Biology of Human Tumors

Skin Barrier Dysfunction and Low Antimicrobial Peptide Expression in Cutaneous T-cell Lymphoma

Hiraku Suga, Makoto Sugaya, Tomomitsu Miyagaki, Hanako Ohmatsu, Makiko Kawaguchi, Naomi Takahashi, Hideki Fujita, Yoshihide Asano, Yayoi Tada, Takaumi Kadono, and Shinichi Sato

Abstract

Purpose: Atopic dermatitis is characterized by decreased expression of filaggrin and loricrin. Patients with atopic dermatitis often suffer from skin infections, which are also frequently seen in patients with cutaneous T-cell lymphoma (CTCL). In this study, we aimed to investigate the skin barrier in CTCL.

Experimental Design: We assessed skin moisture and transepidermal water loss (TEWL) in patients with CTCL. We next examined mRNA expression levels of filaggrin, loricrin, and antimicrobial peptides (AMP) in skin samples of CTCL, using skin from healthy volunteers and patients with atopic dermatitis or psoriasis as controls. Immunostainings for filaggrin, loricrin, and S100 proteins were also performed.

Results: Lower levels of skin moisture accompanied by higher levels of TEWL were seen in lesional skin of CTCL than in normal skin. CTCL lesional skin contained lower levels of filaggrin and loricrin mRNA than normal skin, which was also true with atopic dermatitis and psoriatic skin. mRNA expression levels of filaggrin in CTCL skin negatively correlated with disease severity markers. Expression levels of AMPs in lesional skin of CTCL and atopic dermatitis were significantly lower than in psoriatic skin. Immunohistochemistry confirmed decreased expression of filaggrin and loricrin in CTCL, atopic dermatitis, and psoriatic skin and enhanced expression of S100 proteins in psoriatic skin.

Conclusions: Our results show that there is barrier dysfunction in CTCL skin, similar to what is seen with atopic dermatitis skin. In addition, low AMP expression in CTCL skin was documented when compared with psoriatic skin, which may explain frequent infections that can occur in patients with CTCL. Clin Cancer Res; 20(16); 4339–48. ©2014 AACR.

Introduction

Mycosis fungoides and Sézary syndrome are the most common types of cutaneous T-cell lymphoma (CTCL). Patients with mycosis fungoides typically have a prolonged clinical course and only limited cases progress over years through patch, plaque, and tumor stages, followed by lymph node and visceral involvement (1). Sézary syndrome is characterized by the triad of generalized erythroderma (defined as affecting >80% of total body surface area), lymphadenopathy and presence of more than 1,000 per mm² circulating atypical T cells with cerebriform nuclei, so-called Sézary cells (2). Individuals with Sézary syndrome usually show rapid disease progression compared with patients with mycosis fungoides. Most cases with mycosis fungoides/Sézary syndrome, especially at an advanced stage, show a T helper 2 (Th2)-dominant phenotype, characterized by increased IL4, IL5, IL10, and IL13 production (3, 4). Patients with CTCL often suffer from skin infections with bacteria, viruses, and fungi as well. Among them, Staphylococcus aureus is the most common infection in CTCL (5). In immunocompromised patients with advanced-stage CTCL, skin infections occasionally lead to sepsis, multiple organ failure, and death (6, 7). The underlying basis for these infections has not been elucidated.

The epidermis provides an important physical barrier against environmental insults. Dry skin can cause many serious complications such as discomfort and itching, development of dermatitis, and bacterial and viral infections. Epidermal proteins such as filaggrin and loricrin are important in maintaining skin barrier function. Filaggrin aggregates keratin filaments and provides a cytoskeleton for the cornified envelope (8). Loricrin is initially expressed in the granular layer and comprises 70% of the total protein mass of the cornified layer (8, 9). Skin barrier dysfunction is quite commonly seen in patients with atopic dermatitis, which is caused by loss of function in these proteins (10, 11).

