Trends in Immunology

CellPress

Review

The Multi-Modal Immune Pathogenesis of Atopic Eczema

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Atopic eczema (AE) is one of the most common inflammatory diseases, often constituting a lifelong burden for afflicted individuals. Recent findings have provided new insights into the pathogenesis of AE, revealing contributions of genetics, skin microbiota, and both innate and adaptive immunity in disease onset and progression. We review these findings here, assembling contributing factors conceptually into four modules that can interact in various ways to ultimately lead to epidermal barrier impairment, unchecked type 2 immunity, and chronic disease. We present this modular framework as a basis for understanding the varied presentations of AE, and in this context we propose a diagnostic and therapeutic algorithm aimed at the precise stratification of AE patients and the implementation of individualized medicine in AE standard of care.

AE: A Complex Disease

AE belongs to the most common human inflammatory diseases, with a prevalence of at least 2–3% in the adult population and 10–30% in infants in the western world. Accordingly, AE has a major impact on total global disease burden [1] and represents a challenge for modern health care systems. Affected patients suffer from acute and often persistent or relapsing eczematous skin lesions that are characterized by erythema, papules, and scaly plaques accompanied by intense pruritus. The underlying pathogenesis is a complex interplay of genetic background, environmental influences, and immunological deviation that leads to an impaired epidermal barrier and a dominating type 2 immunity – the hallmarks of AE. Histologically, AE lesions present with signs of apoptosis, spongiosis, and the infiltration of immune cells such as eosinophils and T cells. Whereas lesions in infants are mainly acute and present at the face, trunk, and the extensor site of the limbs, adults often have a distinct distribution pattern with chronic and lichenified lesions at flexures, hands, and often head and neck. Various disease triggers have been described that usually represent harmless environmental allergens derived for example from pollen or house dust mites, indicating that AE is also associated with other atopic diseases such as allergic rhinitis or allergic asthma. However, recent studies suggest that also the composition of the skin microbiota may impact on innate and adaptive immune responses, and thereby influence disease pathogenesis [2,3]. The fact that during adolescence AE often at least partially resolves indicates that the immune system is able to learn and to tolerate harmless disease triggers over time. So far, the mechanisms behind this gain of tolerance are not well understood, and this may partially reflect the fact that AE is a heterogeneous disease, with a broad spectrum regarding clinical phenotype, disease dynamics, trigger factors, and natural clinical course, as well as risk for comorbidities [4]. This heterogeneity is increasingly recognized also from a molecular point of view [5,6], and research efforts are directed into delivering reliable markers for patient stratification and individualized therapies.

Trends

The pathogenesis of atopic eczema (AE) can be better understood if separated, conceptually, into four modules. Distinct combinations of the components of these modules results in the varied presentations of the disease.

Genetics: recent advances highlight the importance of the cutaneous barrier and both innate and adaptive immune deviation.

Microbiota: there is reduced microbiota diversity in AE lesions in the skin, and this reduced diversity has been associated with the disease. The bias towards type 2 immunity seen in AE appears to be also supported by dysbiosis.

Innate immunity: ILC2 and myeloid-derived suppressor cells (MDSCs) contribute to AE pathogenesis, with ILC2s participating in the initiation of disease pathogenesis and MDSCs contributing by failing to terminate inflammation, perpetuating an inflammatory cycle.

Adaptive immunity: acute lesions are triggered by environmental allergens whereas the local microbiota and auto-allergens contribute to chronic disease.

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We discuss here the current understanding of the factors that contribute to AE pathogenesis. We assemble these factors into 'modules', and discuss how these modules can be combined to ultimately lead to epidermal barrier impairment, type 2 immunity, and chronic disease. We present this modular framework as a basis for precise patient stratification – a prerequisite for implementing precision medicine in the field – and in this context we propose a diagnostic and therapeutic algorithm aimed at the implementation of individualized medicine in AE standard of care.

Module 1: The Interplay of Genetic Background and Immunology

The pathogenesis of AE is based on complex genetic traits [7]. Almost 10 years ago a strong association between AE development and loss-of-function mutations in the gene encoding filaggrin was discovered [8]. Filaggrin links keratin filaments with disulfide bonds – a process that leads to epithelial cornification and the generation of a tight physical barrier. In addition, degradation products of filaggrin contribute to skin homeostasis by stabilizing the pH, by 'moisturing' the skin, and by participating in cutaneous antimicrobial defense [9]. Shortly thereafter, family-based studies revealed that loss of filaggrin function predisposes to AE with allergic sensitizations, the so-called extrinsic type of AE [10]. These findings now link the disruption of the 'physical' barrier with immune deviations of the first-line defense, the 'immunological' barrier, and highlight their close interaction and interdependence (Figure 1, Key Figure).

