The immunopathogenesis and immunotherapy of cutaneous T cell lymphoma: Pathways and targets for immune restoration and tumor eradication

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Learning objectives
After completing this learning activity, participants should be able to comprehend how the malignant T-cell evades the host immune response; comprehend the many causes of immune dysregulation in advanced CTCL; and comprehend the numerous immune checkpoints relevant in CTCL.

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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 antitumor immune response. Therapies that stimulate immunity have produced superior progression-free survival compared with conventional chemotherapy, reinforcing the importance of addressing the immune deficient state in the care of patients with CTCL. 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 and Sézary syndrome are now significantly better understood, including the T helper 2 cell phenotype, regulatory T cell 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. (J Am Acad Dermatol 2021;84:587-95.)

Key words: CTCL; cutaneous T cell lymphoma; dermatologic oncology; drug response; immune deficiency; immunopathogenesis; immunotherapy; mycosis fungoides; Sézary syndrome.

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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 the antitumor 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, monoclonal antibodies, oral retinoids, histone deacetylase inhibitors, and total skin electron beam radiation.[4] A newer generation of therapies, including immune checkpoint inhibitors, Toll-like receptor agonists, and chimeric antigen receptor 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 T-helper 2 (T_H2) phenotype, has been known since the 1990s and explains defects in T_H1 immunity, dendritic cell (DC) function, and cytokine production in patients with CTCL.[6] However, the genetic basis for the T_H2 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 the first article in this continuing medical education series, 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, the second article in this series 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 *Staphylococcus 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 antimicrobial 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, *Pneumocystis 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.[13] Both bacterial isolates from patients and recombinant SEs can activate STAT3 and induce expression of interleukin-17 (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 toxic shock syndrome toxin. For example, toxic shock syndrome toxin is specific to Vβ2, and SE type D 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, 2 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, eg, doxycycline's inhibition of nuclear factor-κB,[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 a higher prevalence of HIV, a finding in keeping with the known 15-fold higher incidence of T cell lymphomas in patients with AIDS.[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 posttransplantation patients, CTCL may take a particularly aggressive course.[25] Clearly, medications that inhibit T cell function, such as anti–tumor necrosis factor agents and cyclosporine, can drive sudden progression in undiagnosed CTCL.[26,27] Dupilumab, an anti–IL-4 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 patients 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 T_H1 phenotype, suggesting that the cytokine milieu is supportive of cell-mediated cytotoxicity.[32] These T_H1 cells could represent either reactive benign T helper cells or malignant cells that have a malleable phenotype and have not yet acquired a dominant T_H2 bias.[3] At least 1 study has suggested that the visible inflammation in MF lesions is caused in large part by the reactive immune response.[33] Importantly, the cellular immune response to CTCL depends at least in part on major histocompatibility complex–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 T_H2 profile.[29,36,37] The T_H2 cytokines secreted by malignant cells suppress T_H1 immunity and enforce a global T_H2 bias in benign T helper cells.[38,39] With reduced T_H1 function, the host is substantially deprived of cellular immunity and has impaired immunologic memory to major histocompatibility complex–presented antigens.[40] Patients may possess reactive T cells that are capable of recognizing tumor cells yet are incapacitated by the T_H1/T_H2 imbalance.[41] In keeping with this, $CD8^+$ lymphocytes from patients with SS demonstrate markers of exhaustion, cytokine unresponsiveness, and attenuated cytotoxicity.[42,43] Stimulating T_H1 function by supplementing IL-2, IL-12, and interferon gamma (IFN-γ) restores the lytic capacity of effector T cells.[31] The cytokine IL-2 has also been shown to activate natural killer cells to lyse Sézary cell lines.[44] Apart from suppressing T_H1 function, the T_H2 phenotype of MF and SS cells helps to explain common findings including eosinophilia and increased levels of immunoglobulins E and A.[36] In addition to their T_H2 phenotype, the malignant cells in SS generally also express varying levels of the immune checkpoint molecules programmed cell death protein 1 (PD-1), T cell immunoreceptor with immunoglobulin and ITIM domains, and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4).[45-47] Similarly, T cells from those with human T lymphotropic virus type 1–associated adult T cell leukemias 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. 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 Toll-like receptor 9 agonists, peripheral blood mononuclear cells from patients with SS produce significantly less IFN-α.[51,52] Polymorphonuclear granulocytes from patients with SS have reduced phagocytic activity and intracellular killing against *Klebsiella pneumonia*.[53] These defects in antigen-presenting cells and in innate immunity also favor the development of infections in these patients.

A reduction in the burden of malignant T cells in SS using 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 extracorporeal photopheresis, total skin electron beam, interferons, and Toll-like receptor agonists have been shown to restore some T_H1/T_H2 balance, likely in part by debulking

malignant cells.[56-58] Restoration of DC and natural killer 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, antibodies specific for Vβ TCR families, or high throughput sequencing of the complementarity determining region 3 of the TCRβ gene complex.[63-65] At the transcript level, tumor cells may be distinguished by the expression of T_H2 cytokine messenger RNA.[41] TCR sequencing has also better defined the histogenesis of CTCL, because malignant cells were found to have 2 rearranged copies of Vγ, a marker of "mature" or postthymic 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 T_H2 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, 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, 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 Fas ligand after 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 activation-induced cell death.[72-74] The decreased TCR signaling in CTCL cells appears to be related to a profound suppression of phospholipase C, gamma 1.[74] The Fas ligand 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 nuclear factor-κB signaling, PAK1 and STAT3 overexpression, mammalian target of rapamycin signaling, and IL-7, -9, and -15 interactions.[75-80]

