Mechanisms of Allergic Inflammation

Allerjik İnflamasyonun Mekanizmaları

Mübeccel Akdiş

Swiss Institute of Allergy and Asthma Research (SIAF)
Davos, Switzerland

SUMMARY

Genetic predisposition and environmental instructions tune thresholds for activation, effector functions and life span of T cells, other inflammatory cells and resident tissue cells. Defects in apoptosis and peripheral tolerance in T cells define different allergic phenotypes. High IFN-γ-producing activated allergen-specific T cells predominantly undergo apoptosis in the circulation, skewing the immune response to surviving Th2 cells in atopic diseases. In affected tissues, these cells switch on effector cytokines, induce activation and apoptosis of epithelial cells. On the other hand, in monoallergic non-atopic individuals disturbed balance toward allergen-specific T helper 2 cells instead of T regulatory 1 cells characterize the T cell response. *(Journal of Current Pediatrics 2009; 7: 24-30)*

Key words: Apoptosis, atopy, cytokines, T cells, asthma, atopic dermatitis

ÖZET

Genetik yatkınlık ve çevreden gelen uyarılar T hücrelerinin, diğer inflamatuvar hücrelerin ve vücut dokularında bulunan hücrelerin yaşam sürelerini ve efektör fonksiyonlarını düzenlerler. T hücrelerindeki apoptoz ve periferal tolerans bozuklukları farklı alerjik fenotiplerini belirler. Yüksek IFN-γ yapan aktive olmuş alerjen spesifik T hücreleri dolaşımda erken apoptoza gittikleri için atopik hastalıklarda immun yanıtı Th2 hücreleri yönüne çevirirler. Etkilenen dokularda bu hücreler efektör sitokinleri devreye sokarak epitel hücrelerinin aktivasyonunu ve apoptozunu da tetiklerler. Diğer taraftan monoallerjik nonatopik bireylerde T regulatuvar 1 hücreleri yerine alerjen spesifik Th2 hücreleri yönüne kaymış olan denge T hücre yanıtını belirler. *(Güncel Pediatri 2009; 7: 24-30)*

Anahtar kelimeler: Apoptoz, atopi, sitokinler, T hücreleri, astım, atopik dermatit

Address for Correspondence/Yazışma Adresi:
PD Mübeccel Akdiş, MD, PhD
Head of Immunodermatology
Swiss Institute of Allergy and Asthma Research (SIAF), Obere Strasse 22
CH-7270 Davos, Switzerland
Phone: +4181 4100848 Fax: +4181 4100840
E-mail: akdism@siaf.unizh.ch

Received/Geliş Tarihi: *12.03.2009*
Accepted/Kabul Tarihi: *14.05.2009*

Introduction

T cells constitute a large population of cellular infiltrate in atopic/allergic inflammation and a dysregulated immune response appears to be an important pathogenetic factor. Cardinal events during allergic inflammation can be classified as activation, organ-selective homing, survival and reactivation and effector functions of immune system cells (1). T cells are activated by aeroallergens, food antigens, autoantigens and bacterial superantigens in allergic inflammation. They are under the influence of skin, lung or nose-related chemokine network and they show organ-selective homing. A prolonged survival of the inflammatory cells in the tissues and consequent reactivation is observed in the subepithelial tissues (2-4). Finally, T cells display effector functions, which result in the induction of hyper IgE, eosinophil survival and mucus hyper production (3-5); and interact with bronchial epithelial cells and keratinocytes causing their activation and apoptosis (6,7).

It is still not understood why exposure to allergens causes atopic disorders in some individuals, but not others, however, it is clear that strong interaction of environmental and genetic factors is involved. Four cardinal events during allergic inflammation can be

classified as activation of memory/effector T cells and other effector cells such as mast cells, eosinophils and basophils, their organ-selective homing, prolonged survival and reactivation inside the allergic organs and effector functions (8). T cells are activated by aeroallergens, food antigens, autoantigens and bacterial superantigens in allergic inflammation (3,9). They are under the influence of skin, lung or nose-related chemokine network and they show organ-selective homing (10-12). A prolonged survival of the inflammatory cells and strong interaction with resident cells of the allergic organ and consequent reactivation is observed in the subepithelial tissues (13,14). T cells play important effector roles in atopic dermatitis and asthma with induction of hyper IgE and eosinophil survival (3,14). In addition, activated T cells induce bronchial epithelial cell and keratinocyte apoptosis as major tissue injury events (7,15-17). Peripheral T cell tolerance to allergens can overcome all of the above pathological events in allergic inflammation, because they all require T cell activation.

