TH2 cytokines from malignant cells suppress TH1 responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma

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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 (TH)-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, TH2 and TH17 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 TH2 cytokines. Remaining benign T cells were also strongly TH2 biased, suggesting a global TH2 skewing of the T-cell repertoire. 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.

CONCLUSIONS
A global TH2 bias exists in both benign and malignant T cells in L-CTCL and may underlie the infectious susceptibility of patients. TH2 cytokines from malignant cells strongly inhibited TH1 responses. Our results suggest that therapies that inhibit TH2 cytokine activity, by virtue of their ability to improve TH1 responses, may have the potential to enhance both anticancer and antipathogen responses.