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Skin Homing and Recruitment of Leukocytes in Allergic Contact Dermatitis

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Received: July 25, 2008; Accepted: August 6, 2008; Revised: August 22, 2008

Abstract: Allergic contact dermatitis (ACD) is a common skin disorder that has a high socio-economic impact with regard to the increasing number of industrial allergens that has potential harmful effect on the skin of manual workers. Its management relies on the use of topical anti-inflammatory drugs as well as the avoidance of the allergens inducing the disease. However, with regard to the ubiquitous character of many chemicals in the environment, treatment of the disease remains unsatisfactory. Understanding the molecular basis of the disease is of major importance in prospect of designing new therapeutic modalities. In this article, the various stages of the disease are reviewed as well as the recent advances in the understanding of the molecular basis of the mechanisms of the disease that would help to conceive new concepts for drug intervention. The article also reviews some of the recent patent relevant to the field.

Keywords: Allergic contact dermatitis, allergens, skin homing, haptens, dendritic cells, lymphocytes, ligand, receptor, keratinocytes, chemokines, Langerhans cells, adhesion molecules, cytokines, metalloproteinases, homeostasis.

INTRODUCTION

Allergic contact dermatitis (ACD) is a common skin disorder that has a high socio-economic impact with regard to the increasing number of industrial allergens that has potential harmful effect on the skin of manual workers. The management of the disease based on the avoidance of contact with the substance, the treatment with topical corticosteroid and other immuno-suppressor agents is still unsatisfactory with regard to the ubiquitous character of many chemical substances such as metals that render their strict avoidance illusive. Understanding the molecular mechanisms of the cutaneous allergic process would be of great importance to design new therapeutic molecules and concepts that would allow the treatment of the underlying and fundamental skin abnormalities that are responsible of the disease.

I/ SKIN HOMING

In ACD, chemical allergens or haptens must cross the stratum corneum skin barrier, bind to a protein in the epidermis and form a stable complex that is taken by Langerhans cells (LC) in the epidermis or dendritic cells (DC) in the dermis. The allergen is then transported to regional lymph nodes by LC or DC, where recognition of the allergen by T cells takes place. Re-exposure to the hapten leads to rapid recruitment and activation of specific T cells at the site of inflammation.

Lymphocytes continuously recirculate between blood and tissue. Active mechanisms based on ligand/receptors recognition between cells and endothelium direct lymphocytes from the blood to target tissue [1].

Leukocyte Adhesion and Tissue Migration

Naïve T cells are located in the secondary lymphoid tissues. After skin sensitization, they develop into either

effector or memory T cells. Effector T cells home to sites of inflammation (skin) and are destined to die, whereas memory T cells are long-lived. There is a considerable heterogeneity in the ability of memory T cells to localize within various "extralymphoid" tissues (i.e. the skin). The interaction between circulating T cells and endothelial cells is an important event in the homing process Fig. (1). The tissue selective T cell extravasation in the skin is mediated, at least in part, by the interaction between an adhesion molecule, the cutaneous lymphocyte-associated antigen (CLA) on skin-homing T cells and its vascular counterreceptor, E-selectin, on superficial dermal postcapillary venules.

The recruitment of circulating leukocytes from the blood into tissues depends on three events: vascular attachment of leukocytes to endothelial cells of blood vessels, extravasation and cell migration [2].

During the first stage, initial contact between blood leukocytes and microvascular endothelial cells involves loose interactions mediated by selectins, β 1-integrins [3] and their respective vascular ligands, resulting in a rolling motion of weakly adherent leukocytes. A number of chemokines have recently been shown to regulate the rolling process of lymphocytes on L-selectin ligands [4]. Subsequently, the leukocyte might become firmly attached to the endothelium. Firm adhesion of leukocytes depends on chemokine receptor signaling which results in the necessary integrin affinity/avidity changes required for vascular attachment. Then, adherent leukocytes move across the endothelial cell layer, reach the underlying basement membrane and are released into the tissue.

