

The Role of Leukocytes, Keratinocytes, and Allergen-Specific IgE in the Development of Atopic Dermatitis

Thomas Werfel¹

This review provides an overview of the inflammatory mechanisms and immunological aspects specific to atopic dermatitis. The review discusses publications on the roles of different T-cell subsets (that is, T helper 1 (Th1), Th2, T-regulatory, and Th17 cells), myeloid and plasmacytoid dendritic cells, and eosinophils. A further focus lies on keratinocyte-T-cell interactions, which may be of particular relevance in eczema. Mechanisms in innate and adaptive immunity that result in susceptibility to skin infections and in hyperreactivity to environmental stimuli, influencing the course and severity of atopic dermatitis, are summarized. Because the *Journal of Investigative Dermatology* has recently published reviews of specific features of barrier defects, defects in innate immunity, and, in this issue, genetics, these topics are only briefly discussed here in the context of immunology of atopic dermatitis.

Journal of Investigative Dermatology advance online publication, 9 April 2009; doi:10.1038/jid.2009.71

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that commonly begins in early infancy, runs a course of relapses and remissions, and is associated with a characteristic distribution and morphology of skin lesions. Furthermore, pruritus and consequent sleeplessness are hallmarks of AD. Numerous trigger factors have been identified for AD in recent decades, including inhaled allergens, food allergens, irritative substances, and infectious microorganisms, such as *Staphylococcus aureus* and *Malassezia* species (Werfel and Kapp, 1998; Akdis *et al.*, 2006; Leung *et al.*, 2007; Bieber, 2008).

A complex interaction between susceptibility genes encoding skin barrier molecules and markers of the inflammatory response, host environments, infectious agents, and specific immunologic responses are involved in the pathophysiology of AD. In this review, the focus is on the immunological and

inflammatory mechanisms. The immunohistology of the various phases of the disease are summarized, and the major cells involved in cutaneous inflammation are characterized. Clearly, the different T-cell subpopulations (CD4+ versus CD8+, T helper 1 (Th1) versus Th2 versus Th17; T-regulatory (T-reg) cells) deserve particular attention. In addition, it is now clear that dendritic cells (DCs) and keratinocytes are critical elements in the regulation of skin pathology in AD, and eosinophils may aggravate the inflammatory reaction.

An additional emphasis is placed on the role of specific IgE and T cells as well as the antigens that are recognized by these adaptive elements of the immune system.

IMMUNOHISTOLOGY

Asymptomatic skin in AD differs from normal skin: The underlying barrier defect is associated with filaggrin loss-of-function mutations in more than

30% of patients with AD. This finding was first published by Palmer *et al.* (2006) and then confirmed by several other groups (see reviews: Brown and McLean, 2009; O'Regan and Irvine, 2008). The filaggrin loss-of-function mutations are thought to lead to dry skin associated with a greater skin response to irritants than that of normal healthy skin. Microscopic studies revealed a sparse perivascular T-cell (Th2) infiltrate in unaffected AD skin that is not seen in normal healthy skin (Leung *et al.*, 1983). Mast cell numbers are also slightly enriched in asymptomatic skin.

Acute skin lesions are characterized by intensely pruritic, erythematous papules associated with excoriation and oozing exudation in AD. There is a marked infiltration of mononuclear cells that is histologically similar to that in allergic contact dermatitis.

CD4-positive Th cells dominate the cellular infiltrate in AD (Zachary *et al.*, 1985). The CD4/CD8 ratio of dermis-

¹Department of Immunodermatology and Allergy Research, Hannover Medical School, Hannover, Germany

Correspondence: Professor Thomas Werfel, Department of Immunodermatology and Allergy Research, Hannover Medical School, Ricklinger 5, Hannover, D-30629 Germany. E-mail: werfel.thomas@gmx.de

Abbreviations: AD, atopic dermatitis; CLA, cutaneous lymphocyte-associated antigen; DCs, dendritic cells; Fc ϵ RI, high-affinity receptor for IgE; IDECs, inflammatory dendritic epidermal cells; LCs, Langerhans cells; MHC, major histocompatibility class; pDCs, plasmacytoid DCs

Received 15 May 2008; revised 1 December 2008; accepted 7 January 2009

infiltrating T cells is similar to that in peripheral blood. Many intralesional T cells show signs of activation and can further be distinguished by CD45RO, a marker of T-memory cells, suggesting a previous contact with antigen or allergen, and by the cutaneous lymphocyte-associated antigen (CLA). CLA defines the subset of skin-homing T cells that bind to E-selectin, an adhesion molecule expressed by endothelial cells in inflamed tissues during the first step of leukocyte extravasation (Picker *et al.*, 1990; Santamaria Babi *et al.*, 1995). Many circulating CLA+ T cells display a Th2 phenotype and some are allergen specific (Akdis *et al.*, 1997). IL-12 appears to be a key cytokine in the regulation of CLA; CLA-negative Th2 cells rapidly upregulate $\alpha(1-3)$ -fucosyltransferase VII (involved in the expression of CLA) and CLA molecules (Biedermann *et al.*, 2006).

Mononuclear cells and eosinophil granulocytes can be found mainly in the dermis (Van Reijssen *et al.*, 1992). Mast cell degranulation can be observed in acute lesions. Antigen-presenting cells in lesional and, to a lesser extent, in nonlesional skin bear IgE molecules (Bieber, 2007; Novak *et al.*, 2007).

Chronic inflammation generally causes tissue remodeling, which is also observed in chronic lesions of AD. This can be observed as thickened plaques with increased skin markings (lichenification), increased collagen deposition in the dermis, and dry fibrotic papules. Dermal macrophages are markedly increased in the dermal infiltrate during the chronic phase. Intact eosinophils are less commonly found, but eosinophilic products can be identified in chronic lesions of AD. T cells remain present in the chronic phase, although in smaller numbers than seen in acute AD.

Taken together, both asymptomatic skin and the different stages of eczema are associated with the infiltration of leukocytes (mainly T cells) that characterizes the histology of this disease.

EARLY EVENTS IN AD DEVELOPMENT

Early events initiating atopic skin inflammation involve mechanical trauma and skin barrier disruption, which may

occur after the skin is scratched. This results in the rapid upregulation of proinflammatory mediators such as IL-1 α , IL-1 β , TNF- α , and GM-CSF (Homey *et al.*, 2006). These proinflammatory cytokines bind to receptors on the vascular endothelium, activate cellular signaling, and induce the expression of vascular endothelial cell adhesion molecules. These events initiate the process of adhesion to the endothelium, tethering, and transmigration of infiltrating cells. This process is tightly regulated and involves an active communication process between endothelial cells and leukocytes. T cell-endothelial cell interactions are thus crucial in acute AD. In addition, there is crosstalk between endothelial cells and other cutaneous cells, such as mast cells and perivascular dermal macrophages (Steinhoff *et al.*, 2006).

Once inflammatory cells have infiltrated into the tissue, they respond to chemotactic gradients established by cytokines and chemokines, which originate from sites of injury or infection. These molecules play a central role in defining the nature of the inflammatory infiltrate in AD. For example, IL-16 produced by Langerhans cells (LCs) may help in the recruitment of T cells and has been reported in AD lesions (Reich *et al.*, 2002). Several homeostatic and inflammatory chemokines, including CCL2 (MCP-1), CCL5 (RANTES), CCL17 (TARC), CCL18 (PARC), CCL29 (LARC), CCL22 (MDC), and CCL27 (CTACK), have been shown to be increased in AD and thus may support leukocyte recruitment (Homey *et al.*, 2006). Of note, cutaneous T-cell-attracting chemokine (CCL27) is significantly upregulated in AD and preferentially attracts cutaneous lymphocyte antigen-positive T cells into the skin. Selective recruitment of CCR4-expressing Th2 cells is mediated by macrophage-derived chemokine (CCL22) and thymus and activation-regulated cytokine (CCL17), which are increased in patients with AD. Interestingly, serum levels of a number of chemokines (for example, CCL17, CCL22, and CCL27) correlate with disease activity, suggesting an important role in the pathogenesis of AD (Homey *et al.*, 2006).

The maintenance of chronic AD involves the production of GM-CSF and the Th1-like cytokines IL-12 and IL-18 (Hamid *et al.*, 1994), as well as several remodeling-associated cytokines, such as IL-11 and TGF- β 1, which are expressed preferentially in chronic forms of the disease (Toda *et al.*, 2003).

In summary, early events include endothelial-T-cell interaction and the release of chemokines—the understanding of these events is of particular importance for a recurrent disease such as AD.

T-LYMPHOCYTES

CD4+ and CD8+ T cells in AD

Patients suffering from AD have increased levels of activated circulating T cells. A study revealing increased telomerase activity and shortened telomere length in AD indicates that T cells are chronically stimulated and have an increased cellular turnover *in vivo* (Wu *et al.*, 2000).

The high number of circulating T cells results from increased numbers of CD4+ cells, whereas the absolute number of CD8+ lymphocytes is normal or even decreased in peripheral blood. However, acute psychological stress has been shown to lead to rapid, significantly higher increases in the number of circulating CD8+ T-lymphocytes in AD patients compared with healthy controls. This may indicate that there are larger pools of this cell type close to the circulation that can be translocated into the blood during psychological stress (Schmid-Ott *et al.*, 2001a).

The role of CD8+ T cells in atopic skin inflammation is still not well defined. It has been shown that CLA+ CD8+ T cells isolated from the circulation are as potent as CLA+ CD4+ T cells in the induction of IgE and enhancement of eosinophil survival. This suggests that these cells have more than bystander functions in AD (Akdis *et al.*, 1999). Later, a significant association between the frequency of allergen-specific (that is, Der p 1-specific) CD8+ T cells and disease activity was described (Seneviratne *et al.*, 2002). Recent data from a mouse model indicate that allergen-primed CD8+ T cells are required for the

development of AD-like lesions *in vivo* (Hennino *et al.*, 2007).

In summary, although CD4+ cells clearly dominate over CD8+ cells in the skin in AD, there is some evidence that CD8+ cells are also of relevance in this disease.

T-cell cytokines in AD. The onset of acute AD is strongly associated with the production of Th2 cytokines, notably IL-4, IL-13, and IL-31, levels of which are significantly higher in AD individuals compared with control subjects (Hamid *et al.*, 1994; Neis *et al.*, 2006).

