Cytokine network and dysregulated apoptosis in atopic dermatitis

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Activation and skin-selective homing of peripheral blood memory/effector T cells and effector functions in the skin represent sequential immunological events in the pathogenesis of atopic dermatitis (AD). T cells infiltrating the skin utilize the cutaneous lymphocyte-associated antigen (CLA) and other receptors to recognize and cross the vascular endothelium. In the peripheral blood of AD patients, both $CD4^+$ and $CD8^+$ subsets of $CLA+CD45RO^+$ T cells are in an activated state with high CD25, HLA-DR, and CD40-ligand expression. They express upregulated *Fas* and *Fas*-ligand and undergo activation-induced apoptosis. After homing to skin these T cells form dermal infiltrates which play a key role in the pathogenesis of the disease. Skin-infiltrating T cells in AD are protected from activation-induced cell death, although they express both *Fas* and *Fas*-ligand. They are protected from apoptosis by cytokines such as IL-2, IL-4, and IL-15 and extracellular matrix components such as fibronectin and transferrin. CLA^+, skin-homing T cells may play a role in peripheral blood eosinophilia and hyper IgE production by high IL-5 and IL-13 expression, respectively. These T cells secrete IFN-γ in the skin, which upregulates *Fas* on keratinocytes and renders them susceptible to apoptosis. Keratinocyte apoptosis is induced by *Fas*-ligand, either soluble or expressed on the surface of T cells, leading to eczema formation. Here we discuss the mechanisms of skin-selective T cell homing and activation, and emphasize the concept of dysregulated apoptosis of T cells, eosinophils, and keratinocytes as essential pathogenetic episodes in AD and other eczematous disorders.
☐ *Cutaneous lymphocyte-associated antigen; Fas interferon-γ; interleukin-5; interleukin-13*

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T cell activation and cytokine profile in atopic dermatitis

Numerous studies point to the role of activated $CD4^+$ T cells in atopic dermatitis (AD) and other allergic inflammatory diseases (1). Dermal cellular infiltrate in AD mainly consists of $CD4^+$ and $CD8^+$ T cells with a CD4/CD8 ratio similar to peripheral blood levels (2–4). In recent studies, $CD8^+CLA^+$ T cells have been demonstrated to be as potent as $CD4^+CLA^+$ T cells in the induction of IgE and inhibition of eosinophil apoptosis (2, 3). A number of pathogenetic mechanisms leading to T cell activation in AD, including aeroallergens, food allergens, and superantigens, have been demonstrated. The contribution of aeroallergens and food allergens in the induction and exacerbation of AD by T cell activation has been demonstrated repeatedly (5, 6). 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. $CD8^+$ T cells (7) and even $CD4^-$ $CD8^-$ T cells can respond to superantigenic stimuli (8). Activation of $CD8^+$ T cells in eczema lesions and their contribution to IgE production and eosinophil survival and development of AD can be explained by $CD8^+$ T cell responsiveness to superantigens (2, 3). It can be concluded from a number of studies that bacterial superantigens contribute to the pathogenesis and exacerbation of AD (9, 10).

Previously, a polarized Th2 cytokine pattern was regarded as a specific feature reflecting immune dysregulation in AD. However, current studies demonstrate that IFN-γ predominates over IL-4 in chronic skin lesions and older patch test reactions in AD, whereas IL-5 and IL-13 remain at high levels (3, 11). A number of factors may be involved in increased IFN-γ 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 homing to skin (12–14). Furthermore, IL-18 produced in the microenvironment of skin may act in parallel with IL-12 (15).

Kehry and Yamashita (16) have shown that IgE bound to CD23 on mouse B cells may be used to focus antigen to T cells. This mechanism operates selectively at low doses of allergens and the presentation of extremely low doses of allergen to $CD4^+$ T lymphocytes is greatly enhanced by IgE-facilitated antigen presentation (17, 18). Accordingly, IgE acts as an immunoglobulin specialized in antigen capture or antigen focusing. In the extrinsic type of AD in particular, the presence of high levels of specific IgE in serum and CD23 on APC (activated B cells) (3), together with FcγRI expressing APC (Langerhans cells in the skin) (19), may contribute to overstimulation of the allergen-specific immune responses.

Capture of antigens via surface IgE and signal transduction through the IgE cytoplasmic chain have been shown to be crucial events in specific IgE responses (20). Clinical trials with a neutralizing non-anaphylactogenic anti-IgE mAb treatment have demonstrated an inhibition in bronchial late-phase responses and a decrease in the

number of eosinophils in sputum of allergic asthma patients (21). Correspondingly, the production of IL-4 and IL-5 and lung eosinophilia of house dust mite-sensitized mice is inhibited by anti-CD23 or anti-IgE mAb treatment (22). The recent development of humanized anti-IgE antibodies may also offer the possibility of reduced IgE-facilitated antigen presentation (23). However, elimination of IgE may not be adequate in individuals with persisting T-cell-mediated inflammation, because in animal models of AD allergic inflammation of the skin has been elicited to the same extent in wild type and IgE knockout mice (24).