More recently, increasingly sophisticated genetic approaches and larger cohort sizes have led to the identification of other gene loci associated with AE. To date, 31 susceptibility loci have been identified in European, African, Japanese, and Latino ancestries [11]. Several of these loci, such

Key Figure

The Pathogenetic Mosaic of Atopic Eczema (AE)

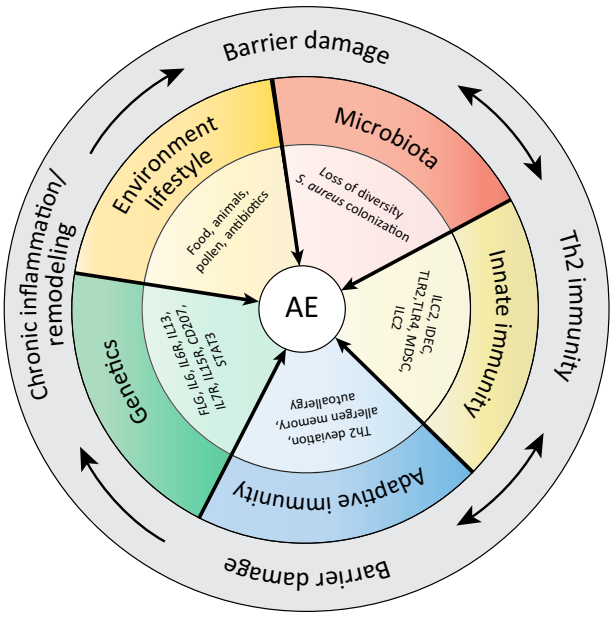

Figure 1. Hallmarks of AE are type 2 immunity and epidermal barrier impairment. Chronic eczema additionally shows a mixed immune response and epithelial remodeling. Those hallmarks may be induced by genetic background, environmental influences, alterations in the cutaneous microbiota, as well as innate and adaptive immune deviation.

as *STAT3* (signal transducer and activator of transcription 3), *IL18R* [interleukin (IL) 18 receptor] and *IL6R* (IL-6 receptor), have been shown to predispose also to inflammatory bowel diseases and rheumatoid arthritis, respectively, in a cohort of ~50 000 AE patients [12]. In line with the antagonistic immunological basis and rare clinical co-occurrence [13] of AE and psoriasis, overlapping loci within the epidermal differentiation complex or the type 2 T helper cell (Th2) locus control region represented opposing risk alleles of psoriasis or AE, respectively [101]. Most susceptibility loci are functionally assigned to the immune system (Table 1), among them those encoding CD207/langerin [11], the T cell trophic IL-7 and IL-15 receptors [11], the Th2-associated cytokine IL-13 [14], the acute phase IL-6 receptor [15], and the transcription factor STAT3 [11]. Of note, IL-6 and IL-13 were also found to 'define eczema' in an intraindividual gene expression comparison of psoriasis and eczema [16]. Taken together, 10 years after identification of the strong genetic background for barrier impairment, novel genetic studies illustrate that genetic variations in distinct immune pathways are associated with AE. Even if these studies do not provide information regarding the causative role of the individual immune genes, they reflect the heterogeneity of the disease and might be used to stratify patients in near future (see Concluding Remarks)

Module 2: The Microbiota and its Role in AE

Analysis of small subunit ribosomal RNA genes (16S rRNA) allows the diversity of microbes in a particular habitat to be assessed [17]. Twin studies using this approach identified interindividual intestinal microbe diversity as well as specific individual bacterial lineages and even similarities among family members [18]. Initial studies comparing cutaneous microbiota also revealed a large inter- and intra-individual diversity [19], and found that gender and exogenous factors such as time since last hand-washing affected cutaneous microbial diversity and community composition [20]. Comparing 20 diverse skin sites from each of 10 different individuals using 16S rRNA gene phylotyping demonstrated that the complexity and stability of the microbial community are dependent on the specific characteristics of the skin site, such as being sebaceous, moist, or dry, and bacterial diversity is highest in the latter [21]. This may be of importance also for

Table 1. Susceptibility Genes with Relevance for the Immune System

Susceptibility Gene/Refs	Variant	Chromosome	Function	Association with other Atopic Diseases
LCE3A (*FLG*) [9]	rs61813875	1q21.3	Involved in epithelial cornification	Allergy
IL13 [14]	rs12188917	5q31.1	Th2 cytokine	Asthma
IL18RA [91]	rs6419573	2q12.1	Receptor for IL-18	Asthma, allergy
IL6R [15]	rs12730935	1q21.3	Receptor for IL-6	Asthma
KIAA109 (*IL2*) [92]	rs17389644	4q27	T cell growth factor	Allergy
HLA-DRB1 [91]	rs4713555	6p21.32	Antigen presentation	Asthma, allergy
MICB [91]	rs145809981	6p21.33	Ligand for the NKG2D type II receptor, binding activates NK cells	Asthma, allergy
NLRP10 [91]	rs4312054	11p15.4	Part of the inflammasome response	–
PPP2R3C [11]	rs2038255	14q13.2	Regulatory subunit of protein phosphatase 2	–
IL15RA [11]	rs6602364	10p15.1	Receptor for IL-15	Allergy, asthma
IL7R [11]	rs10214237	5p13.2	Receptor for IL-7	–
STAT3 [11]	rs12951971	17q21.2	Transcription factor	–
CD207 [11]	rs112111458	2p13.3	Langerin	–

AE with its main symptom being dry skin and its predilection for specific skin sites. Detailed analyses within cutaneous habitats revealed high interpersonal variability, but minimal temporal variability within an individual. Transplantation of the tongue microbiota to the forehead even reversed to the original microbiota within hours, indicating a strong interdependence between skin site and microbiota [22].

