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# The Immunopathogenesis and Immunotherapy of Cutaneous T Cell Lymphoma: Part I, Pathways and Targets for Immune Restoration and Tumor Eradication

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## Abstract

Cutaneous T cell lymphomas (CTCLs) are malignancies of skin-trafficking T cells. Patients with advanced CTCL manifest immune dysfunction that predisposes to infection and suppresses the anti-tumor immune response. Therapies that stimulate immunity have produced superior progression free survival compared to conventional chemotherapy, reinforcing the importance of addressing the immune deficient state in the care of CTCL patients. Recent research has better defined the pathogenesis of these immune deficits, explaining the mechanisms of disease progression and revealing potential therapeutic targets. The features of the malignant cell in mycosis fungoides (MF) and Sézary syndrome (SS) are now significantly better understood, including TH2 phenotype, Treg cytokine production, immune checkpoint molecule expression, chemokine receptors, and interactions with the microenvironment. The updated model of CTCL immunopathogenesis provides understanding into clinical progression and therapeutic response.

### Keywords

cutaneous T cell lymphoma; CTCL; mycosis fungoides; Sezary syndrome; dermatologic oncology; immunotherapy; immune deficiency; immunopathogenesis; drug response

## Introduction

The cutaneous T cell lymphomas (CTCLs) are a heterogenous group of T cell malignancies.[1] The best studied and most common subtypes are mycosis fungoides (MF) and Sézary syndrome (SS), which together account for approximately 60% of cases.[2] With advancing stage, patients with MF or SS typically face worsening immune dysfunction. The state of immune disorder in these patients impacts their risk of serious infections, the robustness of

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the anti-tumor immune response, and the efficacy of therapies that rely on immune stimulation.[3,4]

Therapies that stimulate immunity have long been a mainstay in CTCL management. Indeed, for advanced disease, immune targeted treatments have been associated with longer median progression free survival than traditional chemotherapy.[5] While management of advanced stage CTCL is complex, the use of multimodality therapy is common, including some combination of interferons, extracorporeal photopheresis (ECP), monoclonal antibodies (mAbs), oral retinoids, histone deacetylase (HDAC) inhibitors, and total skin electron beam (TSEB) radiation.[4] A newer generation of therapies, including immune checkpoint inhibitors, Toll-like receptor (TLR) agonists, and chimeric antigen receptor (CAR) T cells, are in development and demonstrate the enthusiasm around immune-stimulating strategies.

Recent research has more thoroughly characterized the cellular biology of immune suppression in CTCL. The nature of the malignant cell in MF and SS, as typically being mature CD4+ T cells with TH2 phenotype, has been known since the 1990s and explains defects in TH1 immunity, dendritic cell (DC) function, and cytokine production in CTCL patients.[6] However, the genetic basis for the TH2 bias, etiology of tropism to the skin, pathogenesis of symptoms including pruritus, and tumorigenic influence of the microenvironment are now substantially better understood and provide intriguing targets for intervention.

In this review, we characterize the immune dysfunction in CTCL and describe the recent advances in our understanding of its pathogenesis. Particular attention is devoted to MF and SS, which are by far the best studied subtypes. Finally, part II considers emerging CTCL immunotherapies, which in the future may help to satisfy the significant remaining need for tolerable and effective treatments for advanced disease.

## Immune dysfunction in CTCL

### The influence of infection, the microbiome, and comorbidities

In MF and SS, the risk of infection is high, corresponds to disease stage, and in some estimates contributes more to mortality than the malignancy *per se*.[3,7] In the early 1990s, a large retrospective cohort study found that staphylococcal, streptococcal, and herpetic skin infections, in decreasing order, are the most common in MF and SS.[7] While many cutaneous infections are treated successfully without hospital admission, some patients develop bacteremia or pneumonia with a high risk of mortality.[7] At a subclinical level, patients with MF and SS, especially the latter, also display a higher incidence of *S. aureus* colonization, particularly in lesional tissue.[8] This finding is reminiscent of the increased *S. aureus* colonization in atopic dermatitis, which shares with MF and SS the impaired induction of anti-microbial peptides, including cathelicidins and β-defensins, in affected skin.[9] Oral vitamin D administration can upregulate cathelicidin production in atopic dermatitis, but this pathway is relatively unexplored in CTCL.[10,11] Rarer infectious complications, such as progressive multifocal leukoencephalopathy (PML), *P. jirovecii* pneumonia, and

