

Apoptosis in tissue inflammation and allergic disease

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Genetic predisposition and environmental instructions tune thresholds for the activation, effector functions and lifespan of T cells, other inflammatory cells and resident tissue cells. Defects in apoptosis and peripheral tolerance in T cells define different allergic phenotypes. In individuals with atopic allergic disease, activated allergen-specific T cells expressing high levels of IFN- γ predominantly undergo apoptosis in the circulation, skewing the immune response to surviving T helper type 2 (Th2) cells. In affected tissues, these cells switch on effector cytokines and induce the activation and apoptosis of epithelial cells. In individuals with non-atopic monoallergic disease, by contrast, a disturbed balance towards allergen-specific Th2 cells instead of T regulatory type 1 (Tr1) cells characterizes the T cell response.

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Abbreviations

AD	atopic dermatitis
AICD	activation-induced cell death
CLA	cutaneous lymphocyte-associated antigen
ECM	extracellular matrix
IL	interleukin
Th cell	T helper cell
TNF-α	tumour-necrosis factor- α
Tr1	T regulatory type 1

Introduction

T cells constitute a large population of the cellular infiltrate in atopic and/or allergic inflammation, and a dysregulated immune response seems to be an important pathogenetic factor in this process. The cardinal events that take place during allergic inflammation can be classified as the activation, organ-selective homing, survival and reactivation, and effector functions of immune system cells (Figure 1) [1].

In allergic inflammation, T cells are initially activated by aeroallergens, food antigens, autoantigens and bacterial

superantigens. They subsequently come under the influence of the skin-, lung- or nose-related chemokine network and show organ-selective homing. These inflammatory T cells have a prolonged survival in tissues, followed by their consequent reactivation in subepithelial tissues [2,3,4]. Finally, they display effector functions that result in the induction of hyper-IgE, eosinophil survival and mucus hyperproduction [3–5], and they interact with bronchial epithelial cells and keratinocytes, causing their activation and apoptosis [6,7].

This article outlines the role of disbalance in activation, apoptosis and survival of T cells and epithelial cells in the pathogenesis of asthma and atopic dermatitis.

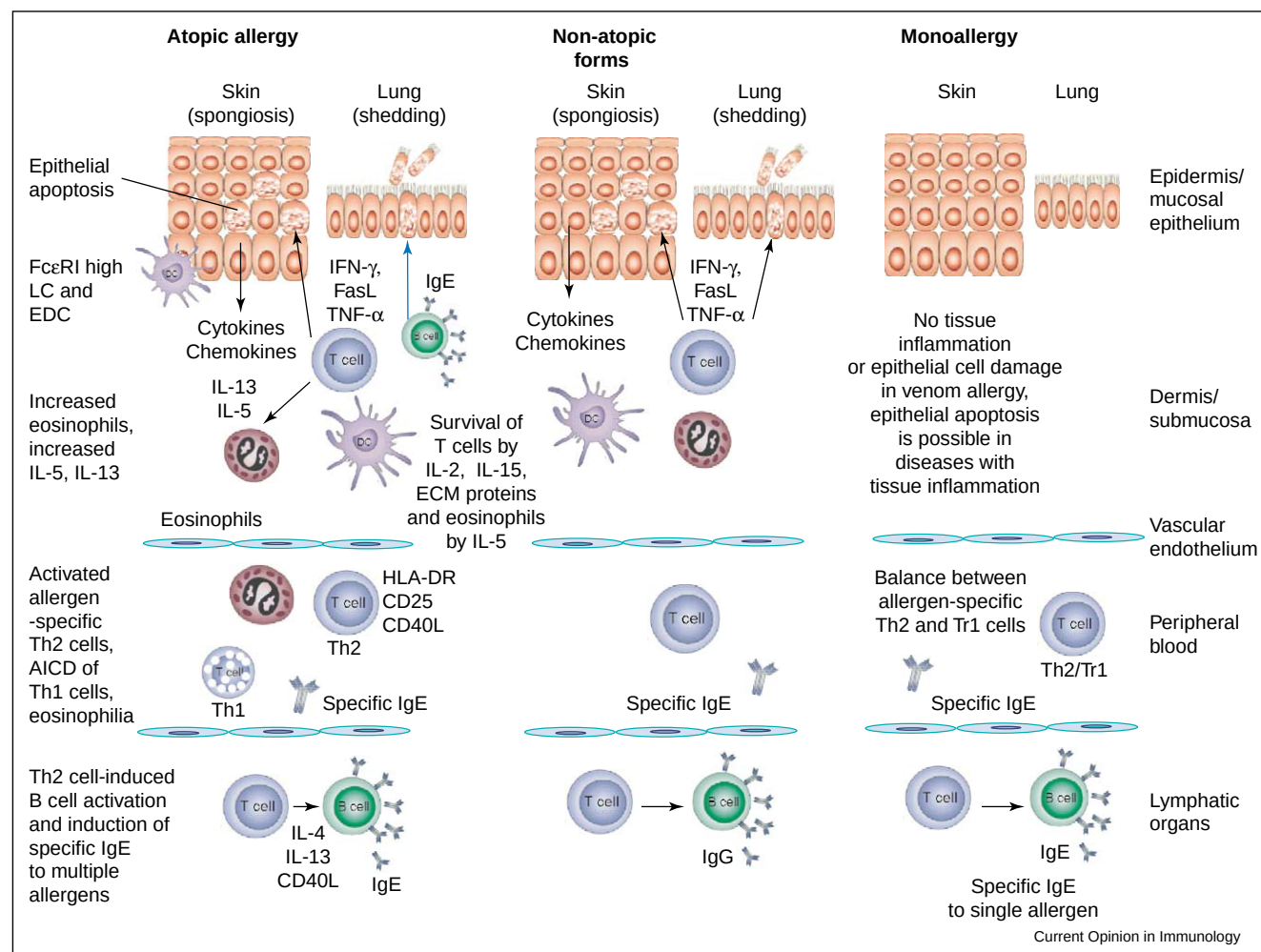
Atopic, monoallergic and non-IgE-associated types of allergic disease

