Title

The Role of Tumor Microenvironment in Mycosis Fungoides and Sézary Syndrome.

Journal

Annals of dermatology, 33(6)

Authors

Liu, Zhaorui

Wu, Xuesong

Hwang, Sam

et al.

Publication Date

2021-12-01

DOI

10.5021/ad.2021.33.6.487

Peer reviewed

Review Article Annals of Dermatology 2021;33(6):487-496 • https://doi.org/10.5021/ad.2021.33.6.487

The Role of Tumor Microenvironment in Mycosis Fungoides and Sézary Syndrome

Zhaorui Liu, Xuesong Wu[1], Sam T. Hwang[1], Jie Liu

Department of Dermatology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing, China, [1]Department of Dermatology, School of Medicine, University of California Davis, Sacramento, CA, United States

Received November 18, 2020
Revised March 21, 2021
Accepted April 6, 2021

Corresponding Author
Jie Liu
Department of Dermatology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, National Clinical Research Center for Dermatologic and Immunologic Diseases, No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing 100730, China
Tel: +86-10-69151536
Fax: +86-10-69151502
E-mail: LiuJie04672@pumch.cn
https://orcid.org/0000-0001-8219-2429

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common subtypes of cutaneous T-cell lymphomas (CTCLs). Most cases of MF display an indolent course during its early stage. However, in some patients, it can progress to the tumor stage with potential systematic involvement and a poor prognosis. SS is defined as an erythrodermic CTCL with leukemic involvements. The pathogenesis of MF and SS is still not fully understood, but recent data have found that the development of MF and SS is related to genetic alterations and possibly to environmental influences. In CTCL, many components interacting with tumor cells, such as tumor-associated macrophages, fibroblasts, dendritic cells, mast cells, and myeloid-derived suppressor cells, as well as with chemokines, cytokines and other key players, establish the tumor microenvironment (TME). In turn, the TME regulates tumor cell migration and proliferation directly and indirectly and may play a critical role in the progression of MF and SS. The TME of MF and SS appear to show features of a Th2 phenotype, thus dampening tumor-related immune responses. Recently, several studies have been published on the immunological characteristics of MF and SS, but a full understanding of the CTCL-related TME remains to be determined. This review focuses on the role of the TME in MF and SS, aiming to further demonstrate the pathogenesis of the disease and to provide new ideas for potential treatments targeted at the microenvironment components of the tumor.

Keywords: Cutaneous T-cell lymphoma, Mycosis fungiodes, Sezary syndrome, Tumor microenvironment

INTRODUCTION

Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL) that accounts for approximately 60% of CTCL[1]. The clinical manifestations of MF vary in different stages. Skin lesions may present with scaly patches or plaques in early stage but gradually formed generalized plaques, tumors or erythroderma in the advanced stage. Sézary syndrome (SS) is an aggressive CTCL variant that is characterized by leukemic involvement, which commonly present with widespread erythema[2]. MF and SS may mimic benign inflammatory diseases, such as eczema, psoriasis, parapsoriasis, vitiligo, folliculitis, and pigmented purpuric dermatoses, making it challenging to make accurate diagnosis[3].

There is still some controversy in the relationship between MF and SS. In the past, SS was considered to be an aggressive variant of MF. However, growing evidence from gene expression profiles, microRNA profiling, and cell marker studies suggests that they may be separate entities with different pathogeneses[4-10]. In recent years, genome sequencing technologies have identified some chromosomal abnormalities that have occurred in MF and SS[4-7]. There have been losses on chromosomes 1, 5, 9, and 13 and gains on chromosomes 7 and 17 for MF, and losses within chromosome 10 and gains within chromosomes 8 and 17 in SS. One study reported miRNA expression of MF and made a comparison with SS profiles[8]. The results showed that

there is no common upregulated miRNA between the tumor stages MF and SS, and they share only 2 of the same downregulated miRNAs, indicating a difference in miRNA expression between MF and SS.

The pathogenic mechanisms underlying oncogenic transformation include not only intrinsic factors such as tumor gene mutation but also extrinsic events in which environmental factors play critical roles. Within patches, plaques, and tumoral CTCL lesions, nonneoplastic T cells such as macrophages, fibroblasts, dendritic cells (DCs), mast cells (MCs), myeloid-derived suppressor cells (MDSCs) and other cells or cytokines comprise the tumor microenvironment (TME). An increasing amount of evidence suggests that the TME plays important roles in tumor occurrence and development of MF and SS, both of which are regarded as Th2-dominant diseases[9]. The main role of the TME in the development of MF/SS can be divided into two aspects: one is to support tumor growth and survival, and the other is to suppress antitumoral immune response. In this review, we will focus on chemokines and various cell in TME that affect the characteristic features of MF and SS. Understanding the interactions between malignant tumor cells and TME will help to find new treatments targeted at the microenvironment components for the disease.

ROLES OF CHEMOKINES DURING THE CLINICAL COURSE OF MYCOSIS FUNGOIDES/SÉZARY SYNDROME

Chemokines and their receptors are widely known to play an important role in directing leukocyte movement, facilitating both innate and adaptive immune responses and contributing to the pathogenesis of various diseases, including CTCL[10]. Malignant T cells in CTCL usually present mature CD4+ T cell phenotypes, accompanied by Th2 or Th17 phenotypes or a T regulatory cells (Tregs) phenotype[11], each of which can express different receptors that react differently with the same chemokines.