toxoplasmosis, have also been observed in CTCL, but do not dominate the picture to the same extent as bacterial and herpesvirus infections.[7,12]

One hypothesis is that microbial products may stimulate disease progression. In erythrodermic CTCL, there is a high incidence of colonization with *S. aureus* strains producing superantigenic staphylococcal enterotoxins (SEs) or toxic shock syndrome toxin (TSST-1).[13] Both bacterial isolates from patients and recombinant SEs can activate STAT3 and induce expression of IL-17 in CTCL cell lines.[14] SEs also trigger expression of the regulatory T cell (Treg) marker FOXP3 in SS cells, in a STAT5 dependent manner.[15] The oncogenic microRNA miR-155 is also STAT5 dependent, raising the possibility that SEs may contribute to the high expression of this molecule in CTCL cells.[16] Only a subset of T cell receptor (TCR) variable region β chains are responsive to specific SEs or TSST-1. For example, TSST-1 is specific to Vβ2, and SED targets Vβ1 and Vβ5.[17] However, these sensitive TCRs are overrepresented in the expanded clones of CTCL in patients colonized with toxicogenic *S. aureus* strains.[13] Even when the clonal TCR is unresponsive to SE, the toxins may activate benign cells which then stimulate neighboring malignant cells.[14,18] Moreover, benign T cells are sensitive to cell death induced by *S. aureus* alpha toxin, whereas malignant cells are resistant.[19] To our knowledge, two small studies have examined the use of antibiotics in CTCL, and both found that treatment led to clearance of *S. aureus* colonization and improvement in clinical symptoms.[20,21] While antibiotics can have off-target effects on pathways relevant to CTCL, e.g. doxycycline's inhibition of NF-kB[22], the studies supporting exogenous, infectious drivers of CTCL are intriguing and promising.[21]

With certain comorbidities, CTCL seems to be more common and sometimes more aggressive. A population based survey suggested that CTCL may be more common in areas with higher prevalence of HIV, a finding in keeping with the known 15-fold higher incidence of T cell lymphomas in AIDS patients.[23,24] The decreased complexity of the TCR repertoire in advanced CTCL is similar to that found in AIDS, illustrating the compromised growth of normal T cells in both conditions.[6] In post-transplantation patients, CTCL may take a particularly aggressive course.[25] Clearly, medications that inhibit T cell function, such as anti-TNF agents and cyclosporine, can drive sudden progression in undiagnosed CTCL.[26,27] Dupilumab, an anti-IL4 receptor antibody, may also hasten CTCL progression through unknown mechanisms, perhaps by depleting benign tumor reactive lymphocytes.[28] Collectively, these associations reinforce the role of T cell immune function in controlling disease progression.

## The importance of cellular immunity

An in-situ host immune response is thought to control progression among many with patch stage MF, perhaps accounting for the indolent course of those with limited clinical disease. On histopathology, the presence of a reactive CD8+ cytotoxic T cell infiltrate is common and its intensity is associated with a more favorable prognosis.[6,29] In peripheral blood, circulating CD8+ T cells display increased activation markers and possess lytic capacity against autologous malignant cells.[30,31] The CD4+ T cells in early stage MF lesions tend to display a TH1 phenotype, suggesting that the cytokine milieu is supportive of cell-mediated cytotoxicity.[32] These TH1 cells could represent either reactive benign helper T cells or

malignant cells which have a malleable phenotype and have not yet acquired a dominant TH2 bias.[3] At least one study has suggested that the visible inflammation in MF lesions is due in large part to the reactive immune response.[33] Importantly, the cellular immune response to CTCL depends at least in part on MHC-dependent recognition of tumor antigens, indicating that these malignancies manifest enough acquired mutations that a healthy immune system would recognize them.[30,34,35]

