




Targeting IL-4 for the Treatment of Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) is an immune-mediated inflammatory skin disease characterized by a predominant type 2 immune response. Type 2 immunity is driven by multiple cytokines, including interleukin (IL)-4 and IL-13 that are considered central to AD pathogenesis and key therapeutic targets. The dual inhibition of these two cytokines or the selective inhibition of IL-13 proved elevated efficacy in treating AD, whereas the selective inhibition of IL-4 has been poorly investigated as IL-4 inhibiting agents did not show any advance in clinical development programs. This review describes the pathogenic role of IL-4 in AD and briefly resumes the main features of compounds selectively blocking IL-4.

Keywords: atopic dermatitis, IL-4, IL-4 inhibitor, dupilumab, pascalizumab, pitrakinra

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease resulting from genetic predisposition and environmental factors that cause skin barrier impairment and predominant type 2 immune responses.¹ Genetic susceptibility involves the keratinocyte differentiation process (ie, filaggrin) generating a defective epidermal barrier as well as immune dysregulation with a prevalent Th2 cytokine gene expression.¹ The immune activation can be altered by the dysbiosis of the skin microbiota characterized by the marked colonization of *Staphylococcus aureus*.² Thereby, AD pathogenesis represents a complicated mechanism wherein skin barrier, immune system, microbes, and, lately, the itch-mediating peripheral and central nervous system are interconnected. The pathogenic model has profoundly changed over the last two decades, overcoming the previous hypotheses based on (i) the immunoglobulin E (IgE)-mediated immune response (type 1 hypersensitivity), (ii) the primary role of the epidermal barrier impairment (“outside-in” theory), or (iii) the primary role of the aberrant immune activation (“inside-out” theory).^{3–5} The discovery of the role for multiple immune pathways has led to new concepts in AD pathogenesis, and subsequently, to novel therapeutic strategies. It is now clear that the exaggerated immune response and the skin barrier impairment are both necessary for the development of AD, that may be considered a heterogeneous disease, being characterized by different phenotypes/endotypes.^{1,6,7} The immune hallmark of AD is the type 2 inflammation that includes the activation of T helper (h) 2 cells, T cytotoxic (c) 2 cells, innate lymphoid cells (ILC)2, γ/δ T cells, eosinophils, and mast cells, B cells, while other immune pathways such as Th22, Th17, Th9 and Th1 contribute to the pathogenic mechanism, particularly in some AD subtypes.^{7,8}

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Type 2 immunity is driven by multiple cytokines, including interleukin (IL)-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33 and thymic stromal lymphopoietin (TSLP). In particular, IL-4 and IL-13 are considered central to AD pathogenesis and key therapeutic targets.^{5,8-10} Because type 2 inflammation also characterizes other atopic disorders, such as food allergies, asthma, allergic rhinitis and conjunctivitis, which are strongly associated with AD, therapeutic strategies blocking type 2 cytokines may be relevant in treating AD and concomitant atopic disorders.¹¹ In this review, we provide a brief overview about the pathogenic role of IL-4 and the therapeutic agents blocking this cytokine.

Methods

Search of the English-language literature regarding the pathogenic role of IL-4 in AD was carried out, in addition to therapeutic agents targeting IL-4 signaling. Different databases, namely PubMed, Embase, ResearchGate, Google Scholar and Scopus, have been consulted using the following terms: interleukin 4, IL-4, IL-4-inhibitor, IL-4-blocker, atopic dermatitis, atopic eczema, pathogenesis, pathogenic mechanism. Ongoing clinical trials and preliminary results concerning investigational use of IL-4 inhibitors in AD were searched on Clinicaltrial.gov. Data from recent international meetings were also taken into account.

