



REVIEW

Inflammasome pathways in atopic dermatitis: insights into inflammatory mechanisms and therapeutic targets[☆]



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Abstract Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a complex interaction between genetic, immunological, and environmental factors. The combination of immune dysregulation and skin barrier dysfunction plays a crucial role in the pathogenesis of the disease. The inflammasome, an important intracellular complex of pattern recognition receptors (PRRs), plays a crucial role in the cutaneous inflammatory response, activating caspase-1 and promoting the release of pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-18. The role of inflammasome components in regulating the inflammatory response in AD highlights how the activation of these complexes exacerbates inflammation and contributes to the worsening of the disease and tissue damage. The review included observational and experimental studies investigating inflammasome activation in AD and other inflammatory skin diseases. The main mechanisms of inflammasome activation and their impact on the inflammatory environment and skin barrier integrity were discussed. Understanding the role of the inflammasome in AD is essential for the development of new therapeutic approaches aimed at both modulating the immune response and restoring the skin barrier, improving more effective clinical management and patients' quality of life.

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease. Skin manifestations include erythema, lichenification, xerosis, papules and desquamation. AD is characterized by intense pruritus, one of the main symptoms, which aggravates others, such as a sensation of pain,¹

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sleep disorders, fatigue^{2,3} and neuropsychiatric symptoms (attention deficit hyperactivity disorder, depression and anxiety).^{3,4} Together, all these manifestations contribute to impairing of patient's quality of life, leading to psychosocial suffering and stigma.²

The etiopathogenesis of AD is a complex multifactorial interaction between various elements: environmental factors, genetic susceptibility,⁵ changes in the function of the skin barrier, the microbiota and the immune system.⁶ Together, these factors contribute to the development, progression and chronicity of the disease. As complications, AD patients are more susceptible to infections such as those caused by the *herpes simplex virus* (HSV)⁷ and mainly by *Staphylococcus aureus* (*S. aureus*).^{8,9} Patients with AD are also susceptible to environmental impacts, indicating that climatic factors, temperature, humidity, air pollution,¹⁰ and exposure to ultraviolet rays¹¹ can interact directly with the skin barrier and significantly influence the development and exacerbation of AD symptoms.¹²

The review addresses the relevance of the interaction between alterations in skin barrier proteins, the innate and adaptive immune response, and connections with the inflammasome complex, and the consequent impact on the pheno-endotypical features of AD.

Key changes in the immune response of atopic dermatitis

Impaired skin barrier

In AD patients, changes in the skin barrier (SB) lead to increased transepidermal water loss (TEWL), defects in the metabolism of pro-filaggrin,¹³ and lower expression of filaggrin and claudin 1 (protein located in tight junctions – TJ).^{14,15} In addition, there is a decrease in ceramide levels,^{13,16} cholesterol sulfate and accumulation of sphingosylphosphorylcholine, due to increased expression of the enzyme sphingomyelin deacylase.^{17,18} Other contributors include decreased antimicrobial peptides (AMPs), increased serine protease (SP), reduced SP inhibitors and disrupted TJs.¹⁹

In addition, keratinocytes of AD patients show dysfunction in their response to environmental stimuli, undergoing apoptosis and leading to interruptions in SB function. Also, loss-of-function mutations in the filaggrin gene,²⁰ in the claudin 1 protein and single nucleotide polymorphisms in the SP SPINK5 inhibitor and SP KLK7 have been described in AD.^{21,22}

Fragility in the SB is well described as a key factor in the pathogenesis of AD, amplifying inflammatory manifestations and aggravating the symptoms associated with the disease.²³ The sum of these factors contributes to greater susceptibility to infections and inflammation, due to increased skin permeability to allergens and irritants, favoring the penetration of pathogens (Fig. 1).

Mechanisms of adaptive immunity

The Th1/Th2 paradigm in AD has been revised, with evidence of a significant role for the IL-17 and IL-22-secreting Th17 and IL-22-secreting Th22 cell subtypes.^{24–27} Thus, dur-

ing the acute phase of AD, in addition to Th2 cytokines such as IL-4, IL-13 and IL-31, there is a predominance of IL-22, as well as smaller amounts of Th17 cells.²⁸ In the chronic phase of the disease, there is an amplification of Th2 and Th22 cytokine axes, with augmented Th1 cells but no further increases in Th17 cells.²⁸ These cytokines reduce the differentiation of epidermal cells and may contribute to the reduction of filaggrin and antimicrobial peptides (AMPs).²⁹ Analysis of acute lesions, compared to non-lesioned skin or chronic lesions, showed up-regulation of the S100A7, S100A8 and S100A9 genes and concomitant activation of Th2 and Th22 cytokines.²⁷ In addition, there is an increase in IL-22 in the dermis and serum of individuals with AD, suggesting a systemic impact on the immune response (Fig. 1).³⁰

The IL-22-producing cells that infiltrate the AD skin lesion are CD4+ T-helper lymphocytes (Th22) and CD8+ T-cytotoxic lymphocytes (Tc22); clinical severity of AD correlated with the number of Tc22 cells, but not with Th22 cells.³¹ In addition, cells from AD patients were responsive to stimulation with staphylococcal enterotoxins, with a decreased response by Th22 cells and increased responsiveness by Tc22 cells, suggesting the role of both T22 cells in the immune imbalance of AD.³⁰ Stimulation with enterotoxins also promoted up-regulation of anergy-related genes (EGR2 and IL13) in AD patients, associated with impairment of the effector response of CD4+CD38+ T cells.³²

As for Th17 cells, their role in defense against bacterial pathogens is well-known and they may be crucial in the pathogenesis of chronic inflammatory skin diseases.³¹ However, there is currently no consensus on the role of these cells in the immunopathogenesis of AD. There is an increase of IL-17 in the skin and serum levels in AD patients.¹⁵ It is also known that IL-17 exerts a role as an amplifier of skin lesions and the increase in circulating Th17 cells correlates with disease severity.³³

T-cells positive for cutaneous lymphocyte antigen (CLA+; skin homing receptor) mediate pathogenic inflammation in AD. Circulating CLA+ T cells are elevated in AD, respond to allergens, infiltrate skin lesions and participate in the initiation and perpetuation of AD lesions.³⁴ In addition, bacterial toxins are also able to increase the expression of CLA.³⁵

In addition to the involvement of cellular immunity, high IgE levels in AD are strongly correlated with the prevalence of IgE autoreactivity and disease severity. More findings reveal an increase of IgG4 and IgE anti-SEB (staphylococcal enterotoxin B) antibodies.³⁶ Likewise, numerous infiltrated cells in the skin lesions of individuals with AD are positive for IgE or its high-affinity Fc IgE receptor (FcεRI).³⁷

Mechanisms of innate immunity

In addition to the physical barrier mechanisms previously discussed, epithelial cells, mainly keratinocytes, are crucial components of the skin's innate immunity. These cells behave as sentinels for danger signals or microbial pathogens, triggering immune responses and a cascade of cytokine production.^{38,39}

Keratinocytes in AD skin express high levels of thymic stromal lymphopoietin (TSLP), IL-7-like cytokine, which induces the activation and migration to the lymph nodes of dendritic cells (DCs). The DCs stimulated by TSLP induce naive T cells to produce IL-5, IL-13 and TNF-α, and initiate