Chemokine receptor expression on tumor cells differs according to different stages of MF. During early stage, the majority of malignant lymphocytes express CXCR3[12,13], an interferon (IFN)-inducible chemokine receptor, which reacts with chemokine CXCL9-11, which are all induced by the Th1 cytokine IFN-γ[14]. There are numerous cells that express the above chemokines, such as keratinocytes, Langerhans cells and fibroblasts, which are mainly distributed in the epidermis and the superficial dermis. The interaction between the above chemokines and their ligands are potentially important for the epidermotropic phenomenon in early stage of MF[15].

A shift from Th1 to Th2 cytokines during the development and progression of MF has been identified. In advanced stage of MF, as malignant T cells tend to express more CCR4 than CXCR3, epidermotropism of tumor cells becomes less evident and tend to infiltrate the dermis[15]. CCR4 is regarded as a Th2-dominant receptor. Sugaya et al.[16] discovered that CCR4 expression is seen in infiltrating malignant T cells in all stages of MF and SS, but the frequency of CCR4 expression is positively related to the tumor stage progression. CCR4 is the receptor for CCL[17] and CCL22, where CCL17 is mainly expressed by endothelial cells and CCL22 is primarily secreted by DCs in dermis17, and it has been shown that DCs may attract T cells for cell-cell antigen stimulation of T cells via CCR4 interactions[18].

CCR4 represents a promising target for CTCL treatment[19]. Clinical trials that used mogamulizumab, an anti-CCR4 monoclonal antibody, demonstrated encouraging results in advanced MF patients[20-22]. In addition, CCR4 expression was also found in circulating malignant T cells and skin tumor cells in SS patients. Fierro et al.[23] found that the leukemic CD4+CD26- subpopulation in SS selectively expressed CCR4 at a high level without an increase in Th1 chemokines such as CXCR3.

CCR10 is overexpressed on infiltrating tumor cells, as well as in the peripheral blood of MF[24,25], while CCL27 is a ligand for CCR10 and is mainly produced by activated keratinocytes. CCL27 is able to selectively attract memory T cells that express CCR10 into inflammatory sites[25,26]. Therefore, the CCR10 and CCL27 interaction explains the preferential migration and retention of tumor cells within the skin in MF/SS and in other cancers such as melanoma[27].

CCR7 is a lymph node-homing chemokine receptor that has been found to be expressed in the peripheral blood of SS, playing an important role in the pathogenesis of SS[28]. Picchio et al.[29] found that CXCL13 expression is increased in skin lesions and in the lymph nodes of SS patients, while CXCL13 is a selective agonist for CCR7. The addition of CXCL13 to CCL19 or CCL21 strongly enhances the migration of CCR7+SS cells. In addition, the neutralization of the CCR7 receptor causes the impaired chemotaxis of SS cells.

CXCR4 usually combines with CXCL12 specifically, inducing chemotaxis of lymphocytes to inflammatory sites, thus

helping to enhance chemotaxis for cancer cells. Daggett et al.[30] found that CXCL12 is highly expressed on skin tumor cells MF, demonstrating that the interaction between CXCL12 and CXCR4 is important in the progression of MF. Furthermore, the CXCL12 and CXCR4 interaction also regulates tumor angiogenesis by promoting the production of vascular endothelial growth factor (VEGF)[31].

CCL18 was frequently expressed by macrophages and DCs in the dermis in CTCL. Miyagaki et al.[32] discovered that circulating CCL18 levels in the peripheral blood of CTCL patients were higher than that of normal controls. They also found that high serum levels of CCL18 often correlated with a poor prognosis. In addition, the interleukin (IL)-4-induced CCL18 transcription was inhibited by the Th1 cytokine IFN-γ, indicating that CCL18 is related to the Th2-dominant TME.

Th2-DOMINANT MICROENVIRONMENT DURING THE PATHOGENESIS OF MYCOSIS FUNGOIDES/SÉZARY SYNDROME

MF and SS are considered to be Th2-type diseases and there is a shift in cytokine expression from Th1 to Th2 profile during the disease progression. Early studies showed that Th1 cytokines, which include IFN-γ, IL-2 and IL-12, comprise a majority of the cytokines expressed in early stage of MF[33], while in late stage, tumor cells in MF and SS lesions present with a Th2 phenotype, accompanied with an elevated expression of Th2-prone cytokines such as IL-4, IL-5, IL-10, and IL-13[34-36]. By using T-bet as a specific maker for Th1 and GATA3 as a marker for Th2, Hsi et al.[37] found that in early stage of MF, T-bet expression was increased and became dominant but as the disease progressed to advanced stage, GATA3 expression gradually became more pronounced and eventually occupied predominance.

Th2 cytokines are able to inhibit Th1 responses and promote a Th2-dominant TME in CTCLs[38], making it a possible anticancer therapy by suppressing Th2 cytokines expression and enhancing Th1 response. IFN-γ produced by Th1 cells is capable of improving antitumor responses and has proved to be an effective treatment for CTCL[39,40]. Recently, Vieyra-Garcia et al.[41] found that nontumor T cells in TME were related to the Th2-recruiting chemokines before PUVA treatment, while Th1-recruiting chemokines were observed after phototherapy, suggesting that PUVA may contribute to a change from the Th2 to the Th1 phenotype in MF.

