Staphylococcal enterotoxins stimulate lymphoma-associated immune dysregulation

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Patients with cutaneous T-cell lymphoma (CTCL) are frequently colonized with Staphylococcus aureus (SA). Eradication of SA is, importantly, associated with significant clinical improvement, suggesting that SA promotes the disease activity, but the underlying mechanisms remain poorly characterized. Here, we show that SA isolates from involved skin express staphylococcal enterotoxins (SEs) that induce crosstalk between malignant and benign T cells leading to Stat3-mediated interleukin-10 (IL-10) production by the malignant T cells. The SEs did not stimulate the malignant T cells directly. Instead, SEs triggered a cascade of events involving cell-cell and asymmetric cytokine interactions between malignant and benign T cells, which stimulated the malignant T cells to express high levels of IL-10. Much evidence supports that malignant activation of the Stat3/IL-10 axis plays a key role in driving the immune dysregulation and severe immunodeficiency that characteristically develops in CTCL patients. The present findings thereby establish a novel link between SEs and immune dysregulation in CTCL, strengthening the rationale for antibiotic treatment of colonized patients with severe or progressive disease. (Blood. 2014;124(5):761-770)

Introduction

Cutaneous T-cell lymphomas (CTCLs) are a group of neoplastic diseases characterized by expansion of malignant T cells in the skin. The 2 predominant clinical forms of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). MF typically presents as patch, plaque, or tumor lesions, whereas SS is characterized by erythroderma and the presence of malignant T cells in the skin and blood.1,4 During disease progression, there is a decline in the number and activity of benign immune cells leading to suppression of cell-mediated immunity and ultimately severe immunodeficiency.5–16 Much evidence supports that malignant T cells drive the immune dysregulation to impede antitumor immunity and that suppression of the patient’s cellular immunity is associated with increased disease activity.17–22 Two factors that seem to hold a central position in driving the immune dysregulation are signal transducer and activator of transcription 3 (Stat3) and the immunoregulatory cytokine interleukin-10 (IL-10). In keeping, the malignant activity of Stat3 and the expression of IL-10 during disease progression in parallel with the evolving immune dysregulation.23–26 Activation of Stat3 in malignant cells can lead to secretion of soluble mediators facilitating activation of Stat3 in infiltrating benign immune cells, thereby suppressing cell-mediated cytotoxicity and promoting accumulation of immunosuppressive regulatory T cells. Furthermore, aberrant activation of Stat3 in malignant cells can induce expression of immunoregulatory factors including IL-10.27 IL-10 possesses strong immunosuppressive capacities and can dampen immune responses by several means. Among these, IL-10 promotes accumulation of tolerogenic macrophages and dendritic cells and represses Th1-mediated immune responses while favoring differentiation of anergic and immunosuppressive T cells.28–30 IL-10 can, accordingly, suppress the antibacterial immune defense and increase the risk of septicemia.31 Supporting that IL-10 also plays an important role in cancer-associated immunosuppression, blocking IL-10 activity in combination with immunostimulatory agents can restore antitumor immune responses in animal models with resulting tumor inhibition or regression.28–30 Indeed, IL-10 represses the expression of Th1 cytokines from CTCL cells, and malignant CTCL cells inhibit dendritic cell maturation as well as activation of benign T cells in an IL-10–dependent manner.32–35 More

Key Points

• Staphylococcal enterotoxins stimulate benign T cells to induce activation of the immunoregulatory Stat3/IL-10 axis in malignant T cells.

• Colonization with enterotoxin-producing Staphylococcus aureus may promote immune dysregulation in cutaneous T-cell lymphoma.

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importantly, as in many other forms of cancer, high levels of IL-10 have been associated with progressive disease and resistance to therapy in CTCL.\textsuperscript{24,25,28-30,36} As a consequence of the compromised skin barrier and evolving immune dysfunction, CTCL patients very frequently acquire bacterial infections, which comprise a major clinical problem.\textsuperscript{37} In particular, there is a high prevalence of \textit{Staphylococcus aureus} (SA), which is present in approximately 40% of the patients.\textsuperscript{38-40} Intriguingly, eradication of SA by antibiotics is associated with significant clinical improvement in colonized patients, including a reduced involved body-surface area as well as decreased redness and pruritus of the skin.\textsuperscript{38,39,41} It has further been reported that staphylococcal sepsis in SS patients is accompanied by increased disease activity often in absence of fever.\textsuperscript{38,42} Therefore, it has been suspected for decades that SA fosters the disease activity in CTCL, but the underlying mechanisms remain poorly characterized, and it is not common practice to initiate antibiotic treatment of colonized patients.\textsuperscript{38,39,41,43-46} One of the central means by which SA

