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The role of cytokines in atopic dermatitis: a breakthrough in immunopathogenesis and treatment

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Abstract

Atopic dermatitis is a multifactorial inflammatory skin disease with a complex immunopathogenesis that is characterized by an underlying imbalance of T-cell subsets. Although cytokines of type 2 immunity consistently predominate in the acute phase of atopic dermatitis, there is strong evidence supporting the contribution of cytokines of type 1 immunity, type 3 immunity, and other cytokines in the development and progression of the disease. This review explores the cytokine network in atopic dermatitis, and it highlights areas and causes of controversy in the immunopathogenesis of the disease. In addition, it presents the current therapeutic targets currently being investigated, including monoclonal antibodies and small molecules that inhibit cytokines and downstream signaling molecules in atopic dermatitis. We conclude that atopic dermatitis has a complex and controversial cytokine profile. Understanding the role of cytokines in the immunopathogenesis of the disease is essential for identifying personalized targets for better management and disease control.

Keywords: atopic dermatitis, cytokines, immunopathogenesis, T cells, interleukin, inflammatory skin disease

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Introduction

Atopic dermatitis (AD) is a chronic relapsing-remitting disease typically presenting with dry skin, pruritus, an age-specific distribution of dermatitis, and a positive history of atopy. In the United Kingdom, AD affects 11 to 20% of children and 5 to 10% of adults (1) in comparison to only 2.1 to 4.9% of adults across North America, Europe, and Japan (2). AD has a complex underlying multifactorial pathogenesis involving genetic and environmental factors that interact with the skin and the immune system, leading to loss of skin barrier integrity, dysregulation of innate and adaptive immune responses, and dysbiosis of the skin microbiome (3, 4). Understanding these findings helps in managing AD patients. Although management highly depends on disease severity and distribution, avoidance of triggers and frequent moisturization to restore skin integrity are mandatory. Topical treatments include agents with anti-inflammatory properties such as corticosteroids and calcineurin inhibitors. However, acceleration of treatment to phototherapy, cyclosporin, and cytokine-targeted agents is carried out in a step-by-step manner (5).

Cytokines play a major pathogenic role in AD. Although the pathologic findings mentioned above could be inherent in the patient's genes, these could be also induced by a cytokine imbalance, as evident in in vitro and in vivo experimental models of AD. A cytokine imbalance can suppress filaggrin, keratins, and epidermal lipids, contributing to loss of skin barrier integrity and a subsequent increase in transepidermal water loss, skin dryness, and intractable pruritus. A cytokine imbalance may also inhibit important antimicrobial peptides, which in turn impairs the skin microbiome and promotes cutaneous infections.

Cytokines can be classified according to the type of immunity they are involved in: type 1 immunity, type 2 immunity, or type 3 immunity. This review highlights the imbalance of cytokines in AD according to this classification. It presents their role in exhibiting disease manifestations, and it addresses cytokines and cytokine antagonists with therapeutic potential.

The T-cell subset imbalance is striking in atopic dermatitis

AD is characterized by an imbalance of T-cell subsets. For instance, peripheral blood CD4+ and CD8+ cells are high in AD. In the differentiation of CD4+ cells, CD4+ T-helper (Th)2 cells predominate in comparison to CD4+ Th1 cells (6–9). Likewise, skin-infiltrating lymphocytes are predominantly CD4+ T cells that proliferate in response to interleukin (IL)-2, IL-3, and IL-4, and they seem to be resistant to tumor necrosis factor (TNF)-α–induced pro-apoptotic signals (10). When continuously grown in vitro, chromosomal aberrations and loss of the T-cell antigen complex are observed (11). Th2 cytokines are also elevated in sera and skin lesions (12–14). Overproduction of Th2 cytokines induces the molecular and histologic features of AD. Interestingly, they induce nucleic acid fragmentation and upregulation of Fas, a death receptor (12), which contradicts the observation of a lack of response to TNF-α–induced proapoptotic signals mentioned above. In the murine model of AD, activation of Fas increases epidermal thickness, collagen deposition, and local inflammatory inflammation consisting of CD4+ cells, macrophages, and neutrophils (15).

The regulatory T-cell marker FoxP3 is expressed on both CD4+ CD25+ and CD8+ CD25+ T-cell subsets, although the latter is diminished in AD (16, 17). Uncontrolled inflammation might be attributed to reduced peripheral blood counts and impaired cutaneous infiltration of CD4+ CD25+ FoxP3+ T cells, possibly due to recued conversion to FoxP3+ cells, which also correlates with disease severity (18). However, there is some evidence suggesting an increase in FoxP3+ T-cell circulation in peripheral blood (19, 20) and skin (21) with perivascular, peri-adnexal, and interstitial infiltration of CD25+ FoxP3+ cells (22) positively correlating with AD severity (23). Taking into account that FoxP3+ cells might exhibit

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attenuated function (24), this may explain the controversy above. We would suggest classifying FoxP3+ defects in AD into quantitative (cell counts) or qualitative (cell function) defects. In quantitative defects, conversion to FoxP3+ cells is reduced, and hence the cell count is unexpectedly low in inflammation. In contrast, in qualitative defects, FoxP3+ cells try to compensate for their dysfunction by increasing their count, and this explains the uncontrolled inflammation in a setting of high counts of regulatory T-cells. The observed controversy in FoxP3+ level might be also explained from another point of view, depending on the subset of cells that is defected. The imbalance in T-cell subsets involves two arms: pro- and anti-inflammatory. In scenarios involving "hyperactive" Th2 cells and normally active regulatory T cells, the regulatory T cells respond by increasing their count to suppress the Th2–induced inflammation, and this may explain the high counts of regulatory T cells. In contrast, in scenarios involving normally active Th2 cells and "hypoactive" regulatory T cells, the negative control exerted on Th2 cells is lost and peripheral blood counts accordingly show a low level of regulatory T cells in an inflammation setting. The second hypothesis is evident experimentally, whereby depletion of FoxP3+ T cells permits further Th2 cytokine release and subsequent exacerbation of the AD model (25).

An imbalance of T-cell subsets could be employed at birth to predict the risk of AD. Multiple factors have been described as affecting cord blood FoxP3 expression, including maternal AD (26) and maternal cytokines—namely, IL-13, IL-17, and interferon (IFN)-γ. In general, neonates born with low counts of regulatory T cells (27) and a higher count of Th2 cells (26) are at risk of AD.

In addition to the aforementioned "intrinsic defects" in T cells, the distribution of T-cell subsets has been suggested to be phase-dependent. Acute AD is associated with a significant increase in Th22 (IL-22), Th2 (IL-4, IL-5, IL-13, IL-31, and IL-33), Th-9 (IL-9), and to a less degree Th17 cytokines, whereas Th1 cytokines predominate in the chronic phase (28). Consistently, in vitro expansion of T cells isolated from AD patients shows a primary predominance of Th2 that subsequently converts to Th1 cytokines (29). The high level of Th2 cytokines could be attributed to the overexpression of a suppressor of cytokine signaling 3, a molecule that mediates Th2 response by negative regulation of Th1 pathways (30). In addition, dermal Langerhans cells promote naive CD4+ cell polarization toward Th2 cells (31). Moreover, Langerhans cells heavily express CD1a, which has the favorable capacity to present lipid antigens to T cells (32). In AD lesions, keratinocytes and inflammatory cells showed a massive expression of CD1a in comparison to other skin diseases and healthy controls (21). However, CD1a+ cells also present endogenous lipids to T cells and induce IL-22 release (33). Thus, some studies speculate that AD is a Th2/Th22–centric disease (34). Type 2 and 22 helper and cytotoxic T cells are selectively expanded in severe AD (35). Consistently, CD30, a molecule expressed on active Th2 cells, is elevated in the sera (36) and skin of AD patients, and it positively correlates with disease severity (36). Being preferably expressed on Th2 cells, detection of CD30 indicates disease acuity (37), and it better reflects AD activity than CD26, a molecule expressed on activated Th1 cells (38).

It has also been suggested that the imbalance is age-dependent. For instance, the cutaneous lymphocyte-associated antigen (CLA)+ Th2/Th1 is observed in early-onset AD with some Th17 polarization, whereas the adult form involves Th22 and cytotoxic T cells (39, 40). In contrast, another age-dependent observation noted a progressive increase of IL-17, IL-22, and IFN-γ levels, with two peaks noted in regulatory T cells at 6 to 11 years and IL-9 at 12 to 17 years (41).

In addition, it has also been suggested that a T-cell subset imbalance is race-dependent. Dominance of Th2 cells is common among European Americans and Asians; however, Th17 and Th22 cells characterize AD in Asians (39, 42), in whom IL-26, another upregulated cytokine in AD (43), may contribute to Th17 and Th2 dominance (44). On the other hand, AD is skewed toward Th22/Th2 in African Americans (34).

Apart from Th2 cells, type 2 innate lymphoid cells (ILC2s), skin-resident lymphoid cells that lack B- or T-cell receptors, and basophils are increased in AD (45). Both cells are key sources of type 2 cytokines (46). Prostaglandin E2 negatively regulates ILC2s (47). However, ILC2 deficiency does not ameliorate AD in experimental models, suggesting that AD can be independent of ILC2s (48). On the other hand, ILC2 activation results in spontaneous AD independently of the adaptive immune system (49).

Overall, there is a global imbalance in T-cell subsets with a predominance of Th2 cells. A controversy was noted regarding Th1, Th17, and regulatory and cytotoxic T cells. Other factors, such as polymorphisms of toll-like receptor (TLR)-2 and TLR-4, might contribute to this (50).

Cytokines of type 2 immunity are pronounced in the acute phase

Figure 1 summarizes the cytokine network of type 2 immunity in AD.

Interleukin-4

Source, stimulation, and regulation

IL-4 is cardinally elevated in AD (51–54) with a few exceptions (55). IL-4rα is overexpressed in acute rather than chronic AD lesions (56). Many sources of IL-4 have been reported in the setting of AD. For instance, IL-4–producing CD4+ and CD8+ cells are high (57). Peripheral blood mononuclear cells (PBMCs) derived from AD patients show abnormal spontaneous production of IL-4 (55). T-cell hyperproduction of IL-4 interferes with the nuclear factor of activated T cells and activator protein-1, two transcription factors associated with the activation responsive element (58, 59). Mononuclear cells (60), including CD4+ cells and CD8+ cells (61, 62), are increased in the peripheral blood and skin of AD patients (63) and were unexpectedly reported to negatively correlate with disease severity (19). Mastocytes are also a rich source of IL-4. IL-4–bearing mastocytes are higher in the upper dermis of patients with AD and are a major source of IL-4 in 40% of cases (60). Furthermore, cutaneous infiltration of basophils in animal models of AD promotes the development of AD-like lesions by producing IL-4 (64). In addition, CD86 expression on bursa of Fabricius cells (B cells) is higher in AD, and it results in greater IL-4 release (65). Hypersecretion of IL-4 could be used at birth to predict the risk of AD. For instance, Phorbol 12-myristate 13-acetate/ionomycin-activated T cells isolated from the cord blood tend to secrete higher levels of IL-4 and a lower level of IFN-γ in persons that develop AD later in life (66).

Animal models of AD are widely used. IL-4 transgenic mice exhibit a typical phenotype of AD manifestation, such as pruritic inflammatory disease with erythema and crusting, cutaneous infection, and cardinal histologic findings including spongiosis, eosinophilic and mononucleocytic infiltration, mastocyte degran-

ulation, and an elevated level of immunoglobulin (Ig)G1, whereas the total IgE level was strain-dependent (8, 67). In addition, IL-4rα polymorphism in dogs is associated with canine AD (68). This emphasizes the role of genetics in AD. For instance, IL-4 –590C/T, a polymorphism resulting in increased promotor activity of the IL-4 gene, has been intensely studied in AD patients. The TT genotype is associated with AD in Japanese (69), Chinese (70), Swedish (71), and other (72) populations. In contrast, the association between –590C>T and AD was absent in a Saudi cohort (73). IL-4 –589C>T showed a similar significant association in a Chinese population, which also exhibited a higher level of IL-4 (70). In addition, another five polymorphisms within the IL-4 promotor region—namely, –3112C>T, –1803T>C, –327C>A, –326A>C, and –186G>A—were also associated with AD, although none of these affects promotor activity (74). However, in a Swedish population with AD, seven polymorphisms of IL-4rα failed to show a significant association (71). In contrast, IL-4rα rs2234898, a synonymous polymorphism, is associated with adulthood AD in Japan (75). IL-4rα nonsynonymous mutations have also been studied. In a Saudi population, IL-4rα (I50V) is associated with AD, as well as the signal transducer and activator (STAT)-6 (G2946A) (73) and (C2892T) (76).

Various stimuli have been described as triggering IL-4 release

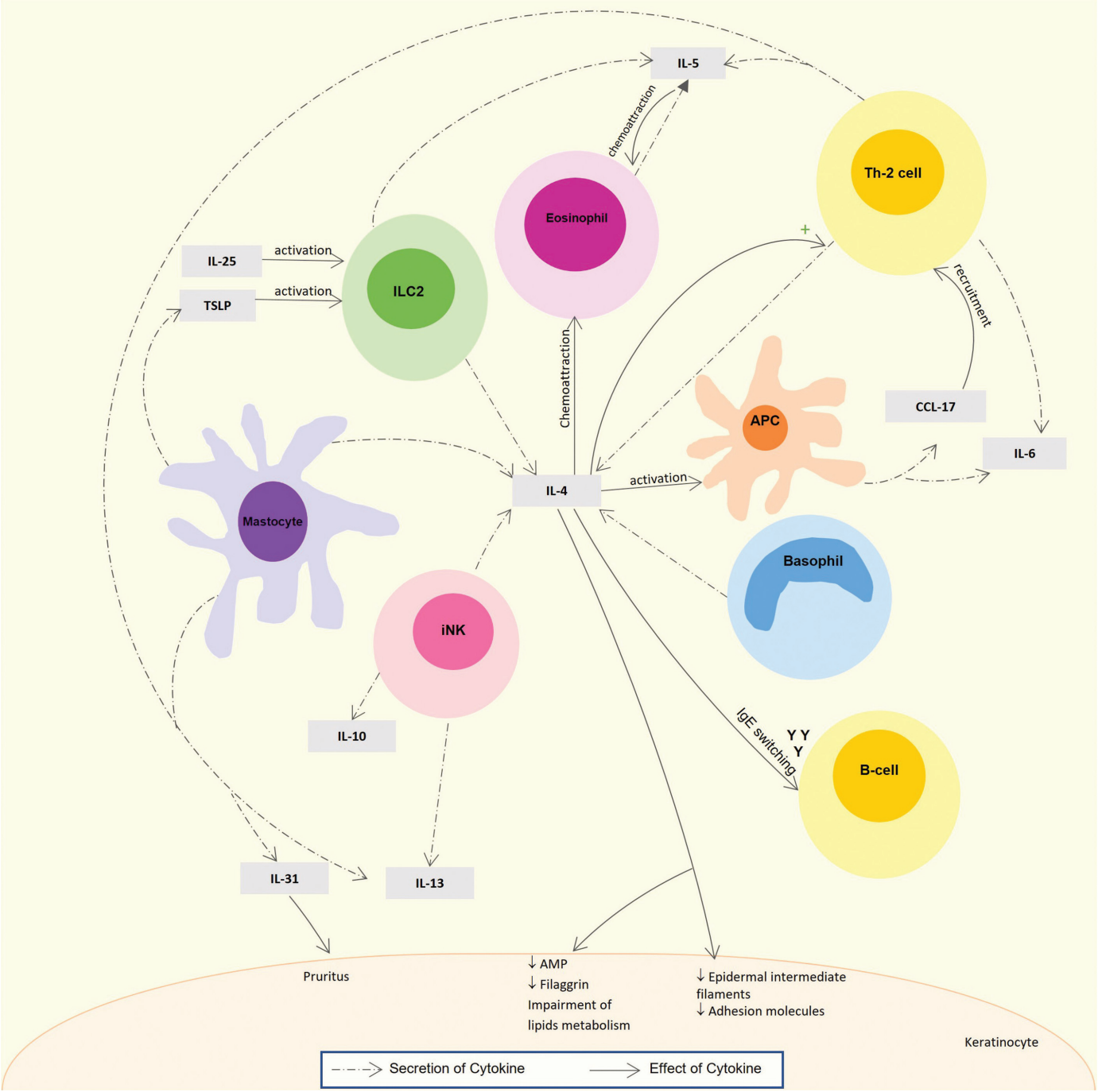

Figure 1 | The cytokine network of type 2 immunity in atopic dermatitis. Type 2 helper T cells are a good source of cytokines of type 2 immunity. Together with type 2 innate lymphoid cells, mastocytes, basophils, and invariant natural killer cells, they release IL-4, which mediates IgE switching, chemoattracts eosinophils, activates antigen-presenting cells to release CCL-17 and IL-6, and impairs the epidermis by reducing the expression of intermediate filaments and adhesion molecules. Together with eosinophils and type 2 innate lymphoid cells, type 2 helper T cells also release IL-5, which in turn chemoattracts eosinophils, contributing to eosinophilia in atopic dermatitis. Together with mastocytes and invariant natural killer cells, type 2 helper T cells secrete IL-13, which impairs the skin barrier integrity by suppressing filaggrin expression and impairing epidermal lipid metabolism. IL-31, a cytokine also released by type 2 helper T cells, contributes to pruritus. IL = interleukin, CCL= chemokine ligand, ILC2 = innate lymphoid cell 2, TSLP = thymic stromal lymphopoietin, iNK = invariant natural killer cell, APC = antigen presenting cell.

in AD. Exogenous IL-4 promotes in vitro IL-4 production from CD4+ CD45RA+ naive T cells (77), and hence in vivo IL-4 might exhibit an autocrine function. In addition, CLA expression on CD4+ cells is elevated in AD (57), and CLA+ naive T cells tend to autonomously produce Th2 cytokines (77). In contrast to naive T cells, CLA expression is diminished in plasmacytoid dendrocytes (78).