The blood vessel at which a leukocyte undergoes extravasation is controlled by the range of adhesion molecules expressed on the cell surface. The exclusion of leukocytes from skin is largely governed by the differential expression of cutaneous lymphocyte-associated antigen, a fucosylated form of P-selectin glycoprotein ligand-1 (PSGL-

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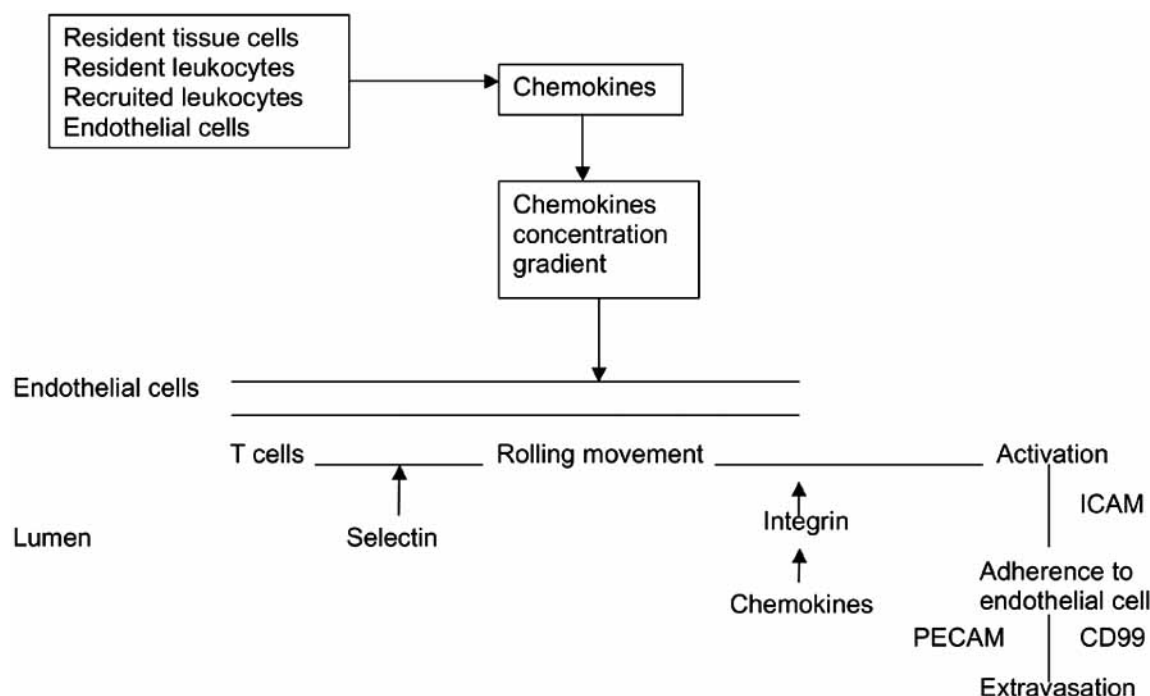


Fig. (1). Regulation of leukocyte movement in the skin.

Chemokines are secreted at sites of inflammation and develop a concentration gradient around the site of inflammation. A selectin-mediated process induces a rolling movement of leukocytes in post capillary venules. Chemokines activate leukocyte integrins leading to firm adherence with endothelial cells. This process needs also interaction between chemokines and intercellular adhesion molecules (ICAM). Diapedesis is regulated by platelet-endothelial cell adhesion molecule 1 (PECAM-1) and CD99.

1) with affinity for skin microvasculature-expressed *E*-selectin (CD62E) [5].

