pluripotent intravenous immunoglobulin [72], which may target eosinophils [73] or other relevant cells in allergic conditions. A better understanding of the disease-driving mechanisms on a molecular and cellular level is key for the development of preventive and more effective treatment options, as well as for advances in personalized medicine.

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The authors have no conflicts of interest to declare.

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Author Contributions

Both O.J.A. and S.G. wrote the manuscript and approved the final version.

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