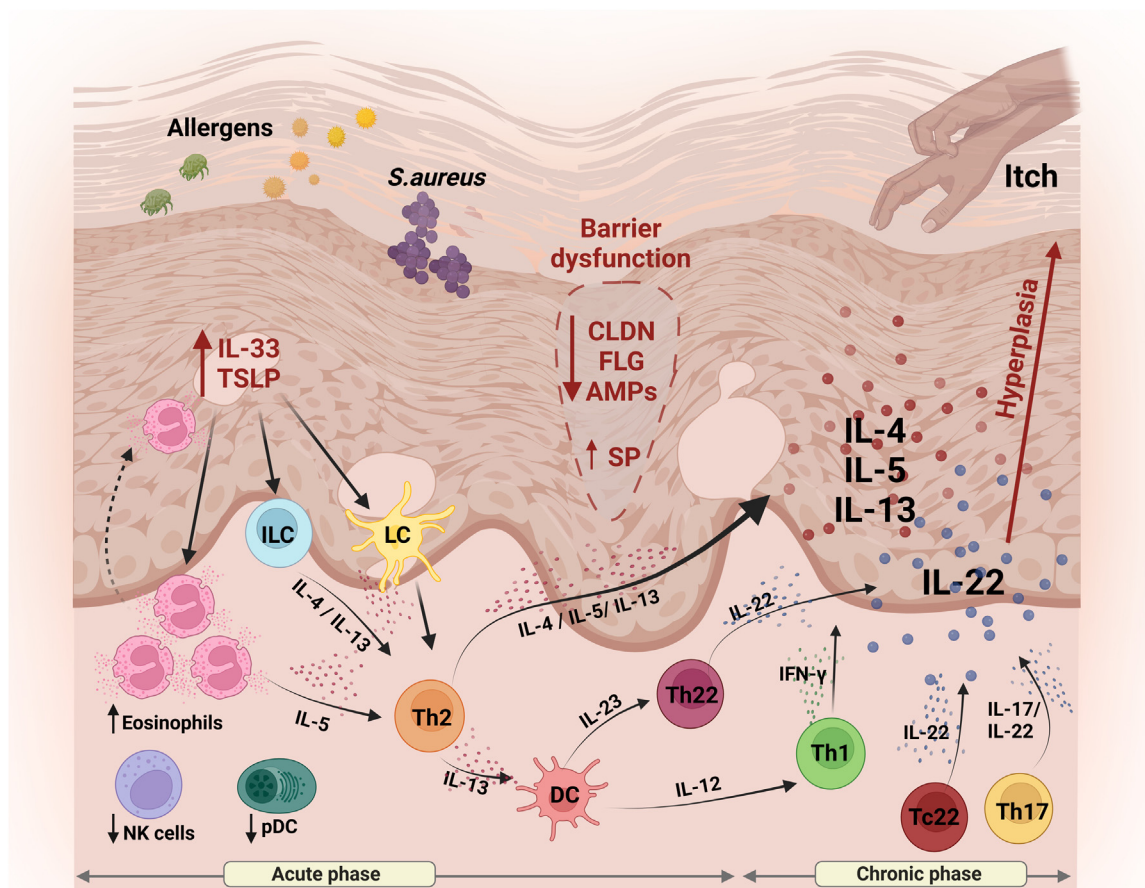


Fig. 1 Schematic representation of skin barrier (SC) alterations and the main aspects of innate and adaptive immunity involved in the pathogenesis of AD. Reduced expression of skin proteins (FLG and CLDNs) results in disruption of the BC and transepidermal water loss, facilitating the entry of external pathogens. Keratinocytes release TSLP and IL-33, amplifying the inflammatory response, attracting and activating Langerhans cells, ILCs and the recruitment of eosinophils. Together, these cells contribute to the release of Th2-type cytokines, including IL-4, IL-5 and IL-13. Dendritic cells, in turn, release IL-12 and IL-23, promoting activation of both the Th1 and Th22 profiles, resulting in the secretion of IFN- γ and IL-22, respectively. Pro-inflammatory cytokines IL-5, IL-13 and IL-31 are released by keratinocytes, which play a role in modulating pruritus, contributing to the perpetuation of the inflammatory process. In addition, IL-22 stimulates keratinocyte proliferation, promoting epidermal hyperplasia. IL, Interleukin; TSLP, thymic stromal lymphopoietin; CLDN, claudin; FLG, filaggrin; AMPs, antimicrobial peptides; SP, serine protease; ILC, innate lymphoid cells; LC, Langerhans cells; DC, dendritic cells; NK, natural killer; pDC, plasmacytoid dendritic cells; Th, T-helper. Figure generated with BioRender.

the production of chemokines by the DCs, which attract Th2 cells, an abundant subtype in AD patients (Fig. 1).^{38,39}

Epithelial cells and immune cells in the skin barrier express pattern recognition receptors (PRRs) that trigger innate immune responses. The arsenal of PRRs includes members of the Toll-like receptors (TLRs) family, C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG) cytoplasmic receptors, peptidoglycan recognition proteins (PGLYRPs) and NOD-like receptors (NLRs).^{40,41} The latter will be focused below with more details.

There are reports on the dysfunction of the TLR2, TLR9, and NOD1/2 receptors in AD patients. TLR2 recognizes peptide glycans from gram-positive bacteria and is among the most extensively studied receptors in infectious complications of AD patients. In monocytes and keratinocytes from AD patients, there was impairment of TLR2-mediated inflammatory cytokine production (IL-1 β and TNF- α).^{42,43}

In addition, the release of AMPs potentiates the strength of TJs and reinforces the defensive barrier against the invasion of microorganisms. In individuals with AD, there is a decrease in the functionality of TLRs, compromising this protective mechanism. This scenario contributes to greater susceptibility to skin infections, especially *S. aureus*.⁴⁴ *S. aureus* virulence factor itself is also an important element of the inflammation in AD patients, capable of inducing TSLP and IL-33, rather than AMPs (Fig. 1).⁴⁵

With regards to cell subtypes in AD, there is evidence of reduced function or migration to the skin of polymorphonuclear effector cells, natural killer (NK) cells and plasmacytoid dendritic cells (pDC).⁴² On the other hand, an increase in circulating eosinophils and eosinophil granule proteins has been reported in the sera and urine of patients.⁴⁶ It is worth noting that during AD crises, there is an increase in circulating IL-5 and eosinophilic chemotax-

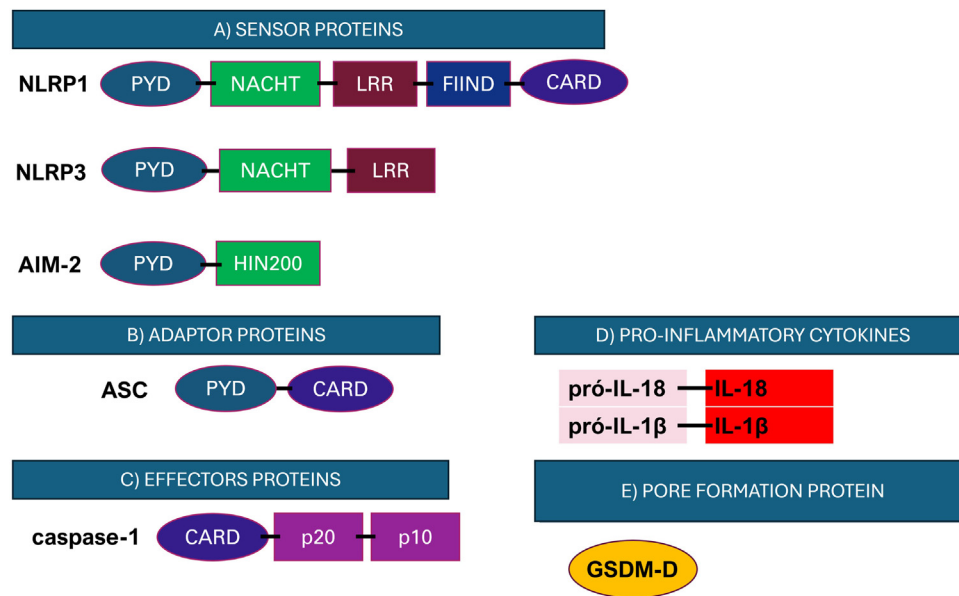


Fig. 2 Representation of the structure of the main components of the inflammasome. (A) Initiator proteins comprise cytosolic receptors; (B) ASC adaptor protein; (C) Caspase-1 effector protein; (D) Inflammatory cytokines and (E) GSDM-D pore-forming protein. NLRP, NACHT, LRR and PYD domains-containing protein; CARD, caspase recruitment domain; NACHT, Nucleotide-Binding Oligomerization Domain; LRR, Leucine-Rich Repeats; PYD, pyrin domain; HIN200, interferon-induced proteins; FIIND, function-to-find domain. Figure generated with BioRender.

ins, contributing to the extravasation of eosinophils into the skin (Fig. 1).

In AD lesional skin, there is an increased presence of activated NK cells, in contrast to their reduction in peripheral blood.⁴⁷ The authors recently found increased NK CLA+ cells in the peripheral blood of patients with severe AD and augmented expression of CD56 and granzyme in the dermis of these individuals. In addition, these cells were responsive to in vitro stimulation with microbial agonists.⁴⁸ There are reports on elevated group 2 Innate lymphoid cells (ILC2), which produce type 2 cytokines (IL-4, IL-5, IL-9 and IL-13) on the lesional skin of AD patients. More findings describe activation of ILCs by TSLP, IL-33 and IL-25, highly expressed in AD.⁴⁹

Defining inflammasomes and their role in inflammatory skin diseases

Inflammasome is an intracellular protein complex that can be activated in response to pathogens and signs of tissue damage. Its primary function is the maturation and secretion of pro-inflammatory cytokines which are fundamental for the elimination of pathogens and for tissue healing.⁵⁰ As a signaling pathway linked to the innate immune response, the inflammasome cascade is well characterized in myeloid cells, but some skin cells such as keratinocytes express its components.⁵¹ Despite its crucial role in the innate immune response, deregulated activation of the inflammasome may contribute to the development of inflammatory diseases such as rheumatoid arthritis, autoimmune diseases, inflammatory syndromes and skin diseases.⁵²

The inflammasome signaling cascade begins with the activation of initiator proteins (Fig. 2). These proteins are PRRs that recognize danger signals, such as pathogen-associated

molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).^{53,54} After activation, the initiator proteins interact with the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), which plays an essential role in the assembly of the inflammasome complex. Oligomerization of ASC via its PYD domain promotes the recruitment of pro-caspase-1, acting as a bridge between receptor interactions and pro-caspase-1.⁵⁵ This association results in the autoactivation of the pro-caspase, converting it into the effector protein caspase-1, an inflammatory caspase that cleaves its substrates pro-IL-18, pro-IL-1 β into their mature and bioactive forms IL-18 and IL-1 β (Fig. 2).^{56–58}

In addition to the processing and maturation of cytokines, the activation of caspase-1 by the inflammasome cascade may also promote the cleavage of the Gasdermin D (GSDM-D) protein.⁵⁹ GSDM-D was first described in 2015 and is expressed in immune cells and epithelial cells. After cleavage, the N-terminal portion of GSDM-D is released and inserts itself into the cell membrane, resulting in the formation of pores in the plasma membrane that lead to the release of the cytokines IL-1 β and IL-18, and a highly inflammatory cell death process called pyroptosis.^{55,57,60–62}

In addition to the canonical activation of the inflammasome mentioned above, the cytokines IL-18 and IL-1 β can also be produced through non-canonical activation of the inflammasome, when lipopolysaccharide (LPS) is directly recognized by the inflammatory caspases -4 and -5 in humans and caspase-11 in mice.^{63,64} The main activation mechanisms of the canonical and non-canonical pathways are presented in Fig. 3.