Functional analyses in mice on immune consequences of microbiota were mostly performed by analyzing the gut, but cutaneous immunity also seems to depend on skin microbiota [3]. Mono-association of germ-free mice with the skin commensal *Staphylococcus epidermidis* rescued IL-17A production in the skin, but not the gut, and restored immune effector responses to cutaneous *Leishmania major* inoculation [3]. Consecutive work with this model demonstrated that skin-resident dendritic cell subsets orchestrate *S. epidermidis*-specific T cell responses in the absence of inflammation. However, this response increases barrier immunity by upregulating IL-1 and S100 proteins through IL-17A. Thus, microbe-sensing shapes the immune system in a compartmentalized fashion, with skin commensals shaping skin-specific immunity [3] and cutaneous microbes preparing the immune system to mount an effective immune defense [2].

A study on 12 children with AE and 11 controls investigated the predilection sites of AE: the antecubital and popliteal creases. Uniformly, AE lesions exhibited reduced bacterial diversity, and analyses detected largely staphylococci, with *Staphylococcus aureus* being the most dominant, but *S. epidermidis* was also frequent. Interestingly, even intermittent treatment of AE before new AE development significantly increased bacterial diversity during these flares [23] (Figure 2). Thus, the hen and egg problem still needs to be solved: does the initial Th2-type inflammation, which is associated with reduced barrier function and decreased production of antimicrobial peptides (AMP), allow the temporal shift from a balanced microbiome to a mono-culture of staphylococci, or does the temporal change in the microbiota and loss of diversity initiate skin inflammation in AE?

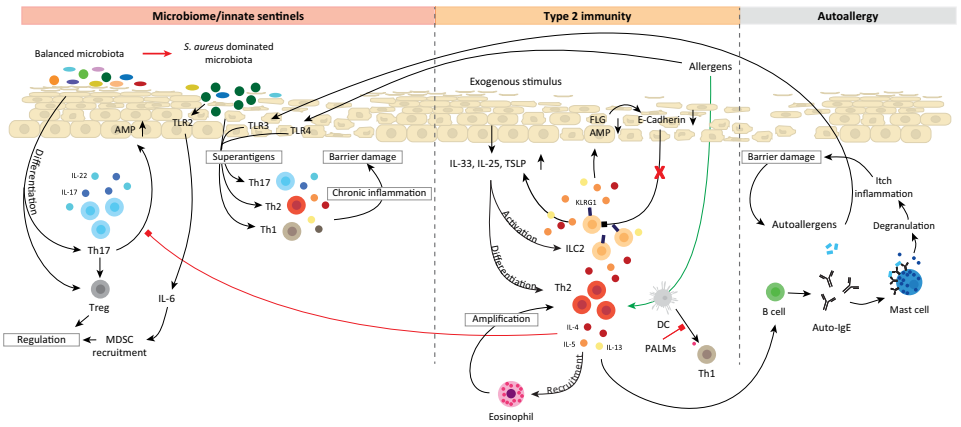

Figure 2. Central Pathogenesis Cascades in Atopic Eczema (AE). (Left) A balanced microbiota induces a type 17 T helper cell (Th17) immune response with induction of antimicrobial peptides by the epidermis. In AE, the type 2 dominated microenvironment inhibits Th17 immunity, consequently the microbial diversity is limited and *Staphylococcus aureus* overgrows the healthy microbiome. Subsequently, *S. aureus*-derived superantigens, and also stimulation of the innate immune system by allergens or autoallergy via Toll-like receptors (TLRs), induce a mixed proinflammatory immune response, leading to further epidermal barrier damage. (Middle column) Epidermal barrier damage – caused by genetic background or external triggers – induces a type 2-dominated microenvironment, comprising both Th2 cells and type 2 innate lymphoid cells (ILC2s), that further reduces epidermal barrier and opens a *circulus vitiosus*. (Right) Antigens released in the process of epithelial damage or autoantigens mimicking microbial antigens induce secretion of autoreactive IgE antibodies in the type 2-dominated microenvironment. Via activation of mast cells and TLRs, such autoantigens contribute to a mixed proinflammatory immune response in the skin. Abbreviations: AMP, antimicrobial peptide; DC, dendritic cell; FLG, filaggrin; IL, interleukin; KLRG, killer cell lectin-like receptor G1; PALM, pollen associated lipid mediator; Treg, regulatory T cell.

Recently, cutaneous inflammation and high immunoglobulin (Ig)E levels were shown to be a consequence of loss of diversity of the cutaneous microbiome in a mouse with epidermal ADAM17 (a disintegrin and metalloprotease 17) deficiency leading to a skin-specific immune barrier defect [24]. These mice develop dry skin at the age of 3 weeks and pruritic skin lesions similarly to ADAM17-deficient patients. Investigating the underlying mechanisms, the authors detected dysbiosis with loss of microbial diversity, eczema, and Th2 immunity. *S. aureus* was dominant in the skin at week 6, the time of severe eczema. Eradication of these cutaneous mono-cultures by antibiotic treatment allowed recovery of the mice. Based on the ADAM17 deficiency, this model may reflect microbial dermatitis more than AE, but the data argue for a role for microbial dysbiosis as an initiating factor of AE.

These data suggest that, rather than the steady-state microbiota, dysbiosis (i) can be responsible for AE flares, as also indicated by human analyses [23], and (ii) can also induce the Th2 immune bias found in patients with AE. However, evidence that the cutaneous steady-state microbiota directly induces a Th2 immune response is lacking. Nevertheless, some mouse studies investigating intestinal immune responses suggest that this may be functional: (i) commensal bacteria-derived signals were shown to upregulate basophils, IgE, and type 2 immunity via MYD88 (myeloid differentiation primary response gene 88) [25]; (ii) in a model of malnutrition (vitamin A deficiency) also affecting intestinal microbiota, IL-13-producing innate lymphoid cells type 2 (ILC2s; see below) were dramatically upregulated at the expense of IL-17-producing ILC3s [26]; and (iii) the microbiota-induced IL-17 axis was dramatically suppressed in favor of type-2 immunity and pathology in the absence of the transcription factor RORγt (retinoid-related orphan receptor γt) [27]. However, no data have yet demonstrated a role for skin steady-state microbiota in inducing cutaneous type 2 immunity as in AE.

