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Novel Insights into Atopic Dermatitis

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Abstract

Recent research into the pathophysiology and treatment of atopic dermatitis (AD) showed notable progress. An increasing number of aspects of the immune system are being implicated in AD, including the epithelial barrier, T_H2 cytokines, and mast cells. Major advances in therapeutics were made in biologic cytokine and receptor antagonists and among Janus kinase inhibitors. Herein, we focus on these areas and address new insights into AD epidemiology, biomarkers, endotypes, prevention, and comorbidities. Going forward, we expect future mechanistic insights and therapeutic advances to broaden physicians' ability to diagnose and manage AD patients, and perhaps find a cure for this chronic condition.

Keywords

atopic dermatitis; T_H2; epithelial barrier; janus kinase inhibitors

Introduction

Progress in our understanding of AD has advanced rapidly in the last year. This includes a deeper understanding of the epidemiology, treatment, genetics, and pathophysiology of AD. In particular, advances in understanding the mechanistic role of cytokine mediators, innate immunity, the epithelial barrier in AD pathogenesis will be emphasized. Furthermore,

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a wealth of clinical trial and other data on current and novel treatments for AD will be reviewed as well. Altogether, these advances will increase our ability to diagnose and treat patients with AD and provide hope for an eventual cure.

Epidemiology

The Global Burden of Disease Study estimated that the general prevalence of AD was 15-20% among children and up to 10% among adults (1). Although traditionally thought to have a lower prevalence in Africa compared to Europe, more recent studies have demonstrated AD occurring at increased frequency in children, as high as 31% in Ghana, which may possibly be connected to increased urbanization (2, 3). Population studies of AD in sub-Saharan Africa have also highlighted the increasing prevalence in this region, with over 15% of children affected (2). Given the limited resources in these regions, there is a need for additional cooperation with pharmaceutical companies to improve management in these areas (2). AD outcomes may also be influenced by structural racism, defined by Martinez *et al.* as “the totality of ways in which society fosters discrimination by creating and reinforcing inequitable systems through intentional policies and practices sanctioned by government and institutions.” For example, proximal pathways of structural racism include pollutant and other environmental hazard exposure, which may lead to “biologic embedding” through reinforcement of aberrant innate and adaptive immune responses (4, 5). What this construct emphasizes is the means by which generational exposure differences can reinforce aberrant immune responses, such as AD, through epigenetic and other mechanisms. This helps to emphasize how social and public policy decisions can have unintended adverse consequences on differential disease manifestations in populations long after such decisions are made. Biagini *et al.* evaluated phenotypic differences between White and Black children experiencing the atopic march. They found that Black children exhibit higher asthma risk despite having a more intact skin barrier as demonstrated by lower lesional and nonlesional transepidermal water loss and higher non-lesional *FLG* expression (6). In response to these issues, the American Academy of Allergy, Asthma & Immunology Committee on the Underserved provided a report highlighting the need for a multilevel approach across patients, healthcare providers, government, non-profits, and professional societies to better address disparities in atopy (7). Within AD, this report emphasized the lack of studies addressing disparities specifically within AD and suggests that effective intervential trials in AD need to improve reporting of and accounting for race and ethnicity in their results.

Environmental Pollutants

Recent work provided additional data on the role of pollutants in AD. In a cross-sectional study of 209,168 individuals from 2008–2013 from the Republic of Korea that examined the long-term average concentration of air pollutants before the diagnosis of AD, the authors identified significant associations between AD incidence and exposure to particulate matter (<2.5μm and <10μm in diameter), sulfur dioxide, nitrogen dioxide, and carbon monoxide. These associations held after adjusting for age, sex, income, comorbidities, and meteorologic variables (8). In another study from Tasmania, increasing nitrogen dioxide was associated with increased AD rates in males (9). These reports expand on the literature demonstrating the contributions of the anthropogenic environment to AD.

Clinical classification

The clinical classification of AD was recently thoroughly reviewed (10), providing detailed images of the clinical heterogeneity of eczematous lesions, as well as an overview of the clinical aspects of AD; this may be of value to clinicians seeking images of AD. We focus here on AD endotypes and biomarkers, as these were areas of notable progress.

Endotypes and Biomarkers: Defining novel endotypes and biomarkers is expected to play a major role in AD diagnosis and treatment. However, multiple studies illustrated the profound immune complexity associated with such AD classifications. Two studies from Bakker *et al.* reported unbiased, principal components analyses of human AD serum cytokine profiles. The first study evaluated pediatric AD, identifying four clusters: T_H2 cell/retinol-dominant, skin-homingdominant, T_H1 cell/T_H2 cell/T_H17 cell/IL-1-dominant, and T_H1 cell/IL-1/eosinophil-inferior. Disease severity was associated with a skin-homing dominant group (11). Only one of these clusters resembled a previously reported adult endotype. The second study identified four severe AD disease clusters: skin-homing chemokines/IL-1R1-dominant, T_H1/T_H2/T_H17-dominant, T_H2/T_H22/PARC-dominant, and T_H2/eosinophil-inferior (12). A third study evaluated humans across the lifespan using skin biopsies of lesional and non-lesional skin, demonstrating a shared T_H2/T_H22-signature that differs depending on the age of the patients, with greater T_H17 skewing in infants and adults (13). A fourth study used a transcriptomic analysis of lesional and non-lesional skin biopsies to define another group of four clusters, similar to the aforementioned studies (14). While all these studies produce somewhat similar clustering results, we note that adult and pediatric AD as well as severe AD each demonstrate substantial immune heterogeneity when classified in this manner, and it is difficult to derive a specific classification system at this time.