Atopic, Monoallergic and Non-IgE-Associated Types of Allergic Diseases

Atopic dermatitis (AD), allergic rhinitis, and asthma are atopic diseases that develop on a complex genetic background. Although they target different organs, in most patients they are characterized by the presence of elevated total serum IgE levels. The atopic form of allergic diseases is often initiated with the atopic march in infancy and the inflammation may involve one of the organs such as skin, lung and nose or appear in combination (18). The cutaneous manifestations of atopy represent the beginning of the atopic march. Approximately half of AD patients develop asthma, particularly with severe AD, and two thirds develop allergic rhinitis (18). The start of the allergic march is characterized by IgE mediated sensitization to food allergens and later only to inhalatory allergens, and that food allergy is very frequently associated with inhalatory allergies. The second type of allergic diseases is monoallergy, so called allergic-breakthrough characterized by development of allergen-specific IgE in the absence of high serum total IgE in non-atopic individuals (19). It may 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 as rhinitis, asthma and dermatitis (20,21). Especially venom allergic and allergic rhinitis patients in this group show highly successful response to allergen-specific immunotherapy (20,22). One of the key question in monoallergies has been to understand how an individual develops allergy to a single protein, while tolerating thousands of others exposed by ingestion or inhalation. Different sub-types of regulatory and suppressor cells and mechanisms that may play a role in peripheral tolerance have been demonstrated, and their biology has been the subject of intensive investigation during the last few years. T regulatory (Tr) 1 cells consistently represent the dominant subset specific for common environmental allergens in healthy individuals, in contrast there is a high frequency of allergen-specific Th2 cells in allergic individuals (23). Effector (allergen-specific Th2) and suppressor (allergen-specific Tr1) T cells exist in both healthy and allergic individuals in certain amounts. Their ratio determines the development of a healthy or an allergic immune response and also plays a role in successful treatment (23-25).

Although most of the patients with AD, asthma and rhinitis show high levels of total and allergen-specific IgE, some of the patients have normal total IgE levels and negative serum allergen-specific IgE. The subgroup of these patients has been termed, non atopic form, non-allergic form, non IgE-associated form or intrinsic-types of asthma, dermatitis and rhinitis (26-29). This subtype can be characterized by the following criteria a) clinical phenotype of asthma, AD or rhinitis; b) negative type I skin hypersensitivity to aero- and food allergens; c) normal serum IgE levels; d) no detectable specific IgE antibodies to aero- and food allergens. These three forms of diseases often overlap in terminology and mechanisms, however exact definitions related with the underlying pathomechanisms may become possible in the near future, because of rapid advancements in the field.

Increased Activation-Induced Cell Death in Th1 Cells as a Mechanism of Peripheral T Helper 2 Dominance in Atopy

It has been proposed that differential organ-specific trafficking of $CD4^+$ Th1 and Th2 cells promote different inflammatory reactions. Skin, lung and nose represent functionally distinct immune compartments

and chronic inflammation of these organs is generally associated with tissue infiltration by T cells (1,9,22,30). A peripheral blood T cell marker has not been identified in allergic asthma, allergic rhinitis as well as other organ-specific autoimmune and inflammatory diseases so far. However, the great majority of T cells homing to skin are of the $CD45RO^+$ memory/effector phenotype and express the skin-selective homing receptor, cutaneous lymphocyte-associated antigen (CLA) (31). Peripheral blood CLA^+ memory/effector cells demonstrate typical features of activated T cells. Both $CD4^+$ and $CD8^+$ subsets of freshly isolated CLA^+ T cells express significantly higher levels of CD25, CD40-ligand and HLA-DR. They show spontaneous proliferation, induce IgE production by B cells and enhance eosinophil survival (3,32,33).

A polarized peripheral blood Th2 cytokine pattern was regarded as a specific feature reflecting immune dysregulation in atopy. Interestingly, a switch in cytokine profile occurs towards Th0/Th1 after skin-homing of T cells in AD. IFN-γ predominates over IL-4 in chronic skin lesions and older patch test reactions, whereas, IL-5 and IL-13 still remain at high levels (34-36). IL-12 and IL-18 produced by keratinocytes and dendritic cells in the microenvironment are likely predominant mediators for the induction of IFN-γ in T cells after homing to skin (37,38). In addition, most of the T cells found in skin-draining lymphatics, which represent skin-de-homing memory/effector T cells, express CLA and increased levels of IFN-γ (39,40).