The notion that a 'wrong microbiota' can be substituted by the 'right microbiota' to alleviate chronic cutaneous inflammation is attractive from a therapeutic perspective, especially given the relative ease of accessibility of the skin. In an early clinical placebo-controlled study we applied lysates of Gram-negative non-pathogenic *Vitreoscilla filiformis* originally found in thermal spa water topically to the skin of AE patients. A significant intergroup difference was found after 30 days of treatment in regard to SCORAD ('scoring atopic dermatitis' scale) and pruritus. demonstrating therapeutic efficacy of signals derived of this lysate [28].

More recently, we demonstrated the underlying mechanism *in vitro* and in AE-prone NC/Nga mice *in vivo*. *In vitro*, exposure of dendritic cells to this lysate of *V. filiformis* promotes the dominant production of the immunoregulatory cytokine IL-10 in a TLR2 and MYD88-dependent manner and co-culture with naïve T cells induced T cells that potently suppressed effector T cells. These suppressive T cells could be classified as type 1 regulatory T cells (TR1 cells) in view of IL-10 and simultaneous interferon (IFN)-γ production [29]. Cutaneous exposure of NC/Nga mice to signals of *V. filiformis*-induced T cell IL-10 and suppressed FITC (fluorescein isothiocyanate)-induced contact hypersensitivity and T cell proliferation. These data indicate that, in principle, signals from the 'right' bacteria may be beneficial for patients with AE.

In the former studies, lysates were applied to the skin and not living bacteria. Thus, it remains to be established whether seeding of live bacteria onto the skin might provide sustained immune signals with immune-regulatory properties. In the case of severe and recurrent *Clostridium difficile* gut infection in humans, a clinical trial was performed comparing the following groups: one group receiving *C. difficile* eradication with vancomycin, one group with this treatment followed by bowel lavage, and one group with both and with fecal transplantation. Fecal transplantation proved to be highly successful, with more than 90% being cured without relapse, compared to about 20% and 30% in the respective other groups, indicating that establishing a new intestinal microbiota population led to recovery [30]. These findings suggest that

microbiota-based approaches hold promise for the treatment of AE and other cutaneous inflammatory conditions. However, the development of specific therapies will require further characterization of the microbial populations associated with different stages of AE, and also of the mechanisms by which these impact on the different immune cell populations in the skin.

Effects of Type 2 Immunity on the Microbiota

Immediate cutaneous innate immune responses to microbes include the regulation of AMPs. AMPs are broad-spectrum antibiotics controlling both Gram-negative and Gram-positive bacteria, enveloped viruses, and fungi, regulate cutaneous microbiota composition, and represent the first-line defense in response to pathogenic bacteria [31]. A major advance in the understanding of AMP regulation came from the comparison of two chronic inflammatory skin diseases: psoriasis and AE. While psoriasis skin is almost never infected, AE is almost always colonized and often even infected with *S. aureus* [32]. In this context, differences observed in AMP expression have received a great deal of attention because these seemed to perfectly explain differences in cutaneous *S. aureus* overgrowth. First, reduced upregulation of the AMPs cathelicidin (LL-37) and β-defensins (HBD-2) in AE versus psoriasis was observed [33]. The dichotomy of these two chronic inflammatory skin diseases is best documented by their immune profiles. AE is dominated by Th2 cells, with IL-4 and IL-13 being highest in the early acute phase of AE, while in psoriasis driving adaptive immune cells from the outset are Th1 and Th17 and their cytokines tumor necrosis factor (TNF), IL-12/23, and IL-17A [34–37]. Importantly, application of IL-4 is even an effective therapy in psoriasis by blocking the Th1/Th17 pathways [38,39].

Subsequently it was discovered that Th2 cytokines IL-4 and IL-13 are responsible for the reduced upregulation of LL-37 in keratinocytes in AE [40], marking reduced AMP levels in AE as a consequence of Th2 inflammation (Figure 2). Because Th2 cytokines also downregulate epidermal filaggrin expression, it became clear that levels of filaggrin are influenced not only by the genotype but also by cutaneous Th2 inflammation [41]. Thus, reduced AMP and barrier function pave the way for the cutaneous *S. aureus* overgrowth in AE.

