Curr Treat Options Allergy (2020) 7:258–273
DOI 10.1007/s40521-020-00263-x

Contact Dermatitis (A Gimenez-Arnau, Section Editor)

Implication of T Helper Cytokines in Contact Dermatitis and Atopic Dermatitis

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Published online: 21 May 2020

This article is part of the Topical Collection on *Contact Dermatitis*

Keywords Contact dermatitis · Atopic dermatitis · Cytokines · T helper cells

Abstract

Purpose of review Cytokines play a key role in lesion development in inflammatory skin diseases such as contact dermatitis and atopic dermatitis and are of great interest as therapeutic targets. This is reflected in the increasing number of clinical studies and case reports as well as preclinical mouse models that provide substantial data on the participation of cytokines in these pathologies. In this review, we provide a detailed and comprehensive account of the advances in the field.
Recent results The importance and therapeutic potential of Th2 cytokines in allergic contact dermatitis (ACD) and atopic dermatitis (AD) are well documented. Recent results have added another member, IL-24, to the list of key players in both diseases. In addition, IL-9, which is associated with Th9 cells, has been found to be strongly increased in ACD patients, opening up another promising new avenue.
Summary In this review, we describe the expression and role of Th cytokines in skin inflammatory disorders, based on mouse models and existing therapy, focusing on cytokines associated with different subpopulations of T helper cells.

Introduction

The term "eczema" encompasses several distinct types of skin conditions including contact dermatitis and atopic dermatitis. Contact dermatitis is a localized skin reaction caused by contact with a foreign agent, with symptoms generally limited to the contact site. It is divided into two types: irritant contact dermatitis (ICD) that accounts for 80% of contact dermatitis and allergic contact dermatitis (ACD). Contact dermatitis is mainly an occupational hazard, for example, in healthcare workers and hairdressers who most often present with eczema on the hands. Atopic dermatitis (AD) is a chronic inflammatory relapsing condition that appears in patients with genetic predisposition. Lesions affect different parts of the body with a pattern that can change with age and time. AD is due to epidermal barrier dysfunction as well as immune tolerance dysfunction. The patients present increased transepidermal water loss (TEWL) with dry skin, pruritus, and chronic eczema and are more susceptible to microbes such as *Staphylococcus aureus*, fungi, and viruses that can enter the skin more easily. Typically, AD patients have elevated IgE antibodies in blood. Furthermore, individuals with atopic dermatitis are at higher risk of developing ICD or ACD because of this damaged barrier [1].

These three pathologies, AD, ICD, and ACD, have similar clinical symptoms, sometimes making the classification of dermatitis very difficult. In addition, for ICD and ACD, the allergens responsible can be hard to identify because of the delay in the reaction. Fortunately, the pathophysiology of these diseases is distinct, providing some clarity. In this paper, we will review what is known about the expression and role of Th cytokines in these three disorders, based on mouse models and existing therapy (Table 1). We will distinguish between the cytokines produced by different subpopulations of T helper cells, as well as cytokines involved in the polarization of different T helper cells. Th1 cells arise under the influence of IL-12p70 and mainly produce IFN-γ; Th2 cells require IL-4 for polarization and produce IL-4, IL-5, IL-13, and IL-24; Th9 cells, producing mainly IL-9, require TGF-β and IL-4; Th17 cells require TGF-β and IL-6 and produce IL-17A and IL-17F, IL-22, and IL-26; and finally, Th22 cells mostly produce IL-22 and are polarized following TNFα, IL-6, and IL-1β stimulation.

ICD

Irritant contact dermatitis (ICD) results from the activation of an inflammatory cascade in response to a direct skin injury by an external chemical or physical agent. Although it was previously considered a non-specific reaction, there is growing evidence showing that ICD is a complex interplay of events involving skin barrier disruption, cellular changes, and the release of pro-inflammatory mediators [2, 3]. The first step is the damage of keratinocytes by an irritant. This disruption leads to the release of IL-1α initially sequestered in keratinocytes [4]. IL-1α stimulates further secretion of pro-inflammatory cytokines such as IL-1β, TNFα, IL-6, and IL-8 by epidermal and dermal cells. In turn, these cytokines induce the activation of dendritic cells and T cells and the upregulation of adhesion molecules such as ICAM-1 on endothelial cells and fibroblasts. Chemokines and adhesion molecules then attract additional immune cells including neutrophils, eosinophils, and T lymphocytes, further increasing inflammation [5, 6, 7••].