Figure 1. SEs stimulate malignant T cells to express IL-10 in the presence of benign T cells. (A) SA was isolated from the skin of CTCL patients. Shown are representative pictures of the involved skin lesions. (B-D) Malignant (SeAx) and benign (MF1850) T-cell lines were mono- and cocultured in the absence (--) or presence of SA isolated from involved and uninvolved skin of (B) an SS patient and (C-D) MF patients. After 24 hours, the concentrations of IL-10 in the cell culture supernatants were determined by ELISA. (E) Malignant (SeAx) and benign (MF1850) T-cell lines were mono- and cocultured with media (--), supernatant from SA from involved skin (SA sup.) or SA sup. plus a pool of antibodies against HLA-DP, HLA-DQ, and HLA-DR (anti-MHC-II, 10 \(\mu\)g/mL) for 24 hours. Subsequently, the concentrations of IL-10 in the culture supernatants were determined by ELISA. Error bars represent standard error of the mean (SEM) of 3 replicate cultures. (F) Representative flow cytometric analysis of MHC-II expression on the malignant (SeAx) and benign (MF1850) T-cell lines. Dashed lines represent isotype control staining and solid lines with anti MHC-II staining. (G) Malignant (SeAx) and benign (MF1850) T-cell lines were mono- and cocultured with vehicle (phosphate-buffered saline [PBS]) or soluble egg antigens [SEA] (50 ng/mL) for 24 hours and the relative expression of IL-10 and GAPDH mRNA measured by qPCR. In each sample, the level of IL-10 mRNA was normalized to that of GAPDH mRNA and depicted as fold change when compared with malignant T cells cultured with PBS. Error bars represent SEM of 3 independent experiments. (H) Malignant (SeAx) and benign (MF1850) T-cell lines were mono- and cocultured with vehicle (PBS) or SEA (50 ng/mL) for 24 hours and the concentration of IL-10 in the cell culture supernatants analyzed by ELISA. Error bars represent SEM of 3 independent experiments. (I) Malignant (SeAx) and benign (MF1850) T-cell lines were mono- and cocultured with vehicle (PBS) or SEA (50 ng/mL) for 16 hours. Subsequently, the cocultured malignant and benign T cells were sorted by FACS and the relative level of IL-10 and GAPDH mRNA in all samples determined by qPCR. In each sample, the level of IL-10 mRNA was normalized to that of GAPDH mRNA and depicted as fold change when compared with malignant T cells cultured with PBS. Malign. (Benign) indicates IL-10 expression in malignant T cells that had been cocultured with benign T cells, and vice versa for Benign (Malign.). Error bars represent SEM of 3 independent experiments.
manipulates the host’s immune system by secreting staphylococcal enterotoxins (SEs). SEs (and SE-like toxins) constitute a large family of secreted proteins (SEA-SEE, SEG-SEJ, SElK-R, SElU, and SElK-R) that functions as superantigens. Thus, SEs bypass the normal antigen-restricted activation of T cells by binding outside the antigen-binding groove of major histocompatibility complex class II (MHC-II) molecules on one cell and to the Vβ region of T-cell receptors (TCRs) on a T cell.45 Little is known about the functional differences of SEs, but each SE interacts with a restricted repertoire of MHC-II alleles and TCR Vβ segments47 and thereby targets specific T-cell subsets. The host’s reaction to SEs seems to be dependent on the site of exposure. Whereas SEs are best known for their ability to cause food poisoning after ingestion, cutaneous colonization with SA strains producing high levels of SEs is commonly observed in chronic inflammatory skin diseases as atopic dermatitis and psoriasis, where they are believed to exacerbate the disease.48,49 SA isolates from flammatory skin diseases as atopic dermatitis and psoriasis, where they are believed to exacerbate the disease.48,49 SA isolates from atopic dermatitis and psoriasis, where they are believed to exacerbate the disease.48,49 SA isolates from the responsive TCR Vβ repertoire in CTCL, indicating that SEs are expressed and active in vivo.38,43-46,50 Accordingly, the TCR Vβ subtypes most frequently reported to be overrepresented (Vβ 5.1 and 8) in CTCL38,44,46,50 are responsive to SEs, and Jackow et al.38 observed that patients colonized with TSST-1–positive SA (ET-41) had an overexpansion of T cells expressing the responsive TCR Vβ subtype (Vβ 2.1). Based on these findings, we hypothesized that SA might promote immune dysregulation in CTCL patients via secretion of SEs.