Th1 and Th2 cytokines may contribute to the pathogenesis of local skin inflammation in AD with the relative contribution of each cytokine dependent on the duration of the skin lesion. In previous studies, the majority of allergen-specific T cells derived from skin lesions that had been provoked by epicutaneous application of inhalant allergens were found to produce predominantly Th2 cytokines such as IL-4, IL-13, or IL-5. This was initially considered to be a specific feature reflecting immune dysregulation in AD (Sager *et al.*, 1992; Van Reijssen *et al.*, 1992). It was subsequently shown that the expression of IFN- γ rather than of IL-4 predominates in spontaneous or older patch test lesions in AD (Grewe *et al.*, 1995; Thepen *et al.*, 1996). Importantly, patient treatments that resulted in lesion improvement could be correlated with downregulation of IFN- γ expression, but not of IL-4, in the skin (Grewe *et al.*, 1995). Also, allergen-specific T-cell clones from spontaneous AD lesions differed from allergen-specific T cells isolated from inhalant allergen patch test lesions by virtue of their capacity to produce IFN- γ (Werfel *et al.*, 1996).

The cytokine switch from Th2 in the acute phase toward Th1 in the chronic phase is accepted for AD and appears to be relevant in allergic contact dermatitis as well.

Factors contributing to cytokine milieu in AD. In patients with AD, activated T cells with skin-homing properties, which express high levels of IFN- γ , may predominantly undergo apoptosis in the circulation, skewing the immune

response to surviving Th2 cells as a mechanism for Th2 predominance in the circulation and in acute lesions (Akdis *et al.*, 2003; Akkoc *et al.*, 2008). Moreover, patients with AD have a genetic background of a general systemic Th2 polarization (Brown and McLean, 2009), which contributes to the higher number of circulating T cells capable of producing Th2 cytokines.

IL-4, which is a strong inducer of a type 2 cytokine milieu itself, is produced by "early" skin-infiltrating T cells, but it may also come from mast cells, basophils, or eosinophils during an acute eczematous skin reaction. It is interesting to note that the high frequency of IL-4-producing T cells in the skin is not necessarily associated with atopy given that mRNA for IL-4 and T cells expressing IL-4 are also found in nickel-induced patch test reactions (Neis *et al.*, 2006; Szepietowski *et al.*, 1997; Werfel *et al.*, 1997b).

Acute lesions show a reduced expression of IL-12, a key cytokine of Th1 polarization, which was shown at the mRNA level by *in situ* hybridization in acute skin lesions (Hamid *et al.*, 1996). The reason for the relative lack in the expression of IL-12 is not completely understood. sCD40L was shown to inhibit IL-12 upregulation by an intracellular ERK-dependent signal-transducing pathway (Wittmann *et al.*, 2002). These results were reproduced later and extended to skin-infiltrating CD40L+ T cells, which may thus contribute to the relative inability to upregulate IL-12 in acute eczema, leading to a refractory state of constitutive antigen-presenting cells (Wittmann *et al.*, 2004).

A number of factors may be involved in the switch from Th2 to Th1 cytokines in older lesions. The polarization of T cells along the Th1 lineage, resulting in IFN- γ production, is supported by IL-12, IL-23, IL-27, and IL-18 (Hunter, 2005). IL-12 subunits have been found to be expressed by antigen-presenting cells and by human keratinocytes. However, it is not clear whether keratinocytes are indeed a relevant source of bioactive IL-12. IL-23 has recently been shown to be produced by DCs and by human cultured keratinocytes in healthy skin

and in psoriasis—its role in AD has to be defined (Piskin *et al.*, 2006). Interaction with activated T cells via CD40-CD40L may enhance IL-23 production by keratinocytes, which may enhance IFN- γ production by memory T cells (Wittmann and Werfel, 2006).

IL-18 is another cytokine that functions in parallel with IL-12 (Dinarello, 2007). Keratinocytes functionally respond to IL-18 with upregulation of major histocompatibility class (MHC) I, reinforcement of the IFN- γ -induced MHC class II expression, and production of the chemokine CXCL10 (Wittmann *et al.*, 2005). This supports the notion that IL-18 is involved in the pathogenesis of local Th1 responses in chronic inflammatory skin diseases.

The molecular mechanism of the cytokine switch from Th2 in the acute phase to Th1 in the chronic phase is complex and involves different Th2 cytokine-producing cells in the acute phase (for example, T cells, basophils, mast cells) and Th1-polarizing cytokines, which are produced primarily by antigen-presenting cells.

Effects of T-cell cytokines on the inflammatory reaction in the skin in AD. In lymphoid organs, IL-4 and IL-13 mediate the IgE isotype switch in B cells. In acute eczema, IL-4 and IL-13 induce a variety of local responses, such as the induction of the adhesion molecules on endothelial cells and Fc receptors on eosinophils or chemokines (Leung *et al.*, 2004). In contrast to IL-5, IL-4 induces apoptosis in eosinophils (Wedi *et al.*, 1998).

Recent findings demonstrate that IL-4 and IL-13 have effects on keratinocytes: both cytokines function via the same receptor (Purwar *et al.*, 2007b). IL-13- or IL-4-stimulated keratinocytes attract CCR4+ CD4+ Th2 cells via CCL22 (Purwar *et al.*, 2006). Moreover, IL-13 induces the expression of MMP-9 in keratinocytes (Purwar *et al.*, 2007a), which may play a crucial role in atopic skin inflammation by facilitating the migration of leukocytes into the epidermis.

Some AD patients have a filaggrin loss-of-function mutation leading to reduced filaggrin expression in the skin (Brown and McLean, 2009). Recently it

was shown that filaggrin expression was reduced in AD even in the absence of a loss-of-function mutation (Howell *et al.*, 2007). Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibited significantly reduced filaggrin gene expression compared with medium alone. Neutralization of IL-4 and IL-13 may improve skin barrier integrity (Howell *et al.*, 2007). This indicates that the atopic immune response directly contributes to the skin barrier defect in AD.

A “new” Th2-associated cytokine, IL-31, has been shown to be highly expressed in acute eczema (that is, in both acute atopic and acute allergy contact dermatitis) (Neis *et al.*, 2006). IL-31 is produced by T cells that express CLA and localize to the skin (Bilsborough *et al.*, 2006). It appears to be a link between skin-infiltrating T cells and pruritus in the skin, as demonstrated in a mouse model (Takaoka *et al.*, 2006). In humans, IL-31 is significantly overexpressed in itching skin inflammation such as AD (Sonkoly *et al.*, 2006; Raap *et al.*, 2008). Staphylococcal superantigens and histamine induce IL-31 expression in atopic individuals (Gutierrez *et al.*, 2009). These data suggest that IL-31 may be an itch-causing mediator in patients with AD derived from skin-infiltrating T cells.

In chronic lichenified AD skin lesions, fewer IL-4 and IL-13 mRNA-expressing cells are present, but greater numbers of IL-5, GM-CSF, IL-12, and IFN- γ mRNA-expressing cells are detected (Hamid *et al.*, 1994). The rise in IL-5 expression during the transition from acute to chronic AD probably plays a role in the prolongation of eosinophil survival and function (Wedi *et al.*, 1999). Some of the other cytokines mentioned above support the function of macrophages and promote the Th1-type inflammation more characteristic of chronic AD (Fiset *et al.*, 2006). Effects of IFN- γ on keratinocytes are discussed below.

In summary, T-cell cytokines have numerous effects on skin inflammation, ranging from the induction of chemokines and downmodulation of barrier-associated molecules to the induction of pruritus.

Th17 lymphocytes in AD

Recently, a novel and unique subset of IL-17-producing CD4⁺ Th17 cells, distinct from Th1 and Th2 cells, was discovered. Th17 cells appear to be involved in protection against bacterial pathogens. In addition, Th17 cells may also be crucial in the pathogenesis of various chronic inflammatory diseases that were formerly categorized as Th1-mediated disorders. Whereas IL-17 may play an important role in the pathogenesis of psoriasis and contact hypersensitivity, its role in AD is still under investigation (van Beelen *et al.*, 2007). In skin biopsy specimens recovered from acute and chronic skin lesions from patients with AD, IL-17 mRNA was preferentially associated with acute lesions (Toda *et al.*, 2003). In a recent study, the percentage of Th17 cells was shown to be higher in the peripheral blood of AD patients and associated with the severity of AD. Immunohistochemically, IL-17⁺ cells infiltrated the papillary dermis of atopic eczema more markedly in acute lesions than in chronic lesions (Koga *et al.*, 2008).

Epicutaneous immunization with ovalbumin, which causes allergic skin inflammation with many characteristics of the skin lesions of AD in a mouse model, was found to drive IL-17 expression. Epicutaneous, but not intraperitoneal, immunization of mice with ovalbumin drove the generation of IL-17-producing T cells in both the spleen and the draining lymph nodes and increased serum IL-17 levels. DCs trafficking from skin to lymph nodes expressed more IL-23 and induced more IL-17 secretion by naive T cells. This was inhibited by neutralizing IL-23 *in vitro* and by intradermal injection of anti-TGF- β -neutralizing antibody *in vivo*. These data suggest that initial cutaneous exposure to protein antigens may selectively induce the production of IL-17 in AD (He *et al.*, 2007).

Taking together these findings, Th17 cells are present in the skin of AD. The role of these cells in acute eczema for the course of AD remains to be elucidated.

T-reg cells in AD

T-reg cells control the activation of autoreactive and T-effector cells and are crucial for the maintenance of

peripheral tolerance to self-antigens. CD4⁺ Foxp3⁺ T-reg cells have been referred to as “naturally occurring” T-reg cells to distinguish them from adaptive T-reg cells, which are generated upon activation. A major population of adaptive T-reg cells is characterized by the secretion of high levels of IL-10 or transforming growth factor (Akdis *et al.*, 2005). Mutations in FOXP3, a nuclear factor expressed in natural T-reg cells and a subpopulation of adaptive T-reg cells, result in immune dysregulation polyendocrinopathy enteropathy X-linked syndrome characterized by hyper-IgE, food allergy, and eczema (Torgerson and Ochs, 2007), which suggests a possible role of T-reg cells in AD.

Increased numbers of peripheral blood CD4⁺ CD25⁺ T cells and an overexpression of FOXP3 have been found in the blood of AD patients compared with psoriasis patients and healthy controls (Ou *et al.*, 2004). Staphylococcal enterotoxin B inhibits natural T-reg cells *in vitro* (Ou *et al.*, 2004). Superantigens have been shown to upregulate glucocorticoid-induced TNF-receptor-related protein ligand on monocytes, resulting in the proliferation of natural T-reg cells and abrogation of their immunosuppressive activity (Cardona *et al.*, 2006).