However, the cellular immune response is profoundly depressed in progressive MF and SS. As the disease burden grows, there is a reduction in CD8+ infiltrate in skin lesions and a shift of cytokine production toward a TH2 profile.[29,36,37] The TH2 cytokines secreted by malignant cells suppress TH1 immunity and enforce a global TH2 bias in benign helper T cells.[38,39] With reduced TH1 function, the host is substantially deprived of cellular immunity and has impaired immunological memory to MHC-presented antigens.[40] Patients may possess reactive T cells that are capable of recognizing tumor cells yet are incapacitated by the TH1/TH2 imbalance.[41] In keeping with this, CD8+ lymphocytes from patients with SS demonstrate markers of exhaustion, cytokine unresponsiveness, and attenuated cytotoxicity.[42,43] Stimulating TH1 function by supplementing IL-2, IL-12, and IFN-γ restores the lytic capacity of effector T cells.[31] The cytokine IL-2 has also been shown to activate natural killer (NK) cells to lyse Sézary cell lines..[44] Apart from suppressing TH1 function, the TH2 phenotype of MF and SS cells helps to explain common findings including eosinophilia and increased levels of immunoglobulins IgE and IgA.[36] In addition to their TH2 phenotype, the malignant cells in SS generally also express varying levels of the immune checkpoint molecules PD-1, TIGIT, and CTLA4.[45–47] Similarly, T cells from those with HTLV-1 associated adult T cell leukemias (ATLL) have demonstrated biomarkers of Tregs, expressing high levels of FOXP3, and other T cell lymphomas may have yet different immunosuppressive phenotypes.[48–50]

There are additional defects in DCs and polymorphonuclear granulocytes (PMNs). In SS, there is a stage-dependent decline in the number of circulating DCs in the blood and in the IL-12 production of each cell.[51] In response to challenge with influenza virus or TLR9 agonists, peripheral blood mononuclear cells from SS patients produce significantly less IFN-α.[51,52] PMNs from SS patients have reduced phagocytic activity and intracellular killing against *K. pneumonia.*[53] These defects in antigen presenting cells (APCs) and in innate immunity also favor the development of infections in these patients.

A reduction in the burden of malignant T cells in SS through the use of immunotherapy can lead to the restoration of more normal immune function. The normal T cell repertoire that is lost in advanced disease tends to be restored after elimination of the malignant clone.[54,55] Treatments including ECP, TSEB, interferons, and TLR agonists have been shown to restore some TH1/TH2 balance, likely in part by debulking malignant cells.[56–58] Restoration of dendritic and NK cell populations is also typical.[4] Importantly, there is a reasonable concern that traditional chemotherapy regimens, being immunotoxic, may delay immune reconstitution relative to treatments that stimulate immunity.[4]

## Cellular mechanisms of immune evasion and progression

### The definition of the malignant cell

The tumor cells in MF and SS are noted morphologically as ‘atypical’ lymphocytes with convoluted, cerebriform nuclei.[4] While these qualitative features are useful, more objective measures have been developed for quantitating malignant cells. Flow cytometry evaluation of peripheral blood can reveal the characteristic deletion of markers including CD7 and CD26, the latter being much more frequent.[59–62] The expansion of clonal T cell populations can be detected by polymerase chain reaction (PCR), antibodies specific for Vβ TCR families, or high throughput sequencing (HTS) of the complementarity determining region 3 (CDR3) of the TCRB gene complex.[63–65] At the transcript level, tumor cells may be distinguished by the expression of TH2 cytokine mRNA.[41] TCR sequencing has also better defined the histogenesis of CTCL, because malignant cells were found to have two rearranged copies of Vγ, a marker of ‘mature’ or post-thymic T cells.[66]

