

Dysregulated Expression of Antimicrobial Peptides in Skin Lesions of Patients with Cutaneous T-cell Lymphoma

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Mycosis fungoides and Sézary syndrome belong to the group of primary cutaneous T-cell lymphomas. Because of the inflammatory appearance of the skin lesions, we hypothesized that antimicrobial peptides might be dysregulated in these conditions, similar to in inflammatory skin conditions. Samples from 20 patients with cutaneous T-cell lymphoma were analysed using immunohistochemistry and enzyme-linked immunoassay (ELISA) of skin washing fluids of hBD-2, hBD-3, RNase 7 and psoriasin. Immunohistochemistry results were compared with previous analyses of healthy and psoriatic skin. ELISA and immunohistochemistry revealed a higher expression of psoriasin in lesional cutaneous T-cell lymphoma compared with non-lesional and healthy samples. Immunohistochemistry showed an increase in hBD-2 in lesional cutaneous T-cell lymphoma skin compared with healthy skin. The expression profile of antimicrobial peptides in cutaneous T-cell lymphoma appears to be dysregulated, indicating a potential role of antimicrobial peptides in cutaneous T-cell lymphoma. A larger prospective study and functional studies are needed to improve our understanding of the role of antimicrobial peptides in cutaneous T-cell lymphoma.

Key words: mycosis fungoides; T-cell lymphoma; defence; tumour; antimicrobial peptides.

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Antimicrobial peptides (AMPs) have been explored in many skin diseases over the past 20–30 years. These peptides play an important role, not only in local infection control, but also in maintaining skin and surface homeostasis, respectively. AMPs have been found in the lung, gut and mucosal tissue, on virtually every body surface that faces the environment (1, 2). Healthy skin expresses certain levels of AMPs, differing body site to body site. However, the expression of AMPs, e.g. human beta-defensin 2 and 3 (hBD-2 and hBD-3), in healthy skin is usually low (3). Inflammatory skin diseases, like psoriasis, which is one of the prototype diseases for AMP exploration revealed an extensive upregulation of psoriasin (=S100A7) and RNase 7 in previous studies (4, 5). Cutaneous T-cell lymphoma (CTCL), explicitly mycosis fungoides (MF), representing the most common form of CTCL, shares some common clinical characteristics

SIGNIFICANCE

Antimicrobial peptides are important for infection control and are known to be dysregulated in inflammatory skin conditions. In early stages of cutaneous T-cell lymphoma the lesions resemble inflammatory skin conditions. In later stages, patients often die due to infections. These clinical facts have led to an increased interest in the potential involvement of antimicrobial peptides. The current study shows that antimicrobial peptides are dysregulated in lesional cutaneous T-cell lymphoma skin. It is likely that antimicrobial peptides play a critical role in cutaneous T-cell lymphoma disease pathogenesis and maintenance. Furthermore, the antimicrobial peptide dysregulation potentially contributes to the infection risk with fatal outcome in higher disease stages.

with inflammatory skin conditions. In the early stages of the disease, the patients typically present with erythematous patches and plaques with epidermal involvement potentially mimicking inflammatory skin diseases, such as psoriasis or, more frequently, eczema. Many patients are diagnosed with a latency of several months or years because of the resemblance to inflammation (6). The clinical features shared with chronic inflammatory skin diseases and previously published data for patients with CTCL, suggesting a disequilibrium in the expression of AMP compared with healthy skin, led to the development of the current project. This is the first study that addresses the expression of AMP in skin washing fluids of patients with CTCL. As patients in higher disease stages of CTCL are likely to develop systemic infections and may die of septic complications, the analysis of AMP expression in CTCL might provide insight into mechanisms that are important for a better understanding of the disease and, possibly, infection control in these patients.

MATERIALS AND METHODS

Patients and specimens

Patients of the Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, were recruited from the cutaneous lymphoma clinics. All patients were diagnosed with MF or Sézary syndrome (SS) according to the current classification of the European Organization for the Research and Treatment of Cancer and International Society for Cutaneous Lymphomas (EORTC-ISCL). Clinical information, including age, sites of involvement, stage at first diagnosis, and current disease stage, were obtained from the patients' clinical charts. The patients' consent was obtained

ned prior to the performance of any procedure according to local ethics approval (D559/16).