Here, we show that SEs induce cell–contact–dependent and independent crosstalk between malignant and benign T cells, which leads to robust Janus kinase 3 (Jak3)/Stat3-mediated expression of IL-10 by the malignant T cells. The present data thereby provide a novel mechanistic explanation of how SA colonization may promote immune dysregulation in CTCL.

**Methods**

**Reagents**

Western blotting antibodies against Jak3 and Erk1/2 were from Santa Cruz Biotechnology (Santa Cruz, CA) and the antibody against Stat3 from Cell Signaling Technology (Beverly, MA). Antibodies against MHC-I and MHC-II molecules were from Leinco Technologies (St. Louis, MO), and the IL-2 neutralizing antibody and isotype control antibodies were from R&D Systems (Minneapolis, MN). Fluorochrome-conjugated antibodies against CD4, CD7, CD26, the IL-10 receptor (IL-10R), MHC-II, and the respective fluorochrome-conjugated isotype control antibodies used for flow cytometry and fluorescence-activated cell sorting (FACS) were from R&D Systems, Biologent (San Diego, CA), BD Biosciences (Franklin Lakes, NJ), and Leinco Technologies. The pan Jak inhibitor (JaktiP6) was from Calbiochem (San Diego, CA), and the Jak3 inhibitor Tofacitinib (CP-690550) was from Selleck Chemicals (Houston, TX). Finally, SEs and biotin-labeled SEA were from Toxin Technology (Sarasota, FL), and dimethylsulfoxide was from Sigma-Aldrich (St. Louis, MO).

**Patients and SA isolation**

Peripheral blood mononuclear cells (PBMCs) were isolated from the blood of 9 patients diagnosed with SS in accordance with the World Health Organization–European Organization for Research and Treatment of Cancer classification.1 A characteristic of malignant T cells in SS patients is that they typically lack expression of the cell-surface markers CD7 and/or CD26 and often display reduced expression of CD4 when compared with benign T cells.1,51 As exemplified in supplemental Figure 1 (available at the Blood Web site), all SS patients included in the study displayed a clear abnormal accumulation of CD4⁺CD7⁻ and/or CD4⁺CD26⁻ T cells in their PBMCs. Accordingly, malignant (CD4⁺CD7⁻, CD4⁺CD26⁻), and benign (CD4⁺CD7⁺, CD4⁺CD26⁺) T-cell populations were defined on the basis of CD4, CD7, and/or CD26 surface expression. The malignant TCR Vβ usage was characterized with the IOTest Beta Mark kit (Beckman Coulter, Indianapolis, IN). In 4 patients, the malignant population expressed a single TCR Vβ subtype, whereas the malignant population expressed high levels of several TCR Vβ subtypes in 1 patient. We did not identify a predominant malignant TCR Vβ subtype in the remaining patients, which is probably because the IOTest Beta Mark kit only covers approximately 70% of the TCR Vβ repertoire. SA bacteria were isolated from 2 patients diagnosed with MF and 1 patient diagnosed with SS. In brief, bacteriologic samples were collected from involved and uninvolved skin surfaces using sterile cotton swabs wetted with 0.1% Triton X-100 in 0.075 M phosphate buffer (pH 7.9) and transferred to Stuart’s transport medium. Subsequently, the bacteriologic samples were cultivated on blood agar and incubated overnight at 37°C in air supplemented with 5% CO₂. Representative colonies of the 10 most dominant colony types were isolated, subcultivated, and identified by matrix-assisted laser desorption/ionization time-of-flight spectroscopy. The SA isolates were examined for production of SEs (SEA-SEE and TSST-1) using the latex agglutination kits SET-RPLA and TST-RPLA (Oxoid, Basingstoke, Hampshire, United Kingdom) and the RIDASCREEN SET A,B,C,D,E kit (R-Biopharm AG, Darmstadt, Germany). In accordance with the Declaration of Helsinki, the samples were obtained with informed consent and after approval by the Committee on Health Research Ethics (#22559).