Among the inflammasome receptors, the family of NOD-type receptors is the best characterized.⁶⁵ These receptors have a tripartite structure composed of a central

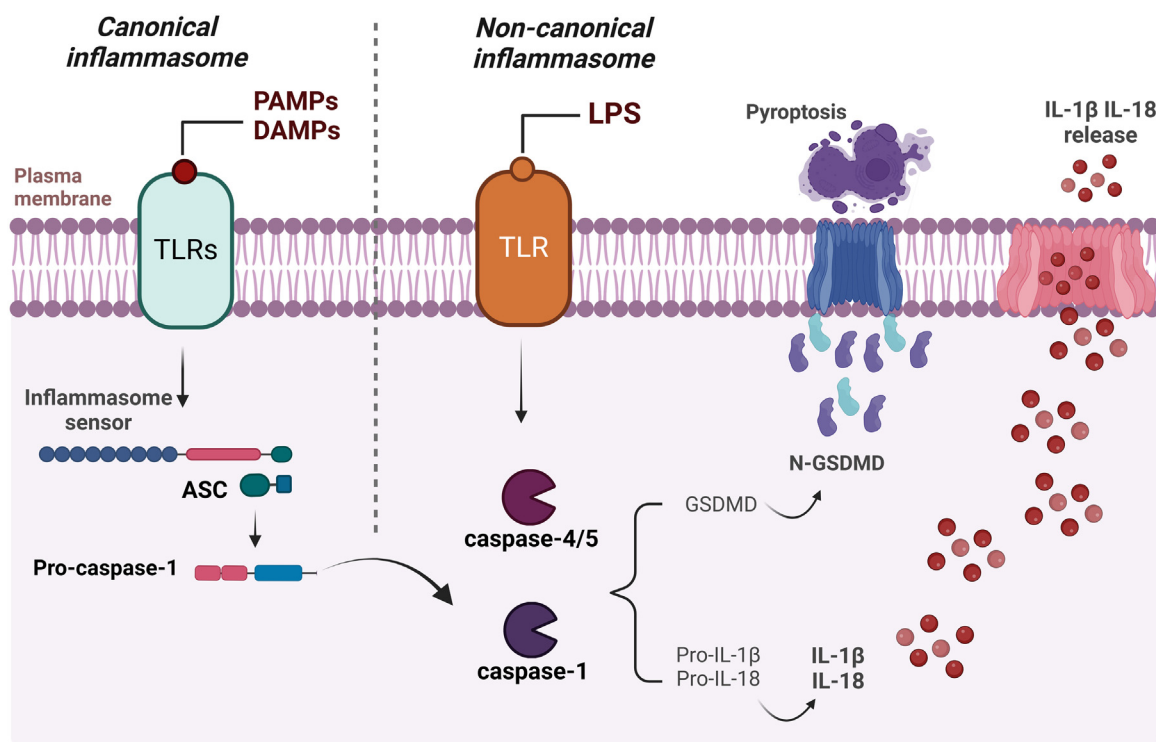


Fig. 3 Schematic representation of canonical and non-canonical inflammasome activation. The formation of the inflammasome via the canonical pathway occurs when PAMPs, DAMPs or other cytosolic disturbances are detected, resulting in the recruitment and activation of caspase-1, either directly or through the recruitment of the adaptor protein ASC. Caspase-1 initiates the process of maturation of pro-IL-1 β and pro-IL-18 into their active forms, in addition to cleaving GSDMD-D. This, in turn, interacts with the plasma membrane, creating pores and resulting in the release of intracellular content, including the inflammatory cytokines IL-1 β and IL-18. Activation of the non-canonical inflammasome begins with the detection of cytosolic LPS by caspase-4/caspase-5 (or pro-caspase-11 in mice), triggering the cleavage of GSDMD-D and subsequent pyroptosis. Figure generated with BioRender.

nucleotide-binding and oligomerization domain (NACHT), usually accompanied by leucine-rich repeats (LRRs), a C-terminal domain that recognizes and regulates ligands, and a variable N-terminal domain, which can be a caspase recruitment domain (CARD) or pyrin (PYD), responsible for the effector functions of the complex.⁶⁵ The NLR family has three distinct subfamilies: NODs (NOD1-2), NLRPs (NLRP1-14), and IPAF (ice protease-activating factor).⁶⁵

The NLRP1 inflammasome was first described in 2001 through the identification of the N-terminal PYD domain by Martinon et al.⁶⁴ The authors demonstrated the interaction of NLRP-1 with caspase-1 dependent on the presence of the ASC protein constituting the inflammasome complex.⁶⁴ NLRP1 is expressed in various immune cells, mainly in the skin by keratinocytes, and appears to play a central role as the main receptor involved in the formation of the inflammasome.⁶⁶ Indeed, UVB irradiation in primary keratinocytes causes translocation of the ASC protein to the nucleus with the formation of aggregates known as speck and this complexation is dependent on NLRP1.⁶⁷ NLRP1 also recognizes the main virulence factor of *Bacillus anthracis* and bacterial muramyl dipeptide.⁶⁸ In humans, gain-of-function mutations in the NLRP1 gene lead to syndromes mediated by inflammasome activation in keratinocytes characterized by skin inflammation and susceptibility to skin cancer.⁶⁹

The most well-known inflammasome is NLRP3, which is expressed by epithelial cells, macrophages, lymphoid cells,

chondrocytes and skin keratinocytes.⁷⁰ This receptor can be activated by a range of PAMPs and DAMPs that do not interact directly with the receptor, but induce cytoplasmic changes that lead to its activation, such as ion flows, extracellular ATP, nucleic acids, bacterial toxins, among others, and is involved in various skin diseases.⁷¹⁻⁷⁵ In keratinocytes, UVB radiation triggers NLRP3 in increased concentrations of cytoplasmic calcium (Ca²⁺), leading to the secretion of IL-1 β .^{66,76}

In patients with progressing vitiligo, NLRP3 and IL-1 β concentrations are increased in perilesional epidermal samples when compared to healthy controls.⁷⁷ In psoriasis there is higher expression of NLRP3 and of several inflammasome components such as caspase-1 and IL-1 β .^{78,79} A close relationship has been described between the pathogenesis of leprosy, colorectal cancer, rheumatoid arthritis, abdominal aortic aneurysms, inflammatory bowel disease, ulcerative colitis and AD, and the NLRP3 rs35829419 gene polymorphism.^{80,81} Bacteria (*S. aureus* and *Escherichia coli* e.g.) and environmental exposure to ultraviolet radiation led to the activation of the NLRP3 inflammasome in keratinocytes.^{71,82} NLRP3 is also necessary for the pyroptotic cell death of macrophages infected with *S. aureus*.⁷⁴

AIM-2 is a receptor first described as a tumor cell growth suppressor gene in melanoma that does not belong to the NLR family, but is capable of forming the inflammasome complex after binding directly to dsDNA (double-stranded DNA).^{83,84} Under homeostasis, DNA remains contained in

the nucleus and mitochondria, but exposure of DNA in the cytosol indicates active infection or cell damage. The AIM2 receptor responds to the cytosolic presence of the host's own DNA and amplifies sterile inflammation, as described in autoinflammatory or autoimmune diseases.⁸⁵ Furthermore, AIM2 also recognizes exogenous DNA released during bacterial infections, such as *S. aureus*,⁸⁶ or viral infections such as cytomegalovirus (CMV), and also upon detection of HPV-16 in keratinocytes, triggering an increase in the secretion of IL-1 β .^{72,87,88}

In psoriasis, cytosolic dsDNA also stimulates the activation of AIM2 expression and IL-1 β secretion. Interestingly, LL-37 inhibits the ability of DNA to induce IL-1 β production due to LL-37's strong association with DNA, which prevents it from becoming involved in the AIM-2 inflammasome and contributing to the pathophysiology of the disease.⁸⁹ In patients with lupus erythematosus, an intense expression of AIM-2 was observed in macrophages, possibly due to decreased DNA methylation in these individuals, contributing to the pathogenesis of the disease.^{90,91} Moreover, in lesions from patients with lichen planus, there is a specific increase in the AIM-2 protein in both the dermis and the epidermis, with improved dermal expression of the IL-1 β protein.⁹² Based on these findings, AIM-2 may be a therapeutic target in inflammatory and oncologic conditions, and also in autoimmune diseases.^{93,94}

Inflammasomes and atopic dermatitis

Considering the inflammatory profile of AD, the inflammasome cascade may exert a relevant role in the pathogenesis of the disease. In fact, the activation of inflammasomes by allergens or pathogens leads to increased levels of IL-1 β on the skin in autoinflammatory diseases, promoting conditions for the development of chronic inflammation.⁹⁵

Polymorphisms and mutations in the NOD1 and NOD2 genes are associated with high levels of IgE in AD patients and are relevant factors indicating susceptibility to atopy.^{96,97} Similarly, polymorphisms in the NLR4 gene, which also codes for an NLR, are associated with AD;⁹⁷ however, functional studies on the role of this receptor in the pathogenesis of the disease are still scarce.