Studies have identified distinct molecular and genetic signatures in MF and SS, which suggest the two may be distinct entities rather than different stages of the same disease. Immunophenotyping analysis has suggested that Sézary cells and MF cells may have central memory and effector memory phenotypes, respectively.[67] A genomic study found highly recurrent chromosomal abnormalities in MF that were not common in SS and vice versa.[68] Therefore, despite many shared features, such as a predominant CD4+CLA+CD26− phenotype with TH2 cytokine elaboration, MF and SS may have distinct molecular signatures that may prove important for future targeted therapies.

### Common mutations and dysregulations

A resistance to apoptosis is a fundamental feature of malignant cells, and several pathways combine to induce this resistance in CTCL. Typically, benign lymphocytes rely on Fas-mediated pathways to undergo regulated cell death after repeated TCR stimulation.[69] This process, also referred to as activation induced cell death (AICD), is important to maintain homeostasis during the clonal expansion of activated lymphocytes.[70] The activation of T cells leads to the expression of Fas ligand (FasL), which complexes with the Fas receptor and leads to T cell apoptosis.[70] However, both CTCL cell lines and patient derived tumor cells have exhibited delayed expression of FasL following activation.[71] Moreover, studies have identified inactivating splice variants and other mutations in the *Fas* gene as well as reduced TCR-proximal signaling that downregulates AICD.[72–74] The decreased TCR signaling in CTCL cells appears to be due to a profound suppression of phospholipase C, gamma 1 (PLCG1).[74] The FasL that CTCL cells *do* express may be sufficient to induce apoptosis in neighboring benign lymphocytes, and this ‘bystander cytotoxicity’ may be a mechanism by which CTCL cells evade the host immune response.[71] Additional pathways implicated in apoptosis resistance include constitutive NF-kB signaling, PAK1 and STAT3 overexpression, mTOR signaling, and IL-7, 9, and 15 interactions.[75–80]

The pathogenesis of the TH2 phenotype of MF and SS cells is now significantly better understood. In benign helper T cells, cytokine and TCR-mediated pathways induce TH differentiation. The principal transcription factors that determine TH1 and TH2 phenotype,

respectively, are T-bet and GATA3.[81] Most TH determining pathways converge on these transcription factors. For example, the TH2 polarizing cytokines IL-4 and IL-13 signal through cytokine receptor associated JAKs to activate STAT6, which enhances the transcription of GATA3.[81] Meanwhile, signaling through the TCR promotes GATA3 expression by PI3K-mTOR pathways and by downregulating RUNX1.[81,82] The activation of STAT5 and STAT3 also appear necessary for TH2 differentiation.[83,84] In MF and SS, the acquisition of the TH2 phenotype is associated with a loss of the TH1 polarizing STAT4 and a gain of STAT6.[85] These changes appear to be due in part to aberrant histone acetylation and expression of the oncogenic miR-155 microRNA.[85] Notably, blocking STAT3 in tumor cell lines abrogates the expression of IL-5 and IL-13 and encourages apoptosis.[39,77] In both early and advanced stages of disease, constitutive STAT3 and STAT5 activity is observed. In early stages this may be due to cytokine signaling from the tumor microenvironment, while in advanced stages these transcription factors may become cytokine-independent and driven by constitutively active JAK signalling.[86]

The application of whole exome sequencing to patient derived SS cells has identified genes with common mutations and copy number alterations. Based on mutation frequency alone, *TP53, PLCG1, CCR4, FAS*, and *TNFRSF1B* emerge as likely driver genes[87,88], all of which have been implicated in prior studies of CTCL pathogenesis.[72,74] Mutations were also observed in well-known tumor suppressor, signaling, and epigenetic regulating proteins including *RB1, CDKN1B, MAPK1, BRAF, TET2*, and *CREBBP*.[88] Overall, these genetic studies help elucidate the derangements behind tumor proliferation, resistance to apoptosis, and immune surveillance.