Among the cytokines produced during an ICD reaction, IL-6 seems to have a particular influence on pathogenesis. Indeed, *Il6*-deficient mice present a more severe dermatitis compared with WT mice following exposure to irritants. This is accompanied by increased pro-inflammatory cytokine expression and inflammatory cell recruitment [8]. The same group has shown that IL6Rα deficiency in keratinocytes or in myeloid cells results in increased epidermal hyperplasia and

Table 1. Cytokines described as induced in skin inflammatory diseases and cytokine-targeting therapy tested in patients

Pathology		Th1-associated cytokines	Th2-associated cytokines	Th9-associated cytokines	Th17-associated cytokines	Th22-associated cytokines	Tested therapy	Ref.
ICD		IFN-γ			IL-6, IL-17	IL-1β, IL-6, TNF-α, IL-22		[8–19, 20•, 21•, 22]
ACD	Nickel	IFN-γ (+) > IL-17 (–)	IL-4, IL-5, IL-13 [40–52]	IL-9	IL-17, IL-26	IL-22	>IL-4Rα	
ACD	Fragrance	(+) > IL-17 (–)	IL-5, IL-13 [53–55] + unpub. data	IL-9		IL-22	>IL-4Rα	
ACD	MI	IFN-γ (–) > IL-17 (–)	IL-4, IL-5, IL-13 [50, 58, 59] + unpub. data	IL-9			>IL-4Rα	
ACD	PPD		IL-4, IL-5, IL-13, IL-24	IL-9				[60, 61•, 62•]
AD		(+) > IL-13 (+) > IL-17 (–) > IL-22 (+) > p40 (–) > IL-31 (+) JAK inhib. (+)	IL-4, IL-5, IL-13, IL-24 [71, 72, 76•, 77••, 78, 79, 81–83, 86, 87••, 88•, 89, 90, 91, 93–104]	IL-9	IL-17, IL-26	IL-22	>IL-4Rα	

(–) no improvement of clinical symptoms with therapy
(+) improvement of clinical symptoms with therapy
Unpub. data unpublished data from our lab

inflammatory monocyte influx into lesional skin in mouse models of ICD, further demonstrating the protective effect of IL-6 in this type of dermatitis [9, 10]. These observations suggest a more complex, pleiotropic role of IL-6, traditionally viewed as a pro-inflammatory cytokine.

The key role of IL-1α and TNFα in ICD is mainly supported by the correlation between gene polymorphisms and a modified risk of developing ICD: individuals with the IL1A-889 T (versus C) polymorphism have a decreased risk of developing ICD [11]; TNFA-308 polymorphisms are also associated with increased risk of ICD, whereas TNFA-238 polymorphisms are associated with reduced risk [12, 13]. The central role of TNFα is further illustrated by the effect of anti-TNF antibodies, which inhibit the irritant reactions induced by trinitrochlorobenzene (TNCB) when administered in vivo [14].

While ICD is primarily driven by innate immunity, we can by no means exclude the participation of T lymphocytes. In acute ICD, the cellular infiltrate is mainly composed of $CD4^+$ lymphocytes, and increased levels of the Th1-associated cytokines IL-2 and IFN-γ are observed [15, 16]. Moreover, Th phenotype has a strong influence on disease, with Th1-dominant C57BL/6 mice manifesting worse dermatitis than Th2-dominant Balb/c mice, in response to three different irritants. The stronger ICD response in C57BL/6 mice is associated with higher expression of IL-1β and IL-6 [17, 18].

Since Th17 cells are known to be involved in ACD, we may wonder if this subtype also plays a role in ICD. Simon et al. indeed described a marked increase of IL-17 expression 4 days after exposure to sodium lauryl sulfate, a potent irritative agent, in patients diagnosed with ICD [19]. A second group demonstrated the anti-inflammatory effect of SR1001, which inhibits the transcriptional activity of RORα and RORγ, in a mouse model of ICD [20•]. Given that RORα and RORγ are key transcriptional factors in Th17 cells, these results may again suggest a role of Th17 in ICD. Recently, IL-22, another cytokine produced by Th17 cells, has also been studied in the context of ICD. Frempah et al. showed that, in addition to more severe inflammation, IL-6a$^{\Delta ker}$ mice had increased expression of IL-22 and IL-22Ra in their skin when subjected to an irritant. In addition, the keratinocyte proliferation induced by IL-22 is diminished by IL-6. Thus, the authors propose that the action of IL-6 on ICD in this model is mediated via the reduction of IL-22-induced keratinocyte proliferation [21•]. In another study, however, inhibition of JAK, which is essential for IL-22 signaling, was not found to affect croton oil-induced ICD [22].