TUMOR-ASSOCIATED MACROPHAGES

Tumor-associated macrophages (TAMs) are a critical part of the primary immune response in TME. The macrophages can be divided into two types: one is an antitumorigenic cell (M1) and the other is a protumorigenic cell (M2)[42]. During the late stage of CTCL, TAMs usually exhibit an M2 phenotype, along with a decreased level of IL-12 but an increased expression of IL-10. TAMs can also produce abundant vascular endothelial growth factor (VEGF), which can drive angiogenesis to support tumor growth and development[43]. Recent clinical histological studies have demonstrated abundant macrophage infiltration in MF patients. Sugaya et al.[44] demonstrated increased CD163+ TAM cells in lesions of CTCL patients compared with healthy individuals. In CTCL, the numbers of CD163+ or CD68+ cells correlated with a poor patient outcome. Moreover, TAMs decreased after effective topical steroid and ultraviolet light treatment, linking TAMs with tumor pathogenesis. Besides, Furudate et al.[45] also found that CD206+ macrophages are increased in parallel with tumor progression in MF.

TAMs are capable of regulating tumor progression by producing chemokines. Furudate et al.[46] found a decreased expression of CCL17 and CCL18, as well as an increased production of CXCL10 and CXCL11 by M2 macrophages after IFN-α2a and IFN-γ treatment. Furudate et al.[45] suggested that increased periostin in the stromal area may promote M2 polarization and TAM recruitment in the early stage of MF. Tanita et al.[47] studied the immunomodulatory effects of bexarotene on TAMs in MF patients and results suggested that the clinical benefits are partially attributed to suppressive effects on the production of CCL22 by M2-polarized TAMs. These data suggest that TAM could be a therapeutic target for the treatment of MF.

A phase II clinical trial[48] confirmed the clinical effect and safety of a CD30 antibody, brentuximab vedotin, in the treatment of MF and SS. Moreover, the results showed that CD30 was coexpressed in TAMs as well as in tumor cells, indicating that the CD30 antibody may disrupt tumor progression by targeting not only malignant T cells but also TAMs. Wu et al.[49] studied the role of macrophages in a CTCL murine model and found that depletion of M2-like TAMs delayed murine T-cell lymphoma tumor development. Recently, by using the same model, Wu et al.[50] detected an increased IL-10 level in TME. Compared to wild-type mice, xenografted cutaneous lymphoma in IL-10 knockout mice showed a smaller tumor size and

a decreased number of infiltrating microphages, suggesting a critical role of TAMs in pathogenesis and treatment of CTCL. In addition, tumor cells express CD47 to bind signal-regulatory protein on TAMs, and this interaction is able to send a "do-not-eat-me" signal from the tumor cells and thus helps cancer cells to escape from phagocytosis[51,52].

CANCER-ASSOCIATED FIBROBLASTS

Cancer-associated fibroblasts (CAFs) are a group of fibroblasts that are closely related to tumor progression and migration, mainly by secreting certain specific chemokines and cytokines in TME[53]. In CTCL, CAFs are related to the change from the Th1- to the Th2-dominant TME along with the tumor progression. Miyagaki et al.[54] found that in early stage, dermal fibroblasts expressed high levels of herpesvirus entry mediator (HVEM), CXCL9, CXCL10, and CXCL11, with Th1 cells expressing IFN-γ and LIGHT (a ligand for HVEM), while in late stage, CAFs expressed less HVEM and increased Th2 cells' expression of LIGHT only and not IFN-γ. CCL17 was widely expressed by fibroblasts and DCs, while CXCL9-11 expression was decreased.

Periostin, a glycoprotein that is predominantly secreted by dermal fibroblasts, is able to induce chronic inflammatory responses by stimulating thymic stromal lymphopoietin and then act on DCs to induce a Th2-dominant TME in CTCL[55,56]. Takahashi et al.[56] identified periostin expression in dermal fibroblasts stimulated by IL-4 or IL-13 *in vitro* and *ex vivo* and found that compared to the healthy controls, CAFs expressed significantly increased periostin in CTCL skin lesions. In addition, higher serum periostin levels were also observed in CTCL patients.

CCR3 is the only receptor for eotaxins and is mainly expressed on Th2 cells and eosinophils. Miyagaki et al.[57] found a higher expression of eotaxin-3 by fibroblasts from the lesional skin in CTCL than from the normal skin and that an increased expression of eotaxin-3 and CCR3 mRNA was related to a more advanced stage. The study above indicates that eotaxins produced by fibroblasts may interact with CCR3 expressed by Th2 cells and then help to form a Th2-dominant TME in the pathogenesis of CTCL.

DENDRITIC CELLS

DCs enable primary immune responses and play a crucial part in TME. In CTCL, proliferating malignant T cells are in close association with immature DCs. Berger et al.[58] reported that CTCL cells appear to retard DC maturation, and when cocultured with immature DCs, CTCL cells can be reproducibly grown in culture.

It is assumed that mature DCs take part in antitumor immune responses while immature DCs induce tumor tolerance[59]. There are three different DC subsets that are discerned by their receptor expression pattern, which include Langerhans cells, dermal DCs and plasmacytoid DCs. Schwingshackl et al.[59] found that all three subsets of DCs were increased and that DC-SIGN+ dermal DCs constituted the majority of the DCs. Among these, most DCs show immature phenotypes in the epidermis and dermis, while the few mature DCs in the dermis are almost all Langerin+ cells.