Attachment of chemokine(s) receptor will result in rapid changes to the adhesive properties of integrins on the leukocytes and its subsequent firm adhesion, which is a prerequisite for leukocyte transmigration. Chemokines and their receptors represent an important event in the control of leukocyte extravasation. Leukocytes move from a site of firm adhesion to the nearest junction to begin diapedesis, is a critical step during extravasation. This process requires interaction of the integrins CD11a/CD18 and CD11b/CD18 with intercellular adhesion molecule 1 (ICAM-1) and ICAM-2 [6]. As a counterpart for ICAM-2, the human DC-specific adhesion receptor DC-specific ICAM-3-grabbing nonintegrin (CD209) is responsible for DC rolling and trans-endothelial migration [7]. Leukocyte diapedesis is regulated by 2 distinct molecules: platelet-endothelial cell adhesion molecule 1 (PECAM-1) and CD99 [7]. In addition to the above-mentioned molecules, a new family of junctional adhesion molecules (JAMs) has been identified [8]. JAM-A binds to its ligand, lymphocyte function-associated antigen-1 (LFA-1). JAM-B on endothelial cells binds its ligand, JAM-C, on T cells, natural killer cells, and DCs. JAM-C binds specifically to CD11b/CD18 on leukocytes.

Leukocyte transendothelial migration and their subsequent tissue localization are two distinct processes, suggesting unrelated control by chemokines.

Chemokines Produced by Keratinocytes

Keratinocytes produce large quantities of interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) in response to

trauma, UV radiation or cytokines [9]. Locally available cytokines (IL-1 β , IL-18) in mouse play an important role in the migration, maturation and subsequent localisation of LC within lymph nodes, following skin sensitization [10, 11]. Therapeutic intervention has been tried by Plitz *et al.* by using IL-18 binding protein (IL-18 BP) to neutralize IL-18 in a contact hypersensitivity murine model. The authors demonstrated significantly reduced clinical symptoms. Also, IL-18 BP reduced the number of T cells homing to sites of inflammation [12]. Transforming growth factor- β (TGF- β), indispensable for immigration of LC precursors in the epidermis, is produced by keratinocytes. Immigration of LC precursors into the epidermis induces keratinocytes to secrete monocyte chemoattractant protein 1 (MCP-1)/ CC chemokine ligand 2 (CCL2), which constitutively recruits DCs and LCs to skin [13]. MCP-1 and RANTES/CCL5 trigger arrest of rolling monocytes on endothelial cells [14], which precedes extravasation movement of leukocytes.

Matrix Metalloproteinases

LC precursors attach to and degrade basement membrane proteins to cross the basement membrane of the dermal-epidermal junction. Matrix-degrading metalloproteinases (MMPs) which are proteolytic enzymes, are key enzymes in the extracellular matrix turnover and mediators of cell migration. Gelatin-binding MMP-2 and MMP-9 and simple hemopexin domain-containing MMP-3 have been demonstrated on the surface of immature, mature, or both dermal and epidermal DCs and LCs from the skin. MMPs are mainly known for their extracellular matrix-degrading activity. However, they can also modulate inflammation through proteolytic activation or inactivation of cytokines,

chemokines, and growth factors. Stromal-derived factor-1 (SDF-1)/ chemokine CXCL12 [15], MCP-3/CCL7 [16], IL-8/CXCL8 are either activated or inactivated by MMPs suggesting that MMPs are both effectors and regulators of inflammatory responses. In an *in vivo* study, Kobayashi [17] showed that MMP-9 is involved in LC migration and maturation. An MMP-9-specific monoclonal antibody (mAb) inhibits hapten-induced LC emigration. In murine models emigration of LCs from skin explants is reduced by MMP-2-specific mAb.

II/ T LYMPHOCYTE ACTIVATION

Naïve T cells migrate only to secondary lymphoid organs, where they are activated by antigen-presenting cells. This activation, confers to T cells the capacity to home to non-lymphoid tissues (skin, gut), that are connected to the secondary lymphoid organs where antigen was first encountered [18]. During activation of naïve T cells in secondary lymphoid tissues, a combination of adhesion molecules and chemokine receptors are generated to target T cells to the corresponding peripheral tissue. So, an important role of local microenvironments for the 'imprinting' of tissue tropism is now progressively recognized [19].