Based on these various studies, we may reasonably hypothesize that both Th1-cytokines and Th17-cytokines are implicated in the pathogenesis of ICD. Indeed, our own group has unpublished data showing increased expression of IFN-γ and IL-17 in the skin of patients with ICD, whereas IL-9 is not expressed. Further studies are certainly needed, however, to clearly elucidate the role of these cytokines in ICD.

ACD

ACD is a delayed type IV hypersensitivity reaction that leads to the activation of allergen-specific T cells. ACD development can be described in two phases: sensitization and elicitation. Sensitization occurs when a susceptible person encounters the allergen for the very first time. The allergen penetrates the skin,

associates with a carrier, and is captured by dendritic cells (Langerhans cells in the epidermis or dermal dendritic cells). These dendritic cells migrate to the skin-draining lymph nodes, where they present antigens to T cells. Hapten-specific T cells differentiate into effector cells and proliferate and reach the circulation without inducing any detectable inflammation. Indeed, no clinical symptoms are observed during this phase. Some inflammatory cytokines such as TNFα, IL-1, and IL-18 are produced by keratinocytes, inducing the migration and maturation of dendritic cells [23••].

The elicitation phase occurs after a second exposure to the hapten, leading to a rapid and specific response against the allergen and the appearance of symptoms of eczema. As during the sensitization phase, the first signals lead to antigen non-specific inflammation. The second step is an antigen-specific inflammation, mediated by antigen-specific T cells that are activated by dendritic cells. Memory T cells that differentiated during the sensitization phase release their cytokines rapidly, setting off an inflammatory cascade and, therefore, infiltration of additional cells. The T cell subset that predominantly mediates response differs from allergen to allergen.

Metal ions, fragrances, preservatives, and dyes are the major allergens in ACD, with nickel being the most common allergen. Fragrances are the second common cause of ACD. Among preservatives causing ACD, isothiazolinone-associated molecules such as methylisothiazolinone (MI) are frequently and abundantly found in cosmetics and non-cosmetic products (before introduction of restrictions), while in hair dyes, several aromatic amine precursors such as para-phenylenediamine (PPD) can cause ACD. More recently, ACD caused by glucose sensors or insulin pumps containing isobornyl acrylate (IBOA) has been described in diabetic patients.

Effective management of ACD currently depends on the identification of the putative allergen with patch testing, in order to avoid any potential causal agents. However, antigen avoidance is sometimes not possible: first, because it is not always easy to determine which antigen is involved and, second, because it is not always possible to enforce avoidance, as when ACD results from an antigen present at work, present widely in the environment or in indispensable materials (e.g., prostheses, glucose sensors, or insulin pumps).

To study the mechanisms underlying ACD, several mouse models of contact hypersensitivity (CHS) have been developed. The most common CHS models however use strong sensitizers that are not usually found in the human environment, such as dinitrofluorobenzene (DNFB), trinitrochlorobenzene (TNCB), or oxazolone.

The role of CD4 or CD8 T cells and the subtypes of T helper cytokines produced in ACD varies depending on allergen [24–27]. Below, we describe T helper cytokine production induced by selected allergens.

Mouse models of ACD: DNFB/TNCB/oxazolone

DNFB, TNCB, and oxazolone are three strong sensitizers used in mouse CHS models. Skin inflammation is accompanied by cytokine induction in all of these ACD models; however, the specific cytokines produced, IFN-γ, IL-4, IL-17, or IL-22, alone or in combination, are model-specific. While several studies have provided evidence for the participation of these Th1, Th2, and Th17 cytokines, IL-9 and Th9 cells have not to our knowledge been explored.

IFN-γ seems to play a detrimental role in mouse models of ACD, as inhibition of the IFN-γ pathway results in an impaired CHS response, implying that Th1 cells induce inflammation [28]. Mechanistically, IFN-γ may induce Th1 chemokine production by keratinocytes, whereas it inhibits Th2 chemokines. Inducible nitric oxide synthesis (iNOS) and myeloperoxidase (MPO) are less expressed in *Ifngr*-deficient mice, suggesting that IFN-γ may also affect the production of reactive oxygen species (ROS), which are key factors in CHS inflammation [29].