Role of IL-4 in AD Pathogenesis

Gene encoding for IL-4 protein maps on human chromosome 5, clustering with other genes involved in AD pathogenesis such as IL-13 and IL-5, other than IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF).^{12,13} IL-4 is a glycosylated, type I cytokine produced by Th2 cells, Tc2 cells, NK T cells, γ/δ T cells, ILC2, eosinophils, mast cells, and activated basophils.^{5,14} IL-4 signals through two different receptor complexes: a type I receptor composed by composed of IL-4R α chain and common γ chain/IL-2 R γ subunit, and expressed on hematopoietic cells, and a type II receptor consisting of IL-4R α and IL-13R α 1 subunits, and expressed on nonhematopoietic cells.^{15,16} Whilst the type I receptor specifically transduces signals for IL-4, the type II receptor can be activated by either IL-4 or IL-13.^{5,15,16} IL-4 acts on both immune and tissue cells, mediating multiple steps of the pathogenic cascade in AD. On the T cell compartment, IL-4 drives the differentiation of naïve CD4+ T cells into Th2 cells, and similarly induces the development of Tc2

and ILC2 cells.¹⁷⁻²⁰ On the B cell compartment, IL-4 induces IgE production.²¹ To amplify type 2 inflammation, IL-4 also modulates dendritic cell activity, reducing their expression of IL-12 and MHC class II and costimulatory molecules, and increasing the production of IL-10, and thus, favoring the differentiation of both naïve CD4+ and CD8+ T cells toward type 2 cells.²²

The expansion of type 2 T cells results in an elevated frequency of circulating Tc2 and cutaneous lymphocyte-associated antigen (CLA)+ IL-4-producing T cells, detected in AD patients and reflecting a significantly higher number of both Th2 cells infiltrating both AD lesional and nonlesional skin.²³⁻²⁸ IL-4 also amplifies CCR4+ Th2 cell recruitment to the skin inducing the expression CCR4-binding chemokines, such as CCL22, CCL5, CCL17, CCL2, in monocytes and dendritic cells.²⁹⁻³¹ In addition, it stimulates the expression of CCL26 (eotaxin-3) in keratinocytes, a key chemokine for eosinophil recruitment and, similarly, it induces in fibroblasts the expression of CCL11 (eotaxin-1), another critical cytokine for eosinophil recruitment.^{32,33}

Mouse models have defined the centrality of IL-4 in AD pathogenesis, highlighting its capability in inducing all AD histopathological features.^{34,35} The overexpression of IL-4 induces IgE production, enhances skin inflammation, favors bacterial skin infection, and mediates pruritus.^{34,35} On the contrary, the lack of IL-4 reduces allergen-challenged skin reactivity, and attenuates IgE levels and skin eosinophilia.^{36,37} Besides the effect on immune cells, IL-4 also influences keratinocyte differentiation and their innate immune activation. In vitro, IL-4 stimulation alters early and terminal keratinocytes differentiation, suppressing the expression of both terminal keratinocyte differentiation proteins (ie, filaggrin, loricrin and involucrin), and genes related to differentiating keratinocytes at early stages (ie, keratin [Krt]1, Krt5, Krt10, Krt14, desmoglein [Dsg]1a, and desmocollin [Dsc]1).³⁸⁻⁴¹ In addition, IL-4 alters extracellular lipid content in in vitro AD model similarly to the aberrant stratum corneum lipid structure observed in both AD mice model and human AD skin.⁴² IL-4 attenuates antimicrobial peptide (AMP) production, suppressing upregulation of beta defensin (HBD)-2, HBD-3, LCN2, and LL-37, even antagonizing IL-17-induced AMP production in keratinocytes.⁴³⁻⁴⁷ IL-4 also triggers fibroblast production of collagen, fibronectin, and fibrinogen, serving as adhesion molecules for *Staphylococcus aureus*.⁴⁸⁻⁵⁰ Thereby, IL-4 contributes to skin barrier function impairment and to the increased susceptibility to bacterial