While the complexity of these classifications renders the practical deployment of such unbiased approaches difficult, other studies evaluated hypothesis-driven or single-marker approaches to explain facets of AD. A study of 248 participants with varied AD severity showed that serum sphingosine-1-phosphate is elevated in AD and associated with severity (15). Another study evaluating children across the lifespan found that specific features, including SCORAD (SCORing Atopic Dermatitis) severity index at age three, trigger factors, and low vascular endothelial growth factor serum levels correlated with AD persistence (16). A third publication demonstrated that RNA-seq profiles from tape stripping of atopic skin in children correlated with clinical features and transepidermal water loss (TEWL). This suggests that non-invasive tape stripping might be a suitable alternative to biopsies for pediatric research in AD (17). Atopic dermatitis-specific lipid alterations have also been noted by tape stripping analysis, further supporting this sampling method (18). Lastly, one review evaluated the role of primary atopic disorders to describe how heritable monogenic allergic disorders can be detected using next-generation sequencing. The authors emphasized that in patients with red flags (e.g., short stature, infections, markedly elevated IgE), early onset of disease, or treatment refractoriness, sequencing can be considered for facilitated diagnosis (19).

Pathophysiology

Recent advances provided multiple additions to our understanding of AD pathophysiology, categorized here by mediators, cell types, and the epithelial barrier (Figure 1).

Mediator data—While the roles of IL-4 and IL-13 are well characterized in AD, novel insights were reported on their role in AD pathogenesis. One study that included both human samples and mechanistic modelling demonstrated that IL-4 and IL-13 modulate abnormalities in sex steroid hormone synthesis via 3β-hydroxysteroid dehydrogenase 1, and may partly underlie the disrupted AD skin barrier (20). Another study used AD patient peripheral eosinophils to demonstrate how IL-4 upregulates, via the JAK/STAT pathway, expression and function of the histamine receptor 4, which is highly expressed on such eosinophils (21). These studies notably connect type 2 cytokines to structural and pathologic aspects of AD and help explain how immune signaling promotes disease outcomes.

Multiple studies evaluated the role of other cytokines in AD. One manuscript used CyTOF to study T cell polarization in the blood of AD patients versus controls, finding a correlation of IL-21 expression in IL-13^+ T cells with AD severity, thus implying a role for IL-21 in AD (22). IL-25 (IL-17E), an IL-17 family member, has received attention as an epithelial barrier damage “alarmin.” The role of IL-25 in epithelial immunology was outlined, emphasizing its role as a key driver of type 2 innate lymphoid cell (ILC2) and T_H2 production of cytokines, including IL-4 and IL-13 (23).

IL-31, a cytokine in the gp130/IL-6 family, is a pruritogen previously implicated in AD itch; one group performed a drug screen in multiple cell lines for IL-31 transcriptional inhibitors and demonstrated a role for 4-(2-(4-isopropylbenzylidene)hydrazineyl)benzoic acid in antagonizing IL-31 production and function in itch in AD (24). Another manuscript evaluated TRP vanilloid channel 3 (TRPV3), an epidermal-keratinocyte localized cation channel warm temperature detector. TRPV3 was noted to be upregulated in lesional AD skin and to mediate IL-31-induced itching in a serpin E1-dependent manner (25).

Several studies increased our understanding of the role of the extended IL-1 family of cytokines including IL-33, IL-36, and IL-37 in AD pathogenesis. Trier *et al.* demonstrated that IL-33 receptor expression on sensory neurons is not required for AD pruritus but is required for dry skin itch using human plasma samples and a mouse model (26). Kindi *et al.* used human keratinocytes in culture and human skin explants to show that the *S. aureus* virulence factor second immunoglobulin-binding protein is essential for inducing IL-33 and downstream type 2 cytokine responses (27). Keratinocyte-derived IL-36 appears to provide a key mechanism for IgE development and B cell class switching in AD (28). IL-37 and its receptor (IL-18R) expression is reduced in AD, suggesting that IL-37 may play a regulatory role (29).

Leukotriene C_4 was shown to be a potent itch inducer acting through its physiological receptor $CysLT_2R$ in sensory neurons in a model of dermatitis (30). Lastly, one study showed that peripheral blood CCL17 (thymus- and activation-regulated chemokine) elevation was associated with presence of AD, though sensitivity and specificity were not adequate to provide diagnostic conclusions with high reliability (31).