Module 3: Innate Immune Cells and their Role in Chronic Inflammation

ILCs: New Players on the Ground

ILCs represent the innate counterpart of T helper cells with comparable cytokine secretion pattern, but lack specific antigen receptors and hematopoietic lineage markers. Similarly to T helper cells, ILC are grouped according to their secreted cytokines into three subsets: ILC1 (IFNγ$^+$), ILC2 (IL-5$^+$, IL-13$^+$) and ILC3 (IL-17$^+$, IL-22$^+$) (reviewed in [42]). Whereas the phenotype and function of mouse ILCs at mucosal surfaces are relatively well understood, understanding their contribution to skin diseases, particularly in the human system, is still in its infancy. However, several recent studies indicate the contribution of ILC2s to the pathogenesis and overall type 2 phenotype of AE: (i) ILC2 cells are enriched in AE lesions [43] and reside in the dermis next to mast cells [44]; (ii) activation of ILC2s is induced by lipids and several cytokines such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) that show a clear association with AE [45] (Figure 2) and are augmented after barrier disruption; (iii) abundant secretion of IL-13 in lesional skin by ILC2 and Th2 cells further triggers the epithelial production of TSLP and may close a vicious circle of ILC2 activation [46,47]; and (iv) inhibitory signals for ILC2s are less abundant in AE lesions because filaggrin mutations result in downregulation of E-cadherin in epidermal keratinocytes. This impedes binding of E-cadherin to the inhibitory immunoreceptor KLRG1 (killer cell lectin-like receptor G1) on ILC2s, and allows continuous activation [43] (Figure 2).

Despite the progress made in understanding the activation of ILC2s in AE, the contribution of these cells to disease pathology is still under debate. Mice deficient in recombination activating

gene 2 (*Rag1*$^{-/-}$) that have been treated with anti-CD90.2 antibodies lack ILC2 cells and react with reduced AE-like skin inflammation after calcipotriol challenge [43]. Together with the secretion of type 2 cytokines and the contribution to the overall type 2 response observed in AE, this gives hints that they are involved in disease; however, final proof is missing to date. Being equipped with surface receptors for the 'alarmins' IL-33, IL-25, and TSLP, ILC2 cells function as sensors of barrier disruption leading to their activation and secretion of amphiregulin. By the transfer of wild-type ILC2 cells into amphiregulin-deficient mice, their role in epithelial repair mechanisms has been unraveled in the murine intestine [48]. If this should also be the case for the human intestine, the repair function of ILC2s in AE lesions is abrogated despite the overwhelming presence of alarmins. By diminishing the production of AMPs in keratinocytes via IL-13 [49], ILC2 cells might even actively contribute to further barrier disruption. In addition to the capacity to sense barrier disruption, ILC2 cells recognize the presence of particular allergens. Application of house dust mite extract to human and mouse skin leads to the accumulation and activation of ILC2s [43]. Therefore, ILC2s might be innate sensors that react to disease triggers in first-line defense and functionally contribute to barrier disruption and type 2 immunity.

Innate Triggers as Drivers of Chronic Inflammation

Recent evidence suggests that ILCs and other innate immune cells contribute to chronic inflammation in AE. The multimodal system of immune sensing involves triggering Toll-like receptors (TLR) such as TLR2. TLR2 is most abundantly engaged on skin because it is the dominant innate receptor sensing Gram-positive bacteria [32,50,51]. TLR2 is known to form heterodimers with TLR1 and TLR6 to interact with a broad spectrum of ligands [52]. It is obvious that a diversity of ligands and its receptors allow fine-tuning of consecutive responses, but the functional consequences of this diversity are only now being characterized. Recently, it was shown that cutaneous sensing of ligands for TLR1/2 induces moderate cutaneous inflammation, whereas activation of TLR2/6 leads to severe inflammation mediated by resident skin cells that strongly upregulate IL-6 [53]. Following TLR2-induced IL-6 induction, accumulation of myeloid-derived suppressor cells (MDSCs) potently suppressed T cell-mediated recall responses. However, in the Th2-dominated microenvironment of AE, the attempt to terminate dermatitis instead amplified inflammation by allowing microbes to spread, which ultimately led to severe complications such as eczema herpeticum [53].

In addition to the regulation of TLR2 activation, it is now well established that a 'second hit' for innate sentinels functionally alters downstream cascades. In contrast to healthy skin, TLR2 ligands in AE are sensed by innate immune cells in a dominant Th2 cytokine milieu. This microenvironment inhibits antimicrobial Th17 immune responses [39], and potently suppresses the production of IL-10, while upregulating the secretion of IL-12 by accessory immune cells such as dendritic cells [53,54]. In this way, the Th2 cytokines IL-4 and IL-13 change the outcome of TLR2-mediated innate immune sensing [39,55–57]. This second hit for innate sentinels leads to a transformation of a self-limited Th2-mediated dermatitis into a persistent and chronic cutaneous inflammation [55]. These data from mouse models provide a rationale for the beneficial effects of inhibiting Th2 cytokines that are functional not only in the early Th2-dominated phase of inflammation but also at later stages of established chronic inflammation. In addition, these data show that signals derived from the skin microbiota, both if its diversity is high or reduced, play a very important role in regulating cutaneous immunity, in driving AE inflammation, and in orchestrating its resolution.

Module 4: Adaptive Immunity and the Nature of Allergens

Adaptive immunity is activated by the specific recognition of potentially harmful antigens. Whereas in allergic rhinitis misdirected Th2 responses against harmless environmental antigens are directly causative for the symptoms, the contribution of these antigens in AE is under debate.

