**Human Cancer Biology**

**T_{H}2 Cytokines from Malignant Cells Suppress T_{H}1 Responses and Enforce a Global T_{H}2 Bias in Leukemic Cutaneous T-cell Lymphoma**

Emmanuella Guenova1, Rei Watanabe1, Jessica E. Teague1, Jennifer A. Desimone1, Ying Jiang3, Mitra Dowlatabadi1, Christoph Schlapbach1, Knut Schaekel5, Alain H. Rook4, Marianne Tawa2, David C. Fisher2, Thomas S. Kupper1,2, and Rachael A. Clark1,2

**Abstract**

**Purpose:** In leukemic cutaneous T-cell lymphoma (L-CTCL), malignant T cells accumulate in the blood and give rise to widespread skin inflammation. Patients have intense pruritus, increased immunoglobulin E (IgE), and decreased T-helper (T_{H})-1 responses, and most die from infection. Depleting malignant T cells while preserving normal immunity is a clinical challenge. L-CTCL has been variably described as a malignancy of regulatory, T_{H}2 and T_{H}17 cells.

**Experimental Design:** We analyzed phenotype and cytokine production in malignant and benign L-CTCL T cells, characterized the effects of malignant T cells on healthy T cells, and studied the immunomodulatory effects of treatment modalities in patients with L-CTCL.

**Results:** Twelve out of 12 patients with L-CTCL overproduced T_{H}2 cytokines. Remaining benign T cells were also strongly T_{H}2 biased, suggesting a global T_{H}2 skewing of the T-cell repertoire. Culture of benign T cells away from the malignant clone reduced T_{H}2 and enhanced T_{H}1 responses, but separate culture had no effect on malignant T cells. Coculture of healthy T cells with L-CTCL T cells reduced IFN-g production and neutralizing antibodies to interleukin (IL)-4 and IL-13 restored T_{H}1 responses. In patients, enhanced T_{H}1 responses were observed following a variety of treatment modalities that reduced malignant T-cell burden.

**Conclusions:** A global T_{H}2 bias exists in both benign and malignant T cells in L-CTCL and may underlie the infectious susceptibility of patients. T_{H}2 cytokines from malignant cells strongly inhibited T_{H}1 responses. Our results suggest that therapies that inhibit T_{H}2 cytokine activity, by virtue of their ability to improve T_{H}1 responses, may have the potential to enhance both anticancer and antipathogen responses.

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**Introduction**

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin lymphomas arising from malignant transformation of T cells that home to and populate the skin (1, 2). In leukemic variants of CTCL (L-CTCL), malignant T cells can accumulate in the blood and lymph nodes and also produce widespread inflammatory skin lesions. L-CTCL is often refractory to multiple therapies, and patients often ultimately require hematopoietic stem cell transplantation (3). The median survival for patients with L-CTCL varies with the extent of malignant T-cell burden but is generally 2 to 5 years and patients die most commonly from infection (4–7).

CTCL has been proposed to be a malignancy of 3 separate T-cell populations: FOXP3^{+} regulatory T cell (Treg), T-helper (T_{H})-2 T cells, and T_{H}17 T cells (8–10). Clinically, patients with L-CTCL have abnormalities suggestive of a T_{H}2-driven immunologic process, including decreased antigen-specific T-cell responses, impaired cell-mediated cytotoxicity, peripheral eosinophilia, and elevated levels of serum immunoglobulin E (IgE) and immunoglobulin A (IgA; refs. 11–13). Prior studies have shown increased levels of T_{H}2 cytokines and T_{H}2-associated genes in T cells from patients with L-CTCL (9, 14–17) but a recent report claims that malignant T cells in the disease are actually T_{H}17 biased (10).

We conducted comprehensive analyses of the cytokine production of benign and malignant T cells from L-CTCL.
with identifiable malignant T-cell clones. We report here that both malignant and benign T cells in patients with L-CTCL were strongly TH2 biased, that this bias was intrinsic in malignant T cells but extrinsic in benign cells, and that inhibition of TH2 cytokines led to recovery of TH1 responses in benign T cells.