Cellular data

Mast cells and basophils: Mast cells and basophils play a major role in atopy, including AD. Antagonism between T_H1 and T_H2 immune processes mediated by mast cells was recently described by Levya-Castillo *et al.* The study demonstrated how a T_H2 cytokine, IL-13, produced by cutaneous mast cells in response to tape stripping, directly inhibits dendritic cell expression of IL-12, in turn decreasing IFN-γ release from $CD4^+$ T cells (32, 33). Another study provided evidence that a microRNA, miR103a-3p, contained in mast cell-derived extracellular vesicles, may play a role in AD by promoting innate lymphoid cell (ILC) 2 upregulation of IL-5, especially in the presence of IL-33 (34). Basophil biology received further attention, with one study using a mouse AD model to show that basophils supply a substantial amount of IL-4 in the skin during AD to induce barrier dysfunction (35).

The role of ILCs is increasingly recognized in AD. Evidence for ILC lineage changes (i.e., between ILC1, ILC2, and ILC3/17) or "infidelity" has increased (36). Alkon *et al.* used single cell RNA sequencing to demonstrate that in AD ILCs commonly co-express both type 2 (*GATA3, IL13*) and type 3/17 (*RORC, IL22, IL26*) genes within the same cell, particularly in AD lesional skin (37). This lineage plasticity perhaps relates to the protean immune profiles of AD noted in "Endotypes" above and cautions against reductionist approaches to simpler classifications.

Innate immunity: As our understanding of innate immunity's role as arbiter of immune responses continues to grow, multiple articles described insights into the role of innate immune responses and AD. CXCR4+ natural killer T cells (NKT cells), seen as a bridge between innate and adaptive immunity, were shown to be enriched in AD skin, facilitating a tissue-resident status contributing to lesional pathogenesis (38). Another study used human skin transcriptomics to suggest that natural killer cells (vs. NKT cells), are enriched and dysfunctional in both non-lesional and lesional AD skin (39). Mucosal associated invariant T (MAIT) cells, another T cell at the innate/adaptive interface, were implicated in AD pathogenesis, and ablation of non-polymorphic MHC class I related-1 molecule (MR1, a critical receptor for antigen presentation to MAIT cells) prevented AD development in the MC903 mouse model of AD (40). Notably, phototherapy appeared to model this effect of the MR1 receptor, likely through photodegradation of folate into inhibitory MR1 ligands (40). These studies strongly link innate/adaptive overlap T and NK cell types to key roles in AD.

Another study addressed the role of Langerhans cells (LCs) and follicular helper T cells (T_{FH}) in AD pathogenesis using two AD mouse models, one driven by thymic stromal lymphopoietin (TSLP) overproduction and the other by ovalbumin (OVA) sensitization. This led to the observation that LCs drive T_{FH} responses when stimulated directly by TSLP, but that LCs inhibit T_{FH} responses during OVA sensitization (41).

A recent article profiled transcriptomes of developing human fetal skin, healthy adult skin, and adult skin with AD and psoriasis (42). This study noted in situ reemergence of prenatal vascular endothelial cell and macrophage cellular programs in AD and psoriasis lesional skin (42). Another study used peripheral blood from AD patients and controls to identify a circular RNA, hsa_circ_0004287, which inhibited macrophage activation in AD

and psoriasis in a subsequent mouse model. The authors posited this as a therapeutic target for AD (43).

More data became available to demonstrate the role of JAK signaling in AD. One study demonstrated that inflammatory dendritic epidermal cell differentiation and function is impaired by JAK inhibition, further rationalizing the utility of JAK inhibitors in AD (44).

Finally, a study suggested a proinflammatory role for p62 (sequestrome 1), a multifunctional adaptor protein target of rapamycin (45). With the prior NK and T cell studies, these works emphasize the role of purely innate cells, such as dendritic cells and monocyte-derived cells, in AD pathogenesis.

Epithelial barrier—The skin epithelial barrier serves as the visible canvas for AD, and interest in the role of barrier function and its related phenomena figured prominently in recent work. This was especially in relation to research gaps in AD genetic susceptibility, epigenetic responses to microbiota, and how barrier restoration and microbiota manipulations affect AD (46). One study addressed the role of genome wide association study (GWAS)-derived single-nucleotide polymorphisms (SNPs) on skin barrier pathology using targeted chromosome conformation capture. This study showed that many SNPs identified by GWAS may unexpectedly affect distal genes, as only 35% of target genes were the nearest gene to known GWAS variants (47). Using a GWAS-based approach with followon mechanistic work, DeVore *et al.* defined Caspase Recruitment Domain Family Member 14 (CARD14) as a regulator of FLG expression in the skin of children with AD and further showed that CARD14 regulates FLG homeostasis in a manner dependent upon rs11652075 (48), a variant in the CARD14 gene that intriguingly is also associated with psoriasis (49).