The balance between production and death is important in the control of cell numbers within physiological ranges. Cell accumulation in the tissues may be a consequence of either increased cell production or decreased cell death. Because apoptosis of mature T cells is a powerful mechanism for deleting T cells, it raises the interesting possibility that unequal apoptosis of Th1 and Th2 effector cells may lead to preferential deletion of one subset over another. It has been demonstrated that, a fraction of circulating CLA^+ $CD45RO^+$ T cells show direct evidence for in vivo initiated activation-induced cell death (AICD) (2). Immediately after purification, these cells show active caspase-8 and increased caspase degradation, in contrast to their CLA^- counterpart and CLA^+ T cells of healthy individuals and 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 could be inhibited by caspase cascade inhibition and by blocking Fas/Fas-ligand interaction. Characterization of cytokine profile of T cells, which resist or undergo AICD revealed unequal death in Th1 and Th2 cells. In the absence of survival factors and Fas-pathway inhibitors, a Th2-skewed cytokine profile was observed in $CD45RO^+$ T cells as well as CLA^+ $CD45RO^+$ T cell clones (2). Supporting these findings, high IFN-γ-secreting Th1 cells were shown to be short lived that do not efficiently develop into long term memory Th1 cells in mice (41,42). By using in vitro generated Th1 and Th2 cells, it was suggested that unequal susceptibility to AICD may be related to increased expression of a Fas-associated phosphatase, FAP-1 in Th2 cells (43). In addition, AICD susceptibility of Th1 subsets in HIV infection was found related to variable levels of Bcl-2 expression (44). Furthermore, upregulation of phosphatidylinositol 3'-kinase, which inhibits caspase-8 cleavage at the death-inducing complex has been reported as a mechanism for Th2 resistance to Fas-mediated apoptosis (45). Instruction of different 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 some evidence has been shown for human diseases (46,47). In addition, Notch pathways are used by antigen-presenting cells to instruct T cell differentiation. Of the two Notch ligand families, Delta induces Th1, while Jagged induces Th2 cell differentiation (48).

In the inflammatory forms of allergic diseases, dermis and submucosa turns into a secondary lymphoid organ-like tissue with migrating T cells and dendritic cells. Tissue infiltration of different types of dendritic cells and increased expression of the high affinity receptor for IgE (FcεRI) has been repeatedly reported in AD in comparison to non-atopic form (49). B cell infiltration and local IgE switch has been reported in the atopic asthma and rhinitis (50). A prerequisite for chronic inflammations is the prolonged survival of inflammatory cells in the affected organs. Loss of attachment to matrix causes apoptosis in many cell types including T cells (51). This phenomenon, referred to as anoikis (homelessness), was assumed to prevent cells that have lost contact with their original surroundings, from establishing themselves at inap-

propriate locations. Inflammatory cells reside in a protein network in the tissues, the ECM, which exerts a profound control over them. T cells infiltrating the AD skin are protected from apoptosis by ECM proteins and cytokines, although they express both Fas and Fas-ligand. The effects of ECM are primarily mediated by integrins that can recognize several ECM proteins; conversely, a single ECM protein can bind to several integrins (51). Cell adhesion to the ECM has been implicated in protection from apoptosis in anchorage-dependent cell types (51). Apparently, integrin signaling by ECM represents an important survival signal to T cells, although they do not require anchorage in the tissues. In addition, the common γ-chain shared by IL-2, IL-4 and IL-15 receptors as well as all other known T cell growth factor receptors is an essential survival signaling component for T cells (52).

T Cells Induce Epithelial Cell Activation and Apoptosis

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 target and enhancer of the inflammatory response in asthma and AD (6,7). The respiratory epithelium was demonstrated as 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 the findings in the lung, apoptosis of keratinocytes induced by T cells and mediated by Fas is a crucial event in the formation of eczematous lesions in 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. On the other hand, TNF-α upregulates both Fas and Fas-ligand as well as its own receptors, TNF-RI and II on bronchial epithelial cells. Moderate to severe epithelial apoptosis was demonstrated to be relevant in vivo using bronchial biopsies in asthma and lesional skin biopsies in AD. It has to be noted here that receptor affinity and activation thresholds for IFN-γ and Th2 cytokines IL-4, IL-5 and IL-13 show a significant difference. For example, 1 ng/ml of IFN-γ can induce KC apoptosis, whereas 50 ng/ml of IL-4 and IL-13 are required to induce IgE production by B cells and IL-5 to prolong eosinophil life span in vitro (6,24). This suggests that a Th2-like T cell, which 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 (6,7,53). It seems probable that during the course of eczema, keratinocyte stem cells located directly at the basal membrane are protected from T-cell induced apoptosis because of strong anti-apoptotic signals from dermal fibrocytes and ECM proteins (51).