**Materials and Methods**

**Blood samples**

The protocols of this study were conducted in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board of the Partners Human Research Committee (Partners Research Management, Boston, MA). Blood from healthy individuals was obtained as discarded tissue following leukopheresis. Blood and lesional skin from patients with CTCL were obtained from patients seen at the Dana-Farber/Brigham and Women's Cancer Center (Boston, MA) Cutaneous Lymphoma Program. Patients with L-CTCL described in this manuscript met the World Health Organization–European Organization for Research and Treatment of Cancer criteria for L-CTCL/Sezary Syndrome (18). Patient characteristics are included in Table 1 based on the malignant T-cell burden. In this cohort of patients, expected survival is approximately 5 years (4–7). Peripheral blood mononuclear cell (PBMC) were isolated by ficoll centrifugation, and clonal and nonclonal CD4+ T cells from patients with CTCL were isolated using magnetic bead separation (Miltenyi Biotec) after staining with TCR Vβ-specific antibodies (Beckman Coulter Inc.).

**Flow cytometry**

Analysis of T cells was conducted using directly conjugated monoclonal antibodies obtained from BD Biosciences, eBioscience, Biolegend, or R&D Systems. Vβ staining was conducted using the IOtest Beta Mark TCR Vβ Repertoire kit (Beckman Coulter) as per manufacturer’s instructions. Isotype-matched negative control antibodies

**Translational Relevance**

Patients with leukemic cutaneous T-cell lymphoma (L-CTCL) have an average 2 to 5 years of survival, die most commonly from infection, and have clinical abnormalities consistent with a T-helper (TH)-2–driven immunologic process. We find that both malignant and benign T cells in L-CTCL are markedly TH2 biased, demonstrating a global TH2 skewing. Culture of benign T cells away from the malignant clone reduced TH2 and enhanced TH1 responses, but separate culture had no effect on malignant T cells. Coculture of healthy T cells with L-CTCL T cells reduced IFNγ production and neutralizing antibodies to interleukin (IL)-4 and IL-13 restored TH1 responses. In patients, enhanced TH1 responses were observed following a variety of treatment modalities that reduced malignant T-cell burden, suggesting that TH2 cytokines produced by malignant T cells play a critical role in downregulating TH1 responses in vivo. Results suggest that neutralization of TH2 cytokines may be beneficial in enhancing immune responses both to pathogens and to the malignancy itself.

**Table 1. Clinical patient characteristics**

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<th>Patient ID #</th>
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Abbreviations: I, IFN-α/β; ECP, extracorporeal photochemotherapy; V, vorinostat; B, bexarotene, D, denileukin diftitox; TS, topical steroids; SS, systemic steroids; G, gemcitabine; A, alemtuzumab; P, pralatraxate; R, romidepsin; PUVA, psoralen + UVA treatment.
were used to set the gates for positive staining. For analysis of cytokine production, T cells were stimulated with either control medium or 50 ng/mL phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich) and 750 ng/mL ionomycin (Life Technologies) plus 10 μg/mL Brefeldin A (BD) for 4 hours. Cells were surface stained, fixed, permeabilized, stained with anticytokine antibodies, and examined by flow cytometry. Analysis was conducted on Becton Dickinson FACSCanto instruments and data were analyzed using FACSDiva software (V5.1).

**Dendritic cell priming of clonal and nonclonal T cells from patients with CTCL**

The 6-sulfo LacNaC-expressing dendritic cells (slanDC) were isolated as previously described (19). Lipopolysaccharide (LPS; Sigma-Aldrich) was used at 100 ng/mL. For T-cell priming, LPS-stimulated dendritic cells were harvested and cocultured with autologous clonal and nonclonal T cells from patients with CTCL in the presence of 1 ng/mL of staphylococcal enterotoxin B (Sigma-Aldrich). Following 12 days of culture, T cells were restimulated for intracytoplasmatic flow cytometry analysis of cytokine production after treatment with PMA and ionomycin.

**Cocultures of healthy PBMC with L-CTCL cells**

A total of 2 × 10^6/mL PBMC from healthy donors (including lymphocytes, monocytes, basophils, and dendritic cells) were cocultured over 12 days with 1 × 10^6/mL fluorescently labelled PBMC from patients with L-CTCL in Iscove's modification of Dulbecco's media (Mediatech) supplemented with 20% heat-inactivated fetal calf serum, antibiotics and 1-glutamine. 100 IU/mL interleukin (IL)-2 and 15 ng/mL IL-15 (Peprotech) were supplemented every other day. Where indicated, only cell-substrate, but not direct cell–cell interaction was allowed, and Transwell inserts (Corning Inc.) were used to separate L-CTCL from healthy PBMC.