In a study evaluating the systemic proteomic differences between mild and moderate/severe AD, He *et al.* noted that mild AD showed high levels of T_H2/T_H22 cell activation localized to the skin and lacked the systemic inflammation of moderate/severe AD (50). The same group used RNA-sequencing to show that tape stripping is capable of differentiating among AD, psoriasis, and normal skin (51). Another study suggested that tape stripping demonstrates the ability to detect T_H2 skin response in AD and correlates with severity of AD better than skin biopsy (52). Skin-based impedance spectroscopy may offer a future in vivo technique for assessing epithelial barrier component integrity, including for claudin 1 and 4 dysfunction (53). This may provide a noninvasive measure of therapeutic effect in AD (54). Another study used RNA sequencing to evaluate existing biopsy specimens from trials of cyclosporine and dupilumab to demonstrate a “core” AD RNA signature involving itch and keratinocyte dysfunction, along with a “dynamic” signature dominated by type 2 cytokines responsive to both therapies (55).

Atopic itch, which is generated in part at the epithelial barrier, has long been known as both a symptom and enhancer of AD. Self-DNA liberated by barrier disruption, presumably due to physical disruption from scratching, was shown to interfere with antimicrobial peptides (56). In another study, overexpression of PAR2, which acts as a sensor for proteolytic enzymes, enhanced house dust mite-induced itch in a mouse model (57). Coupled with the

IL-31 and IL-33 data above(26), our understanding of the pathogenic role of pruritus in AD continues to grow.

Microbiome & Metabolism

Related to barrier defects, microbiota alteration has been observed in multiple AD studies (46). The most prominent example is *S. aureus*, which attaches to the stratum corneum by binding to the N-terminal region of corneodesmosin (58), and also produces biofilms that are significantly associated with AD severity (59). *S. aureus* can also interact with the host immune system and affected tissue by inducing pro-inflammatory responses from T_H2 cells (60), or working with T_H2 and its cytokines to induce allergic inflammation and phenotypes (61).

Besides *S. aureus, S. epidermidis* also acts similarly to affect AD, and recent work highlighted that its cysteine protease EcpA can degrade desmoglein-1 and LL-37 and disrupt the skin barrier. Expression of these molecules is associated with disease severity (62). Therefore, the distributions and expression of different skin microbial species can serve as signatures to stratify the AD patients with different phenotypes, degree of severity, and treatment response, due to microbial networking with the host immune system (63).

Microbiota in other tissues can also play role in AD. A study investigating the microbiome of airway and gut showed that infancy in urban area increases risk of asthma, AD, and allergic sensitization at a later age, suggesting a predisposed microbial composition (64). Another study of school-age children found a less consistent association between microbial diversity in stool with atopic diseases; association of α-diversity with risk of eczema was non-significant (65). Bacteriotherapy efforts have attempted to use *S. hominis* A9 as topical therapy for AD. Though disease severity was not improved, *S. aureus* composition was significantly decreased (66). However, the immune system and microbiome interactions are complicated, particularly given microbiome variability across skin sites (67). These studies highlight the importance of gathering samples from diverse backgrounds and the necessity of joint efforts spanning microbiology and systems biology to study the causal relationships and disease mechanisms of the microbiome in AD.

Genetics

AD is a complex condition, and previous GWAS have highlighted multiple disease susceptibility regions (68). Recent studies have focused on using existing resources to advance our understanding of the AD genetic architecture as well as unravel disease-causing variants. One study used biobank resources to successfully identify 30 genome-wide significant regions, including 5 novel loci. This work highlights the feasibility of deploying different emerging biobank datasets in future genetic AD studies (69). Differences in the linkage disequilibrium between ethnic groups can enhance resolution in fine-mapping causal variants. A trans-ethnic meta-analysis using Caucasian and Japanese cohorts was able to identify putative causal variants: a missense variant (R243W) with a deleterious effect in *NLRP10* and a variant altering expression of *CCDC80* (70). Information from chromatin interaction has also been used to infer the mechanism for AD-associated signals, highlighting the need to integrate multi-omic information in understanding their biological

effects (71). AD genetic studies also facilitate efforts for other sub-phenotypes or related traits, including the identification and understanding of genetic signals associated with eczema herpeticum (72) and total IgE level (73). One important translational implication for AD GWAS is to use polygenic risk scores to model the disease risk. One study showed that genetic scores derived from GWAS are predictive of AD with up to an odds ratio (OR) of 3.86 for severe disease (74). Another study demonstrated the importance in using a cohort with similar demographics as the target population in model training, achieving an area under the receiver operating characteristic curve (AUROC) of 0.88 when predicting moderate-to-severe AD (75).

Prevention

Work in AD prevention has continued apace. There is a longstanding interest in whether prophylactic skin barrier enhancement via emollient application prevents AD. A large systematic review and meta-analysis of prophylactic emollients within 6 weeks of birth reported a benefit only in those at high risk for AD when emollients were used continuously (76). A Cochrane review concluded that “emollients during the first year of life in healthy infants are probably not effective for preventing eczema”(77). This conclusion was supported by the PreventADALL study, a cluster-randomized trial of 2,400 infants, which evaluated whether either early food introduction or prophylactic emollients could prevent food allergy or AD among the general population. While early feeding reduced the risk of food allergy, early feeding did not impact AD development, and emollient prophylaxis showed no significant effect on food allergy or AD (78). However, one study of maternal diet during pregnancy did find that offspring of mothers with greater yogurt and/or vegetable intake displayed reduced odds of AD, although causation still has yet to be established (79). Thus, while emollient use may not provide definitive AD prevention, other avenues, including immune metabolic regulation remain open for investigation.