In the skin, adaptive T-reg cells, but no FOXP3⁺ natural T-reg cells, were detectable in AD in a series of biopsies from eight AD patients (Verhagen *et al.*, 2006). However, in recent studies, the numbers of FOXP3⁺ natural T-reg cells were similar or higher in AD patients compared with healthy controls (Franz *et al.*, 2007; Schnopp *et al.*, 2008). It is noteworthy that the number of natural T-reg cells did not change significantly after medium-dose UVA-1 radiation (Schnopp *et al.*, 2007).

In summary, most recent studies have identified T-reg cells in the skin of AD patients. It remains to be determined whether the differences in functional activities of T-reg cells shown *in vitro* are relevant for the course of AD *in vivo*.

DCs

Myeloid DCs in AD

DCs are specialized antigen-presenting cells found in lymphoid tissues and in

peripheral organs such as the skin. Two major subtypes of DCs have been shown to play an important role in the pathophysiology of AD in humans: myeloid DCs and plasmacytoid DCs (pDCs) (Novak *et al.*, 2007).

Myeloid DCs can be further differentiated into two subtypes that have been found in lesional skin of AD patients: LCs and inflammatory dendritic epidermal cells (IDECs). Both LCs and IDECs express the high-affinity receptor for IgE (FcεRI) (Bieber, 2007), but they have different functions in AD. LCs play a predominant role in the initiation of the allergic immune response and prime naive T cells into T cells of the Th2 type with high IL-4-producing capacity, which predominate in the initial phase of AD (Novak *et al.*, 2004). Activated LCs can also present allergen-derived peptides to antigen-specific T cells in the skin. The aggregation of FcεRI on the surface of LCs induces the release of chemotactic factors (for example, CCL2, CCL22, CCL17, or IL-16) and may facilitate allergen presentation to T cells (Maintz and Novak, 2007).

IgE-bearing FcεRI+ IDECs become more prominent in chronic AD lesions. After allergen challenge, invasion of high numbers of IDECs has been shown, emphasizing their crucial role in the development of eczema (Kerschenlohr *et al.*, 2003). IDECs are also found exclusively at inflammatory sites, suggesting an involvement in cell recruitment and IgE-mediated antigen presentation to T cells. In contrast to LCs, these cells promote Th1 cytokine production from T cells. In this context it has been shown that stimulation of FcεRI on the surface of IDECs induces the release of IL-12 and IL-18. This may contribute to the switch from the initial Th2 immune response in acute AD to the Th1 polarization of T cells in the chronic phase (Novak *et al.*, 2004).

In summary, both resident and infiltrating myeloid DC populations are crucial in AD. The expression of Fc receptors for IgE on these cells may be of importance for facilitated allergen presentation in AD.

pDCs

Activated pDCs are able to produce antiviral type I interferons. pDCs in the peripheral blood of patients with AD have been shown to bear the trimeric variant of FcεRI on their cell surface, which is occupied by IgE molecules. pDCs can take up allergens by FcεRI-IgE, process them, and promote Th2-type immune responses (Novak *et al.*, 2007). Increased numbers of pDCs have been found in the peripheral blood of AD patients, but only low numbers of pDCs are detectable in skin lesions in AD, in contrast to other inflammatory skin diseases (Wollenberg *et al.*, 2002).

The lack of pDCs in the skin has been shown to contribute to the high susceptibility of AD patients to viral skin infections, such as herpes simplex-induced eczema herpeticum.

KERATINOCYTE-T-CELL INTERACTIONS

There is growing evidence supporting keratinocytes as enhancer cells of the inflammatory response in AD (Wittmann and Werfel, 2006; Holgate, 2007). Keratinocytes play a role in innate immunity by expressing Toll-like receptors and producing antimicrobial peptides in response to invading microbes (McGirt and Beck, 2006; De Benedetto *et al.*, 2009).

Keratinocytes secrete a unique profile of chemokines and cytokines after exposure to proinflammatory cytokines (Figure 1A and B). Keratinocyte-derived thymic stromal lymphopoietin (TSLP) may be of particular importance in AD (Soumelis and Liu, 2004; Homey *et al.*, 2006): This protein is not detected in normal skin or in nonlesional skin in patients with AD, but it is highly expressed in lesions in both acute and chronic AD. TSLP instructs human DCs to create a Th2-permissive microenvironment by inducing the expression of OX40L, which triggers the differentiation of inflammatory Th2 cells (Ito *et al.*, 2005). Recently it was shown that TSLP, synergistically with IL-1 and TNFα, stimulates the production of high levels of Th2 cytokines by human mast cells. In that study, TSLP was shown to be released by primary epithelial cells in response to microbial

products, physical injury, or inflammatory cytokines (Allakhverdi *et al.*, 2007). Moreover, a recent paper demonstrated a strong link between TSLP and skin barrier disruption (Demehri *et al.*, 2008).

The general role of chemokines in the initiation and perpetuation of AD has been reviewed by Homey *et al.* (2006). Keratinocytes stimulated with proinflammatory cytokines have been identified as an important cellular source of chemokines, which attract T cells of different subtypes (Wittmann and Werfel, 2006). For example, CXCR3 ligands such as CXCL10 preferentially attract Th1 cells (Albanesi *et al.*, 2001). CCL22 and CCL17 preferentially attract Th2 cells by binding to CCR4 (Purwar *et al.*, 2006). CCL2 is effective on both Th1 and Th2 subsets. CCL27, which is constitutively expressed by keratinocytes, binds to CCR10 expressed on most skin-homing lymphocytes (Homey *et al.*, 2002).

Keratinocytes are also important cellular sources of cytokines such as the T-cell growth factor IL-15 in the skin (Han *et al.*, 1999) (Figure 1B). IL-15 has been implicated in the pathogenesis of different skin diseases by virtue of its action on the maintenance of T cells—possibly intraepithelial T cells.

Keratinocytes respond to both Th1 and Th2 cytokines from T cells (Figure 1C). Among them, IFN-γ is one of the most potent keratinocyte-activating factors. It induces surface molecules (for example, ICAM-1, MHC class I and II, CD40, and Fas), chemokines (for example, CCL2, CCL3, CCL4, CCL5, CCL18, CCL22, and CXCL10) and cytokines (for example, IL-1, IL-6, IL-18, and TGF-β) in keratinocytes. Many other molecules, such as matrix metalloproteinases, growth factors, enzymes, and transcription factors/pathway molecules, are also upregulated. (Homey *et al.*, 2006; Wittmann and Werfel, 2006). Pastore *et al.* (1998, 2000) observed differences in the responsiveness to cytokines of keratinocytes from AD patients as compared with healthy controls or psoriasis patients (Giustizieri *et al.*, 2001).

It has been shown that IFN-γ induces Fas on keratinocytes, which

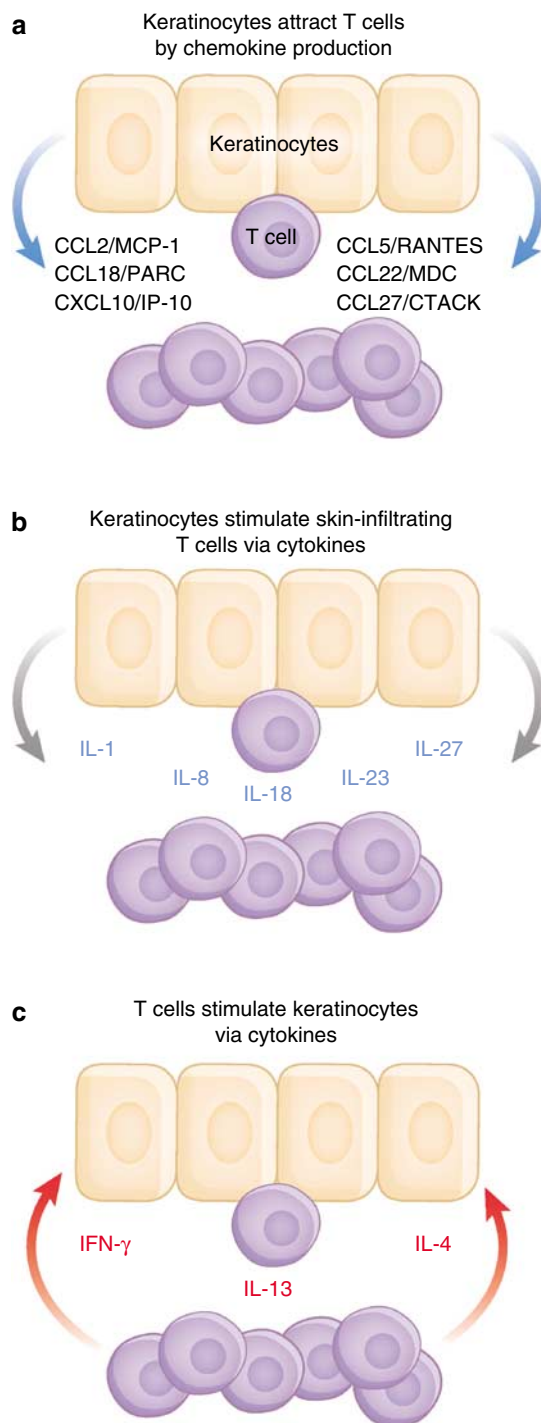


Figure 1. Keratinocyte–T-cell interactions. (a) Keratinocytes attract T cells by chemokine production. (b) Keratinocytes stimulate skin-infiltrating T cells via cytokines. (c) T cells stimulate keratinocytes via cytokines.

renders them susceptible to apoptosis induction by infiltrating FasL⁺ T cells (Trautmann *et al.*, 2000). This has been interpreted as an important event in eczema, mainly in AD. There is further evidence that cleavage of E-cadherin and sustained desmosomal cadherin

contacts between keratinocytes that are undergoing apoptosis result in spongiiform morphology in the epidermis. This morphology is regarded as a hallmark of eczematous lesions (Trautmann *et al.*, 2001). Suppression of keratinocyte activation and apoptosis

thus remains a potential target for the treatment of AD (Akdis *et al.*, 2006).