In a subset of newborns and babies a clear association of skin inflammation with ingestion of particular food allergens such as egg, cow milk, or peanut proteins is well established [58], whereas in adults sensitization to airborne allergens derived from pollen or house dust mites is more frequent [59,60]. Interestingly, only a subset of sensitized AE patients (maximum 39%) react to direct application of allergen to the skin (atopy patch test, APT) with an eczematous lesion [61], indicating that the allergen itself might not be the direct driver of disease in the majority of patients. This again reflects the heterogeneity of AE pathogenesis, and leaves us with the question of why the adaptive immune system recognizes harmless environmental substances as 'danger'. One possible explanation is that several major allergens act *per se* as danger signal, for example by binding to TLRs (reviewed in [62]) and subsequent induction of potent innate immune responses [62,63] via activation of antigen-presenting cells that in turn shape immune responses towards a type 2 profile (Figure 2). In addition, pollen have been shown to be more than merely allergen-carriers because they contain active lipid substances, the so-called pollen-associated lipid mediators, that act on antigen-presenting cells and foster the development of Th2 responses via the inhibition of the Th1-differentiating cytokine IL-12 [64,65]. Therefore, common allergens may bridge innate and adaptive immunity to skew immune responses towards type 2 dominance.

Besides allergens acting both as classical antigens and inducers of innate immune signals, colonizing microorganisms influence inflammation and the type of immune response. Bacterial exotoxins derived from *S. aureus* frequently act as superantigens that stimulate adaptive immunity independently of antigen recognition in AE [66] (Figure 2). Human *in vitro* studies have shown that superantigens are potent inducers of T cell IL-17 and IL-22 secretion [49,67] and might be important for the shift of an initial, allergen-driven Th2 to a subsequent microbe-triggered Th1/Th17/Th22 response. This mixed immune response explains also the different clinical and histological phenotype of acute versus chronic eczema, with the latter even resembling the Th17-driven disease psoriasis [7].

A strong argument for specific environmental immune stimuli as the primary cause of AE is actually found in the comparison of AE with psoriasis. Even if patients with concomitant psoriasis and AE are extremely rare, they represent a highly interesting model to compare pathogenesis independently of the genetic background [16]. The observation of both naturally occurring eczema and patch test-induced eczema immediately adjacent to psoriasis plaques argues that. at least in subgroups of the diseases, specific local immune stimuli are the primary triggers of both psoriasis and AE [34,68,69]. While in the case of AE such primary triggers may be aeroallergens, such as house dust mite or pollen, factors leading to chronic eczema with its broader immune response are instead triggered by microorganisms or self-antigens.

In this regard, the autoimmune phenomenon of so-called 'autoallergy' may play an important role as an epiphenomenon of chronic inflammation (Figure 2). Various autoallergens are described in AE. They may be either cross-reactive with microbial antigens, as is the case for the autoantigen human thioredoxin [70], or primary autoantigens, named Hom S1–S5 [71]. There is evidence that autoallergy is associated with a more severe form of AE [72] where the heavily disrupted epithelial barrier might be the reason for autoallergen release. Because autoallergens again preferentially induce a Th1, Th17, and Th22 immune response, they contribute to the mixed immune response type in chronic eczema [73,74].

Taken together, hyper-Th2 immunity is a hallmark of AE pathogenesis that can be triggered by common aeroallergens and their vehicles. Chronic, broad adaptive immune responses are involved, and these are induced by tissue-specific immune responses, the local microbiota and auto-antigens.

Concluding Remarks

Dissecting the pathogenesis of AE into different modules allows the heterogeneity of this complex disease to be better characterized. This heterogeneity is increasingly reflected by distinct therapeutic approaches. Therefore, the last section of this review introduces therapeutic strategies and proposes a therapeutic algorithm based on patient stratification (Figure 3). Such an algorithm must recognize the heterogeneity of AE: in some cases causative treatment or even prevention may be possible, while symptomatic treatments should be personalized based on the individual contributions of the different pathogenesis modules discussed above (also see Outstanding Questions).

Concepts for prevention of AE follow the hypothesis that single or few immune triggers initiate the immune cascade in AE pathogenesis, which may be true in a subset of patients, for example food-allergic newborns or adults with a positive APT. A shift of paradigms currently occurs concerning primary prevention: while avoidance of allergens was advocated for a long time, recent evidence suggests that allergen sensitization as a triggering factor in early AE might be benefit from continuous early or even prenatal habituation. This has been shown convincingly for peanut allergy [75] but also for contact with pet animals [76]. Insights into the relevance of the microbiota led to a second hypothesis – that influencing the microbiota could prevent AE. Clinical trials feeding newborns at risk of developing AE with bacterial lysates [77] or prebiotics [78] gave promising results that would encourage further large-scale studies, whereas others failed to confirm these findings [79,80]. Thus, large-scale studies are warranted, but the outcome will crucially depend on precise patient stratification and the time-point of application. Because recent studies indicate compartmentalization of microbe-driven immune orchestration [2,3], influencing skin microbiota in a more differentiated fashion than by anti-infectives or antibiotics should be the goal of future clinical trials.

Secondary prevention concepts are most successful in children, where food allergens may directly exacerbate AE [58]. Here, oral provocation tests are the gold standard, and a subsequent strict diet frequently leads to improvement of eczema in a subset of patients. In sharp contrast, food allergens play a minor role in adult AE, and strategies to prevent contact with house dust mites or even aeroallergens are highly complicated.

Acute cases of manifest AE that can be traced to a single trigger factor may benefit from causative approaches such as allergen-specific immunotherapy. While a recent meta-analysis comes to the conclusion that immunotherapy is beneficial for the outcome of AE [81], the largest individual randomized double blind placebo control (RDBPC) trial to date does not report an overall meaningful improvement of AE [82]. This reflects again the heterogeneity of AE pathogenesis and underlines the need of clear parameters to stratify AE patients as well as biomarkers predicting the individual outcome of an immunotherapy.