**Figure 2.** SEA induces expression of IL-10 from primary malignant T cells. (A) PBMCs were isolated from 7 SS patients and cultured with vehicle (PBS) or SEA (200 ng/mL). After 24 hours, the concentrations of IL-10 in the cell culture supernatants were determined by ELISA. Error bars represent SEM. (B) Flow cytometric analysis of IL-10 expressing malignant (CD4⁻CD26⁺) T cells, benign (CD4⁺CD26⁻) T cells, and CD4-negative cells (CD4⁻) in SS PBMCs cultured with vehicle (PBS) or SEA (200 ng/mL) for 24 hours. (C) Representative flow cytometric analysis of MHC-II expression on malignant (CD4⁺CD26⁻) and benign (CD4⁺CD26⁺) T cells in PBMCs isolated from the blood of an SS patient. Dashed lines represent isotype control staining and solid lines with fill MHC-II staining. Flow cytometric analysis of MHC-II expression on malignant and benign T cells from 5 SS patients are summarized in supplemental Figure 7.
Cultured in human serum (HS) media (RPMI-1640 [Sigma-Aldrich], 2 mM L-glutamine [Sigma-Aldrich], and 100 mg/mL penicillin/streptomycin [Sigma-Aldrich]). Prior to experimental setup, the cell lines were starved overnight in HS media (without IL-2), and, likewise, all experiments were performed in HS media (without IL-2). Allantoigen-specific CD4+ human T-cell lines from healthy donors have been described and characterized previously.54

**Results**

SE-producing SA from infected CTCL lesions induces expression of IL-10 in cocultures of malignant and benign T cells

To investigate the potential role of SA in CTCL immune dysregulation, we initially isolated SA from the skin of CTCL...
IL-2 by benign T cells. Cell-cell contacts between malignant and benign T cells as well as secretion of IL-2 by benign T cells.

Figure 4. SEA induces IL-10 expression via a mechanism that is dependent on cell-cell contacts between malignant and benign T cells as well as secretion of IL-2 by benign T cells. (A) Malignant (SeAx) and benign (MF1850) T cells were mono- and cocultured with vehicle (PBS) or SEA (50 ng/mL). In cocultures, the malignant and benign T cells were either cultured in transwells where the 2 subsets are separated by a cell-impermeable filter (indicated by a line) or together without a cell-impermeable filter (no line). The supernatants were harvested after 24 hours and the concentrations of IL-10 determined by ELISA. Error bars represent SEM of 3 independent experiments. (B) Malignant (SeAx) and benign (MF1850) T cells were cultured alone and together with SEA for different periods of time. At each given time point, the cells were harvested and the cocultured cells were sorted into pure populations of malignant and benign T cells by FACS. Finally, the relative levels of IL-2, IL-10, and GAPDH mRNA in each sample were analyzed by qPCR. The levels of IL-2 and IL-10 mRNA were normalized to that of GAPDH and are shown as fold change when compared with benign and malignant T cells without SEC or SEA stimulation. (C) Malignant (SeAx) and benign (MF1850) T cells were mono- and cocultured in the presence of SEA (100 ng/mL) together with an IL-2 neutralizing antibody (Anti-IL-2, 10 μg/mL), an isotype control antibody (10 μg/mL), or vehicle (PBS) for 24 hours before the concentrations of IL-10 in the cell culture supernatants were determined by ELISA. Error bars represent SEM of 3 independent experiments.

Figure 4 (continued) depicted as fold change when compared with benign and malignant T cells respectively at time point zero. Malign. (Benign) indicates cytokine expression in malignant T cells that had been cocultured with benign T cells, and vice versa for Benign (Malign.). Data are representative of 2 independent experiments. (C) Malignant (SeAx) and benign (MF1850) T cells were mono- and cocultured in the presence of SEA (100 ng/mL) together with an IL-2 neutralizing antibody (Anti-IL-2, 1 μg/mL), an isotype control antibody (1 μg/mL), or vehicle (PBS) for 24 hours before the concentrations of IL-10 in the cell culture supernatants were determined by ELISA. Error bars represent SEM of 3 independent experiments.
SEA induces secretion of IL-10 from primary malignant T cells in the presence of benign T cells