Recently, Vieyra-Garcia et al.[41] found c-Kit+ DCs may activate tumor cells through CD40 and CD40L interactions in CTCL. Their data suggest that c-Kit+OX40L+CD40L+ DCs are able to activate benign T cells to cause inflammation and may transmit tumorigenic signals.

MAST CELLS

MCs originate from the myeloid stem cells and are part of the innate immune system, which take part in allergies and inflammation, as well as the regulation of adaptive T cell-mediated immune responses[60]. Recently, MCs were described as regulators in the TME of CTCL with protumorigenic functions. Rabenhorst et al.[61] found that MCs were increased in CTCL lesions and had a positive relationship with the tumor stage progression and microvessel density. They also reported delayed development of cutaneous lymphoma in mast cell-deficient mice. Eder et al.[62] also identified high MC counts within CTCL, especially in MF, but instead of a higher prominence with disease progression, they found that compared to the IIA and IIB stages, there were higher mast cell counts in the IA and IB stages in MF.

MYELOID-DERIVED SUPPRESSOR CELLS

MDSCs are a group of immature myeloid cells that act in can-

cer tolerance and function as immunosuppressive cells. Geskin et al.[63] found that the activity of MDSCs, which is reflected by intracellular reactive oxygen species, was elevated in MF patients of stage IB and above, while the number of MDSCs was not increased. IFN-α2b therapy was related to a decreased function in MDSCs, suggesting that inhibiting MDSCs may be one of the reasons for the effective treatment of IFN. Maliniemi et al.[64] found that CD33+ MDSCs express indoleamine 2,3-deoxygenase 1 (IDO1) in all studied CTCL subtypes including MF, while IDO1 induces immune tolerance in the TME and is recognized as a potential therapeutic target.

B CELLS

The role of B cells has been investigated in cancer development, revealing that B cells may mediate both pro- and antitumorigenic effects. On one hand, B cells present antigen and induce tumor-reactive T cell activity, which have antitumorigenic effects. On the other hand, they may promote an immunosuppressive milieu and support tumor growth. In addition, regulatory B cells (Bregs) may upregulate the secretion of IL-10, TGF-β, and granzyme B, leading to the induction of tumor immunosuppressive cells, i.e., Tregs, myeloid-derived suppressor cells, and M2-macrophages, as well as the inhibition of the antitumor activities of cytotoxic T cells. The role of tumor-infiltrating B cells has been reported recently in CTCL. First, an increased B cell density was found in CTCL skin samples. Moreover, B cell infiltration was discovered to be correlated inversely with a progression-free survival. The CD20-targeting antibody rituximab and the type II CD20-directed mAb obinutuzumab are being used in multiple clinical trials for CTCL, and the efficacy of targeting B cells and modulating the TME will be further confirmed by following the patients and analyzing their biological samples.

Table 1 summarized the related cells above and their functions in TME.

Table 1. Different cell types and their characteristics and functions in TME

Cell type	Characteristics and functions in TME
Tumor-associated macrophages (TAMs)	• Mainly exhibit an M2 phenotype • Increased in parallel with tumor progression • Increase CXCL10, CXCL11 and decrease CCL17, CCL18 production after treatment • Produce VEGF to support tumor angiogenesis • Produce CCL22 • Increase IL-10 expression
Cancer-associated fibroblasts (CAFs)	• Promote Th2-dominant TME • Express HVEM, CXCL9, CXCL10, and CXCL11 in early stage, increased Th2 expression in late stage • Produce CCL17 and decrease expression of CXCL9-11 • Express periostin and then act with DCs • Express eotaxin-3 and interact with CCR3
Dendritic cells (DCs)	• Immature DCs induce tumor tolerance • Activate tumor cells through CD40 and CD40L interactions • Transmit tumorigenic signals
Mast cells (MCs)	• Act as regulators with protumorigenic functions • Increase in parallel with tumor progression • Positively related to microvessel density
Myeloid-derived suppressor cells (MDSCs)	• Elevated activity in late stage MF • Possible target of IFN treatment • Induce immune tolerance of tumor cells
B cells	• Both pro- and antitumorigenic effects • Upregulate secretion of IL-10, TGF-β and granzyme B • Induce tumor immunosuppressive cells as Tregs, MDSCs and TAMs

TME: tumor microenvironment, IL: interleukin, MF: mycosis fungoides, IFN: interferon, TGF: transforming growth factor.

T-CELL EXHAUSTION VIA IMMUNE CHECKPOINTS

Exhausted T-cells have the features of the presence of immune checkpoints such as PD-1, LAG-3, CTLA-4, TIM-3 and others[65]. Kantekure et al.[66] found that PD-1 expression was frequently observed in early stage of CTCL and that there was a lower expression of PD-1 at tumor stage, while PD-L1 expression seemed to have a positive coloration with the tumor stage progression. Querfeld et al.[65] found that both CD4+ and CD8+ T cells in CTCL expressed more immune checkpoints than those from normal skin. Samimi et al.[67] reported that PD-1 was highly expressed on malignant T cells, indicating that the elevated expression of PD-1 plays a role in the immunosuppression of SS. Recent report suggested PD-1-PD-L1 therapies may also function through a direct effect on TAMs, and when PD-L1/PD-1 signaling is blocked by antibodies, CD163+ TAMs activated and polarized into M1-like TAMs[68]. Since the profiles of chemokines are different between M1 and M2 polarized macrophages, M1-polarized macrophages not only induce cytotoxic reaction against lymphoma cells, but also work together with other immunosuppressive cells[69].