Th2 cells are also likely involved in these allergic models, as *Stat6*-deficient mice, in which IL-4 and IL-13 production are impaired, display a weaker ACD reaction [30]. This decrease in symptoms is associated with reduced inflammatory cell infiltration and lower IgE levels. The three CHS models have also been tested in $Il4^{-/-}$ or $Il13^{-/-}$ mice, but with conflicting results [31] that likely depend on experimental variables, as effects of antigen, mouse strain, or site of application are observed. In the DNFB model, IL-19 and IL-24, two other Th2 cytokines, are also increased [32], and $Il19^{-/-}$ mice are more affected than WT mice, suggesting a protective role of this cytokine [33]. In addition, with oxazolone and TNCB models, a shift from a Th1-dominated response to a chronic Th2-associated response is observed upon repeated challenges [34].

The Th17 cytokines IL-17 and IL-22 are highly produced at the beginning of the inflammatory process in these models and decline in chronic response, when IL-4 is increased [35, 36]. $Il17^{-/-}$ mice are protected in DNFB- and TNCB-induced CHS [37], as are *Il17r*-deficient mice, which display lower neutrophilic infiltration of the skin, suggesting an ultimately protective role of Il-17 and Th17 cells [29].

Nickel

Nickel is the major contact allergen in industrialized countries, with the prevalence of nickel allergy as high as 8–19% in the adult European population [24, 38]. Nickel is ubiquitous, in everything from coins and jewelry to metal tools, dental materials, and surgical implants. Clinically, nickel-induced positive patch test and irritative reaction caused by patch test are sometimes very similar, meaning that some patch tests are wrongly considered positive. Nickel allergy was historically associated with Th1/Th17 response, but Th2 cytokines have emerged to be extremely important.

First described as a Th1 response [39], it is now considered a mixed Th1/Th2 response, with IFN-γ, IL-4, IL-5, and IL-13 production, which have been extensively described [40–44]. Other metals such as chromium, palladium, and gold also stimulate a mixed Th1/Th2 profile in allergic patient PBMCs [40].

Multiple Th17 cytokines have been associated with nickel-induced ACD. Cells producing IL-17 and IL-22 are present in inflamed skin of nickel-allergic patients, and ACD PBMCs display a Th17 and Th1 profile upon nickel stimulation [45]. IL-22 is also increased in serum of allergic patients [46]. IL-26 is produced in skin lesions of ACD patients and is increased in plasma of ACD patients. It was also shown to be produced by PBMCs of patients (5 out of 10 of whom were nickel-allergic) after stimulation. Finally, siRNA-mediated depletion of IL-26 decreased the capacity of ACD PBMCs to kill keratinocytes, demonstrating its role in this disease mechanism [47].

IL-9 production and the presence of Th9 cells have also been described in the skin of nickel-allergic patients. PBMCs from these patients secrete high levels of IL-9 and IFN-γ but low levels of IL-4 after 96 h of nickel stimulation. IL-9 could play an indirect regulatory role on IFN-γ production because IL-9 addition in these experiments does not modify IFN-γ but induces the production of IL-4, and IL-4 addition inhibits IFN-γ production [48].

Unfortunately, a detailed dissection of the mechanisms underlying nickel allergy is hampered by the lack of good mouse models that mimic it, probably because nickel is not a strong enough sensitizer. Tests using targeted treatments in patients have however yielded insights into the key cytokines involved. In a study on ten nickel-allergic patients, anti-IL-17A antibody (secukinumab) slightly decreased clinical score, but not inflammation or skin thickness in a patch test [49], arguing against its efficacy as a therapeutic strategy. By contrast, dupilumab, an antibody directed against IL-4Rα that blocks IL-4 and IL-13, has been reported to decrease patch test scores and improve ACD symptoms in several case reports on nickel-allergic patients [50–52]. This would suggest that blocking Th2 cytokine action could be useful in nickel-induced ACD, although the effect of the antibody on cytokine production and T cell infiltration remains to be studied.

Fragrances

Fragrance allergies account for a large proportion of cosmetic allergies [24], with a prevalence of 1–4% in the general population.

Fragrance allergy is associated with strong Th2/Th9/Th22 responses but a very small contribution of Th1 and Th17 cytokines. Strong induction of Th2-related genes such as IL-5-, IL-13-, and Th2-associated chemokines is observed in the skin of allergic patients. IL-22 and IL-9 are also strongly induced ([53] and unpublished data from our lab).