**Statistical analysis**

For studies described in Fig. 1, the nonparametric Kruskal–Wallis test and Dunn test were used for comparisons between the 3 groups. For studies described in Figs. 2 to 5, a standard 2-sample Student t test was used. The data were previously tested for normal distribution (Shapiro–Wilk test) and homogeneity of variance. One-way between group ANOVA was used for statistical analysis of differences between 3 or more groups. P values ≤ 0.05 were considered as significant.

**Results**

**Both benign and malignant T cells are Th2 biased in patients with L-CTCL**

CTCL has been proposed to be a malignancy of FOXP3+ Tregs, but more recent studies showed that only a subset of patients had malignant T cells with a Treg phenotype (8, 20, 21). We identified 12 patients in whom the malignant T-cell clone could be conclusively identified by staining with commercially available TCR Vβ antibodies and analyzed benign and malignant T cells by flow cytometry (Fig. 1A). This approach allows direct analysis of the phenotype and functional characteristics of the malignant T-cell clone, while at the same time providing similar information about remaining benign T cells.

We studied cytokine production and found that both the benign and malignant T cells in patients with L-CTCL were strongly Th2 biased. Both benign and malignant T cells from patients with L-CTCL produced markedly higher levels of IL-4 than T cells from healthy individuals (Fig. 1A and B). A mean 42.7% of malignant T cells (SEM 7.8, n = 12) and 28.1% of benign T cells (SEM 7.0, n = 12) produced IL-4 in patients with L-CTCL, compared with 0.65% of T cells from healthy individuals (SEM 0.18, n = 12). IL-13 production was significantly higher in malignant T cells and in the benign T cells of 5 patients, and IL-10 production was also increased in malignant clones. Th1 responses were globally decreased in both benign and malignant T cells from patients with L-CTCL, with significantly reduced production of IFNγ in both populations (Fig. 1). Production of TNFα was also markedly decreased in both the benign and malignant T cells from patients with L-CTCL compared with normal controls (Fig. 1). In a subset of patients, malignant T-cell clones produced more IL-2 (Fig. 1), consistent with a report that malignant T cells in L-CTCL have a phenotype suggestive of central memory T cells (Tcm,AL), a cell type known to use autocrine production of IL-2 to maintain survival (22, 23). However, given the heterogeneity among patients, this result was not statistically significant.

**Benign T cells show enhanced Th1 and reduced Th2 responses when cultured separately from clonal malignant T cells**

Th12 cells can suppress the production of Th11 cytokines by other T cells in vitro (24, 25). To evaluate whether clonal malignant T cells suppress benign T-cell responses, we separated nonclonal benign from clonal malignant T cells from the blood of patients with L-CTCL using magnetic beads and cultured these T cells separately in the presence of autologous LPS-activated dendritic cell. IFNγ production increased and IL-4 production decreased in nonclonal T cells cultured away from the malignant clone, whereas clonal T cells showed no significant changes in IFNγ or IL-4 production (Fig. 2A and B). Real-time PCR analyses showed that expression of the Th12-associated transcription factor GATA-3 declined and expression of the Th11-associated transcription factor T-bet increased in benign T cells after cultured away from the malignant clone (Fig. 2C). In clonal malignant T cells, there was no change in the expression of GATA-3 and T-bet after separate culture. Expression of the Th17-associated transcription factor RORc was low in both malignant and benign T cells before and after culture. T cells isolated from the skin lesions of patients with L-CTCL had similar responses; IFNγ increased in nonclonal T cells after separate coculture but remained unchanged in malignant T cells (Fig. 2D).
IL-4 and IL-13 produced by L-CTCL T cells suppress TH1 responses of T cells from healthy donors

To evaluate the ability of L-CTCL T cells to suppress non-TH2 cytokine production, we cultured PBMC from healthy individuals with fluorescently labeled PBMC from patients with L-CTCL with a high malignant T-cell burden. Coculture was conducted in direct contact or in Transwell systems, which separated healthy from L-CTCL cells. After coculture with L-CTCL cells, T cells from healthy patients showed reduced production of IFN-γ (Fig. 3). Suppression was observed in both direct contact and Transwell cultures, suggesting that a soluble factor was responsible for TH1 suppression. To determine whether TH1 cytokine production was reduced in both the benign (non-clonal) and malignant (clonal) T cells from patients with L-CTCL as compared with normal controls (nml). Twelve healthy individuals and 12 patients with L-CTCL are shown. Increased IL-4 production and loss of IFNγ and TNFα production were observed in both malignant and benign T cells from patients with L-CTCL. The production of IL-13 and IL-10 was also elevated in the malignant clones.