Antimicrobial peptides (AMP) are part of the innate immune response and are found among all classes of life...
Translational Relevance

Skin is a barrier against pathogens such as bacteria, viruses, and fungi. Atopic dermatitis is characterized by decreased skin expression of filaggrin and loricrin, leading to abnormalities in skin barrier function and increased susceptibility to infections. Patients with cutaneous T-cell lymphoma (CTCL), which is a T helper 2–dominant disease like atopic dermatitis, often suffer from skin infection as well, leading us to investigate the skin barrier in CTCL. In this study, we have shown that mRNA levels of filaggrin and loricrin in lesional skin of advanced CTCL are decreased compared with normal skin, which negatively correlate with disease severity markers such as CCL17 and IL22. Antimicrobial peptide expression in lesional skin of CTCL was significantly lower than in psoriatic skin. Identification of skin barrier dysfunction in patients with CTCL, as shown here, may potentially lead to therapeutic strategies to prevent infections in these patients, leading to improved disease-associated morbidity.

Materials and Methods

Patients and samples

mRNA was obtained from biopsy materials of lesional skin of CTCL ($n = 26$, 17 males and 9 females; mean ± SD: age: $57.6 ± 12.3$ years; 7 cases with patch mycosis fungoides, 8 cases with plaque mycosis fungoides, 5 cases with tumor mycosis fungoides, 2 cases with erythrodermic mycosis fungoides, and 4 cases with Sézary syndrome). Atopic dermatitis ($n = 6$, all extrinsic type), and psoriasis ($n = 5$), and normal skin adjacent to benign skin tumors ($n = 6$) using RNeasy Fibrous Tissue Mini Kit (QIAGEN). All patients were either untreated or treated with only topical corticosteroids at the time of biopsy. The diagnosis of mycosis fungoides and Sézary syndrome and the stages of CTCL were based on clinical criteria as well as on histologic and IHC assessment according to World Health Organization classification and the criteria of the International Society for Cutaneous Lymphomas (2, 22). When classifying patients into patch mycosis fungoides, plaque mycosis fungoides, tumor mycosis fungoides, or erythrodermic mycosis fungoides/Sézary syndrome, the most severe skin lesion was taken into consideration. Atopic dermatitis was diagnosed according to Hanifin and Rajka criteria (23). Healthy controls had no history of CTCL, atopic dermatitis, psoriasis, or any inflammatory skin diseases. Indeed, we specifically excluded patients under treatment for various internal and inflammatory disorders other than CTCL, atopic dermatitis, and psoriasis. All samples were collected after informed consent during daily clinical practice. The medical ethical committee of the University of Tokyo (Tokyo, Japan) approved all described studies, and the study was conducted according to the Declaration of Helsinki Principles.

Skin moisture and TEWL

We evaluated skin moisture and TEWL in lesional skin of patients with CTCL ($n = 11$, 8 males and 3 females; $59.4 ± 11.3$ years; 4 cases with patch mycosis fungoides, 2 cases with plaque mycosis fungoides, 3 cases with tumor mycosis fungoides, and 2 cases with erythrodermic mycosis fungoides/Sézary syndrome) and healthy volunteers ($n = 8$, 6 males and 2 females; $54.4 ± 20.3$ years). Skin moisture and TEWL were evaluated at least 24 hours after the last application of moisturizers and/or topical corticosteroids as previously described (24, 25). CTCL lesions located in the lower abdominal area or equivalent normal skin areas in healthy volunteers were chosen as the test regions. Moreover, we examined skin moisture and TEWL in perilesional normal-appearing skin in the same patients with CTCL. Perilesional skin was located at least 3 cm outside of the border of CTCL lesional skin. None of patients with CTCL in this study had ichthyosis vulgaris. The measurements were performed in the months of April and May, when the humidity was 40% to 50% and the room temperature was kept at $20^\circ$C. First, we put water-soaked gauze on the test region. Next, we softly wiped the region with dry gauze. Five minutes later, we evaluated skin moisture and TEWL by using Skicon-200EX (IBS Co. Ltd.) and Tewometer TM 300 (Courage & Khazaka), respectively. Skin moisture levels...
were displayed on the machine within 1 second after application of the probe onto the skin. Regarding TEWL levels, values were displayed on a recorder, and the mean value during the period 40 seconds after application of the probe onto the skin was calculated. Skin moisture levels were evaluated 5 times in one skin lesion, and TEWL values were measured twice. Mean values were calculated.

