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

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 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 (Th2) 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 reduced 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-adenexal, 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 naïve 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 (44).

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 Th22 dominance (44). On the other hand, AD is skewed toward Th22/Th1 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-4Ra 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 crustng, cutaneous infection, and cardinal histologic findings including spongiosis, eosinophilic and mononuclearcytic 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-4 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 promoter 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 promoter region—namely, −3112C>T, −1803T>C, −327C>A, −326A>C, and −1866G>A—were also associated with AD, although none of these affects promoter 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...
in AD. Exogenous IL-4 promotes in vitro IL-4 production from CD4+ CD45RA+ naïve 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+ naïve T cells tend to autonomously produce Th2 cytokines (77). In contrast to naïve 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 promoter hypermethylation (84). In addition, IL-18 promotes TSLP secretion through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway (85), and NF-kB-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-4 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 IL-4 receptor, does not cure AD (77). IL-4 is still present in AD skin, but the role of IL-4 in the pathogenesis of AD is still uncertain (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-4 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-4Ra is a common subunit shared between IL-4R and IL-13R. In AD lesions, IL-4Ra 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 chemokatin, 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-1β, IL-2, IL-19, IL-20, and IL-31Ra. 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; lymphotixin-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 chemotaxing 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 FceRI 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-31ra 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-5ra 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 (179), whereas IL-10 and IL-10 rs2228145 is associated with more persistent AD (171).

Monocyte-derived 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-13ra 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 (592), 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 CD2− independent manner (157).

Underlying polymorphisms of IL-13 and IL-13ra may account for IL-13 and IL-13ra overexpression (196). In AD, IL-13 was found to be associated with five polymorphisms: IL-13 rs3091907, rs20541, and rs12956685 as well as IL-13ra1 rs2265753 and rs2254672 (197–201), where IL-13 rs20541 also correlates with the serum IgE level (202). Taking into consideration that soluble CD14 correlates positively with AD (203), CD14 rs22569190 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+ CCR4+ 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 IV 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, 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). Parallely, 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 neuropetide 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-31ra 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 co-express IL-13 and IL-22 and rarely IFN-γ and IL-17 (13). Although different IL-31 polymorphisms—namely, IL-31 rs10847385 and rs7976857—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 adulthood. 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,
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-10 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 promoter region of IL-12rβ—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, CD1α+ 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, transdermal 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 pro-inflammatory 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-1ra 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 mononuclearcyte 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 of 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 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.

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<th>Current status</th>
<th>National clinical trial</th>
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<td>Janus kinase antagonists</td>
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<tr>
<td>LY3009104 (baricitinib)</td>
<td>JAK-1 and -2 antagonist</td>
<td>EMA 2020, Phase 3</td>
<td>NCT03952559, NCT03559270, NCT03435081, NCT03334422, NCT03334396, NCT03428100, NCT03733301, NCT03334435</td>
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<td>Janus kinase antagonists</td>
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<tr>
<td>A 301 (ATI 502)</td>
<td>Small molecule against JAK-1 and -2</td>
<td>Phase 3</td>
<td>NCT03002571</td>
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<tr>
<td>ABT-494 (upadacitinib)</td>
<td>Small molecule against JAK-1</td>
<td>Phase 3</td>
<td>NCT03738397, NCT03661138, NCT04195698, NCT03607422, NCT04666675, NCT03569293, NCT03568318</td>
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<tr>
<td>INCB018424 (ruxolitinib)</td>
<td>JAK-1 and -2 antagonist</td>
<td>Phase 3</td>
<td>NCT03745651, NCT03745638, NCT04921969</td>
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<tr>
<td>LEO 124249 (delgocitinib)</td>
<td>Small molecule; pan-JAK antagonist</td>
<td>Phase 3</td>
<td>NCT04871711, NCT04872101, NCT04949841</td>
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<td>PF04965842 (abrocitinib)</td>
<td>Small molecule against JAK-1</td>
<td>Phase 3</td>
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<td>SHR0302</td>
<td>Small molecule against JAK-1, JAK-2, JAK-3, and TYK-2</td>
<td>Phase 3</td>
<td>NCT04875169</td>
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<td>ARQ-252</td>
<td>Small molecule against JAK-1</td>
<td>Phase 2</td>
<td>NCT03654755, NCT03531957, NCT03728504</td>
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<td>ASN002</td>
<td>Small molecule against spleen tyrosine kinase and JAK</td>
<td>Phase 2</td>
<td>NCT04378569</td>
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<td>ATI-1777</td>
<td>Small molecule against JAK-1 and -3</td>
<td>Phase 2</td>
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<td>Jaktinib</td>
<td>Pan JAK antagonist</td>
<td>Phase 2</td>
<td>NCT04598269, NCT04598269</td>
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<td>PF-06700841</td>
<td>JAK-1 and TYK-2 antagonist</td>
<td>Phase 2</td>
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<td>Tofacitinib</td>
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<td>CEE321</td>
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<td>Phosphodiesterase-4 antagonists</td>
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<td>Crisaborole</td>
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<td>ARQ-151 (roflumilast)</td>
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<td>Phase 3</td>
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<td>OPA-15406 (MM36)</td>
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<td>Phase 3</td>
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<td>Apremilast</td>
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<td>DRM02</td>
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<td>Phase 2</td>
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<td>GW842470X</td>
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<td>Hemay808</td>
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<td>Phase 2</td>
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<td>LEO 29102</td>
<td>PDE-4 inhibitor</td>
<td>Phase 2</td>
<td>NCT03452595, NCT01037881, NCT0219633, NCT01850849</td>
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