

EDITORIAL

Immunological differences between intrinsic and extrinsic types of atopic dermatitis

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Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease characterized by typically distributed eczematous skin lesions with lichenification, pruritic excoriations, severely dry skin, and susceptibility to cutaneous infections [1]. Although most of the patients with AD show high concentrations of total and allergen-specific IgE in blood and skin, some of the patients have normal total IgE levels and negative serum allergen-specific IgE [2]. Diagnostic criteria of AD by Hanifin and Rajka [1] or Williams et al. [3] can be fulfilled in the absence of elevated total IgE and specific IgE to food or environmental allergens. The subgroup of AD patients with normal IgE levels and without specific IgE sensitization has been termed non-atopic dermatitis, non-allergic form of AD, atopiform dermatitis or intrinsic-type AD (IAD) as a counterpart to the term IgE-associated, allergic or extrinsic-type AD (EAD) [4–6]. This subtype can be characterized by the following criteria: (a) clinical phenotype of AD; (b) absence of other atopic diseases; (c) negative type I skin hypersensitivity to aero- and food allergens; (d) normal serum IgE levels; (e) no detectable specific IgE antibodies to aero- and food allergens. The frequency of IAD has been reported to be between 10% and 45% in different studies [6]. In the recently proposed nomenclature by the European Academy of Allergology and Clinical Immunology, AD has been renamed as atopic eczema/dermatitis syndrome (AEDS) and divided into non-allergic and allergic AEDS, the latter being subdivided into 'IgE-associated AEDS' and 'non-IgE-associated allergic AEDS' [7].

Various immunological parameters have been investigated in biopsy samples of lesional skin and patch test reactions as well as peripheral blood in patients with EAD and IAD (Fig. 1). T cell activation, skin-selective homing, and effector functions such as induction of keratinocyte apoptosis, IgE and eosinophilia represent cardinal features of allergic inflammation in AD [8]. Aeroallergens, food allergens and superantigens are involved in the activation of T cells in allergic inflammation in EAD [9–11]. T cell activating factor has long been questioned in IAD. It has recently been demonstrated that allergens such as house dust mite (*Dermaphagoides pteronyssinus*) and birch pollen induce atopy patch test reactivity in IAD patients with the presence of specific IgG, but not IgE antibodies [12]. Following activation, skin-selective homing of peripheral blood T cells represents the early step in AD. The dermal mononuclear cell infiltrate predominantly comprises CD4⁺ T cells as well as CD8⁺ T cells, with a CD4/CD8 ratio similar to that in peripheral blood, without showing any difference between IAD and EAD [11, 13]. The cutaneous lymphocyte-associated antigen

(CLA) represents the homing receptor involved in selective migration of memory/effector T cells to the skin. CLA is expressed on Th1 cells during the differentiation process and can be induced on Th2 cells by stimulation with bacterial superantigen and/or IL-12 [14, 15]. Both CD4⁺ and CD8⁺ T cells bearing CLA represent activated memory/effector T cell subsets, which contribute to hyper-IgE and eosinophilia in EAD [13, 16].

Different cytokine patterns of involved T cells have been suggested to play an important role in immunological differences such as induction of IgE and eosinophilia between IAD and EAD. Jeong et al. [17] have analysed the expression of various cytokines by RT-PCR in chronic lesional skin biopsies of both types of AD patients. In this issue, they report four different types of expression patterns of tissue cytokines. IL-5, IL-13 and IL-1 β mRNA levels were significantly high in both types of AD, with significantly higher expression in EAD than IAD. IL-4, IL-10, IL-12, IFN- γ and granulocyte macrophage-colony stimulating factor levels were high in AD without showing any difference between the two subtypes. IL-6 and TGF- β did not show any increased expression in AD, whereas TNF- α mRNA was decreased in both types of AD compared to non-atopic controls. Similar to their findings, increased IL-5 and IL-13 expression in T cells isolated from skin biopsies of EAD has been observed compared with IAD [11]. Accordingly, T cells isolated from skin biopsies of EAD, but not from the IAD, induced high IgE production in co-cultures with normal B cells that was mediated by IL-13. In addition, B cell activation with high CD23 expression has been reported in the peripheral blood of EAD but not IAD patients [11, 18, 19]. Furthermore, increased spontaneous IL-4 release was reported in peripheral blood mononuclear cells of EAD patients in comparison with IAD [19]. Together, these studies suggest increased IL-4- and IL-13-induced B cell activation and IgE production as well as IL-5-induced eosinophilia in EAD.