**Quantitative reverse transcriptase PCR assay**

cDNA was synthesized using iScript cDNA Synthesis Kit (Bio-Rad Laboratories). Quantitative reverse transcriptase PCR was performed as described previously based on SYBR Green assay (26). Primers for human filaggrin, loricrin, S100A7, S100A8, S100A9, hBD-1, hBD-2, hBD-3, and GAPDH were as follows: filaggrin: forward, 5'-GAA GAC AAG GAT CGC ACC AC-3' and reverse, 5'-ATG GTG TCC TGA CCC TCT TG-3'; loricrin: forward, 5'-TCA TGA TGC TAC CCC AGG TTT G-3' and reverse, 5'-CAG AATCAG ATG CAG CCG GAG A-3'; S100A7: forward, 5'-CTT CCT TAG TGC CGT TGA CAA AAA-3' and reverse, 5'-AAA GAC AGA AAC TCA GAA AAA TCA ATC TT T-3'; S100A8: forward, 5'-ATG CCG TCT ACA GGG ATG AC-3' and reverse, 5'-ACG CCC ATC TTT ATC ACC AG-3'; S100A9: forward, 5'-CAG CTG GAA CGC AAC ATA GA-3' and reverse, 5'-TCA GCT GCT TTG CAT TT-3'; hBD-1: forward, 5'-AGA TGG CCT CAG GTG GTA ACT TT-3' and reverse, 5'-GGG CAG GCA GAA TAG AGA CAT T-3'; hBD-2: forward, 5'-GAT GCC TCT TGC AGG TGT TTT TT-3' and reverse, 5'-GGA TGA CAT ATG GCT CCA TTC TT-3'; hBD-3: forward, 5'-GTT CAG AGG CCT AGC AGT GAT GAG C-3' and reverse, 5'-TCA GTC CTC CAT GAC CTG GAA-3'; GAPDH: forward, 5'-ACC CACTC GCC ACC TTT GA-3' and reverse, 5'-CAT ACC AGG AAA TGA GCT TGA CAA-3'.

**Immunohistochemistry**

We performed IHC staining for filaggrin, loricrin, S100A7, and S100A8 with lesional skin of 20 cases of CTCL.

**Statistical analyses**

Statistical analyses were performed using the Mann–Whitney U test and the Student t test for comparison of 2 groups. For testing equality of population means among 3 or more groups, the Kruskal–Wallis test and the Scheffe F test were used. Correlation coefficients were determined by using the Spearman rank correlation test. P < 0.05 was considered statistically significant.

**Results**

**Lower levels of skin moisture accompanied by higher levels of TEWL in lesional skin of CTCL**

To investigate skin barrier function in patients with CTCL, we evaluated skin moisture and TEWL in lesional and nonlesional skin of CTCL and in normal skin. Skin moisture levels in CTCL lesional skin were significantly lower than those found in nonlesional skin and normal skin (Fig. 1, P < 0.01, each). Moreover, skin moisture levels in nonlesional skin from patients with CTCL were lower than in normal control skin (Fig. 1, P < 0.01).

![Figure 1. Skin moisture and TEWL in lesional and nonlesional skin from patients with CTCL and in normal control skin. The measured values from individual patients were plotted by dots. **, P < 0.05; ***, P < 0.01.](https://www.aacrjournals.org/ClinCancerRes;20(16)August15,2014/4341)
TEWL values in CTCL lesional skin were significantly higher than those in nonlesional skin and normal skin (Fig. 1, \( P < 0.01 \), each). There were also significant differences in TEWL values between nonlesional CTCL skin and normal control skin (Fig. 1, \( P < 0.05 \)). Thus, skin barrier function was abnormal in both lesional and nonlesional skin of patients with CTCL when compared with normal control skin.