## Surface factors

The cellular ‘surfaceome’ has acquired a new importance in the age of immunotherapy. With the advent of therapeutic mAbs, affinity-directed toxins, and (CAR) T cells, we are witnessing how surface proteomics can direct tumor eradication.

In CTCL, we now have a much higher resolution picture of cell surface proteomics. The immune checkpoint receptors are a particularly well-characterized group. In SS, both benign and malignant CD4+ T cells exhibit a stage-dependent increase in PD-1 expression, and the blockade of the PD-1 axis can restore TH1 cytokine production.[45] With elimination of the malignant clone, PD-1 expression can normalize.[45] Mechanistically, PD-1/PD-L1 complexes inhibit reactive immune T cells and promote induction of FOXP3+ Tregs and TH2 cells.[89,90] A study of MF skin biopsies found that tumor cells strongly express the ligand PD-L1, while a separate report examining leukemic CTCL found lower PD-L1 expression.[90,91] The anti PD-L1 antibodies atezolizumab and avelumab are currently being studied for mature T cell malignancies including CTCL (NCT03905135 and NCT03357224). The immune checkpoint receptors TIGIT and CTLA-4 are also overexpressed on Sézary cells, the latter likely due to proteasome dysfunction and GATA3 upregulation.[46,47,92] The receptor CD47, which inhibits macrophage-mediated phagocytosis of tumor cells, is also elevated on Sézary cells through the influence of TH2 cytokines, and its expression is correlated with worse overall survival.[93]

To date, the screening of CTCL lines for tumor-*specific* plasma membrane proteins has produced only a limited number of candidates for immunotherapeutic targeting.[94] Examples include a set of cancer/germline antigens that include cTAGE-1, MAGE-A9, and NY-ESO-1.[95,96] However, the search for tumor-*associated* proteins has been more fruitful. These proteins are upregulated relative to benign cells, and some provide promising targets as well as insight into clinical manifestations. The chemokine receptors CCR4 and CCR7 facilitate T cell homing into the skin and lymph nodes, respectively.[97] The former is upregulated in both CTCL cells and Tregs, making it an attractive dual target.[98] CCR7 is overexpressed mainly on leukemic CTCL cells.[67] The chemokine receptor CXCR4 also plays a role in skin trafficking, and the absence of CD26, which normally degrades the ligand of CXCR4, may also facilitate skin tropism.[99] Other associated biomarkers of Sézary cells include the sialomucin core protein CD164, Fc receptor-like protein 3 (FCRL3), syndecan-4 (SD-4), and vimentin.[100–102] The latter two are present on all activated T cells and may simply reflect the constitutively activated phenotype of Sézary cells. Tumor-associated antigens can be effective targets, with acceptable on-target off-tumor toxicity, as demonstrated by good results with anti-CCR4 and anti-CD52 mAbs. The discovery of other tumor-associated antigens is a promising direction of research.

## The influence of the microenvironment

The interactions of cytokines, chemokines, and stroma contribute to CTCL tumorigenesis, suggesting potential therapeutic targets. The influences of TH2 and Treg cytokines are summarized in Fig 1..[103,104] The cytokine IL-31 has a dose-dependent relationship with the clinical manifestation of pruritus.[105,106] A set of chemokines including CCL17, CCL22, CCL27, and the stromal cell-derived factor 1 (SDF1) are implicated in directional migration into the skin.[107] Importantly, in their normal function, these chemokines also exert pro-survival influences on their target cells, likely including PI3K/Akt signaling.[107] In *in vitro* studies, the cytokines IL-2, IL-4, IL-7, IL-13, and IL-15 have all been implicated as lymphoma growth factors[108–110].