THERAPEUTIC STRATEGIES BASED ON TUMOR MICROENVIRONMENT MODULATION

CTCL can be challenging to treat in the aggressive late stage, especially with visceral involvement or following relapses. For patients with T4 stage MF, the 10-year overall survival drops to 27% (compared to 86% in the T1 stage), and more than 50% of the observed deaths occur in the first 4 years after diagnosis. Thus, novel therapeutic strategies, especially biological therapy (i.e., immunotherapy), are needed to offer the best promise in managing such cases. Leuchte et al.[70] wrote an elegant comprehensive review on innovative treatment concepts in CTCL derived from the growing knowledge of the TME in tumor biology. In general, the successful translation of medications from benchside testing to bedside application has been limited.

In all the listed clinical trials funded by the NIH in the United States, there are thirteen active trials employing biological drugs/medications. These include the immune checkpoint inhibitors and therapeutic monoclonal antibodies targeting CD30, CD52, or ICOS (the T cell inducible costimulator), immune-modulating agents (cytokines (IL-12, IL-15) or drugs (imiquimod/resiquimod, lenalidomide)), and immune cell therapy (allogenic stem cell transplant), most of which modulate the TME.

Therapeutic monoclonal antibodies represent a new advancement in CTCL treatment. While a few of the therapeutic antibodies directly target cancer cells, such as the antibody for KIR3DL2 receptor, which is expressed by tumor cells, most monoclonal antibodies kill tumor cells indirectly though the modulation of the TME. An anti-PD antibody was approved for treat several other malignancies.

CTCL contains an increased proportion of PD-1+ and PD-L1+ cells, which provide the rationale for applying checkpoint inhibitors. In addition, the next-generation sequencing of CTCL cells revealed an outstandingly high mutational burden and a high rate of chromothripsis, both of which predict a superior response to immune checkpoint blockade. However, resistance to anti-PD1 antibody treatment often occurs in cancer patients, and even patients initially responding to treatment can eventually develop acquired resistance. Peranzoni and Donnadieu[71] demonstrated that depletion of TAMs restored T cell migration and infiltration into tumor islets and improved the efficacy of anti-PD-1 immunotherapy in a mouse model of squamous cell carcinoma. We have assessed a combined regimen by simultaneously administrating an anti-PD1 antibody and a CCR2 inhibitor that blocks CCR2-mediated chemotaxis of monocytes in a syngeneic mouse implantation model of T-cell lymphoma in skin. CCR2 inhibitor-induced TAM depletion synergized with the anti-PD1 antibody, producing an encouraging antitumor effect, which warrants a future translational study[72].

Mogamulizumab a CCR4 antibody, another potent anti-CTCL biological, has completed two clinical trials with results showing the effective targeting of not only malignant T cells but also Tregs and Th2 lymphocytes, which express CCR4. In addition to therapeutic antibodies, the immunomodulatory drug lenalidomide and Toll-like receptor agonists enhance antitumor immune responses by increasing IL-2, IL-12, and IFN-γ and decreasing IL-1, IL-6, and IL-10. The topical formulation in imiquimod and resiquimod would improve compliance and reduce side effects and toxicity to other organs compared to systemic medications. Moreover, small molecule compounds inhibiting signaling pathways such as NF-κB, JAK/STAT, or mTOR also regulate Tregs, DC, NKs and inhibit TGF-β and IL-

10 in the TME, which enhance the antitumor effects from their principal mechanisms functioning through tumor intrinsic survival and growth pathways.

The intimate relationship between tumor cells and the TME determines every step of tumorigenesis. Targeting the TME, either through active host immunity or counteracting the activities of cancer-associated partners, provides more options in CTCL clinical management.

CONCLUSION

The TME has been identified as one of the critical driving factors in tumor occurrence, progression, and invasion in CTCL. In this article, we have reviewed the roles of the TME in MF and SS, including the essential chemokines involved, Th2-dominant microenvironment, T cell exhaustion via immune checkpoints, and the different cell types in the TME. These cell types include TAMs, CAFs, DCs, MCs, and MDSCs.

The interaction between tumor cells and the microenvironment affects the progression of MF and SS. Determining the mechanism and dynamic changes in this process will provide a better understanding of the pathogenesis in CTCL and serve as a basis for potential TME component-targeted treatments or alternative immunotherapies for refractory/relapse MF and SS in the future.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING SOURCE

The study was funded by Beijing Natural Science Foundation (Grant No.7182127) and National Natural Science Foundation of China (Grant No. 82173449). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

ORCID

Zhaorui Liu, https://orcid.org/0000-0002-9811-9063
Xuesong Wu, https://orcid.org/0000-0003-0093-6338
Sam T. Hwang, https://orcid.org/0000-0001-7930-9964
Jie Liu, https://orcid.org/0000-0001-8219-2429