**Decreased mRNA expression of filaggrin and loricrin combined with increased mRNA expression of S100 family in CTCL skin**

We next analyzed expression levels of skin barrier–associated proteins and AMPs in lesional skin of CTCL, atopic dermatitis, psoriasis, and healthy individuals. Filaggrin mRNA expression levels in lesional skin of plaque, tumor, or erythroderma of CTCL were significantly decreased compared with normal skin (Fig. 2). Similar results were obtained with regard to loricrin mRNA. Filaggrin and loricrin mRNA expression levels in lesional skin of atopic dermatitis and psoriasis were also decreased compared with normal controls (Fig. 2), which was consistent with previous reports (10, 11). S100A7 mRNA expression levels in lesional skin of patch, plaque, tumor, erythroderma of CTCL, atopic dermatitis, and psoriasis were significantly higher than in normal controls (Fig. 2; \( P < 0.05 \), \( P < 0.01 \), \( P < 0.05 \), and \( P < 0.01 \), respectively). Similarly, lesional skin of plaque, tumor, erythroderma of CTCL, atopic dermatitis, and psoriasis expressed significant higher levels of S100A8 mRNA than in normal skin (Fig. 2; \( P < 0.01 \), \( P < 0.05 \), \( P < 0.05 \), and \( P < 0.01 \), respectively). S100A9 mRNA expression levels in lesional skin of plaque, tumor of CTCL, and psoriasis were significantly higher than in normal controls (Fig. 2; \( P < 0.01 \), \( P < 0.05 \), and \( P < 0.05 \), respectively). With regard to hBD-1, in lesional skin of plaque, tumor, erythroderma of CTCL, and atopic dermatitis, significantly decreased mRNA expression levels were detected compared with normal controls (Fig. 2; \( P < 0.05 \), each). Although previous reports showed that hBD-1 expression correlated with disease activity in psoriasis (15, 27), it was not elevated in lesional skin of psoriasis compared with normal skin. Of note, mRNA levels

![Figure 2](image-url)
of S100A7 and S100A8 in CTCL lesional skin were significantly decreased as compared with levels in psoriatic skin (Fig. 2; $P < 0.01$, each). There were no significant differences in hBD-2 and hBD-3 expression among the groups (data not shown). Thus, filaggrin and loricrin mRNA expression levels were decreased in CTCL lesional skin combined with increased S100 family protein expression, although the latter was not as high as seen in psoriatic skin.

**Correlations between filaggrin expression in lesional skin of CTCL and disease activity**

We evaluated correlations between expression levels of filaggrin and those of loricin, S100 family, hBD-1, hBD-2, hBD-3, and disease severity markers in CTCL lesional skin. We have previously reported that expression levels of CCL17, CCL18, CCR4, IL4, and IL22 are associated with disease progression in CTCL (3, 28–31). LIGHT [lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D for herpesvirus entry mediator (HVEM)], a receptor expressed by T lymphocytes is also correlated with disease progression in CTCL, whereas HVEM expression in CTCL skin negatively correlates with disease progression (28). Filaggrin expression levels positively correlated with those of loricin (Fig. 3A), which is consistent with the fact that both molecules are barrier function–related proteins downregulated by $T_{h}2$ cytokines (32, 33). Filaggrin expression levels negatively correlated with those of CCL17, CCL18, CCR4, IL4, IL22, and LIGHT and positively correlated with those of HVEM (Fig. 3A), suggesting a significant negative correlation between disease progression in CTCL and filaggrin expression. Moreover, we evaluated associations between filaggrin expression in CTCL lesional skin and serum levels of sIL2R or CCL17 (Fig. 4B). Thus, AMP expression was not increased in proportion to IL17A or IL22 expression in CTCL skin, probably because $T_{h}2$ cytokines, abundantly expressed in advanced CTCL skin, blocked AMP expression by lesional keratinocytes as was reported in vitro (18, 19).