Role of IL-5 and IL-13 in atopic dermatitis

Although most patients with AD show high concentrations of total and allergen-specific IgE in blood and skin, some of them express normal IgE levels and show no allergen-specific IgE antibodies. The diagnostic criteria of AD by Hanifin & Rajka (25) can be fulfilled also in the absence of elevated total IgE and specific IgE to food or environmental allergens. This suggests that elevated IgE levels and IgE sensitization are not prerequisites in the pathogenesis of the disease. The disease in the subgroup of AD patients with normal IgE levels and without specific IgE sensitization has been termed the non-allergic form of AD (NAD), non-atopic eczema, non-AD or intrinsic-type AD (3, 26). Recent data suggest that T cells are involved in the pathogenesis of both AD and NAD. $CD4^+$ and $CD8^+$ subsets of skin-infiltrating T cells, as well as skin-homing CLA^+ T cells from peripheral blood, respond equally well to the superantigen SEB, and produce IL-2, IL-5, IL-13, and IFN-γ in both forms of the disease (2, 3). Interestingly, skin T cells from AD patients express higher IL-5 and IL-13 levels compared to those of NAD patients. Thus, T cells isolated from skin biopsies of AD, but not from NAD, induce high IgE production in co-cultures with normal B cells, that is, mediated by IL-13. In addition, B cell activation with high CD23 expression is observed in the peripheral blood of AD patients but not NAD patients (3). These findings suggest a lack of IL-13-induced B-cell activation and consequent IgE production in non-atopic eczema, although high numbers of T cells are present in lesional skin of both types (3). More importantly, IL-4 and IL-13 neutralization in B-cell co-cultures with peripheral blood CLA^+ skin-homing T cells or skin-infiltrating T cells has demonstrated that IL-13 represents the major cytokine for induction of hyper-IgE production in AD (2–4).

Cytokine determinations from peripheral blood CLA^+ T cells and skin biopsies of AD patients show increased IL-5 expression (2, 3, 27). Accordingly, supernatants from CLA^+ T cells of both $CD4^+$ and $CD8^+$ subsets extend the life span of freshly purified eosinophils in vitro, whereas supernatants of CLA^- T cells do not influence eosinophil survival. Neutralization of cytokines demonstrated the predominant role of IL-5 secreted from CLA^+ T cells to prolong eosinophil survival in AD (2).

Skin-selective T cell homing and chemokine network in atopic dermatitis

The great majority of T cells homing to the skin are of the $CD45RO^+$ memory/effector phenotype and express the selective skin-homing receptor CLA (28). The CLA epitope is characterized by specific binding to the monoclonal antibody HECA-452 (28). CLA binds to its vascular counter receptor, E-selectin (CD62E), which is expressed on inflamed superficial dermal postcapillary venules and endothelial cells (29). CLA^+ $CD45RO^+$ T cells migrate across activated endothelium using CLA/E selectin, VLA-4/VCAM-1, and LFA-1/ICAM-1 interactions (30). 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 (28). In both AD and contact dermatitis, T cells specific to skin-related allergens are confined to the CLA^+T-cell population (31). The CLA^+ memory/effector cells demonstrate typical features of in vivo activation in AD (4). Freshly isolated, unstimulated CLA^+ T cells show significantly higher levels of CD25 (IL-2 receptor-α chain), CD40-ligand, and HLA-DR expression. CLA^+ T cells contain and spontaneously release high amounts of preformed IL-5 and IL-13, but only very little IL-4 and IFN-γ in their cytoplasm, as demonstrated by intracellular cytokine staining immediately after purification (2, 4). Moreover, CLA^+ memory/effector T cells induce IgE production by B cells and enhance eosinophil survival by inhibiting eosinophil apoptosis in AD (2, 4).

