Role of T Cells in Atopic Eczema

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32.1 Skin-Selective Homing of T Cells

It has been proposed that differential organ-specific trafficking of $CD4^+$ Th1 and Th2 cells promote different inflammatory reactions. Skin represents a functionally distinct immune compartment, and chronic inflammation of the skin is generally associated with tissue infiltration by T cells [1–3]. The great majority of these T cells homing to skin are of the $CD45RO^+$ memory/effector phenotype and express the skin-selective homing receptor, cutaneous lymphocyte-associated antigen (CLA) [4]. The CLA epitope consist of a sialyl-$Lewis^x$ carbohydrate and corresponds to a posttranslational modification of the P-selectin glycoprotein ligand 1 (PSGL-1) [5, 6]. It is characterized by specific binding to the monoclonal antibody (mAb) HECA-452 [4]. CLA binds to its vascular counter receptor, E-selectin (CD62E), which is expressed on inflamed superficial dermal postcapillary venules and endothelial cells [7, 8]. CLA^+ $CD45RO^+$ T cells migrate across activated endothelium using CLA/E-selectin, VLA-4/VCAM-1, and LFA-1/ICAM-1 interactions [9]. The generation of CLA on T cells undergoing naive to memory transition in skin-draining lymph nodes [10] requires α (1,3)-fucosyltransferase (FucT-VII) activity [5, 6]. Thus, CLA expression predominantly reflects the regulated activity of the glycosyltransferase, FucT-VII. CLA is upregulated by IL-12 that also enhances FucT-VII expression [11–14].

Induction of CLA expression by superantigens may play an important role in the pathogenesis of disorders associated with superantigen-producing staphylococci such as atopic eczema (AE) [11, 15, 16]. 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 APC. They can upregulate the expression of CLA by IL-12 production [17] and influence the functional profile of naive 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 [12]. Local production of IL-1 and TNF may induce expression of E-selectin on vascular endothelium [18] allowing an initial migration of CLA^+ memory/effector cells. Thereby they increase their efficiency of recirculation to the skin. Together, these mechanisms tend to markedly amplify the initial cutaneous inflammation. Moreover, inflamed skin may favor the progression of the staphylococcal skin colonization.

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 [4, 19]. CLA is expressed on less than 10% of liver infiltrating lymphocytes of acute allograft rejection and primary biliary cirrhosis patients although E-selectin is highly expressed on endothelium [20]. In addition, CLA^+ T cells were enriched on skin-infiltrating lymphocytes but not on lymphocytes in the joints of psoriatic arthritis [21]. In AE, circulating allergen-specific memory/effector T cells expressing CLA have been demonstrated to be activated and regulate IgE by secretion of an IL-13-dominated cytokine pattern and delay eosinophil apoptosis by IL-5 [22–24]. Studies focused on an intralesional cytokine pattern of mostly CLA-expressing, skin-infiltrating T cells in AE demonstrated higher IFN-γ and less IL-4, but still high IL-5 and IL-13 production [25–28].

32.2 Mechanisms of Cutaneous Lymphocyte-Associated Antigen Expression on Human T Cells

Infection or other damage induces the local production of distinct cytokines by tissue cells and antigen-presenting cells initiating the differentiation of T cells reacting to the antigen into either type 1 or type 2 cells [29]. IL-12 drives naive T cell differentiation toward type 1 phenotype and IL-4 drives toward type 2 [29, 30]. CD4+ Th1 cells are involved in cell-mediated inflammatory reactions. Their cytokines activate cytotoxic and inflammatory functions and induce delayed-type hypersensitivity reactions. Th2 cytokines support antibody production, particularly IgE responses, and eosinophil differentiation and function-associated allergic responses [29]. There is now clear evidence for heterogeneity of CD8+ T cell functions. CD8+ T cells may not act solely as effector cells concerning the elimination of viral and other intracellular pathogens (Tc1). They can also secrete Th2 cytokines and help B cells for Ab production (Tc2) [31, 32]. In allergic inflammations of the skin a considerable amount of CD8+ T cells, in addition to CD4+ T cells, were found to infiltrate skin, suggesting an important role for T cells of both subsets [24, 25].