Novel treatments

Progress on novel treatments also continued in the past year (Figure 2, Table 1). Tapinarof, a topical therapeutic aryl hydrocarbon receptor modulating agent, was evaluated in a phase 2b, double-blind, randomized, vehicle-controlled study of adolescents and adults with AD. Participants received tapinarof cream or vehicle for 12 weeks, which resulted in improvements in Eczema Area and Severity Index (EASI) and Patient-Oriented Eczema Measure (POEM) (80), corroborating results from a 2019 study (81).

A phase 3 trial of asivatrep, a transient receptor potential vanilloid subfamily V member 1 (TRPV1) antagonist, reported global improvements in AD symptomatology at 8 weeks among participants on twice-daily 1.0% application of drug compared to placebo (82). TRPV1 is a nonselective cation channel expressed in keratinocytes, mast cells, and cutaneous sensory nerves.

Nemolizumab, a monoclonal antibody targeting the IL-31 receptor, also underwent clinical trials. In a post hoc analysis of a phase 2b trial of moderate-to-severe AD among participants with EASI ≥ 16 at baseline, nemolizumab therapy resulted in improvements in inflammation, pruritus, and sleep (83). A 24-week, double-blind, multicenter nemolizumab

dose-finding study in which participants were randomized to placebo, 10, 30, or 90 mg subcutaneous monthly injections showed similar improvements, with a maximal dose effect at 30 mg (84). A 16-week, double-blind, phase 3 trial reported that nemolizumab treatment in AD induced a greater reduction in pruritus than placebo plus topical agents (85). Lastly, a meta-analysis of 14 cohorts among 6 randomized/controlled studies of nemolizumab in AD showed “a promising effect based on the difference in the average change in pruritus visual analog score and EASI versus placebo”(86).

A prospective, uncontrolled, multicenter cohort examining dupilumab, an IL-4 receptor inhibitor, showed a 70% decrease in EASI at 16 weeks and a 76.6% decrease at 52 weeks (87). A meta-analysis identified dupilumab as having the highest quality trial evidence at 1 year in adults for all treatments in all AD populations (88). Indeed, when dupilumab is ineffective, there is limited data on the optimal next step of therapy (89). One study reported a real-world 6-month observation of dupilumab, where dupilumab showed elevated rates of conjunctivitis over mycophenolate, methotrexate, or cyclosporine, but was not associated with increased infections (90). An intriguing study of longitudinal immune responses to dupilumab suggested that not just T_H2 but also T_H17 responses correlate with EASI, suggesting that non-T_H2 immune responses (such as T_H17) play a role in AD pathophysiology and dupilumab responses (91).

Secukinumab is a monoclonal antibody that binds IL-17A. In a phase 2, randomized, double-blinded trial, secukinumab did not improve AD among 41 subjects (92). While the role of T_H17 signaling in AD is of interest, deployment of T_H17 antagonism in AD has not been successful.

Janus kinase (JAK) inhibitors (JAKi) hold promise for AD treatment (93). Upadacitinib is an oral JAK1-selective JAKi with a rapid onset of action (94). The AD Up study reported favorable results at both 16 weeks (95) and 52 weeks (96) for this medication in combination with topical corticosteroids. Similar results were reported from the Measure Up 1 and 2 studies (97). Abrocitinib is another oral JAK1-selective JAKi. One phase 3, double-blinded trial compared abrocitinib to placebo or dupilumab. Abrocitinib was overall comparable to dupilumab but more effectively reduced itch (98). In another study, abrocitinib responders were assigned to blinded continuation vs. discontinuation. Those with flares were effectively rescued with the drug, suggesting that therapy holidays are feasible (99). The third JAKi currently in clinical trials for AD, baricitinib, is an oral JAK1/2 inhibitor. In a phase 3 trial of adults with moderate-to-severe AD who responded inadequately or were intolerant to topical therapy, baricitinib improved EASI vs. placebo at 16 weeks of therapy (100). Delgocitinib is a topical pan-JAKi (inhibiting all four members of the JAK family: JAK1, JAK2, JAK3 and TYK2) clinically approved for AD in Japan (101). One delgocitinib study of pediatric patients reported substantial improvements in EASI versus vehicle at 4 weeks that were maintained with continued application at one year during a study extension (102). Ruxolitinib cream is a topical JAK1/JAK2 JAKi. Two phase 3 trials reported 8-week efficacy for ruxolitinib in Investigator’s Global Assessment (IGA) and itch reduction vs. vehicle (103).