In addition to polymorphisms, the skin of AD patients shows an increase in inflammasome components, which may favor inflammation. In fact, the highest expression of AIM-2 was found in keratinocytes from AD patients and is directly associated with acute and chronic inflammation related to SB rupture.^{98,99} These patients have intense pruritus, and the mechanical act of scratching impairs SB, causing intracellular products to be released and detected by the AIM-2 receptor. Moreover, bacterial DNA can be released after a process of bacteriolysis mediated by AMPs, and keratinocytes are able to capture exogenous DNA through receptor-mediated endocytosis.⁸⁶

The expression of NLRP1 and NLRP3 receptors is also increased in the damaged skin of AD patients and is directly associated with the severity of the disease, highlighting the importance of this signaling cascade for the inflammatory pathology of this and other skin diseases.^{70,98,100} In 2010, Grigoryev et al.,¹⁰⁰ showed that NLRP1 gene expression is inversely correlated with AD severity in skin

explants, suggesting that local inflammation could inhibit NLRP1 expression, or that reduced expression of this protein promotes skin inflammation. Furthermore, higher NLRP1 expression and caspase-1 activity were seen in mild AD patients and is associated with IL-1 β and IL-18 production.¹⁰¹ Several studies have described the relevance of variations in the NLRP1 gene in skin diseases such as vitiligo, psoriasis and leprosy, showing that NLRP1 plays a particular role in the skin.^{102–104}

Considering NLRP3, the expression of this receptor is directly associated with an increase in IL-33 in the lesions of AD patients, but this association is independent of the activation of the inflammasome cascade.⁷⁰ In addition, Cho et al.¹⁰⁵ demonstrated that IL-17 and IL-22 secreted by Th17 cells can activate NLRP3 and stimulate the secretion of IL-1 β and caspase-1 in immortalized HaCaT keratinocytes, suggesting that other pathways such as the Th17/Th22 axis play a role in the activation of the inflammasome complex. In vitro tests showed that inhibition of Drp1 (dynamin-related protein-1) – responsible for NLRP3 activation – with the compound mdivi-1 inhibited NLRP3 activation, IL-1 β and IL-18 production, as well as induction of pyroptosis.¹⁰⁶ This compound was also shown to be effective in improving the symptoms associated with AD, as well as reducing the serum IgE levels and the production of IL-4, IL-5 and IL-13 in skin lesions in a murine model of AD.¹⁰⁶ In addition, omega-3 supplementation decreases NLRP3 activation via NF- κ B, and decreases the expression of Th2 cytokines in experimental mouse models of AD, suggesting that this receptor is a target for therapeutic strategies for the disease.¹⁰⁷

Conversely, Niebuhr et al.¹⁰⁸ showed reduced expression of NLRP3 and caspase-1 in AD skin. In addition, a reduction in NLRP3 and ASC transcripts was observed in keratinocytes stimulated with Th2 cytokines (IL-4, IL-5 and IL-13).¹⁰⁸ These cytokines can also reduce caspase-1-dependent IL-1 β secretion in monocytes from AD patients stimulated with staphylococcal α -toxin, suggesting interference of the NLRP3 inflammasome in the Th2 response profile, which is relevant in the pathogenesis of AD.¹⁰⁸ The controversial findings may be the result of differences between animal and human studies, with great variability in the number of participants, indicating the need for further analysis to better understand the role of NLRP3 in the AD inflammatory response.

Recently, Ramos et al.⁹⁸ showed that there is an alteration of other components of the inflammasome beyond NLRP3 and NLRP1 receptors in AD. The authors found that ASC expression by immunohistochemistry is increased in the dermis of AD patients, as well as caspase-1.⁹⁸ Furthermore, human primary keratinocytes show enhanced ASC expression when stimulated with UV.⁶⁷

Ramos et al.⁹⁸ also identified that individuals with AD have a higher expression of GSDM-D, which may favor inflammation and local tissue damage. Interestingly, in a murine experimental model of AD induced by oxazolone, the inhibition/deletion of the GSDM-D gene decreased IL-1 β and IL-18 levels, confirming the involvement of pyroptosis in amplifying the inflammatory response in AD.¹⁰⁹ In this regard, the GSDM-D deletion promotes an improvement in AD-like lesions by decreasing the cellular infiltrate and reducing IgE and IL-4 levels.¹⁰⁹ GSDM-D is also elevated in psoriatic skin

Table 1 Association of the inflammasome with pheno-endotypical features of AD.

Inflammasome component	Main findings	References
NOD1 e NOD2	NOD1 and NOD2 gene polymorphisms associated with high IgE levels and susceptibility to atopy	96,97
NLRP1	NLRP1 expression inversely correlated with AD severity	100
NLRP3	NLRP3 gene polymorphism associated with the development of AD γ -hemolysin from <i>S. aureus</i> leads to NLRP3 activation Reduced expression of NLRP3 and caspase-1 in AD patients, relationship with Th2 response profile	80,81 112 108
NLRC4	NLRC4 gene polymorphisms associated with AD	97
AIM-2	Increased expression of AIM-2 in keratinocytes, associated with inflammation and breakdown of the skin barrier	98,99
ASC Caspase-1	Increased expression of ASC and caspase-1 in lesions of AD patients, associated with inflammation	67,98
GSDM-D	GSDM-D deletion in a murine model reduces IL-1 β , IL-18 and AD symptoms, indicating involvement in pyroptosis	109
IL-18	Elevated IL-18 levels in serum and peripheral blood mononuclear cells of AD patients	114

lesions, but serum levels of this protein are similar to the healthy control group.¹¹⁰

In counterpart, the relationship between the inflammasome cascade and colonizing bacteria in the skin microbiota of AD patients has also been studied. Recent evidence indicates that several inflammasomes are activated during an *S. aureus* infection, including NLRP3, via NF- κ B, increasing the transcription of pro-IL-1 β , activation of caspase-1, and secretion of IL-1 β , together with IL-18.¹¹¹ In macrophages, *S. aureus* γ -hemolysins can activate the NLRP3 inflammasome and caspase-1 without the participation of the P2 $\times$ 7 receptor or the Myd88/TLR adaptor. In addition, inoculation of *S. aureus* into keratinocytes led to increased secretion of IL-1 β and IL-18, and silencing of NLRP1 inhibited the production of these cytokines, suggesting that skin colonization may lead to activation of this receptor directly interfering with the inflammatory response in the disease.¹¹²

In skin diseases associated with dysregulation of the inflammasome, the effector cytokines IL-1 β and IL-18 are highly expressed, playing a significant role in the onset and exacerbation of inflammation.¹¹³ In fact, cutaneous keratinocytes are the main sources of these cytokines in the skin, and the increased expression of inflammasome components associated with exposure to *S. aureus* antigens may lead to an increase in IL-18 and IL-1 β in AD patients.^{66,114} In fact, CD68+ macrophages produce IL-1 β in the dermis of AD patients,⁹⁸ and increased epidermal expression of this cytokine is observed in AD patients with filaggrin gene mutations.¹¹⁵ Interestingly, several observations suggest that both IL-1 α and IL-1 β contribute to the development of skin inflammation with AD.¹¹⁶ Additionally, mast cells and keratinocytes from AD patients produce IL-18 in response to exposure to allergens or pathogens such as dust mites and *S. aureus*.¹¹⁷ The IL-18 produced stimulates basophils, mast cells, and CD4 T-cells to produce Th2 cytokines in acute AD lesions, while in chronic lesions, IL-18 stimulates Th1 cells to produce IFN- γ together with IL-12.¹¹⁸

The inflammatory profile triggered by inflammasome activation is also systemically reflected. Orfali et al.¹¹⁴ showed high concentrations of IL-18 in the serum of AD

patients according to the severity of the disease, regardless of the presence of staphylococcal enterotoxins. IL-18 is also increased in the culture supernatants of mononuclear cells from patients stimulated with staphylococcal enterotoxin type A (SEA).¹¹⁴ However, studies on IL-18 deficient mice show an absence of this cytokine, leading to a reduction in the worsening of skin lesions.¹¹⁹ The main changes in inflammasomes related to the pheno-endotypical features in AD are summarized in Table 1.