The role of dendrocytes in promoting IL-4 production is controversial. For instance, CD1c+ myeloid dendrocytes show diminished release of TNF-α and IL-12p70, which subsequently tends to induce IL-4–bearing helper T cells (79).

Neuropeptides stimulate the secretion of IL-4 as well. Substance P and vasoactive intestinal peptide are elevated in AD, accounting for pruritus. Upon exposure to these neuropeptides, IL-4 secretion from AD-isolated PBMCs is pronounced (80). Prostaglandin E2 is an eicosanoid that is elevated in AD. It drives IL-4 secretion through the 3',5'-cyclic adenosine monophosphate and phosphodiesterase enzyme (81).

Thymic stromal lymphopoietin (TSLP) is elevated in AD (82), and it positively correlates with AD severity (83). TSLP increase may be attributed to epigenetic factors such as promotor hypomethylation (84). In addition, IL-1β promotes TSLP secretion through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (85), and NF-κB-dependent secretion of TSLP is observed through the TLR-3/ΔNp73 axis (86). Mastocytes are involved in TSLP production as well, although the exact mechanism is still unknown (87). TSLP transgenic mice exhibit AD-like manifestations accompanied by increased IL-4–producing CD4+ cells, which also co-express increased levels of IL-5, TNF-α, IgE, and IgG1 (88). IL-13, IL-31, and TNF-α were also reported to induce keratinocytes to produce TSLP (89). Taking into account that Th2 cells express TSLP receptor, direct interaction between the two is expected (90). TSLP exerts its effect on other cells. For instance, it activates fibrocytes to produce collagen, predisposing AD subjects to the risk of fibrosis (91). It also stimulates ILC2s (92) and regulates eosinophil migration in AD (93). TSLP also activates invariant natural killer cells to produce Th2 cytokines such as IL-4 and IL-13 (94). IgG isolated from AD patients may also induce invariant natural killer cells to secrete IL-4 (95). In contrast, natural killer cells, including the CD4+ and CD8+ subpopulations, were found to be deficient in AD and, where IL-4rα is blocked, the natural killer cell count is restored (96, 97), suggesting that IL-4 exerts negative feedback on these cells. Consistently, upon expansion of CD4– CD8– double negative invariant natural killer cells, AD is suppressed (98).

Although IL-4 is a key player in AD, knocking out STAT-6, an important IL-4 signaling molecule, would still produce AD-like lesions in mice. However, these mice fail to produce IgE and Th2 cytokines. Cutaneous caspase-1, IFN-γ, IL-12, and IL-18 were all elevated. This suggests that type 2 immunity is not mandatory for AD development (99).

Effect

IL-4 exerts its effect by binding to its receptor. IL-4rα is a common subunit shared between IL-4r and IL-13r. In AD lesions, IL-4rα is expressed on melanocytes, vascular endothelial cells, and perivascular inflammatory and stromal cells, explaining the post-inflammatory hyperpigmentation observed in AD and other inflammatory skin diseases (100). IL-4 impairs the skin barrier in AD. It downregulates keratin-1 and -10, two epidermal intermediate filaments; desmoglein-1 and desmocollin-1, two adhesion molecules; and ceramide, an epidermal lipid (89, 101, 102). However, it upregulates the C-C motif chemokine ligand (CCL)-3L1, CCL-8, CCL-24, CCL-25, CCL-26, the C-X-C motif chemokine ligand (CXCL)-6, and CXCL-16, seven AD-related chemokines. Among these, CCL-8 has the capacity to recruit IL-5+ Th2 cells (103). Production of CCL-26, an eosinophil chemotaxin, takes place through the IL-4 / Janus kinase (JAK)-1 and -2/STAT-6 pathway (104). In addition, IL-4 upregulates other proinflammatory molecules such as IL-1α, IL-12rβ2, IL-25, IL-19, IL-20, and IL-31rα. On the other hand, IL-4 downregulates anti-microbial peptides or the factors involved in their production, such as IFN-κ and TLRs, explaining the low count of TLR-2+ and TLR-4+ PBMCs (14, 105, 106). In addition, IL-4 may impair the mobilization of anti-microbial peptides from cytoplasm (107). IL-4 also downregulates the NLR family pyrin domain containing 3 (108). All these mechanisms expose AD patients to a high risk of cutaneous bacterial, viral, and fungal infections (20). IL-4 downregulates TNF-α; lymphotoxin-β, an IgE-suppressor; and TNF superfamily member-18, a T-cell regulator (109, 110).

AD-derived PBMCs are hyperresponsive to IL-4 (111). IL-4 promotes the expansion of cutaneous lymphocytes in the presence of IL-2 (61), and it augments PBMC proliferation independently from IL-2 (112). IL-4 exerts a chemotactic effect on eosinophils in AD patients (113). CCL-3 (114) and CCL-11 (52, 115) are overexpressed in AD lesions. IL-4 upregulates the fibroblast-release of CCL-11, an eosinophil-activating and chemoattracting agent (116). Putting it all together, IL-4 imposes direct and indirect chemotactic roles on eosinophils, increasing their count in AD, which also correlates with AD severity (63).

IL-4 drives spontaneous IgE production, explaining the elevation of IgE in AD (117). Although IL-4 is associated with an increased IgE level by mediating IgE class switching (118), development of AD is IgE-independent (119). IgE production positively correlates with age (120) and severity of AD (121), and it is antagonized by IFN-γ, which is typically suppressed by IL-4 (59) and, subsequently, the regulatory mechanism of IgE production is lost (122). At birth, maternal and cord-blood IgE may predict the risk of AD (123, 124), whereas at 6 months of age the IgE level may predict the prognosis of AD during later childhood (125). Soluble CD23, a low-affinity IgE receptor, is elevated in AD (51) and is independently augmented by IL-4 and IFN-γ, although the latter may antagonize the former's effect (7, 126). CD23 is expressed on CD20+ B cells as well as non-B and non-T cells (CD3– CD20–) (127). The high-affinity IgE receptor FcεRI is overexpressed in plasmacytoid dendrocytes, impairing the expression of major histocompatibility complexes-1 and -2, enhancing the production of IL-10, and promoting plasmacytoid dendrocyte apoptosis (78). The intracellular expression of the receptor's alpha chain is attributed to IL-4, whereas the expression of the surface receptor is induced through a different mechanism (128).

CCL-17, CCL-18, and CCL-22, all dendrocyte-activated chemokines, are differentially pronounced in AD (43, 54, 64, 83, 115, 129–132). Interestingly, IL-4 activates different antigen-presenting cells, contributing to this observation. It enhances IL-31/IL-31rα interaction, which in turn augments CCL-17 and CCL-22 (133). In addition, IL-4 induces Forkhead Box Q1, a transcription factor, in human monocytes and macrophages, and it stimulates their migration. This is accompanied by a lower expression of claudin-1 and plexin-C1, two migration-regulating genes (134). CCL-22, but not CCL-17, correlates well with AD activity (135, 136), whereas both CCL-17 and CCL-22 correlate with AD severity (137). In contrast, IL-10, an anti-inflammatory cytokine, was also found to induce

HaCaT cells, immortalized human keratinocytes, to release CCL-17 (138). Being a C-C motif chemokine receptor (CCR)-4 ligand, CCL-17 secretion recruits CLA+ CCR-4+ T cells (139), explaining the high counts of CCR-4+ CD4+ T cells (140), which positively correlates with AD and the IgE level (9). Chemokine-like factor-1, a CCR-4 ligand, is highly expressed in AD scales and positively correlates with the IgE level as well (52).

In IL-4 transgenic mice, skin-barrier proteins as well as immunocytes and cytokines are dysregulated. IL-4 downregulates filaggrin (141–143). It also suppresses the epidermal expression of loricrin. p300/CBP is a common molecule that is competed for in two pathways: loricrin synthesis and IL-4/STAT-6. IL-4 overexpression consumes p300/CBP, which in turns suppresses loricrin production. Upon inhibition of STAT-6, loricrin expression normalizes (105). In addition, IL-4 alters the composition and metabolism of cutaneous lipids (89, 144) and tight junctions (145), contributing to the skin-barrier defect observed in AD. At the level of the immune system, IL-4 overexpression doubles cytokines levels several hundredfold (146). In addition, lymphocytes appear to spontaneously proliferate, and the total number of dendrocytes, macrophages, and natural killer cells increases in lymphoid tissue with potential migration toward the skin (147). Adhesion molecules, including intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), E-selectin, L-selectin, P-selectin, and P-selectin glycoprotein ligand-1, are also overexpressed (148, 149). In contrast, L-selectin is diminished in plasmacytoid dendrocytes (78).

CCL-27, a T-cell homing cytokine, is elevated in AD and psoriasis, suggesting disease non-specificity. Its level in AD positively correlates with AD severity, IL-2r level, eosinophil count, and CCL-17 level (150). Both the CCL-27 and its receptor, CCR-10, are essential for the development of AD inflammation, which regresses with CCL-27–antagonizing antibodies (151). CCR-4, the CCL-17 receptor, and CCR-10 may co-express in lymphocytes in AD (152).

CX3CR1, also known as fractalkine, is another disease non-specific chemokine. Its expression is upregulated in endothelial cells in AD and psoriatic lesions. However, an elevated serum level is specific to AD and correlates with disease severity (153).

In addition, angiogenesis is affected. Animal models of AD show an increase in interendothelial junctional cleft length and number, and an increase in capillary sprout density, and they exhibit an overall disorganized network of capillaries (154), which can be attributed to the increased expression of vascular endothelial growth factor but not its receptors (155). IL-4 (109), IL-6, and IFN-γ induce vascular endothelial growth factor-A, which also correlates with AD severity, together with other pro-angiogenic molecules (156).

Interleukin-5

IL-5 is upregulated in AD and correlates with disease severity (137). IL-5 is secreted from PBMCs (157) in addition to dermal eosinophils isolated from AD lesions (158) and ILC2s, as evident in filaggrin-deficient mice (49). In contrast, some studies have shown that the IL-5 serum level in AD is comparable to that in healthy subjects (159). IL-5rα is also elevated in acute and chronic AD lesions in comparison to normal skin (56).

The role of IL-5 in AD development was studied further in IL-4, IL-5, and IL-13 transgenic mice that develop an AD phenotype (160). IL-5 is important for eosinophil development, proliferation, and survival (161), and hence peripheral blood eosinophilia is more common in AD (162). Peripheral blood eosinophilia in AD could be attributed to IL-5 genotypes. For instance, the IL-5 –703C allele is more prevalent among AD patients with eosinophilia (eosinophils > 15%) (163).

IL-5 has been speculated to play a role in AD pathogenesis (161) For instance, IL-5 is capable of downregulating the NLR family pyrin domain containing 3 (108), and hence it works synergistically with other Th2 cytokines in predisposing AD patients to a high risk of cutaneous infection.

Interleukin-6

IL-6 is elevated in AD with a few contradictory reports (156). It positively correlates with disease severity (19, 35) and negatively with filaggrin expression (164). IL-6 increase is attributed to various factors, including increased production and reduced degradation. For instance, reduced activity of mastocyte-released chymase, an IL-6–degrading molecule, was reported in AD patients (165). Fibroblasts are a major source of IL-6 (166). In addition, PBMCs isolated from AD patients show a significantly greater release of IL-6 compared to healthy controls (167). Likewise, dendrocytes isolated from AD infants show increased release of IL-6, which diminishes after 1 year (168). This provides another potential tool for early prediction of AD.

Multiple reports have confirmed the role of IL-6 in AD pathogenesis. For instance, interruption of IL-6r improves the severity of AD; however, it increases the risk of bacterial superinfection (169). IL-6 rs1800795 (–174C>G) is associated with an increased risk of AD (170), whereas IL-6r rs2228145 is associated with more persistent AD (171).

Interleukin-9

IL-9, IL-9r, and Th9 cell counts are high in AD (172), in which the first positively correlates with disease severity (173). IL-9 was found to mediate AD in T-box transcription factor TBX21 and STAT-6 double knockout mice. IL-9 release is enhanced by TSLP (174), and the cytokine itself promotes IL-8 secretion (175). IL-9 –4091G>A is associated with AD (176).

Interleukin-10

The level of IL-10 is controversial in AD. For instance, AD derived from PBMCs may show diminished (177) or pronounced (178) spontaneous expression of IL-10. IL-10 negatively correlates with AD severity (19). TLR-10 is thought to drive IL-4–mediated IL-10 suppression, which in turns promotes disease chronicity (179). Monocyte-derived dendrocytes exhibit increased IL-10 release (180); however, the IL-10–producing regulatory B-cell count is low in AD (181). Two factors might enhance IL-10 production in AD; IgG induces IL-10 production from invariant natural killer cells (95) and high-affinity IgE receptor induces IL-10 production from plasmacytoid dendrocytes (78).

Being an anti-inflammatory cytokine, IL-10 plasmid ameliorates AD-like manifestations in vivo (182), suggesting that IL-10 plays a protective role in AD (138). However, IL-10 also downregulates antimicrobial peptides, and hence it increases the risk of cutaneous infections (183). In addition, dendrocytes isolated from AD infants show increased release of IL-10, which diminishes after 1 year (168). This provides another potential tool for early prediction of AD.

Looking into IL-10 polymorphisms might be helpful. IL-10 –819G>A is associated with AD (184), whereas IL-10 –1082G>A is associated with a higher IL-10 level in AD (185), although it lacks a direct association with the disease itself (186). In addition, IL-10 genotyping seems to interfere with the IgE level in AD. A common haplotype, TSS-distal haplotype (TGAC), is associated with a high IgE level (187). In contrast, two other haplotypes are associated with low IgE (188).

Interleukin-13

IL-13 and IL-13rα are elevated in AD (54, 115, 132, 189, 190). In canines with AD, IL-13 was proposed to have a more important role in exhibiting AD phenotype than IL-4 (191). IL-13 is released from PBMCs, including CD4+ and CD8+ T cells, yet the highest release is found from epidermal Langerhans cells (16, 52, 100, 180, 192, 193). In AD lesions, two-thirds of IL-13 is produced by T cells and mastocytes (192), where a unique IL-13+ IL-22+ subpopulation has been identified (194). Taking into consideration that IL-13 mediates IgE class switching (118), CD4+ IL-13+ cell count and serum level correlate with the IgE level and disease severity (63, 137, 193). Being a Th2 cytokine, IL-13 is pronounced in acute AD more than in chronic AD (195) in a CD-2–independent manner (157).

Underlying polymorphisms of IL-13 and IL-13rα may account for IL-13 and IL-13rα1 overexpression (196). For instance, AD was found to be associated with five polymorphisms: IL-13 rs3091307, rs20541, and rs1295685 as well as IL-13rα1 rs2265753 and rs2254672 (197–201), where IL-13 rs20541 also correlates with the serum IgE level (202). Taking into consideration that soluble CD-14 correlates positively with AD (203), CD-14 rs2569190 was found to be associated with a lower level of IL-13 production and it seems to be protective (200).

IL-13 also interferes with the composition and metabolism of cutaneous lipids (89, 144). In addition, it impairs the synthesis and secretion of antimicrobial peptides (14, 106, 107), and it downregulates the NLR family pyrin domain containing 3 (108). Nevertheless, IL-13 induces keratinocytes to secrete CCL-22, a CD4+ CCR-4+ T-cell chemoattractant (204). It also induces keratinocytes to secrete matrix metalloproteases, which may degrade the basement membrane in AD. IL-13 was also found to suppress in vitro production of type 4 collagen, a major component of the basement membrane; p63, a transcription factor; integrin α6; involucrin; filaggrin; and corneodesmosin (141–143, 205, 206). IL-13–induced filaggrin suppression is mediated via the transcription factor ovolike transcriptional repressor-1 (207). However, and unlike IL-4, IL-13 fails to exhibit a chemotactic effect on eosinophils (113).

Interleukin-25

The level of IL-25 is controversial. Diminished cord blood IL-25 has been reported in association with a high risk of infantile AD (208). Consistently, serum IL-25 is decreased in AD patients (106). However, cutaneous IL-25 overexpression has been reported in AD (49), probably produced by dermal dendrocytes (209). Parallelly, the relationship between Th2 cytokines and IL-25 is bidirectional. For instance, IL-4 has the capacity to augment IL-25 production (109). Reciprocally, IL-25 stimulates ILC2s to produce type 2 cytokines (92). Although it correlates with the degree of skin dryness and acute lesions in AD (210), the effect of IL-25 on the expression of structural epidermal proteins such as filaggrin is controversial (209, 211).

Interleukin-31

IL-31 is a novel Th2 cytokine that generally tends to be elevated in AD (82, 212, 213), with a few exceptions (214). It positively correlates with the level of other Th2 cytokines, such as IL-4 and IL-13, and the IgE level, whereas its correlation with AD severity and pruritus is controversial (212, 213, 215). Resembling IL-4 and IL-13 activity against filaggrin, IL-31 also downregulates it (141–143). IL-31 expression is elevated in models with itching behavior, explaining how observed AD-associated pruritus (216) is ameliorated upon blockage (217). The suggested mechanism of pathogenesis involves the IL-31/IL-31r/STAT3/β-endorphin axis (218), and it employs neuropeptide natriuretic polypeptide β (219).