Both CXCR3⁺ CD4⁺ and CCR4⁺ CD4⁺ T cells migrate in response to IFN- γ -treated human primary keratinocytes (Purwar *et al.*, 2006). It is interesting to note that IFN- γ also induces CCL22 production in human keratinocytes. Many IFN- γ -inducible molecules are reinforced by IL-4 or IL-13 in human keratinocytes, such as CD54, CCL2, CCL5, and CXCL10 (Albanesi *et al.*, 2000; Purwar *et al.*, 2006).

Keratinocytes have been shown to express the IL-1 and IL-33 receptor, ST2, in the acute phase of eczema in AD. A significant genetic association between AD and a single-nucleotide polymorphism has been found in the distal promoter region of the ST2 gene (Shimizu *et al.*, 2005). This polymorphism is associated with an upregulation of the transcriptional activity of the ST2 gene. The ligand of ST2, IL-33, induces the expression of IL-4, IL-5, and IL-13 *in vivo*, which may explain higher IgE serum levels found in patients with the ST2 polymorphism in AD.

Taken together, these observations suggest that keratinocytes are important regulatory and effector cells in skin diseases involving the epidermis as a particular feature.

EOSINOPHILS

Eosinophils play an important role in AD, characterized by activated eosinophils in the peripheral blood and in the lesional skin (Leiferman *et al.*, 1985; Kapp, 1993; Simon *et al.*, 2004). Increased numbers of circulating eosinophils are frequently observed in patients with AD. Inhibition of eosinophil apoptosis in AD, probably mediated by IL-5 and GM-CSF, appears to be a relevant mechanism for the eosinophil accumulation observed in AD (Wedi *et al.*, 1999). Interestingly, acute psychosocial stress leads to further increases in eosinophil counts and IL-5⁺ T cells in the peripheral blood (Schmid-Ott *et al.*, 2001a, b).

Eosinophils are recruited to tissue sites mainly by chemokines (for example, eotaxin and RANTES (regulated on activation, normal T-cell expressed and secreted)). A survey on the chemokine receptor repertoire of human peripheral

blood eosinophils draws a confusing picture of receptors (Homey *et al.*, 2006). However, the expression of CCR3 on eosinophils seems to be of particular importance; a number of findings suggest that CCR3-driven pathways are essential for the recruitment of eosinophils to sites of atopic skin inflammation (Hoechstetter *et al.*, 2000). In the skin lesions of AD, CCR3 ligands are candidates that mediate the influx of eosinophils into the skin (Gombert *et al.*, 2005).

The interaction of eosinophil surface molecules with endothelial cell vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 are important for eosinophil extravasation and activation. Activated eosinophils are capable of releasing a variety of potent cytotoxic granule proteins and chemical mediators contributing to tissue inflammation (Elsner and Kapp, 1999), as shown by the deposition of eosinophil products in the inflamed skin (Bruijnzeel-Koomen *et al.*, 1992).

Eosinophils play a relevant role in neuroimmunologic interactions—enhanced levels of brain-derived growth factor can be detected in the sera and plasma of patients with AD. Brain-derived growth factor has been shown to reduce eosinophil apoptosis while enhancing chemotaxis of eosinophils *in vitro* (Raap *et al.*, 2006).

In summary, eosinophils infiltrate the skin of AD patients and aggravate the inflammatory response.

DEFECTS IN THE INNATE IMMUNE RESPONSE IN AD

Most patients with AD are colonized with *Staphylococcus aureus* and experience exacerbation of their skin disease after infection with this organism (De Benedetto *et al.*, 2009). In patients with AD with bacterial infection, treatment with anti-staphylococcal antiseptics and antibiotics can result in the improvement of skin lesions (Breuer *et al.*, 2002). Binding of *S. aureus* to skin is enhanced by AD skin inflammation. This is supported by clinical studies demonstrating that treatment with topical corticosteroids or tacrolimus reduces *S. aureus* counts in AD.

Recent evidence suggests that a deficiency of the antimicrobial peptides dermcidin, cathelicidin LL-37, human β -defensin (HBD)-2, and HBD-3 contributes to the susceptibility of atopic patients to skin infections (McGirt and Beck, 2006). Defensins are broad-spectrum antibiotics that kill bacterial and fungal pathogens. LL-37 has been shown to display antimicrobial activity against viral pathogens in addition to bactericidal and fungicidal actions (Howell *et al.*, 2006). The expression of antimicrobial peptides by keratinocytes is increased in response to inflammatory cytokines. However, IL-4 and IL-13 have been shown to downregulate the expression of β -defensins and of LL-37 in the skin in AD (Ong *et al.*, 2002; Nomura *et al.*, 2003; Howell *et al.*, 2006). This can predispose to *S. aureus* colonization and to severe eczema herpeticum.

Recently it was shown that monocytes from AD patients are functionally defective in their ability to produce proinflammatory cytokines on Toll-like receptor 2 stimuli (Hasannejad *et al.*, 2007; Niebuhr *et al.*, 2009). Moreover, Toll-like receptor 2 with a single-nucleotide polymorphism was found in higher frequency in patients with severe AD compared with control groups (Ahmad-Nejad *et al.*, 2004). Cells with this polymorphic Toll-like receptor 2 show altered responses to peptidoglycans and lipoteichoic acid from staphylococcal cell walls, which may further contribute to the innate immune defect in AD (Niebuhr *et al.*, 2008 and Mrabet-Dahbi *et al.*, 2008).

Patients with the head and neck variant of AD are frequently colonized with *Malassezia* species (Scheynius *et al.*, 2002). *Malassezia sympodialis* cells produce, express, and release allergens to a greater extent when cultured at the higher pH resembling the high pH in the skin of AD. This was particularly true of the major allergen Mala s 12, suggesting that the skin barrier in AD patients provides an environment that can enhance the release of allergens from *M. sympodialis*, which can in turn contribute to the inflammation (Selander *et al.*, 2006).

Together, these findings indicate that a number of constitutive and

acquired defects of innate immunity may explain the predisposition of the skin in AD to bacterial, viral, or fungal infection or colonization.

IgE IMMUNOREACTIVITY

In approximately 80% of adult patients with AD, the disease is associated with increased serum IgE levels ($>150 \text{ kU l}^{-1}$), sensitization to aeroallergens and food allergens, and/or concomitant food allergy, allergic rhinitis, and asthma (Werfel and Kapp, 1998; Leung *et al.*, 2004). Recent epidemiologic data suggest a contributory role for IgE-mediated immunologic processes in the onset and course of AD, especially in patients with severe disease. (Williams and Flohr, 2006).

However, 20% of adult patients with eczematous skin lesions clinically and histologically indistinguishable from AD lack sensitization and other clinical manifestations of the atopic diseases. This subtype of AD often has a late onset (>20 years of age) and a lack of IgE sensitization to inhalant or food allergens (Werfel and Kapp, 1999; Novak and Bieber, 2003). In children, a transient form of AD with low IgE serum levels and without any detectable sensitization has been observed; it develops into the extrinsic variant of AD with increasing IgE serum levels and development of sensitization to aeroallergens and food allergens later in life (Novembre *et al.*, 2001).

Despite the clinical similarity, AD patients with IgE-mediated allergy exhibit higher tissue eosinophilia, enhanced lesional cytokine expression, and higher surface expression of the Fc ϵ RI on epidermal DCs compared with non-allergic eczema patients.

Specific IgE may play a critical role in cutaneous inflammation in the activation of mast cells and DCs via high-affinity Fc receptors (Bieber, 2007). IgE-mediated histamine release from cutaneous mast cells may aggravate AD through the itch-scratch cycle. Moreover, increased cutaneous inflammation, mediated via histamine receptors, on T-lymphocytes (Jutel *et al.*, 2001; Gutzmer *et al.*, 2009), antigen-presenting cells (Gutzmer *et al.*, 2005; Gutzmer *et al.*, 2005; Dijkstra *et al.*, 2007), and keratinocytes (Giustizieri

et al., 2004) is probable. IgE-facilitated allergen presentation by DCs and activation of DCs via high-affinity Fc receptors in the skin are discussed above (Bieber, 2007).

Despite many *in vitro* and *ex vivo* findings, the importance of IgE to the clinical severity of AD is difficult to evaluate. In a recent study of adult patients with AD, it became clear that patients with greater IgE-mediated sensitization suffer from more severe disease (Salt *et al.*, 2007). In proof-of-concept trials, some—but not all—patients treated with anti-IgE antibodies improved in terms of eczema severity (Lane *et al.*, 2006; Vigo *et al.*, 2006; Belloni *et al.*, 2007; Forman and Garrett, 2007). However, extremely high total IgE serum levels in AD present a major problem for treatment with anti-IgE. A controlled study with anti-IgE is therefore required (Beck and Saini, 2006).

In summary, specific IgE not only is relevant to immediate reactions but may contribute to delayed eczematous skin reactions in AD as well.

ALLERGEN-SPECIFIC T CELLS

Primary T-cell immunodeficiency disorders are frequently associated with high serum IgE levels and eczematous skin lesions, which clear after successful bone marrow transplantation (Akdis *et al.*, 2006). In animal models of AD, the eczematous rash does not occur in the absence of T cells (Spergel *et al.*, 1999).

FOOD ALLERGENS

Food allergy and AD may occur in the same patient. In addition to typical immediate types of allergic reactions (that is, noneczematous reactions), which are observed in AD patients, foods can provoke flares of AD; this has been demonstrated in placebo-controlled food challenge studies (Werfel and Breuer, 2004). The serum levels of food-specific IgE can be predictive for the outcome of oral provocation tests with foods, as observed in cohort studies with children with AD who had immediate reactions to foods (Sampson, 2001; Mehl *et al.*, 2005). Specific T cells have been shown to be involved in the late eczematous response to food; higher proliferative

responses to food proteins and specific T-cell clones can be generated from patients with food-induced eczema (Reekers *et al.*, 1996; Werfel *et al.*, 1997a; van Reijsen *et al.*, 1998). In addition, milk-induced eczema has been reported to be associated with a higher rate of CLA⁺ lymphocytes upon *in vitro* stimulation with casein (Abernathy-Carver *et al.*, 1995).

A murine model of food-induced AD confirmed the important role of food-specific T cells in eczema. C3H/HeJ mice were orally sensitized to cow's milk or peanuts and then subjected to low-grade allergen exposure. An eczematous eruption developed in approximately one-third of mice after low-grade exposure to milk or peanut proteins. Histologic examination of the lesional skin revealed spongiosis and a cellular infiltrate consisting of CD4⁺ lymphocytes, eosinophils, and mast cells. IL-5 and IL-13 mRNA expression was elevated only in the skin of mice with the eczematous eruption (Li *et al.*, 2001).

