

REVIEW

Increased incidence of skin infections in atopy: evidence for an antigen-specific homing defect?

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Introduction

Skin problems in atopic patients occur frequently and are not restricted to eczemata, itch and dryness. In addition, the skin of the atopic patient is often colonized and infected by dermatophytes such as *Trichophyton rubrum*, bacteria such as *Staphylococcus (S.) aureus*, and viruses such as herpes simplex virus (HSV). The incidence of infection with these pathogens is significantly higher in atopics [1–7]. Although this phenomenon has been known for many years, the causes underlying this increased incidence are not completely understood. In this review we summarize experimental data suggesting an antigen-specific defect in T cell re-circulation into the skin associated with the atopic phenotype and limited to antigens that are immunologically unique regarding their ability to induce a Th1 or a Th2 response in different individuals.

A role for defective skin barrier in increased incidence of skin infection

Human skin has unique properties, of which functioning as a physicochemical barrier is one of the most apparent. The human integument is able to resist the penetration of many molecules and microbes. Following disruption of this barrier, for example by burn destruction or placement of cutaneous catheters, many microbes can easily penetrate the skin leading to an increased incidence of infections. In atopic dermatitis, the skin barrier is disturbed, which is thought to be at least partially caused by a marked reduction in the amount of ceramides in the stratum corneum resulting from increased expression of sphingomyelin deacylase [8]. As ceramides are important for the stratum corneum's water-holding property, insufficient ceramide content in atopic skin may result in dry and itchy skin. The itch is followed by scratching of the skin that helps to destroy the physical barrier and allows microbes to invade the skin. Additionally, certain stratum corneum lipids such as sphingosines have antimicrobial activity and are reduced in skin from atopic individuals [9]. In conclusion, several changes in the physicochemical composition of atopic skin can lead to reduced resistance to skin infections. However, besides these altered physicochemical changes of the skin, immunological

aberrations may be involved in the increased incidence of skin infections. The latter will be discussed in this review in more detail.

S. aureus, *Trichophyton* and HSV can induce a specific Th2 response in atopics

Upon first encounter with the host's skin immune system, antigen-presenting cells take up antigens from infectious organisms residing on the skin, process them and present antigenic peptides in the context of certain costimulatory molecules to naïve T cells in the skin-draining lymph nodes. It has been proposed that it is the microenvironment in the lymph node that is responsible for allergic sensitization in atopics. Factors that may contribute to allergic sensitization in atopics are increased concentrations of IL-4 and PGE₂, or decreased concentrations of IL-12 and/or IFN- α , or a combination of both constellations [10,11].

Most antigens induce either a delayed-type hypersensitivity (DTH) reaction (e.g. tetanus toxoid) or an immediate hypersensitivity (IH) reaction (e.g. antigens derived from *Onchocerca volvulus*). In contrast, antigens derived from pathogens that infect atopics more frequently than healthy subjects exhibit unique immunological properties in their ability to elicit either DTH (Th1) or IH (Th2) reactions in different individuals. This has been analysed in detail for antigens derived from dermatophytes such as *Trichophyton rubrum* and *T. tonsurans* antigens Tri r 2 and Tri t 1. In different individuals, these antigens can induce either high titres of specific IgG and IgE antibodies associated with IH skin test reactions or low to intermediate titres of specific IgG antibodies and DTH skin responses. Additionally, cell lines derived from IH and DTH responders produce a Th2- and a Th1-dominated cytokine pattern, respectively (Table 1) [12–16]. Given the above mentioned changes in the local microenvironment of atopic individuals, it may be postulated that these antigens preferentially induce a Th2-dominated immune response.