The qualitative aspect of skin sensitization is related to heterogeneity in cytokines secretion profile by lymphocytes subgroups. In humans exists heterogeneity among T helper (Th; CD4) cells [20]. Some cytokines are produced by both Th1 and Th2, while others are associated with one of the two groups. Th1 cells are characterized by the production of IL-2 and interferon- γ (IFN- γ), and Th2 cells secrete cytokines required for the immediate-type allergic reactions (IL-4, IL-5, IL-9, IL-10 and IL-13). There is also heterogeneity among T cytotoxic cells (Tc; CD8). Tc1 and Tc2 have cytokine production phenotypes similar, respectively to Th1 and Th2 cells [21].

The pathogenesis of allergic contact dermatitis requires that effector T lymphocytes are recruited into the sites of dermal exposure and this involves interactions between lymphocytic cells and environment. The allergen-specific Th1 are the major cells of this stage. However, other cell types could be of great importance [22].

Some controversy arose about the activation of which lymphocyte subpopulations (CD4 and/or CD8 of the type 1 or type 2) are involved in ACD. In humans, CD8 T lymphocytes might represent the critical subpopulation in the development of the disease. Cavani *et al.* [23] examined nickel-specific T cell responses in nickel allergic and nickel non-allergic patients. Only in the allergic group there were CD8 nickel specific T lymphocytes responses, although both groups showed CD4 T lymphocyte responses to nickel *in vitro*. Some data suggest that CD8 Tc1-type cells are major mediators of allergic skin reactions, although for full development of contact sensitivity there may be a requirement for CD8 and CD4 type 1 effector cells to act jointly [24].

In mice, contact with allergens will induce a selective type 1 response with the production by draining lymph node cell (LNC) of high levels of IFN- γ but comparatively low levels type 2 cytokines. This, support the view that selective type 1 responses favour the generation of skin sensitisation. Following oral intake of nickel and placebo in nickel-

sensitive and healthy individuals, the study of lymphocyte subpopulation and cytokine profile in peripheral blood, suggested migration of CD8+ 'memory' CLA+ T lymphocytes from the blood to peripheral tissues and activation of type 2 T lymphocytes [25]. However, the responses at the molecular level are more complex. It has been shown that following mice sensitization by dinitrochlorobenzene (DNCB), the high levels production by LNC of IFN- γ were derived from both CD4 and CD8 cells, while the lower levels of type 2 cytokines were produced only by CD4 cells. These data indicate that both Th1- and Tc1- type cells are induced in skin sensitization with a less marked intervention of Th2-type cells.

Development of allergic contact dermatitis to haptens depends upon a balance between CD8+ T lymphocytes and CD4+ T cells, which comprise both effector and regulatory cells. Thus differential recruitment of CD8+ and CD4+ lymphocytes to sites of hapten challenge may have considerable impact on disease expression. CCL17/ thymus and activation-regulated chemokine (TARC) and CCL22/ macrophage-derived chemokine (MDC) induced a 3-fold higher migration of CD4+ compared with CD8+ lymphocytes. In contrast, CXCL10/ inducible protein 10 (IP-10) was 2-fold more potent in attracting CD8+ cells. These findings were consistent with the higher expression of CCR4 and CXCR3 on CD4+ and CD8+ T cell lines, respectively. Moreover, CC chemokine receptor 4 (CCR4) expression was high on nickel-specific T helper 2, intermediate on T helper 1 and cytotoxic 2, and almost undetectable on T cytotoxic 1 clones [25]. On the contrary, CXC chemokine receptor 3 (CXCR3) was expressed by T cytotoxic 1 and 2 and T helper 1, but not T helper 2 clones [25].

It seems that distinct chemokines and cell types control the accumulation of CD8+ and CD4+ T cells within inflamed skin.

The recruitment of T cell subsets during inflammatory skin diseases is promoted by chemokines preferentially released by distinct resident cell populations. The diverse chemokine responsiveness of CD8+ and CD4+ T cells suggests novel therapeutic interventions based on the selective modulation of their recruitment into the skin [26].