Atopic allergy, the first type of allergic disease to be discussed in this review, includes atopic dermatitis (AD), allergic rhinitis and asthma, and develops on a complex genetic background. Although these disorders target different organs, in most affected individuals they are characterized by the presence of an increase in total serum IgE. The atopic form of allergic disease is often initiated with the atopic march in infancy and the inflammation might involve a single organ such as skin, lung or nose or a combination of these organs [8]. The cutaneous manifestations of atopy represent the beginning of the atopic march. Roughly half of the individuals affected with AD, particularly those with severe AD, develop asthma and two-thirds develop allergic rhinitis [8]. The start of the atopic march is characterized by IgE-mediated sensitization to food allergens, which is frequently associated with inhalatory allergies that develop subsequently.

The second type of allergic disease is monoallergy — the so-called ‘allergic breakthrough’ that is characterized by the development of allergen-specific IgE in the absence of high serum total IgE in non-atopic individuals [9]. Monoallergy can develop at any time of the life without any predisposing factor. It is manifested as an anaphylactoid type of allergy without any target organ inflammation in venom, some food and drug allergies, or with organ involvement in rhinitis, asthma and dermatitis [10,11]. In particular, individuals in this group with venom allergy or with allergic rhinitis show a highly successful response to allergen-specific immunotherapy [10,12].

One of the key issues in monoallergies is to understand why an individual develops an allergy to a single protein while tolerating thousands of others encountered through ingestion or inhalation. Different subtypes of regulatory

Figure 1



Immune mechanisms in atopic, non-atopic and monoallergic forms of allergic disease. In the peripheral blood of atopic individuals (left), CD45RO⁺ T cells are in an activated state (CD25⁺, CD40 ligand [CD40L]⁺, HLA-DR⁺). The Th1-like compartment of these cells mainly undergoes Fas-mediated activation-induced cell death (AICD), skewing the immune response to Th2 cells. In the inflammatory forms of allergic disease, dermis and submucosa turn into a secondary lymphoid-organ-like tissue with migrating T cells and dendritic cells. T cells infiltrating the skin of individuals with atopic dermatitis (AD), despite expressing both Fas and Fas ligand (FasL), do not show any apoptosis, because they are protected from apoptosis by cytokines and proteins of the extracellular matrix (ECM). Interferon-γ (IFN-γ), tumour-necrosis factor-α (TNF-α) and FasL are effector molecules in the skin and lung, which induce the apoptosis of epidermal keratinocytes, resulting in spongiosis and bronchial epithelial cell apoptosis leading to shedding. Epithelial cells undergoing apoptosis release IFN-γ-induced chemokines (IP-10, Mig and ITAC) that attract more CXCR3⁺ T cells towards the epidermis, which might further augment the inflammation and epithelial apoptosis. In atopic allergy, T cells are capable of prolonging eosinophil lifespan and activating B cells for the expression of CD23 and production of IgE. Local production of IgE by B cells has been shown in atopic asthma and rhinitis. In AD, epidermal dendritic cells (EDCs) and Langerhans cells (LCs) express large amounts of the high-affinity IgE receptor (FcεRI). In non-atopic forms of allergic disease (middle), no specific IgE is expressed, but allergen-specific IgG is present in the circulation. In monoallergic diseases (right), Th2 cells and IgE specific for a single allergen constitute the immune response. The balance between Th2 cells and T regulatory type 1 (Tr1) cells is crucial for development of monoallergy and also for successful treatment.