Histopathological evaluation

Formalin-fixed and paraffin-embedded (FFPE) tissue specimens and stained slides from the Department of Dermatology were retrieved and reviewed by a dermatopathologist (UW). Only patients with a definite diagnosis of MF and histological specimen consistent with the diagnosis of MF were included in the immunohistochemical analysis. Immunohistochemical staining for RNase 7, hBD-2, hBD-3, and psoriasin were performed as described previously (3, 5). Positive and negative controls were included for every staining. Quantitative scoring was performed by a dermatopathologist (UW) separately scoring every epidermal layer in all fields of vision (FV) using 400-fold magnification. The following levels of immunoreactivity were distinguished: 0=no, 1=faint, 2=moderate, 3=high (Fig. 1). The number of counted FV was multiplied with the corresponding scores and subsequently divided by the total number of fields of vision according to the following formula:

$$\frac{(FV1 \cdot 1) + (FV2 \cdot 2) + (FV3 \cdot 3)}{FV_{\text{Overall}}}$$

where FV_n=number of fields of vision with value n; and FV_{Overall}=total number of fields of vision.

The quotient calculated using this formula (IHC score) could take every rational number between 0 and 3. Slides for immunohistochemical evaluation for RNase 7, hBD-2, hBD-3, and psoriasin were available from 12 patients.

ELISA

Protein levels of RNase 7, psoriasin, and hBD-2 in the skin washing fluids were measured using ELISA, as described previously (7). The ELISA detection limit was 0.3 ng/ml for psoriasin and RNase 7, respectively, and 0.075 ng/ml for hBD-2. Washing fluids of lesional and non-lesional skin of CTCL patients with ELISA were evaluable for 10 patients.

Comparison of histopathological evaluation

For the comparison of expression in the immunohistochemistry, data from previous projects in healthy human skin and psoriasis were used (3, 5), in which expression of AMPs had been evaluated using the same approach as used for the analysis of our CTCL cohort.

Statistical methods

GraphPad Prism software (San Diego, CA, USA) was used for all statistical calculations.

Table I. Cohort characteristics of the patients with cutaneous T-cell lymphomas included in the study (patient cohort: n=20)

| Characteristics | |
|--|------------|
| Age at initial diagnosis, years, median (range) | 63 (41–78) |
| Sex, male/female, n | 13/7 |
| Examined lesion type, patch: plaque: tumour | 8: 11: 1 |
| Diagnosis mycosis fungoides: Sézary syndrome | 18:2 |
| Clinical stage (according to current recommendation of EORTC/ISCL) (8) | |
| IA | 8 |
| IB | 5 |
| IIB | 5 |
| IVB | 2 |

EORTC-ISCL: European Organization for the Research and Treatment of Cancer and International Society for Cutaneous Lymphomas.

RESULTS

Clinical features

The study cohort comprised 20 patients with CTCL. All patients were classified according to the current TNMB classification and clinical stages of the European Organization for Research and Treatment of Cancer and the International Society for Cutaneous Lymphoma (EORTC/ISCL) (8). The clinical characteristics of the patients included in the present study are shown in Table I. Most of the patients were in the early disease stages of MF (clinical stages IA, IB: 13/20; 65%) and the majority of lesions examined in our study were defined as plaque lesions (11/20; 55%). Two patients with Sézary syndrome were included in the study.

Immunohistochemical expression of antimicrobial peptides in cutaneous T-cell lymphoma lesional skin

The expression of all AMPs was present mainly in the stratum corneum, to a lower extent also in the stratum granulosum, spinosum and, rarely, in the stratum basale. The highest expression was observed for psoriasin, with a mean value of 1.02. For RNase 7 a mean expression of 0.92 was observed. hBD-2 and hBD-3 both equalled a mean value of 0.37 in the semiquantitative evaluation. Representative examples of the stainings are shown in Fig. 2.

ELISA from skin washing fluids

In the ELISA from skin washing fluids lesional and non-lesional samples of CTCL patients were analysed