As in the case of nickel allergy, a case series showed that dupilumab markedly alleviated ACD symptoms in patients with fragrance allergies, with at least 90% improvement in body surface area involvement [54]. Thus, Th2 cytokines are highly promising targets in the treatment of this allergy.

In contrast, a clinical trial (4 patients including 3 with fragrance allergy) testing secukinumab, a monoclonal antibody inhibiting IL-17A, showed little to no effect [55]. PGA, PaGA, and DLQI scores showed minimal to no reduction after 12 weeks of treatment, demonstrating that IL-17 is not a major cytokine in this context.

Methylisothiazolinone

Isothiazolinone derivatives are used as preservatives, particularly in cosmetics and detergents, thanks to their anti-bacterial and anti-fungal properties. MI-induced ACD affects 0.5% of the European population [56], although recent legislation to reduce MI in cosmetic products has decreased rates [57]. Currently, MI is still present in industrial products such as paints and in some rinse-off cosmetics.

Few studies have analyzed T cells and cytokines associated with MI-induced ACD. Masjedi et al. showed that IFN-γ is increased in some allergic patients, and IL-4 or IL-5 in some; importantly, however, IL-13 is induced in most [58].

While there are no published data on IL-9 and Th9 cells in MI-induced ACD to our knowledge, we have observed high levels of IL-9 in PBMCs from 12 allergic patients (unpublished data), suggesting a role for this arm.

In a case report on a nickel and MI allergic patient, dupilumab, inhibiting IL-4 and IL-13 signaling, failed to decrease the MI patch test score, while it had an effect on the nickel patch test score [50]. In another case report, IL-17A inhibition did not prevent MI-induced ACD in a patient who developed the allergy despite being on ixekizumab, as part of his treatment for psoriasis [59]. An effective cytokine-targeting strategy against MI-induced ACD is therefore yet to be demonstrated.

Para-phenylenediamine

PPD is found in hair dyes and black henna tattoos. PPD-induced ACD affects 0.8% of the general population. The main T cell populations involved in these allergic patients are Th2 and Th9 cells.

PBMCs from PPD-allergic patients secrete high levels of Th2 cytokines such as IL-4, IL-5, and IL-13 [60]. IL-4 and IL-24, another Th2 cytokine, are also highly produced in skin biopsies taken from allergic patients after PPD patch tests, as are the related cytokines IL-19 and IL-20 [61•, 62•]. In ACD PBMCs, however, only IL-24 production is induced after allergen stimulation.

IL-9, the main Th9 cell-derived cytokine, is also strongly induced in skin biopsies and stimulated PBMCs from allergic patients [62•]. As with nickel allergy, IL-9 may have a regulatory role in PPD allergy as suggested by the comparison of its production with that of IL-4.

As far as we know, no cytokine-targeting treatment has been tested in PPD-allergic patients. However, a good mouse model of PPD-induced CHS has been developed, in which (as in humans) Th2 and Th9 cytokines are key players. Indeed, *Stat6*$^{-/-}$ mice display an impaired ACD reaction associated with reduced *IL4* and *IL5* expression [63]. Whereas we have data showing increased IL-4 (but no IL-17) expression in PPD-induced CHS, another group reported no evidence of Th2 involvement in the model in BALB/c mice [64]. IL-24, which is also described as a Th2 cytokine, plays a detrimental role in PPD-induced CHS in mice: *Il24*$^{-/-}$ mice are less affected than WT mice and have a lower neutrophil infiltrate in the skin [61•]. Our data demonstrate that IL-9, in contrast, plays an anti-inflammatory role in the PPD-induced CHS model, as *Il9r*-deficient mice are more affected than WT mice [62•]. This may be a result of the capacity of Il-9 to activate regulatory T cells [65].

Isobornyl acrylate

Since 2014, several cases of isobornyl acrylate (IBOA) allergies have been described among diabetic patients using glucose sensors or insulin pumps. IBOA is found in many compounds (glues, coatings, etc.) and also in the plastic components of some medical devices [66•, 67]. As far as we know, nothing is known about the T cells and cytokines involved in this allergy, and studies assessing these are much needed. It is however a prime example in which antigen avoidance would be extremely challenging (except if manufacturers

were to change device composition), making alternatives such as biologics highly attractive.