IL-31 interacts directly with eosinophils via IL-31r, which in the presence of keratinocytes promotes the production of IL-1, IL-6, CXCL-1, CXCL-8, and CCL-2 (54, 220), explaining the observed elevation in CXCL-1 (43). IL-31rα is also expressed on keratinocytes, nerve fibers, and skin-infiltrating macrophages in AD. In peripheral blood, IL-31 expression is restricted to CD45RO+ CLA+ T cells, whereby CLA+ cells show a greater capacity to secrete IL-31 in comparison to healthy controls (221, 222). In comparison to acute AD, IL-31–bearing T cells are more frequent in chronic AD and coexpress IL-13 and IL-22 and rarely IFN-γ and IL-17 (13). Although different IL-31 polymorphisms—namely, IL-31 rs10847385 and rs7974857—fail to show a significant association with AD (223), another two polymorphisms are associated with AD. For instance, the rs6489188AA genotype seems to be protective, whereas the rs11608363AA genotype is more prevalent in AD (224).

Cytokines of type 1 immunity are attenuated in the acute phase

Figure 2 summarizes the cytokine network of type 1 immunity in AD.

Interferon-γ

The IFN-γ level is generally low in AD (177) with a few exceptions (115, 132). It is suppressed by IL-4 and vasoactive intestinal peptide, whereby the latter molecule is a neuropeptide known to be elevated in AD. However, the effect of substance P is controversial (80, 225). Interestingly, the IFN-γ level fails to recover upon IL-2 stimulation, suggesting a potential intrinsic dysfunction (226). Although IFN-γ mRNA transcripts are elevated, its release is reduced (227). Other studies found that IFN-γ is spontaneously produced intracellularly, and that IFN-γ–producing cells are rather increased in AD. However, upon stimulation, IFN-γ extracellular secretion is unexpectedly low (226, 228). In contrast, multiple independent studies have concluded that IFN-γ–producing CD4+ cells, CD45RO+ in particular (229), and CD8+ cells are significantly low in the peripheral blood of AD patients (57, 62). One study estimated that 25% of CD4+ T cells and 30% of CD4– T cells are capable of producing IFN-γ (230). Furthermore, there is some evidence suggesting that the IFN-γ level in AD is age-dependent; it increases in infancy and decreases in childhood. This observation points toward a potential regulatory function of IFN-γ in inhibiting mononucleocyte differentiation toward Th2 and subsequently controlling the production of allergen-specific IgE during infancy (231). However, there are many other contradicting reports documenting normal serum levels of IFN-γ in the setting of a normal (232) or elevated (6) IL-4 level, a high level of IFN-γ in the setting

of high IL-4 (53), and a high level of Th1 cytokines in the setting of a normal IgE level (233) given that IFN-γ typically tends to inhibit IgE production (122).

These controversial observations may point toward different mechanisms contributing to the low level of IFN-γ, including a potential genetic component resulting in suppression of IFN-γ transcription, defect of post-transcriptional mechanisms, and dysfunction of CD4+. However, the rarely seen high level of IFN-γ might be attributed to the weakness of IFN-γ responses in cutaneous monocytes and monocyte-derived dendrocytes, probably due to decreased expression of IFN-γ receptor-2 (234). Subsequently, to compensate for IFN-γ receptor-2 under-expression, IFN-γ is up-regulated. Another explanation for the variation in IFN-γ expression is the variation in AD subtypes. Because AD is classified into intrinsic or extrinsic, IFN-γ was reported to be high in the former type and low in the latter type (157) and, if the subtype of AD was not specifically looked for, contradictory observations are reported. Interestingly, IFN-γ–producing CD1a-reactive T cells were enriched in AD blood and skin in response to an allergen (house dust mite) challenge (235).

IFN-γ expression is TSLP-independent, as already evident in TSLP transgenic mice (88). IFN-γ does not seem to contribute to the increased risk of infection in AD, and it may instead exert a protective effect. For instance, IFN-γ induces human β-defensin-3,

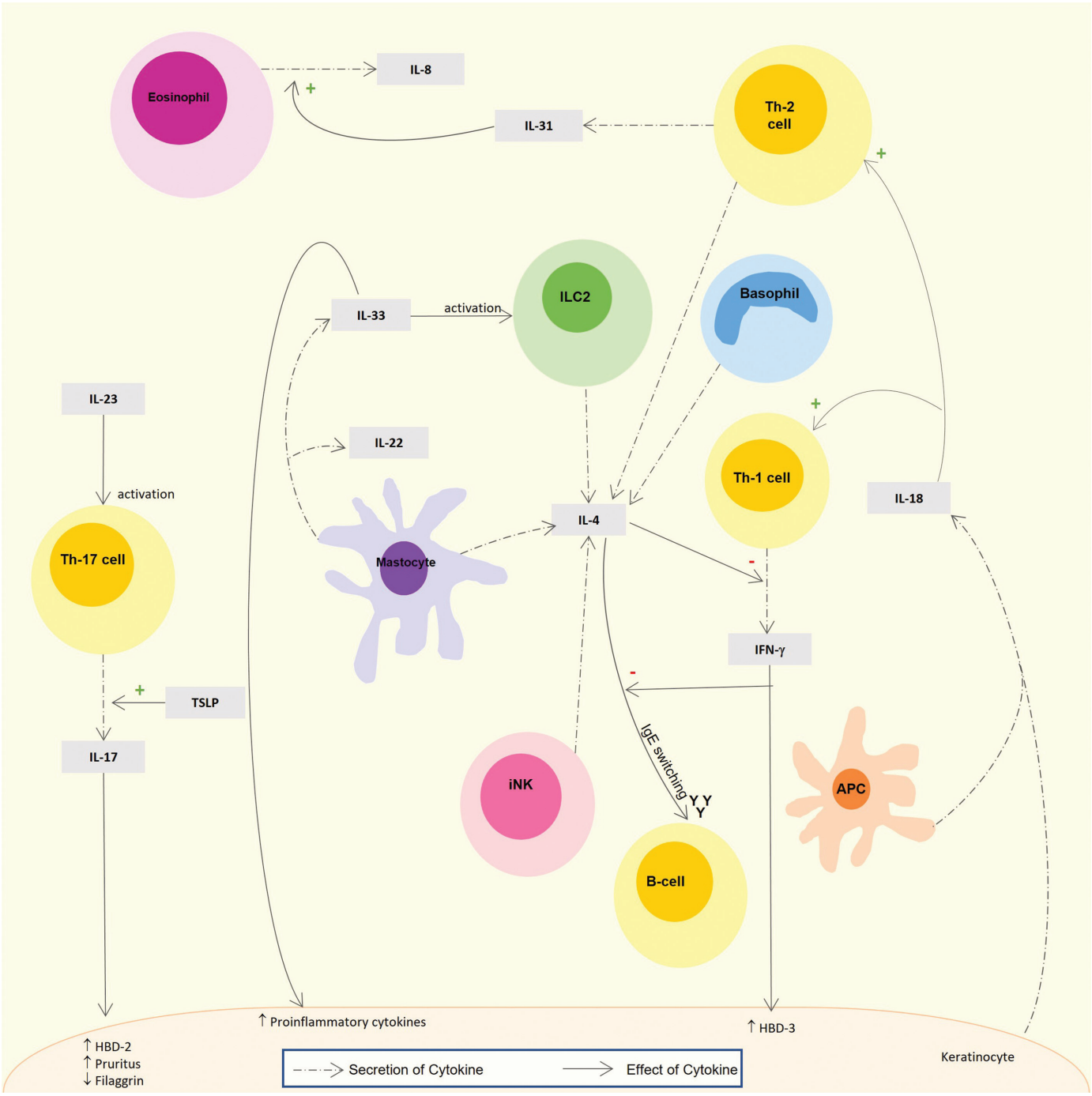

Figure 2 | The cytokine network of type 1 immunity, type 3 immunity, and miscellaneous cytokines in atopic dermatitis. Type 1 helper T cells are the cardinal source of cytokines of type 1 immunity. Type 1 helper T cells release IFN-γ, which promotes the release of human beta defensin-3 and suppresses IL-4–mediated IgE switching. Type 1 helper T-cell activation is promoted by IL-18, a cytokine released by keratinocytes and antigen-presenting cells. However, type 1 helper T-cell suppression is mediated by cytokines of type 2 immunity, including IL-4. Likewise, cytokines of type 3 immunity are cardinally secreted by type 17 helper T cells upon IL-23 activation with further enhancement by the thymic stromal lymphopoietin. Upon release, IL-17 promotes human beta defensin-2 release and suppresses filaggrin expression. IL = interleukin, HBD = human beta defensin, ILC2 = innate lymphoid cell 2, TSLP = thymic stromal lymphopoietin, iNK = invariant natural killer cell, APC = antigen presenting cell.

an antimicrobial peptide suppressed by IL-4, IL-10, and IL-13 (14, 236). In addition, IFN-γ suppresses ILC2 proliferation and production of type 2 cytokines (96).

Interleukin-2

Although IL-2 production is either low (237) or normal (6) in AD, its receptor, IL-2r, is elevated in AD sera and skin (7, 53, 167, 237–240) and it correlates with AD activity and severity (239). It has been proposed that high levels of IL-1α may enhance IL-2r expression (241). The effect of IL-2 varies in AD based on the target cell. Although IL-2 promotes the differentiation of PBMCs toward CD8+ T cells, it also promotes the differentiation of skin-derived lymphocytes toward CD4+ T cells (61). In AD patients and healthy controls, intradermal injection of IL-2 induced pruritus, erythema, spongiosis, exocytosis, dermal mononucleocyte infiltration, and ICAM-1 expression (242).

Interleukin-12

IL-12 is elevated in AD (115, 121, 132, 238), and IL-12–secreting cells are higher in chronic rather than acute AD, suggesting that IL-12 may promote AD chronicity (195). This is consistent with the aforementioned phase-dependent immunity (acute vs. chronic). Some reports have documented a positive correlation between IL-12p40 and AD severity (121). Consistently, blockage of IL-12p40 resulted in complete remission of AD in one-third of patients, partial remission in another third, and lack of response in the remaining third (243). Considering that IL-12p40 is shared between IL-12 and IL-23, the observed promising outcome cannot be fully attributed to IL-12; it may instead reinforce the importance of IL-23/IL-17 axis.

Expression of IL-12rβ seems to be regulated by epigenetic factors (244). In addition, two polymorphisms of the promotor region of IL-12r—namely, IL-12rβ –111A>T and –2C>T—are associated with an increased risk of AD (245). There are at least five other polymorphisms and haplotypes within the IL-12r gene that predispose patients to AD (246–248).

Interleukin-15

Epidermal and dermal IL-15 overexpression was observed in AD. IL-15 is particularly expressed by keratinocytes, CD1a+ dendrocytes, CD11b+ dendrocytes, CD68+ macrophages, and vimentin+ fibroblast (249). In contrast, IL-15 was not detectable in interstitial fluids collected from chronic AD (190), was reduced upon in vitro stimulation of AD-derived monocytes (250), and was comparable to controls in cases with severe AD (156).

Interleukin-18

With a few contradictory reports (251), IL-18 is elevated in AD patients and animal models (35, 83, 117, 121, 129, 190, 252–254), possibly due to decreased degradation (254). The level of IL-18 positively correlates with disease severity, transepidermal water loss (83, 117, 121, 137), and eosinophil counts (253), but its correlation with the serum IgE level is controversial (252, 253). IL-18 rs795467 (255) and rs187238 (256) may be associated with AD. The former polymorphism has been reported to be associated with psoriasis, rather than AD, in a Japanese cohort (257), whereas the latter polymorphism correlates with CCL-17 and IgE levels (129). Consistently, and as discussed above, in the absence of type 2 immunity in animal models, development of AD-like lesions was possible (99) and IL-18 seems to contribute to AD-like manifestations (258) by inducing Th1 cytokines. For instance, in the presence of IL-2, IL-18 induces PBMCs to secrete IL-13 and IFN-γ (259). However, response to IL-18 blockage is still inconclusive (260, 261).

Interleukin-33

IL-33, secreted by mastocytes and keratinocytes (87, 262), is elevated in AD (82). Filaggrin deficiency induces IL-33 (263), which in turns induces keratinocytes to secrete a wide spectrum of proinflammatory cytokines and antimicrobial peptides (262, 264). On the other hand, it is evident that IL-33 is capable of suppressing human β-defensin (264). In AD patients, corneal IL-33 correlates with the severity of pruritus and lichenification (265). In contrast, in IL-33 transgenic mice lacking B and T cells, IL-33 activates ILC2s, resulting in AD-like inflammatory lesions (92). IL-33 indirectly polarizes T cells toward type 2 immunity. It overexpresses OX40L on ILC2s, which in turns deviates OX40+ T cells toward type 2 immunity (266). Polymorphism of its receptor, SH2 –226999 G>A, was found to be associated with the expression level of both the receptor and IgE (267). In the mouse model of AD, IL-33 mediates AD through ILC2s (268).

Tumor necrosis factor-β

TNF-β, released by Th1–like cells, is low in AD. TNF-β–treated PBMCs were found to inhibit Th2 cytokines and to promote IFN-γ secretion (269). On the other hand, there is a single report documenting the TNF-β increase among AD patients (115). TNF-β 252A>G was studied in a Saudi cohort, and the results showed a significantly greater prevalence of GG and AA genotypes and a significantly lower prevalence of GA genotypes in AD cases compared to controls (270). However, the distribution of these genotypes does not appear to be dose-dependent, and hence the role of A/G alleles in AD is questionable.

Cytokines of type 3 immunity are controversial

The level of IL-17A and IL-17F is controversial. IL-17A was reported to be elevated and positively correlated with AD severity, particularly the intrinsic subtype (20, 132, 263). IL-23, a Th17 activator; IL-19; and IL-22 are also pronounced (132, 238). Levels of IL-17A and IL-22 positively correlate with transepidermal water loss (83, 137), and IL-22 promotes the production of human β-defensin-2, an antimicrobial peptide (106). In contrast, transcripts of both IL-17A and IL-23A were reported high in pruritic AD lesions in comparison to nonpruritic AD lesions (215). IL-17–producing T cells account for 2% of the peripheral blood in AD patients (230) and correlate with disease severity as well (42). In contrast, in AD skin, intracellular production of IL-17 was limited to papillary dermal CD3+ CD4+ T cells.

IL-17 promotes naive T-cell polarization toward Th2 cells (271). It also induces keratinocyte production of granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, IL-8, CXCL-10, vascular endothelial growth factor, and human β-defensin-2 (42), and this explains the observed CXCL-10 elevation in AD (43, 115, 130, 131). Accordingly, it seems that IL-17 induces many genes involved in the innate immunity. IL-17 also suppresses the expression of filaggrin (272) and cutaneous tight junction-related genes and proteins (272). The IL-23/IL-17 axis might be diminished in AD.

Considering that IL-17 promotes human β-defensin production, IL-17 reduction is proposed to promote cutaneous infections. The observed decrease in Th17 cells negatively correlates with CCL-17 expression, IgE levels, and eosinophil count (273).

IL-17 overexpression might be attributed to genetic factors. For instance, IL-17 –152G>A is more common among AD patients (263) and predisposes them to a more severe phenotype (274). However, IL-17F rs763780 failed to show any significant association with AD (275). IL-17 production is also inducible by TSLP (276) and AD-derived IgG (95). IL-17 seems to contribute to expressing the AD phenotype. In a CD4–depleted animal model of AD, animals were still capable of displaying AD manifestations mediated by IL-17 and IL-22 (277).

IL-22 is elevated in AD (132, 278). It is secreted by both mastocytes (279) and Th22 cells, and it positively correlates with CCL-17 (278). There is a growing body of evidence suggesting that IL-22 contributes remarkably to AD pathogenesis. For instance, IL-22 downregulates profilaggrin or filaggrin expression in keratinocytes (280). In addition, it induces epidermal hyperplasia and mediates keratinocyte proliferation (281).

Figure 2 summarizes the cytokine network of type 3 immunity in AD.

Miscellaneous

Figure 2 summarizes the other cytokine interaction in AD.

Interleukin-1

IL-1α, IL-1β, and IL-1rα are generally high in AD (190), and PBMC production of IL-1 is increased in vitro with further augmentation by histamine (240). On the other hand, AD-derived monocytes show reduced IL-1 release (282). IL-1β correlates with AD severity (137). IL-1 has also been implicated in putting severe AD patients at high risk of cardiovascular disease (283). Genetic polymorphisms have been investigated. The IL-1r pst-I 1970 T allele seems to play a protective role against AD, whereas the C allele is more prevalent among AD patients (284). No association has been observed between AD and IL-1β –511T>C or IL-1β +3953T>C (285).

Interleukin-8

The level of IL-8, a cytokine released by PBMCs (286), is controversial. Although it is low in AD patients (156), it is still detectable in the majority of AD cases in comparison to other skin diseases (287), and it has even been reported to be significantly elevated in AD compared to controls (83, 190, 238, 288). AD-derived T cells have shown a weak in vitro chemotactic response to IL-8 (289). The increase of IL-8 and weakness of T-cell response could be viewed from two aspects. T cells might have an intrinsic defect in their response to IL-8 and, hence, IL-8 tries to compensate by increasing its release. The other explanation is that IL-8 is originally elevated (because of an intrinsic defect or in response to a stimulus), and thus T cells attenuate their chemotactic response as a self-protective mechanism. AD scales contain a high level of IL-8, positively correlating with AD severity (137). IL-31 and IL-33 stimulate IL-8 secretion from eosinophils and fibroblasts, respectively (166). However, lesional skin biopsies have exhibited variable patterns of IL-8 stain (290).

Interleukin-16

Low levels of IL-16 transcripts have been detected in AD-derived keratinocytes and Langerhans cells (40% of CD1a+ cells). Although it is low in AD, IL-16 is absent in normal keratinocytes and Langerhans cells. The increase of IL-16 is significant in acute rather than chronic AD (291) and its level correlates with the severity of AD, the level of IgE, and the number of CD4+ infiltrating cells (288, 292, 293).

Interleukin-36

IL-36 is elevated in the skin and sera of AD patients (43, 294).