Skin from atopic dermatitis (AD) patients is often heavily colonized by *S. aureus* and the incidence of impetigo contagiosa is increased as compared with healthy subjects [2,3,5]. Although *S. aureus* usually induces a Th1-dominated response and IgG production, IH reactions with the detection of *S. aureus*-specific IgE antibodies are frequently reported in atopic patients [17,18]. Additionally, in these patients *S. aureus*-specific DTH skin reactions are reduced and IH skin reactions have been documented [19]. IH responses with the detection of IgE antibodies

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Table 1. Features of immediate hypersensitivity responses to pathogens such as *Trichophyton rubrum* as compared with delayed-type hypersensitivity responses

	Immediate hypersensitivity response	Delayed-type hypersensitivity response
Specific IgG concentration	High	Low to intermediate
Specific IgE concentration	High	Negative
Cytokine profile	Th2-dominated	Th1-dominated
Skin test	Negative DTH	Positive DTH
Skin homing potential	Low	High
Immune response	Weak, i.e. chronic or recurrent infections	Strong, i.e. acute, spontaneously regressing infections

have also been reported to occur towards *S. aureus* products such as the superantigens staphylococcal enterotoxin (SE) A, SEB, SEC, SED and toxic shock syndrome toxin-1 (TSST-1) [20,21]. Skin testing with these superantigens in patients suffering from atopic dermatitis resulted in IH skin reactions and flare-up reactions [22].

Specific IgE production has also been observed in response to antigens derived from HSV. Incubation of human leucocytes with HSV has been shown to induce histamine release [23]. HSV-specific IgE antibodies have been reported independently by several groups. Using an immunization protocol known to induce high IgE concentrations and a Th2-prone CD4 lymphokine profile (i.e. cyclophosphamide-treated mice immunized subcutaneously with low concentrations of HSV with aluminium hydroxide as adjuvant), cell-bound and circulating HSV-specific IgE have been detected. Additionally, in Th2-prone AIDS patients [24,25] HSV-specific IgE antibodies have been observed [26,27].

Reduced immunity in Th2 vs. Th1 responses

Immunity against bacteria, viruses and dermatophytes results from a concerted action of the host's non-specific and specific immune system. T cells contribute in several ways by inducing immunoglobulin production by B cells or by direct or indirect cytokine or chemokine production. Additionally, T cells that invade the infected organ can either kill the respective pathogen or induce an inflammatory reaction that supports the immune function of other cell types, e.g. macrophages in DTH responses.

In Th2 states, the immune response towards several fungi, bacteria and viruses is reduced; this has been shown in mice and humans [16,28–31]. In murine HSV infections, a pathogenic role for Th2 responses in the severity of encephalomyelitis has been demonstrated [31]. Additionally, the immune response to *S. aureus* in a *S. aureus*-induced septic arthritis model has also been shown to be decreased in wild-type compared with IL-4-deficient mice that had a significantly decreased bacterial burden [32]. Evidence for a defective Th2 immunity against several pathogens comes also from intervention studies: treatment with Th1 cytokines such as IL-12 or IL-18 was efficient as anti-infective therapy [33–36]. In BALB/c mice infected with *Mycobacterium tuberculosis*, IL-12 given at the initiation of the infection doubled their mean survival time and diminished bacterial burdens, whereas treatment with IFN- γ had no such effects [33]. Additionally, IL-12-transduced dendritic cells have

been shown to be capable of inducing or down-modulating antigen-specific Th1 or Th2 responses, respectively, in intracellular infections. Furthermore, antigen-specific proliferative CD4⁺ T cell responses are enhanced compared with CD4⁺ T cells co-cultured with non-transduced dendritic cells [34]. IL-12 cDNA as an adjuvant for a HSV DNA vaccine has been shown to induce antigen-specific Th1 type responses that resulted in reduced HSV-derived morbidity and mortality [35]. The caspase 1-dependent production of the Th1 cytokine IL-18 has also been proposed to represent an important pathway for the expression of Th1 reactivity to *Candida albicans*; administration of IL-18 to caspase 1-deficient mice restored resistance to infection [36].

In humans, reduced immunity in Th2-type responses has been proposed to contribute to chronic dermatophyte infections. Thus, IH responses to *Trichophyton* have been associated with chronic infection, whereas DTH responses correlate with acute, spontaneously regressing infections [37–39]. As a result, it has been proposed that cell-mediated responses to dermatophytes play a role in the eradication of *Trichophyton* infection, while type I hypersensitivity reactions are non-protective [13–16]. The impaired immune response associated with IH could be explained, in part, by reduced cytolytic potential of human Th2 cells as compared with Th1 cells by virtue of their associated cytokines [40]. Alternatively, a more general defect in cell-mediated immunity as observed in children with eczema herpeticum [41] and in atopic dermatitis may contribute [42]. In this work, reduced proliferation in response to Con A [41], PPD and HSV [42] has been observed. Deficient IFN- γ production potentially caused by diminished IL-12 and/or IL-2 concentration during priming [43] may be of additional importance.