The above findings point out the relevance of inflammasome components in AD as potential biomarkers of the disease and possible targets for future immunomodulatory interventions (Fig. 4).

Targeted therapies and relevance of individualized therapy for key changes in AD

The use of emollients and topical corticosteroids is the first line of treatment for AD.¹²⁰ Conventional systemic therapy options for AD include cyclosporine (CsA), methotrexate, azathioprine, mycophenolate mofetil, and systemic glucocorticoids, with limited proven efficacy and potential side effects.¹²¹ With the development of new target-specific therapies aimed at inflammatory mediators, new opportunities have arisen for restoring the skin barrier, as well as for restoring the innate and adaptive immune systems in AD.¹²¹

One of the target therapies is dupilumab (DUPI), a humanized monoclonal antibody that targets IL-4R α , a subunit shared by the IL-4 and IL-13 receptors. Pivotal studies have shown significant clinical improvement and a favorable safety profile in individuals with moderate to severe AD, confirming the central role of Th2 cytokines in this disease.¹²¹ It was shown that blocking IL-4/IL-13 signaling, in addition to suppressing systemic Th2-type inflammation, increased microbial diversity, reducing the abundance of *S. aureus*, with the recovery of the altered transcriptome of epidermal proteins associated with AD. DUPI also increased the expression of FLG, LEKTI (protease inhibitor), and HBD-3

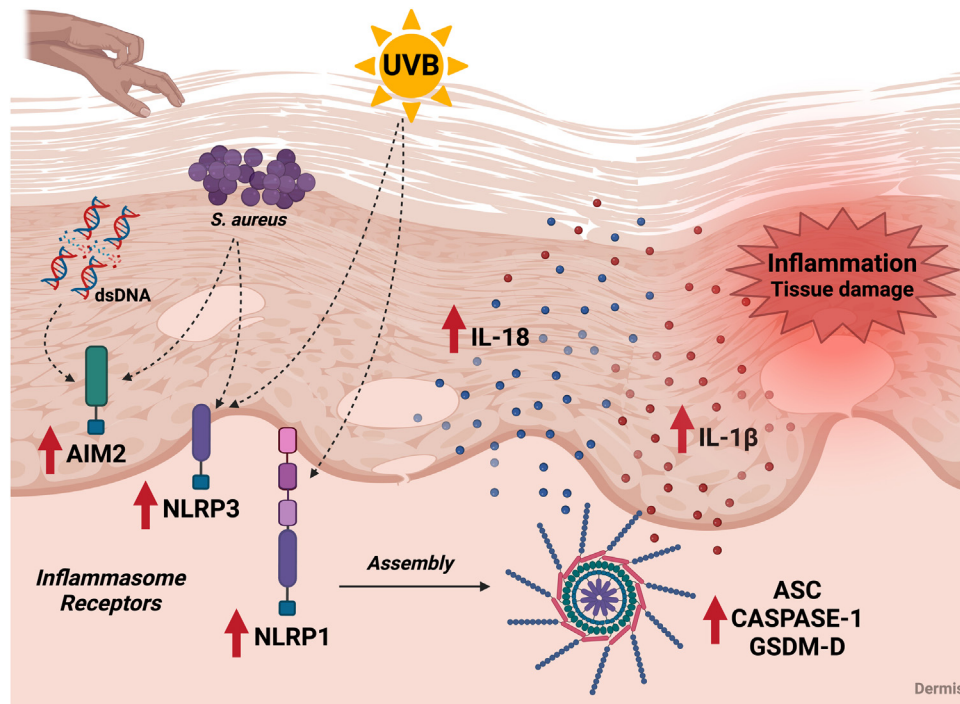


Fig. 4 Association of the inflammasome cascade with AD immunopathology. Components of the inflammasome signaling pathway are increased in the skin of AD patients. In the skin of patients, inflammasome receptors can be activated by exposure to ultraviolet radiation, by contact with *S. aureus* antigens, and by possible DNA molecules released by cell damage. These receptors promote the oligomerization of ASC and caspase-1, leading to the maturation of IL-1 β and IL-18, which are also elevated in AD patients. In addition, activation of the inflammasome leads to an increase in GSDM-D and promotion of pyroptosis. The release of pro-inflammatory and cell death cytokines contributes to tissue damage and local and systemic inflammation during the disease. UVB, ultraviolet radiation; *S. aureus*, *Staphylococcus aureus*; dsDNA, double stranded DNA. Figure generated with BioRender.

(antimicrobial peptide) after 6–8 weeks of treatment, as well as the degree of hydration of the stratum corneum, with a consequent improvement in the severity of AD after 12 weeks. Transcriptomic data from the European clinical registry (TREAT Germany) of adults with moderate to severe AD, in a comparative study of the use of DUPI vs. CsA, showed that treatment with DUPI for 12 weeks led to the normalization of BC-related genes, to a greater extent than CsA,^{122,123} and decreased expression of chemokines related to the Th2 response (e.g. CCL13, CCL17, CCL18 and CCL22). There was normalization of the expression of markers related to barrier function (e.g., CLDN8, ELOVL3, FLG, K1, K10 e LOR).^{19,124–126}

Other IL-13 antagonists (lebriquizumab and tralokinumab) have shown clinical efficacy in AD patients, demonstrating the critical role of IL-13 in the pathogenesis of AD. Since IL-4 and IL-13 reduce the expression of CB proteins such as filaggrin, loricrin, and involucrin, treatment with IL-13 antagonists is expected to positively influence the recovery of CB integrity, but more studies are needed to corroborate these findings.¹⁹

Janus Kinase (JAK) inhibitors that target JAK/STAT signaling, such as baricitinib, upadacitinib and abrocitinib, have shown promising results in some studies regarding the restoration of SB, demonstrating an increase in filaggrin expression, as well as a reduction in inflammatory signaling.¹⁹ There is a lack of publications focusing on the role of JAK inhibitors and new immunobiologicals in the recovery of SB and its components, especially targeting ele-

ments of the inflammatory response such as OX-40 Ligand (OX-40L) and OX-40 (amlitelimab and rocatinlimab),¹²⁷ as well as IL-31 (nemolizumab).¹²⁸

Regarding the therapeutic potential of inhibiting inflammasomes, NLRP3 inhibitors and their respective mechanisms in allergic diseases have been described. These include MCC950, a diarylsulfonylurea-based compound that inhibits NLRP3 activity and interferes with chloride efflux; OLT1177, an orally active b-sulfonyl cyanide molecule that binds directly to NLRP3 and inhibits ATPase activity, preventing NLRP3-ASC, NLRP3-caspase-1 interaction; CY-09, an inhibitor of cystic fibrosis transmembrane conductance regulator (CFTR) channels that inhibits NLRP3 ATPase activity; Tranilast, a tryptophan metabolite that inhibits NLRP3 oligomerization and improves NLRP3 ubiquitination; Oridonin (ent-kaurane diterpene), the main active component of *Rabdosia rubescens* that blocks the interaction between NLRP3 and NEK7; RRx-001, a pleiotropic anticancer agent that blocks the interaction between NLRP3 and NEK7. Natural products and their derivatives are also suggested as potential therapeutic strategies such as XQLD (*Xiaoqinglong Decoction*) which inhibits NLRP3 inflammasome-mediated pyroptosis; APS (*Astragalus Polysaccharide*), an inhibitor of NLRP3 activation and a blocker of NF- κ B phosphorylation, decreasing NOD2 expression; MFXD (*Mahuang Fuzi Xixin Decoction*), which inhibits the NLRP3/Caspase-1/GSDMD-N signaling pathway; *Schisandrin B*, which inhibits NLRP3 activation; *Houttuynia cordata*, which decreases the

expression of NLRP3, ASC, caspase-1, GSDMD, IL-1 β , and IL-18; and *Angelica Yinzi*, which inhibits NLRP3 activation and MAPKs/NF κ B signaling.^{129,130} Currently, there is a clinical trial for AD patients with GSK1070806, an anti-IL-18 monoclonal antibody. In phase 1b of the study NCT04975438 (<https://clinicaltrials.gov/study/NCT04975438?tab=history&a=7#study-results-card>), patients with no previous systemic treatment with biologics (non-responsive to topical therapies), and patients non-responsive or intolerant to DUPI were evaluated, with promising results. An ongoing phase 2b will evaluate the clinical effect, safety and tolerability of GSK1070806 in AD (NCT05999799 - <https://clinicaltrials.gov/study/NCT05999799?intr=GSK1070806&rank=2>).