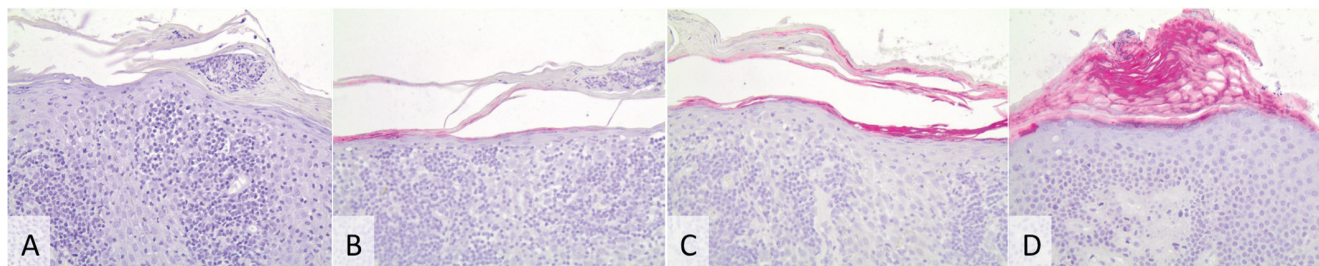


Fig. 1. Scoring of expression in immunohistochemistry on the example of the stratum corneum. (A) No expression, (B) faint, (C) moderate, and (D) high. (A–D) Original magnification 200×.

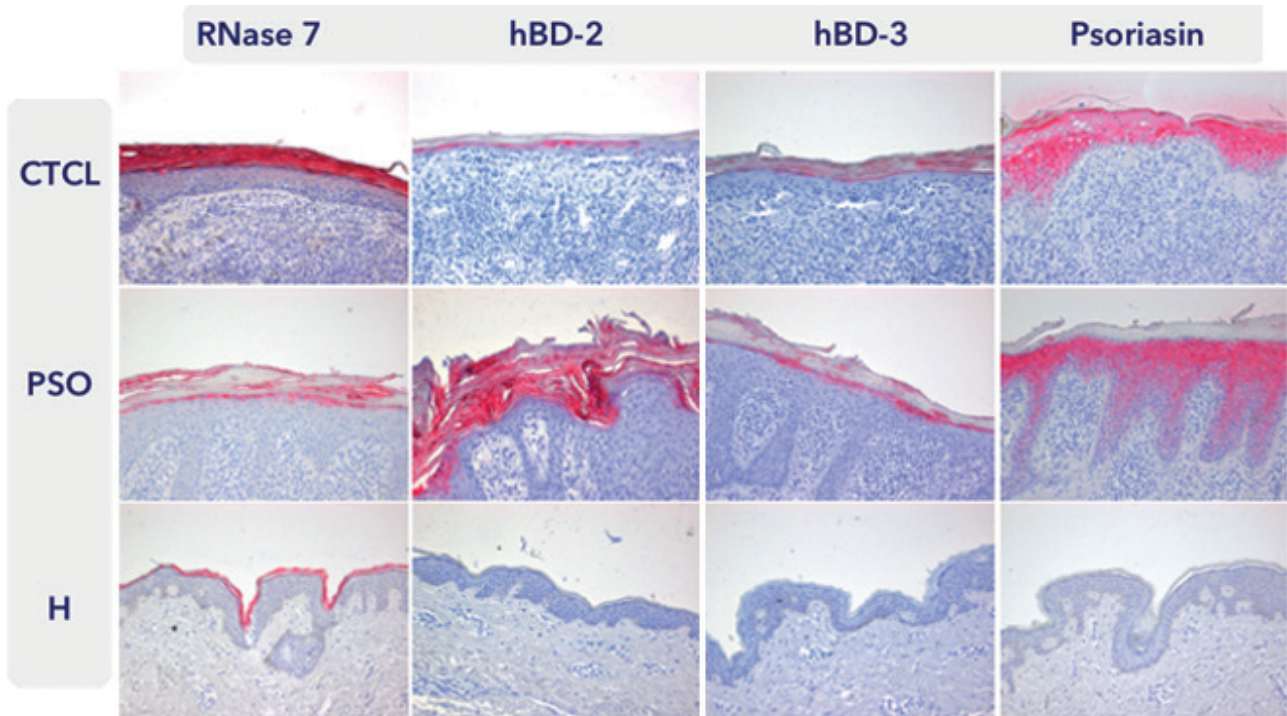


Fig. 2. Representative examples of immunohistochemistry staining in patients with cutaneous T-cell lymphomas (CTCL), psoriasis (PSO) and healthy controls (H) for the stained antimicrobial peptides RNase 7, human beta-defensin (hBD)-2 and -3 and psoriasin.

and compared. The only AMP that showed a statistically significant discrepancy between lesional and non-lesional skin was psoriasin ($p < 0.0001$). For RNase 7 and hBD-2 the expression in the ELISA was similar in the comparison of lesional and non-lesional skin (RNase 7 $p = 0.7703$; hBD-2 $p = 0.2912$) (**Fig. 3**). Lesional and non-lesional skin washing fluids could be retrieved from 10 patients.