REFERENCES

1. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-1714.
2. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 2014;70:205.e1-e16.
3. Sarantopoulos GP, Palla B, Said J, Kinney MC, Swerdlow SM, Willemze R, et al. Mimics of cutaneous lymphoma: report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop. Am J Clin Pathol 2013;139:536-551.
4. van Doorn R, van Kester MS, Dijkman R, Vermeer MH, Mulder AA, Szuhai K, et al. Oncogenomic analysis of mycosis fungoides reveals major differences with Sezary syndrome. Blood 2009;113:127-136.
5. McGirt LY, Jia P, Baerenwald DA, Duszynski RJ, Dahlman KB, Zic JA, et al. Whole-genome sequencing reveals oncogenic mutations in mycosis fungoides. Blood 2015;126:508-519.
6. Choi J, Goh G, Walradt T, Hong BS, Bunick CG, Chen K, et al. Genomic landscape of cutaneous T cell lymphoma. Nat Genet 2015;47:1011-1019.
7. Bastidas Torres AN, Cats D, Mei H, Szuhai K, Willemze R, et al. Genomic analysis reveals recurrent deletion of JAK-STAT signaling inhibitors HNRNPK and SOCS1 in mycosis fungoides. Genes Chromosomes Cancer 2018;57:653-664.
8. van Kester MS, Ballabio E, Benner MF, Chen XH, Saunders NJ, van der Fits L, et al. miRNA expression profiling of mycosis fungoides. Mol Oncol 2011;5:273-280.
9. Rubio Gonzalez B, Zain J, Rosen ST, Querfeld C. Tumor microenvironment in mycosis fungoides and Sézary syndrome. Curr Opin Oncol 2016;28:88-96.
10. Wu XS, Lonsdorf AS, Hwang ST. Cutaneous T-cell lymphoma: roles for chemokines and chemokine receptors. J Invest Dermatol 2009;129:1115-1119.
11. Fujii K. New therapies and immunological findings in cutaneous T-cell lymphoma. Front Oncol 2018;8:198.
12. Lu D, Duvic M, Medeiros LJ, Luthra R, Dorfman DM, Jones D. The T-cell chemokine receptor CXCR3 is expressed highly in low-grade mycosis fungoides. Am J Clin Pathol 2001;115:413-421.

13. Nikoo A. The expression of CXCR3 and CD30 in mycosis fungoides. Arch Iran Med 2012;15:146-150.
14. Kuo PT, Zeng Z, Salim N, Mattarollo S, Wells JW, Leggatt GR. The role of CXCR3 and its chemokine ligands in skin disease and cancer. Front Med (Lausanne) 2018;5:271.
15. Sugaya M. Chemokines and cutaneous lymphoma. J Dermatol Sci 2010;59:81-85.
16. Sugaya M, Morimura S, Suga H, Kawaguchi M, Miyagaki T, Ohmatsu H, et al. CCR4 is expressed on infiltrating cells in lesional skin of early mycosis fungoides and atopic dermatitis. J Dermatol 2015;42:613-615.
17. Yoshie O, Matsushima K. CCR4 and its ligands: from bench to bedside. Int Immunol 2015;27:11-20.
18. Wu M, Fang H, Hwang ST. Cutting edge: CCR4 mediates antigen-primed T cell binding to activated dendritic cells. J Immunol 2001;167:4791-4795.
19. Jour G, Aung PP, Merrill ED, Curry JL, Tetzlaff MT, Nagarajan P, et al. Differential expression of CCR4 in primary cutaneous gamma/delta (γδ) T cell lymphomas and mycosis fungoides: significance for diagnosis and therapy. J Dermatol Sci 2018;89:88-91.
20. Duvic M, Pinter-Brown LC, Foss FM, Sokol L, Jorgensen JL, Challagundla P, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. Blood 2015;125:1883-1889.
21. Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J Clin Oncol 2014;32:1157-1163.
22. Perera LP, Zhang M, Nakagawa M, Petrus MN, Maeda M, Kadin ME, et al. Chimeric antigen receptor modified T cells that target chemokine receptor CCR4 as a therapeutic modality for T-cell malignancies. Am J Hematol 2017;92:892-901.
23. Fierro MT, Comessatti A, Quaglino P, Ortoncelli M, Osella Abate S, Ponti R, et al. Expression pattern of chemokine receptors and chemokine release in inflammatory erythroderma and Sézary syndrome. Dermatology 2006;213:284-292.
24. Notohamiprodjo M, Segerer S, Huss R, Hildebrandt B, Soler D, Djafarzadeh R, et al. CCR10 is expressed in cutaneous T-cell lymphoma. Int J Cancer 2005;115:641-647.
25. Fujita Y, Abe R, Sasaki M, Honda A, Furuichi M, Asano Y, et al. Presence of circulating CCR10+ T cells and elevated serum CTACK/CCL27 in the early stage of mycosis fungoides. Clin Cancer Res 2006;12:2670-2675.
26. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. FEBS J 2018;285:2944-2971.
27. Murakami T, Cardones AR, Finkelstein SE, Restifo NP, Klaunberg BA, Nestle FO, et al. Immune evasion by murine melanoma mediated through CC chemokine receptor-10. J Exp Med 2003;198:1337-1347.
28. Sokolowska-Wojdylo M, Wenzel J, Gaffal E, Lenz J, Speuser P, Erdmann S, et al. Circulating clonal CLA(+) and CD4(+) T cells in Sezary syndrome express the skin-homing chemokine receptors CCR4 and CCR10 as well as the lymph node-homing chemokine receptor CCR7. Br J Dermatol 2005;152:258-264.
29. Picchio MC, Scala E, Pomponi D, Caprini E, Frontani M, Angelucci I, et al. CXCL13 is highly produced by Sézary cells and enhances their migratory ability via a synergistic mechanism involving CCL19 and CCL21 chemokines. Cancer Res 2008;68:7137-7146.
30. Daggett RN, Kurata M, Abe S, Onishi I, Miura K, Sawada Y, et al. Expression dynamics of CXCL12 and CXCR4 during the progression of mycosis fungoides. Br J Dermatol 2014;171:722-731.
31. Ping YF, Yao XH, Jiang JY, Zhao LT, Yu SC, Jiang T, et al. The chemokine CXCL12 and its receptor CXCR4 promote glioma stem cell-mediated VEGF production and tumour angiogenesis via PI3K/AKT signalling. J Pathol 2011;224:344-354.
32. Miyagaki T, Sugaya M, Suga H, Ohmatsu H, Fujita H, Asano Y, et al. Increased CCL18 expression in patients with cutaneous T-cell lymphoma: association with disease severity and prognosis. J Eur Acad Dermatol Venereol 2013;27:e60-e67.
33. Saed G, Fivenson DP, Naidu Y, Nickoloff BJ. Mycosis fungoides exhibits a Th1-type cell-mediated cytokine profile whereas Sezary syndrome expresses a Th2-type profile. J Invest Dermatol 1994;103:29-33.
34. Papadavid E, Economidou J, Psarra A, Kapsimali V, Mantzana V, Antoniou C, et al. The relevance of peripheral blood T-helper 1 and 2 cytokine pattern in the evaluation of patients with mycosis fungoides and Sézary syndrome. Br J Dermatol 2003;148:709-718.
35. Vowels BR, Lessin SR, Cassin M, Jaworsky C, Benoit B, Wolfe JT, et al. Th2 cytokine mRNA expression in skin in cutaneous T-cell lymphoma. J Invest Dermatol 1994;103:669-673.
36. Miyagaki T, Sugaya M. Immunological milieu in mycosis fungoides and Sézary syndrome. J Dermatol 2014;41:11-18.
37. Hsi AC, Lee SJ, Rosman IS, Carson KR, Kelley A, Viele V, et al. Expression of helper T cell master regulators in inflammatory dermatoses and primary cutaneous T-cell lymphomas: diagnostic implications. J Am Acad Dermatol 2015;72:159-167.
38. Guenova E, Watanabe R, Teague JE, Desimone JA, Jiang Y, Dowlatshahi M, et al. TH2 cytokines from malignant cells suppress TH1

responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma. Clin Cancer Res 2013;19:3755-3763.
39. Spaccarelli N, Rook AH. The use of interferons in the treatment of cutaneous T-cell lymphoma. Dermatol Clin 2015;33:731-745.
40. Urosevic M, Fujii K, Calmels B, Laine E, Kobert N, Acres B, et al. Type I IFN innate immune response to adenovirus-mediated IFN-gamma gene transfer contributes to the regression of cutaneous lymphomas. J Clin Invest 2007;117:2834-2846.
41. Vieyra-Garcia P, Crouch JD, O'Malley JT, Seger EW, Yang CH, Teague JE, et al. Benign T cells drive clinical skin inflammation in cutaneous T cell lymphoma. JCI Insight 2019;4:e124233.
42. Ghione P, Moskowitz AJ, De Paola NEK, Horwitz SM, Ruella M. Novel immunotherapies for T cell lymphoma and leukemia. Curr Hematol Malig Rep 2018;13:494-506.
43. Assaf C, Hwang ST. Mac attack: macrophages as key drivers of cutaneous T-cell lymphoma pathogenesis. Exp Dermatol 2016;25:105-106.
44. Sugaya M, Miyagaki T, Ohmatsu H, Suga H, Kai H, Kamata M, et al. Association of the numbers of CD163(+) cells in lesional skin and serum levels of soluble CD163 with disease progression of cutaneous T cell lymphoma. J Dermatol Sci 2012;68:45-51.
45. Furudate S, Fujimura T, Kakizaki A, Kambayashi Y, Asano M, Watabe A, et al. The possible interaction between periostin expressed by cancer stroma and tumor-associated macrophages in developing mycosis fungoides. Exp Dermatol 2016;25:107-112.
46. Furudate S, Fujimura T, Kakizaki A, Hidaka T, Asano M, Aiba S. Tumor-associated M2 macrophages in mycosis fungoides acquire immunomodulatory function by interferon alpha and interferon gamma. J Dermatol Sci 2016;83:182-189.
47. Tanita K, Fujimura T, Sato Y, Lyu C, Kambayashi Y, Ogata D, et al. Bexarotene reduces production of CCL22 from tumor-associated macrophages in cutaneous T-cell lymphoma. Front Oncol 2019;9:907.
48. Kim YH, Tavallaee M, Sundram U, Salva KA, Wood GS, Li S, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. J Clin Oncol 2015;33:3750-3758.
49. Wu X, Schulte BC, Zhou Y, Haribhai D, Mackinnon AC, Plaza JA, et al. Depletion of M2-like tumor-associated macrophages delays cutaneous T-cell lymphoma development in vivo. J Invest Dermatol 2014;134:2814-2822.
50. Wu X, Hsu DK, Wang KH, Huang Y, Mendoza L, Zhou Y, et al. IL-10 is overexpressed in human cutaneous T-cell lymphoma and is required for maximal tumor growth in a mouse model. Leuk Lymphoma 2019;60:1244-1252.
51. Russ A, Hua AB, Montfort WR, Rahman B, Riaz IB, Khalid MU, et al. Blocking "don't eat me" signal of CD47-SIRPα in hematological malignancies, an in-depth review. Blood Rev 2018;32:480-489.
52. Folkes AS, Feng M, Zain JM, Abdulla F, Rosen ST, Querfeld C. Targeting CD47 as a cancer therapeutic strategy: the cutaneous T-cell lymphoma experience. Curr Opin Oncol 2018;30:332-337.
53. Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E. In search of definitions: cancer-associated fibroblasts and their markers. Int J Cancer 2020;146:895-905.
54. Miyagaki T, Sugaya M, Suga H, Morimura S, Ohmatsu H, Fujita H, et al. Low herpesvirus entry mediator (HVEM) expression on dermal fibroblasts contributes to a Th2-dominant microenvironment in advanced cutaneous T-cell lymphoma. J Invest Dermatol 2012;132:1280-1289.
55. Murota H, Lingli Y, Katayama I. Periostin in the pathogenesis of skin diseases. Cell Mol Life Sci 2017;74:4321-4328.
56. Takahashi N, Sugaya M, Suga H, Oka T, Kawaguchi M, Miyagaki T, et al. Thymic stromal chemokine TSLP acts through Th2 cytokine production to induce cutaneous T-cell lymphoma. Cancer Res 2016;76:6241-6252.
57. Miyagaki T, Sugaya M, Fujita H, Ohmatsu H, Kakinuma T, Kadono T, et al. Eotaxins and CCR3 interaction regulates the Th2 environment of cutaneous T-cell lymphoma. J Invest Dermatol 2010;130:2304-2311.
58. Berger CL, Hanlon D, Kanada D, Dhodapkar M, Lombillo V, Wang N, et al. The growth of cutaneous T-cell lymphoma is stimulated by immature dendritic cells. Blood 2002;99:2929-2939.
59. Schwingshackl P, Obermoser G, Nguyen VA, Fritsch P, Sepp N, Romani N. Distribution and maturation of skin dendritic cell subsets in two forms of cutaneous T-cell lymphoma: mycosis fungoides and Sézary syndrome. Acta Derm Venereol 2012;92:269-275.
60. Ammendola M, Sacco R, Sammarco G, Luposella M, Patruno R, Gadaleta CD, et al. Mast cell-targeted strategies in cancer therapy. Transfus Med Hemother 2016;43:109-113.
61. Rabenhorst A, Schlaak M, Heukamp LC, Förster A, Theurich S, von Bergwelt-Baildon M, et al. Mast cells play a protumorigenic role in primary cutaneous lymphoma. Blood 2012;120:2042-2054.
62. Eder J, Rogojanu R, Jerney W, Erhart F, Dohnal A, Kitzwögerer M, et al. Mast cells are abundant in primary cutaneous T-cell lymphomas: results from a computer-aided quantitative immunohistological study. PLoS One 2016;11:e0163661.
63. Geskin LJ, Akilov OE, Kwon S, Schowalter M, Watkins S, Whiteside TL, et al. Therapeutic reduction of cell-mediated immunosuppres-