Conclusion

AD is one of the most common chronic inflammatory skin diseases, and its persistence occurs as a consequence of the combination of genetic, environmental and immunological factors, affecting both adults and children. Skin barrier dysfunction, together with bacterial colonization and dysregulation of the innate and adaptive immune system, play a central role in maintaining inflammation and therefore the chronicity of AD. This review highlights the crucial role of inflammasomes, especially NLRP1/3 and AIM-2, in regulating the inflammatory response in skin diseases such as AD, including the release of the pro-inflammatory cytokines IL-18 and IL-1 β , which are essential in perpetuating skin inflammation. A deeper understanding of immune pathways, such as the inflammasome cascade, opens new perspectives for therapeutic interventions. Targeting treatments to modulate the immune response and restore the skin barrier may offer more effective management of the disease and improve the AD patients' quality of life.

Author's contribution

Yasmim Álefe Leuzzi Ramos: Critical review of the literature; drafting of the manuscript; preparation of figures; final approval of the final version of the manuscript.

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Franciane Mouradian Emidio Teixeira: Critical review of the literature; drafting of the manuscript; preparation of figures; final approval of the final version of the manuscript.

Valeria Aoki: Conception and design of the study; critical review of the content; analysis and interpretation of the data; critical review of the literature; final approval of the final version of the manuscript.

Maria Notomi Sato: Conception and design of the study; critical review of the content; analysis and interpretation of the data; critical review of the literature; final approval of the final version of the manuscript.

Raquel Leão Orfali: Conception and design of the study; data collection; writing of the article and critical review of the content; obtaining, analyzing and interpreting the data; critical review of the literature; final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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References

1. Vakharia PP, Chopra R, Sacotte R, Patel KR, Singam V, Patel N, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol.* 2017;119:548–52.e3.
2. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol.* 2015;135:56–66.
3. Yu SH, Attarian H, Zee P, Silverberg JI. Burden of sleep and fatigue in US adults with atopic dermatitis. *Dermatitis.* 2016;27:50–8.
4. Strom MA, Fishbein AB, Paller AS, Silverberg JI. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. *Br J Dermatol.* 2016;175:920–9.
5. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. *Curr Allergy Asthma Rep.* 2009;9:265–72.
6. Yamazaki Y, Nakamura Y, Núñez G. Role of the microbiota in skin immunity and atopic dermatitis. *Allergol Int.* 2017;66:539–44.
7. Gao PS, Rafaels NM, Hand T, Murray T, Boguniewicz M, Hata T, et al. Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum. *J Allergy Clin Immunol.* 2009;124:507–13, 513.e1–7.
8. Geoghegan JA, Irvine AD, Foster TJ. *Staphylococcus aureus* and atopic dermatitis: a complex and evolving relationship. *Trends Microbiol.* 2018;26:484–97.
9. Saintive S, Abad E, de C Ferreira D, Stambovsky M, Cavalcante FS, Gonçalves LS, et al. What is the role of *Staphylococcus aureus* and herpes virus infections in the pathogenesis of atopic dermatitis? *Future Microbiol.* 2017;12:1327–34.
10. Hendricks AJ, Eichenfield LF, Shi VY. The impact of airborne pollution on atopic dermatitis: a literature review. *Br J Dermatol.* 2020;183:16–23, <http://dx.doi.org/10.1111/bjd.18781>.
11. Bonamonte D, Filoni A, Vestita M, Romita P, Foti C, Angelini G. The role of the environmental risk factors in the pathogenesis and clinical outcome of atopic dermatitis. *Biomed Res Int.* 2019;2019:2450605.
12. Wang SP, Stefanovic N, Orfali RL, Aoki V, Brown SJ, Dhar S, et al. Impact of climate change on atopic dermatitis: a review by the International Eczema Council. *Allergy.* 2024;79:1455–69.
13. Peng W, Novak N. Pathogenesis of atopic dermatitis. *Clin Exp Allergy.* 2015;45:566–74.
14. Addor FA, Takaoka R, Rivitti EA, Aoki V. Atopic dermatitis: correlation between non-damaged skin barrier function and disease activity. *Int J Dermatol.* 2012;51:672–6.
15. Batista DI, Perez L, Orfali RL, Zaniboni MC, Samorano LP, Pereira NV, et al. Profile of skin barrier proteins (filag-

- grin, claudins 1 and 4) and Th1/Th2/Th17 cytokines in adults with atopic dermatitis. *J Eur Acad Dermatol Venerol*. 2015;29:1091–5.
16. Schröder JM, Harder J. Antimicrobial skin peptides and proteins. *Cell Mol Life Sci*. 2006;63:469–86.
 17. Hoffjan S, Stemmler S. On the role of the epidermal differentiation complex in ichthyosis vulgaris, atopic dermatitis and psoriasis. *Br J Dermatol*. 2007;157:441–9.
 18. Verdier-Sévrain S, Bonté F. Skin hydration: a review on its molecular mechanisms. *J Cosmet Dermatol*. 2007;6:75–82.
 19. Yang G, Seok JK, Kang HC, Cho YY, Lee HS, Lee JY. Skin barrier abnormalities and immune dysfunction in atopic dermatitis. *Int J Mol Sci*. 2020;21:2867.
 20. McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol*. 2013;131:280–91.
 21. Nishio Y, Noguchi E, Shibasaki M, Kamioka M, Ichikawa E, Ichikawa K, et al. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. *Genes Immun*. 2003;4:515–7.
 22. Zaniboni MC, Samorano LP, Orfali RL, Aoki V. Skin barrier in atopic dermatitis: beyond filaggrin. *An Bras Dermatol*. 2016;91:472–8.
 23. Smith AR, Knaysi G, Wilson JM, Wisniewski JA. The skin as a route of allergen exposure: part I. Immune components and mechanisms. *Curr Allergy Asthma Rep*. 2017;17:6.
 24. Leung DY, Soter NA. Cellular and immunologic mechanisms in atopic dermatitis. *J Am Acad Dermatol*. 2001;44:S1–12.
 25. Ong PY, Leung DY. Atopic dermatitis. *Clin Allergy Immunol*. 2002;16:355–79.
 26. Berker M, Frank LJ, Geßner AL, Grassl N, Holtermann AV, Höppner S, et al. Allergies - A T cells perspective in the era beyond the T. *Clin Immunol*. 2017;174:73–83.
 27. Gittler JK, Shemer A, Suarez-Farinas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130:1344–54.
 28. Czarnewicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143:1–11.
 29. Niebuhr M, Scharonow H, Gathmann M, Mamerow D, Werfel T. Staphylococcal exotoxins are strong inducers of IL-22: a potential role in atopic dermatitis. *J Allergy Clin Immunol*. 2010;126:1176–83.e4.
 30. Orfali RL, da Silva Oliveira LM, de Lima JF, de Carvalho GC, Ramos YAL, Pereira NZ, et al. Staphylococcus aureus enterotoxins modulate IL-22-secreting cells in adults with atopic dermatitis. *Sci Rep*. 2018;8:6665.
 31. Nogales KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing $\text{I}\beta\text{I}22^{\text{T}}$ cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol*. 2009;123:1244–52.e2.
 32. Orfali RL, Yoshikawa FSY, Oliveira LMDs, Pereira NZ, de Lima JF, Ramos YÁL, et al. Staphylococcal enterotoxins modulate the effector CD4. *Sci Rep*. 2019;9:13082.
 33. Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol*. 2008;128:2625–30.
 34. Jung T, Schulz S, Zachmann K, Neumann C. Expansion and proliferation of skin-homing T cells in atopic dermatitis as assessed at the single cell level. *Int Arch Allergy Immunol*. 2003;130:143–9.
 35. Ferran M, Santamaria-Babi LF. Pathological mechanisms of skin homing T cells in atopic dermatitis. *World Allergy Organ J*. 2010;3:44–7.
 36. Orfali RL, Sato MN, Santos VG, Titz TO, Brito CA, Duarte AJ, et al. Staphylococcal enterotoxin B induces specific IgG4 and IgE antibody serum levels in atopic dermatitis. *Int J Dermatol*. 2015;54:898–904.
 37. Furue M, Chiba T, Tsuji G, Ulzii D, Kido-Nakahara M, Nakahara T, et al. Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. *Allergol Int*. 2017;66:398–403.
 38. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, et al. Thymus and activation-regulated chemokine in atopic dermatitis: serum thymus and activation-regulated chemokine level is closely related with disease activity. *J Allergy Clin Immunol*. 2001;107:535–41.
 39. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002;3:673–80.
 40. Kumagai Y, Akira S. Identification and functions of pattern-recognition receptors. *J Allergy Clin Immunol*. 2010;125:985–92.
 41. Kuo IH, Yoshida T, De Benedetto A, Beck LA. The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2013;131:266–78.
 42. De Benedetto A, Agnihotri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol*. 2009;129:14–30.
 43. Hasannejad H, Takahashi R, Kimishima M, Hayakawa K, Shiohara T. Selective impairment of Toll-like receptor 2-mediated proinflammatory cytokine production by monocytes from patients with atopic dermatitis. *J Allergy Clin Immunol*. 2007;120:69–75.
 44. Turksen K, Troy TC. Barriers built on claudins. *J Cell Sci*. 2004;117:2435–47.
 45. Al Kindi A, Williams H, Matsuda K, Alkahtani AM, Saville C, Bennett H, et al. Staphylococcus aureus second immunoglobulin-binding protein drives atopic dermatitis via IL-33. *J Allergy Clin Immunol*. 2021;147:1354–68.e3.
 46. Breuer K, Kapp A, Werfel T. Urine eosinophil protein X (EPX) is an in vitro parameter of inflammation in atopic dermatitis of the adult age. *Allergy*. 2001;56:780–4.
 47. Mack MR, Brestoff JR, Berrien-Elliott MM, Trier AM, Yang TB, McCullen M, et al. Blood natural killer cell deficiency reveals an immunotherapy strategy for atopic dermatitis. *Sci Transl Med*. 2020;12:eaay1005.
 48. de Lima JF, Teixeira FME, Ramos YÁL, de Carvalho GC, Castelo Branco ACC, Pereira NV, et al. Outlining the skin-homing and circulating CLA⁺NK cells in patients with severe atopic dermatitis. *Sci Rep*. 2024;14:2663.
 49. Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, Wang X, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med*. 2013;210:2939–50.
 50. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. *Nat Rev Immunol*. 2016;16:407–20.
 51. Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijk L, Martinon F, et al. Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. *J Histochem Cytochem*. 2007;55:443–52.
 52. Yao J, Sterling K, Wang Z, Zhang Y, Song W. The role of inflammasomes in human diseases and their potential as therapeutic targets. *Signal Transduct Target Ther*. 2024;9:10.
 53. He Y, Hara H, Núñez G. Mechanism and regulation of NLRP3 inflammasome activation. *Trends Biochem Sci*. 2016;41:1012–21.
 54. Martinon F, Tschopp J. Inflammasome caspases and inflammasomes: master switches of inflammation. *Cell Death Differ*. 2007;14:10–22.
 55. Fink SL, Bergsbaken T, Cookson BT. Anthrax lethal toxin and Salmonella elicit the common cell death pathway of caspase-1-