Once AE is manifest, it is treated symptomatically. While moderate AE is treated with a multilayered concept of topical treatments restoring the epidermal barrier and broadly anti-inflammatory topical steroids, more-severe cases require systemic treatment [83]. Here, the main concepts are to target acute-phase or non-Th2 inflammation, Th2 immunity, influence the cutaneous microbiota, and restore the epidermal barrier. Table 2 gives an overview about currently developed specific symptomatic therapies in AE. Dupilumab, an antibody broadly inhibiting Th2 responses by targeting IL-4Rα, is the first drug that showed efficacy at the large-scale population level. Previous attempts to inhibit Th2 responses by interfering with IL-5, IL-13, or IgE showed a more heterogeneous response rate, and were thus not followed up. Again, the lesson learned from dupilumab is that previous holistic study designs probably fail to identify the AE subpopulation that responds to Th2-targeting therapy. Besides Th2-inhibiting therapeutics, drugs targeting acute-phase inflammation have been trialed in AE. The most promising one may

Outstanding Questions

What is the primary cause of AE pathogenesis? AE is characterized by chronic cutaneous inflammation based on (i) epidermal barrier damage, (ii) altered skin microbiota, and (iii) abnormal type 2 immunity. Each of these also modulates dysfunction of the other two. Regarding AE initiation, however, the question of what came first – the hen or the egg – remains unresolved.

How can AE patients be stratified to realize the ultimate goal of implementing individualized medicine in diagnosis and therapy? Dissecting AE pathogenesis into different modules is the first step of precision medicine for AE. However, the level of contribution of each of the modules will be different and 'individual' for AE patients. Thus, AE as a heterogeneous disease can be stratified at a molecular level for individual AE endotypes. However, valid biomarkers that define AE endotypes for groups of patients and predict the risk for comorbidities, the natural clinical course of AE, or optimal therapeutic response have yet to be identified.

What are the factors leading to remission or resolution of AE? AE drastically improves and even clears in the vast majority of afflicted children before adulthood. Currently, one cannot predict which baby will undergo remission and which will suffer from life-long severe disease. Similarly, single AE lesions may heal, but the process of spontaneous AE resolution has not been characterized. Understanding remission and resolution of AE will pave the way to new therapeutic strategies.