Accordingly, the regulation of CLA on primed human Th1 and Th2 cells in $CD4^+$, and Tc1 and Tc2 cells in $CD8^+$ subsets has been investigated [33]. Purified $CD45RA^+$, $CD4^+$, and $CD8^+$ T cells were cultured with IL-2 in the presence of IL-12 or IL-4. IL-12 but not IL-4 induced CLA expression on both $CD4^+$ and $CD8^+$ T cells. Consequently, after differentiation, Th1 and Tc1 cells expressed CLA, whereas Th2 and Tc2 cells did not express CLA on their surface. Anti-CD3 stimulation in the absence of serum in the culture medium was sufficient to induce CLA on Th2 cells. We further investigated factors that regulate CLA expression in serum containing medium. IL-4 inhibited CLA and related α-fucosyltransferase mRNA expression. IL-12 and/or staphylococcal enterotoxin B (SEB) stimulation upregulated CLA expression on either Th2 and Tc2 cells of CD4+ or CD8+ subsets. Stimulation of the cells with SEB in the presence of autologous irradiated PBMC induced CLA expression on both Th1 and Th2 cells. Neutralization of IL-12 in these cultures significantly downregulated the surface CLA expression on both Th1 and Th2 cells, demonstrating that superantigen-induced IL-12 plays a major role on the induction of skin-selective homing ligand [33].

It has been investigated whether T cells show any limitation in the expression of skin-selective homing ligand in continuous cultures of $CD45RO^+$ T cells [33]. For this purpose, CLA^+ and CLA^- subsets of $CD45RO^+$, $CD4^+$, and $CD8^+$ T cells were purified from peripheral blood. The cells were incubated in resting conditions for 14 days in cultures containing low amounts of IL-2. CLA was downregulated on resting T cells within 2 weeks. Subsequently, all four T cell subsets were restimulated with anti-CD2, anti-CD3, anti-CD28 mAbs in the presence of IL-2 and IL-12. CLA was highly induced on both CLA^+ and CLA^- cells after 7 days. The cells were rested again for additional 14 days. CLA was downregulated a second time on all subsets. These experiments demonstrate that there is no restriction for CLA expression in T cell subsets. CLA is downregulated on resting T cells and can be induced repeatedly on CLA^- T cells.

In addition, an essential question was whether there is a limitation of CLA expression on human T cells by using non-skin-related, antigen-specific T cell clones. Regulation of CLA expression by cytokines was investigated in bee venom phospholipase A_2-specific T cell clones. Five different T cell clones of Th1, Th2, Th0, and Tr1 phenotypes were analyzed for CLA expression. Cells were stimulated with the phospholipase A_2 antigen in the presence of autologous irradiated PBMC as APC and IL-2. The addition of IL-4 to cultures significantly decreased CLA expression in T cell clones of Th2, Th0, and Tr1 phenotypes, but there was no significant effect on Th1 clones. IL-12 enhanced CLA expression in all five clones but to a lesser extend in the Th2 clone.

In conclusion, these studies demonstrate that the expression of skin-homing ligand differs in T cell populations after they have differentiated from naive T cells. Apparently, this is a consequence of the regulatory influences by exogenous cytokines and superantigens on those T cell subsets. There was no principle limitation for CLA expression on T cells. CLA can be induced on Th2 and Tc2 cells, on CLA^- T cells and on non-skin-related, antigen-specific T cell clones by IL-12. T cell stimulation via T cell receptor was sufficient; however, it was strictly controlled by serum factors. IL-12 responsiveness of Th2 cells was an important permissive factor for CLA expression in the presence of serum.

32.3 T Cell Chemotaxis in Atopic Eczema

Chemokines are potent leukocyte chemoattractants, cellular activating factors, and histamine releasing factors, which makes them particularly important in the pathogenesis of allergic inflammation. All of the chemokine receptors belong to the G-protein-coupled receptor family, comprising seven transmembrane domains, NH2-terminal glycosylation sites, and phosphorylation sites for protein kinases. The superfamily of seven-transmembrane G-protein-coupled receptors is the largest and most diverse group of membrane-spanning proteins [34]. Within all identified human genes, approximately 1,000 encode G-protein-coupled receptors. Many established G-protein-coupled receptor systems have been successfully exploited by the pharmaceutical industry to become the target for approximately 40 % of the currently available drugs [34]. Classical models of G-protein-coupled receptors require the occupation of receptors by an agonist to initiate activation of signal transduction pathways. Recently, the expression of G-protein-coupled receptors in recombinant systems revealed a constitutive spontaneous receptor activity, which is independent of receptor occupancy by an agonist [35]. An agonist with a preferential affinity for the active state of the receptor stabilizes the receptor in its active conformation leading to continuous activation signal. An inverse agonist (antagonist in the old terminology) with a preferential affinity for the inactive state, stabilizes the receptor in this conformation and consequently induces an inactive state, which is characterized by blocked signal transduction [36].

