

Immune regulation in atopic dermatitis

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Atopic dermatitis is a chronic inflammatory skin disease with a pathogenesis of complex immune dysregulation and interplay of genetic, environmental and psychological factors. Activation and skin-selective homing of peripheral-blood T cells, and effector functions in the skin, represent sequential immunological events in the pathogenesis of atopic dermatitis. Both CD4⁺ and CD8⁺ T cells bearing the cutaneous-lymphocyte-associated antigen represent activated memory/effector T cell subsets and induce IgE, mainly via IL-13, and prolong eosinophil lifespan, mainly via IL-5. Dysregulated apoptosis in skin-homing T cells and keratinocytes contributes to the elicitation and progress of atopic dermatitis. T cell survival is enhanced in the skin by cytokines and extracellular-matrix proteins. These activated T cells induce keratinocyte apoptosis, leading to eczema formation.

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Abbreviations

AD	atopic dermatitis
CLA	cutaneous-lymphocyte-associated antigen
NAD	nonallergic dermatitis

Introduction

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease characterized by typically distributed eczematous skin lesions with lichenification, pruritic excoriations, severely dry skin and a susceptibility to cutaneous infections [1,2]. The prevalence of AD has steadily increased during the past few decades [3]. There is believed to be a significant genetic contribution to the pathogenesis, on the basis of familial occurrence and studies on twins. However, there are wide variations in prevalence between similar ethnic groups, suggesting that environmental factors are critical in determining disease expression. In addition to environmental allergens and food, other factors — emotional stress, climatic factors, hormones, irritating substances, and systemic and local infections — have been demonstrated as provocative factors in AD [4]. Recent investigations have greatly increased our understanding of the immunological mechanisms that are involved in the pathogenesis of AD. However, complex inter-relationships of the immune system with genetic, environmental and psychological factors still remain to be investigated. This review examines the mechanisms of skin-selective T cell homing and activation

and introduces the concept of dysregulated apoptosis of T cells, eosinophils and keratinocytes as an important pathogenetic event in the development, chronicity and exacerbation of AD.

The role of skin-homing T cells in atopic dermatitis

Skin represents a functionally distinct immune compartment and chronic inflammation of the skin is generally associated with tissue infiltration by T cells [5,6]. The great majority of these T cells homing to the skin are of the CD45RO⁺ memory/effector phenotype and they express the selective skin-homing receptor, cutaneous-lymphocyte-associated antigen (CLA) [7].

The CLA epitope is characterized by specific binding to the monoclonal antibody HECA-452 [7]. CLA consists of a sialyl Lewis-x carbohydrate and corresponds to a post-translational modification of the P-selectin glycoprotein ligand 1 (PSGL-1) [8]. The generation of CLA on T cells undergoing naïve-to-memory transition in skin-draining lymph nodes requires α (1,3)-fucosyltransferase (FucT-VII) activity [8,9]. Thus, CLA expression predominantly reflects the regulated activity of FucT-VII [8,9]. CLA binds to its vascular counter-receptor, E-selectin (CD62E), which is expressed on inflamed superficial dermal postcapillary venules and endothelial cells [10]. CLA⁺CD45RO⁺ T cells migrate across activated endothelium using CLA–E-selectin, VLA-4–VCAM-1 and LFA-1–ICAM-1 interactions [11]. In addition, CLA is expressed by the malignant T cells of chronic-phase cutaneous T cell lymphoma (mycosis fungoides and Sezary syndrome) but not by non-skin-associated T cell lymphomas [7].

In both AD and contact dermatitis, T cells specific for skin-related allergens are confined to the CLA⁺ T cell population [12]. Peripheral-blood CLA⁺CD45RO⁺ (memory/effector) T cells demonstrate typical features of *in vivo* activation in AD [13]. Freshly isolated, unstimulated CLA⁺ T cells show significantly higher levels of expression of CD25 (the IL-2-receptor α chain), CD40-ligand and HLA-DR. Additional evidence for *in vivo* activation of CLA⁺ T cells is evident from the spontaneous proliferation that they exhibit immediately after purification, without further activation. CLA⁺ T cells contain and spontaneously release high amounts of preformed IL-5 and IL-13 but they have only very little IL-4 and IFN- γ in their cytoplasm, as demonstrated by intracellular cytokine staining immediately after purification [13,14••]. Moreover, CLA⁺ memory/effector T cells induce IgE production in B cells and enhance eosinophil survival by delaying eosinophil apoptosis in AD [13,14••]. In comparison, the peripheral-blood CLA[–]CD45RO⁺ T cell population represents a resting memory T cell fraction, induces IgG in B cells and

does not show any effect on eosinophil survival and apoptosis [13,14^{••}].