Although, the factors driving induction of T cell homing process are largely unknown, Dudda *et al.* showed that soluble factors produced during the interaction of T cells with CD11c+DC isolated from skin, modulate expression of the corresponding tissue-selective homing receptors (E-selectin ligands) on murine CD8+ cells [27].

Recent works have focused on the intervention of additional cell types that could have an important role in the contact allergic reaction. Using skin biopsies in positive patch test reactions in humans, Gober *et al.* [28] showed that natural killer T cells (NKT cells) play an important role in the efferent late phase of the allergic inflammation, since they concentrate in the site reaction of the skin and are activated, as they express IFN- γ and IL-4.

Innate immunity has also been implicated in the mediation of contact hypersensitivity reaction [29]. O'Leary [30] showed that in mutant mice, lacking the *Rag2* gene, B cells, T cells and NKT cells are absent and the natural killer

cells (NK cells) are the only circulating lymphocytes. These mice are able to develop contact-sensitivity reactions against dinitrofluorobenzene and the reaction is almost as strong as in normal mice [30], demonstrating that NK cells play all the roles necessary to produce contact sensitivity.

III/ HUMAN IMMUNE SURVEILLANCE T CELLS AND CONTROL OF ALLERGY

Effective immune surveillance is essential for maintaining protection and homeostasis of peripheral tissues. The majority of human T cells in healthy skin express the chemokine receptor CCR8 and respond to its selective ligand I-309/CCL1 [31]. These CCR8⁺ T cells are absent in small intestine and colon tissue, and are very rare in peripheral blood, suggesting healthy skin as their physiological target site [32]. Potential precursors of skin surveillance T cells in peripheral blood may correspond to the minor subset of CCR8+CD25⁻ T cells. CCL1 is constitutively expressed at strategic cutaneous locations, including dermal microvessels and epidermal antigen-presenting cells. CCL1 with its only receptor CCR8 is essential for controlling cutaneous homeostatic T cell traffic [32].

The chemokine CCL27 which attracts skin-homing T cells, is produced by keratinocytes [33]. Its production is increased in allergic contact dermatitis [34]. TNF- α promotes CCL27 production in human keratinocytes partially by activating nuclear factor κ B (NF- κ B) and prostaglandin E₂ (PGE₂) suppresses TNF- α -induced CCL27 production by inhibiting NF- κ B activity [35].

IL-17 level is increased in ACD skin lesions where it might regulate inflammation. IL-17 alone or synergistically with IFN- γ or TNF- α , enhances production of IL-6, IL-8, granulocyte macrophage colony stimulating factor (GM-CSF), or intercellular adhesion molecule 1 by keratinocytes and promotes infiltration, retention and activation of leukocytes in the epidermis through these molecules [36].

The *in vivo* injection of CCL27 induces recruitment of T cells to the skin, and conversely, injection of anti-CCL27 antibody impairs T-cell recruitment to ACD skin lesions in mice [37] indicating a pivotal role of CCL27 in T-cell skin infiltration. *in vitro*, T cell-derived IL-17 might reduce TNF- α -induced CCL27 secretion in keratinocytes and thus at least partially alleviate T-cell infiltration into ACD skin lesions. The inhibition of CCL27 secretion by IL-17 is mediated by induction of cyclooxygenase-2 (COX-2). COX-2 inhibitors counteract the IL-17- induced inhibition of CCL27 secretion and might exacerbate skin inflammation [35].

IL-17 is released from a newly recognized Th cell subset (Th17 cells) [38]. Nickel-specific Th clones from patients with contact dermatitis expressed IL-17 [39]. Also, IL-17-deficient mice exhibited reduced contact hypersensitivity induced by dinitrofluorobenzene and trinitrochlorobenzene implying that IL-17 could play a role in contact hypersensitivity [39].