In particular, the eotaxin subfamily of chemokines and their receptor CC chemokine receptor 3 have emerged as central regulators of allergic response. One of the actions of glucocorticoids is to inhibit the transcription and/or stability of chemokine mRNA. The ideal pharmaceutical agent would interfere with selective function of critical chemokine and/or their receptors in the pathophysiology of asthma, but not in protective immune responses. A variety of approaches, including antibody neutralization experiments and gene targeting, have shown nonredundant specific roles for selected chemokines in allergic diseases. For example, eotaxin 1 gene-deficient mice have been shown to have impairment in the recruitment of eosinophils during the early part of the late-phase response in the lung in experimental models of asthma [37]. In addition, the use of neutralizing antibodies against RANTES, Macrophage inflammatory protein MIP-1α, MCP-1, MCP-5, and eotaxin-1 has indicated the individual importance of each of these chemokines in the development and regional localization of inflammatory cells during allergen-induced pulmonary infiltration and airway hyper responsiveness (AHR) [38]. For instance, neutralization of eotaxin 1 reduced eosinophil infiltration and AHR transiently after each allergen challenge, whereas neutralization of MCP-5 abolished AHR while altering the trafficking of eosinophils through the lung interstitium. An endobronchial challenge with allergen results in an increase in the level of chemokines in the bronchioalveolar lavage fluid. The chemoattractant activity of lavage fluid of patients with asthma is partially inhibited by antibodies against RANTES, MCP-3, MCP-4, and eotaxin-1.

Recently, cutaneous T cell-attracting chemokine CTACK/CCL27 and its receptor CRP-2/CCR10 were demonstrated to play a role in preferential attraction of CLA-bearing T cells to the skin [39, 40]. CTACK is predominantly expressed in the skin and selectively attracts a tissue-specific subpopulation of memory lymphocytes. It is also reported as ALP in mouse. The terms „Eskine“ and „ILC“ were also used for the same chemokine [39]. It is designated as CCL27 in the new systematic chemokine nomenclature. CTACK is constitutively expressed in mouse skin suggesting that other mechanisms of chemoattraction during flares of AE must exist. In a mouse model of AE, the Th2-selective chemokine the thymus and activation-regulated chemokine (TARC) is selectively induced by mechanical injury. NC/Nga mice spontaneously develop AE-like lesions and TARC is highly expressed in the basal epidermis with lesions, whereas it is not expressed in the skin without lesions [41]. Similarly, the expression of macrophage-derived chemokine (MDC) was increased several fold in the mouse skin with AE-like lesions [41]. IL-16 is a cytokine with selective chemotactic activity for $CD4^+$ T cells. An in situ hybridization study for IL-16 mRNA has demonstrated positive signals for IL-16 both in the basal layer of epidermis and in the dermis of AE skin samples [42]. In addition, the numbers of epidermal and dermal IL-16 mRNA+ cells were found significantly increased in acute in comparison to chronic AE skin lesions [42]. Furthermore, the same study demonstrated that upregulation of IL-16 mRNA expression in acute AE was associated with increased numbers of $CD4^+$ cells.

A second step of chemotaxis inside the allergic inflammatory tissues also occurs after transendothelial migration of the inflammatory cells [43]. By IFN-γ stimulation, chemokines such as IFN-γ-inducible protein 10 (IP-10), monokine induced by IFN-γ (Mig) and interferon-γ-inducible α chemoattractant (iTac) are strongly upregulated in keratinocytes. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies of AD patients. Accordingly, an increased T cell chemotaxis was observed towards IFN-γ-treated keratinocytes. Supporting these findings, enhanced IP-10, Mig and iTac expression was observed in lesional AE skin by immunohistochemical staining. Taken together, these studies suggest that targeting chemokine and/or chemokine receptor pathways involved in allergic inflammation is a promising therapy strategy.