Patients sensitized to pollen allergens often develop an IgE-response to cross-reactive food allergens. Consumption of birch pollen-related foods such as hazelnuts, carrots, apples, and celery (that is, foods that are cross-reactive to birch pollen allergens, mainly the major allergen Bet v1) may lead to an exacerbation of eczema in a subpopulation of patients with AD sensitized to birch pollen antigens. A birch pollen-specific T-cell response could be detected in lesional skin of these responding patients (Reekers *et al.*, 1999): Birch pollen-related food may also induce allergic symptoms in a subgroup of children with AD (Breuer *et al.*, 2004). Recently, Bohle *et al.* (2006) showed that T-cell cross-reactivity between Bet v1 and related food allergens can occur independent of IgE cross-reactivity *in vitro* and *in vivo*. In patients with AD, the resulting immune reaction that manifested as late eczematous skin reactions to cooked food was shown to elicit T cell- but not IgE-mediated responses.

In summary, T-cell responses and specific IgE to food allergens may explain flare-ups of eczema upon oral food challenges in sensitized patients with AD.

AEROALLERGENS

Pruritus and skin lesions can develop after intranasal or bronchial inhalation challenge with aeroallergens in patients with AD. Epicutaneous application of aeroallergens (house dust mites, weeds, animal danders, and molds) on asymptomatic skin of patients with AD elicits eczematous reactions in a subgroup of patients with AD. The so-called atopy patch test has been used in recent years as a model for studying allergen-induced changes in the skin of AD patients (Darsow *et al.*, 2004; Turjanmaa *et al.*, 2006). Aeroallergen-specific T cells were first isolated from skin sites from atopy patch test lesions (Sager *et al.*, 1992; Van Reijsen *et al.*, 1992). Similar techniques were applied later to isolate aeroallergen-specific T cells from spontaneous lesional skin (Werfel *et al.*, 1996).

A combination of effective measures to control house dust mites has been reported to improve AD, but the clinical effect varied in different clinical studies (Tan *et al.*, 1996; Holm *et al.*, 2001; Oosting *et al.*, 2002).

Specific immunotherapy directly addresses an adaptive mechanism in hypersensitivity reactions. A recent meta-analysis of specific immunotherapy studies revealed positive effects of subcutaneous immunotherapy in the majority of studies performed to date on AD (Bussmann *et al.*, 2006). In the largest cohort study, subcutaneous immunotherapy with mite allergens was effective in moderate to severe AD (Werfel *et al.*, 2006). In contrast, sublingual immunotherapy with mite allergens, which has recently been studied in children with AD, was effective only in patients with mild eczema (Pajno *et al.*, 2007). During specific immunotherapy of AD, the level of the tolerogenic cytokine IL-10 increased in the sera of patients, whereas the levels of CCL17 and IL-16 decreased (Bussmann *et al.*, 2007).

In summary, evidence of the clinical role of adaptive immune responses to aeroallergens for AD come from atopy patch tests and therapy studies on specific immunotherapy.

MICROBIAL ALLERGENS

S. aureus can exacerbate AD by secreting exotoxins. Some of them function

as superantigens, which stimulate activation of T cells and MHC+ antigen-presenting cells, macrophages, or keratinocytes. Major effects elicited by superantigens are summarized in Figure 2A. Some patients with AD produce specific IgE antibodies directed against staphylococcal superantigens (Figure 2B), to an extent that correlates with skin disease severity (Bunikowski *et al.*, 1999; Breuer *et al.*, 2000).

Superantigens have been shown to penetrate into the dermis (Skov *et al.*, 2000), and higher doses have been shown to induce cutaneous inflammation when applied to the skin in patch tests (Strange *et al.*, 1996). Low doses that do not induce visible clinical inflammation are still able to amplify aeroallergen-induced patch test responses (Langer *et al.*, 2007).

There is increasing evidence that the opportunistic yeast *Malassezia* species is a contributing factor in AD. Several studies have demonstrated the presence of specific serum IgE, a positive skin prick test response, and a positive patch test response against *Malassezia* species in adults with AD (Scheynius *et al.*, 2002). IgE sensitization to *Malassezia* species is specific for patients with AD; it is not seen in patients with asthma or allergic rhinitis (Scalabrin *et al.*, 1999; Schmid-Grendelmeier *et al.*, 2006).

Within “non-allergic” patients with atopic eczema, some exhibit IgE sensitization against microbial antigens, such as *S. aureus* enterotoxins and *Candida albicans* or *M. sympodialis* antigens (Novak *et al.*, 2003). The presence of specific IgE to *Malassezia* antigens in the non-allergic variant of AD was confirmed in a recent study (Casagrande *et al.*, 2006). In a larger cohort, however, it was found that antimicrobial IgE antibodies were uncommon in patients with AD with low IgE levels (Reefer *et al.*, 2007).

In summary, microbial allergens may worsen the skin condition in AD.

SELF-ALLERGENS

Autoimmunity to human proteins may also contribute to the pathophysiology of AD. IgE against autoantigens has been shown to stimulate type 1 hypersensitivity reactions and DCs (Valenta, 2009). Autoallergens induce the proliferation of CLA+ autoreactive T cells in the blood, and T-cell clones specific for autoallergens can be generated from the skin of patients with AD (Heratizadeh *et al.*, submitted). Interestingly, autoallergen-specific IgE was found as early as in infancy in AD (Mothes *et al.*, 2005). Cross-reactivity between inhaled allergens and autoantigens may lead to autoimmunity: For example, IgE against manganese superoxide dismutase (MnSOD) from the skin-colonizing yeast *M. sympodialis* cross-reacts with human MnSOD. Patients with AD sensitized to human MnSOD have been shown to also be sensitized against the *M. sympodialis* MnSOD (Schmid-Grendelmeier *et al.*, 2005).

Lens epithelium-derived growth factor/dense fine speckles 70 kDa protein (LEDGF/DFS70) is another defined autoantigen in patients with AD. Autoantibodies to this protein have been found in Japan in approximately 30% of AD patients. It is located predominantly in the nucleus of the basal epidermal cells and translocates into the cytoplasm during differentiation. Once in the cytoplasm, LEDGF/DFS70 accumulates in the keratohyalin granules in the granular layer (Sugiura *et al.*, 2007).

The role of self-allergens remains to be elucidated in more detail in future studies. The concept of AD as an autoimmune disease has therapeutic implications and may explain the chronicity of the disease in “autoallergic” patients.

CONCLUSION

Immunological responses to defined allergens, inflammatory reactions to microbial agents, and a complex interplay of cells and mediators belonging to the skin immune system contribute to the clinical appearance of AD. Allergens may reach the skin from the bloodstream or through the epidermis, as depicted in Figure 3. Specific IgE, which is bound to Fc receptors on DCs (LC, IDECs, dermal DCs) and on cutaneous mast cells, may facilitate allergen presentation to specific T cells (Th2 cells in the acute phase, Th1 cells in the chronic phase). Figure 3 highlights only some key mediators of AD—the Th2 cytokine IL-4 and histamine in the acute phase and Th1-related cytokines IL-12 and IL-18 in the chronic phase. A number of other mediators are currently being investigated, with IL-17 and IL-31 representing extensively studied cytokines with regard to AD at present. More knowledge of these factors may contribute to the development of specific approaches for phase-dependent therapies in this chronic relapsing skin disease.

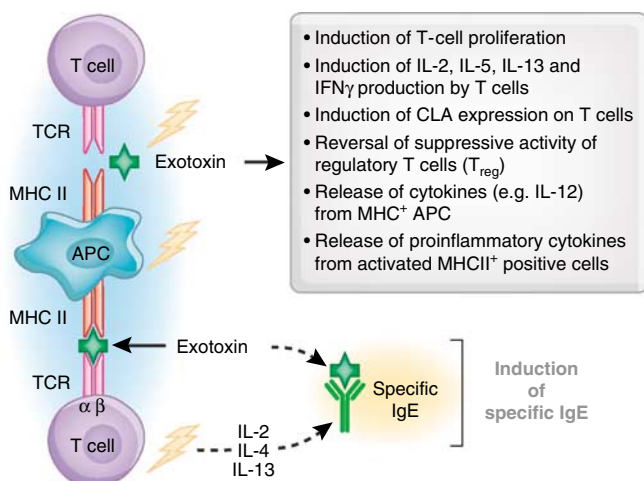


Figure 2. Function of staphylococcal exotoxins as superantigens or as allergens. Staphylococcal exotoxins can function as superantigens as depicted on the upper part of the figure. In this way exotoxins induce strong effects on both T cells and antigen-presenting cells, as summarized in the gray box. Exotoxins can also function as allergens in atopic dermatitis (depicted in the lower part of the figure) inducing specific IgE and specific Th2 responses.

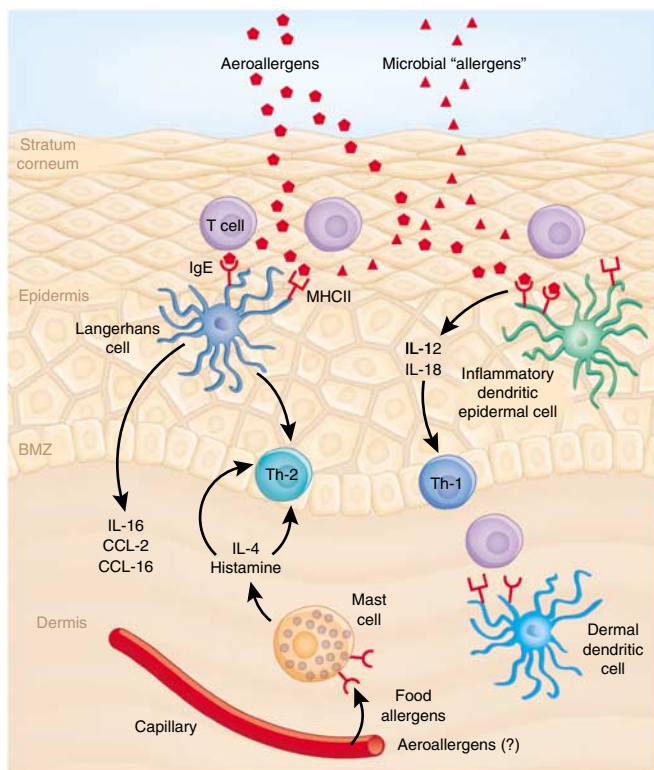


Figure 3. Effects of allergens on the cutaneous inflammation in atopic dermatitis. Allergens can enter the skin both through the bloodstream (for example, food allergens) or through the stratum corneum (for example, inhaled allergens). In the skin, IgE bound on Fc receptors on cutaneous mast cells and on dendritic cells contributes, together with specific T cells, to the inflammatory response.