Comorbidities

AD is the first step of the atopic march development of food allergies, allergic rhinitis, and asthma. Increasing severity of early-onset AD, but not late-onset, is associated with aeroallergen sensitization and allergic rhinitis later in childhood (104). In a study of 321 infants at risk for peanut allergy, AD was strongly associated with peanut allergy development, whereas other factors such as family history were not a major risk factor without concomitant AD (105). A visual summary of these and other AD comorbidities can be found in Figure 3.

Despite the substantial population prevalence of AD, previously unrecognized comorbidities continue to be identified. In a 3-million-person study from the United Kingdom from 1998–2016, AD was linked with significantly elevated all-cause mortality (hazard ratio 1.04), which was higher for infectious, digestive, and genitourinary causes of death. Furthermore, individuals with severe AD had a hazard ratio of 1.62 vs. those without AD (106). In another study of adults with AD using insurance claims data, the authors noted increased odds of anxiety, autoimmune diseases, infections, malignancies, atherosclerosis, and metabolic syndrome in AD patients (107). While such studies cannot establish causation, these observations may help explain why increased mortality is associated with AD (106). Indeed, cardiac disease has been linked to AD, as vascular inflammation in AD is associated with enhanced T_H2 responses and clinical severity, which may explain the cardiovascular comorbidities observed in AD populations (108).

Elevated body mass index (BMI) is also associated with AD. Using 30,608 cases and 389,849 controls in the UK Biobank Resource, one group demonstrated a small but significant OR of 1.02 elevated risk of AD per each $1kg/m^2$ increase in BMI (109). Children with elevated BMI in early childhood were noted in another study to have a higher rate of subsequent AD later in childhood (110).

In a year defined by COVID-19, one meta-analysis analyzed AD and COVID-19, finding that skin conditions such as AD were associated with a greater risk of COVID-19 (OR 1.55) but a decreased risk of mechanical ventilation (OR 0.22) (111). Together, the studies above together suggest a complex, possibly bidirectional association between mortality-associated conditions and AD that requires more evaluation.

Conclusions

In summary, progress in AD research remains strong, and with increasing data on epidemiology, pathophysiology, and therapy, we are poised to further combat this challenging condition. Ongoing areas of investigation include improvements in prevention, approaches to deconvolute the immune and genetic complexity of AD, and methods to mitigate comorbid conditions. In the future, the areas of greatest need include those areas listed in Table 2. Future work will continue to address these gaps in the field even as new areas of need become better understood.

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Abbreviations:

AD	atopic dermatitis
T_H	T helper cell
IL	interleukin
TEWL	transepidermal water loss
Ig	immunoglobulin
SCORAD	SCORing Atopic Dermatitis
ILC	innate lymphoid cell
NK T cell	natural killer T cell
MR1	MHC class I related-1 molecule
TRPV3	TRP vanilloid channel 3
MAIT	mucosal associated invariant T
GWAS	genome wide association study
TSLP	thymic stromal lymphopoietin
OVA	ovalbumin
AUROC	area under the receiver operating characteristic curve
EASI	Eczema Area and Severity Index
POEM	Patient-Oriented Eczema Measure
TRPV1	transient receptor potential vanilloid subfamily V member 1
JAKi	Janus kinase (JAK) inhibitors
BMI	body mass index
IGA	investigator’s global assessment

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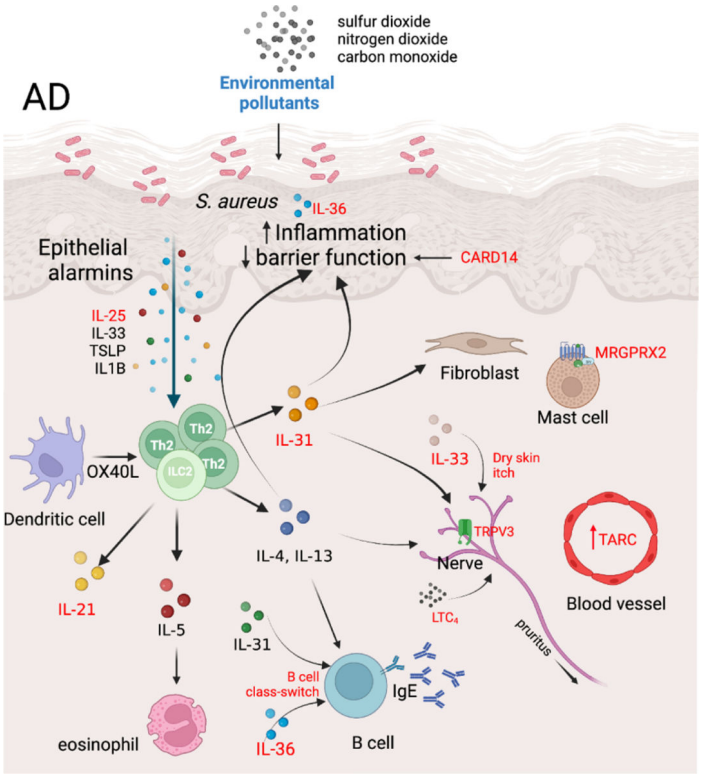

Figure 1. Novel insights and additions to AD pathogenesis.