and suppressor cells and mechanisms have been demonstrated as potentially having a role in peripheral tolerance, and their biology has been the subject of intensive investigation in the past few years. T regulatory type 1 (Tr1) cells consistently represent the dominant subset specific for common environmental allergens in healthy individuals; by contrast, there is a high frequency of

allergen-specific Th2 cells in allergic individuals [13^{••}]. Effector (allergen-specific Th2) and suppressor (allergen-specific Tr1) T cells exist in both healthy and allergic individuals in regulated amounts. The ratio of these cells determines the development of a healthy or an allergic immune response and also has a role in successful treatment [13^{••},14,15[•]].

Although most individuals with AD, asthma and rhinitis show high levels of total and allergen-specific IgE, some individuals have normal total IgE levels and negative serum levels of allergen-specific IgE. This third type of allergic disease has been variously termed the non-atopic form, non-allergic form, non-IgE-associated form or intrinsic type of asthma, dermatitis and rhinitis [16–19]. This subtype of allergic disease can be characterized by the following criteria: clinical phenotype of asthma, AD or rhinitis; negative type I skin hypersensitivity to aeroallergens and food allergens; normal serum IgE levels; and no detectable specific IgE antibodies to aeroallergens or food allergens.

These three forms of allergic disease often overlap in terminology and mechanism; however, it might be possible to derive exact definitions related to the underlying pathomechanisms in the near future because of rapid advancements in the field.

Mechanism of peripheral Th2 dominance in atopy

It has been proposed that the differential organ-specific trafficking of CD4⁺ Th1 and Th2 cells promotes different inflammatory reactions. Skin, lung and nose represent functionally distinct immune compartments, and chronic inflammation of these organs is generally associated with the infiltration of tissues by T cells [1,12,20,21].

Phenotype of T cells in atopic allergy

So far, a peripheral blood T cell marker has not been identified in allergic asthma, allergic rhinitis or other organ-specific autoimmune and inflammatory diseases; however, most T cells that home to skin are of the CD45RO⁺ memory or effector (memory/effector) phenotype and express cutaneous lymphocyte-associated antigen (CLA), a skin-selective homing receptor [22]. Peripheral blood CLA⁺ memory/effector cells show typical features of activated T cells. Both CD4⁺ and CD8⁺ subsets of freshly isolated CLA⁺ T cells express significantly high levels of CD25, CD40 ligand and HLA-DR. They show spontaneous proliferation, induce IgE production by B cells and enhance eosinophil survival [3,23,24].

In peripheral blood, a cytokine pattern polarized towards Th2 cells is regarded as a specific feature that reflects immune dysregulation in atopy. Notably, a switch in cytokine profile towards Th0 and Th1 cells occurs after T cells home to the skin in AD. Expression of interferon- γ (IFN- γ) predominates over interleukin 4 (IL-4) in chronic skin lesions and older patch-test reactions, but IL-5 and IL-13 expression remains at high levels [25–27]. IL-12 and IL-18, produced by keratinocytes and dendritic cells in the microenvironment, are probably the predominant mediators of the induction of IFN- γ in T cells that have homed to the skin [28,29]. In addition, most of the T

cells found in draining lymphatics of the skin, which represent skin-dehoming memory/effector T cells, express CLA and increased levels of IFN- γ [30,31].

Increased activation-induced death of Th1 cells in peripheral blood

The balance between production and death is important for maintaining cell numbers within physiological ranges. An accumulation of cells in tissue can be a consequence of either an increase in cell production or a decrease in cell death. Apoptosis of mature T cells is a powerful mechanism for deleting T cells, which raises the interesting possibility that an unequal apoptosis of Th1 and Th2 effector cells can lead to preferential deletion of one subset over another. Consistent with this, it has been demonstrated that a fraction of circulating CLA⁺CD45RO⁺ T cells show direct evidence for activation-induced cell death (AICD) initiated *in vivo* [2**].