Having established that SEs induce expression of IL-10 by malignant T-cell lines when cocultured with benign T-cell lines, we next addressed whether SEA induced a similar response in primary CTCL cells. Indeed, SEA induced variable but potent secretion of IL-10 in the presence of benign T cells, demonstrating that they had the capacity to bind SEs (Figure 2B). Substantiating that the induction of IL-10 was not mediated by direct stimulation of the malignant T cells, none of the malignant TCR Vβ subtypes identified in the patients were responsive to SEA (data not shown). Concordant with the findings made with the T-cell lines, these results indicated that SEs induced expression of IL-10 in primary malignant T cells but that the response required the presence of benign T cells. To confirm this conclusion, we purified primary malignant and benign T cells from SS patients and cultured them with or without SEA. The purified malignant and benign CTCL T cells generally exhibited no detectable or very low levels of spontaneous IL-10 expression in monocultures, and the expression was not significantly influenced by the addition of SEA (Figure 3A). Importantly, SEA induced a marked increase in the expression of IL-10 when the primary malignant T cells were cultured with benign SS T cells (Figure 3A). Likewise, SEA mediated a potent induction of IL-10 when primary malignant T cells were cultured together with the benign CTCL T-cell line MF1850 and benign CD4 T cells from healthy donors (Figure 3B-C). The SEA-induced secretion of IL-10 from primary malignant T cells was thus dependent on the presence of benign T cells but did not rely on a specific nature of benign T cells derived from CTCL patients.

SEA induces expression of IL-10 via a mechanism that is dependent on cell-cell contact and IL-2

To investigate the mechanisms underlying the SE-induced expression of IL-10, malignant and benign T cells were cocultured in wells with or without cell-impermeable filters that allow transport of soluble messengers but prevent cell-cell contacts. As shown in Figure 4A, the SEA-induced expression of IL-10 was strongly inhibited in transwell cocultures as compared with cocultures without cell-impermeable filters, suggesting that cell-cell contact between the 2 cell types is required to induce robust IL-10 expression. SEs have previously been shown to induce secretion of IL-2 from benign CD4 T cells. In agreement, SEA stimulated benign CTCL cells to express IL-2 mRNA and protein (Figure 4B and supplemental Figure 8). Because IL-2 can promote the expression of IL-10 by malignant T cells, we speculated that IL-2 was involved in the SE-mediated induction of IL-10. Therefore, mono- and cocultured malignant and benign T cells were treated with SEA and
Figure 6. IL-10R expression is low or absent on the malignant T cells. (A) Representative flow cytometric analysis of IL-10 receptor (IL-10R) expression on the benign T-cell line, MF1850, and the malignant T-cell line, SeAx. (B) Representative flow cytometric analysis of IL-10R expression on benign (CD4\(^{+}\)CD26\(^{-}\)) and malignant (CD4\(^{+}\)CD26\(^{-}\)) T cells in PBMCs from an SS patient. (C) Graph showing the average percentage of IL-10R-positive benign (CD4\(^{+}\)CD26\(^{-}\)) and malignant (CD4\(^{+}\)CD26\(^{-}\)) T cells in PBMCs isolated from 5 SS patients. Bars represent SEM. FSC-H, forward scatter height; SSC-A, side scatter area.

SE-induced expression of IL-10 is dependent on the Jak3/Stat3 pathway in malignant T cells

Because the Jak3/Stat3 pathway can promote the expression of IL-10 in malignant T cells,\(^{35,59}\) we investigated its possible involvement. Both a pan-Jak inhibitor (Figure 5A) and a Jak3 inhibitor (Figure 5B) efficiently blocked the SEA-mediated IL-10 expression. Likewise, transfection of the malignant T cells with Jak3-specific siRNA lead to efficient depletion of Jak3 (Figure 5C) and totally abrogated the SEA-induced expression of IL-10 in cocultures of malignant and benign T cells (Figure 5D). On the other hand, depleting Jak3 in the benign T cells had no effect on the expression of IL-10 (Figure 5C-D). Depletion of Stat3 in the malignant but not in the benign T cells also significantly inhibited the SEA-induced expression of IL-10 (Figure 5E-F). Altogether, these results demonstrate that the SE-induced expression of IL-10 was mediated via a Jak3/Stat3-dependent mechanism in malignant T cells.