Atopic dermatitis

Because compromised barrier function puts atopic dermatitis patients at risk of developing ICD or ACD [1], the therapy used in atopic dermatitis that helps limit subsequent development of ACD and ICD warrants discussion. Atopic dermatitis can be subdivided into two groups: extrinsic or allergic AD (IgE-associated) and intrinsic or non-allergic AD. Extrinsic or allergic AD is strongly associated with loss-of-function mutations in genes involved in the function of the cornified envelope, such as profilaggrin (*FLG*), loricrin (*LOR*), and involucrin (*IVL*) [68–70], that allow for the penetration of microbes, irritants, or allergens into the epidermis. As expected with IgE-associated diseases, AD is mainly mediated by Th2 cytokines such as IL-4, IL-5, and IL-13, and levels of these cytokines correlate with disease severity [71]. AD is also associated polymorphisms in *IL4* and *IL13*, and transgenic mice that overexpress Th2 cytokines develop spontaneous atopic dermatitis [72–74]. These cytokines induce decreased production of epidermal differentiation complex genes and antimicrobial peptide, respectively contributing to a defective skin barrier and an increase of skin infection by *Staphylococcus aureus* in patients with AD [75]. Moreover, the success of therapy with dupilumab, which inhibits receptor binding of IL-4 and IL-13, formally demonstrates the principal role of Th2 cytokines in this disease [76•, 77••]. Clinical trials in phase II and III have shown excellent safety and efficacy [76•, 78], and the phase III randomized study SOLO 1 and 2 showed AESI50 and EASI75 responses of 67% and 47.7%, respectively, compared with 13.3% and 23.3% for placebo controls [76•]. A second phase III clinical trial (CHRONOS) showed long-term safety and efficacy after 52 weeks of dupilumab treatment every other week, with EASI75 responses of 69% vs 23% in the placebo control [79]. Dupilumab treatment is associated with a decrease in AD markers such as Th2-, Th22-, and Th17-associated cytokines and epidermal hyperplasia markers, whereas expression of differentiation markers such as filaggrin increases [80•]. Currently, we do not know whether both IL-4 and IL-13 play central roles in AD processes. Clinical studies in phase II using anti-IL-13 antibodies (lebrikizumab or tralokinumab) showed moderate to efficacious improvement of EASI75 responses, particularly with monotherapy, where EASI75 response at week 16 reached 60.6% vs 24.3% in the placebo control group [81–83]. These results strongly suggest that IL-13 does at any rate play an important role in development of AD, even if differences in study design between the dupilumab and lebrikizumab trials prevent us from drawing any clear conclusions regarding the respective roles of the two cytokines. To further demonstrate the role of IL-13, Myles et al. showed that IL-24, another Th2 cytokine, is the mediator of IL-13-induced barrier dysfunction [84], downregulating filaggrin expression and thereby causing a deficit in skin barrier function. IL-24 is also likely responsible for increased infection by *S. aureus* via downregulation of IL-1β- and IL-17A-dependent pathways [85]. These results strongly suggest that IL-24 might be a potential target in this disease. Blockade of IL-31 with nemolizumab is another encouraging therapy, targeting the Th2-associated itch cytokine [86]. Phase IIb clinical trials have shown that the

treatment is well tolerated and AD patients present decreased pruritus, an effect likely responsible for the alleviation of sleep difficulties [86].

Although AD is mainly associated with a type II immune response, it is becoming obvious that other T helper cell populations also play a role, depending on AD subtypes, which in turn are based on IgE level, chronicity, mutations in genes involved in skin barrier function, race, and age. This last parameter was highlighted in a beautiful comprehensive study that compared AD profiles of different age groups and showed that cutaneous ($CD4^+CLA^+$) and systemic ($CD4^+CLA^-$) T helper profiles evolve with age [87••]. Th1 profile is very low at birth both in healthy and AD patients. It increases in adulthood, initially to similar levels in healthy and AD patients, seeming to correlate with disease activity in the chronic form of the AD. In contrast, CLA^+Th2 were similarly expanded in affected compared to control individuals, whatever the age. CLA^-Th2 is also increased after infancy, demonstrating a systemic immune activation that correlates with disease chronicity. IL-22 expression also significantly increased in affected adolescents and adults compared with their respective controls.