Differential regulation of selectin ligands in Th1 vs. Th2 lymphocytes and their role in immunosurveillance

Lymphocyte migration is an essential requirement for efficient surveillance of tissues for infectious pathogens and for recruitment of effector cells at sites of infection. Adhesion of lymphocytes to the endothelium involves a complex series of adhesive interactions between lymphocytes and their endothelial counterparts. Interaction of lymphocyte carbohydrate moieties with E- and P-selectin is followed by lymphocyte activation by chemokines resulting in an activation of T cells and integrins expressed by T cells. The chemokine-induced activation of integrins is necessary for subsequent strong adhesion of T cells to

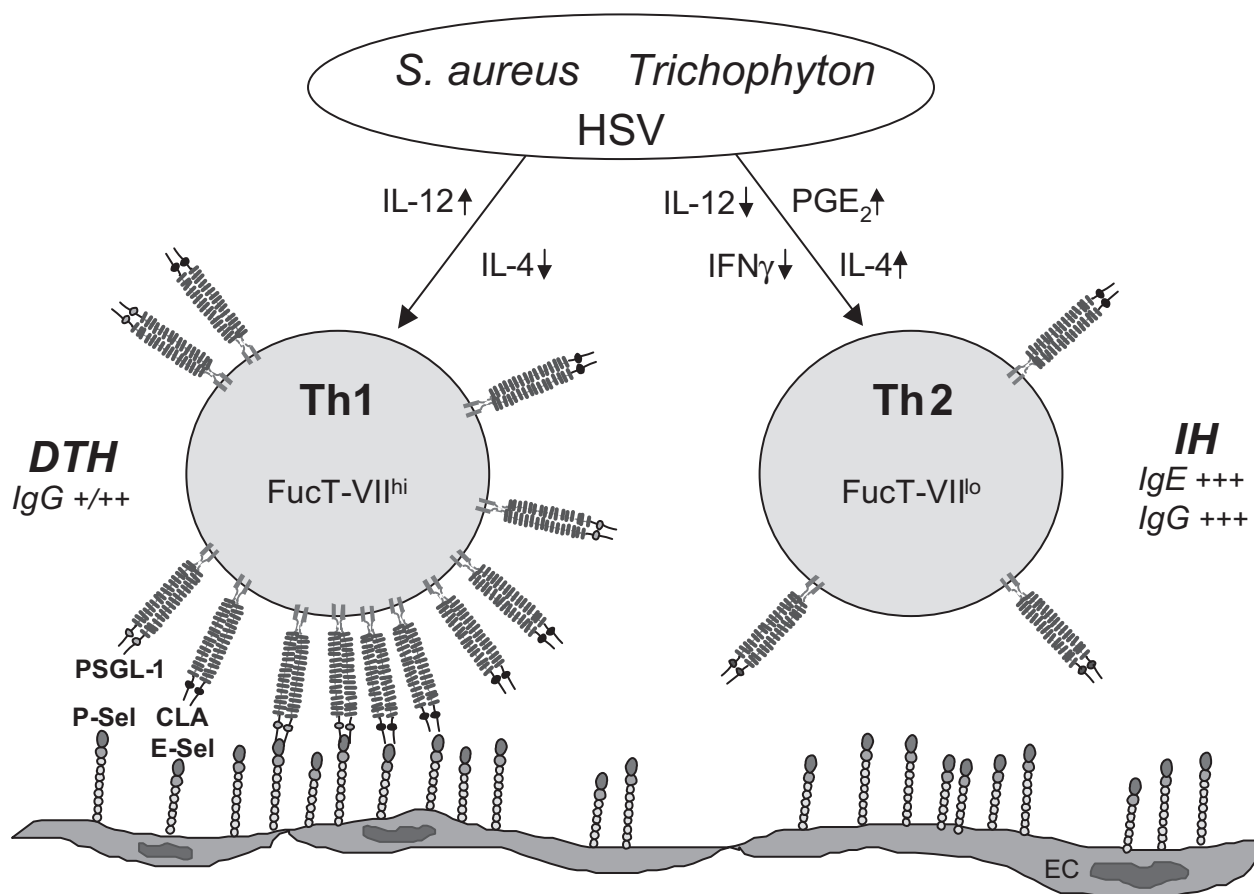


Fig. 1. Differential regulation of selectin ligands in Th1 vs. Th2 lymphocytes. Antigens from *Staphylococcus aureus* (*S. aureus*), herpes simplex virus (HSV) and dermatophytes (e.g. *trichophyton*) exhibit unique immunological properties in their ability to elicit either a Th1-dominated/delayed-type hypersensitivity (DTH) or a Th2-dominated/immediate hypersensitivity (IH) response in different individuals. Skin of atopic individuals is frequently and more severely infected by these pathogens than healthy individuals. The local microenvironment of atopic individuals (high IL-4, low IL-12) preferentially induces a Th2-dominated immune response. These Th2 cells are less effective than Th1 cells in the immune surveillance of skin, partially due to their low expression of fucosyltransferase VII (FucT-VII), which is responsible for E- and P-selectin ligand (CLA and activated PSGL-1) expression. Th2 cells show less rolling on E- and P-selectin expressing skin endothelial cells (EC).

the endothelium. These interactions – initial tethering and rolling, T cell integrin activation by chemokines and strong integrin-mediated adhesion to the endothelium – are a prerequisite of sufficient T cell homing into peripheral organs [44–47] and are altered in Th2 cells, which may lead to diminished immunosurveillance [48].