infections. In addition, IL-4 both directly and indirectly, stimulates itch sensory neurons. Indeed, IL-4 is capable of directly activating itch sensory neurons *in vitro*, and, in mice, intradermal injections of IL-4 induced rapid and significant increase of scratching.^{51,52} It has been shown, by employing sensory neuron-specific genetic deletion of IL-4R α , that chronic itch is dependent on neuronal IL-4R α and Janus kinase 1 signaling.⁵² Rather than triggering acute itch, activation of neuronal IL-4R α sensitizes sensory neurons to multiple other pruritogens. IL-4 significantly amplifies scratching behavior to low doses of known pruritogens like histamine.⁵² The indirect effects of IL-4 in potentiating itch signal may be also due to its capability to enhance the interaction between IL-31, identified as key pruritogen cytokine, and its receptor (IL-31R α), and increasing the expression of IL-31 receptor, in a dose-dependent manner, in bone marrow-derived dendritic cells.⁵³ The presence of IL-4 increases CCL-17 and CCL-22 production regulated by IL-31, conversely to IL-31 stimulation alone.⁵³ Finally, IL-4, together with granulocyte/macrophage colony stimulating factor, supports the differentiation of monocytes into monocyte-derived dendritic cells, which are abundantly present in AD lesional skin and potently contribute to sustain T cell activation in AD skin.⁵⁴

Therapeutic Relevance of Targeting IL-4

Inhibition of type 2 inflammation proved elevated efficacy in treating AD. The first approved monoclonal antibody, dupilumab, which blocks IL-4R α and thus the activity of both IL-13 and IL-4, primed the therapeutic strategy of blocking type 2 cytokines, their receptors, or their coupled intracellular signal transducers such as Janus kinases (JAK) - signal transducer and activator of transcription (STAT) pathway.^{55,56} Notwithstanding IL-4 signaling is considered a very interesting potential therapeutic target for the treatment of AD, a few attempts in neutralizing soluble IL-4 have been previously performed, but no pharmacologic entity blocking IL-4 is apparently in the current treatment pipeline for AD. The pharmaceutical development of monoclonal antibodies blocking the IL-4R α subunit, is predominant.⁵⁷ The therapeutic advantage of blocking this receptor subunit is to contemporarily neutralize the signaling of both IL-4 and IL-13 that show overlapping, but not redundant functions in potentiating type 2 inflammation. Indeed, IL-4, driving

T cell differentiation, is thought to have a key pathogenic role in the early steps of AD pathogenesis, whereas IL-13 does not promote Th2 differentiation and its effects seem to be more focused on peripheral tissue cells and the effector phase of the immune response.^{56,58} Thereby, T cells respond to IL-4 stimulation only as they do not express IL-13 receptors with the exception of Th17 cells that are reported to express a functional IL-13 receptor lessening IL-17 production.⁵⁹ The hypothesis of an early relevant intervention of IL-4 in the pathogenesis of AD is in line with other findings describing an elevated IL-4 expression in acute lesional skin, which further increase in chronic AD lesions.^{60,61} Because IL-4 mainly acts on both T cell and ILC differentiation towards a type 2 response, but tissue cell activation in AD is suggested to be preferentially driven by IL-13, the dual blockade of these cytokines has the advantage of blocking multiple steps of the pathogenic cascade, reflecting a both rapid and maintained therapeutic response. The neutralization of IL-4 signaling alone may not directly suppress tissue cell response, which might translate therapeutically into a late-onset response, compared to simultaneous IL-4/IL-13 blockade.