- dependent pyroptosis via distinct mechanisms. *Proc Natl Acad Sci U S A*. 2008;105:4312–7.
56. Wang B, Tian Y, Yin Q. AIM2 inflammasome assembly and signaling. *Adv Exp Med Biol*. 2019;1172:143–55.
 57. Sollberger G, Strittmatter GE, Garstkiewicz M, Sand J, Beer HD. Caspase-1: the inflammasome and beyond. *Innate Immun*. 2014;20:115–25.
 58. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117:3720–32.
 59. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature*. 2015;526:660–5.
 60. Devant P, Kagan JC. Molecular mechanisms of gasdermin D pore-forming activity. *Nat Immunol*. 2023;24:1064–75.
 61. Dai Z, Liu WC, Chen XY, Wang X, Li JL, Zhang X. Gasdermin D-mediated pyroptosis: mechanisms, diseases, and inhibitors. *Front Immunol*. 2023;14:1178662.
 62. Brennan MA, Cookson BT. Salmonella induces macrophage death by caspase-1-dependent necrosis. *Mol Microbiol*. 2000;38:31–40.
 63. Kayagaki N, Wong MT, Stowe IB, Ramani SR, Gonzalez LC, Akashi-Takamura S, et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science*. 2013;341:1246–9.
 64. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell*. 2002;10:417–26.
 65. Schroder K, Tschopp J. The inflammasomes. *Cell*. 2010;140:821–32.
 66. Feldmeyer L, Keller M, Niklaus G, Hohl D, Werner S, Beer HD. The inflammasome mediates UVB-induced activation and secretion of interleukin-1beta by keratinocytes. *Curr Biol*. 2007;17:1140–5.
 67. Smatlik N, Drexler SK, Burian M, Röcken M, Yazdi AS. ASC speck formation after inflammasome activation in primary human keratinocytes. *Oxid Med Cell Longev*. 2021;2021:7914829.
 68. Frew BC, Joag VR, Mogridge J. Proteolytic processing of Nlrp1b is required for inflammasome activity. *PLoS Pathog*. 2012;8:e1002659.
 69. Zhong FL, Mamai O, Sborgi L, Boussofara L, Hopkins R, Robinson K, et al. Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. *Cell*. 2016;167:187–202.e17.
 70. Zheng J, Yao L, Zhou Y, Gu X, Wang C, Bao K, et al. A novel function of NLRP3 independent of inflammasome as a key transcription factor of IL-33 in epithelial cells of atopic dermatitis. *Cell Death Dis*. 2021;12:871.
 71. Rathinam VA, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. *Nat Immunol*. 2012;13:333–42.
 72. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. *Cell*. 2014;157:1013–22.
 73. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 2011;469:221–5.
 74. Muñoz-Planillo R, Kuffa P, Martínez-Colón G, Smith BL, Rajendran TM, Núñez G. K⁺ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity*. 2013;38:1142–53.
 75. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36:401–14.
 76. Faustin B, Reed JC. Sunburned skin activates inflammasomes. *Trends Cell Biol*. 2008;18:4–8.
 77. Li S, Kang P, Zhang W, Jian Z, Zhang Q, Yi X, et al. Activated NLR family pyrin domain containing 3 (NLRP3) inflammasome in keratinocytes promotes cutaneous T-cell response in patients with vitiligo. *J Allergy Clin Immunol*. 2020;145:632–45.
 78. Su F, Xia Y, Huang M, Zhang L, Chen L. Expression of NLRP3 in psoriasis is associated with enhancement of interleukin-1β and caspase-1. *Med Sci Monit*. 2018;24:7909–13.
 79. Tervaniemi MH, Katayama S, Skoog T, Siitonen HA, Vuola J, Nuutila K, et al. NOD-like receptor signaling and inflammasome-related pathways are highlighted in psoriatic epidermis. *Sci Rep*. 2016;6:22745.
 80. Bivik C, Verma D, Winge MC, Lieden A, Bradley M, Rosdahl I, et al. Genetic variation in the inflammasome and atopic dermatitis susceptibility. *J Invest Dermatol*. 2013;133:2486–9.
 81. Zhang Q, Fan HW, Zhang JZ, Wang YM, Xing HJ. NLRP3 rs35829419 polymorphism is associated with increased susceptibility to multiple diseases in humans. *Genet Mol Res*. 2015;14:13968–80.
 82. Watanabe H, Gaide O, Pétrilli V, Martinon F, Contassot E, Roques S, et al. Activation of the IL-1beta-processing inflammasome is involved in contact hypersensitivity. *J Invest Dermatol*. 2007;127:1956–63.
 83. Ratsimandresy RA, Dorfleutner A, Stehlik C. An update on PYRIN domain-containing pattern recognition receptors: from immunity to pathology. *Front Immunol*. 2013;4:440.
 84. DeYoung KL, Ray ME, Su YA, Anzick SL, Johnstone RW, Trapani JA, et al. Cloning a novel member of the human interferon-inducible gene family associated with control of tumorigenicity in a model of human melanoma. *Oncogene*. 1997;15:453–7.
 85. Kumari P, Russo AJ, Shivcharan S, Rathinam VA. AIM2 in health and disease: Inflammasome and beyond. *Immunol Rev*. 2020;297:83–95.
 86. Feng S, Yang Y, Liu Z, Chen W, Du C, Hu G, et al. Intracellular bacteriolysis contributes to pathogenicity of. *Virulence*. 2022;13:1684–96.
 87. Reinholz M, Kawakami Y, Salzer S, Kreuter A, Dombrowski Y, Koglin S, et al. HPV16 activates the AIM2 inflammasome in keratinocytes. *Arch Dermatol Res*. 2013;305:723–32.
 88. Ma Z, Ni G, Damania B. Innate sensing of DNA virus genomes. *Annu Rev Virol*. 2018;5:341–62.
 89. Dombrowski Y, Peric M, Koglin S, Kammerbauer C, Göss C, Anz D, et al. Cytosolic DNA triggers inflammasome activation in keratinocytes in psoriatic lesions. *Sci Transl Med*. 2011;3:82ra38.
 90. Yang CA, Huang ST, Chiang BL. Sex-dependent differential activation of NLRP3 and AIM2 inflammasomes in SLE macrophages. *Rheumatology (Oxford)*. 2015;54:324–31.
 91. Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Subero JI, Rodriguez-Ubreva J, et al. Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. *Genome Res*. 2010;20:170–9.
 92. Domingues R, Pietrobon AJ, Carvalho GC, Pereira NZ, Pereira NV, Sotto MN, et al. Lichen planus: altered AIM2 and NLRP1 expression in skin lesions and defective activation in peripheral blood mononuclear cells. *Clin Exp Dermatol*. 2019;44:e89–95.
 93. Chai D, Shan H, Wang G, Li H, Fang L, Song J, et al. AIM2 is a potential therapeutic target in human renal carcinoma and suppresses its invasion and metastasis via enhancing autophagy induction. *Exp Cell Res*. 2018;370:561–70.
 94. Wang J, Gao J, Huang C, Jeong S, Ko R, Shen X, et al. Roles of AIM2 gene and AIM2 inflammasome in the pathogenesis and treatment of psoriasis. *Front Genet*. 2022;13:929162.
 95. Abramovits W, Rivas Bejarano JJ, Valdecantos WC. Role of interleukin 1 in atopic dermatitis. *Dermatol Clin*. 2013;31:437–44.
 96. Weidinger S, Klopp N, Rummel L, Wagenpfeil S, Novak N, Baurecht HJ, et al. Association of NOD1 polymorphisms with atopic eczema and related phenotypes. *J Allergy Clin Immunol*. 2005;116:177–84.
 97. Macaluso F, Nothnagel M, Parwez Q, Petrasch-Parwez E, Bechara FG, Epplen JT, et al. Polymorphisms in NACHT-