Interleukin-37

The available evidence suggests that IL-37 is elevated in AD (43) with a few exceptions (295). Being an anti-inflammatory cytokine, IL-37 activates FoxP3+ regulatory T cells and ameliorates experimental AD (296). In addition, IL-37 seems to contribute to atherosclerosis in AD (297).

Granulocyte-macrophage colony-stimulating factor

Some studies have documented high expression of GM-CSF receptor (189), possibly attributed to the low spontaneous release of GM-CSF as evident in AD-derived PBMCs (178). On the other hand, AD lesions exhibit a strong GM-CSF stain. GM-CSF is mainly produced by keratinocytes and is cable of stimulating PBMCs in a dose-dependent manner. Keratinocyte-secreted GM-CSF may contribute to AD chronicity by enhancing mononucleocyte survival (298, 299). Consistently, the α-subunit of GM-CSF is also increased in chronic AD lesions in comparison to the acute phase (56). In addition, intradermal injection of GM-CSF results in a progressive accumulation of CD1a+ cells (298), explaining the high number of cutaneous CD1a+ cells in intrinsic and extrinsic AD (300). On the other hand, IL-4, IL-5, and IFN-γ induce eosinophils to express the α and β subunits of GM-CSF receptor (189). Genotyping of GM-CSF may help in predicting AD severity (301).

Macrophage migration inhibitory factor

Macrophage migration inhibitory factor, a cytokine with a T-cell activation function, is elevated in the sera and diffusely expressed in the epidermis of AD patients (302). Unstimulated AD-derived PBMCs spontaneously secrete high levels of this factor, and with stimulation, its level is further augmented (303). Consistently, lacrimal fluids collected from patients with severe AD contain a significantly greater concentration of this cytokine in comparison to those with a milder disease (304). This factor is also elevated in animals with AD (305). When neutralized, experimental AD is ameliorated (306).

Tumor necrosis factor-α

The level of TNF-α is controversial. Although some studies have found its serum and cutaneous levels to be elevated (53, 156), others have reported a lower level of TNF-α secretion (177, 178), probably due to IL-4 suppressive effect (109). Expression of TNF-α

receptor 1 and 2 subunits is increased in AD (307). Polymorphisms of TNF-α are controversial as well. No association was observed between AD and TNFA –238G>A or –308G>A in one study (285), whereas AD was found to be associated with the GG genotype of both polymorphisms in a second study (308) and with the –308GA genotype in a third study (270).

Transforming growth factor-β

The role of TGF-β is controversial in AD. For instance, AD is associated with a low-producer genotype of TGF-β, namely 869TT (309). Consistently, TGF-β level is significantly low in AD (288). Likewise, PBMCs from AD patients show a decreased level of TGF-β (178). Conversely, expression of TGF-β and its receptors was reported to be high (54, 238). Parallelly, experimental models suggest that blockage of TGF-β receptor alleviates AD-like manifestations and also improves levels of TNF-α, TGF-β1, TGF-βr1, IL-1β, IL-6, and IgE (310). Nevertheless, TGF-β was found to inhibit IgE production. For instance, knocking out the TGF-β signaling molecule augments the level of antigen-specific IgE (311).

Cytokines and cytokine antagonists in the management of atopic dermatitis

Understanding the pathogenesis of AD is essential in the advancement of drug development. Augmented cytokines could be selectively antagonized by designing antibodies neutralizing the cytokine itself or blocking its receptor. Small molecules interfering with the downstream signaling pathway have been developed, inhibiting JAK and phosphodiesterase-4 in particular. Table 1 summarizes the status of cytokines and cytokine antagonists as retrieved and filtered from www.clinicaltrials.gov. We categorized these agents into antagonists of cytokines in type 2 immunity (IL-4, IL-5, IL-13, IL-31, TSLP, and CCR-4), IL-2, antagonists of cytokines in type 3 immunity (IL-23/IL-17 axis and IL-22), antagonists of the IL-1 family (IL-1, IL-18, and IL-36), antagonists of JAK, antagonists of phosphodiesterase-4, and antagonists of IL-1 receptor-associated kinase-4. The current literature review suggests that many of these cytokines are inconclusively elevated, and hence we assume that these antagonists are being "retargeted" toward AD control.

Nevertheless, where a cytokine is diminished, recombinant cytokine "replacement" could help in restoring its normal level. For instance, there are multiple reports of systemic administration of IFN-γ in AD (312).

To date, four agents have obtained Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) approval (313), including Dupilumab, an IL-4rα antagonist (FDA and EMA 2017); Crisaborole, a phosphodiesterase-4 antagonist (FDA 2016, EMA 2020); Baricitinib, a small-molecule JAK inhibitor (EMA 2020); and Tralokinumab, an IL-13 antagonist (EMA 2021).

Conclusions

The cytokine profile in AD is complex and controversial, but cytokines of type 2 immunity strikingly predominate. The observed controversy could be attributed to the variations of underlying mechanisms of pathogenesis. In addition, multiple confounding factors seem to interfere with cytokine expression, including disease phase (acute vs. chronic), disease type (intrinsic vs. extrinsic), patient factors (epigenetics, polymorphisms, age, and race), and experimental models that might not exactly match AD in humans. Monoclonal antibodies and small molecules targeting cytokines and downstream signaling molecules are promising.

Table 1 | **The current status of cytokines and cytokine antagonists in atopic dermatitis.**

Agent	Structure and mechanism of action	Current status	National clinical trial
Antagonists of cytokines of type 2 immunity			
Interleukin-4			
Dupilumab	Human IgG4 monoclonal antibody against IL4rα, a shared subunit with IL-13	FDA and EMA 2017, phase 4	NCT03667014 NCT03389893 NCT04447417 NCT03293030 NCT05042258 NCT04033367 NCT04520308 NCT04358224 NCT04823130 NCT04718870 NCT04895423
AK120	Monoclonal antibody against IL-4rα, a shared subunit with IL-13	Phase 2	NCT04256174
CBP-201	Monoclonal antibody against IL-4rα, a shared subunit with IL-13	Phase 2	NCT05017480 NCT04444752
Interleukin-5			
Benralizumab	Humanized recombinant IgG1κ monoclonal antibody against IL-5rα	Phase 2	NCT04605094 NCT03563066
Mepolizumab	Humanized IgG1 monoclonal antibody against IL-5	Phase 2	NCT03055195
Interleukin-13			
Tralokinumab	Human IgG4 monoclonal antibody against IL-13	EMA 2021 Phase 3	NCT03587805 NCT03761537 NCT04587453 NCT03363854 NCT03160885 NCT03131648 NCT03526861

Table 1 | **Continued.**

Agent	Structure and mechanism of action	Current status	National clinical trial
LY3650150 (lebrikizumab)	Humanized IgG4 monoclonal antibody against IL-13rα1	Phase 3	NCT04626297 NCT04250350 NCT04392154 NCT04178967 NCT04146363 NCT04250337 NCT04760314
CC93538 (*cendakimab*)	Humanized monoclonal antibody against IL-13	Phase 2	NCT04800315
ASLAN004	Human monoclonal antibody against IL-13rα1	Phase 1	NCT04090229
Interleukin-31			
CIM331 (*nemolizumab*)	Humanized IgG2 monoclonal antibody against IL-31rα	Phase 3	NCT03985943 NCT03989349 NCT03989206 NCT05056779
BMS-981164	Monoclonal antibody against IL-31	Phase 1	NCT01614756
TSLP			
MEDI9929 (AMG 157, tezepelumab)	Human IgG2λ monoclonal antibody against TSLP	Phase 2	NCT02525094 NCT03809663
MK-8226	Recombinant human IgG1 monoclonal antibody against TSLP receptor	Phase 1	NCT01732510
CCR-4			
RPT193	Small molecule against CCR-4	Phase 1	NCT04271514
Cytokines of type 1 immunity			
Interleukin-2			
LY3471851	Recombinant IL-2	Phase 1	NCT04081350
Antagonists of cytokines of type 3 immunity			
Interleukin-23 / interleukin-17 axis			
MOR106	Human monoclonal antibody against IL-17C	Phase 2	NCT03864627 NCT03568071
Risankizumab	Human monoclonal antibody against IL-23	Phase 2	NCT03706040
Secukinumab	Human IgG1κ monoclonal antibody against IL-7A	Phase 2	NCT02594098 NCT03568136
Ustekinumab	Monoclonal antibody against p40, a shared subunit between IL-12r and IL-23r	Phase 2	NCT01806662 NCT01945086
Interleukin-22			
ILV-094 (fezakinumab)	IL-22	Phase 2	NCT01941537
LEO 138559	Human monoclonal antibody against IL-22r, a common receptor with IL-20	Phase 1	NCT04922021 NCT03514511
Antagonists of the interleukin-1 family			
Interleukin-1			
JNJ-77474462 (*bermekimab*)	Human IgG1κ monoclonal antibody against IL-1α	Phase 2	NCT04791319 NCT04990440 NCT04021862 NCT03496974
Anakinra	Recombinant IL-1r antagonist	Phase 1	NCT01122914
Interleukin-18			
CMK389	IL-18 antagonist	Phase 2	NCT04836858
Interleukin-33			
ANB020 (etokimab)	IgG1 monoclonal antibody against IL-33	Phase 2	NCT03533751
LY3375880	Monoclonal antibody against IL-33	Phase 2	NCT03831191
MEDI3506	Monoclonal antibody against IL-33	Phase 2	NCT04212169
MSTT1041A (*astegolimab*)	Human IgG2monoclonal antibody against IL-33r	Phase 2	NCT03747575
REGN3500	Human monoclonal antibody against IL-33	Phase 2	NCT03738423 NCT03736967
CNTO 7160	IgG2σ monoclonal antibody against IL-33r	Phase 1	NCT02345928
PF-06817024	Monoclonal antibody against IL-33	Phase 1	NCT02743871
Interleukin-36			
BI 655130 (spesolimab)	Monoclonal antibody against IL-36r	Phase 2	NCT03822832 NCT04086121

Table 1 | **Continued.**

Agent	Structure and mechanism of action	Current status	National clinical trial
Miscellaneous (other cytokines and downstream signaling molecules)			
Janus kinase antagonists			
LY3009104 (baricitinib)	JAK-1 and -2 antagonist	EMA 2020, Phase 3	NCT03952559 NCT03559270 NCT03435081 NCT03334422 NCT03334396 NCT03428100 NCT03733301 NCT03334435
A 301 (*ATI 502*)	Small molecule against JAK-1 and -2	Phase 3	NCT03002571
ABT-494 (*upadacitinib*)	Small molecule against JAK-1	Phase 3	NCT03738397 NCT03661138 NCT04195698 NCT03607422 NCT04666675 NCT03569293 NCT03568318 NCT03745651
INCB018424 (ruxolitinib)	JAK-1 and -2 antagonist	Phase 3	NCT03745638 NCT04921969
LEO 124249 (delgocitinib)	Small molecule; pan-JAK antagonist	Phase 3	NCT04871711 NCT04872101 NCT04949841
PF04965842 (abrocitinib)	Small molecule against JAK-1	Phase 3	NCT03796676 NCT03349060 NCT03575871 NCT03627767 NCT03720470 NCT03422822
SHR0302	Small molecule against JAK-1, JAK-2, JAK-3, and TYK-2	Phase 3	NCT04875169
ARQ-252	Small molecule against JAK-1	Phase 2	NCT04378569
ASN002	Small molecule against spleen tyrosine kinase and JAK	Phase 2	NCT03654755 NCT03531957 NCT03728504
ATI-1777	Small molecule against JAK-1 and -3	Phase 2	NCT04598269
Jaktinib	Pan JAK antagonist	Phase 2	NCT04539639
PF-06700841	JAK-1 and TYK-2 antagonist	Phase 2	NCT03903822
Tofacitinib	Small molecule against JAK-1 and -3	Phase 2	NCT02001181 NCT04246372
CEE321	Pan-JAK antagonist	Phase 1	NCT04612062
Phosphodiesterase-4 antagonists			
Crisaborole	Small molecule, inhibitor of PDE-4	FDA 2016 EMA 2020 phase 4	NCT04214197 NCT03539601 NCT04023084 NCT03832010 NCT03868098
ARQ-151 (roflumilast)	Small molecule, inhibitor of PDE-4	Phase 3	NCT04804605 NCT04773587 NCT04845620 NCT04773600 NCT03961529
OPA-15406 (MM36)	Small molecule, inhibitor of PDE-4	Phase 3	NCT03911401 NCT03908970
Apremilast	Small molecule, inhibitor of PDE-4	Phase 2	NCT02087943 NCT01393158 NCT04306965 NCT00931242 NCT03160248
DRM02	Small molecule, inhibitor of PDE-4	Phase 2	NCT01993420
E6005 (RVT-501)	PDE-4 inhibitor	Phase 2	NCT01461941 NCT03394677 NCT02950922
GW842470X	PDE-4 inhibitor	Phase 2	NCT00354510
Hemay808	Small molecule, inhibitor of PDE-4	Phase 2	NCT04352595
LEO 29102	PDE-4 inhibitor	Phase 2	NCT01037881
PF-07038124	Small molecule, inhibitor of PDE-4	Phase 2	NCT04664153
LEO 39652	PDE-4 inhibitor	Phase 1	NCT02219633 NCT01850849

Table 1 | **Continued.**

Agent	Structure and mechanism of action	Current status	National clinical trial
NF-κB Decoy	Oligonucleotides	Phase 1 Phase 2	NCT00125333
KT-474	Small molecule, IRAK-4 degrader	Phase 1	NCT04772885

CCR = C-C motif chemokine receptor, EMA = European Medicines Agency, FDA = Food and Drug Administration, IFN = interferon, Ig = immunoglobulin, IL = interleukin, IRAK = interleukin-1 receptor-associated kinase, JAK = Janus kinase, NF-κB = nuclear factor-B, PDE-4 = phosphodiesterase-4, TSLP = thymic stromal lymphopoietin, TYK-2 = tyrosine kinase-2.