The pathogenesis of the T_H2 phenotype of MF and SS cells is now significantly better understood. In benign T helper cells, cytokine and TCR-mediated pathways induce T helper differentiation. The principal transcription factors that determine T_H1 and T_H2 phenotype, respectively, are T-bet and GATA3.[81] Most T helper–determining pathways converge on these transcription factors. For example, the T_H2 polarizing cytokines IL-4 and IL-13 signal through cytokine receptor–associated Janus kinases to activate STAT6, which enhances the transcription of GATA3.[81] Meanwhile, signaling through the TCR promotes GATA3 expression by PI3K–mammalian target of rapamycin pathways and by downregulating RUNX1.[81,82] The activation of STAT5 and STAT3 also appear necessary for T_H2 differentiation.[83,84] In MF and SS, the acquisition of the T_H2 phenotype is associated with a loss of the T_H1-polarizing STAT4 and a gain of STAT6.[85] These changes appear to be caused in part by 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 caused by cytokine signaling from the tumor microenvironment, while in advanced stages these transcription factors may become cytokine-independent and driven by constitutively active Janus kinase 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 previous 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 monoclonal antibodies, affinity-directed toxins, and chimeric antigen receptor 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 T_H1 cytokine production.[45] With elimination of the malignant clone, PD-1 expression can normalize.[45] Mechanistically, PD-1/programmed death-ligand 1 (PD-L1) complexes inhibit reactive immune T cells and promote induction of $FOXP3^+$ Tregs and T_H2 cells.[89,90] A study of MF skin biopsy specimens 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 (clinicaltrials.gov studies NCT03905135 and NCT03357224). The immune checkpoint receptors T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) and CTLA-4 are also overexpressed on Sézary cells, the latter likely caused by 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 T_H2 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 C-C chemokine receptor type 4 (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 C-X-C motif chemokine receptor 4 also plays a role in skin trafficking, and the absence of CD26, which normally degrades the ligand of C-X-C motif chemokine receptor 4, may also facilitate skin tropism.[99] Other associated biomarkers of Sézary cells include the sialomucin core protein CD164, Fc receptor—like protein 3, syndecan-4, and vimentin.[100-102] The latter 2 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 monoclonal antibodies. 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 T_H2 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, are implicated in directional migration into the skin.[107] Importantly, in their normal function, these chemokines also exert prosurvival 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 antigen-presenting cells 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 a major histocompatibility complex class 2—dependent manner.[103] The presence of immature DCs in culture allows for the prolonged proliferation of CTCL cells, an effect that is inhibited by blocking CD40 or the clonotypic TCRs.[111] Conversely, CTCL cells do not proliferate when encountering mature DCs.[112] The T_H1 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 antigen-presenting

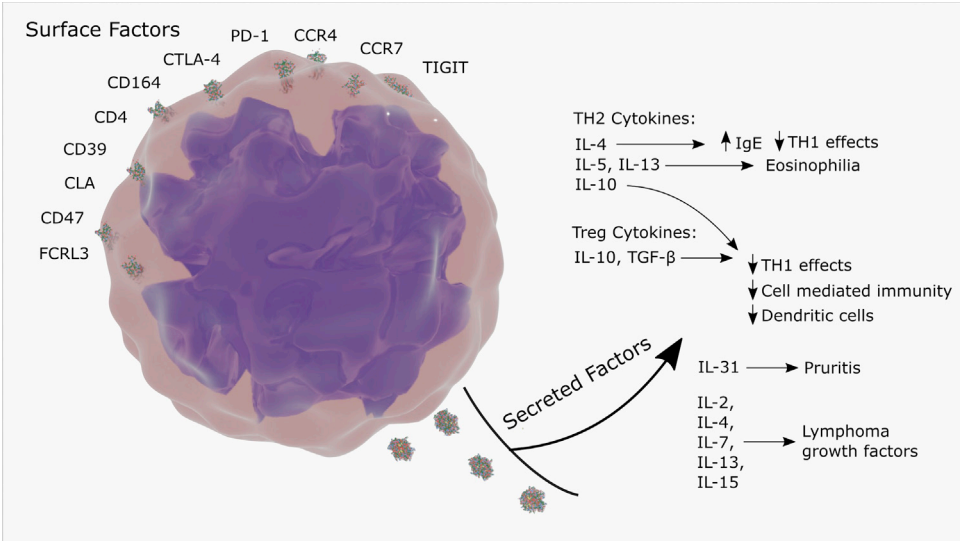

Fig 1. Sézary syndrome. Malignant cells dysregulate the host immune response through surface and secreted factors. *CCR4*, C-C chemokine receptor 4; *CCR7*, C-C chemokine receptor 4; *CLA*, cutaneous lymphocyte-associated antigen; *CTLA-4*, cytotoxic T lymphocyte-associated antigen-4; *FCRL3*, Fc receptor-like protein 3; *IgE*, immunoglobulin E; *IL*, interleukin; *PD-1*, programmed cell death-1; *TGF*, transforming growth factor; *TH*, T helper; *TIGIT*, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains; *Treg*, regulatory T cell.

cell maturation may explain why therapies like total skin electron beam and extracorporeal photopheresis, which can induce massive apoptosis of malignant cells, are effective additions to many multimodality regimens.

CONCLUSION

In 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 antitumor 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. The next article in this continuing education series reviews the current and emerging immunotherapies for CTCL in more detail.

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Answers to CME examination

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