Langerhans cells and epidermal dendritic cells are professional antigen-presenting cells in AD skin. An increased expression of the high-affinity receptor for IgE (Fc ϵ RI) was repeatedly reported in EAD in comparison with IAD [12, 20]. Whether dendritic cells and Langerhans cells display abnormal hyperstimulatory function for T cells and IgE-facilitated antigen presentation plays a role remain to be elucidated in both types of AD. High numbers of eosinophils are recruited to inflamed tissues in asthma and AD, and prolonged eosinophil life span has been suggested in both diseases [21, 22]. Jeong et al. [17] report significantly increased numbers of eosinophils in the dermis in EAD compared with IAD.

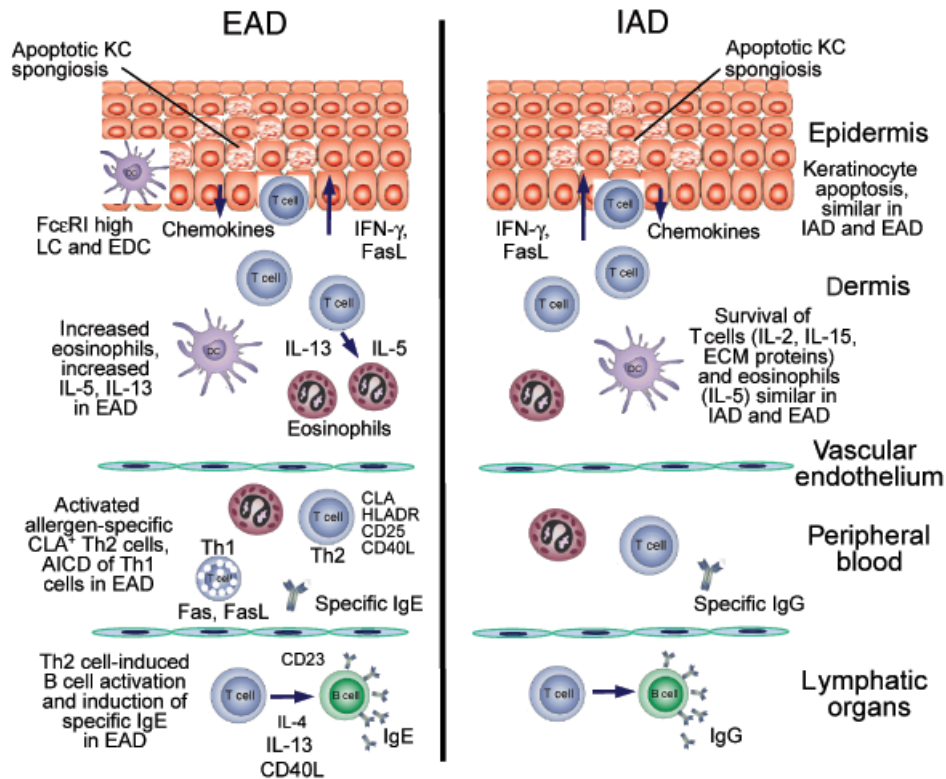


Fig. 1. Immune effector mechanisms in extrinsic-type dermatitis (EAD) and intrinsic-type (IAD). In the peripheral blood of EAD patients, both CD4⁺ and CD8⁺ subsets of CLA⁺ CD45RO⁺ T cells are in an activated state (CD25⁺, CD40-ligand (L)⁺, HLADR⁺). Mainly the Th1-like compartment of them undergoes Fas-mediated activation-induced cell death (AICD). In contrast, T cells infiltrating the skin of AD patients – despite expressing both Fas and FasL – do not show any apoptosis, because they are protected from apoptosis by cytokines and ECM proteins. These T cells secrete IFN-γ, which up-regulates Fas on keratinocytes and renders them susceptible to apoptosis in the skin. Keratinocyte apoptosis leading to spongiosis is induced by FasL expressed by activated T cells. Keratinocytes undergoing apoptosis in acute eczematous lesions release IFN-γ-induced chemokines (IP-10, Mig and ITAC) that attract more CXCR3⁺ T cells towards the epidermis, which may further augment the inflammation and keratinocyte apoptosis. In EAD, T cells isolated from skin or CLA⁺ CD45RO⁺ T cells from peripheral blood secrete high levels of IL-5 and IL-13, and are therefore capable of prolonging eosinophil life span and activating B cells for CD23 expression and inducing IgE production in EAD. In IAD no specific IgE, but IgG is found in the circulation against allergens. Epidermal dendritic cells (EDC) and Langerhans cells (LC) express high levels of FcεRI in EAD.