Selective Inhibitors of IL-4 Signaling

In 2017, both the European Medicines Agency and the US Food and Drug Administration approved dupilumab for the treatment of moderate to severe AD. Clinical outcomes derived from Phase 3 trials have been confirmed by a large number of real-life studies, demonstrating high clinical effectiveness and very favorable safety profile.^{62,63} Targeting the same receptor subunit, other drugs, namely CBP 201 (manufacturer: Suzhou Connect Biopharmaceuticals), AK 120 (manufacturer: Akeso Biopharma), are now tested in Phase II and Phase I trials, respectively (Table 1).^{64,65} With a different mechanism-of-action, pitrakinra, is able to block both IL-4 and IL-13. It represents an IL-4 double mutein, recombinant protein that binds to IL-4R α receptor subunit without signaling through, thus not determining receptor activation.⁶⁶ So far, pascolizumab (SB 240683), is the only humanized monoclonal antibody neutralizing IL-4 that was developed for the treatment of asthma.⁶⁷ A pilot study, a phase I/II, randomized, double-blind, placebo controlled, parallel-group trial, enrolling 120 patients with symptomatic steroid-naïve asthma, was conducted but results are

Table I Therapeutic Agents Targeting IL-4 That are Marketed or Under Clinical Development for the Treatment of AD

Compound	Type of Molecule	Target	Phase of Development
Pitrakinra	Inactive human recombinant protein similar to IL-4 (also a PEGylated variant of subcutaneous pitrakinra was investigated)	IL-4 alpha receptor subunit	Phase IIb in AD - unknown future development program
Dupilumab	Fully human monoclonal IgG4 antibody	IL-4 alpha receptor subunit	FDA and EMA approved
CBP 201	Monoclonal antibody	IL-4 alpha receptor subunit	Phase II
AK 120	Monoclonal antibody	IL-4 alpha receptor subunit	Phase I
Pascolizumab (SB 240683)	Humanized monoclonal IgG1 antibody	IL-4	Phase II in asthma - unknown future development program

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; IL-, interleukin.

not reported and no further development has been planned.⁶⁸

Conclusions

The role of IL-4 in AD is well established and multiple lines of evidence support its relevant contribution in mediating multiple clinical features, including skin inflammation and pruritus. Nevertheless, its therapeutic relevance is still debated as it is usually considered a valid target for AD in conjunction with IL-13 neutralization. Conversely to IL-13 alone that constitutes a target for various compounds currently tested in clinical trials, the selective inhibition of IL-4 is not considered an advantageous therapeutic intervention for type 2 mediated disorders. However, further investigations on developing new IL-4 targeting agents will be worthy to expand and diversify the therapeutic armamentarium in AD and other type 2 inflammation mediated itchy skin disorders.

Disclosure

Andrea Chiricozzi served as advisory board member and consultant, and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme, and UCB-Pharma

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Giampiero Girolomoni has been principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Celgene, Celltrion, Eli-Lilly, Genzyme, Leo Pharma, Menlo therapeutics, Novartis, OM Pharma, Pfizer, Regeneron, Samsung, Sandoz and UCB Pharma.

The authors report no conflicts of interest for this work.

References

- Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res.* 2012;22(5):850. doi:10.1101/gr.131029.111
- Coca A, Cooke R. On the classification of the phenomena of hypersensitiveness. *J Immunol.* 1923;8:163–182.
- Elias PM, Steinhoff M. “Outside-to-inside” (and now back to “outside”) pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol.* 2008;128(5):1067–1070. doi:10.1038/jid.2008.88
- Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2016;138:336–349.
- Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought? *J Allergy Clin Immunol.* 2017;140(3):633–643. doi:10.1016/j.jaci.2017.07.006
- Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol.* 2017;139(4):S65–S76. doi:10.1016/j.jaci.2017.01.011
- Lloyd CM, Snelgrove RJ. Type 2 immunity: expanding our view. *Sci Immunol.* 2018;3:eaat1604.