CONFLICT OF INTEREST

The author states no conflict of interest.

REFERENCES

- Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DY (1995) Milk-induced eczema is associated with the expansion of T-cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 95:913–8
- Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U *et al.* (2004) The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol* 113:565–7
- Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P *et al.* (2006) Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol* 118:152–69 and *Allergy* 61: 969–87
- Akdis M, Akdis CA, Weigl L, Disch R, Blaser K (1997) Skin-homing, CLA+ memory T-cells are activated in atopic dermatitis and regulate IgE by an IL-13-dominated cytokine pattern: IgG4 counter-regulation by CLA- memory T-cells. *J Immunol* 159: 4611–9
- Akdis M, Blaser K, Akdis CA (2005) T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. *J Allergy Clin Immunol* 116:961–8
- Akdis M, Simon HU, Weigl L, Kreyden O, Blaser K, Akdis CA (1999) Skin homing (cutaneous lymphocyte-associated antigen-positive) CD8+ T-cells respond to superantigen and contribute to eosinophilia and IgE production in atopic dermatitis. *J Immunol* 163:466–75
- Akdis M, Trautmann A, Klunker S, Daigle I, Kucuksezir UC, Deglmann W *et al.* (2003) T helper (Th) 2 predominance in atopic diseases is due to preferential apoptosis of circulating memory/effector Th1 cells. *FASEB J.* 17:1026–35
- Akkoc T, de Koning PJ, Rückert B, Barlan I, Akdis M, Akdis CA (2008) Increased activation-induced cell death of high IFN-gamma-producing T(H)1 cells as a mechanism of T(H)2 predominance in atopic diseases. *J Allergy Clin Immunol* 121:652–8
- Albanesi C, Scarponi C, Sebastiani S, Cavani A, Federici M, De Pita O *et al.* (2000) IL-4 enhances keratinocyte expression of CXCR3 agonistic chemokines. *J Immunol* 165:1395–402
- Albanesi C, Scarponi C, Sebastiani S, Cavani A, Federici M, Sozzani S *et al.* (2001) A cytokine-to-chemokine axis between T-lymphocytes and keratinocytes can favor Th-1 cell accumulation in chronic inflammatory skin diseases. *J Leukoc Biol* 70:617–23
- Allakhverdi Z, Comeau MR, Jessup HK, Yoon BR, Brewer A, Chartier S *et al.* (2007) Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potentially activates mast cells. *J Exp Med* 204:253–8
- Beck LA, Saini S (2006) Wanted: A study with omalizumab to determine the role of IgE-mediated pathways in atopic dermatitis. *J Am Acad Dermatol* 55:540–1
- Belloni B, Ziai M, Lim A, Lemerrier B, Sbornik M, Weidinger S *et al.* (2007) Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. *J Allergy Clin Immunol* 120:1223–5
- Bieber T (2007) The pro- and anti-inflammatory properties of human antigen-presenting cells expressing the high affinity receptor for IgE (Fc epsilon RI). *Immunobiology* 212:499–503
- Bieber T (2008) Atopic dermatitis. *N Engl J Med* 358:1483–94
- Biedermann T, Lametschwandner G, Tangemann K, Kund J, Hinteregger S, Carballido-Perrig N *et al.* (2006) IL-12 instructs skin homing of human Th2 cells. *J Immunol* 177:3763–70
- Bilsborough J, Leung DY, Maurer M, Howell M, Boguniewicz M, Yao L *et al.* (2006) IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T-cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 117:418–25
- Bohle B, Zwölfer B, Heratizadeh A, Jahn-Schmidt B, Antonia YD, Alter M *et al.* (2006) Cooking birch pollen-related food: divergent consequences for IgE- and T-cell-mediated reactivity *in vitro* and *in vivo*. *J Allergy Clin Immunol* 118:242–9
- Breuer K, Haeussler S, Kapp A, Werfel T (2002) *Staphylococcus aureus*: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol* 147:55–61
- Breuer K, Wittmann M, Bosche B, Kapp A, Werfel T (2000) Severe atopic dermatitis is associated with sensitization to staphylococcal enterotoxin B (SEB). *Allergy* 55:551–5
- Breuer K, Wulf A, Constien A, Tetat D, Kapp A, Werfel T (2004) Birch pollen-related food as a provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. *Allergy* 59:988–94
- Brown SJ, McLean WHI (2009) Eczema genetics: current state of knowledge and future goals. *J Invest Dermatol* 129:543–52
- Bruijnzeel-Koomen C, Storz E, Menz G, Bruijnzeel P (1992) Skin eosinophilia in patients with allergic and nonallergic asthma and atopic dermatitis. *J Allergy Clin Immunol* 89:52–9
- Bunikowski R, Mielke M, Skarabis H, Herz U, Bergmann RL, Wahn U *et al.* (1999) Prevalence and role of serum IgE antibodies to

- the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *J Allergy Clin Immunol* 103:119-24
- Bussmann C, Bockenhoff A, Henke H, Werfel T, Novak N (2006) Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? *J Allergy Clin Immunol* 118:1292-8
- Bussmann C, Maintz L, Hart J, Allam JP, Vrtala S, Chen KW *et al.* (2007) Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. *Clin Exp Allergy* 37:1277-85
- Cardona ID, Goleva E, Ou LS, Leung DY (2006) Staphylococcal enterotoxin B inhibits regulatory T-cells by inducing glucocorticoid-induced TNF receptor-related protein ligand on monocytes. *J Allergy Clin Immunol* 117:688-95
- Casagrande BF, Fluckiger S, Linder MT, Johansson C, Scheynius A, Cramer R *et al.* (2006) Sensitization to the yeast *Malassezia sympodialis* is specific for extrinsic and intrinsic atopic eczema. *J Invest Dermatol* 126:2414-21
- Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wuthrich B *et al.* (2004) The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 59:1318-25
- De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA (2009) Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 129:14-30
- Demehri S, Liu Z, Lee J, Lin MH, Crosby SD, Roberts CJ *et al.* (2008) Notch-deficient skin induces a lethal systemic B-lymphoproliferative disorder by secreting TSLP a sentinel for epidermal integrity. *PLoS Biol* 27:6-e123
- Dijkstra D, Leurs R, Chazot P, Shenton FC, Stark H, Werfel T *et al.* (2007) Histamine down-regulates monocyte CCL2 production through the histamine H4 receptor. *J Allergy Clin Immunol* 120:300-7
- Dinarello CA (2007) Interleukin-18 and the pathogenesis of inflammatory diseases. *Semin Nephrol* 27:98-114
- Elsner J, Kapp A (1999) Regulation and modulation of eosinophil effector functions. *Allergy* 54:15-26
- Fiset PO, Leung DY, Hamid Q (2006) Immunopathology of atopic dermatitis. *J Allergy Clin Immunol* 118:287-90
- Forman SB, Garrett AB (2007) Success of omalizumab as monotherapy in adult atopic dermatitis: case report and discussion of the high-affinity immunoglobulin E receptor, FcεR1. *Cutis* 80:38-40
- Franz B, Fritzsche B, Riehl A, Oberle N, Klemke CD, Sykora J *et al.* (2007) Low number of regulatory T cells in skin lesions of patients with cutaneous lupus erythematosus. *Arthritis Rheum* 56:1910-20
- Giustizieri ML, Albanesi C, Fluhr J, Gisondi P, Norgauer J, Girolomoni G (2004) H1 histamine receptor mediates inflammatory responses in human keratinocytes. *J Allergy Clin Immunol* 114:1176-82
- Gombert M, Dieu-Nosjean MC, Winterberg F, Bunemann E, Kubitz RC, Da Cunha L *et al.* (2005) CCL1-CCR8 interactions: an axis mediating the recruitment of T-cells and Langerhans-type dendritic cells to sites of atopic skin inflammation. *J Immunol* 174:5082-91
- Grewe M, Walther S, Gyufko K, Czech W, Schopf E, Krutmann J (1995) Analysis of the cytokine pattern expressed *in situ* in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest Dermatol* 105:407-10
- Gutzmer R, Diestel C, Mommert S, Kother B, Stark H, Wittmann M *et al.* (2005) Histamine H4 receptor stimulation suppresses IL-12p70 production and mediates chemotaxis in human monocyte-derived dendritic cells. *J Immunol* 174:5224-32
- Gutzmer R, Mommert S, Gschwandtner M, Zwingmann K, Stark H, Werfel T (2009) The histamine H4 receptor is functionally expressed on T(H)2 cells. *J Allergy Clin Immunol* 123:619-25
- Hamid Q, Boguniewicz M, Leung DY (1994) Differential *in situ* cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 94:870-6
- Hamid Q, Naseer T, Minshall EM, Song YL, Boguniewicz M, Leung DY (1996) *In vivo* expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol* 98:225-31
- Han GW, Iwatsuki K, Inoue M, Matsui T, Nishibu A, Akiba H *et al.* (1999) Interleukin-15 is not a constitutive cytokine in the epidermis, but is inducible in culture or inflammatory conditions. *Acta Derm Venereol* 79:37-40
- Hasannejad H, Takahashi R, Kimishima M, Hayakawa K, Shiohara T (2007) Selective impairment of Toll-like receptor 2-mediated proinflammatory cytokine production by monocytes from patients with atopic dermatitis. *J Allergy Clin Immunol* 120:69-75
- He R, Oyoshi MK, Jin H, Geha RS (2007) Epicutaneous antigen exposure induces a Th-17 response that drives airway inflammation after inhalation challenge. *Proc Natl Acad Sci U S A* 104:15817-22
- Hennino A, Vocanson M, Toussaint Y, Rodet K, Benetiere J, Schmitt AM *et al.* (2007) Skin-infiltrating CD8+ T-cells initiate atopic dermatitis lesions. *J Immunol* 178:5571-7
- Hochstetter R, Dobos G, Kimmig D, Dulkys Y, Kapp A, Elsner J (2000) The CC chemokine receptor 3 CCR3 is functionally expressed on eosinophils but not on neutrophils. *Eur J Immunol* 30:2759-64
- Holgate ST (2007) The epithelium takes centre stage in asthma and atopic dermatitis. *Trends Immunol* 28:248-51
- Holm L, Bengtsson A, Hage-Hamsten M, Ohman S, Scheynius A (2001) Effectiveness of occlusive bedding in the treatment of atopic dermatitis—a placebo-controlled trial of 12 months' duration. *Allergy* 56:152-8
- Homey B, Alenius H, Muller A, Soto H, Bowman EP, Yuan W *et al.* (2002) CCL27-CCR10 interactions regulate T-cell-mediated skin inflammation. *Nat Med* 8:157-65
- Homey B, Steinhoff M, Ruzicka T, Leung DY (2006) Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol* 118:178-89
- Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, De Benedetto A *et al.* (2007) Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 120:150-5
- Howell MD, Wollenberg A, Gallo RL, Flaig M, Streib JE, Wong C *et al.* (2006) Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol* 117:836-41
- Hunter CA (2005) New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. *Nat Rev Immunol* 5:521-31
- Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N *et al.* (2005) TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med* 202:1213-23
- Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OA, Malolepszy J *et al.* (2001) Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 413:420-5
- Kapp A (1993) The role of eosinophils in the pathogenesis of atopic dermatitis—eosinophil granule proteins as markers of disease activity. *Allergy* 48:1-5
- Kerschenlohr K, Decard S, Przybilla B, Wollenberg A (2003) Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells in patients with extrinsic atopic dermatitis and patients with intrinsic atopic dermatitis. *J Allergy Clin Immunol* 111:869-74
- Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y (2008) Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol* 128:2625-30
- Lane JE, Cheyney JM, Lane TN, Kent DE, Cohen DJ (2006) Treatment of recalcitrant atopic dermatitis with omalizumab. *J Am Acad Dermatol* 54:68-72
- Langer K, Breuer K, Kapp A, Werfel T (2007) *Staphylococcus aureus*-derived enterotoxins enhance house dust mite-induced patch test reactions in atopic dermatitis. *Exp Dermatol* 16:124-9
- Leiferman KM, Ackerman SJ, Sampson HA, Haugen HS, Venencie PY, Gleich GJ (1985) Dermal deposition of eosinophil-granule major basic protein in atopic dermatitis. Comparison with onchocerciasis. *N Engl J Med* 313:282-5
- Leung AK, Hon KL, Robson WL (2007) Atopic dermatitis. *Adv Pediatr* 54:241-73
- Leung DY, Bhan AK, Schneeberger EE, Geha RS (1983) Characterization of the mononuclear