Peripheral eosinophil numbers did not show any difference between the two subtypes as previously reported [19]. Eosinophilic granule proteins, as well as eotaxin and its receptor have been found increased in lesional AD skin [23, 24]. The *in vitro* life span of eosinophils did not differ between IAD and EAD [22].

Allergen-specific T cells derived from skin lesions after epicutaneous application of inhalant allergens in patients with EAD were found to express predominantly Th2 cytokines [25, 26]. A dysregulated, Th2-biased peripheral allergen-specific immune response appears to be an important pathogenetic factor in circulating T cells and early lesions. In AD, circulating memory/effector T cells with skin-specific homing property (CLA⁺ CD45RO⁺) show interesting features of apoptosis [27]. They express high levels of Fas and Fas-ligand and undergo activation-induced cell death (AICD). The freshly purified CLA⁺ CD45RO⁺ T cells of atopic individuals display distinct features of *in vivo* triggered apoptosis such as pro-caspase degradation and active caspase-8 formation. Particularly, the Th1 compartment of activated memory/effector T cells selectively undergoes AICD, skewing the immune response towards surviving Th2 cells in atopic diseases. The apoptosis of circulating memory/effector T cells was confined to atopic individuals, whereas non-atopic

patients such as IAD, psoriasis, intrinsic-type asthma, contact dermatitis, bee venom-allergic patients and healthy controls did not show any evidence for enhanced Th1 cell apoptosis *in vivo*. These recent findings propose a novel mechanism for peripheral Th2 response in atopic diseases. In contrast, T cells infiltrating the skin of AD patients – despite expressing both Fas and Fas-ligand – do not show any apoptosis, because they are protected from apoptosis by cytokines and ECM proteins [27].

Although a polarized Th2 cytokine pattern has been regarded as a general phenomenon for atopy, several studies have demonstrated that IFN-γ increases in chronic skin lesions and older patch test reactions in AD. IL-4 decreases, whereas IL-5 and IL-13 still remain at high levels in ageing lesions [11, 28–30]. It has to be considered that the age of the patient population, the age of the eczema lesion and the isolation site of cells might influence the cellular composition and their cytokine profiles in both types of AD. In their study Jeong et al. [17] demonstrate that IFN-γ is strongly up-regulated in AD lesions without showing any difference between EAD and IAD. The histology of both types of eczematous disorders is characterized by spongiosis in the epidermis. Activated skin-infiltrating T cell-induced epidermal keratinocyte apoptosis has been demonstrated as a

key pathogenic event in eczematous disorders, leading to spongioform morphology [31, 32]. IFN- γ released from activated T cells up-regulates Fas (CD95) on keratinocytes, which renders them susceptible to apoptosis. Keratinocytes show a relatively low threshold for IFN- γ (0.1–1 ng/mL), which suggests that Th0 cells or high amounts of IL-5 and IL-13, but little amounts of IFN- γ -secreting Th2-like cells can induce keratinocyte apoptosis. The lethal hit is delivered to keratinocytes by Fas-ligand expressed on the surface of T cells that invade the epidermis and soluble Fas-ligand released from T cells. Keratinocytes undergoing apoptosis in acute eczematous lesions release IFN- γ -induced chemokines (IP-10, Mig and ITAC), which leads to a second step of chemotaxis of CXCR3 bearing T cells towards the epidermis and may further augment the inflammation and keratinocyte apoptosis [33]. In addition, it has been demonstrated that targeting apoptosis of epidermal keratinocytes may open a new future for drug development in the treatment of atopic dermatitis. Current treatments such as corticosteroids, cyclosporine A, rapamycin and FK506 mainly inhibit the activation of T cells and T cell-induced keratinocyte apoptosis [34].

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