The influence of dysregulated or immature APCs can explain certain aspects of both tumor progression and therapeutic response. Direct contact with immature DCs promotes CTCL cell proliferation and Treg cytokine production in an MHC class 2-dependent manner.[103] The presence of immature DCs in culture allows for the prolonged proliferation of CTCL cells, an effect which is inhibited by blocking CD40 or the clonotypic TCR.[111] Conversely, CTCL cells do not proliferate when encountering mature DCs.[112] The TH1 cytokine IFN-γ stimulates maturation of dendritic cells.[113] While DCs can phagocytose both viable and apoptotic CTCL cells, only the latter induce DC maturation markers.[112] The observation that apoptotic CTCL cells can induce APC maturation may explain why therapies like TSEB and ECP, which can induce massive apoptosis of malignant cells, are effective additions to many multimodality regimens.

## Conclusion

Recent discoveries have advanced our understanding of the pathophysiology of CTCL, particularly MF and SS. The immune deficient state commonly observed in these patients may lead to severe infections or inadequate anti-tumor immunity. Therapies that stimulate

immunity have been associated with longer progression free survival than traditional cytotoxic chemotherapy. The application of new technologies, including high throughput TCR sequencing and genomic analysis, has led to breakthroughs in diagnosis and in understanding tumor proliferation, escape from apoptosis, and dependency on the microenvironment. In the next part, we review in more depth the current and emerging immunotherapies for CTCL.

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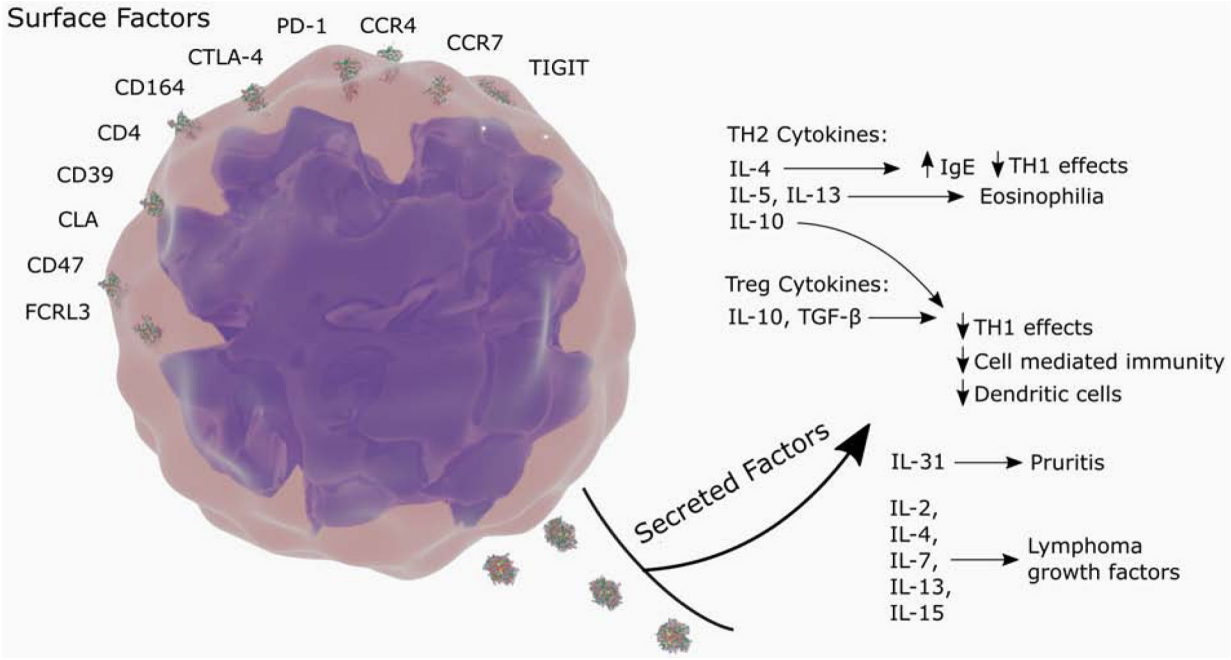


**Figure 1.**

"Sézary syndrome. Malignant cells dysregulate the host immune response through surface and secreted factors."