This figure highlights novel insights and additions to AD pathogenesis (shown in red), and environmental contribution (blue), and their relevance to key AD associated features including T_H2 immune responses, epidermal inflammation and barrier function, mast cell activation, and pruritus. LTC_4, leukotriene C4; MRGPRX2, Mas-related G protein-coupled receptor-X2; TARC, thymus and activation-regulated chemokine; TRPV3, transient receptor potential vanilloid subfamily V member 1; TSLP, thymic stromal lymphopoietin.

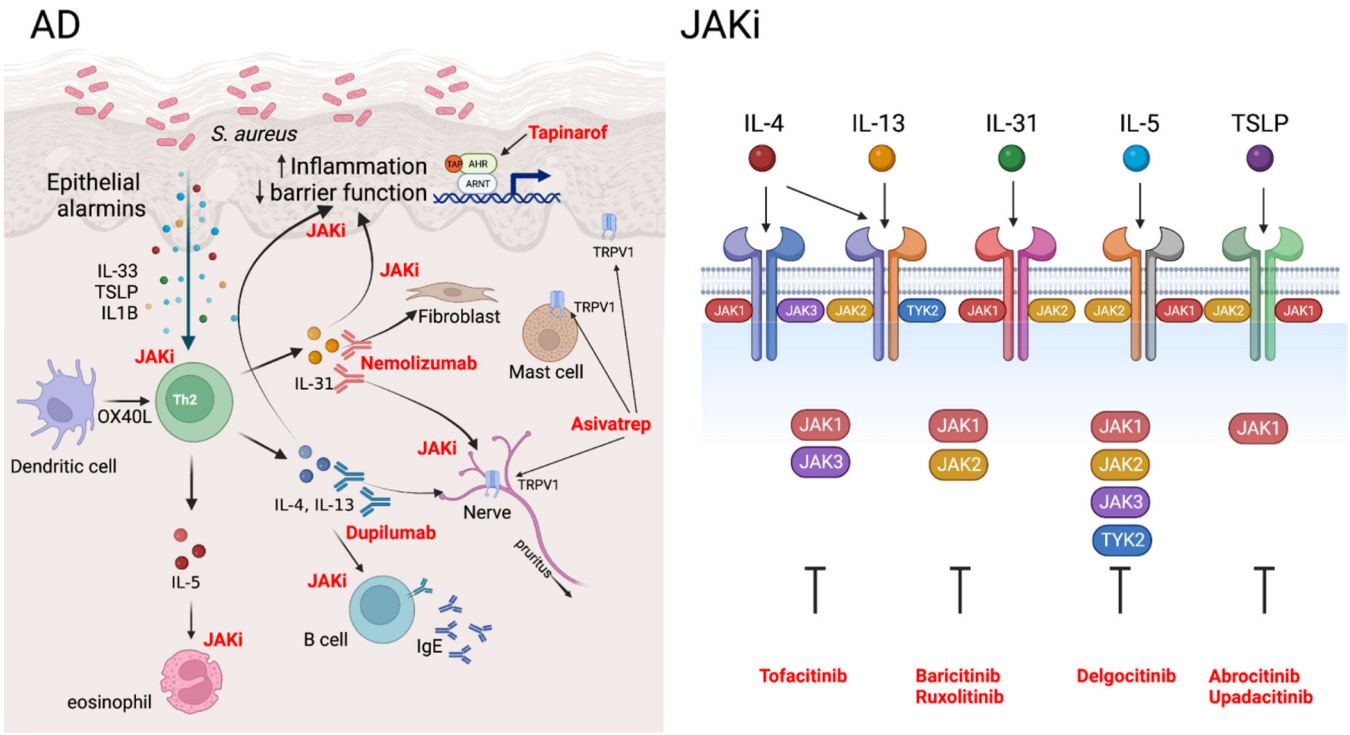

Figure 2. Novel therapeutic advances in AD.

Left panel, Intersection between therapeutic development and atopic dermatitis (AD) pathogenesis with therapeutic agents shown in red next to their biologic mechanisms of action. Right panel, Janus kinase (JAK) family members dimerize to mediate different cytokine responses. JAK inhibitors (JAKi) inhibit multiple aspects of AD pathogenesis through targeting of select JAK family members (right panel modified from Chovatiya *et. al.* (93)).