Comparison of the results of cutaneous T-cell lymphoma with normal skin and psoriatic skin

For comparison, the main values of previous studies performed in our department in psoriasis and healthy

skin were used (3, 5). Compared with normal healthy skin (HC) the expression of psoriasin was twice as high in CTCL (CTCL: 1.02 and HC: 0.48, respectively); however, it was not as high as in lesional skin of psoriatic patients (2.37). hBD-2 expression was strongly induced in lesional CTCL skin compared with HC (CTCL: 0.37 and HC: 0.03) and was also not as high as in psoriasis (0.77). RNase 7 and hBD-3 showed comparable mean values in CTCL skin and HC (RNase 7: 0.92 and 0.81, respectively and hBD-3: 0.37 and 0.29). Interestingly, RNase 7 mean expression in psoriasis was lower than in CTCL and HC (0.68 vs. 0.92 and 0.81, respectively) and, on the other hand, hBD-3 showed higher values for psoriasis in this comparison. However, the differences in

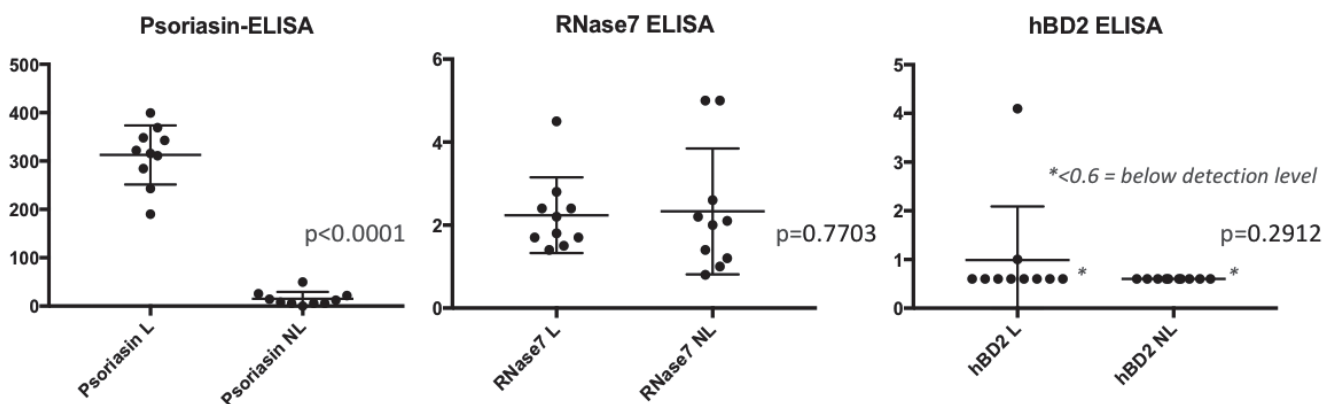


Fig. 3. Enzyme-linked immunoassay (ELISA) expression values of lesional and non-lesional skin of skin washing fluids of patients with cutaneous T-cell lymphomas (CTCL) show a significant difference for psoriasin. For RNase 7 and human beta-defensin (hBD)-2 the expression is in the same ranges.

Table II. Immunohistochemical evaluation and mean values obtained from the immunohistochemistry scoring system of skin samples in comparison of lymphoma, patients with psoriasis, and healthy controls

| | LS CTCL | LS PSO | Healthy control | <i>p</i> -value* |
|--------------------|---------|--------|-----------------|------------------|
| RNase-7 | | | | |
| Stratum corneum | 2.29 | 1.92 | 2.16 | |
| Stratum granulosum | 1.25 | 0.66 | 0.70 | |
| Stratum spinosum | 0.13 | 0.14 | 0.25 | |
| Stratum basale | 0.00 | 0.00 | 0.12 | |
| Mean | 0.92 | 0.68 | 0.81 | 0.331 |
| hBD-2 | | | | |
| Stratum corneum | 0.82 | 2.21 | 0.09 | |
| Stratum granulosum | 0.44 | 0.50 | 0.02 | |
| Stratum spinosum | 0.20 | 0.36 | 0.01 | |
| Stratum basale | 0.00 | 0.00 | 0.00 | |
| Mean | 0.37 | 0.77 | 0.03 | 0.061 |
| hBD-3 | | | | |
| Stratum corneum | 1.09 | 2.44 | 0.69 | |
| Stratum granulosum | 0.37 | 0.88 | 0.20 | |
| Stratum spinosum | 0.01 | 0.34 | 0.17 | |
| Stratum basale | 0.00 | 0.25 | 0.10 | |
| Mean | 0.37 | 0.98 | 0.29 | 0.296 |
| Psoriasis | | | | |
| Stratum corneum | 1.29 | 2.08 | 0.39 | |
| Stratum granulosum | 1.58 | 2.69 | 0.69 | |
| Stratum spinosum | 1.17 | 2.69 | 0.63 | |
| Stratum basale | 0.06 | 2.02 | 0.21 | |
| Mean | 1.02 | 2.37 | 0.48 | 0.057 |