Expression of the IL-10 receptor is low or absent in malignant T cells

It has previously been shown that malignant T cells can suppress the activation of benign T cells in an IL-10–dependent manner,\(^{35}\) raising the question whether IL-10 could also mediate autocrine suppression of the malignant T cells. Therefore, we analyzed surface expression of IL-10R on malignant and benign T cells. IL-10R was expressed in the benign T-cell line, MF1850, but not in the malignant T-cell line, SeAx (Figure 6A). In a similar manner, IL-10R expression was absent or strongly decreased on malignant T cells when compared with benign T cells in PBMCs isolated from the blood of SS patients (Figure 6B-C and data not shown), indicating that malignant T cells generally are resistant to IL-10 stimulation.

Discussion

It has long been suspected that SA via expression of SEs can influence the malignant expansion and evolving immune dysregulation in CTCL patients.\(^{38,39,41-46,50}\) Indeed, prior studies have reported that SEs in some cases can stimulate the proliferation of malignant T cells.\(^{43,54}\) However, a mechanistic connection between SEs and lymphoma-associated immune dysregulation has remained elusive. Here, we demonstrate that SEs can induce vigorous expression of the immunoregulatory cytokine IL-10 in cocultures of malignant and benign T cells, thereby providing a novel link between SEs and immune dysregulation in CTCL. Remarkably, SEs did not induce high expression of IL-10 in monocultured malignant or benign T cells. Instead, SEs modulated the interactions between malignant and benign T cells to induce high malignant expression of IL-10 (Figure 7A-C). Our results suggest a mechanism where SEs induce cell-cell contact–dependent crosstalk between malignant and benign T cells and stimulate the benign T cells to produce IL-2 (Figure 7B). These interactions in turn promote activation of the Jak3/Stat3 pathway in the malignant T cells, which induces expression of IL-10 and subsequently leads to the inhibition of cell-mediated immunity and antitumor responses (Figure 7C). Because both strong activation of Stat3 and high expression of IL-10 have been identified as markers of poor response to treatment in CTCL, the present data indicate that elimination of SA may not only lead to clinical improvement but also enhance the patient’s response to treatment with other therapeutics.\(^{36,60}\)
IL-10 has been reported to promote CTCL immune dysregulation by several means, including direct inhibition of benign T cells.\textsuperscript{17,32-35} It could thus be speculated that IL-10 might similarly suppress the proliferation and cytokine production of malignant T cells. We found that the expression of IL-10R was very low or completely absent on malignant T cells, indicating that they are protected against suppressive effects mediated by IL-10. Likewise, malignant CTCL cells express the immunosuppressive cytokine transforming growth factor \(\beta\) (TGF-\(\beta\)) but often lose surface expression of TGF-\(\beta\) receptor II.\textsuperscript{5,59,61-63} This suggests that the malignant T cells elegantly manipulate and use the immune system while escaping its control. Similar to IL-10R and TGF-\(\beta\) receptor II, malignant T cells from advanced disease typically display decreased surface expression of CD3 and/or exhibit resistance to TCR stimulation and apoptosis.\textsuperscript{51,64} By targeting the benign T cells, SEs may still influence the malignant T cells even as they become resistant to TCR stimulation. Moreover, the proposed indirect mechanism implies that the pathogenic role of SEs is not limited to cases of patients expressing a SE-responsive TCR \(\text{V}\beta\) on the malignant clone. On the contrary, patients harbor benign T cells with a wider repertoire of TCR \(\text{V}\beta\) families, making them vulnerable to this indirect mode of action.

Infections comprise a major clinical problem in CTCL, and patients with advanced disease frequently die of infections rather than complications from the tumor burden.\textsuperscript{37} We hypothesize that SEs are part of a vicious circle where initial deterioration of the skin barrier leads to colonization with SE-producing SA. The SEs then modulate the interactions between malignant and benign immune cells leading to enhanced suppression of the host’s cellular immunity and increased disease activity, thereby contributing to further deterioration of the skin barrier. In turn, weakening of the host’s defenses stabilizes the SA colonization, facilitates its propagation, and increases the susceptibility to secondary infections.

In conclusion, we identify a mechanistic link between colonization with SE-producing SA and immune dysregulation in CTCL, thus strengthening the rationale for antibiotic treatment of colonized patients with severe or progressive disease. Furthermore, the present study supports accumulating evidence that bacterial toxins may promote cancer\textsuperscript{65-70} and conceptually demonstrates how bacterial toxins may contribute to cancer by influencing the crosstalk between tumor and immune cells.

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Authorship


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