The generation of CLA on T cells undergoing naive to memory transition in skin-draining lymph nodes requires α(1,3)-fucosyltransferase (FucT-VII) activity (32). The skin-selective homing ligand expression is regulated by the same mechanisms in both $CD4^+$ and $CD8^+$ T cells (33). The CLA molecule has been expressed on Th1 cells during the differentiation process (33, 34). More importantly, CLA can be induced on Th2 cells by T-cell stimulation with bacterial superantigen and/or IL-12 challenge (33). These Th2 cells demonstrate the same cytokine profile as the T cells found in skin biopsies and in peripheral blood of AD patients (3, 27, 35, 36). They show high IFN-γ, IL-5, and IL-13 production with very little or no IL-4 production. By IL-12 stimulation, CLA could be expressed on the surface of bee venom phospholipase A2-specific Th1, Th2, Th0, and T regulatory 1 clones, representing non-skin-related antigen-specific T cells (33). In addition, CLA could be re-induced on T cells that lost CLA expression upon resting (33). Apparently, skin-selective homing is not restricted to functional and phenotypic T-cell subsets. IL-12 and/or superantigen responsiveness, such as certain T-cell receptor variable β chain expression or IL-12Rβ expression, act as factors that control CLA expression on T cells.

Mechanisms that control infiltration of inflammatory cells into AD skin have been intensively investigated. Recently, cutaneous T-cell-attracting chemokine CTACK/

CCL27 and its receptor CRP-2/CCR10 were demonstrated as playing a role in preferential attraction of CLA^+ T cells to the skin (37, 38). CTACK is predominantly expressed in the skin and selectively attracts a tissue-specific subpopulation of memory lymphocytes. CTACK is constitutively expressed in mouse skin, suggesting that other mechanisms of chemoattraction during flares of AD must exist. In a mouse model of AD, the Th2-selective chemokine thymus and activation-regulated chemokine (TARC) is selectively induced by mechanical injury. NC/Nga mice spontaneously develop AD-like lesions and TARC is highly expressed in the basal epidermis with lesions, whereas it is not expressed in the skin without lesions (39). Similarly, the expression of macrophage-derived chemokine (MDC) was increased several fold in the mouse skin with AD-like lesions (39).

Eotaxin is a CC chemokine and a potent activator of human eosinophils, basophils, and Th2 cells via the chemokine receptor CCR3. Immunohistological staining and mRNA of eotaxin and its receptor CCR3 have been found significantly increased in lesional skin from AD, but not in that from nonatopic controls (40). An in situ hybridization study for IL-16 mRNA has demonstrated positive signals for IL-16 in the basal layer of epidermis and also in the dermis of AD skin samples, suggesting that IL-16 may play a role in initiating skin inflammation (41).

Transmigration studies through IL-1β and TNF-α activated endothelium have demonstrated that IL-8 and IL-8 receptor B are selectively involved in the enhanced transendothelial migration of CLA^+ T cells (42). Together, these studies on chemokine network for skin-homing of T cells demonstrate a complex system of different chemokines and chemokine receptors during different stages of disease and for different T-cell subsets. The involvement of epidermal keratinocytes, dendritic cells, and Langerhans cells on the skin-homing process by releasing chemotactic substances requires further investigation.

Dysregulated apoptosis in atopic dermatitis

To ensure self-tolerance and downregulation of an immune response, the elimination of T cells takes place in the periphery and involves induction of apoptosis (43). Cell death by apoptosis is a tightly regulated process that enables removal of unnecessary, aged, or damaged cells. One way to induce apoptosis is by triggering a family of transmembrane proteins called death receptors, of which *Fas* (CD95) may be the most important. During development of the immune response, T cells are stimulated by antigens presented by antigen-presenting cells, which leads to T-cell activation and clonal expansion. Some of the activated T cells die by activation-induced T-cell death (AICD) under certain conditions (44). The process of AICD is thought to play an important role in maintaining homeostasis of the immune response and prevention of excessive immune reactivity. Activated T cells can kill themselves (suicide) and other cells in the environment in a fratricidal way.

Differences in control of life span have been observed between peripheral blood CLA^+ T cells and T cells infiltrating the eczema lesions. In peripheral blood of AD patients, both $CD4^+$ and $CD8^+$ subsets of CLA^+ $CD45RO^+$ T cells expressed upregulated *Fas* and *Fas* ligand and underwent spontaneous AICD. CLA^- $CD45RO^+$ T cells are in a resting state, do not express *Fas* and *Fas* ligand, and are resistant to anti-*Fas* mAb-induced apoptosis (45). T cells infiltrating the skin of AD patients expressed both *Fas* and *Fas* ligand; yet, they did not show any signs of apoptosis. Apoptosis of CLA^+ $CD45RO^+$ T cells is inhibited by IL-2, IL-4, IL-15 as cytokines; fibronectin, tenascin, laminin and collagen IV as extracellular matrix proteins (ECM) and transferrin, demonstrating a multifactorial survival of skin-infiltrating T cells in the tissue (45). Inflammatory cells reside in a protein network in the tissues, the ECM, which exerts a profound control over them. The effects of ECM are primarily mediated by integrins, a family of cell surface receptors that attach cells to the matrix and mediate mechanical and chemical signals from it. Many ECM signals converge on cell-cycle regulation, directing cells to live or die, to proliferate or to differentiate. In addition to ECM proteins, IL-2, IL-4, and IL-15 also prevent T-cell apoptosis (45). The common γc-chain is an essential signaling component shared by IL-2, IL-4, and IL-15 receptors, as well as by all other known T-cell growth factor receptors. Together, these observations demonstrate that numbers of in vivo activated skin-homing T cells in peripheral blood are controlled by increased apoptosis, and that, in contrast, T cell apoptosis in eczematous skin is prevented by cytokines and extracellular matrix components.