Two types of Ag-experienced T cell subsets are produced during adaptative immune responses: large numbers of short-lived effector T cells and a minor fraction of long-lived memory T cells [37, 40, 41]. Effector T cells are equipped with receptors for inflammatory chemokines and adhesion

molecules that are up-regulated during inflammation and thus, these cells efficiently home to sites of pathogens and disease. Memory T cells are divided into two major subsets characterized by different migratory and functional properties. The subset of CCR+CD62L⁺ memory T cells, termed central memory T(T_{CM}) cells, outnumber by far the memory subset lacking these LN-homing receptors, termed effector memory T (T_{EM}) cells. In humans, T_{CM} were described as being undifferentiated, as they were unable to produce inflammatory cytokines or lytic enzymes, whereas T_{EM} cells were found to immediately initiate effector functions in response to stimulation [42]. Conceptually, antigen encountered at inflammatory sites leads to T cell activation and consequent re-expression of CCR7, which may enable these cells to reach draining LNs via afferent, CCL21-expressing lymphatic vessels.

Recent data suggest the existence of a third class of memory T cell called peripheral immune surveillance T (T_{PS}) cells [5]. T_{PS} are characterized by their preferential localization in healthy peripheral tissues, including normal skin. Unlike T_{CM} and T_{EM}, T_{PS} have the capacity to respond to chemokines expressed constitutively in healthy peripheral tissues. As a result, they are largely excluded from peripheral blood and secondary lymphoid tissues (spleen, LN). Since <5% of total T cells reside in peripheral blood, the majority, >95% of T cell reside in peripheral tissue (LN, spleen, PP, healthy tissue). Recent findings support a role for CCR8 and its single ligand CCL1/I-309 in the control of skin-selective T_{PS} cells [43]. In human skin, a minor fraction of mostly CD8⁺ cutaneous T cells is found in the epidermis, whereas 90% of total cutaneous T cells cluster around post capillary venules of the superficial dermal plexus, the main site of leukocyte extravasation in the skin. The study revealed the presence of CCL1 on blood microvessels as well as epidermis-associated langerhans cells in normal human skin. Of interest, CCL1 was not identified on keratinocytes or dermal fibroblasts, two types of tissue cells that produce a variety of mostly inflammatory chemokines [44]. Furthermore, most of T cells in healthy human skin express functional CCR8, whereas other chemokine receptors were low or even absent. In keeping with the T_{PS} hypothesis, lack of CCR7 and borderline expression of receptors for inflammatory chemokines indicate that memory T cells within healthy skin indeed form a T cell subset that is different from T_{CM} and T_{EM} cells. Within the skin, both the CD4⁺ and CD8⁺ subsets of CCR8⁺ T_{PS} cells produce high levels of the proinflammatory cytokines TNF- α and IFN- γ , whereas secretion of type 2 cytokines (IL-4, IL-5, IL-13) was rarely observed. Conclusion is that cutaneous CCR8⁺ T cells represent the first example of a memory T cell subset that fulfils the criteria of T_{PS} cells [5]. The phenotyping characteristics suggest that skin T_{PS} cells respond to local antigen challenges by contributing to the inflammatory cascade at the site of pathogen entry. It remains to be determined whether activated skin T_{PS} cells can also acquire LN-homing properties, i.e. CCR7 expression as observed in activated γ - β T cells.

In addition to CCL1, a number of other chemokines are expressed, with varying degrees of specificity in normal skin, but are likely candidates for the control of T_{PS} cell traffic. CXCL12 is expressed by blood endothelial cells and