- cell infiltrate in atopic dermatitis using monoclonal antibodies. *J Allergy Clin Immunol* 71:47–56
- Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA (2004) New insights into atopic dermatitis. *J Clin Invest* 113:651–7
- Li XM, Kleiner G, Huang CK, Lee SY, Schofield B, Soter NA *et al.* (2001) Murine model of atopic dermatitis associated with food hypersensitivity. *J Allergy Clin Immunol* 107:693–702
- Maintz L, Novak N (2007) Getting more and more complex: the pathophysiology of atopic eczema. *Eur J Dermatol* 17:267–83
- McGirt LY, Beck LA (2006) Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol* 118:202–8
- Mehl A, Verstege A, Staden U, Kulig M, Nocon M, Beyer K *et al.* (2005) Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children. *Allergy* 60:1034–9
- Mothes N, Niggemann B, Jenneck C, Hagemann T, Weidinger S, Bieber T *et al.* (2005) The cradle of IgE autoreactivity in atopic eczema lies in early infancy. *J Allergy Clin Immunol* 116:706–9
- Mrabet-Dahbi S, Dalpke A, Frey M, Niehbuhr M, Draing C, Brand S *et al.* (2008) The toll-like receptor 2 (TRL-2) R753Q mutation modifies cytokine production and TLR expression in atopic dermatitis. *J Allergy Clin Immunol* 121:1013–9
- Neis MM, Peters B, Dreuw A, Wenzel J, Bieber T, Mauch C *et al.* (2006) Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. *J Allergy Clin Immunol* 118:930–7
- Niebuhr M, Langnickel J, Draing C, Renz H, Kapp A, Werfel T (2008) Dysregulation of toll-like receptor-2 (TLR-2)-induced effects in monocytes from patients with atopic dermatitis: impact of the TLR-2 R753Q polymorphism. *Allergy* 63:728–34
- Niebuhr M, Lutat C, Sigel S, Werfel T (2009) Impaired TLR-2 expression and TLR-2 mediated cytokine secretion in macrophages from patients with atopic dermatitis. *Allergy* (in press)
- Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF *et al.* (2003) Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 171:3262–9
- Novak N, Allam JP, Bieber T (2003) Allergic hyperreactivity to microbial components: a trigger factor of “intrinsic” atopic dermatitis? *J Allergy Clin Immunol* 112:215–6
- Novak N, Bieber T (2003) Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 112:252–62
- Novak N, Peng W, Yu C (2007) Network of myeloid and plasmacytoid dendritic cells in atopic dermatitis. *Adv Exp Med Biol* 601:97–104
- Novak N, Valenta R, Bohle B, Laffer S, Haberstok J, Kraft S *et al.* (2004) Fc epsilon RI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes *in vitro*. *J Allergy Clin Immunol* 113:949–57
- Novembre E, Cianferoni A, Lombardi E, Bernardini R, Pucci N, Vierucci A (2001) Natural history of “intrinsic” atopic dermatitis. *Allergy* 56:452–3
- Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T *et al.* (2002) Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 347:1151–60
- O’Regan GM, Irvine AD (2008) The role of filaggrin loss-of-function mutations in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 8:406–10
- Oosting AJ, Bruin-Weller MS, Terreehorst I, Tempels-Pavlica Z, Aalberse RC, de Monchy JG *et al.* (2002) Effect of mattress encasings on atopic dermatitis outcome measures in a double-blind, placebo-controlled study: the Dutch mite avoidance study. *J Allergy Clin Immunol* 110:500–6
- Ou LS, Goleva E, Hall C, Leung DY (2004) T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. *J Allergy Clin Immunol* 113:756–63
- Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F *et al.* (2007) Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 120:164–70
- Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP *et al.* (2006) Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 38:441–6
- Giustizieri ML, Mascia F, Frezzolini A, De Pità O, Chinni LM, Giannetti A *et al.* (2001) Keratinocytes from patients with atopic dermatitis and psoriasis show a distinct chemokine production profile in response to T cell-derived cytokines. *J Allergy Clin Immunol* 107:871–7
- Pastore S, Corinti S, La Placa M, Didona B, Girolomoni G (1998) Interferon-gamma promotes exaggerated cytokine production in keratinocytes cultured from patients with atopic dermatitis. *J Allergy Clin Immunol* 101:538–44
- Pastore S, Giustizieri ML, Mascia F, Giannetti A, Kaushansky K, Girolomoni G. (2000) Dysregulated activation of activator protein 1 in keratinocytes of atopic dermatitis patients with enhanced expression of granulocyte/macrophage-colony stimulating factor. *J Invest Dermatol* 115:1134–43
- Pickler LJ, Michie SA, Rott LS, Butcher EC (1990) A unique phenotype of skin-associated lymphocytes in humans. Preferential expression of the HECA-452 epitope by benign and malignant T-cells at cutaneous sites. *Am J Pathol* 136:1053–68
- Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB (2006) *In vitro* and *in situ* expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol* 176:1908–15
- Purwar R, Kraus M, Werfel T, Wittmann M (2007a) Modulation of Keratinocyte-Derived MMP-9 by IL-13: A Possible Role for the Pathogenesis of Epidermal Inflammation. *J Invest Dermatol* 128:59–66
- Purwar R, Werfel T, Wittmann M (2006) IL-13-stimulated human keratinocytes preferentially attract CD4+CCR4+ T-cells: possible role in atopic dermatitis. *J Invest Dermatol* 126:1043–51
- Purwar R, Werfel T, Wittmann M (2007b) Regulation of IL-13 receptors in human keratinocytes. *J Invest Dermatol* 127:1271–4
- Raap U, Werfel T, Goltz C, Deneka N, Langer K, Bruder M *et al.* (2006) Circulating levels of brain-derived neurotrophic factor correlate with disease severity in the intrinsic type of atopic dermatitis. *Allergy* 61:1416–8
- Raap U, Wichmann K, Bruder M, Ständer S, Wedi B, Kapp A *et al.* (2008) Correlation of IL-31 serum levels with severity of atopic dermatitis. *J Allergy Clin Immunol* 122:421–3
- Reefer AJ, Satinover SM, Wilson BB, Woodfolk JA (2007) The relevance of microbial allergens to the IgE antibody repertoire in atopic and nonatopic eczema. *J Allergy Clin Immunol* 120:156–63
- Reekers R, Beyer K, Niggemann B, Wahn U, Freihorst J, Kapp A *et al.* (1996) The role of circulating food antigen-specific lymphocytes in food allergic children with atopic dermatitis. *Br J Dermatol* 135:935–41
- Reekers R, Busche M, Wittmann M, Kapp A, Werfel T (1999) Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 104:466–72
- Reich K, Hugo S, Middel P, Blaschke V, Heine A, Gutgesell C *et al.* (2002) Evidence for a role of Langerhans cell-derived IL-16 in atopic dermatitis. *J Allergy Clin Immunol* 109:681–7
- Sager N, Feldmann A, Schilling G, Kreitsch P, Neumann C (1992) House dust mite-specific T-cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. *J Allergy Clin Immunol* 89:801–10
- Salt BH, Boguniewicz M, Leung DY (2007) Severe refractory atopic dermatitis in adults is highly atopic. *J Allergy Clin Immunol* 119:508–9
- Sampson HA (2001) Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 107:891–6
- Santamaria Babi LF, Picker LJ, Perez Soler MT, Drzimalla K, Flohr P, Blaser K *et al.* (1995) Circulating allergen-reactive T-cells from patients with atopic dermatitis and allergic contact dermatitis express the skin-selective homing receptor, the cutaneous