Psoriasis shows the highest overexpression in the comparison except for RNase 7. Lymphoma patients display an upregulation in psoriasis and hBD-2 compared with healthy skin.

*LS CTCL vs Healthy control. *p*-values were calculated using paired *t*-test.

LS: lesional skin; CTCL: cutaneous T-cell lymphoma; PSO: psoriasis vulgaris.

the levels of AMP expression between groups were not statistically significant (**Table II**).

DISCUSSION

CTCL comprise a spectrum of heterogeneous entities with a wide variety of clinical presentation and disease aggressiveness (9). In the present study we therefore decided to limit our investigation of AMP expression to the most common subtypes, MF and SS; the latter representing a rarer subtype, but being classified according to the same criteria as MF (8). In both of these entities the skin lesions may resemble inflammatory skin conditions. In the clinical setting differential diagnoses encompass eczema with variants such as atopic and nummular eczema and eczema of the elderly, psoriasis, pityriasis rubra pilaris, etc. In the following text, we refer to both of these entities as CTCL and emphasize that we do not want to imply that the results of the current study extend to CTCL other than MF and SS. MF in the early stages usually presents with a favourable course of disease (10). However, from higher stages onwards (tumour stage T3 to clinical stage IIB) including SS the outcome is poor, and 5-year survival rates are reported as between 24% and 36% (11–13).

Healthy human skin is characterized by the expression of AMPs in variable amounts. Depending on the localization and age, intra-individual variability has been noted (3). In general, the expression of AMPs in

healthy human skin is rather low or not even measurable in inducible AMPs, such as hBD-2 and hBD-3. This inducibility relates to inflammatory or mechanical triggers, and was reported previously for inflammatory skin conditions, both psoriasis and atopic eczema (14). Due to the inflammatory aspect of CTCL patients, the skin lesions often resemble other inflammatory skin conditions. With regard to previously published data, we aimed to assess the expression of AMPs in skin washing fluids from lesional and non-lesional skin of patients with CTCL and, in addition, to characterize the expression of AMPs in immunohistochemistry. This is the first study to assess AMP expression in the skin washing fluids of patients with CTCL.

In the present study, expression of AMPs within the different epidermal layers was detected in most cases in the upper epidermal layers. This finding is similar to previous reports about AMP expression in healthy skin or inflammatory skin conditions and is described as a kind of shield against the environment and microbes that could potentially be harmful (15). Using immunohistochemistry, a high level of expression of psoriasis was detected in lesional CTCL skin. In line with these findings the ELISA results for skin washing fluids in the current study revealed strongly increased levels of psoriasis in lesional CTCL skin compared with non-lesional CTCL skin. Psoriasis, also known as S100A7, is typically highly upregulated in psoriasis, and is known to contribute to a dysregulated differentiation of keratinocytes (4). Whether this mechanism is a contributing factor for the characteristic “inflammatory” clinical picture of CTCL skin lesions has not yet been explored. Psoriasis appears to have several functions, not all of which are well understood. A major purpose is its antimicrobial capacity against microbes (16). However, it has been discussed that psoriasis might also play a role in cancer. Its influence on the immune response has been associated with breast cancer progression (17). Furthermore, a role in cancer progression is under discussion for more cancer types, e.g. pancreatic, lung and prostate cancer (18–20). Therefore, a potential contribution of psoriasis to disease maintenance and progression in CTCL appears to be plausible.