8. Roesner LM, Zeitvogel J, Heratizadeh A. Common and different roles of IL-4 and IL-13 in skin allergy and clinical implications. *Curr Opin Allergy Clin Immunol*. 2019;19(4):319–327. doi:10.1097/ACI.0000000000000553
9. Kim JE, Jung K, Kim JA, et al. Engineering of anti-human interleukin-4 receptor alpha antibodies with potent antagonistic activity. *Sci Rep*. 2019;9(1):7772. doi:10.1038/s41598-019-44253-9
10. Bagnasco D, Ferrando M, Varricchi G, et al. A Critical Evaluation of Anti-IL-13 and Anti-IL-4 Strategies in Severe Asthma. *Int Arch Allergy Immunol*. 2016;170:122–131.
11. McKenzie AN, Li X, Largaespada DA, et al. Structural comparison and chromosomal localization of the human and mouse IL-13 genes. *J Immunol*. 1993;150:5436–5444.
12. Takahashi M, Yoshida MC, Satoh H, et al. Chromosomal mapping of the mouse IL-4 and human IL-5 genes. *Genomics*. 1989;4(1):47–52. doi:10.1016/0888-7543(89)90313-3
13. Werfel T. The role of leukocytes, keratinocytes, and allergen-specific IgE in the development of atopic dermatitis. *J Invest Dermatol*. 2009;129(8):1878–1891. doi:10.1038/jid.2009.71
14. Izuhara K, Yang G, Miyajima A, et al. Structure of the IL4 receptor and signal transduction mechanism of IL4. *Res Immunol*. 1993;144:584–590.
15. Keegan A, Nelms K, Paul WE. The IL-4 receptor–signaling mechanisms. *Adv Exp Med Biol*. 1994;365:211–215.
16. Huang LR, Chen FL, Chen YT, et al. Potent induction of long-term CD8+ T cell memory by short-term IL-4 exposure during T cell receptor stimulation. *Proc Natl Acad Sci U S A*. 2000;97:3406–3411.
17. Pelly VS, Kannan Y, Coomes SM, et al. IL-4-producing ILC2s are required for the differentiation of TH2 cells following Heligmosomoides polygyrus infection. *Mucosal Immunol*. 2016;9(6):1407–1417. doi:10.1038/mi.2016.4
18. Swain SL, Weinberg AD, English M, et al. IL-4 directs the development of Th2-like helper effectors. *J Immunol*. 1990;145:3796–3806.
19. Roesner LM, Werfel T, Heratizadeh A. The adaptive immune system in atopic dermatitis and implications on therapy. *Expert Rev Clin Immunol*. 2016;12(7):787–796. doi:10.1586/1744666X.2016.1165093
20. Pène J, Rousset F, Brière F, et al. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons gamma and alpha and prostaglandin E2. *Proc Natl Acad Sci U S A*. 1988;85:6880–6884.
21. Iezzi G, Boni A, Degl’Innocenti E, et al. Type 2 cytotoxic T lymphocytes modulate the activity of dendritic cells toward type 2 immune responses. *J Immunol*. 2006;177(4):2131–2137. doi:10.4049/jimmunol.177.4.2131
22. 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;143:373–378.
23. Okazaki H, Kakurai M, Hirata D, 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(8):1236–1242. doi:10.1046/j.1365-2745.2002.01383.x
24. Hijnen D, Knol EF, Gent YY, et al. CD8(+) T cells in the lesional skin of atopic dermatitis and psoriasis patients are an important source of IFN- γ , IL-13, IL-17, and IL-22. *J Invest Dermatol*. 2013;133:973–979.
25. Czarnecki T, Gonzalez J, Shemer A, et al. Severe atopic dermatitis is characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17, cells within the skin-homing T-cell population. *J Allergy Clin Immunol*. 2015;136(1):104–115.e7. doi:10.1016/j.jaci.2015.01.020