A variety of modalities that reduce tumor burden enhance the TH1 responses of benign T cells

It has been previously reported that immunomodulatory therapies for CTCL, including IFN-α2b and extracorporeal photopheresis, led to enhanced TH1 responses in responding patients (26). IFN-α2b and extracorporeal photopheresis, both have immunomodulatory effects beyond their ability to reduce the number of malignant T cells. If TH1 cytokines produced by malignant T cells are indeed responsible for the decreased TH1 responses, pruritus, susceptibility to infections, and benign T cell TH2 skewing observed in these individuals, then a variety of treatment modalities that...
have in common only the depletion of malignant T cells should all produce enhanced TH1 responses, regardless of the underlying mechanism of action of the therapy used. To study this issue, we evaluated the cytokine production of benign T cells before and after therapy with a variety of treatment modalities (Fig. 5). We found that successful therapy with variety of modalities, including UVB phototherapy, extracorporeal photopheresis, low-dose alemtuzumab, and systemic chemotherapy with gemcitabine, all had similar effects on the cytokine production of benign T cells. In all therapies and in all patients examined, when the number of circulating malignant T cells declined, benign T cells subsequently produced less IL-4 and more IL-2 and IFN-g (Fig. 5). In addition to the patients shown, similar findings were observed in 6 additional patients treated with a combination of therapies that also included topical corticosteroids, electron beam therapy, and narrow band UVB (data not shown). In all patients included in this analysis, complete remission of at least 4 months was achieved. With respect to the patients shown in Fig. 5, the first patient (Fig. 5A) remains in remission on UVB and topical steroids but photopheresis was discontinued. Following a complete remission with alemtuzumab therapy, the second patient (Fig. 5B) subsequently relapsed with progressive skin disease not controlled by alemtuzumab and ultimately died from progressive disease. The third patient (Fig. 5C) experienced a complete remission following gemcitabine, and underwent stem cell transplantation.

**Figure 2.** Benign T cells show reduced TH2 and enhanced TH1 responses when cultured separately from clonal malignant T cells. A and B, nonclonal benign and clonal malignant T cells were isolated from the blood of patients with L-CTCL using magnetic beads. Clonal and nonclonal T cells were cultured separately with LPS-activated autologous dendritic cell for 12 days and then assayed for cytokine production by intracellular flow cytometry. IFN-g production increased and IL-4 production decreased in nonclonal T cells cultured away from the malignant clone but clonal T cells showed no significant changes in IFN-g or IL-4 production. Representative dot plots (A) and the mean and SEM of 3 patients with L-CTCL (B) are shown. C, changes in the expression of T-bet- and T-cell-associated transcription factors parallel observed changes in cytokine production in benign and malignant T cells cultured separately. In benign T cells cultured away from the malignant clone, expression of GATA-3 (TH2) decreased, and expression of t-BET (TH1) increased, whereas expression levels of both transcription factors remained unchanged in malignant T cells. Expression of ROR-g (TH17) was low in both cell populations both before and after culture. D, TH1 responses are also enhanced in lesional skin T cells cultured away from the malignant clone. T cells were isolated from lesional skin, separated into nonclonal and clonal T cells, and then cultured separately with LPS-activated autologous dendritic cell. Nonclonal T cells from lesional skin showed a marked enhancement of IFN-g production after cultured away from the malignant clone. * P < 0.05.

**Discussion**

There has been some disagreement about the cytokine production and functional polarization of malignant T cells in L-CTCL. L-CTCL has been proposed to be a uniform malignancy of FOXP3+ Tregs, TH17 cells, and TH2 cells (8–10). All of the patients in our cohort showed a marked TH2 bias in malignant T cells, in agreement with earlier studies that the vast majority of patients with L-CTCL have TH2-biased malignant T cells (9, 14–17, 27). Patients with L-CTCL have characteristics suggestive of a TH17-driven immunologic process, including elevated levels of IgE and IgA, eosinophilia, and reduced T-bet responses (11–13). These patients also suffer from marked pruritus of the skin, high rates of colonization with *Staphylococcus aureus*, and a high susceptibility to cutaneous infections, similar to patients with atopic dermatitis, a prototypic TH2 disease (28). We did not observe any patients with malignant T cells of a TH1 phenotype.