sion in mycosis fungoides and Sézary syndrome. Cancer Immunol Immunother 2018;67:423-434.
64. Maliniemi P, Laukkanen K, Väkevä L, Dettmer K, Lipsanen T, Jeskanen L, et al. Biological and clinical significance of tryptophan-catabolizing enzymes in cutaneous T-cell lymphomas. Oncoimmunology 2017;6:e1273310.
65. Querfeld C, Leung S, Myskowski PL, Curran SA, Goldman DA, Heller G, et al. Primary T cells from cutaneous T-cell lymphoma skin explants display an exhausted immune checkpoint profile. Cancer Immunol Res 2018;6:900-909.
66. Kantekure K, Yang Y, Raghunath P, Schaffer A, Woetmann A, Zhang Q, et al. Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. Am J Dermatopathol 2012;34:126-128.
67. Samimi S, Benoit B, Evans K, Wherry EJ, Showe L, Wysocka M, et al. Increased programmed death-1 expression on CD4+ T cells in cutaneous T-cell lymphoma: implications for immune suppression. Arch Dermatol 2010;146:1382-1388.
68. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature 2017;545:495-499.
69. Fujimura T, Aiba S. Significance of immunosuppressive cells as a target for immunotherapies in melanoma and non-melanoma skin cancers. Biomolecules 2020;10:1087.
70. Leuchte K, Schlaak M, Stadler R, Theurich S, von Bergwelt-Baildon M. Innovative treatment concepts for cutaneous T-cell lymphoma based on microenvironment modulation. Oncol Res Treat 2017;40:262-269.
71. Peranzoni E, Donnadieu E. Improving efficacy of cancer immunotherapy through targeting of macrophages. Hum Vaccin Immunother 2019;15:189-192.
72. Wu X, Singh R, Hsu DK, Zhou Y, Yu S, Han D, et al. A small molecule CCR2 antagonist depletes tumor macrophages and synergizes with anti-PD-1 in a murine model of cutaneous T-cell lymphoma (CTCL). J Invest Dermatol 2020;140:1390-1400.e4.