Mechanisms controlling infiltration of inflammatory cells into AD skin have been intensely investigated. Recently a chemokine, CTACK/CCL27, and its receptor, CRP-2/CCR10, were demonstrated to play a role in the preferential attraction of CLA⁺ T cells to the skin [15^{••},16]. In addition, eotaxin and the chemokine-receptor CCR3, which mediates the action of eotaxin on eosinophils and Th2 cells, were found to be highly expressed in AD skin [17]. IL-16, a chemoattractant for CD4⁺ T cells, is also found to be highly expressed in acute, in comparison to chronic, AD skin lesions [18]. Furthermore, transendothelial migration of skin-homing T cells involves the participation of IL-8-receptor type B [19].

Mechanisms of T cell activation in atopic dermatitis

Numerous studies have pointed to the role of activated CD4⁺ T cells in AD, asthma and other atopic diseases. The dermal cellular infiltrate in AD consists of mainly CD4⁺ and CD8⁺ T cells with a CD4 : CD8 ratio similar to that in peripheral blood [14^{••},20]. In recent studies, CD8⁺CLA⁺ T cells were demonstrated to be as potent as CD4⁺CLA⁺ T cells in induction of IgE and enhancement of eosinophil survival [14^{••},20]. A number of pathogenetic mechanisms — including aeroallergens, food allergens and superantigens — have been highlighted as being involved in T cell activation in AD; these are detailed below.

The role of aeroallergens in T cell activation in AD has been extensively studied [21,22]. Aeroallergens can induce both immediate-type and delayed-type responses in the skin [22]. The frequency of aeroallergen-specific T cells has been investigated in AD lesions: frequencies were found to be less than 1% in non-challenged AD lesions [23]. Besides, such allergen-specific T cells can be detected in the skin of atopic patients after allergen administration, without any signs of AD lesions [24].

The contribution of food allergens in the exacerbation of AD by T cell activation has also been studied [25]. Normally, allergen-specific T cell responses in food and aeroallergen allergy are confined to CD4⁺ T cells. This, however, does not explain the activation and recruitment of CD8⁺ T cells in AD skin lesions.

It is known that bacterial superantigens can interact with certain V β elements of the TCR, leading to activation, expansion, anergy or deletion of T cells. It is evident from mouse studies that superantigen-mediated responses of T cells are not restricted to CD4⁺ T cells. CD8⁺ T cells [26] and even CD4⁺CD8⁺ T cells can respond to superantigenic stimuli [27]. This suggests an explanation for the existence and activation of CD8⁺ T cells in eczema lesions and their contribution to IgE production, eosinophil survival and development of eczema [14^{••},20].