References

1. Cork MJ, Danby SG, Ogg GS. Atopic dermatitis epidemiology and unmet need in the United Kingdom. J Dermatolog Treat. 2020;31:801–9.
2. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy. 2018;73:1284–93.
3. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers. 2018;4:1.
4. Eyerich K, Eyerich S, Biedermann T. The multi-modal immune pathogenesis of atopic eczema. Trends Immunol. 2015;36:788–801.
5. Howe W. Treatment of atopic dermatitis (eczema) [Internet]. UpToDate. 2021 [cited 2021 Apr 29]. Available from: https://www.uptodate.com/contents/treatment-of-atopic-dermatitis-eczema.
6. Kagi MK, Wuthrich B, Montano E, Barandun J, Blaser K, Walker C. Differential cytokine profiles in peripheral blood lymphocyte supernatants and skin biopsies from patients with different forms of atopic dermatitis, psoriasis and normal individuals. Int Arch Allergy Immunol. 1994;103:332–40.
7. Walker C, Kagi MK, Ingold P, Braun P, Blaser K, Bruijnzeel-Koomen CA, et al. Atopic dermatitis: correlation of peripheral blood T cell activation, eosinophilia and serum factors with clinical severity. Clin Exp Allergy. 1993;23:145–53.
8. Reichle ME, Chen L, Lin SX, Chan LS. The Th2 systemic immune milieu enhances cutaneous inflammation in the K14-IL-4-transgenic atopic dermatitis model. J Invest Dermatol. 2011;131:791–4.
9. Okazaki H, Kakurai M, Hirata D, Sato H, Kamimura T, Onai N, et al. Characterization of chemokine receptor expression and cytokine production in circulating CD4+ T cells from patients with atopic dermatitis: up-regulation of C-C chemokine receptor 4 in atopic dermatitis. Clin Exp Allergy. 2002;32:1236–42.
10 Reinhold U, Kukel S, Goeden B, Neumann U, Kreysel HW. Functional characterization of skin-infiltrating lymphocytes in atopic dermatitis. Clin Exp Immunol. 1991;86:444–8.
11. Kaltoft K, Pedersen CB, Hansen BH, Lemonidis AS, Frydenberg J, Thestrup-Pedersen K. In vitro genetically aberrant T-cell clones with continuous growth are associated with atopic dermatitis. Arch Dermatol Res. 1994;287:42–7.
12. Kamsteeg M, Bergers M, de Boer R, Zeeuwen PL, Hato SV, Schalkwijk J, et al. Type 2 helper T-cell cytokines induce morphologic and molecular characteristics of atopic dermatitis in human skin equivalent. Am J Pathol. 2011;178:2091–9.
13. Szegedi K, Kremer AE, Kezic S, Teunissen MB, Bos JD, Luiten RM, et al. Increased frequencies of IL-31–producing T cells are found in chronic atopic dermatitis skin. Exp Dermatol. 2012;21:431–6.
14. Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF, et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. J Immunol. 2003;171:3262–9.
15. Bien K, Zmigrodzka M, Orlowski P, Fruba A, Szymanski L, Stankiewicz W, et al. Involvement of Fas/FasL pathway in the murine model of atopic dermatitis. Inflamm Res. 2017;66:679–90.
16. Jassies-van der Lee A, Rutten VP, Bruijn J, Willemse T, Broere F. CD4+ and CD8+ skin-associated T lymphocytes in canine atopic dermatitis produce interleukin-13, interleukin-22 and interferon-γ and contain a CD25+ FoxP3+ subset. Vet Dermatol. 2014;25:456-e72.
17. Zhang BX, Lyu JC, Liu HB, Feng DQ, Zhang DC, Bi XJ, et al. Attenuation of peripheral regulatory T-cell suppression of skin-homing CD8(+)T cells in atopic dermatitis. Yonsei Med J. 2015;56:196–203.
18. Garcia EM, Galicia-Carreon J, Novak N. In vitro conversion into CD4+CD25+Foxp3+ induced regulatory T cells is reduced in atopic dermatitis patients. Int Arch Allergy Immunol. 2020;181:353–6.
19. Samochocki Z, Alifier M, Bodera P, Jeziorkowska R, Rosiak E, Jurkiewicz B, et al. T-regulatory cells in severe atopic dermatitis: alterations related to cytokines and other lymphocyte subpopulations. Arch Dermatol Res. 2012;304:795–801.
20. Lesiak A, Smolewski P, Sobolewska-Sztychny D, Sysa-Jedrzejowska A, Narbutt J. The role of T-regulatory cells and toll-like receptors 2 and 4 in atopic dermatitis. Scand J Immunol. 2012;76:405–10.
21. Szegedi A, Barath S, Nagy G, Szodoray P, Gal M, Sipka S, et al. Regulatory T cells in atopic dermatitis: epidermal dendritic cell clusters may contribute to their local expansion. Br J Dermatol. 2009;160:984–93.
22. Caproni M, Antiga E, Torchia D, Volpi W, Barletta E, Gitti G, et al. FoxP3-expressing T regulatory cells in atopic dermatitis lesions. Allergy Asthma Proc. 2007;28:525–8.
23. Ito Y, Adachi Y, Makino T, Higashiyama H, Fuchizawa T, Shimizu T, et al. Expansion of FOXP3-positive CD4+CD25+ T cells associated with disease activity in atopic dermatitis. Ann Allergy Asthma Immunol. 2009;103:160–5.
24. Zhang YY, Wang AX, Xu L, Shen N, Zhu J, Tu CX. Characteristics of peripheral blood CD4+CD25+ regulatory T cells and related cytokines in severe atopic dermatitis. Eur J Dermatol. 2016;26:240–6.
25. Fyhrquist N, Lehtimaki S, Lahl K, Savinko T, Lappetelainen AM, Sparwasser T, et al. Foxp3+ cells control Th2 responses in a murine model of atopic dermatitis. J Invest Dermatol. 2012;132:1672–80.
26. Fu Y, Lou H, Wang C, Lou W, Wang Y, Zheng T, et al. T cell subsets in cord blood are influenced by maternal allergy and associated with atopic dermatitis. Pediatr Allergy Immunol. 2013;24:178–86.
27. Hinz D, Bauer M, Roder S, Olek S, Huehn J, Sack U, et al. Cord blood Tregs with stable FOXP3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year. Allergy. 2012;67:380–9.
28. Antunez C, Torres MJ, Mayorga C, Cornejo-Garcia JA, Santamaria-Babi LF, Blanca M. Different cytokine production and activation marker profiles in circulating cutaneous-lymphocyte-associated antigen T cells from patients with acute or chronic atopic dermatitis. Clin Exp Allergy. 2004;34:559–66.
29. Higashi N, Bang K, Gesser B, Lund M, Thestrup-Pedersen K. Cytokine expression of skin T-lymphocytes from patients with atopic dermatitis. Acta Derm Venereol. 2001;81:3–7.
30. Horiuchi Y, Bae SJ, Katayama I. Overexpression of the suppressor of cytokine signalling 3 (SOCS3) in severe atopic dermatitis. Clin Exp Dermatol. 2006;31:100–4.
31. Elentner A, Finke D, Schmuth M, Chappaz S, Ebner S, Malissen B, et al. Langerhans cells are critical in the development of atopic dermatitis-like inflammation and symptoms in mice. J Cell Mol Med. 2009;13:2658–72.
32. Otsuka A, Nomura T, Rerknimitr P, Seidel JA, Honda T, Kabashima K. The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. Immunol Rev. 2017;278:246–62.
33. Colonna M. Skin function for human CD1a-reactive T cells. Nat Immunol. 2010;11:1079–80.
34. Sanyal RD, Pavel AB, Glickman J, Chan TC, Zheng X, Zhang N, et al. Atopic dermatitis in African American patients is TH2/TH22-skewed with TH1/TH17 attenuation. Ann Allergy Asthma Immunol. 2019;122:99–110.e6.
35. Olivry T, Mayhew D, Paps JS, Linder KE, Peredo C, Rajpal D, et al. Early activation of Th2/Th22 inflammatory and pruritogenic pathways in acute canine atopic dermatitis skin lesions. J Invest Dermatol. 2016;136:1961–9.
36. Caproni M, Bianchi B, D'Elios MM, De Carli M, Amedei A, Fabbri P. In vivo relevance of CD30 in atopic dermatitis. Allergy. 1997;52:1063–70.
37. Dummer W, Rose C, Brocker EB. Expression of CD30 on T helper cells in the inflammatory infiltrate of acute atopic dermatitis but not of allergic contact dermatitis. Arch Dermatol Res. 1998;290:598–602.
38. Katoh N, Hirano S, Suehiro M, Ikenaga K, Yamashita T, Sugawara N, et al. Soluble CD30 is more relevant to disease activity of atopic dermatitis than soluble CD26. Clin Exp Immunol. 2000;121:187–92.
39. Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. J Allergy Clin Immunol. 2016;138:1639–51.
40. Brunner PM, He H, Pavel AB, Czarnowicki T, Lefferdink R, Erickson T, et al. The blood proteomic signature of early-onset pediatric atopic dermatitis shows systemic inflammation and is distinct from adult long-standing disease. J Am Acad Dermatol. 2019;81:510–9.
41. Czarnowicki T, He H, Canter T, Han J, Lefferdink R, Erickson T, et al. Evolution of pathologic T-cell subsets in patients with atopic dermatitis from infancy to adulthood. J Allergy Clin Immunol. 2020;145:215–28.
42. 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.
43. Zhu J, Wang Z, Chen F. Association of key genes and pathways with atopic dermatitis by bioinformatics analysis. Med Sci Monit. 2019;25:4353–61.

44. Kamijo H, Miyagaki T, Hayashi Y, Akatsuka T, Watanabe-Otobe S, Oka T, et al. Increased IL-26 expression promotes T helper type 17- and T helper type 2-associated cytokine production by keratinocytes in atopic dermatitis. J Invest Dermatol. 2020;140:636–44.e2.
45. Mashiko S, Mehta H, Bissonnette R, Sarfati M. Increased frequencies of basophils, type 2 innate lymphoid cells and Th2 cells in skin of patients with atopic dermatitis but not psoriasis. J Dermatol Sci. 2017;88:167–74.
46. 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.
47. Sawada Y, Honda T, Nakamizo S, Nakajima S, Nonomura Y, Otsuka A, et al. Prostaglandin E2 (PGE2)-EP2 signaling negatively regulates murine atopic dermatitis-like skin inflammation by suppressing thymic stromal lymphopoietin expression. J Allergy Clin Immunol. 2019;144:1265–73.e9.
48. Schwartz C, Moran T, Saunders SP, Kaszlikowska A, Floudas A, Bom J, et al. Spontaneous atopic dermatitis in mice with a defective skin barrier is independent of ILC2 and mediated by IL-1β. Allergy. 2019;74:1920–33.
49. Saunders SP, Moran T, Floudas A, Wurlod F, Kaszlikowska A, Salimi M, et al. Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity. J Allergy Clin Immunol. 2016;137:482–91.
50. Tyurin YA, Shamsutdinov AF, Kalinin NN, Sharifullin AA, Reshetnikova ID. Association of toll-like cell receptors TLR2 (p.Arg753GLN) and TLR4 (p.Asp299GLY) polymorphisms with indicators of general and local immunity in patients with atopic dermatitis. J Immunol Res. 2017;2017:8493545.
51. Ohshima Y, Katamura K, Miura M, Mikawa H, Mayumi M. Serum levels of interleukin 4 and soluble CD23 in children with allergic disorders. Eur J Pediatr. 1995; 154:723–8.
52. Yang GY, Chen X, Sun YC, Ma CL, Qian G. Chemokine-like factor 1 (CLFK1) is overexpressed in patients with atopic dermatitis. Int J Biol Sci. 2013;9:759–65.
53. Nuttall TJ, Knight PA, McAleese SM, Lamb JR, Hill PB. T-helper 1, T-helper 2 and immunosuppressive cytokines in canine atopic dermatitis. Vet Immunol Immunopathol. 2002;87:379–84.
54. Wohlfahrt JG, Kunzmann S, Menz G, Kneist W, Akdis CA, Blaser K, et al. T cell phenotype in allergic asthma and atopic dermatitis. Int Arch Allergy Immunol. 2003;131:272–82.
55. Well S, Diel F. In vitro interleukin 4 and interferon-gamma production by mononuclear cells from atopic dermatitis patients. Mediators Inflamm. 1993;2:411–5.
56. Taha RA, Leung DY, Ghaffar O, Boguniewicz M, Hamid Q. In vivo expression of cytokine receptor mRNA in atopic dermatitis. J Allergy Clin Immunol. 1998;102: 245–50.
57. Teraki Y, Hotta T, Shiohara T. Increased circulating skin-homing cutaneous lymphocyte-associated antigen (CLA)+ type 2 cytokine-producing cells, and decreased CLA+ type 1 cytokine-producing cells in atopic dermatitis. Br J Dermatol. 2000;143:373–8.
58. Chan SC, Brown MA, Willcox TM, Li SH, Stevens SR, Tara D, et al. Abnormal IL-4 gene expression by atopic dermatitis T lymphocytes is reflected in altered nuclear protein interactions with IL-4 transcriptional regulatory element. J Invest Dermatol. 1996;106:1131–6.
59. Yamazaki F, Aragane Y, Maeda A, Matsushita K, Ueno K, Yudate T, et al. Overactivation of IL-4–induced activator protein-1 in atopic dermatitis. J Dermatol Sci. 2002;28:227–33.
60. Horsmanheimo L, Harvima IT, Jarvikallio A, Harvima RJ, Naukkarinen A, Horsmanheimo M. Mast cells are one major source of interleukin-4 in atopic dermatitis. Br J Dermatol. 1994;131:348–53.
61. Reinhold U, Kukel S, Goeden B, Neumann U, Wehrmann W, Kreysel HW. Interleukin-4 promotes the expansion of skin-infiltrating lymphocytes from atopic dermatitis in vitro. J Invest Dermatol. 1991;96:370–5.
62. Nakazawa M, Sugi N, Kawaguchi H, Ishii N, Nakajima H, Minami M. Predominance of type 2 cytokine-producing CD4+ and CD8+ cells in patients with atopic dermatitis. J Allergy Clin Immunol. 1997;99:673–82.
63. La Grutta S, Richiusa P, Pizzolanti G, Mattina A, Pajno GB, Citarrella R, et al. CD4(+)IL-13(+) cells in peripheral blood well correlates with the severity of atopic dermatitis in children. Allergy. 2005;60:391–5.
64. Vestergaard C, Yoneyama H, Murai M, Nakamura K, Tamaki K, Terashima Y, et al. Overproduction of Th2-specific chemokines in NC/Nga mice exhibiting atopic dermatitis–like lesions. J Clin Invest. 1999;104:1097–105.
65. Jirapongsananuruk O, Hofer MF, Trumble AE, Norris DA, Leung DY. Enhanced expression of B7.2 (CD86) in patients with atopic dermatitis: a potential role in the modulation of IgE synthesis. J Immunol. 1998;160:4622–7.
66. Herberth G, Heinrich J, Roder S, Figl A, Weiss M, Diez U, et al. Reduced IFN-gamma- and enhanced IL-4–producing CD4+ cord blood T cells are associated with a higher risk for atopic dermatitis during the first 2 yr of life. Pediatr Allergy Immunol. 2010;21:5–13.
67. Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. J Invest Dermatol. 2001;117:977–83.
68. Tanaka K, Yamamoto-Fukuda M, Takizawa T, Shimakura H, Sakaguchi M. Association analysis of non-synonymous polymorphisms of interleukin-4 receptor-α and interleukin-13 genes in canine atopic dermatitis. J Vet Med Sci. 2020;82:1253–9.
69. Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, et al. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. J Med Genet. 1998;35:502–4.
70. Shang H, Cao XL, Wan YJ, Meng J, Guo LH. IL-4 gene polymorphism may contribute to an increased risk of atopic dermatitis in children. Dis Markers. 2016;2016: 1021942.
71. Söderhäll C, Bradley M, Kockum I, Luthman H, Wahlgren CF, Nordenskjöld M. Analysis of association and linkage for the interleukin-4 and interleukin-4 receptor b;alpha; regions in Swedish atopic dermatitis families. Clin Exp Allergy. 2002;32:1199202.
72. Liang J, Liu Y, Xue R, Chen L, Chen H, Shao L, et al. Interleukin 4 –590C/T (rs2243250) polymorphism is associated with increased risk of atopic dermatitis: meta-analysis of case-control studies. Dermatitis. 2017;28:144–51.
73. Hussein YM, Alzahrani SS, Alharthi AA, Alhazmi AS, Ghonaim MM, Alghamdy AA, et al. Gene polymorphism of interleukin-4, interleukin-4 receptor and STAT6 in children with atopic dermatitis in Taif, Saudi Arabia. Immunol Invest. 2016;45: 223–34.
74. Hosomi N, Fukai K, Oiso N, Kato A, Ishii M, Kunimoto H, et al. Polymorphisms in the promoter of the interleukin-4 receptor alpha chain gene are associated with atopic dermatitis in Japan. J Invest Dermatol. 2004;122:843–5.
75. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. Br J Dermatol. 2000; 142:1003–6.
76. Lee YL, Yen JJ, Hsu LC, Kuo NW, Su MW, Yang MF, et al. Association of STAT6 genetic variants with childhood atopic dermatitis in Taiwanese population. J Dermatol Sci. 2015;79:222–8.
77. Jung T, Moessner R, Neumann C. Naive CD4+ T cells from patients with atopic dermatitis show an aberrant maturation towards IL-4–producing skin-homing CLA+ cells. Exp Dermatol. 2003;12:555–62.
78. Novak N, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R, et al. Characterization of FcepsilonRI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. J Allergy Clin Immunol. 2004;114:364–70.
79. Lebre MC, van Capel TM, Bos JD, Knol EF, Kapsenberg ML, de Jong EC. Aberrant function of peripheral blood myeloid and plasmacytoid dendritic cells in atopic dermatitis patients. J Allergy Clin Immunol. 2008;122:969–76.e5.
80. Kang H, Byun DG, Kim JW. Effects of substance P and vasoactive intestinal peptide on interferon-gamma and interleukin-4 production in severe atopic dermatitis. Ann Allergy Asthma Immunol. 2000;85:227–32.
81. Hanifin JM, Chan SC. Monocyte phosphodiesterase abnormalities and dysregulation of lymphocyte function in atopic dermatitis. J Invest Dermatol. 1995;105: 84–88S.
82. Nygaard U, Hvid M, Johansen C, Buchner M, Folster-Holst R, Deleuran M, et al. TSLP, IL-31, IL-33 and sST2 are new biomarkers in endophenotypic profiling of adult and childhood atopic dermatitis. J Eur Acad Dermatol Venereol. 2016;30: 1930–8.
83. Lyubchenko T, Collins HK, Goleva E, Leung DYM. Skin tape sampling technique identifies proinflammatory cytokines in atopic dermatitis skin. Ann Allergy Asthma Immunol. 2021;126:46–53.e2.
84. Luo Y, Zhou B, Zhao M, Tang J, Lu Q. Promoter demethylation contributes to TSLP overexpression in skin lesions of patients with atopic dermatitis. Clin Exp Dermatol. 2014;39:48–53.
85. Bernard M, Carrasco C, Laoubi L, Guiraud B, Rozieres A, Goujon C, et al. IL-1β induces thymic stromal lymphopoietin and an atopic dermatitis-like phenotype in reconstructed healthy human epidermis. J Pathol. 2017;242:234–45.
86. Kumagai A, Kubo T, Kawata K, Kamekura R, Yamashita K, Jitsukawa S, et al. Keratinocytes in atopic dermatitis express abundant ΔNp73 regulating thymic stromal lymphopoietin production via NF-κB. J Dermatol Sci. 2017;88:175–83.
87. Svanberg S, Li Z, Ohlund P, Roy A, Abrink M. Mast cells limit ear swelling independently of the chymase mouse mast cell protease 4 in an MC903-induced atopic dermatitis–like mouse model. Int J Mol Sci. 2020;21:6311.
88. Yoo J, Omori M, Gyarmati D, Zhou B, Aye T, Brewer A, et al. Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. J Exp Med. 2005;202:541–9.
89. Danso MO, van Drongelen V, Mulder A, van Esch J, Scott H, van Smeden J, et al. TNF-α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. J Invest Dermatol. 2014;134:1941–50.
90. Tatsuno K, Fujiyama T, Yamaguchi H, Waki M, Tokura Y. TSLP directly interacts with skin-homing Th2 cells highly expressing its receptor to enhance IL-4 production in atopic dermatitis. J Invest Dermatol. 2015;135:3017–24.
91. Oh MH, Oh SY, Yu J, Myers AC, Leonard WJ, Liu YJ, et al. IL-13 induces skin fibrosis in atopic dermatitis by thymic stromal lymphopoietin. J Immunol. 2011;186: 7232–42.
92. Puar N, Chovatiya R, Paller AS. New treatments in atopic dermatitis. Ann Allergy Asthma Immunol. 2021;126:21–31.
93. Noh JY, Shin JU, Park CO, Lee N, Jin S, Kim SH, et al. Thymic stromal lymphopoietin regulates eosinophil migration via phosphorylation of l-plastin in atopic dermatitis. Exp Dermatol. 2016;25:880–6.