Immediately after purification, CLA⁺CD45RO⁺ T cells show active caspase-8 and increased caspase degradation, in contrast to their CLA[−] counterparts, CLA⁺ T cells of healthy subjects and individuals with several non-atopic disorders, such as intrinsic types of asthma and AD, psoriasis, contact dermatitis and bee venom allergy. In addition, AICD of CLA⁺ T cells can be inhibited by blocking both the caspase cascade and interactions between Fas and Fas ligand. Characterization of the cytokine profile of T cells that resist or undergo AICD has revealed that there is unequal death in the Th1 and Th2 populations. In the absence of survival factors or inhibitors of the Fas pathway, a cytokine profile skewed towards Th2 cells has been observed in both CD45RO⁺ T cells and CLA⁺ CD45RO⁺ T cell clones [2**].

In support of these findings, Th1 cells that secrete high levels of IFN- γ are short-lived and do not efficiently develop into long-term memory Th1 cells in mice [32,33]. The results of studies using *in vitro* generated Th1 and Th2 cells suggest that their unequal susceptibility to AICD might be related to an increase in the expression of a Fas-associated phosphatase, FAP-1, in Th2 cells [34]. In addition, AICD susceptibility of Th1 subsets in HIV infection is related to variable levels of Bcl-2 expression [35].

Furthermore, upregulation of phosphatidylinositol 3-kinase, which inhibits cleavage of caspase-8 at the death-inducing complex, has been reported as a mechanism for Th2 resistance to Fas-mediated apoptosis [36]. The instruction of distinct Th cell fates via different transcription factors, such as T-BET for Th1 cells and GATA-3 for Th2 cells, has been demonstrated in several mouse models, and evidence suggests that it might occur in human diseases [37,38*]. In addition, Notch pathways are used by antigen-presenting cells to instruct T cell differentiation. Of the two Notch ligand families, Delta

induces Th1, whereas Jagged induces Th2 cell differentiation [39**].

Prolonged T cell survival in allergic inflammatory tissues

In the inflammatory forms of allergic diseases, dermis and submucosa turn into a secondary lymphoid-organ-like tissue containing migrating T cells and dendritic cells. Tissue infiltration by different types of dendritic cell and an increase in expression of the high-affinity receptor for IgE (FcεRI) have been repeatedly reported in AD in comparison to the non-atopic form of allergic disease [40]. In addition, B cell infiltration and local IgE switching have been reported in atopic asthma and rhinitis [41].

A prerequisite for chronic inflammation is the prolonged survival of inflammatory cells in the affected organs. Loss of attachment to the matrix causes apoptosis in many cell types including T cells [42]. This phenomenon, referred to as 'anoikis' (homelessness), is assumed to prevent cells that have lost contact with their original surroundings from establishing themselves at inappropriate locations.

Inflammatory cells are located in the extracellular matrix (ECM) — a protein network in the tissues that exerts a profound control over the infiltrating cells. Although they express both Fas and Fas ligand, T cells that infiltrate the skin in AD are protected from apoptosis by ECM proteins and cytokines. The effects of the ECM are primarily mediated by integrins that can recognize several ECM proteins; conversely, a single ECM protein can bind to several integrins [42]. Cell adhesion to the ECM has been implicated in protection from apoptosis in anchorage-dependent cell types [42]. Apparently, integrin signalling by the ECM is an important survival signal to T cells, which do not require anchorage in the tissues. In addition, the common γ chain that is shared by IL-2, IL-4 and IL-15 receptors, as well as all other known T cell growth factor receptors, is an essential signalling component for T cell survival [43].

T cells induce epithelial cell activation and apoptosis

The infiltration of T cells into the dermis, which leads to an interaction between T cells and keratinocytes and a marked keratinocyte pathology, is associated with eczematous skin lesions [6]. Transendothelial migration and influx into skin represent the first phase leading to dermal perivascular infiltration by T cells in AD. Notably, a second step of chemotaxis includes the migration of T cells closer to and into the epidermis, where they augment T-cell-mediated effector functions [44].

It has been shown that IFN- γ is one of the most active cytokines during interactions between T cells and keratinocytes [45]. IFN- γ upregulates MHC class I molecules and Fas, and induces the *de novo* synthesis of MHC class

II molecules on keratinocytes [46]. IFN- γ also induces the expression of several cytokines, including IL-1 α , IL-1 receptor agonist, tumour-necrosis factor- α (TNF- α) and granulocyte-macrophage colony stimulating factor [47,48]. Via IFN- γ stimulation, chemokines such as IP-10 (IFN- γ -inducible protein-10), Mig (monokine induced by γ -IFN) and ITAC (IFN- γ -inducible α -chemoattractant) are strongly upregulated in keratinocytes [44]. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies taken from individuals with AD [44].