Until now, very few groups have examined the expression of AMPs in CTCL. Gambichler et al. analysed the expression of hBD-1, hBD-2 and hBD-3 on mRNA level (21). They described, in 13 patients with MF, upregulation of hBD-2 and hBD-3 compared with healthy skin and in intra-individual comparison of lesional and non-lesional tissue. hBD-1 appeared to be downregulated (21). The current immunohistochemistry analysis also revealed a stronger expression of hBD-2 in lesional CTCL compared with healthy skin, corroborating the previous description. This result is novel, as this is the first description of an immunohistochemistry study of

hBD-2 expression in CTCL. For hBD-3 we observed only a slightly higher expression in immunohistochemistry. It is suggested that the high levels of hBD-2 present in lesional psoriatic skin may trigger the disease due to the immunomodulatory activities (e.g. chemotactic activity) of hBD-2 (22). Thus, it is intriguing to speculate that an increased level of hBD-2 might trigger the inflammatory process in CTCL, a hypothesis that remains to be verified. Gambichler et al. also compared their findings with those for patients with atopic dermatitis (AD), another common inflammatory skin condition, and reported a comparable expression profile of AMPs for MF and AD (21). Overlaps in T-cell polarization between these 2 diseases might explain this finding.

Suga et al. (23) also examined mRNA expression levels and immunohistochemistry for psoriasin in 26 skin samples of CTCL. At the mRNA level, psoriasin was also overexpressed in lesional CTCL skin compared with healthy tissue. On immunohistochemistry, psoriasin was highly expressed in psoriatic skin and slightly higher in CTCL compared with healthy skin, on analysis of different stages of the disease in a total of 20 cases of CTCL. Their analyses do not give specifics about the localization within the epidermal compartment (23). In the current study, the clear difference in expression, with higher expression in CTCL compared with healthy skin, might be due to the more detailed analysis performed in our study. In any case, in our study, psoriasis also proved to be the prototype of overexpression of psoriasin.

In a cohort of 21 patients with MF from China, significant upregulation in CTCL skin compared with healthy controls was reported based on immunohistochemistry, which is in agreement with the findings of the current study cohort. However, only the abstract of this work is available in English, and, therefore, only limited comparison with our data was possible (24).

Analyses in a mouse model revealed that bacterial triggers might play an important role in the development of CTCL (25). As AMPs are critical in the regulation of presence of microbiota on the skin (26), the AMP expression profile might be highly relevant to the pathogenesis and the maintenance of a “pro-lymphoma” milieu. Hypothetically, 2 reasons for the AMP dysregulation in CTCL seem plausible: the dysregulation might simply reflect a regular response to bacterial colonization on the skin surface, or it might be due to a dysregulated signalling potentially triggered by the malignant inflammation of the CTCL itself (27).

In patients with CTCL, the skin is frequently found to be colonized with *Staphylococcus aureus* (28, 29). Therefore, a role for *S. aureus* in the development and maintenance of CTCL is under discussion, and different approaches show that *S. aureus* and its toxins, respectively, impact on critical pathways in lymphomagenesis, e.g. via STAT3 and IL-17 signalling (25, 30). It has been demonstrated that, in some cases, antibiotic treatment can

improve the clinical presentation of CTCL and, sometimes, even lead to complete remission. It has been shown that this treatment line leads to a reduction in inflammation, and inhibits aberrant signalling and proliferation of the malignant T cells in skin lesions colonized by *S. aureus* in patients with advanced CTCL (31). This suggests that microbial colonization, in part by *S. aureus*, influences the disease activity of CTCL (32).

Patients with atopic dermatitis (AD) are also known to frequently harbour *S. aureus* on their skin surface (33). In this entity it has been described that a reduced mobilization of hBD-3 might lead to a defective killing of *S. aureus* (34). Compared with patients with psoriasis, those with AD and those with CTCL have only minimal differences regarding the incidence of presence of *S. aureus* on their lesions (29, 35). In all of these diseases, the extent of *S. aureus* colonization is higher than in healthy skin. However, in psoriasis the patients rarely develop infections related to *S. aureus*, which leads to the assumption that the presence of bacteria does not necessarily correlate with infection risk. To date, we have obtained knowledge that AMPs influence the microbiota and vice versa (1). The knowledge of AMP expression in CTCL might lead to better understanding of the disease. Projects focusing on pathway signalling and microbiome analysis complementing AMP expression data could help to provide insight into the pathogenesis and maintenance of this disease.

In summary, this is the first study to assess AMP expression in lesional and non-lesional skin from skin washing fluids, together with immunohistochemistry results, using a very detailed evaluation scheme. According to our data and the data found in the literature, AMPs are dysregulated in patients with CTCL. To gain a better understanding of the influence of AMPs on disease development and evolution, more functional studies are needed. These could help in advancing treatment strategies from another angle and might also add to the prevention of infectious complications, which frequently result in a fatal outcome in the higher stages of the disease.

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