Table 1. Immunological characterization of atopic, non-atopic and monoallergic forms of allergic diseases

	Clinical outcome	Total IgE	Specific IgE	Th1 AICD	Specific Th2	Eosinophilia	Epithelial apoptosis	Type 1 skin test reactivity
Atopic diseases	AD asthma rhinitis	high	+ (multiple specificity)	+	+	+	+	+ (multiple specificity)
Non-atopic diseases (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)

Conclusion

Different immune response profiles and activation and apoptosis thresholds define at least three types of allergic diseases (Table 1). In atopic diseases, T cell turnover between skin and circulation is associated with a switch of cytokine profiles as Th0/Th1-like inside the skin and Th0/Th2-like in the circulation. T cell-mediated effector functions such as epithelial shedding and spongiosis formation depends on IFN-γ, TNF-α and Fas-ligand production in the skin and lung. In contrast, hyper-IgE production depends on 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, may eventually cause an imbalance in Th cell subsets leading to peripheral blood Th2 response in poly-allergic individuals with AD. This is often associated with peripheral blood and sometimes tissue eosinophilia. In monoallergic form, allergen-specific Th2 and IgE responses are confined to the single allergen and esosinophilia is not observed. Changes in the fine balance between allergen-specific Tr1 and allergen-specific Th2 cells are very crucial in the development and also treatment of monoallergies. In the non IgE-associated type of allergic diseases, Th2 cytokine production is much lower compared to atopic form. Total IgE and specific IgE are not observed, but eosinophilia is reported occasionally. Epithelial apoptosis in the lung and skin may occur in all forms with tissue inflammation.

Acknowledgements

The authors laboratory is supported by the Swiss National Foundation Grant: 32-100266, United Bank of Switzerland, Zurich and Niarchos Foundation, Monaco.

References

1. Akdis CA, Akdis M, Trautmann A, Blaser K. Immune regulation in atopic dermatitis. Curr Opin Immunol 2000; 12:641-6.
2. Akdis M, Trautmann A, Klunker S, Daigle I, Kücüksezer UC, Deglmann W, et al. T helper (Th) 2 predominance in atopic disease is due to preferential apoptosis of circulating memory/effector Th1 cells. Faseb J 2003; 17:1026-35.
3. Akdis M, Simon H-U, Weigl L, Kreyden O, Blaser K, Akdis CA. 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 1999;163:466-75.
4. Simon H-U, Blaser K. Inhibition of programmed eosinophil death: A key pathogenic event for eosinophilia. Immunol Today 1995; 16:53-5.
5. Whittaker L, Niu N, Temann UA, Stoddard A, Flavell RA, Ray A, et al. Interleukin-13 mediates a fundamental pathway for airway epithelial mucus induced by CD4 T cells and interleukin-9. Am J Respir Cell Mol Biol 2002; 27:593-602.
6. Trautmann A, Akdis M, Kleeman D, Altznauer F, Simon H-U, Graeve T, et al. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. J Clin Invest 2000; 106:25-35.
7. Trautmann A, Schmid-Grendelmeier P, Krüger K, Crameri R, Akdis M, Akkaya A, et al. T cells and eosinophils cooperate in the induction of bronchial epithelial apoptosis in asthma. J Allergy Clin Immunol 2002; 109:329-37.
8. Akdis CA, Akdis M, Trautmann A, Blaser K. Immune regulation in atopic dermatitis. Curr Opin Immunol 2000; 12:641-6.
9. Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DYM. Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. J Clin Invest 1995; 95:913-8.
10. Klunker S, Trautmann A, Akdis M, Verhagen J, Schmid-Grendelmeier P, Blaser K, et al. A second step of chemotaxis after transendothelial migration: Keratinocytes undergoing apoptosis release IP-10, Mig and iTac for T cell chemotaxis towards epidermis in atopic dermatitis. J Immunol 2003;171:1078-84.
11. Luster AD. The role of chemokines in linking innate and adaptive immunity. Curr Opin Immunol 2002; 14:129-35.
12. Gutierrez-Ramos JC, Lloyd C, Kapsenberg ML, Gonzalo JA, Coyle AJ. Non-redundant functional groups of chemokines operate in a coordinate manner during the inflammatory response in the lung. Immunol Rev 2000; 177:31-42.
13. Akdis M, Trautmann A, Klunker S, Daigle I, Kücüksezer UC, Deglmann W, et al. T helper (Th) 2 predominance in atopic diseases is due to preferential apoptosis of circulating memory/effector Th1 cells. Faseb J 2003; 17:1026-35.
14. Simon H-U, Blaser K. Inhibition of programmed eosinophil death: A key pathogenic event for eosinophilia. Immunol Today 1995; 16:53-5.
15. Trautmann A, Akdis M, Kleemann D, Altznauer F, Simon HU, Graeve T, et al. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. J Clin Invest 2000; 106:25-35.
16. Trautmann A, Akdis M, Brocker EB, Blaser K, Akdis CA. New insights into the role of T cells in atopic dermatitis and allergic contact dermatitis. Trends Immunol 2001; 22:530-2.
17. Trautmann A, Akdis M, Schmid-Grendelmeier P, Disch R, Brocker EB, Blaser K, et al. Targeting keratinocyte apoptosis in the treatment of atopic dermatitis and allergic contact dermatitis. J Allergy Clin Immunol 2001; 108:839-46.
18. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003; 112:118-27.
19. Katz DH, Bargatze RF, Bogowitz CA, Katz LR. Regulation of IgE antibody production by serum molecules. V. Evidence that coincidental sensitization and imbalance in the normal damping mechanism results in "allergic breakthrough". J Immunol 1979; 122:2191-7.