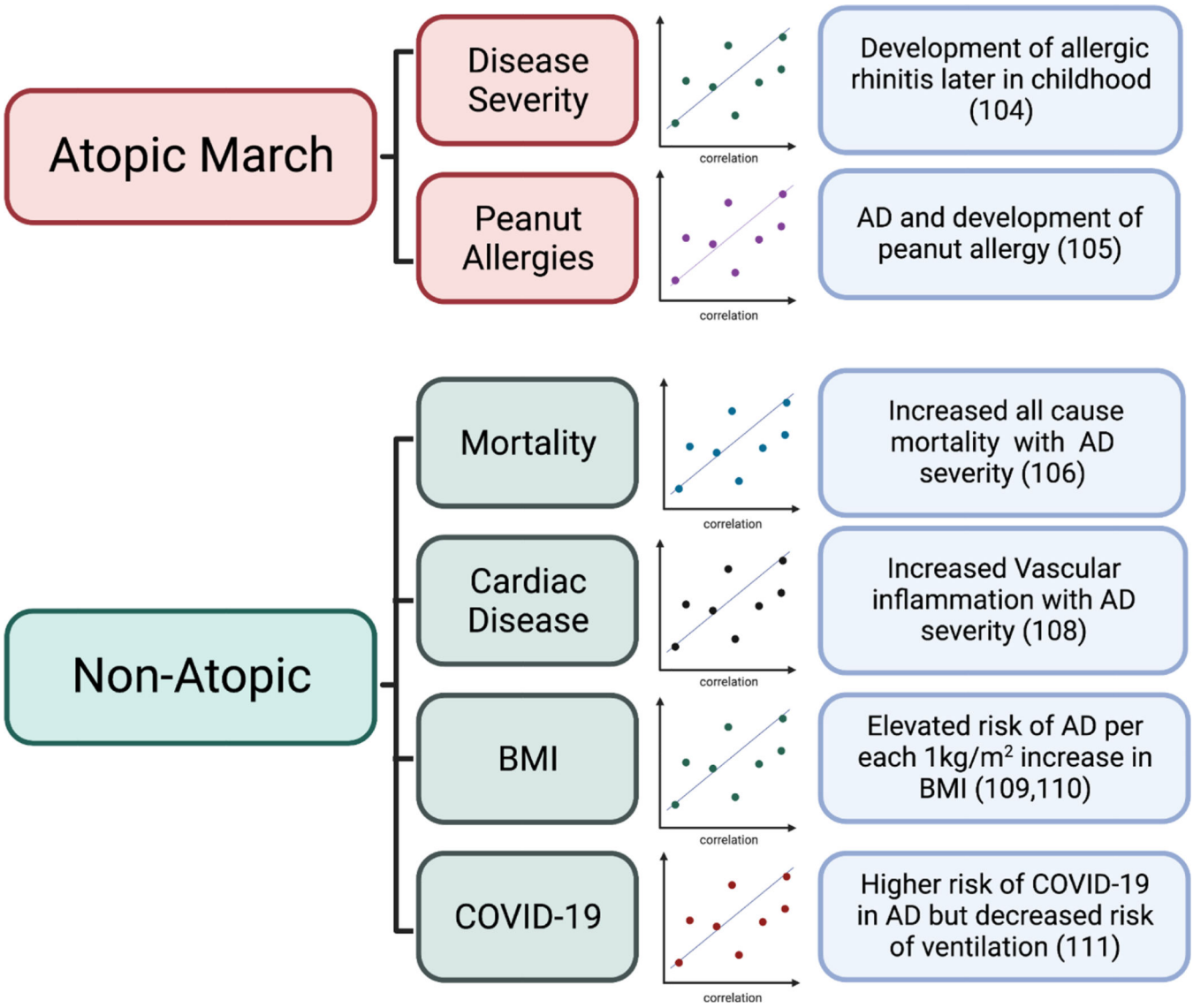

Figure 3. Novel Insights into AD Comorbidities.

Highlighted comorbidities associated with “Atopic March” or “Non-Atopic” aspects of AD pathogenesis. This includes association of AD disease severity with development of allergic rhinitis and association between AD and development of peanut allergy. Non-Atopic associated comorbidities include association between AD and all-cause mortality, AD associated vascular inflammation, influence of body mass index (BMI) with AD risk, and COVID-19.

Table 1:

Novel immunomodulators for AD

Name	Route of delivery	Mechanism of action	Specific target
Dupilumab	Injection	Cytokine antagonist	IL-4Rα
Nemolizumab	Injection	Cytokine antagonist	IL-31
Secukinumab	Injection	Cytokine antagonist	IL-17A
Asivatrep	Topical	Cation channel antagonist	TRPV1
Tapinarof	Topical	Aryl hydrocarbon receptor modulator	
Abrocitinib	Oral	JAKi	JAK1
Baricitinib	Oral	JAKi	JAK1, JAK2
Delgocitinib	Topical	JAKi	JAK1, JAK2, JAK3, TYK2
Ruxolitinib	Topical	JAKi	JAK1, JAK2
Tofacitinib	Oral	JAKi	JAK1, JAK3
Udapacitinib	Oral	JAKi	JAK1

Table 2:

Areas of need for future work

Area	Specific improvement	Population in need
Epidemiology	Inclusion of disadvantaged groups in clinical trials and other clinical studies.	Disadvantaged groups
Endotypes	Simple definitions for endotyping accessible to all institutions.	All patients
Prevention	Low-impact interventions to prevent AD in all risk groups, especially from infancy.	Primarily children
Comorbidity	Improved understanding of the mechanisms of comorbidity development to facilitate mitigation.	All patients