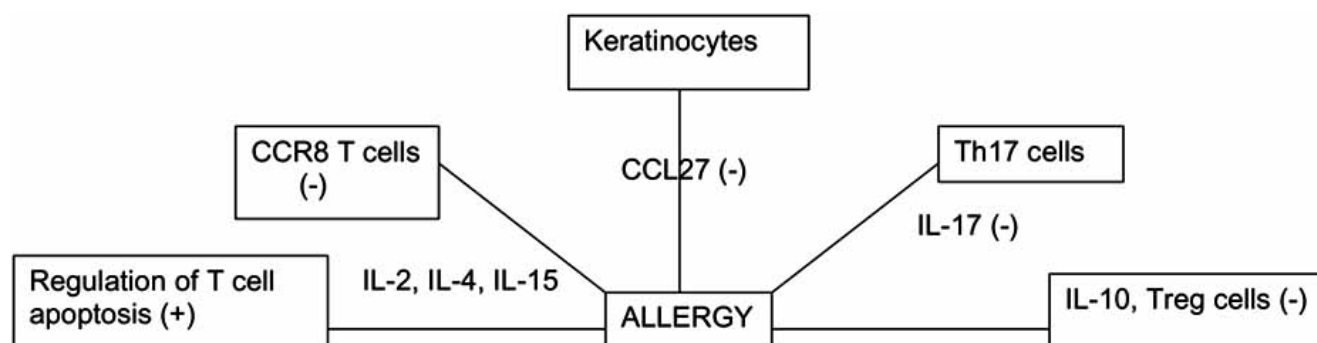


Fig. (2). Regulation of allergic contact dermatitis.

CCR8+ T cells, keratinocyte-secreted CCL27, Th-17-secreted IL-17 and IL-10 inhibit allergic skin reaction. Inhibition of T cell apoptosis by IL-2, IL-4 and IL-15 may lead to chronic allergic contact dermatitis.

DC in normal skin. Its single receptor CXCR4 is expressed on all leukocytes [45].

CCL17/TARC, one of two ligands of CCR4 as well as CCL20/ liver and activation-regulated chemokine (LARC), the single ligand for CCR6, are occasionally detected on cutaneous blood endothelial cells. However, these chemokines are greatly induced by proinflammatory stimuli on blood endothelial and tissue cells, and are readily observed in diseased skin [46]. In addition, expression of CCR4 and CCR6 is low to undetectable on T cells in healthy skin. Together, these observations suggest that the principal function of these two chemokine systems, is related to the control of inflammatory infiltrates.

CCL27/ cutaneous T-cell-attracting chemokine (CTACK), one of the two ligands for CCR10, is a recently identified chemokine with skin-selective expression. In normal skin, CCL27 is primarily found on keratinocytes and microvascular endothelial cells but, in clear contrast to CCL1, is strongly up-regulated during inflammation [46]. The majority of CCR10+ T cells in peripheral blood are skin-homing (CLA+) CD4+ memory T cells, yet these cells constitute only a minor fraction of T cells from healthy skin [34] arguing against a prominent role of this chemokine in the traffic control of cutaneous CD4+ and CD8+ T_{PS} cells. Rather as for CCR4 and CCR6 ligands, a role for this chemokine system in controlling T cell traffic in the skin is probably limited to conditions of inflammation.

The aberrant regulation of T cell apoptosis leads to the accumulation of T cells in the dermis. Cytokines IL-2, IL-4 and IL-15, and components of the extracellular matrix (fibronectin) in eczematous skin prevent T cell apoptosis and might contribute to chronicity in eczema [47] Fig. (2).

Contact hypersensitivity was also found to be regulated by CD4+CD25+ T regulatory cells, since expansion of CD8+ populations were limited and duration of contact hypersensitivity reduced [48].

IL-10 secreting Tregulatory cells type 1 are supposed to be of importance in controlling allergic contact dermatitis [49]. Recently, IL 10 production by mast cells has been shown to limit inflammatory manifestations in allergic contact dermatitis [50]. Thus, the use of IL 10 analogs (AK 155) [51] might play a role in the development of contact allergy.

CURRENT & FUTURE DEVELOPMENTS

Treatment of ACD remains unsatisfactory, mainly when the disease progresses toward chronic stage. New therapeutic options should focus in the future on the design of new molecules based on the better understanding of the molecular aspect of the various steps that govern the allergic process. The skin homing process with its various stages, skin cells chemokines and T lymphocytes cytokines secretion, as well as the control of apoptosis phenomenon and human immune surveillance, should be considered as various steps that could be targeted by appropriate molecules to control the allergic reaction.

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