20. Muller UR. Recent developments and future strategies for immunotherapy of insect venom allergy. Curr Opin Allergy Clin Immunol 2003; 3:299-303.
21. Pichler WJ. Lessons from drug allergy: against dogmata. Curr Allergy Asthma Rep 2003;3:1-3.
22. Durham SR, Walker SM, Varga E-V, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999; 341:468-75.
23. Akdis M, Verhagen J, Taylor A, Karamloo F, Karagiannidis C, Crameri R, et al. Immune Responses in Healthy and Allergic Individuals Are Characterized by a Fine Balance between Allergen-specific T Regulatory 1 and T Helper 2 Cells. J Exp Med 2004; 199:1567-75.
24. Akdis CA, Blesken T, Akdis M, Wüthrich B, Blaser K. Role of IL-10 in specific immunotherapy. J Clin Invest 1998; 102:98-106.
25. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K, et al. IL-10 and TGF-b cooperate in regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol 2003; 33:1205-14.
26. Humbert M, Menz G, Ying S, Corrigan CJ, Robinson DS, Durham SR, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. Immunol Today 1999; 20:528-33.
27. Schmid-Grendelmeier P, Simon D, Simon H-U, Akdis CA, Wüthrich B. Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). Allergy 2001; 56:841-9.
28. Moneret-Vautrin DA, Hsieh V, Wayoff M, Guyot JL, Mouton C, Maria Y. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. Ann Allergy 1990; 64:513-8.
29. Akdis CA, Akdis M. Immunological differences between intrinsic and extrinsic types of atopic dermatitis. Clin Exp Allergy 2003; 33:1618-21.
30. Robinson DS, Hamid QA, Ying S, Tsicopoulos A, Barkans J, Bentley AM, et al. Predominant Th2-like bronchoalveolar T lymphocyte population in atopic asthma. N Engl J Med 1992; 326:298-304.
31. Picker LJ, Michie SA, Rott LS, Butcher EC. 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 1990; 136:1053-61.
32. Santamaria Babi LF, Picker LJ, Perez Soler MT, Drzimalla K, Flohr P, Blaser K, et al. 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 1995; 181:1935-40.
33. Akdis M, Akdis CA, Weigl L, Disch R, Blaser K. 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 1997; 159:4611-9.
34. Grewe M, Bruijnzeel-Koomen CAFM, Schöpf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T, et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 1998; 19:359-61.
35. Thepen T, Langeveld-Wildschut EG, Bihari IC, van Wichen DF, Van Reijsen FC, Mudde GC, et al. Biphasic response against aeroallergen in atopic dermatitis showing a switch from an initial Th2 response to a Th1 response in situ: An immunochemical study. J Allergy Clin Immunol 1996; 97:828-37.
36. Akdis CA, Akdis M, Simon D, Dibbert B, Weber M, Gratzl S, et al. T cells and T cell-derived cytokines as pathogenic factors in the nonallergic form of atopic dermatitis. J Invest Dermatol 1999; 113:628-34.
37. Müller G, Saloga J, Germann T, Bellinghausen I, Mohamadzadeh M, Knop J, et al. Identification and induction of human keratinocyte-derived IL-12. J Clin Invest 1994; 94:1799-805.
38. Stoll S, Jonuleit H, Schmitt E, Müller G, Yamauchi H, Kurimoto M, et al. Production of functional IL-18 by different subtypes of murine and human dendritic cells (DC): DC-derived IL-18 enhances IL-12-dependent Th1 development. Eur J Immunol 1998; 28:3231-9.
39. Yawalkar N, Hunger RE, Pichler WJ, Braathen LR, Brand CU. Human afferent lymph from normal skin contains an increased number of mainly memory/effector $CD4^+$ T cells expressing activation, adhesion and co-stimulatory molecules. Eur J Immunol 2000; 30:491-7.
40. Hunger RE, Yawalkar N, Braathen LR, Brand CU. The HECA-452 epitope is highly expressed on lymph cells derived from human skin. Br J Dermatol 1999; 141:565-9.
41. Liu Y, Janeway CA, Jr. Interferon gamma plays a critical role in induced cell death of effector T cell: a possible third mechanism of self-tolerance. J Exp Med 1990; 172:1735-9.
42. Wu CY, Kirman JR, Rotte MJ, Davey DF, Perfetto SP, Rhee EG, et al. Distinct lineages of T(H)1 cells have differential capacities for memory cell generation in vivo. Nat Immunol 2002; 3:852-8.
43. Zhang X, Brunner T, Carter L, Dutton RW, Rogers P, Bradley L, et al. Unegual death in T helper cell (Th) 1 and Th2 effectors: Th1, but not Th2, effectors undergo rapid Fas/FasL-mediated apoptosis. J Exp Med 1997; 185:1837-49.
44. Ledru E, Lecoeur H, Garcia S, Debold T, Gougeon M-L. Differential susceptibility to activation-induced apoptosis among peripheral Th1 subsets: correlation with Bcl-2 expression and consequences for AIDS pathogenesis. J Immunol 1998; 160:3194-206.
45. Varadhachary AS, Peter ME, Perdow SN, Krammer PH, Salgame P. Selective up-regulation of phosphotidyinositol 3'-kinase activity in Th2 cells inhibits caspase-8 cleavage at the death-inducing complex: A mechanism for Th2 resistance from Fas-mediated apoptosis. J Immunol 1999; 163:4772-9.
46. Finotto S, Neurath MF, Glickman JN, Qin S, Lehr HA, Green FH, et al. Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. Science 2002; 295:336-8.