94. Wu WH, Park CO, Oh SH, Kim HJ, Kwon YS, Bae BG, et al. Thymic stromal lymphopoietin-activated invariant natural killer T cells trigger an innate allergic immune response in atopic dermatitis. J Allergy Clin Immunol. 2010;126:290–9, 299.e1-4.
95. Santos LS, Sgnotto FDR, Sousa TR, Orfali RL, Aoki V, Duarte A, et al. IgG from atopic dermatitis patients induces non-atopic infant thymic invariant natural killer T (iNKT) cells to produce IL-4, IL-17, and IL-10. Int J Dermatol. 2020;59:359–64.
96. 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.
97. Gyimesi E, Nagy G, Remenyik E, Sipka S, Zeher M, Biro T, et al. Altered peripheral invariant natural killer T cells in atopic dermatitis. J Clin Immunol. 2011;31:864–72.
98. Park HJ, Lee SW, Park SH, Van Kaer L, Hong S. Selective expansion of double-negative iNKT cells inhibits the development of atopic dermatitis in Vα14 TCR transgenic NC/Nga mice by increasing memory-type CD8(+) T and regulatory CD4(+) T cells. J Invest Dermatol. 2021;141:1512–21.
99. Yagi R, Nagai H, Iigo Y, Akimoto T, Arai T, Kubo M. Development of atopic dermatitis–like skin lesions in STAT6-deficient NC/Nga mice. J Immunol. 2002;168:2020–7.
100. Miranda E, Roberts J, Novick S, Lapointe JM, Bruijnzeel-Koomen C, Thijs J, et al. Immunohistochemical characterization of the IL-13:IL-4 receptor α axis in the skin of adult patients with moderate to severe atopic dermatitis and healthy controls. J Invest Dermatol. 2021;141:440–3.e4.
101. Totsuka A, Omori-Miyake M, Kawashima M, Yagi J, Tsunemi Y. Expression of keratin 1, keratin 10, desmoglein 1 and desmocollin 1 in the epidermis: possible downregulation by interleukin-4 and interleukin-13 in atopic dermatitis. Eur J Dermatol. 2017;27:247–53.
102. Sawada E, Yoshida N, Sugiura A, Imokawa G. Th1 cytokines accentuate but Th2 cytokines attenuate ceramide production in the stratum corneum of human epidermal equivalents: an implication for the disrupted barrier mechanism in atopic dermatitis. J Dermatol Sci. 2012;68:25–35.
103. Islam SA, Chang DS, Colvin RA, Byrne MH, McCully ML, Moser B, et al. Mouse CCL8, a CCR8 agonist, promotes atopic dermatitis by recruiting IL-5+ T(H)2 cells. Nat Immunol. 2011;12:167–77.
104. Bao L, Shi VY, Chan LS. IL-4 regulates chemokine CCL26 in keratinocytes through the Jak1, 2/Stat6 signal transduction pathway: implication for atopic dermatitis. Mol Immunol. 2012;50:91–7.
105. Bao L, Mohan GC, Alexander JB, Doo C, Shen K, Bao J, et al. A molecular mechanism for IL-4 suppression of loricrin transcription in epidermal keratinocytes: implication for atopic dermatitis pathogenesis. Innate Immun. 2017;23:641–7.
106. Kanda N, Watanabe S. Increased serum human β-defensin-2 levels in atopic dermatitis: relationship to IL-22 and oncostatin M. Immunobiology. 2012;217:436–45.
107. Kisich KO, Carspecken CW, Fiéve S, Boguniewicz M, Leung DYM. Defective killing of Staphylococcus aureus in atopic dermatitis is associated with reduced mobilization of human β-defensin-3. J Allergy Clin Immunol. 2008;122:62–8.
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. Bao L, Shi VY, Chan LS. IL-4 up-regulates epidermal chemotactic, angiogenic, and pro-inflammatory genes and down-regulates antimicrobial genes in vivo and in vitro: relevant in the pathogenesis of atopic dermatitis. Cytokine. 2013;61:419–25.
110. Scarponi C, Nardelli B, Lafleur DW, Moore PA, Madonna S, De Pita O, et al. Analysis of IFN-kappa expression in pathologic skin conditions: downregulation in psoriasis and atopic dermatitis. J Interferon Cytokine Res. 2006;26:133–40.
111. Furue M, Ogata F, Ootsuki M, Ishibashi Y. Hyperresponsibility to exogeneous interleukin 4 in atopic dermatitis. J Dermatol. 1989;16:247–50.
112. Furue M, Ohtsuki M, Ogata F, Ishibashi Y. Responsiveness to interleukin 4 and interleukin 2 of peripheral blood mononuclear cells in atopic dermatitis. J Invest Dermatol. 1991;96:468–72.
113. Dubois GR, Bruijnzeel-Koomen CA, Bruijnzeel PL. IL-4 induces chemotaxis of blood eosinophils from atopic dermatitis patients, but not from normal individuals. J Invest Dermatol. 1994;102:843–6.
114. Yawalkar N, Uguccioni M, Scharer J, Braunwalder J, Karlen S, Dewald B, et al. Enhanced expression of eotaxin and CCR3 in atopic dermatitis. J Invest Dermatol. 1999;113:43–8.
115. Brunner PM, Suarez-Farinas M, He H, Malik K, Wen HC, Gonzalez J, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. Sci Rep. 2017;7:8707.
116. Gahr N, Folster-Holst R, Weichenthal M, Christophers E, Schroder JM, Bartels J. Dermal fibroblasts from acute inflamed atopic dermatitis lesions display increased eotaxin/CCL11 responsiveness to interleukin-4 stimulation. Br J Dermatol. 2011;164:586–92.
117. Aral M, Arican O, Gul M, Sasmaz S, Kocturk SA, Kastal U, et al. The relationship between serum levels of total IgE, IL-18, IL-12, IFN-gamma and disease severity in children with atopic dermatitis. Mediators Inflamm. 2006;2006:73098.
118. Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. Nat Rev Immunol. 2003;3:721–32.
119. Chen L, Overbergh L, Mathieu C, Chan LS. The development of atopic dermatitis is independent of immunoglobulin E up-regulation in the K14-IL-4 SKH1 transgenic mouse model. Clin Exp Allergy. 2008;38:1367–80.
120. Bordignon V, Sinagra JL, Trento E, Pietravalle M, Capitanio B, Cordiali Fei P. Antigen specific cytokine response in pediatric patients with atopic dermatitis. Pediatr Allergy Immunol. 2005;16:113–20.
121. Zedan K, Rasheed Z, Farouk Y, Alzolibani AA, Bin Saif G, Ismail HA, et al. Immunoglobulin E, interleukin-18 and interleukin-12 in patients with atopic dermatitis: correlation with disease activity. J Clin Diagn Res. 2015;9:WC01-5.
122. Vollenweider S, Saurat JH, Rocken M, Hauser C. Evidence suggesting involvement of interleukin-4 (IL-4) production in spontaneous in vitro IgE synthesis in patients with atopic dermatitis. J Allergy Clin Immunol. 1991;87:1088–95.
123. Wen HJ, Wang YJ, Lin YC, Chang CC, Shieh CC, Lung FW, et al. Prediction of atopic dermatitis in 2-yr-old children by cord blood IgE, genetic polymorphisms in cytokine genes, and maternal mentality during pregnancy. Pediatr Allergy Immunol. 2011;22:695–703.
124. Jin JJ, Zou YX, Zeng SW. Risk factors for and expression of immune and inflammatory factors in atopic dermatitis in Chinese population: a birth cohort study. Mol Cell Probes. 2016;30:168–73.
125. Kawamoto N, Fukao T, Kaneko H, Hirayama K, Sakurai S, Arai T, et al. Total IgE at 6 months predicts remittance or persistence of atopic dermatitis at 14 months. Allergy Asthma Proc. 2013;34:362–9.
126. Halpern M, Schwartz S. Regulation of the low affinity IgE Fc receptor (CD23) in atopic dermatitis. Int Arch Allergy Immunol. 1993;100:197–200.
127. Nakamura K, Okubo Y, Minami M, Furue M, Ishibashi Y. Phenotypic analysis of CD23+ peripheral blood mononuclear cells in atopic dermatitis. Br J Dermatol. 1991;125:543–7.
128. Novak N, Bieber T, Kraft S. Immunoglobulin E–bearing antigen-presenting cells in atopic dermatitis. Curr Allergy Asthma Rep. 2004;4:263–9.
129. Gohar MK, Atta AH, Nasr MM, Hussein DN. Serum thymus and activation regulated chemokine (TARC), IL-18 and IL-18 gene polymorphism as associative factors with atopic sermatitis. Egypt J Immunol. 2017;24:9–22.
130. Narbutt J, Lesiak A, Sysa-Jedrzeiowska A, Zakrzewski M, Bogaczewicz J, Stelmach I, et al. The imbalance in serum concentration of Th1– and Th-2–derived chemokines as one of the factors involved in pathogenesis of atopic dermatitis. Mediators Inflamm. 2009;2009:269541.
131. Pavel AB, Zhou L, Diaz A, Ungar B, Dan J, He H, et al. The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature. J Am Acad Dermatol. 2020;82:690–9.
132. Lang CCV, Renert-Yuval Y, Del Duca E, Pavel AB, Wu J, Zhang N, et al. Immune and barrier characterization of atopic dermatitis skin phenotype in Tanzanian patients. Ann Allergy Asthma Immunol. 2021;127:334–41.
133. Miake S, Tsuji G, Takemura M, Hashimoto-Hachiya A, Vu YH, Furue M, et al. IL-4 augments IL-31/IL-31 receptor alpha interaction leading to enhanced Ccl 17 and Ccl 22 production in dendritic cells: implications for atopic dermatitis. Int J Mol Sci. 2019;20:4053.
134. Ovsiy I, Riabov V, Manousaridis I, Miche J, Moganti K, Yin S, et al. IL-4 driven transcription factor FoxQ1 is expressed by monocytes in atopic dermatitis and stimulates monocyte migration. Sci Rep. 2017;7:16847.
135. Hashimoto S, Nakamura K, Oyama N, Kaneko F, Tsunemi Y, Saeki H, et al. Macrophage-derived chemokine (MDC)/CCL22 produced by monocyte derived dendritic cells reflects the disease activity in patients with atopic dermatitis. J Dermatol Sci. 2006;44:93–9.
136. Holm JG, Hurault G, Agner T, Clausen ML, Kezic S, Tanaka RJ, et al. Immunoinflammatory biomarkers in serum are associated with disease severity in atopic dermatitis. Dermatology. 2021;237:513–20.
137. McAleer MA, Jakasa I, Hurault G, Sarvari P, McLean WHI, Tanaka RJ, et al. Systemic and stratum corneum biomarkers of severity in infant atopic dermatitis include markers of innate and T helper cell-related immunity and angiogenesis. Br J Dermatol. 2019;180:586–96.
138. Vestergaard C, Kirstejn N, Gesser B, Mortensen JT, Matsushima K, Larsen CG. IL-10 augments the IFN-gamma and TNF-alpha induced TARC production in HaCaT cells: a possible mechanism in the inflammatory reaction of atopic dermatitis. J Dermatol Sci. 2001;26:46–54.
139. Vestergaard C, Bang K, Gesser B, Yoneyama H, Matsushima K, Larsen CG. A Th2 chemokine, TARC, produced by keratinocytes may recruit CLA+CCR4+ lymphocytes into lesional atopic dermatitis skin. J Invest Dermatol. 2000;115:640–6.
140. Nakatani T, Kaburagi Y, Shimada Y, Inaoki M, Takehara K, Mukaida N, et al. CCR4 memory CD4+ T lymphocytes are increased in peripheral blood and lesional skin from patients with atopic dermatitis. J Allergy Clin Immunol. 2001;107:353–8.
141. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol. 2009;124:R7–12.
142. Cornelissen C, Marquardt Y, Czaja K, Wenzel J, Frank J, Luscher-Firzlaff J, et al. IL-31 regulates differentiation and filaggrin expression in human organotypic skin models. J Allergy Clin Immunol. 2012;129:426–33.e1–8.
143. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, Debenedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol. 2007;120:150–5.