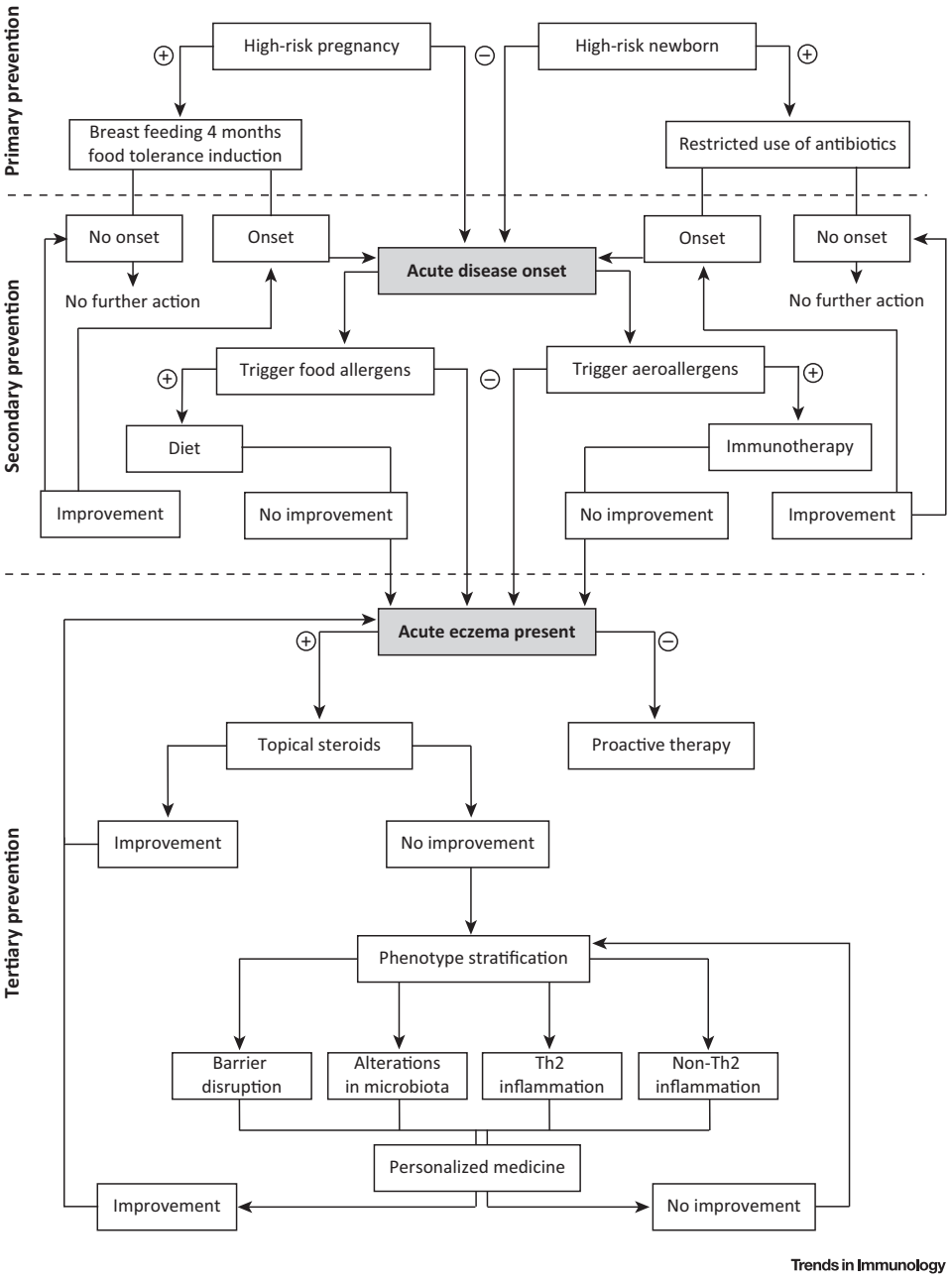

Figure 3. A Proposed Diagnostic and Therapeutic Algorithm for Atopic eczema (AE). Primary prevention of AE may be achieved by breast-feeding and low-dose food tolerance of the unborn via the maternal diet, as well as by restricted use of antibiotics for the newborn. In case of acute eczema onset, triggers should be identified to eventually guide therapeutic approaches. Manifest eczema is treated symptomatically with topical steroids, and severe eczema by using a stratified therapeutic algorithm based on individual predisposition: microbiota-centered, targeting the epidermal barrier or type 2 T helper cell (Th2) function or acute phase immunity. Eczema in remission should be treated with the concept of proactive therapy.

be tocilizumab that neutralizes IL-6. Here, a small case series showed good clinical efficacy, but infectious side-effects led the authors to terminate the study [84]. A larger trial using ustekinumab that targets IL-12p40 is currently running. Here again, smaller case studies report heterogeneous outcomes [85,86]. Thus, targeting acute-phase or non-Th2-inflammation in AE will again require personalized medicine, namely a preselection of patients with dominant non-Th2

Table 2. Symptomatic Therapeutic Approaches in AE

Target	Biological	Level of Evidence	Key Outcome/Refs
Th2 Immunity			
Il-4Rα	Dupilumab (further substances: AMG-317, Pitrakinra)	Phase III	EASI 50: 47/55 [93]
IL-5	Mepolizumab	Stopped after phase II	EASI 50: 0/18 [94]
IgE	Omalizumab (further substances: MEDI4212, QGE031)	Stopped after proof-of-concept	Heterogeneous reports ranging from EASI or SCORAD 50 0/20 [95] to 21/21 [96]
CD20	Rituximab	Case series	EASI 50: 6/6 [97], long-term: 0/2 [98]
IL-31	BMS-981164	Phase I ongoing	https://clinicaltrials.gov/ct2/show/NCT01614756
IL-31R	CIM331	Phase II ongoing	https://clinicaltrials.gov/ct2/show/NCT01986933
TSLP	AMG-157	Phase I completed	https://clinicaltrials.gov/ct2/show/NCT00757042
CRTH2	QAW039	Phase II completed	https://clinicaltrials.gov/ct2/show/NCT01785602
Non-Th2 Immunity			
IL-1R1	Anakinra	Phase I completed	https://clinicaltrials.gov/ct2/show/NCT01122914
IL-6	Tocilizumab	Case series	EASI 50: 3/3 [84]
IL-22	ILV-094	Phase II ongoing	https://clinicaltrials.gov/ct2/show/NCT01941537
IL-23p40	Ustekinumab	Case series; phase II ongoing	Heterogeneous reports: successful [34,85] versus non-effective [86]
TNF-α	Etanercept	Case series	EASI 50: 0/2 [99]
	Recombinant IFN-γ	Phase III	EASI 50: 18/40 [100]

inflammation and additionally at lower risk of developing infections. A good model for the success of such a stratification is mepolizumab, an anti-IL-5 antibody used to treat asthma. While initial holistic studies failed to show clinical efficacy [87], the antibody seems to be highly efficient in a subgroup of patients with severe asthma and persistent eosinophilic inflammation [88,89].

Taken together, the numerous therapeutic strategies of AE reflect its complex pathogenesis. Key to success is a precise stratification of individual patients. This stratification must be based on individual risk to develop AE as determined by family history and eventually genetic characterization, sensitization profile, clinical course of the disease, comorbidities, clinical and histological phenotype of AE, and analysis of skin microbiota, as well as molecular biomarkers in the circulation or lesional skin. A model algorithm for well-characterized patients is proposed in Figure 3. The benefit of primary prevention is not fully clear yet, but it seems that sensitization against food allergens as triggers of newborn AE might be beneficially modulated by intake of the food by the pregnant mother – a shift of paradigms. It is also not clear yet whether newborns at risk might benefit from an early and consequent therapy with barrier-restoring topical ointments,

but the immunology of AE provides a clear indication for such a suggestion. Furthermore, there is first evidence that microbiota-restoring topical agents might have a place here in near future.

Once AE is manifest, it should be treated early and vigorously. Previously affected skin is treated intermittently with low-dose steroids or calcineurin inhibitors – the concept of pro-active therapy [90]. In an acute stage of the disease, triggers may be identified and specific immunotherapy might be beneficial in a subgroup of AE patients. The current state of the art for the treatment of established AE is symptomatic treatment. Here also, several strategies have evolved in recent years, and a well-phenotyped and -stratified patient may take benefit from targeting epidermal barrier impairment, dysbiosis, Th2 inflammation, or non-Th2 inflammation. A major task for the future of AE treatment is to develop a clear algorithm accompanied by biomarkers predicting the optimal and personalized therapeutic strategy.

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