32.4 Role of IL-5 and IL-13 in Atopic Eczema

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 and Rajka [44] 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 subgroup of eczema patients with normal IgE levels and without specific IgE sensitization has been termed the nonallergic form of AE (NAE), nonatopic eczema, non-AE or intrinsic-type AE [25, 45]. Recent data suggest that T cells are likely involved in the pathogenesis of AE and NAD. $CD4^+$ and $CD8^+$ subsets of skin-infiltrating T cells as well as skin-homing CLA^+ T cells from peripheral blood, equally responded to superantigen, and produce IL-2, IL-5, IL-13, and IFN-γ in both forms of the disease [24, 25]. Interestingly, skin T cells from AE patients express higher IL-5 and IL-13 levels compared to NAE patients. Thus, T cells isolated from skin biopsies of AE, but not from the NAE, induced high IgE production in cocultures with normal B cells which is mediated by IL-13. In addition, B cell activation with high CD23 expression is observed in the peripheral blood of AE, but not NAE patients [25]. These findings suggest a lack of IL-13-induced B cell activation and consequent IgE production in nonatopic eczema, although high numbers of T cells are present in lesional skin of both types [25]. More importantly, IL-4 and IL-13 neutralization 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 AE [23 – 25].

Cytokine determinations from peripheral blood CLA^+ T cells and skin biopsies of AD patients show increased IL-5 expression [24, 25]. 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 in prolonged eosinophil survival in AE [24].

32.5 Role of Apoptosis in Allergic Inflammation

Recent studies on allergic diseases have demonstrated three major pathogenetic events in allergic inflammation in which dysregulated survival or apoptosis of effector cells and/or target cells play an essential role (Fig. 32.1). These events are: prolonged survival of eosinophils and T cells in the subepithelial tissue [24, 46, 47], increased apoptosis of bronchial epithelial cells in asthma and skin keratinocytes in AE [48, 49], and increased death of Th1 cells in the circulation leading to Th2 predominance in atopic diseases [47].

To assure self-tolerance and downregulation of an immune response, the elimination of T cells takes place in the periphery and involves induction of apoptosis [50]. 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 the development of the immune response, T cells are stimulated by antigens presented by APC that 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 [51]. 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.