144. Berdyshev E, Goleva E, Bronova I, Dyjack N, Rios C, Jung J, et al. Lipid abnormalities in atopic skin are driven by type 2 cytokines. JCI Insight. 2018;3:e98006.
145. Gruber R, Bornchen C, Rose K, Daubmann A, Volksdorf T, Wladykowski E, et al. Diverse regulation of claudin-1 and claudin-4 in atopic dermatitis. Am J Pathol. 2015;185:2777–89.
146. Bao L, Zhang H, Mohan GC, Shen K, Chan LS. Differential expression of inflammation-related genes in IL-4 transgenic mice before and after the onset of atopic dermatitis skin lesions. Mol Cell Probes. 2016;30:30–8.
147. Chen L, Martinez O, Venkataramani P, Lin SX, Prabhakar BS, Chan LS. Correlation of disease evolution with progressive inflammatory cell activation and migration in the IL-4 transgenic mouse model of atopic dermatitis. Clin Exp Immunol. 2005;139:189–201.
148. Chen L, Lin SX, Amin S, Overbergh L, Maggiolino G, Chan LS. VCAM-1 blockade delays disease onset, reduces disease severity and inflammatory cells in an atopic dermatitis model. Immunol Cell Biol. 2010;88:334–42.
149. Wuthrich B, Joller-Jemelka H, Kagi MK. Levels of soluble ICAM-1 in atopic dermatitis. A new marker for monitoring the clinical activity? Allergy. 1995;50:88–9.
150. Kakinuma T, Saeki H, Tsunemi Y, Fujita H, Asano N, Mitsui H, et al. Increased serum cutaneous T cell-attracting chemokine (CCL27) levels in patients with atopic dermatitis and psoriasis vulgaris. J Allergy Clin Immunol. 2003;111:592–7.
151. Chen L, Lin SX, Agha-Majzoub R, Overbergh L, Mathieu C, Chan LS. CCL27 is a critical factor for the development of atopic dermatitis in the keratin-14 IL-4 transgenic mouse model. Int Immunol. 2006;18:1233–42.
152. Vestergaard C, Deleuran M, Gesser B, Gronhoj Larsen C. Expression of the T-helper 2-specific chemokine receptor CCR4 on CCR10-positive lymphocytes in atopic dermatitis skin but not in psoriasis skin. Br J Dermatol. 2003;149:457–63.
153. Echigo T, Hasegawa M, Shimada Y, Takehara K, Sato S. Expression of fractalkine and its receptor, CX3CR1, in atopic dermatitis: possible contribution to skin inflammation. J Allergy Clin Immunol. 2004;113:940–8.
154. Agha-Majzoub R, Becker RP, Schraufnagel DE, Chan LS. Angiogenesis: the major abnormality of the keratin-14 IL-4 transgenic mouse model of atopic dermatitis. Microcirculation. 2005;12:455–76.
155. Koczy-Baron E, Jochem J, Kasperska-Zajac A. Increased plasma concentration of vascular endothelial growth factor in patients with atopic dermatitis and its relation to disease severity and platelet activation. Inflamm Res. 2012;61:1405–9.
156. Samochocki Z, Bogaczewicz J, Sysa-Jedrzejowska A, McCauliffe DP, Kontny E, Wozniacka A. Expression of vascular endothelial growth factor and other cytokines in atopic dermatitis, and correlation with clinical features. Int J Dermatol. 2016;55:e141–6.
157. Simon D, Von Gunten S, Borelli S, Braathen LR, Simon HU. The interleukin-13 production by peripheral blood T cells from atopic dermatitis patients does not require CD2 costimulation. Int Arch Allergy Immunol. 2003;132:148–55.
158. Tanaka Y, Delaporte E, Dubucquoi S, Gounni AS, Porchet E, Capron A, et al. Interleukin-5 messenger RNA and immunoreactive protein expression by activated eosinophils in lesional atopic dermatitis skin. J Invest Dermatol. 1994;103:589–92.
159. Simon MR, Cooper KD, Norris RB, Blok B, King CL. Antigen presenting cell-independent cytokine and spontaneous in vitro IgE production in patients with atopic dermatitis: increased interferon-gamma production and lack of effects of in vivo low-dose interferon-gamma treatment. J Allergy Clin Immunol. 1995;96:84–91.
160. Lee GR, Flavell RA. Transgenic mice which overproduce Th2 cytokines develop spontaneous atopic dermatitis and asthma. Int Immunol. 2004;16:1155–60.
161. Brandt EB, Sivaprasad U. Th2 cytokines and atopic dermatitis. J Clin Cell Immunol. 2011;2:110.
162. Jenerowicz D, Czarnecka-Operacz M, Silny W. Peripheral blood eosinophilia in atopic dermatitis. Acta Dermatovenerol Alp Pannonica Adriat. 2007;16:47–52.
163. Yamamoto N, Sugiura H, Tanaka K, Uehara M. Heterogeneity of interleukin 5 genetic background in atopic dermatitis patients: significant difference between those with blood eosinophilia and normal eosinophil levels. J Dermatol Sci. 2003;33:121–6.
164. Ilves T, Tiitu V, Suttle MM, Saarinen JV, Harvima IT. Epidermal expression of filaggrin/profilaggrin is decreased in atopic dermatitis: reverse association with mast cell tryptase and IL-6 but not with clinical severity. Dermatitis. 2015;26:260–7.
165. Ilves T, Harvima IT. Decrease in chymase activity is associated with increase in IL-6 expression in mast cells in atopic dermatitis. Acta Derm Venereol. 2015;95:411–6.
166. Wong CK, Leung KM, Qiu HN, Chow JY, Choi AO, Lam CW. Activation of eosinophils interacting with dermal fibroblasts by pruritogenic cytokine IL-31 and alarmin IL-33: implications in atopic dermatitis. PLoS One. 2012;7:e29815.
167. Toshitani A, Ansel JC, Chan SC, Li SH, Hanifin JM. Increased interleukin 6 production by T cells derived from patients with atopic dermatitis. J Invest Dermatol. 1993;100:299–304.
168. Yao W, Chang J, Sehra S, Travers JB, Chang CH, Tepper RS, et al. Altered cytokine production by dendritic cells from infants with atopic dermatitis. Clin Immunol. 2010;137:406–14.
169. Navarini AA, French LE, Hofbauer GF. Interrupting IL-6-receptor signaling improves atopic dermatitis but associates with bacterial superinfection. J Allergy Clin Immunol. 2011;128:1128–30.
170. Gharagozlou M, Farhadi E, Khaledi M, Behniafard N, Sotoudeh S, Salari R, et al. Association between the interleukin 6 genotype at position –174 and atopic dermatitis. J Investig Allergol Clin Immunol. 2013;23:89–93.
171. Esparza-Gordillo J, Schaarschmidt H, Liang L, Cookson W, Bauerfeind A, Lee-Kirsch MA, et al. A functional IL-6 receptor (IL6R) variant is a risk factor for persistent atopic dermatitis. J Allergy Clin Immunol. 2013;132:371–7.
172. Sismanopoulos N, Delivanis DA, Alysandratos KD, Angelidou A, Vasiadi M, Therianou A, et al. IL-9 induces VEGF secretion from human mast cells and IL-9/IL-9 receptor genes are overexpressed in atopic dermatitis. PLoS One. 2012;7:e33271.
173. Ciprandi G, De Amici M, Giunta V, Marseglia A, Marseglia G. Serum interleukin-9 levels are associated with clinical severity in children with atopic dermatitis. Pediatr Dermatol. 2013;30:222–5.
174. Makita S, Takatori H, Matsuki A, Kawashima H, Iwata A, Tanaka S, et al. T-bet and STAT6 coordinately suppress the development of IL-9–mediated atopic dermatitis–like skin inflammation in mice. J Invest Dermatol. 2021;141:1274–85.e5.
175. Hong CH, Chang KL, Wang HJ, Yu HS, Lee CH. IL-9 induces IL-8 production via STIM1 activation and ERK phosphorylation in epidermal keratinocytes: a plausible mechanism of IL-9R in atopic dermatitis. J Dermatol Sci. 2015;78:206–14.
176. Namkung JH, Lee JE, Kim E, Park GT, Yang HS, Jang HY, et al. An association between IL-9 and IL-9 receptor gene polymorphisms and atopic dermatitis in a Korean population. J Dermatol Sci. 2011;62:16–21.
177. Dunstan JA, Hale J, Breckler L, Lehmann H, Weston S, Richmond P, et al. Atopic dermatitis in young children is associated with impaired interleukin-10 and interferon-gamma responses to allergens, vaccines and colonizing skin and gut bacteria. Clin Exp Allergy. 2005;35:1309–17.
178. Lee HJ, Lee HP, Ha SJ, Byun DG, Kim JW. Spontaneous expression of mRNA for IL-10, GM-CSF, TGF-beta, TGF-alpha, and IL-6 in peripheral blood mononuclear cells from atopic dermatitis. Ann Allergy Asthma Immunol. 2000;84:553–8.
179. Kaesler S, Volz T, Skabytska Y, Koberle M, Hein U, Chen KM, et al. Toll-like receptor 2 ligands promote chronic atopic dermatitis through IL-4–mediated suppression of IL-10. J Allergy Clin Immunol. 2014;134:92–9.
180. Aleksza M, Lukacs A, Antal-Szalmas P, Hunyadi J, Szegedi A. Increased frequency of intracellular interleukin (IL)-13 and IL-10, but not IL-4, expressing CD4+ and CD8+ peripheral T cells of patients with atopic dermatitis. Br J Dermatol. 2002;147:1135–41.
181. Yoshihara Y, Ishiuji Y, Yoshizaki A, Kurita M, Hayashi M, Ishiji T, et al. IL-10–producing regulatory B cells are decreased in patients with atopic dermatitis. J Invest Dermatol. 2019;139:475–8.
182. Jung BG, Cho SJ, Ko JH, Lee BJ. Inhibitory effects of interleukin-10 plasmid DNA on the development of atopic dermatitis–like skin lesions in NC/Nga mice. J Vet Sci. 2010;11:213–20.
183. Howell MD, Novak N, Bieber T, Pastore S, Girolomoni G, Boguniewicz M, et al. Interleukin-10 downregulates anti-microbial peptide expression in atopic dermatitis. J Invest Dermatol. 2005;125:738–45.
184. Zhao J, Chen ZY, Li LF. Association between the IL-10-1082G/A, IL-10-592A/C, and IL-10-819G/A polymorphisms and atopic dermatitis susceptibility: a meta-analysis. Genet Test Mol Biomarkers. 2019;23:332–41.
185. Lesiak A, Zakrzewski M, Przybylowska K, Rogowski-Tylman M, Wozniacka A, Narbutt J. Atopic dermatitis patients carrying G allele in –1082 G/A IL-10 polymorphism are predisposed to higher serum concentration of IL-10. Arch Med Sci. 2014;10:1239–43.
186. Chen S, Zhao L. Association between the IL10 –1082A>G (rs1800896) single-nucleotide polymorphism and atopic dermatitis: a systematic review and meta-analysis. Dermatitis. 2013;24:161–5.
187. Lacy K, Archer C, Wood N, Bidwell J. Association between a common IL10 distal promoter haplotype and IgE production in individuals with atopic dermatitis. Int J Immunogenet. 2009;36:213–6.
188. Simon D, Simon HU. New drug targets in atopic dermatitis. Chem Immunol Allergy. 2012;96:126–31.
189. Ogawa K, Hashida R, Miyagawa M, Kagaya S, Sugita Y, Matsumoto K, et al. Analysis of gene expression in peripheral blood eosinophils from patients with atopic dermatitis and in vitro cytokine-stimulated blood eosinophils. Clin Exp Immunol. 2003;131:436–45.
190. Szegedi K, Lutter R, Res PC, Bos JD, Luiten RM, Kezic S, et al. Cytokine profiles in interstitial fluid from chronic atopic dermatitis skin. J Eur Acad Dermatol Venereol. 2015;29:2136–44.
191. Majewska A, Gajewska M, Dembele K, Maciejewski H, Prostek A, Jank M. Lymphocytic, cytokine and transcriptomic profiles in peripheral blood of dogs with atopic dermatitis. BMC Vet Res. 2016;12:174.
192. Obara W, Kawa Y, Ra C, Nishioka K, Soma Y, Mizoguchi M. T cells and mast cells as a major source of interleukin-13 in atopic dermatitis. Dermatology. 2002;205:11–7.
193. Ezzat MH, Hasan ZE, Shaheen KY. Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. J Eur Acad Dermatol Venereol. 2011;25:334–9.
194. Teraki Y, Sakurai A, Izaki S. IL-13/IL-22–coproducing T cells, a novel subset, are increased in atopic dermatitis. J Allergy Clin Immunol. 2013;132:971–4.
195. Hamid Q, Naseer T, Minshall EM, Song YL, Boguniewicz M, Leung DY. In vivo expression of IL-12 and IL-13 in atopic dermatitis. J Allergy Clin Immunol. 1996;98:225–31.

196. Wongpiyabovorn J, Suto H, Ushio H, Izuhara K, Mitsuishi K, Ikeda S, et al. Up-regulation of interleukin-13 receptor alpha1 on human keratinocytes in the skin of psoriasis and atopic dermatitis. J Dermatol Sci. 2003;33:31–40.
197. Namkung JH, Lee JE, Kim E, Kim HJ, Seo EY, Jang HY, et al. Association of polymorphisms in genes encoding IL-4, IL-13 and their receptors with atopic dermatitis in a Korean population. Exp Dermatol. 2011;20:915–9.
198. Liu X, Nickel R, Beyer K, Wahn U, Ehrlich E, Freidhoff LR, et al. An IL13 coding region variant is associated with a high total serum IgE level and atopic dermatitis in the German multicenter atopy study (MAS-90). J Allergy Clin Immunol. 2000; 106:167–70.
199. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Kakinuma T, et al. Interleukin-13 gene polymorphism G4257A is associated with atopic dermatitis in Japanese patients. J Dermatol Sci. 2002;30:100–7.
200. Lee SY, Yu J, Ahn KM, Kim KW, Shin YH, Lee KS, et al. Additive effect between IL-13 polymorphism and cesarean section delivery/prenatal antibiotics use on atopic dermatitis: a birth cohort study (COCOA). PLoS One. 2014;9:e96603.
201. Lee E, Kim JH, Lee SY, Kang MJ, Park YM, Park MJ, et al. Association of IL13 genetic polymorphisms with atopic dermatitis: fine mapping and haplotype analysis. Ann Allergy Asthma Immunol. 2020;125:287–93.
202. Zitnik SE, Ruschendorf F, Muller S, Sengler C, Lee YA, Griffioen RW, et al. IL13 variants are associated with total serum IgE and early sensitization to food allergens in children with atopic dermatitis. Pediatr Allergy Immunol. 2009;20:551–5.
203. Wuthrich B, Kagi MK, Joller-Jemelka H. Soluble CD14 but not interleukin-6 is a new marker for clinical activity in atopic dermatitis. Arch Dermatol Res. 1992; 284:339–42.
204. Purwar R, Werfel T, Wittmann M. IL-13–stimulated human keratinocytes preferentially attract CD4+CCR4+ T cells: possible role in atopic dermatitis. J Invest Dermatol. 2006;126:1043–51.
205. Shin JW, Choi YJ, Choi HR, Na JI, Kim KH, Park IA, et al. Defective basement membrane in atopic dermatitis and possible role of IL-13. J Eur Acad Dermatol Venereol. 2015;29:2060–2.
206. Lee UH, Kim BE, Kim DJ, Cho YG, Ye YM, Leung DY. Atopic dermatitis is associated with reduced corneodesmosin expression: role of cytokine modulation and effects on viral penetration. Br J Dermatol. 2017;176:537–40.
207. Furue K, Ito T, Tsuji G, Ulzii D, Vu YH, Kido-Nakahara M, et al. The IL-13-OVOL1-FLG axis in atopic dermatitis. Immunology. 2019;158:281–6.
208. Gamez C, Metcalfe J, Prescott SL, Palmer DJ. Lower cord blood IL-17 and IL-25, but not other epithelial cell-derived cytokines are associated with atopic dermatitis in infancy. Int Arch Allergy Immunol. 2021;182:474–8.
209. Deleuran M, Hvid M, Kemp K, Christensen GB, Deleuran B, Vestergaard C. IL-25 induces both inflammation and skin barrier dysfunction in atopic dermatitis. Chem Immunol Allergy. 2012;96:45–9.
210. Nakamura N, Tamagawa-Mineoka R, Maruyama A, Nakanishi M, Yasuike R, Masuda K, et al. Stratum corneum interleukin-25 expressions correlate with the degree of dry skin and acute lesions in atopic dermatitis. Allergol Int. 2020;69: 462–4.
211. Al-Shobaili HA, Ahmed AA, Alnomair N, Alobead ZA, Rasheed Z. Molecular genetic of atopic dermatitis: an update. Int J Health Sci (Qassim). 2016;10:96–120.
212. Ozceker D, Bulut M, Ozbay AC, Dilek F, Koser M, Tamay Z, et al. Assessment of IL-31 levels and disease severity in children with atopic dermatitis. Allergol Immunopathol (Madr). 2018;46:322–5.
213. Lu J, Wu K, Zeng Q, Xiang Y, Gao L, Huang J. Serum interleukin-31 level and pruritus in atopic dermatitis: a meta-analysis. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2018;43:124–30.
214. Cheon BR, Shin JE, Kim YJ, Shim JW, Kim DS, Jung HL, et al. Relationship between serum 25-hydroxyvitamin D and interleukin-31 levels, and the severity of atopic dermatitis in children. Korean J Pediatr. 2015;58:96–101.
215. Nattkemper LA, Tey HL, Valdes-Rodriguez R, Lee H, Mollanazar NK, Albornoz C, et al. The genetics of chronic itch: gene expression in the skin of patients with atopic dermatitis and psoriasis with severe itch. J Invest Dermatol. 2018;138: 1311–7.
216. Hawro T, Saluja R, Weller K, Altrichter S, Metz M, Maurer M. Interleukin-31 does not induce immediate itch in atopic dermatitis patients and healthy controls after skin challenge. Allergy. 2014;69:113–7.
217. Grimstad O, Sawanobori Y, Vestergaard C, Bilsborough J, Olsen UB, Gronhoj-Larsen C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. Exp Dermatol. 2009;18:35–43.
218. Lee CH, Hong CH, Yu WT, Chuang HY, Huang SK, Chen GS, et al. Mechanistic correlations between two itch biomarkers, cytokine interleukin-31 and neuropeptide β-endorphin, via STAT3/calcium axis in atopic dermatitis. Br J Dermatol. 2012;167:794–803.
219. Pitake S, Ralph PC, DeBrecht J, Mishra SK. Atopic dermatitis linked cytokine interleukin-31 induced itch mediated via a neuropeptide natriuretic polypeptide B. Acta Derm Venereol. 2018;98:795–6.
220. Cheung PF, Wong CK, Ho AW, Hu S, Chen DP, Lam CW. Activation of human eosinophils and epidermal keratinocytes by Th2 cytokine IL-31: implication for the immunopathogenesis of atopic dermatitis. Int Immunol. 2010;22:453–67.
221. Bilsborough J, Leung DY, Maurer M, Howell M, Boguniewicz M, Yao L, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. J Allergy Clin Immunol. 2006;117:418–25.
222. Kato A, Fujii E, Watanabe T, Takashima Y, Matsushita H, Furuhashi T, et al. Distribution of IL-31 and its receptor expressing cells in skin of atopic dermatitis. J Dermatol Sci. 2014;74:229–35.
223. Hong CH, Yu HS, Ko YC, Chang WC, Chuang HY, Chen GS, et al. Functional regulation of interleukin-31 production by its genetic polymorphism in patients with extrinsic atopic dermatitis. Acta Derm Venereol. 2012;92:430–2.
224. Sokolowska-Wojdylo M, Glen J, Zablotna M, Rebala K, Sikorska M, Florek A, et al. Association of distinct IL-31 polymorphisms with pruritus and severity of atopic dermatitis. J Eur Acad Dermatol Venereol. 2013;27:662–4.
225. Gordon DJ, Ostlere LS, Holden CA. Neuropeptide modulation of Th1 and Th2 cytokines in peripheral blood mononuclear leucocytes in atopic dermatitis and non-atopic controls. Br J Dermatol. 1997;137:921–7.
226. Reinhold U, Wehrmann W, Kukel S, Kreysel HW. Evidence that defective interferon-gamma production in atopic dermatitis patients is due to intrinsic abnormalities. Clin Exp Immunol. 1990;79:374–9.
227. Tang ML, Varigos G, Kemp AS. Reduced interferon-gamma (IFN-gamma) secretion with increased IFN-gamma mRNA expression in atopic dermatitis: evidence for a post-transcriptional defect. Clin Exp Immunol. 1994;97:483–90.
228. Tang M, Kemp A. Production and secretion of interferon-gamma (IFN-gamma) in children with atopic dermatitis. Clin Exp Immunol. 1994;95:66–72.
229. Matsuyama T, Urano K, Ohkido M, Ozawa H, Ohta A, Kaneko S, et al. The quantitative and qualitative defect of CD4+ CD45RO+ memory-type T cells are involved in the abnormality of TH1 immunity in atopic dermatitis patients. Clin Exp Allergy. 1999;29:687–94.
230. Grieco T, Faina V, Porzia A, Paolino G, Morrone S, Bottoni U, et al. Atopic dermatitis IL17A- and IFN-γ–producing lymphocytes: investigation in blood, chronic lesions and APT. J Eur Acad Dermatol Venereol. 2017;31:e438–9.
231. Kimura M, Tsuruta S, Yoshida T. Unique profile of IL-4 and IFN-gamma production by peripheral blood mononuclear cells in infants with atopic dermatitis. J Allergy Clin Immunol. 1998;102:238–44.
232. Dolen JG, Mathur A. Undetectable interferon-alpha serum levels in a patient with atopic dermatitis. J Interferon Cytokine Res. 1995;15:973–5.
233. Kabashima-Kubo R, Nakamura M, Sakabe J, Sugita K, Hino R, Mori T, et al. A group of atopic dermatitis without IgE elevation or barrier impairment shows a high Th1 frequency: possible immunological state of the intrinsic type. J Dermatol Sci. 2012;67:37–43.
234. Gros E, Petzold S, Maintz L, Bieber T, Novak N. Reduced IFN-γ receptor expression and attenuated IFN-γ response by dendritic cells in patients with atopic dermatitis. J Allergy Clin Immunol. 2011;128:1015–21.
235. Jarrett R, Salio M, Lloyd-Lavery A, Subramaniam S, Bourgeois E, Archer C, et al. Filaggrin inhibits generation of CD1a neolipid antigens by house dust mite-derived phospholipase. Sci Transl Med. 2016;8:325ra18.
236. Howell MD, Boguniewicz M, Pastore S, Novak N, Bieber T, Girolomoni G, et al. Mechanism of HBD-3 deficiency in atopic dermatitis. Clin Immunol. 2006;121: 332–8.
237. Kapp A, Neuner P, Krutmann J, Luger TA, Schopf E. Production of interleukin-2 by mononuclear cells in vitro in patients with atopic dermatitis and psoriasis. Comparison with serum interleukin-2 receptor levels. Acta Derm Venereol. 1991;71: 403–6.
238. Fedenko ES, Elisyutina OG, Filimonova TM, Boldyreva MN. Burmenskaya OV, Rebrova OY, et al. Cytokine gene expression in the skin and peripheral blood of atopic dermatitis patients and healthy individuals. Self Nonself. 2011;2:120–4.
239. Furue M, Sugiyama H, Tsukamoto K, Ohtake N, Tamaki K. Serum soluble IL-2 receptor (sIL-2R) and eosinophil cationic protein (ECP) levels in atopic dermatitis. J Dermatol Sci. 1994;7:89–95.
240. Thestrup-Pedersen K, Larsen CS, Kristensen M, Zachariae C. Interleukin-1 release from peripheral blood monocytes and soluble interleukin-2 and CD8 receptors in serum from patients with atopic dermatitis. Acta Derm Venereol. 1990;70:395–9.
241. Greally P, Hussain MJ, Price JF, Coleman R. Interleukin-1 alpha and soluble interleukin-2 receptor in atopic dermatitis. Arch Dis Child. 1992;67:1413.
242. Wahlgren CF, Tengvall Linder M, Hagermark O, Scheynius A. Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. Arch Dermatol Res. 1995;287:572–80.
243. Husein-ElAhmed H, Steinhoff M. Effectiveness of ustekinumab in patients with atopic dermatitis: analysis of real-world evidence. J Dermatolog Treat. 2021:1–6.
244. Chen XF, Zhang LJ, Zhang J, Dou X, Shao Y, Jia XJ, et al. MiR-151a is involved in the pathogenesis of atopic dermatitis by regulating interleukin-12 receptor β2. Exp Dermatol. 2018;27:427–32.
245. Takahashi N, Akahoshi M, Matsuda A, Ebe K, Inomata N, Obara K, et al. Association of the IL12RB1 promoter polymorphisms with increased risk of atopic dermatitis and other allergic phenotypes. Hum Mol Genet. 2005;14:3149–59.
246. Namkung JH, Lee JE, Kim E, Kim S, Kim S, Shin ES, et al. Association of single nucleotide polymorphisms in the IL-12 (IL-12A and B) and IL-12 receptor (IL-12Rbeta1 and beta2) genes and gene-gene interactions with atopic dermatitis in Koreans. J Dermatol Sci. 2010;57:199–206.
247. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, et al. Interleukin-12 p40 gene (IL12B) 3'-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. J Dermatol Sci. 2002;30: 161–6.