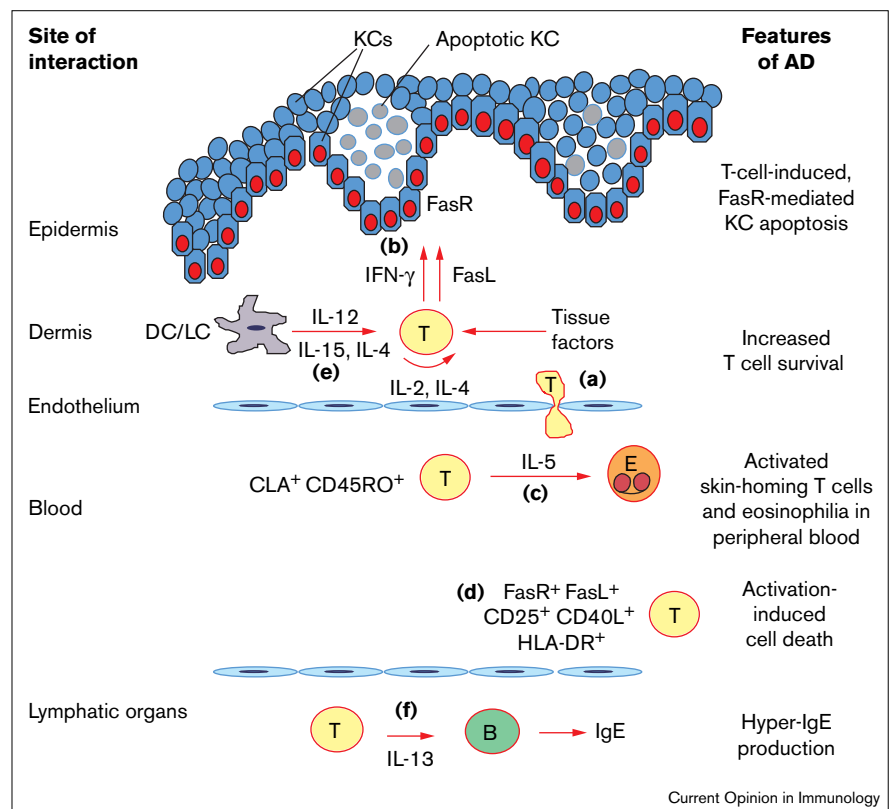
From a number of studies it could be concluded that bacterial superantigens contribute to the pathogenesis and exacerbation of AD: staphylococcal superantigens were isolated from AD skin [28]; superantigen patch-tests elicit skin inflammation in AD patients [29] and in human–SCID-mouse chimeric model [30]; in addition, IgE antibodies specific for bacterial superantigens exist in AD [31]. It was also demonstrated that CD8⁺ T cells isolated from the skin of AD patients or CLA⁺CD8⁺ T cells isolated from peripheral blood of AD patients and healthy individuals efficiently proliferate following superantigenic stimulation [14^{••}]. Furthermore, purified CD4⁺ or CD8⁺ T cells cultured from skin biopsies secrete a Th2-like cytokine profile — with very high IL-5 and IL-13 levels — following stimulation by the superantigen, staphylococcal enterotoxin B (SEB) [14^{••}].

Induction of CLA expression by superantigens may play an important role in the pathogenesis of disorders — such as AD — that are associated with superantigen-producing staphylococci [32]. Staphylococcal superantigens secreted at the skin surface may penetrate through the inflamed skin and stimulate epidermal macrophages or Langerhans cells to produce IL-1, TNF and IL-12. Superantigen-stimulated Langerhans cells may migrate to skin-associated lymph nodes and serve as antigen-presenting cells. They can upregulate the expression of CLA on T cells by producing IL-12 [32,33] and can influence the functional profile of virgin T cells; moreover, superantigens presented by keratinocytes, Langerhans cells and macrophages can stimulate T cells in the skin and this second round of stimulation can induce CLA formation [34]. Local production of IL-1 and TNF may induce expression of E-selectin on vascular endothelium [35], allowing an initial migration of CLA⁺ memory/effector cells.

If skin lesions are provoked in AD patients by epicutaneous application of allergens, the majority of allergen-specific T cells produce predominantly Th2 cytokines such as IL-4, IL-5 and IL-13; so do peripheral-blood T cells that home to the skin [12,13,14^{••},36]. A polarized Th2 cytokine pattern was previously regarded as a specific feature reflecting immune dysregulation in AD but current studies demonstrate that IFN- γ predominates over IL-4 in chronic skin lesions and older patch-test reactions in AD; however, IL-5 and IL-13 still remain at high levels [20,23,37,38]. A number of factors may be involved in the increased IFN- γ levels in older skin lesions. IL-12 produced by Langerhans cells, eosinophils and keratinocytes appears to be a predominant mediator for the induction of IFN- γ in T cells after they home to skin [33,39,40]. Furthermore, IL-18 produced in the skin microenvironment may function in parallel to IL-12 [41]. Recently, characterization of the cells in the afferent skin-derived lymph from healthy individuals demonstrated the dominance of a type-1 cytokine profile, with IFN- γ in T cells and IL-12 in dendritic cells [42[•]]. Such studies performed in AD patients may further help our understanding of the immune regulation mechanisms.