An inflammatory process is associated almost invariably with tissue damage and healing. There is growing evidence to incriminate the epidermis and bronchial epithelium as both the target and enhancer of the inflammatory response in asthma and AD [6,7]. The respiratory epithelium is an essential target of the inflammatory attack by T cells and eosinophils in asthma [7]. Bronchial epithelial cells show morphological characteristics of apoptosis mediated by activated T cells and eosinophils.

Similar to findings in the lung, the apoptosis of keratinocytes induced by T cells and mediated by Fas is a crucial event in the formation of eczematous lesions in both AD and allergic contact dermatitis [6]. In both asthmatic lung and eczematous skin, epithelial cells express functional Fas as an apoptosis receptor. IFN- γ upregulates Fas and renders keratinocytes susceptible to apoptosis. By contrast, TNF- α upregulates both Fas and Fas ligand, as well as its own receptors, TNF-RI and TNF-RII, on bronchial epithelial cells. Moderate to severe epithelial apoptosis is relevant *in vivo* in bronchial biopsies taken from individuals with asthma and lesional skin biopsies taken from individuals with AD [6,7].

It should be noted here that the receptor affinity and activation thresholds for IFN- γ and the Th2 cytokines IL-4, IL-5 and IL-13 show a significant difference. For example, 1 ng/ml of IFN- γ can induce keratinocyte apoptosis, whereas 50 ng/ml of IL-4 or IL-13 is required to induce IgE production by B cells and also 50 ng/ml of IL-5 is needed to prolong eosinophil lifespan *in vitro* [6,14]. This suggests that a Th2-like T cell that produces small quantities of IFN- γ can also induce epithelial cell apoptosis. Apparently, bronchial epithelial apoptosis leads to epithelial shedding in asthma and keratinocyte apoptosis leads to spongioform morphology in AD [6,7,49]. It seems probable that, in eczema, keratinocyte stem cells located directly at the basal membrane are protected from T-cell-induced apoptosis because of strong antiapoptotic signals from dermal fibrocytes and ECM proteins [42].

Conclusions

Different immune response profiles and activation and apoptosis thresholds define at least three types of allergic

Table 1

Immunological characterization of atopic, non-atopic and monoallergic forms of allergic disease.

	Clinical outcome	Total IgE	Specific IgE	Th1 AICD	Specific Th2	Eosinophilia	Epithelial apoptosis	Type 1 skin test reactivity
Atopic disease	AD, asthma, rhinitis	High	+ (multiple specificity)	+	+	+	+	+ (multiple specificity)
Non-atopic disease (non-IgE-associated, intrinsic)	Dermatitis, asthma, rhinitis	Normal	—	—	—	±	+	—
Monoallergy (allergic-breakthrough)	Without organ involvement (venom allergy)	Normal	+ (single specificity)	—	+	—	—	+ (single specificity)
	With organ involvement (dermatitis, asthma, rhinitis)	Normal	+ (single specificity)	—	+	—	+	+ (single specificity)

Abbreviations: AD, atopic dermatitis; AICD, activation-induced cell death.

disease (Table 1). In atopic diseases, T cell turnover between skin and circulation is associated with a switch in cytokine profiles from Th0 and/or Th1-like inside the skin to Th0 and/or Th2-like in the circulation. T-cell-mediated effector functions, such as epithelial shedding and spongiosis formation, depend on the production of IFN- γ , TNF- α and Fas ligand in the skin and lung (Figure 1). By contrast, hyper-IgE production depends on the Th2-like profile of circulating memory/effector T cells that home to secondary lymphoid organs. The unequal susceptibility to AICD between Th1 and Th2 cells that controls the T cell fate might eventually cause an imbalance in Th cell subsets, leading to a peripheral blood Th2 response in polyallergic individuals with AD. This is associated frequently with peripheral blood and sometimes with tissue eosinophilia.

In monoallergic diseases, allergen-specific Th2 and IgE responses are confined to the single allergen and eosinophilia is not observed. Changes in the fine balance between allergen-specific Tr1 and allergen-specific Th2 cells is very crucial in the development and also treatment of monoallergies. In non-atopic (non-IgE-associated) forms of allergic disease, Th2 cytokine production is much lower than in atopic forms. Total IgE and specific IgE are not observed, but eosinophilia is reported occasionally. Epithelial apoptosis in the lung and skin might occur in all forms of allergic disease with tissue inflammation.

An understanding of immune mechanisms in the pathogenesis of different types of allergic diseases will open new windows for future treatment of allergic diseases and possible cure.

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