- LRR (NLR) genes in atopic dermatitis. *Exp Dermatol*. 2007;16:692–8.
98. Ramos YÁL, Pereira NV, Aoki V, Sotto MN, Kawakami JT, da Silva LFF, et al. Cutaneous inflammasome driving ASC/gasdermin-D activation and IL-1 β -secreting macrophages in severe atopic dermatitis. *Arch Dermatol Res*. 2024;316:156.
 99. de Koning HD, Bergboer JG, van den Bogaard EH, van Vlijmen-Willems IM, Rodijk-Olthuis D, Simon A, et al. Strong induction of AIM2 expression in human epidermis in acute and chronic inflammatory skin conditions. *Exp Dermatol*. 2012;21:961–4.
 100. Grigoryev DN, Howell MD, Watkins TN, Chen YC, Cheadle C, Boguniewicz M, et al. Vaccinia virus-specific molecular signature in atopic dermatitis skin. *J Allergy Clin Immunol*. 2010;125:153–9.e28.
 101. Vaher H, Kingo K, Kolberg P, Pook M, Raam L, Laanesoo A, et al. Skin colonization with *S. aureus* can lead to increased NLRP1 inflammasome activation in patients with atopic dermatitis. *J Invest Dermatol*. 2023;143:1268–78.e8.
 102. Pontillo A, Laurentino W, Crovella S, Pereira AC. NLRP1 haplotypes associated with leprosy in Brazilian patients. *Infect Genet Evol*. 2013;19:274–9.
 103. Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC, et al. NALP1 in vitiligo-associated multiple autoimmune disease. *N Engl J Med*. 2007;356:1216–25.
 104. Ekman AK, Verma D, Fredrikson M, Bivik C, Enerbäck C. Genetic variations of NLRP1: susceptibility in psoriasis. *Br J Dermatol*. 2014;171:1517–20.
 105. Cho KA, Suh JW, Lee KH, Kang JL, Woo SY. IL-17 and IL-22 enhance skin inflammation by stimulating the secretion of IL-1 β by keratinocytes via the ROS-NLRP3-caspase-1 pathway. *Int Immunol*. 2012;24:147–58.
 106. Li L, Mu Z, Liu P, Wang Y, Yang F, Han X. Mdivi-1 alleviates atopic dermatitis through the inhibition of NLRP3 inflammasome. *Exp Dermatol*. 2021;30:1734–44.
 107. Jang HY, Koo JH, Lee SM, Park BH. Atopic dermatitis-like skin lesions are suppressed in fat-1 transgenic mice through the inhibition of inflammasomes. *Exp Mol Med*. 2018;50:1–9.
 108. Niebuhr M, Baumert K, Heratizadeh A, Satzger I, Werfel T. Impaired NLRP3 inflammasome expression and function in atopic dermatitis due to Th2 milieu. *Allergy*. 2014;69:1058–67.
 109. Lu Y, Sun Y, Peng Y, Zhao X, Wang D, Zhang T, et al. Inhibition of gasdermin D (GSDMD) as a promising therapeutic approach for atopic dermatitis. *Int Immunopharmacol*. 2023;124:110958.
 110. Nowowiejska J, Baran A, Hermanowicz JM, Pryczynicz A, Sieklucka B, Pawlak D, et al. Gasdermin D (GSDMD) is upregulated in psoriatic skin-A new potential link in the pathogenesis of psoriasis. *Int J Mol Sci*. 2023;24:13047.
 111. Melehani JH, Duncan JA. Inflammasome activation can mediate tissue-specific pathogenesis or protection in *Staphylococcus aureus* infection. *Curr Top Microbiol Immunol*. 2016;397:257–82.
 112. Munoz-Planillo R, Franchi L, Miller LS, Nunez G. A critical role for hemolysins and bacterial lipoproteins in *Staphylococcus aureus*-induced activation of the Nlrp3 inflammasome. *J Immunol*. 2009;183:3942–8, <http://dx.doi.org/10.4049/jimmunol.0900729>.
 113. Fenini G, Contassot E, French LE. Potential of IL-1, IL-18 and inflammasome inhibition for the treatment of inflammatory skin diseases. *Front Pharmacol*. 2017;8:278.
 114. Orfali RL, Sato MN, Takaoka R, Azor MH, Rivitti EA, Hanifin JM, et al. Atopic dermatitis in adults: evaluation of peripheral blood mononuclear cells proliferation response to *Staphylococcus aureus* enterotoxins A and B and analysis of interleukin-18 secretion. *Exp Dermatol*. 2009;18:628–33.
 115. Kezic S, O'Regan GM, Lutter R, Jakasa I, Koster ES, Saunders S, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol*. 2012;129:1031–9.e1.
 116. Bernard M, Carrasco C, Laoubi L, Guiraud B, Rozières A, Goujon C, et al. IL-1 β induces thymic stromal lymphopoietin and an atopic dermatitis-like phenotype in reconstructed healthy human epidermis. *J Pathol*. 2017;242:234–45.
 117. Inoue Y, Aihara M, Kirino M, Harada I, Komori-Yamaguchi J, Yamaguchi Y, et al. Interleukin-18 is elevated in the horny layer in patients with atopic dermatitis and is associated with *Staphylococcus aureus* colonization. *Br J Dermatol*. 2011;164:560–7.
 118. Yoshimoto T, Tsutsui H, Tominaga K, Hoshino K, Okamura H, Akira S, et al. IL-18, although antiallergic when administered with IL-12, stimulates IL-4 and histamine release by basophils. *Proc Natl Acad Sci U S A*. 1999;96:13962–6.
 119. Chen JL, Niu XL, Gao YL, Ma L, Gao XH, Chen HD, et al. IL-18 knockout alleviates atopic dermatitis-like skin lesions induced by MC903 in a mouse model. *Int J Mol Med*. 2020;46:880–8.
 120. Aoki V, Lorenzini D, Orfali RL, Zaniboni MC, Oliveira ZNP, Rivitti-Machado MC, et al. Consensus on the therapeutic management of atopic dermatitis - Brazilian Society of Dermatology. *An Bras Dermatol*. 2019;94:67–75.
 121. Orfali RL, Lorenzini D, Bressan A, Tanaka AA, Cerqueira AMM, Hirayama ADS, et al. Consensus on the therapeutic management of atopic dermatitis – Brazilian Society of Dermatology: an update on phototherapy and systemic therapy using e-Delphi technique. *An Bras Dermatol*. 2023;98:814–36.
 122. Möbus L, Rodriguez E, Harder I, Stölzl D, Boraczynski N, Gerdes S, et al. Atopic dermatitis displays stable and dynamic skin transcriptome signatures. *J Allergy Clin Immunol*. 2021;147:213–23.
 123. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). *Br J Dermatol*. 2018;178:1083–101.
 124. Möbus L, Rodriguez E, Harder I, Schwarz A, Wehkamp U, Stölzl D, et al. Elevated NK-cell transcriptional signature and dysbalance of resting and activated NK cells in atopic dermatitis. *J Allergy Clin Immunol*. 2021;147:1959–65.e2.
 125. Yoshida T, Beck LA, De Benedetto A. Skin barrier defects in atopic dermatitis: from old idea to new opportunity. *Allergol Int*. 2022;71:3–13, <http://dx.doi.org/10.1016/j.alit.2021.11.006>.
 126. Beck LA, Cork MJ, Amagai M, De Benedetto A, Kabashima K, Hamilton JD, et al. Type 2 inflammation contributes to skin barrier dysfunction in atopic dermatitis. *JID Innov*. 2022;2:100131.
 127. Guttman-Yassky E, Pavel AB, Zhou L, Estrada YD, Zhang N, Xu H, et al. GBR 830, an anti-OX40, improves skin gene signatures and clinical scores in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;144:482–93.e7.
 128. Orfali RL, Aoki V. Blockage of the IL-31 pathway as a potential target therapy for atopic dermatitis. *Pharmaceutics*. 2023;15:577.
 129. Lu HF, Zhou YC, Hu TY, Yang DH, Wang XJ, Luo DD, et al. Unraveling the role of NLRP3 inflammasome in allergic inflammation: implications for novel therapies. *Front Immunol*. 2024;15:1435892.
 130. Coll RC, Schroder K. Inflammasome components as new therapeutic targets in inflammatory disease. *Nat Rev Immunol*. 2025;25:22–41.