Figure 1

Immune effector mechanisms in AD. **(a)** T cells infiltrating the skin are mostly CD45RO⁺ and use CLA and other receptors to recognize and cross endothelium. **(b)** In the skin, these T cells secrete IFN- γ , which upregulates Fas receptors (FasRs) on keratinocytes (KCs) and renders them susceptible to apoptosis (basal KCs are actively proliferating cells and therefore their nuclei are shown in the figure). This apoptosis of KCs is induced by Fas ligand (FasL), either soluble or expressed on the surface of T cells. **(c)** CLA⁺ CD45RO⁺ T cells from peripheral blood – or CD4⁺ and CD8⁺ T cells isolated from skin (not shown) – secrete high levels of IL-5 and therefore are capable of preventing spontaneous eosinophil (E) apoptosis, thereby prolonging eosinophil lifespan. **(d)** In the peripheral blood of AD patients, both CD4⁺ and CD8⁺ subsets of CLA⁺CD45RO⁺ T cells are in an activated state (CD25⁺CD40L⁺HLA-DR⁺). They express upregulated FasR and FasL and undergo activation-induced apoptosis. **(e)** In contrast, T cells infiltrating the skin of AD patients – despite expressing both FasR and FasL – do not show any apoptosis because they are protected from apoptosis by cytokines such as IL-12, IL-4 and IL-15 (from dendritic cells [DC] and Langerhans cells [LC]) and extracellular-matrix components such as fibronectin and transferrin. **(f)** In the lymphatic organs, these cells induce IgE production by increasing IL-13 production.



Another widely supported view is that dermal dendritic cells and epidermal Langerhans cells display an abnormal hyperstimulatory function for T cells, in addition to their IL-12 and IL-18 production. IgE receptors, Fc ϵ RI and Fc ϵ RII (CD23), are upregulated in CD1a⁺ cells in AD (CD1a is a marker for Langerhans cells and dendritic cells) [43]. Presentation of IgE-binding autoantigens [44^{*}], foreign antigens and microbial superantigens can result in T cell activation by CD1a⁺ cells in AD. A positive feedback, with increased IgE production and further IgE-facilitated allergen presentation, may amplify the response to allergens [43,45]. The recent development of humanized anti-IgE antibodies also offers the hope that it may possibly reduce IgE-facilitated responses [46]. However, elimination of IgE may not be adequate in individuals with continuing T-cell-mediated inflammation because, in animal models of AD, allergic inflammation of the skin was elicited to the same extent in wild-type and IgE-knockout mice [47^{*}].

T-cell-mediated effector mechanisms in atopic dermatitis

A role for IL-13

Although most patients with AD show high concentrations of total and allergen-specific IgE in the blood and skin, some of them express normal total IgE levels and no allergen-specific IgE antibodies. The diagnostic criteria of AD, as detailed by Hanifin and Rajka [1], can be fulfilled

in the absence of elevated total IgE and specific IgE to food or environmental allergens. This suggests that elevated IgE levels and IgE-mediated sensitization are not prerequisites in the pathogenesis of the disease. The subgroup of AD patients with normal IgE levels and without specific IgE-mediated sensitization has been termed nonallergic dermatitis (NAD), non-atopic eczema, non-AD or intrinsic-type AD [20,48].

Recent data suggest that T cells are likely to be involved in the pathogenesis of AD and NAD. CD4⁺ and CD8⁺ subsets of skin-infiltrating T cells, as well as skin-homing CLA⁺ T cells from peripheral blood, responded equally to staphylococcal enterotoxin B and produced IL-2, IL-5, IL-13 and IFN- γ in both forms of the disease [14^{**},20]. Interestingly, skin T cells from AD patients express higher IL-5 and IL-13 levels compared with NAD patients. Thus T cells isolated from skin biopsies from AD patients, but not from NAD patients, induced high IL-13-mediated IgE production in cocultures with normal B cells. In addition, B cell activation — with high CD23 expression — is observed in the peripheral blood of AD patients but not NAD patients [20]. These data suggest a lack of IL-13-induced B cell activation and consequent IgE production in NAD although high numbers of T cells are present in lesional skin of both types [20]. More importantly, IL-4 and IL-13 neutralization studies in B cell cocultures with

peripheral-blood CLA⁺ skin-homing T cells or skin-infiltrating T cells demonstrated that IL-13 represents the major cytokine for induction of hyper-IgE production in AD [13,14^{••},20].

Dysregulated apoptosis

Although the death of certain cells can lead to functional deficiencies, prolonged survival of some effector cells can cause tissue injury and play a role on the pathogenesis of disease [49]. At least three major mechanisms by which dysregulated apoptosis leads to pathology in AD have been recently demonstrated (Figure 1): these mechanisms involve survival/apoptosis of eosinophils, T cells and keratinocytes, as detailed below.

IL-5 from CLA⁺ T cells increases eosinophil survival in atopic dermatitis

Cytokine determinations from peripheral-blood CLA⁺ T cells and skin biopsies of AD patients revealed increased IL-5 expression [14^{••},20]. Accordingly, supernatants from CLA⁺ T cells of both CD4⁺ and CD8⁺ subsets extended the lifespan of freshly purified eosinophils *in vitro* whereas supernatants of CLA⁻ T cells showed no effect on eosinophil survival. Neutralization of cytokines demonstrated the predominant role of IL-5 in prolonged eosinophil survival [14^{••}].