26. Leung DY, Bhan AK, Schneeberger EE, et al. Characterization of the mononuclear cell infiltrate in atopic dermatitis using monoclonal antibodies. *J Allergy Clin Immunol*. 1983;71:47–56.
27. Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130:1344–1354.
28. Andrew DP, Chang MS, McNinch J, et al. STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. *J Immunol*. 1998;161:5027–5038.
29. Vulcano M, Albanesi C, Stoppacciaro A, et al. Dendritic cells as a major source of macrophage-derived chemokine/CCL22 in vitro and in vivo. *Eur J Immunol*. 2001;31(3):812–822. doi:10.1002/1521-4141(200103)31:3<812::AID-IMMU812>3.0.CO;2-L
30. Xiao T, Fujita H, Saeki H, et al. Thymus and activation-regulated chemokine (TARC/CCL17) produced by mouse epidermal Langerhans cells is upregulated by TNF-alpha and IL-4 and down-regulated by IFN-gamma. *Cytokine*. 2003;23:126–132.
31. Nishi N, Yamamoto S, Ou W, et al. Enhanced CCL26 production by IL-4 through IFN-gamma-induced upregulation of type 1 IL-4 receptor in keratinocytes. *Biochem Biophys Res Commun*. 2008;376(1):234–240. doi:10.1016/j.bbrc.2008.08.136
32. Gahr N, Fölster-Holst R, Weichenthal M, et al. Dermal fibroblasts from acute inflamed atopic dermatitis lesions display increased eotaxin/CCL11 responsiveness to interleukin-4 stimulation. *Br J Dermatol*. 2011;164:586–592.
33. 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(4):977–983. doi:10.1046/j.0022-202x.2001.01484.x
34. Lee GR, Flavell RA. Transgenic mice which overproduce Th2 cytokines develop spontaneous atopic dermatitis and asthma. *Int Immunol*. 2004;16(8):1155–1160. doi:10.1093/intimm/dxh117
35. Spergel JM, Mizoguchi E, Oettgen H, et al. Roles of TH1 and TH2 cytokines in a murine model of allergic dermatitis. *J Clin Invest*. 1999;103(8):1103–1111. doi:10.1172/JCI5669
36. He R, Kim HY, Yoon J, et al. Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13. *J Allergy Clin Immunol*. 2009;124(4):761–70.e1. doi:10.1016/j.jaci.2009.07.040
37. Kim BE, Leung DY, Boguniewicz M, et al. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin Immunol*. 2008;126(3):332–337. doi:10.1016/j.clim.2007.11.006
38. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol*. 2007;120(1):150–155. doi:10.1016/j.jaci.2007.04.031
39. Sehra S, Yao Y, Howell MD, et al. IL-4 regulates skin homeostasis and the predisposition toward allergic skin inflammation. *J Immunol*. 2010;184(6):3186–3190. doi:10.4049/jimmunol.0901860
40. Omori-Miyake M, Yamashita M, Tsunemi Y, et al. In vitro assessment of IL-4- or IL-13-mediated changes in the structural components of keratinocytes in mice and humans. *J Invest Dermatol*. 2014;134(5):1342–1350. doi:10.1038/jid.2013.503
41. Berdyshev E, Goleva E, Bronova I, et al. Lipid abnormalities in atopic skin are driven by type 2 cytokines. *JCI Insight*. 2018;3:e98006.
42. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*. 2002;347:1151–1160.
43. Nomura I, Goleva E, Howell MD, et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol*. 2003;171(6):3262–3269. doi:10.4049/jimmunol.171.6.3262
44. Howell MD, Wollenberg A, Gallo RL, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol*. 2006;117(4):836–841. doi:10.1016/j.jaci.2005.12.1345