248. Hoffjan S, Beygo J, Akkad DA, Parwez Q, Petrasch-Parwez E, Epplen JT. Analysis of variation in the IL7RA and IL2RA genes in atopic dermatitis. J Dermatol Sci. 2009;55:138–40.
249. Karlen H, Yousefi S, Simon HU, Simon D. IL-15 Expression pattern in atopic dermatitis. Int Arch Allergy Immunol. 2020;181:417–21.
250. Ong PY, Hamid QA, Travers JB, Strickland I, Al Kerithy M, Boguniewicz M, et al. Decreased IL-15 may contribute to elevated IgE and acute inflammation in atopic dermatitis. J Immunol. 2002;168:505–10.
251. Higashi N, Gesser B, Kawana S, Thestrup-Pedersen K. Expression of IL-18 mRNA and secretion of IL-18 are reduced in monocytes from patients with atopic dermatitis. J Allergy Clin Immunol. 2001;108:607–14.
252. Tanaka T, Tsutsui H, Yoshimoto T, Kotani M, Matsumoto M, Fujita A, et al. Interleukin-18 is elevated in the sera from patients with atopic dermatitis and from atopic dermatitis model mice, NC/Nga. Int Arch Allergy Immunol. 2001;125:236–40.
253. Yoshizawa Y, Nomaguchi H, Izaki S, Kitamura K. Serum cytokine levels in atopic dermatitis. Clin Exp Dermatol. 2002;27:225–9.
254. Tsukuba T, Okamoto K, Okamoto Y, Yanagawa M, Kohmura K, Yasuda Y, et al. Association of cathepsin E deficiency with development of atopic dermatitis. J Biochem. 2003;134:893–902.
255. Kim E, Lee JE, Namkung JH, Park JH, Kim S, Shin ES, et al. Association of the single-nucleotide polymorphism and haplotype of the interleukin 18 gene with atopic dermatitis in Koreans. Clin Exp Allergy. 2007;37:865–71.
256. Trzeciak M, Glen J, Roszkiewicz J, Nedoszytko B. Association of single nucleotide polymorphism of interleukin-18 with atopic dermatitis. J Eur Acad Dermatol Venereol. 2010;24:78–9.
257. Kato T, Tsunemi Y, Saeki H, Shibata S, Sekiya T, Nakamura K, et al. Interferon-18 gene polymorphism –137 G/C is associated with susceptibility to psoriasis vulgaris but not with atopic dermatitis in Japanese patients. J Dermatol Sci. 2009; 53:162–3.
258. Konishi H, Tsutsui H, Murakami T, Yumikura-Futatsugi S, Yamanaka K, Tanaka M, et al. IL-18 contributes to the spontaneous development of atopic dermatitis–like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions. Proc Natl Acad Sci U S A. 2002;99:11340–5.
259. El-Mezayen RE, Matsumoto T. In vitro responsiveness to IL-18 in combination with IL-12 or IL-2 by PBMC from patients with bronchial asthma and atopic dermatitis. Clin Immunol. 2004;111:61–8.
260. Higa S, Kotani M, Matsumoto M, Fujita A, Hirano T, Suemura M, et al. Administration of anti-interleukin 18 antibody fails to inhibit development of dermatitis in atopic dermatitis-model mice NC/Nga. Br J Dermatol. 2003;149:39–45.
261. Tsutsui H, Mizutani H, Nakanishi K. Contribution of interleukin 18 to the development of infection-associated atopic dermatitis. Curr Probl Dermatol. 2011;41: 93–103.
262. Du HY, Fu HY, Li DN, Qiao Y, Wang QW, Liu W. The expression and regulation of interleukin-33 in human epidermal keratinocytes: a new mediator of atopic dermatitis and its possible signaling pathway. J Interferon Cytokine Res. 2016;36:552–62.
263. Savinko T, Matikainen S, Saarialho-Kere U, Lehto M, Wang G, Lehtimaki S, et al. IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. J Invest Dermatol. 2012;132:1392–400.
264. Alase A, Seltmann J, Werfel T, Wittmann M. Interleukin-33 modulates the expression of human beta-defensin 2 in human primary keratinocytes and may influence the susceptibility to bacterial superinfection in acute atopic dermatitis. Br J Dermatol. 2012;167:1386–9.
265. Nakamura N, Tamagawa-Mineoka R, Yasuike R, Masuda K, Matsunaka H, Murakami Y, et al. Stratum corneum interleukin-33 expressions correlate with the degree of lichenification and pruritus in atopic dermatitis lesions. Clin Immunol. 2019;201:1–3.
266. Nakahara T, Kido-Nakahara M, Tsuji G, Furue M. Basics and recent advances in the pathophysiology of atopic dermatitis. J Dermatol. 2021;48:130–9.
267. Shimizu M, Matsuda A, Yanagisawa K, Hirota T, Akahoshi M, Inomata N, et al. Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. Hum Mol Genet. 2005;14:2919–27.
268. Imai Y, Yasuda K, Nagai M, Kusakabe M, Kubo M, Nakanishi K, et al. IL-33–induced atopic dermatitis–like inflammation in mice is mediated by group 2 innate lymphoid cells in concert with basophils. J Invest Dermatol. 2019;139:2185–94. e3.
269. Jirapongsananuruk O, Donahue HL, Trumble AE, Leung DY. The modulation of cytokine and IgE production by tumor necrosis factor-beta in atopic dermatitis. J Invest Dermatol. 2000;114:200–3.
270. Bin Huraib G, Al Harthi F, Arfin M, Al-Sugheyr M, Rizvi S, Al-Asmari A. Cytokine gene polymorphisms in Saudi patients with atopic dermatitis: a case-control study. Biomark Insights. 2018;13:1177271918777760.
271. Nakajima S, Kitoh A, Egawa G, Natsuaki Y, Nakamizo S, Moniaga CS, et al. IL-17A as an inducer for Th2 immune responses in murine atopic dermatitis models. J Invest Dermatol. 2014;134:2122–30.
272. Gutowska-Owsiak D, Schaupp AL, Salimi M, Selvakumar TA, McPherson T, Taylor S, et al. IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion. Exp Dermatol. 2012;21:104–10.
273. Hayashida S, Uchi H, Moroi Y, Furue M. Decrease in circulating Th17 cells correlates with increased levels of CCL17, IgE and eosinophils in atopic dermatitis. J Dermatol Sci. 2011;61:180–6.
274. Narbutt J, Wojtczak M, Zalinska A, Salinski A, Przybylowska-Sygut K, Kuna P, et al. The A/A genotype of an interleukin-17A polymorphism predisposes to increased severity of atopic dermatitis and coexistence with asthma. Clin Exp Dermatol. 2015;40:11–6.
275. Shibata S, Saeki H, Tsunemi Y, Kato T, Nakamura K, Kakinuma T, et al. IL-17F single nucleotide polymorphism is not associated with psoriasis vulgaris or atopic dermatitis in the Japanese population. J Dermatol Sci. 2009;53:163–5.
276. Mizutani N, Sae-Wong C, Kangsanant S, Nabe T, Yoshino S. Thymic stromal lymphopoietin-induced interleukin-17A is involved in the development of IgE-mediated atopic dermatitis–like skin lesions in mice. Immunology. 2015;146:568–81.
277. Christensen GB, Hvid M, Kvist PH, Deleuran B, Deleuran M, Vestergaard C, et al. CD4+ T cell depletion changes the cytokine environment from a TH1/TH2 response to a TC17-like response in a murine model of atopic dermatitis. Int Immunopharmacol. 2011;11:1285–92.
278. Hayashida S, Uchi H, Takeuchi S, Esaki H, Moroi Y, Furue M. Significant correlation of serum IL-22 levels with CCL17 levels in atopic dermatitis. J Dermatol Sci. 2011; 61:78–9.
279. Mashiko S, Bouguermouh S, Rubio M, Baba N, Bissonnette R, Sarfati M. Human mast cells are major IL-22 producers in patients with psoriasis and atopic dermatitis. J Allergy Clin Immunol. 2015;136:351–9.e1.
280. Gutowska-Owsiak D, Schaupp AL, Salimi M, Taylor S, Ogg GS. Interleukin-22 downregulates filaggrin expression and affects expression of profilaggrin processing enzymes. Br J Dermatol. 2011;165:492–8.
281. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, Morel F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol. 2005;174:3695–702.
282. Rasanen L, Lehto M, Reunala T, Jansen C, Leinikki P. Decreased monocyte production of interleukin-1 and impaired lymphocyte proliferation in atopic dermatitis. Arch Dermatol Res. 1987;279:215–8.
283. Yamanaka K, Mizutani H. "Inflammatory skin march": IL-1–mediated skin inflammation, atopic dermatitis, and psoriasis to cardiovascular events. J Allergy Clin Immunol. 2015;136:823–4.
284. Behniafard N, Gharagozlou M, Sotoudeh S, Farhadi E, Khaledi M, Moghaddam ZG, et al. Association of single nucleotide polymorphisms of interleukin-1 family with atopic dermatitis. Allergol Immunopathol (Madr). 2014;42:212–5.
285. Reich K, Westphal G, Konig IR, Mossner R, Schupp P, Gutgesell C, et al. Cytokine gene polymorphisms in atopic dermatitis. Br J Dermatol. 2003;148:1237–41.
286. Hatano Y, Katagiri K, Takayasu S. Increased levels in vivo of mRNAs for IL-8 and macrophage inflammatory protein-1 alpha (MIP-1 alpha), but not of RANTES mRNA in peripheral blood mononuclear cells of patients with atopic dermatitis (AD). Clin Exp Immunol. 1999;117:237–43.
287. Kimata H, Lindley I. Detection of plasma interleukin-8 in atopic dermatitis. Arch Dis Child. 1994;70:119–22.
288. Hon KL, Ching GK, Wong KY, Leung TF, Leung AK. A pilot study to explore the usefulness of antibody array in childhood atopic dermatitis. J Natl Med Assoc. 2008;100:500–4.
289. Zheng M, Sun G, Mrowietz U. The chemotactic activity of T-lymphocytes in response to interleukin 8 is significantly decreased in patients with psoriasis and atopic dermatitis. Exp Dermatol. 1996;5:334–40.
290. Sticherling M, Bornscheuer E, Schroder JM, Christophers E. Immunohistochemical studies on NAP-1/IL-8 in contact eczema and atopic dermatitis. Arch Dermatol Res. 1992;284:82–5.
291. Laberge S, Ghaffar O, Boguniewicz M, Center DM, Leung DY, Hamid Q. Association of increased CD4+ T-cell infiltration with increased IL-16 gene expression in atopic dermatitis. J Allergy Clin Immunol. 1998;102:645–50.
292. Angelova-Fischer I, Hipler UC, Bauer A, Fluhr JW, Tsankov N, Fischer TW, et al. Significance of interleukin-16, macrophage-derived chemokine, eosinophil cationic protein and soluble E-selectin in reflecting disease activity of atopic dermatitis—from laboratory parameters to clinical scores. Br J Dermatol. 2006;154: 1112–7.
293. Reich K, Hugo S, Middel P, Blaschke V, Heine A, Gutgesell C, et al. Evidence for a role of Langerhans cell–derived IL-16 in atopic dermatitis. J Allergy Clin Immunol. 2002;109:681–7.
294. Otobe S, Sugaya M, Nakajima R, Oka T, Takahashi N, Kabasawa M, et al. Increased interleukin-36γ expression in skin and sera of patients with atopic dermatitis and mycosis fungoides / Sezary syndrome. J Dermatol. 2018;45:468–71.
295. Hou T, Tsang MS, Chu IM, Kan LL, Hon KL, Leung TF, et al. Skewed inflammation is associated with aberrant interleukin-37 signaling pathway in atopic dermatitis. Allergy. 2021;76:2102–14.
296. Hou T, Sun X, Zhu J, Hon KL, Jiang P, Chu IM, et al. IL-37 Ameliorating allergic inflammation in atopic dermatitis through regulating microbiota and AMPK-mTOR signaling pathway-modulated autophagy mechanism. Front Immunol. 2020;11: 752.
297. Ewald DA, Malajian D, Krueger JG, Workman CT, Wang T, Tian S, et al. Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. BMC Med Genomics. 2015;8:60.
298. Pastore S, Fanales-Belasio E, Albanesi C, Chinni LM, Giannetti A, Girolomoni G. Granulocyte macrophage colony-stimulating factor is overproduced by keratinocytes in atopic dermatitis. Implications for sustained dendritic cell activation in the skin. J Clin Invest. 1997;99:3009–17.

299. Bratton DL, Hamid Q, Boguniewicz M, Doherty DE, Kailey JM, Leung DY. Granulocyte macrophage colony-stimulating factor contributes to enhanced monocyte survival in chronic atopic dermatitis. J Clin Invest. 1995;95:211–8.
300. Rho NK, Kim WS, Lee DY, Lee JH, Lee ES, Yang JM. Immunophenotyping of inflammatory cells in lesional skin of the extrinsic and intrinsic types of atopic dermatitis. Br J Dermatol. 2004;151:119–25.
301. Rafatpanah H, Bennett E, Pravica V, McCoy MJ, David TJ, Hutchinson IV, et al. Association between novel GM-CSF gene polymorphisms and the frequency and severity of atopic dermatitis. J Allergy Clin Immunol. 2003;112:593–8.
302. Shimizu T, Abe R, Ohkawara A, Mizue Y, Nishihira J. Macrophage migration inhibitory factor is an essential immunoregulatory cytokine in atopic dermatitis. Biochem Biophys Res Commun. 1997;240:173–8.
303. Shimizu T, Abe R, Ohkawara A, Nishihira J. Increased production of macrophage migration inhibitory factor by PBMCs of atopic dermatitis. J Allergy Clin Immunol. 1999;104:659–64.
304. Kitaichi N, Shimizu T, Honda A, Abe R, Ohgami K, Shiratori K, et al. Increase in macrophage migration inhibitory factor levels in lacrimal fluid of patients with severe atopic dermatitis. Graefes Arch Clin Exp Ophthalmol. 2006;244:825–8.
305. Gow DJ, Jackson H, Forsythe P, Gow AG, Mellanby RJ, Hume DA, et al. Measurement of serum macrophage migration inhibitory factor (MIF) and correlation with severity and pruritus scores in client owned dogs with atopic dermatitis. Vet Dermatol. 2019.
306. Hamasaka A, Abe R, Koyama Y, Yoshioka N, Fujita Y, Hoshina D, et al. DNA vaccination against macrophage migration inhibitory factor improves atopic dermatitis in murine models. J Allergy Clin Immunol. 2009;124:90–9.
307. Lopatnikova JA, Alshevskaya AA, Krugleeva OL, Nepomnyschih VM, Gladkikh VS, Lukinov VL, et al. Expression of TNFα receptors on immunocompetent cells is increased in atopic dermatitis. Int Arch Allergy Immunol. 2017;174:151–60.
308. Behniafard N, Gharagozlou M, Farhadi E, Khaledi M, Sotoudeh S, Darabi B, et al. TNF-alpha single nucleotide polymorphisms in atopic dermatitis. Eur Cytokine Netw. 2012;23:163–5.
309. Arkwright PD, Chase JM, Babbage S, Pravica V, David TJ, Hutchinson IV. Atopic dermatitis is associated with a low-producer transforming growth factor beta(1) cytokine genotype. J Allergy Clin Immunol. 2001;108:281–4.
310. Alyoussef A. Blocking TGF-β type 1 receptor partially reversed skin tissue damage in experimentally induced atopic dermatitis in mice. Cytokine. 2018;106:45–53.
311. Anthoni M, Wang G, Deng C, Wolff HJ, Lauerma AI, Alenius HT. Smad3 signal transducer regulates skin inflammation and specific IgE response in murine model of atopic dermatitis. J Invest Dermatol. 2007;127:1923–9.
312. Reinhold U, Wehrmann W, Kukel S, Kreysel HW. Recombinant interferon-gamma in severe atopic dermatitis. Lancet. 1990;335:1282.
313. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nat Rev Drug Discov. 2022;21:21–40.