IL-22 directed therapy seems increasingly relevant for patients with an upregulation of this cytokine, given its regulation of terminal differentiation genes that contribute to skin barrier defects, and inflammatory processes associated with skin disorders. In this context, a randomized double-blind placebo control trial with fezakinumab, an anti-IL-22 antibody, has shown efficacy in severe AD patients but not in moderately affected patients, demonstrating the need for precision medicine. Fezakinumab every 2 weeks for 10 weeks gave a decrease in SCORAD and a downregulation of Th1-, Th2-, and Th17-associated genes in severe AD patients compared with placebo-treated patients [88•].

Other Th17 cytokines such as IL-17 and IL-26 are also upregulated in patients with AD, and correlations between some Th17 cytokines and SCORAD scores have been reported [89, 90]. In addition, Th17 cytokines seem to be more highly expressed in pediatric patients and in Asian patients [91]. IL-17 was reported to regulate Th2 response in spontaneous and induced mouse models of AD [92]. Nevertheless, the function of Th17 in patients is still debated. Unlike IL-22, IL-17 levels in the serum of AD patients do not correlate with disease activity [93]. Therapy targeting the p40 subunit, shared by IL-12 and IL-23 cytokines driving Th1 and Th17 differentiation, has given unclear results in AD [94, 95]. In phase II trials, for example, ustekinumab decreased Th1, Th2, Th17, and Th22 immune responses, suggesting efficacy, but did not improve clinical symptoms. Secukinumab, an anti-IL-17 antibody, was used in a pilot study of 52 weeks (NCT02594098) without clear benefits for patients [77••]. Moreover, anti-IL-17 treatment of psoriatic patients induced cutaneous eruption in 5.8% of patients after 4 months of treatment [96, 97], with about half presenting an atopic dermatitis-like rash [96]. These results suggest that targeting Th17-associated cytokines may not be useful in AD, except perhaps in certain subpopulations such as Asian patients.

Finally, Th9 cytokine is also increased in the skin and serum of children with AD and correlates with disease severity [98]. In addition, the rs31563 SNP (-4091G/A) in the *IL9* gene has been associated with increased susceptibility to AD [99], suggesting that it contributes to pathogenesis, although the mechanism is unknown.

Broad treatment approaches targeting signaling molecules common to multiple cytokine pathways, namely, JAK1, JAK2, and JAK3 [100], have been tested in AD, with some success. Phase II and III randomized, double-blinded studies have shown the efficacy of two topical JAK inhibitors, tofacitinib and delgocitinib [101]. This local therapy blocks various cytokines, including those involved in T helper cell differentiation, or those (such as IL-22) involved in barrier disruption. In addition, phase IIb and phase III studies have confirmed significant improvement in patients after oral monotherapy with baricitinib [102] and the JAK1 selective inhibitors upadacitinib and abrocitinib [103, 104]. It should be noted, however, that additional trials will be needed to define long-term efficacy and safety.

In summary, T helper cells of the Th2 axis seem to be the preponderant pathologic subtype in atopic dermatitis, even if other cytokines contribute to some forms of AD. Clinical trials across different world populations and AD subtypes are required to better define the role of these cytokines and identify the most appropriate treatments for each context.

Conclusions

All T helper cell subtypes can show increases in the three dermatitis disorders; however, it is Th2 that seems to play a central role in AD and ACD, as shown by the success of dupilumab therapy in both pathologies. In AD, IL-13 is clearly important, most probably via the induction of IL-24, which is likely also responsible for increased infection by *S. aureus*. In light of the fact that IL-24 also participates in allergic contact dermatitis, it would be of great interest to develop therapies targeting this cytokine. Moreover, side effects of such therapies may be more limited since keratinocytes, rather than immune cells, are the major target of this cytokine. Besides Th2 cytokines, we have observed that the Th9 cytokine IL-9 is massively increased in ACD induced by several allergens. Among the different T helper cytokines tested, IL-9 is by far the most strongly increased, and its levels correlate with positivity on patch tests, suggesting it is key at least in ACD, but probably also in AD. In addition, the difference in IL-9 expression could be helpful in the diagnosis of ACD and ICD because these two pathologies are sometimes very similar clinically. There is therefore a definite and urgent need for future studies to clearly demonstrate the role of this cytokine in inflammatory skin diseases.

Compliance with ethical standards

Conflict of interest

Perrine Cochez declares that she has no conflict of interest. Mathilde Choteau declares that she has no conflict of interest. Nisha Limaye declares that she has no conflict of interest. Marie Baeck declares that she has no conflict of interest. Laure Dumoutier declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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