With respect to T cell re-circulation into the skin the interaction of the cutaneous lymphocyte-associated antigen (CLA) with its ligand E-selectin is responsible for the initial tethering and rolling of T cells along the vascular wall. CLA is produced by post-translational glycosylation of P-selectin glycoprotein 1 (PSGL-1) via the action of $\alpha(1,3)$ -fucosyltransferase VII (FucT-VII) [49–51]. Interestingly, CLA expression and function and FucT-VII mRNA expression are inversely regulated by Th1 vs. Th2 cytokines: when naive, human or murine CD4⁺ T cells are activated in the presence of the Th1 polarizing cytokine IL-12, levels of FucT-VII mRNA and binding to E- and P-selectin are significantly augmented. In contrast, activation of CD4⁺ T cells in the presence of IL-4, a Th2 polarizing cytokine, inhibited FucT-VII expression and binding to vascular selectins [52–54]. Additionally, Th1 cells, but not Th2 cells, are able to bind *in vivo* to P-selectin and E-selectin of murine skin vessels and only

Th1 cells can efficiently enter inflamed cutaneous sites in Th1-dominated but not in Th2-dominated responses [53]. A critical role of selectin ligand expression for re-circulation and immunosurveillance has also been shown *in vivo* in FucT-VII-deficient mice. FucT-VII-deficient mice are characterized by reduced E- and P-selectin ligand activity and are distinguished by impaired leucocyte extravasation in inflammation and faulty lymphocyte homing [55]. Recently, also FucT-IV has been shown to play a role in leucocyte rolling on skin endothelium [56]. However, a differential expression of FucT-IV in Th1 vs. Th2 cells has not yet been addressed. These alterations can also be observed in mutant mice that are deficient for the receptors of selectin ligands, i.e. the selectin itself. Delayed-type hypersensitivity induced by oxazolone was reduced in E-selectin and P-selectin double deficient mice compared with wild-type and single deficient mice [57]. These data indicate that altered expression of selectins or selectin ligands regulated by fucosyltransferases results in reduced immunosurveillance and increases susceptibility to infections (Fig. 1).