- lymphocyte-associated antigen. *J Exp Med* 181:1935–40
- Scalabrini DM, Bavbek S, Perzanowski MS, Wilson BB, Platts-Mills TA, Wheatley LM (1999) Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and nonasthmatic control subjects. *J Allergy Clin Immunol* 104:1273–9
- Scheynius A, Johansson C, Buentke E, Zargari A, Linder MT (2002) Atopic eczema/dermatitis syndrome and Malassezia. *Int Arch Allergy Immunol* 127:161–9
- Schmid-Grendelmeier P, Fluckiger S, Disch R, Trautmann A, Wuthrich B, Blaser K *et al.* (2005) IgE-mediated and T-cell-mediated autoimmunity against manganese superoxide dismutase in atopic dermatitis. *J Allergy Clin Immunol* 115:1068–75
- Schmid-Grendelmeier P, Scheynius A, Cramer R (2006) The role of sensitization to Malassezia sympodialis in atopic eczema. *Chem Immunol Allergy* 91:98–109
- Schmid-Ott G, Jaeger B, Adamek C, Koch H, Lamprecht F, Kapp A *et al.* (2001a) Levels of circulating CD8(+) T-lymphocytes, natural killer cells, and eosinophils increase upon acute psychosocial stress in patients with atopic dermatitis. *J Allergy Clin Immunol* 107:171–7
- Schmid-Ott G, Jaeger B, Meyer S, Stephan E, Kapp A, Werfel T (2001b) Different expression of cytokine and membrane molecules by circulating lymphocytes on acute mental stress in patients with atopic dermatitis in comparison with healthy controls. *J Allergy Clin Immunol* 108:455–62
- Schnopp C, Rad R, Weidinger A, Weidinger S, Ring J, Eberlein B *et al.* (2007) Fox-P3-positive regulatory T-cells are present in the skin of generalized atopic eczema patients and are not particularly affected by medium-dose UVA1 therapy. *Photodermatol Photoimmunol Photomed* 23:81–5
- Selander C, Zargari A, Mollby R, Rasool O, Scheynius A (2006) Higher pH level, corresponding to that on the skin of patients with atopic eczema, stimulates the release of Malassezia sympodialis allergens. *Allergy* 61:1002–8
- Seneviratne SL, Jones L, King AS, Black A, Powell S, McMichael AJ *et al.* (2002) Allergen-specific CD8(+) T cells and atopic disease. *J Clin Invest* 110:1283–91
- Shimizu M, Matsuda A, Yanagisawa K, Hirota T, Akahoshi M, Inomata N *et al.* (2005) Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. *Hum Mol Genet* 14:2919–27
- Simon D, Braathen LR, Simon HU (2004) Eosinophils and atopic dermatitis. *Allergy* 59:561–70
- Skov L, Olsen JV, Giorio R, Schlievert PM, Baadsgaard O, Leung DY (2000) Application of Staphylococcal enterotoxin B on normal and atopic skin induces up-regulation of T-cells by a superantigen-mediated mechanism. *J Allergy Clin Immunol* 105: 820–6
- Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L *et al.* (2006) IL-31: a new link between T-cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 117:411–7
- Soumelis V, Liu YJ (2004) Human thymic stromal lymphopoietin: a novel epithelial cell-derived cytokine and a potential key player in the induction of allergic inflammation. *Springer Semin Immunopathol* 25:325–33
- Spergel JM, Mizoguchi E, Oettgen H, Bhan AK, Geha RS (1999) Roles of TH-1 and TH-2 cytokines in a murine model of allergic dermatitis. *J Clin Invest* 103:1103–11
- Steinhoff M, Steinhoff A, Homey B, Luger TA, Schneider SW (2006) Role of vasculature in atopic dermatitis. *J Allergy Clin Immunol* 118:190–7
- Strange P, Skov L, Lisby S, Nielsen PL, Baadsgaard O (1996) Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. *Arch Dermatol* 132:27–33
- Sugiura K, Muro Y, Nishizawa Y, Okamoto M, Shinohara T, Tomita Y *et al.* (2007) LEDGF/DFS70, a major autoantigen of atopic dermatitis, is a component of keratohyalin granules. *J Invest Dermatol* 127:75–80
- Szepietowski JC, McKenzie RC, Keohane SG, Aldridge RD, Hunter JA (1997) Atopic and non-atopic individuals react to nickel challenge in a similar way. A study of the cytokine profile in nickel-induced contact dermatitis. *Br J Dermatol* 137: 195–200
- Takaoka A, Arai I, Sugimoto M, Honma Y, Futaki N, Nakamura A *et al.* (2006) Involvement of IL-31 on scratching behavior in NC/Nga mice with atopic-like dermatitis. *Exp Dermatol* 15:161–7
- Tan BB, Weald D, Strickland I, Friedmann PS (1996) Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 347:15–8
- Thepen T, Langeveld-Wildschut EG, Bihari IC, van Wichen DF, Van Reijssen FC, Mudde GC *et al.* (1996) Biphasic response against aeroallergen in atopic dermatitis showing a switch from an initial TH-2 response to a TH-1 response *in situ*: an immunocytochemical study. *J Allergy Clin Immunol* 97:828–37
- Toda M, Leung DY, Molet S, Boguniewicz M, Taha R, Christodoulouopoulos P *et al.* (2003) Polarized *in vivo* expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol* 111:875–81
- Torgerson TR, Ochs HD (2007) Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: forkhead box protein 3 mutations and lack of regulatory T-cells. *J Allergy Clin Immunol* 120:744–50
- Trautmann A, Akdis M, Kleemann D, Altnauer F, Simon HU, Graeve T *et al.* (2000) T-cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J Clin Invest* 106:25–35
- Trautmann A, Altnauer F, Akdis M, Simon HU, Disch R, Brocker EB *et al.* (2001) The differential fate of cadherins during T-cell-induced keratinocyte apoptosis leads to spongiosis in eczematous dermatitis. *J Invest Dermatol* 117:927–34
- Turjanmaa K, Darso U, Niggemann B, Rance F, Vanto T, Werfel T (2006) EAACI/GA2LEN position paper: present status of the atopy patch test. *Allergy* 61:1377–84
- Valenta R, Mittermann I, Werfel T, Garn H, Renz H (2009) Linking allergy to autoimmune disease. *Trends Immunol* 30:109–16
- van Beelen AJ, Teunissen MB, Kapsenberg ML, de Jong EC (2007) Interleukin-17 in inflammatory skin disorders. *Curr Opin Allergy Clin Immunol* 7:374–81
- Van Reijssen FC, Bruijnzeel-Koomen CA, Kalthoff FS, Maggi E, Romagnani S, Westland JK *et al.* (1992) Skin-derived aeroallergen-specific T-cell clones of Th-2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 90:184–93
- Van Reijssen FC, Felius A, Wauters EA, Bruijnzeel-Koomen CA, Koppelman SJ (1998) T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 101:207–9
- Verhagen J, Akdis M, Traidl-Hoffmann C, Schmid-Grendelmeier P, Hijnen D, Knol EF *et al.* (2006) Absence of T-regulatory cell expression and function in atopic dermatitis skin. *J Allergy Clin Immunol* 117:176–83
- Vigo PG, Girgis KR, Pfuetze BL, Critchlow ME, Fisher J, Hussain I (2006) Efficacy of anti-IgE therapy in patients with atopic dermatitis. *J Am Acad Dermatol* 55:168–70
- Wedi B, Raap U, Kapp A (1999) Significant delay of apoptosis and Fas resistance in eosinophils of subjects with intrinsic and extrinsic type of atopic dermatitis. *Int Arch Allergy Immunol* 118:234–5
- Wedi B, Raap U, Lewrick H, Kapp A (1998) IL-4-induced apoptosis in peripheral blood eosinophils. *J Allergy Clin Immunol* 102:1013–20
- Werfel T, Ahlers G, Schmidt P, Boeker M, Kapp A, Neumann C (1997a) Milk-responsive atopic dermatitis is associated with a casein-specific lymphocyte response in adolescent and adult patients. *J Allergy Clin Immunol* 99:124–33
- Werfel T, Breuer K (2004) Role of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 4:379–85
- Werfel T, Breuer K, Rueff F, Przybilla B, Worm M, Grewe M *et al.* (2006) Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 61:202–5
- Werfel T, Hentschel M, Kapp A, Renz H (1997b) Dichotomy of blood- and skin-derived IL-4-producing allergen-specific T-cells and restricted V beta repertoire in nickel-mediated contact dermatitis. *J Immunol* 158:2500–5
- Werfel T, Kapp A (1998) Environmental and other major provocation factors in atopic dermatitis. *Allergy* 53:731–9

- Werfel T, Kapp A (1999) What do we know about the etiopathology of the intrinsic type of atopic dermatitis? *Curr Probl Dermatol* 28:29–36
- Werfel T, Morita A, Grewe M, Renz H, Wahn U, Krutmann J *et al.* (1996) Allergen specificity of skin-infiltrating T-cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. *J Invest Dermatol* 107:871–6
- Williams H, Flohr C (2006) How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol* 118:209–13
- Wittmann M, Alter M, Stunkel T, Kapp A, Werfel T (2004) Cell-to-cell contact between activated CD4+ T-lymphocytes and unprimed monocytes interferes with a TH-1 response. *J Allergy Clin Immunol* 114:965–73
- Wittmann M, Kienlin P, Mommert S, Kapp A, Werfel T (2002) Suppression of IL-12 production by soluble CD40 ligand: evidence for involvement of the p44/42 mitogen-activated protein kinase pathway. *J Immunol* 168:3793–800
- Wittmann M, Purwar R, Hartmann C, Gutzmer R, Werfel T (2005) Human keratinocytes respond to interleukin-18: implication for the course of chronic inflammatory skin diseases. *J Invest Dermatol* 124:1225–33
- Wittmann M, Werfel T (2006) Interaction of keratinocytes with infiltrating lymphocytes in allergic eczematous skin diseases. *Curr Opin Allergy Clin Immunol* 6:329–34
- Wollenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M *et al.* (2002) Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol* 119:1096–102
- Wu K, Higashi N, Hansen ER, Lund M, Bang K, Thestrup-Pedersen K (2000) Telomerase activity is increased and telomere length shortened in T-cells from blood of patients with atopic dermatitis and psoriasis. *J Immunol* 165:4742–7
- Zachary CB, Allen MH, MacDonald DM (1985) *In situ* quantification of T-lymphocyte subsets and Langerhans cells in the inflammatory infiltrate of atopic eczema. *Br J Dermatol* 112:149–56