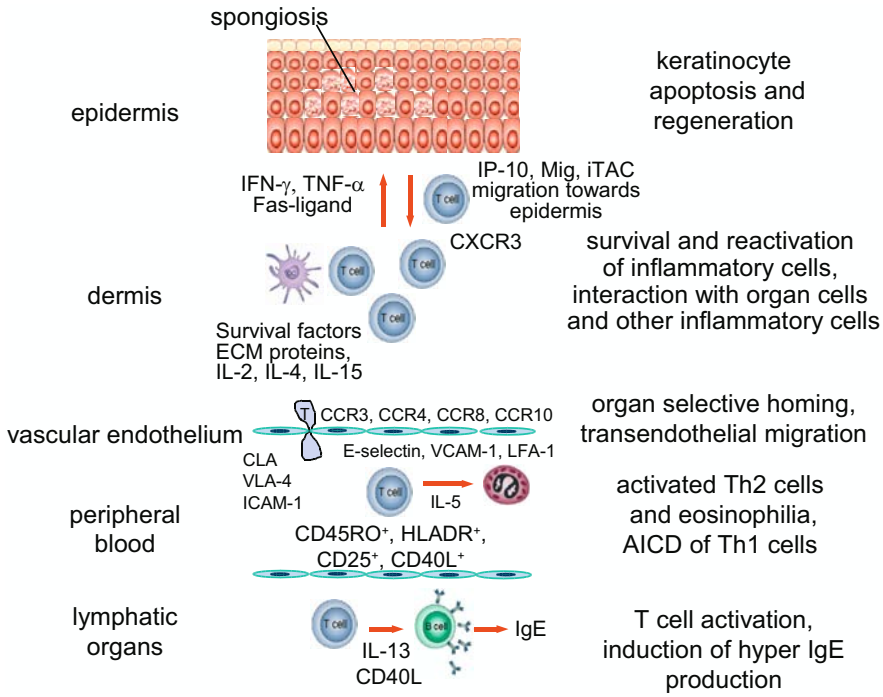

Fig. 32.1. Immune effector mechanisms in AE. T cells infiltrating the skin use cutaneous lymphocyte-associated antigen (CLA) and other receptors (VLA-4/VCAM-1, LFA-1/ICAM-1, CCR3, CCR4, CCR8, CCR10) to recognize and cross the endothelium. In the peripheral blood of AE and asthma patients, circulating allergen-specific Th2 cells are dominant. Dermis in AE represents an immunological organ-like cellular organization with T cells, dendritic cells, which enables a second step of activation by antigens and superantigens. T cells infiltrating the dermis show decreased apoptosis, because they are protected from apoptosis by cytokines and ECM proteins. IL-2, IL-4, IL-15 are survival factors for T cells. A second step of chemotaxis from dermis towards epidermis takes place after transendothelial migration of the inflammatory cells. By IFN-γ stimulation, chemokines such as IFN-γ-inducible protein 10 (IP-10), monokine induced by IFN-γ (Mig), and interferon-γ-inducible α chemoattractant (iTac) are strongly upregulated in keratinocytes. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies of AE patients. T cells play an essential role in the induction of keratinocyte apoptosis. IFN-γ, Fas-ligand, and TNF-α were identified as inducers of apoptosis. Particularly, the Th1 compartment of circulating activated memory/effector T cells selectively undergoes activation-induced cell death, skewing the immune response towards surviving Th2 cells in atopic diseases. Th2 cells secrete high levels of IL-5 and IL-13 and therefore are capable of prolonging eosinophil life span, inducing IgE production, and upregulating homing ligands such as VCAM-1

32.5.1 T Helper (Th) 2 Predominance in Atopy is Due to Preferential Apoptosis of Circulating Memory/Effector Th1 Cells

Differences in control of life span was observed between peripheral blood activated memory/effector T cells and T cells infiltrating the eczema lesions in atopic and nonatopic diseases. In peripheral blood of AE patients both $CD4^+$ and $CD8^+$ subsets of activated memory/effector T cells expressed upregulated Fas and Fas-ligand and undergo spontaneous activation-induced cell death [47]. Freshly purified memory/effector T cells of atopic individuals display distinct features of in vivo-triggered apoptosis such as procaspase 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 AE patients. The apoptosis of circulating memory/effector T cells was confined to atopic individuals, whereas nonatopic patients such as psoriasis, intrinsic-type asthma, contact dermatitis, intrinsic type of AE, bee venom allergic patients, and healthy controls did not show any evidence for enhanced T cell apoptosis in vivo. These results define a novel mechanism for peripheral Th2 response in atopic diseases.

Apoptosis of skin-infiltrating T cells is inhibited by IL-2, IL-4, IL-15, and eosinophils is inhibited by IL-5 and GM-CSF as cytokines; fibronectin, tenascin, laminin, and collagen IV as extracellular matrix (ECM) proteins, together demonstrating a multifactorial survival of effector cells in the tissue [47, 52]. 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 that attach cells to the matrix and mediate mechanical and chemical signals. Integrins can recognize several ECM proteins; conversely, a single ECM protein can bind to several integrins [53]. During inflammation, leukocytes migrate into tissues and interact with ECM proteins. Cell adhesion to the ECM has been implicated in protection from apoptosis in anchorage-dependent cell types [54]. Apparently, integrin signaling by ECM proteins represents an important survival signal to T cells and eosinophils, although they do not require anchorage in the tissues.

In addition, IL-2, IL-4, and IL-15 prevent AICD in skin-homing T cells. 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 signaling component. IL-15 shares many biological activities with IL-2 and signals through the IL-2 receptor β and γ chains. However, IL-15 and IL-2 differ in their control of expression and secretion, their range of target cells, and their functional activities. IL-2 induces or inhibits T cell apoptosis in vitro depending on T cell activation, whereas IL-15 inhibits cytokine deprivation-induced apoptosis in activated T cells [55]. Furthermore, blocking the γ-chain in mice inhibits T cell proliferation and induces T cell apoptosis which leads to stable allograft survival [56].