47. Skapenko A, Leipe J, Niesner U, Devriendt K, Beetz R, Radbruch A, et al. GATA-3 in Human T Cell Helper Type 2 Development. J Exp Med 2004; 199:423-8.
48. Amsen D, Blander JM, Lee GR, Tanigaki K, Honjo T, Flavell RA. Instruction of distinct CD4 T helper cell fates by different notch ligands on antigen-presenting cells. Cell 2004;117:515-26.
49. Kerschenlohr K, Decard S, Darsow U, Ollert M, Wollenberg A. Clinical and immunological rectivity to aeroallergens in "intrinsic" atopic dermatitis patients. J Allergy Clin Immunol 2003; 111:195-7.
50. Cameron L, Gounni AS, Frenkiel S, Lavigne F, Vercelli D, Hamid Q. S epsilon S mu and S epsilon S gamma switch circles in human nasal mucosa following ex vivo allergen challenge: evidence for direct as well as sequential class switch recombination. J Immunol 2003; 171:3816-22.
51. Giancotti FG, Rouslahti E. Integrin signaling. Science 1999; 285:1028-32.
52. Li WC, Ima A, Li Y, Zheng XX, Malek TR, Strom TB. Blocking the common g-chain of cytokine receptors induces T cell apoptosis and long term islet allograft survival. J Immunol 2000; 164:1193-9.
53. Trautmann A, Altznauer F, Akdis M, Simon H-U, Disch R, Bröcker E-B, et al. The differential fate of cadherins during T cell-induced keratinocyte apoptosis leads to spongiosis in eczematous dermatitis. J Invest Derm 2001; 117:927-34.