In contrast to the above mentioned work, Akdis et al., using anti-CD3 stimulation in serum-free cultures, were able to induce CLA expression on Th2 cells, which was not the case in

serum-containing medium. Additionally, IL-12 and/or super-antigen stimulation up-regulated CLA expression on either Th2 or Tc2 cells [58]. Finally, CLA⁺ Th2 cells can be detected in sites of atopic dermatitis [59]. Further work should analyse the rolling capacity of CLA⁺ Th1 or Tc1 cells as compared with Th2 or Tc2 cells on skin endothelium, to clarify whether there might be differences in skin homing of human compared with mouse T cells [53].

Antigen-specific regulation of T cell skin homing

Recently, an antigen-specific regulation of E-selectin ligand expression by T cells has been shown in two different experimental models. Blander et al. activated D10.TCR transgenic CD4 T cells in the presence of a low (i.e. Th2-inducing) or a high (i.e. Th1-inducing) dose of their specific antigen. This allowed them to specifically stimulate CD4 cells with antigen and follow their differentiation without the need for adding polarizing cytokines. Antigen-specific T cells stimulated with low antigen concentrations produced high amounts of IL-4 in the absence of detectable IFN- γ and FucT-VII mRNA was almost undetectable in these cells. In contrast, cells that were activated in the presence of high antigen concentration produced mainly IFN- γ and showed higher levels of FucT-VII than Th2 cells [60]. In chronic dermatophytosis, we activated peripheral blood mononuclear cells by two cycles of stimulation with recombinant *Trichophyton rubrum* 2 (Tri r 2) antigen or with tetanus toxoid (TT) for 6 days, followed by stimulation with IL-2 for 8 days. After re-stimulation with Tri r 2 or TT for 4 days, the Th1 cytokine IFN- γ and Th2 cytokines IL-4 and IL-5 were measured. Tri r 2-stimulated cell lines exhibited a Th2 cytokine pattern and low CLA expression, whereas TT-stimulated cells exhibited a Th1 cytokine pattern and a CLA expression higher than Tri r 2-stimulated cells [61]. This indicates that FucT-VII and CLA expression in Th1 and Th2 cells is regulated not only by Th1/Th2 polarizing cytokines but also in an antigen-specific manner.

Although there is ample evidence from *in vitro* and mouse models that Th2 cells express reduced E-selectin ligands such as CLA and have a reduced capacity in their migration into skin sites, human Th2 cells do also express CLA and invade skin sites of atopic individuals [58,59,62]. However, in none of these studies was rolling of CLA-expressing Th2 cells compared with CLA-expressing Th1 cells. Therefore, it cannot be ruled out that CLA-expressing Th2 cells have a reduced rolling capacity on the endothelium.

Th1 and Th2 cells not only differentially express and bind to selectin ligands, but are different in chemokine receptor expression. Chemokine receptors preferentially expressed by human Th1 cells are CCR5 and CXCR3, whereas CCR3, CCR4, CCR8 and CRTH2 are more abundantly expressed by Th2 cells [48,63–67]. These findings suggest that distinct chemotactic signals contribute to the localization of Th1 and Th2 cells to inflammatory sites and might be important for immunosurveillance towards pathogens. This was indeed found by Maloy et al. [68]. In mice infected with vesicular stomatitis virus (VSV) only the transfer of Th1 cells mediated protection against a recombinant vaccinia virus expressing VSV-G and the ability to mount a VSV-specific DTH. Interestingly, protective capacity correlated with the ability of Th1 cells to rapidly migrate to

inflammatory sites and to respond to the inflammatory Th1-type chemokines IP-10, Mig and MCP-1 that were induced after virus infection [68]. Chemokine-induced migration of Th1 cells mediated protective immunity also in HSV 2 infection in mice [69]. By contrast, production of the selectively Th2-attracting chemokine, viral macrophage inflammatory protein-II (vMIP-II), by human herpes virus 8 (HHV8) has been proposed to subvert the human immune response in Kaposi's sarcoma [70].

Taken together, these observations indicate that Th2 cells are less efficient in binding to E-selectin and responding to chemokines that are induced in infected organs. This may result in a low potential for T cells from atopic individuals to penetrate infected organs such as the skin. Therefore, future therapeutic modalities for the treatment of chronic or recurrent skin infections should include strategies which increase T cell recruitment into infected skin.

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