The histological hallmark of eczematous disorders is a marked keratinocyte pathology. Spongiosis in the epidermis is caused by impairment or loss of cohesion between KC and influx of fluid from dermis, sometimes progressing to vesicle formation. A recent study by Trautmann et al. delineated activated skin-infiltrating T-cell-induced epidermal keratinocyte apoptosis as a key pathogenic event in eczematous disorders (46). IFN-γ released from activated T cells upregulates *Fas* (CD95) on keratinocytes, which renders them susceptible to apoptosis. When the number of *Fas* molecules per keratinocyte reaches a threshold of approximately 40,000, the cell becomes susceptible to apoptosis. Keratinocytes exhibit a relatively low threshold for IFN-γ-induced *Fas* expression (0.1–1 ng/ml). This requirement is largely met by low IFN-γ-secreting T cells that also produce high amounts of IL-5 and IL-13 and thereby contribute to eosinophilia and IgE production (46). The lethal hit is delivered to keratinocytes by *Fas* ligand expressed on the surface of T cells that invade the epidermis, and by soluble Fas ligand released from T cells. Keratinocyte apoptosis was demonstrated in situ in lesional eczematous skin and patch-test lesions of both AD and allergic contact dermatitis. Exposure of normal

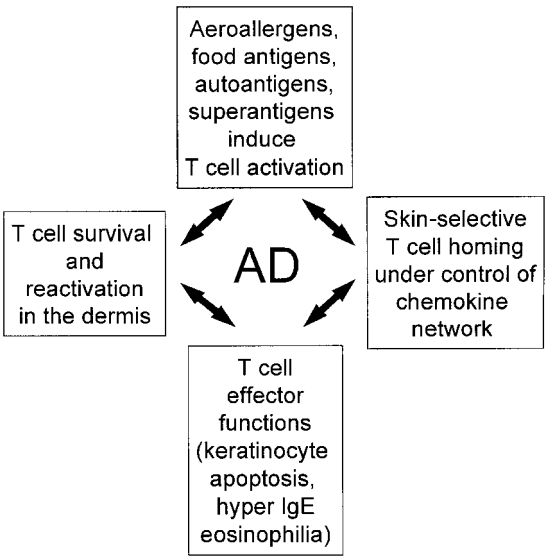

Fig. 1. Mechanisms of T-cell mediated inflammation in AD. T cells are activated by aeroallergens, food antigens, autoantigens, and bacterial superantigens. They are under the influence of a skin-related chemokine network and they show skin-selective homing. In the skin, the cells show increased survival and are continuously stimulated. Activated T cells induce keratinocyte apoptosis as a key pathogenetic event in the formation of eczema.

human skin and cultured skin equivalents to activated T cells demonstrated that keratinocyte apoptosis caused by skin-infiltrating T cells represents a key event in the pathogenesis of eczematous dermatitis (46).

Both $CD4^+$ and $CD8^+$ T cells may play a role in keratinocyte injury depending on their activation status. A direct contact of T cell to keratinocyte is not always required and soluble *Fas* ligand released from activated T cells can also induce keratinocyte apoptosis. IFN-γ appears to be a key cytokine in rendering keratinocytes susceptible to apoptosis (46–48). Recent studies on mice also provide evidence for the role of IFN-γ in eczema formation. IFN-γ knockout mice show significantly decreased allergic eczema formation (24) and transgenic mice expressing IFN-γ in the epidermis spontaneously developed eczema (49).

Conclusions

AD is a chronic inflammatory skin disease with a pathogenesis of complex immune dysregulation and an interplay of genetic and environmental factors. T-cell activation, skin-selective homing, and effector functions in the skin represent sequential immunological events in the pathogenesis of AD (Fig. 1). Dysregulated apoptosis in skin-infiltrating T cells and epidermal keratinocytes contributes to the elicitation and progression of AD. In this context, future studies for treatment of AD should be directed to T cells by inhibition of various modes of activation, by inhibition of skin-homing and by inhibition of cytokines and chemokines that play a role in the pathogenesis. The knowledge of the molecular basis for dysregulated apoptosis is pivotal in understanding the pathology in AD, and may lead to more focused therapeutic applications in the future.

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