32.5.2 T Cells Induce Eczematous Dermatitis

The histological hallmark of eczematous disorders is characterized by a marked keratinocyte pathology. Spongiosis in the epidermis is identified by impairment or loss of cohesion between KC and the influx of fluid from dermis, sometimes progressing to vesicle formation. A study by Trautmann et al. delineated activated skin-infiltrating, T cell-induced epidermal keratinocyte apoptosis as a key pathogenic event in eczematous disorders [48]. IFN-γ released from activated T cells upregulates Fas (CD95) on keratinocytes, which renders them susceptible to apoptosis. When the Fas number on keratinocytes reaches a threshold of approximately 40,000 Fas molecules per keratinocyte, the cells become susceptible to apoptosis. Keratinocytes exhibit a relatively low threshold for IFN-γ-induced Fas expression (0.1 – 1 ng/ml). This requirement is substantially achieved 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 [48]. 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. In these studies, the involvement of cytokines other than IFN-γ was eliminated by experiments with different cytokines and anticytokine-neutralizing antibodies. In addition, apoptosis pathways other than the Fas pathway were ruled out by blocking T cell-induced keratinocyte apoptosis with caspase inhibitors and soluble Fas-Fc protein. Keratinocyte apoptosis was demonstrated in situ in lesional eczematous skin and patch test lesions of both AE and allergic contact dermatitis. Exposure of normal 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 [48]. These studies demonstrate that both $CD4^+$ and $CD8^+$ T cells may play a role in keratinocyte injury according to 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 if keratinocytes are susceptible to apoptosis. IFN-γ appears to be a decisive cytokine to render keratinocytes susceptible to apoptosis.

Spongiosis is a characteristic histopathological appearance in eczematous dermatitis. It is characterized by condensation of the cells, widening of the intercellular space and stretching of remaining intercellular contacts, resulting in a sponge-like appearance of the tissue. Homophilic interactions of the cadherin superfamily of molecules provides inter-keratinocyte adhesiveness in the epidermis. Interestingly, during the early phase of keratinocyte apoptosis one of these cadherin superfamily molecules, E-cadherin is rapidly cleaved whereas desmosomal cadherins (desmocollin and desmoglein) remain intact. Accordingly, loss of E-cadherin contacts and sustained desmosomal cadherin contacts between keratinocytes results in spongiform morphology in the epidermis [57 – 59]. In addition, it has been demonstrated that targeting apoptosis of epidermal keratinocytes may open a new future for drug development in the treatment of asthma and AE. Current treatments such as corticosteroids, cyclosporin A, rapamycin, and FK506 mainly inhibit activation of T cells and T cell-induced keratinocyte apoptosis [59]. Similar apoptotic mechanisms leading to bronchial epithelial cell death were also demonstrated in asthma [49]

32.6 Conclusion

T cells infiltrating the skin use CLA and other receptors to recognize and cross the endothelium. The AE dermis shows an immunological organ-like cellular organization with T cells, and dendritic cells, which enables a second step of T cell activation by antigens and superantigens. A second step of chemotaxis inside the dermis of AE lesions takes place after transendothelial migration of the inflammatory cells. By IFN-γ stimulation, chemokines such as IFN-γ-inducible protein 10 (IP-10), monokine induced by IFN-γ (Mig), and interferon-γ-inducible α chemoattractant (iTac) are strongly upregulated in keratinocytes. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies of AE patients. T cells infiltrating the skin show decreased apoptosis, because they are protected from apoptosis by cytokines and ECM proteins in the dermis. IL-2, IL-4, and IL-15 are survival factors for T cells, IL-5, for eosinophils. T cells play an essential role in the induction of keratinocyte apoptosis. IFN-γ, Fas-ligand and TNF-α were identified as inducers of apoptosis. Particularly, the Th1 compartment of circulating activated memory/effector T cells selectively undergoes activation-induced cell death, skewing the immune response towards surviving Th2 cells in atopic diseases. Th2 cells secrete high levels of IL-5 and IL-13 and therefore are capable of prolonging eosinophil life span, inducing IgE production, and upregulating homing ligands such as VCAM-1.

Future studies to find out novel treatment ways of AE should be focused on inhibition of various modes of T cell activation, inhibition of skin-homing, and modulation of effector molecules that play a role in dysregulated apoptosis/survival of T cells, eosinophils and keratinocytes.

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