Malignant T cells in L-CTCL have a phenotype suggestive of skin tropic T_{CM} (22). T_{CM} are highly migratory, recirculate between the blood, skin, and lymph nodes, have a high proliferative potential, are markedly resistant to apoptosis, and have a variety of cytokine production profiles (23). The T_{CM} phenotype of these cells helps to explain why patients with L-CTCL develop erythroderma, peripheral blood disease, and lymphadenopathy. However, one might expect that malignant T cells would have a heterogeneous pattern of cytokine production that reflects the diverse population...
of TCM from which they arise. The fact that the vast majority of patients have strongly TH2-biased malignant T cells is striking. We found that the TH2 bias of the malignant T cells was remarkably stable in vitro, suggesting that this bias may result from intrinsic abnormalities of the cell or from autocrine factors, for example, galectin-1 produced by malignant T cells, which has previously been implicated in the TH2 skewing of the malignant clone (17). It may also be that TH2 malignant T-cell clones predominate in L-CTCL because they are remarkably effective in suppressing anti-cancer TH1 responses and therefore have a survival advantage.

We were surprised to find that the benign T cells remaining in the circulation of patients with L-CTCL were significantly different from those found in normal individuals. There was a striking and consistent TH2 bias even among the benign T cells in these patients, as well as a reduction in the production of TH1 cytokines (Fig. 1). These results show that a global TH2 bias exists in these patients that leads to skewing of the entire T-cell repertoire, both benign and malignant, toward enhanced production of TH2 cytokines. This overproduction of TH2 cytokines by both malignant and benign T cells likely contributes to the pruritus, reduced TH1 responses, and the susceptibility to infections observed in these patients.

The remaining nonclonal benign T cells in patients with L-CTCL would be expected to have a variety of cytokine production capacities. Given the known ability of TH2 cells to suppress TH1 responses and to force a TH2 bias on other T cells (24, 25), we hypothesized that the malignant T cells may suppress the activity of benign T cells, silencing TH1 responses, as has been suggested previously (26). Indeed, when we separated and cultured nonclonal T cells from the blood and skin lesions of patients away from the malignant clone, we observed improved TH1 responses (Fig. 2). When we cocultured T cells from healthy individuals with L-CTCL
T cells, we saw a marked inhibition of TH1 responses (Fig. 3, 4). Incubation of cocultures with neutralizing antibodies to IL-4 and IL-13 restored TH1 responses, suggesting that TH2 cytokines produced by malignant T cells may be directly responsible for the suppression of TH1 responses we observed in our patients and in T cells from healthy donors. If so, successful treatment of patients with CTCL should reduce TH2 and enhance TH1 responses, as a previous study of 3 patients suggested (26).

To study this question, we evaluated patients with L-CTCL treated with a variety of modalities that had in common only reduction in the number of circulating malignant T cells. Regardless of the underlying mechanism of action of particular therapies, treatments that reduced malignant T-cell burden were invariably associated with enhanced TH1 responses (Fig. 5). Although circumstantial, our results suggest that TH2 cytokines produced by malignant T cells play a critical role in suppressing TH1 responses in our patients.

In summary, we report a marked TH1 bias in both the benign and malignant T cells in patients with L-CTCL and we find that TH12 cytokine production by the malignant
clone likely suppresses Th1 responses in these patients. Th1 responses improved in vitro when the benign T cells were cultured away from the malignant clone, when IL-4 and IL-13 activities were blocked in vitro with neutralizing antibodies, and in patients themselves after treatment with therapies that reduced the number of circulating malignant T cells. The suppression of Th1 responses in these patients by IL-4 and IL-13 suggests that neutralization of these cytokines may be beneficial in enhancing immune responses. Aeroderm, a recombinant small protein antagonist of the IL-4/IL-13 receptor formulated for skin injection, was previously in clinical trials for the treatment of severe atopic dermatitis (29). By inhibiting Th1 responses and enhancing Th1 responses, IL-4/IL-13 antagonists have the potential to enhance immune responses to both skin pathogens and to the malignant T cells themselves.

Disclosure of Potential Conflicts of Interest
T.S. Kupper is a consultant/advisory board member of TremRx. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

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References


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