**Decreased filaggrin and loricrin expression by keratinocytes in lesional skin of CTCL, atopic dermatitis, and psoriasis, and enhanced S100A7 and S100A8 expression in psoriatic skin**

IHC stainings for filaggrin, loricin, S100A7, and S100A8 were performed using lesional skin of patch, plaque, tumor, erythroderma of CTCL, atopic dermatitis, psoriasis, and normal skin. In patch and plaque CTCL cases, filaggrin and loricrin expression by keratinocytes was decreased compared with normal skin (Fig. 5 and Table 1). In almost all cases with tumor and erythroderma of CTCL, atopic dermatitis, and psoriasis, filaggrin and loricrin expression was remarkably decreased (Fig. 5 and Table 1). S100A7 and S100A8 expression was remarkably enhanced only in psoriatic skin. These IHC findings were largely consistent with mRNA levels detected by real-time PCR (Fig. 2). Thus, expression of skin barrier–related proteins by keratinocytes in lesional skin of CTCL, atopic dermatitis, and psoriasis was decreased, whereas AMPs were highly produced by keratinocytes of lesional skin of psoriasis, but not in CTCL or atopic dermatitis skin.

**Discussion**

Our study revealed that skin moisture levels were decreased, and TEWL was increased in lesional skin of CTCL compared with normal skin. Lesional skin of advanced CTCL also expressed lower levels of filaggrin mRNA, which negatively correlated with mRNA levels of disease severity markers. Expression levels of AMPs in lesional skin of CTCL and atopic dermatitis were significantly lower than those in psoriatic skin, which may explain the frequent occurrence of cutaneous infections in patients with CTCL.

Measuring skin moisture and TEWL are noninvasive means to assess barrier function of the stratum corneum. Previously, skin moisture and TEWL were evaluated with various skin diseases such as atopic dermatitis, ichthyosis, and psoriasis, all of which are strongly associated with dry skin (24, 25). To the best of our knowledge, this is the first study to evaluate skin moisture and TEWL in patients with CTCL. Of note, to control for any age-related changes in skin

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function (39), we used normal volunteers of the approximate same age as the patients with CTCL. Skin moisture levels in lesional skin of CTCL were significantly lower than those in normal skin, whereas TEWL in CTCL skin was significantly higher than in normal skin (Fig. 1). Moreover, lower levels of skin moisture combined with higher levels of TEWL were detected in CTCL perilesional skin than in normal skin. Although we did not evaluate perilesional skin histologically in this study, atypical T-cell infiltration is often seen in normal-appearing skin of patients with CTCL. Therefore, direct infiltration of tumor cells as well as Th2-dominant systemic inflammation can cause skin barrier dysfunction in nonlesional skin of CTCL. Thus, we clearly show here that patients with CTCL have dry skin, which can subsequently lead to pain, pruritus, and infections.

The recent identification and confirmation of loss-of-function mutations in filaggrin as a major risk factor for atopic dermatitis sheds new light on the immunopathogenesis of this disease (10, 11). Skin barrier dysfunction and

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**Figure 3.** Correlations between filaggrin expression in lesional skin of CTCL and disease activity. A, significant positive or negative correlations between expression levels of filaggrin in CTCL lesional skin and those of loricrin or disease markers. B, significant negative correlations between filaggrin expression in CTCL lesional skin and serum-soluble IL2 receptor or CCL17 levels. The measured values from individual patients were plotted by dots.
resultant diminished epidermal defense mechanisms to allergens and microbes are regarded as early steps in the onset of atopic dermatitis (16–19). TH2-dominant immune responses such as increased levels of IgE may result from, rather than cause, refractory eczema as has been reported in mice repeatedly exposed to cutaneous allergens (40). A recent report, however, showed that expression of filaggrin and loricrin by primary human keratinocytes was inhibited by adding IL4, IL13, or the combination of IL4 and IL13 (33). Skin biopsies from STAT6 transgenic mice were deficient in loricrin and involucrin, suggesting that TH2 cytokines such as IL4 and IL13 inhibit expression of barrier proteins.