T cell lifespan differs in the peripheral-blood and skin of atopic dermatitis patients

Differences in control of lifespan were observed between peripheral-blood CLA⁺ T cells and T cells infiltrating eczema lesions (eczema is a characteristic of skin lesions in AD and is seen in some other diseases, such as contact dermatitis). In the peripheral blood of AD patients, both CD4⁺ and CD8⁺ subsets of CLA⁺CD45RO⁺ T cells expressed upregulated Fas receptor and Fas ligand and underwent spontaneous activation-induced cell death. CLA⁻CD45RO⁺ T cells were in a resting state, did not express Fas receptor and Fas ligand and were resistant to Fas-mediated apoptosis [50]. In contrast, T cells infiltrating the skin of AD patients expressed both Fas receptor and Fas ligand; however, they did not show any signs of apoptosis. Apoptosis of CLA⁺CD45RO⁺ T cells was inhibited by IL-2, IL-4, IL-15, fibronectin or transferrin, demonstrating multifactorial mechanisms for the survival of skin-infiltrating T cells in the tissue [15^{••}]. Together, these results demonstrate the control of *in-vivo*-activated, skin-homing T cell numbers in peripheral blood using increased apoptosis; in contrast, T cell apoptosis is prevented by cytokines and extracellular-matrix components in the eczematous skin.

T-cell-induced keratinocyte apoptosis as a key pathogenetic mechanism in eczema

A histological hallmark of eczematous disorders is a marked, characteristic keratinocyte pathology. Spongiosis in the epidermis is caused by impairment or loss of cohesion between keratinocytes and by the influx of fluid from the dermis, sometimes progressing to vesicle formation.

Several morphologic changes have been observed in human keratinocytes cocultured with autologous T cells. Resting, unstimulated T cells did not affect the keratinocyte morphology whereas keratinocytes cocultured with activated T cells (freshly purified CD45RO⁺ T cells and *in-vitro*-differentiated CD4⁺ or CD8⁺ type 1 and type 2 T cells) were shrunken, rounded, detached from the plates and finally apoptotic [51^{••}]. IFN- γ released from activated T cells upregulated Fas receptors on keratinocytes, which rendered them susceptible to apoptosis; when the number of Fas receptors on each keratinocyte reached a threshold of approximately 40,000 the cells became susceptible to apoptosis. Keratinocytes exhibited a relatively low threshold for IFN- γ -induced Fas receptor expression (only 0.1–1 ng/ml of IFN- γ was required); this requirement could be fulfilled by cells that secreted low levels of IFN- γ . The activated cells also produced high amounts of IL-5 and IL-13, which can contribute to eosinophilia and IgE production [51^{••}]. The 'lethal hit' is delivered to keratinocytes either by Fas ligand expressed on the surfaces of T cells that invade the epidermis or by soluble Fas ligand released from T cells.

The possibility of the involvement of cytokines other than IFN- γ was eliminated by experiments with different cytokines and neutralizing, anticytokine antibodies. In addition, the critical role of pathways induced following the triggering of Fas receptors was established using caspase inhibitors and a soluble Fas-Fc fusion protein.

Keratinocyte apoptosis was demonstrated *in situ* in lesional eczematous skin and patch tests. Exposure of normal human skin and cultured skin equivalents (i.e. in a three-dimensional whole-skin model of dermal fibroblasts embedded in a biomatrix with a multilayered epidermis containing stratum corneum [51^{••}]) to activated T cells demonstrated that keratinocyte apoptosis, caused by skin infiltrating T cells, is a key event in the pathogenesis of eczematous dermatitis [51^{••}]. Recent studies in mice also provide evidence for the role of IFN- γ in eczema formation: IFN- γ knockout mice showed significantly decreased allergic eczema formation [47[•]] and transgenic mice expressing IFN- γ in the epidermis spontaneously developed eczema [52].

Conclusions

Activated skin-homing T cells that secrete distinct cytokines play a central regulatory role in AD. They induce hyper-IgE production, eosinophilia and keratinocyte apoptosis.

In this context, future studies for the treatment of AD should be directed to the modulation of T cells by inhibition of various modes of activation, inhibition of skin-homing and inhibition of certain cytokines/chemokines that play a role in disease pathogenesis; the dysregulated apoptosis found in AD should also be targeted.

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