45. Howell MD, Fairchild HR, Kim BE, et al. Th2 cytokines act on S100/A11 to downregulate keratinocyte differentiation. *J Invest Dermatol.* 2008;128:2248–2258.
46. Nograles KE, Suárez-Fariñas M, Shemer A, et al. Atopic dermatitis keratinocytes exhibit normal T(H)17 cytokine responses. *J Allergy Clin Immunol.* 2010;125(3):744–746.e2. doi:10.1016/j.jaci.2009.12.934
47. Cho SH, Strickland I, Boguniewicz M, et al. Fibronectin and fibrinogen contribute to the enhanced binding of *Staphylococcus aureus* to atopic skin. *J Allergy Clin Immunol.* 2001;108(2):269–274. doi:10.1067/mai.2001.117455
48. Cho SH, Strickland I, Tomkinson A, et al. Preferential binding of *Staphylococcus aureus* to skin sites of Th2-mediated inflammation in a murine model. *J Invest Dermatol.* 2001;116(5):658–663. doi:10.1046/j.0022-202x.2001.01331.x
49. Bhogal RK, Bona CA. Regulatory effect of extracellular signal-regulated kinases (ERK) on type I collagen synthesis in human dermal fibroblasts stimulated by IL-4 and IL-13. *Int Rev Immunol.* 2008;27:472–496.
50. Campion M, Smith L, Gatault S, et al. Interleukin-4 and interleukin-13 evoke scratching behaviour in mice. *Exp Dermatol.* 2019;28:1501–1504.
51. Oetjen LK, Mack MR, Feng J, et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. *Cell.* 2017;171(1):217–228.e13. doi:10.1016/j.cell.2017.08.006
52. Miate S, Tsuji G, Takemura 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.
53. Pastore S, Fanales-Belasio E, Albanesi C, et al. 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(12):3009–3017. doi:10.1172/JCI119496
54. Calabrese L, Malvaso D, Chiricozzi A, et al. Baricitinib: therapeutic potential for moderate to severe atopic dermatitis. *Expert Opin Investig Drugs.* 2020;1–10.
55. Bieber T. Interleukin-13: targeting an underestimated cytokine in atopic dermatitis. *Allergy.* 2020;75(1):54–62. doi:10.1111/all.13954
56. Le Floch A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4R α antibody, is required to broadly inhibit type 2 inflammation. *Allergy.* 2020;75(5):1188–1204. doi:10.1111/all.14151
57. Oettgen HC, Geha RS. IgE in asthma and atopy: cellular and molecular connections. *J Clin Invest.* 1999;104(7):829–835. doi:10.1172/JCI8205
58. Newcomb DC, Boswell MG, Zhou W, et al. Human TH17 cells express a functional IL-13 receptor and IL-13 attenuates IL-17A production. *J Allergy Clin Immunol.* 2011;127(4):1006–13.e134. doi:10.1016/j.jaci.2010.11.043
59. Tazawa T, Sugiura H, Sugiura Y, et al. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. *Arch Dermatol Res.* 2004;295(11):459–464. doi:10.1007/s00403-004-0455-6
60. Tsoi LC, Rodriguez E, Stölzl D, et al. Progression of acute-to-chronic atopic dermatitis is associated with quantitative rather than qualitative changes in cytokine responses. *J Allergy Clin Immunol.* 2020;145(5):1406–1415. doi:10.1016/j.jaci.2019.11.047
61. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2016;375(24):2335–2348. doi:10.1056/NEJMoa1610020
62. Fargnoli MC, Esposito M, Ferrucci S, et al. Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis. *J Dermatolog Treat.* 2019. 1–7. doi:10.1080/09546634.2019.1682503
63. Available from: <https://clinicaltrials.gov/ct2/show/NCT04178967>. Assessed August 24 2020.
64. Available from: <https://clinicaltrials.gov/ct2/show/NCT04444752>. Assessed August 24 2020.
65. Antoniu SA. Pitakinra, a dual IL-4/IL-13 antagonist for the potential treatment of asthma and eczema. *Curr Opin Investig Drugs.* 2010;11:1286–1294.
66. Hart TK, Blackburn MN, Brigham-Burke M, et al. Preclinical efficacy and safety of pascolizumab (SB 240683): a humanized anti-interleukin-4 antibody with therapeutic potential in asthma. *Clin Exp Immunol.* 2002;130(1):93–100. doi:10.1046/j.1365-2249.2002.01973.x
67. Available from: <https://clinicaltrials.gov/ct2/show/NCT00024544?term=pascolizumab&draw=2&rank=2>. Assessed August 5 2020.
68. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet.* 2020;396:345–360.

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