Figure 4. Correlations between S100A7 expression in lesional skin of CTCL and disease activity. A, significant positive or negative correlations between expression levels of S100A7 and those of S100A8, S100A9, CCL26, or CCR3 in CTCL lesional skin. B, no significant correlations between expression levels of S100A7 and those of IL17A or IL22 in CTCL lesional skin. The measured values from individual patients were plotted by dots.
function–related proteins through a STAT6-dependent mechanism (33). IL4 and IL13, which are highly expressed in skin and blood of patients with either atopic dermatitis or CTCL (30, 41, 42), may in turn downregulate filaggrin and loricrin expression in these patients. Indeed, we found significant negative correlations between filaggrin expression and disease severity markers (including IL4) in CTCL lesional skin (Fig. 3A). On the other hand, expression of filaggrin and loricrin was also decreased in lesional skin of psoriasis patients (Fig. 2), which is consistent with previous reports (13–15). TNFα, expressed in psoriatic skin, down-regulates filaggrin and loricrin expression in vitro. Our results, along with previous reports, suggest that decreased expression of filaggrin is not a specific finding of atopic dermatitis, as this was readily seen in CTCL and psoriasis patients as well.

Whereas CTCL, atopic dermatitis, and psoriasis are all T-cell–associated diseases that share common features such as epidermal hyperplasia, abundant inflammatory cell infiltrates, and decreased expression of filaggrin, the 2 former diseases have different immune and barrier phenotypes from the latter. Atopic dermatitis is a TH2/TH22-polarized disease with an attenuated TH17 axis (43). Expression of IL22 and TH2 cytokines such as IL4 and IL10, but not IL17A, is also elevated in lesional skin of CTCL (30). In contrast, IL17A and IL22 are elevated in psoriatic skin, but not TH2 cytokines. TH2 cytokines inhibit secretion of AMPs such as S100A7, hBD-2, and hBD-3 in primary

### Table 1. Filaggrin, loricrin, S100A7, and S100A8 expression in lesional skin of patch, plaque, tumor, erythroderma of CTCL, atopic dermatitis, psoriasis and in normal skin

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keratinocytes (44–46). Consistently, in CTCL lesional skin, we detected significant negative correlations between expression levels of S100A7 and those of CCL26 or CCR3, a representative T_{H12} chemokine/chemokine receptor pair (Fig. 4A). T_{H12} cytokines also suppress T_{H1} cytokines, which are effective for antitumor immunity and infections (47, 48). Thus, a T_{H12}-dominant cytokine milieu downregulates immunity against infections, which are commonly seen in lesional skin of CTCL as well as in atopic dermatitis skin. Not surprisingly, patients with psoriasis do not have clinical issues with skin infections, as T_{H12} cytokines are not dominant.

We also showed that expression levels of AMPs were higher in psoriatic skin than in CTCL or atopic dermatitis skin (Fig. 2). IL17A, together with IL22, induces AMPs such as S100A7, S100A8, S100A9, and hBD-2 (49). Interestingly, there were positive correlations between expression levels of S100A7 and those of IL17A or IL22 in psoriatic skin (data not shown), whereas no such correlations were found in CTCL skin (Fig. 4B). Because T_{H12} cytokines suppress expression of AMPs as well as IL17A, high expression of T_{H12} cytokines may be the main reason why AMP levels were decreased in CTCL and atopic dermatitis compared with psoriasis. In the skin of patients with erythrodermic CTCL, Staphylococcus aureus-derived superantigen enterotoxins are commonly found, which could exacerbate chronic expansion of T cells, including T-cell receptor V{beta}2-bearing cells (5, 50). Therefore, insufficient induction of AMPs, especially S100A8 and S100A9, may cause infection with staphylococcus in CTCL skin, which may induce expansion of T cells bearing specific T-cell receptors. Although psoriatic skin is often colonized with Staphylococcus aureus, life-threatening infection is rarely seen probably due to sufficient expression of AMPs.

In conclusion, our study has revealed that skin barrier dysfunction is present in CTCL, similar to what has been reported in atopic dermatitis. T_{H2}/T_{H22}-polarized immune status together with an attenuated T_{H17} axis may cause decreases in filaggrin expression and insufficient induction of AMPs. Thus, improving skin barrier function by attenuating T_{H2} responses could lead to better control of cutaneous infections, improving overall disease-associated morbidity in patients with CTCL.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References


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