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Perspectives

Feeding the fire: How inflammation may sustain mycosis fungoides and Sézary syndrome – and options to disrupt

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Abstract

Cutaneous T-cell lymphomas (CTCL), including mycosis fungoides (MF) and Sézary syndrome (SS), are histopathologically characterized by a prominent inflammatory infiltrate, accompanying the malignant cells in the skin. This infiltrate contributes to diagnostic uncertainty and appears to support the persistence of malignant T cells. Growing evidence supports an inflammation-driven disease model, in which cytokine networks, microbial triggers, and direct cellular interactions shape a tumor-permissive microenvironment. In this perspective, we discuss how established skin-directed therapies achieve clinical benefits not only by directly affecting malignant cells, but also by remodeling the lesional immune milieu and reducing supportive inflammatory infiltrates. We also highlight the importance of targeting microenvironmental signaling pathways, focusing on the OX40/OX40L costimulatory axis and JAK/STAT pathway dysregulation as therapeutic targets. Overall, we propose that integrating tumor-directed therapy with approaches that modify the inflammatory niche may offer a rational strategy to improve long-term disease control in MF/SS.

Key words: Cutaneous T-cell lymphoma, Mycosis fungoides, Sézary syndrome, inflammatory infiltrate, tumor microenvironment

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1.0 Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of extranodal non-Hodgkin lymphomas that arise in the skin and often share clinical similarities with common inflammatory dermatoses such as eczema, psoriasis, or chronic dermatitis in their early presentation [1–3]. Histopathologically, lesions are characterized not only by the presence of malignant T cells, but also by a significant inflammatory infiltrate of benign lymphocytes and other immune cells. This infiltrate contributes to the diagnostic challenge and reflects the underlying inflammatory microenvironment [1, 4, 5].

This perspective article aims to discuss how established skin-directed and immunomodulatory therapies, including phototherapy, topical corticosteroids, interferons, retinoids, and radiotherapy, may modulate the inflammatory tumor microenvironment by reducing microenvironmental signals that support the persistence and survival of malignant T cells, while potentially restoring a more effective anti-tumor immune balance. Building on this concept, we explore emerging therapeutic strategies, such as JAK (Janus kinase) inhibitors, OX40/

OX40L pathway blockade and other immunomodulators, which may target the same pathogenic mechanisms more selectively and effectively.

1.1 The role of inflammation in driving tumor progression in MF/SS and its potential inhibition

Mycosis fungoides and Sézary syndrome are diseases in which chronic inflammation contributes to tumor progression. The proliferation and survival of malignant T cells are significantly influenced by their interactions with the surrounding microenvironment. Krejsgaard et al. described this relationship as "malignant inflammation", characterized by a complex interplay of cytokine signaling and cellular interactions that create a pro-tumorigenic inflammatory environment [6]. In the early stages of mycosis fungoides, the cutaneous infiltrate is dominated by reactive $CD8^+$ cytotoxic T cells and Th1-polarized $CD4^+$ T cells, which may contribute to tumor immune surveillance. However, as the disease progresses, the immune landscape gradually shifts towards a Th2-dominant and immunosuppressive phenotype [2–5, 7, 8]. This immunological shift transforms a protective inflammatory response into a self-sustaining lymphocytic microenvironment, where malignant and benign T cells interact to stimulate disease activity [4–6]. Understanding the mechanisms that drive and sustain this process is essential for explaining how current therapies achieve remission by modulating the lesional immune milieu, as well as for developing future treatment strategies [9–12].

2.0 Skin-directed therapies

Current therapeutic strategies for MF/SS are primarily directed at controlling the malignant T-cell clone and improving clinical symptoms. Increasing evidence suggests that several established therapies, particularly skin-directed treatments, may additionally exert therapeutic effects by reshaping the inflammatory tumor microenvironment.

Phototherapy and topical corticosteroids are widely used as first-line treatments for early-stage disease, achieving clinical benefit through immunomodulatory mechanisms. These therapies highlight the importance of targeting the inflammatory milieu that supports the survival of malignant T cells.

2.1 Corticosteroids

Topical corticosteroids are widely used as first-line skin-directed therapy for early-stage mycosis fungoides, as recommended by international consensus guidelines [13]. However, data specifically addressing their molecular effects in MF are limited, and the mechanisms described below are largely inferred from their established immunomodulatory actions in other inflammatory settings.

Mechanistically, glucocorticoids are known to exert broad immunomodulatory effects through binding to cytoplasmic glucocorticoid receptors, which translocate to the nucleus and regulate inflammatory gene expression predominantly through transrepression of key transcription factors such as NF-κB and AP-1, while also inducing anti-inflammatory mediators including annexin A1 (lipocortin-1) and IL-10, thereby inhibiting phospholipase A2, cyclooxygenase-2 and inducible nitric oxide synthase and reducing the production of pro-inflammatory cytokines [14–16].

In addition, glucocorticoids promote apoptosis of T lymphocytes and other inflammatory cells and impair leukocyte recruitment by downregulating endothelial adhesion molecules such as ICAM-1 and E-selectin, while their vasoconstrictive and antimitotic effects further contribute to the resolution of cutaneous inflammation [14–17]. In early-stage MF, clinical series and retrospective analyses have demonstrated substantial activity of potent topical corticosteroids as monotherapy. In a prospective cohort of patch- and early plaque-stage MF, high response rates and complete remissions were observed with class I steroids, establishing their effectiveness in skin-limited disease [18, 19].

More recently, Kartan et al. reported in a retrospective analysis that topical corticosteroid monotherapy was associated with reductions in body surface area and mSWAT (Modified Severity-Weighted Assessment Tool) scores in early-stage MF, with complete responses observed in a subset of patients [20].

Taken together, these mechanisms suggest that topical corticosteroids, beyond symptomatic control, reduce lymphocytic infiltrates in MF lesions and may thereby likely diminish the inflammatory support that sustains the malignant microenvironment.

2.2 Phototherapy

Phototherapy – most commonly psoralen plus ultraviolet A (PUVA) and narrow-band ultraviolet B (NB-UVB) – is recommended as a first-line skin-directed treatment for early-stage MF in international guidelines [21]. Although both modalities are clinically effective, they differ substantially in their molecular and cellular mechanisms of action. As the effects of PUVA on the tumor microenvironment have been more extensively characterized, the following section focuses primarily on PUVA.

PUVA has been used therapeutically in mycosis fungoides since its first description in MF patients by Gilchrest in 1976 [22] and has since been shown to induce durable remissions, including long-term complete responses in a subset of early-stage patients [23]. In a randomized clinical trial, low-dose, low-frequency PUVA induced complete remission in approximately 70% of patients with early-stage MF and was associated with a marked reduction of lesional lymphocytic infiltrates and malignant T-cell clonality [24].

Mechanistically, PUVA exerts both proapoptotic and immunomodulatory effects: UV-induced DNA photoproducts trigger apoptosis of epidermotropic T cells, while broad transcriptional changes in keratinocytes and immune cells reshape the inflammatory milieu of lesional skin [9].

Accumulating evidence suggests that phototherapy kills malignant cells directly [25], and may also disrupt the microenvironmental support on which these cells depend. In MF skin, malignant T cells cluster with benign T cells and CCL18 expressing dendritic cells to form „inflammatory synapse networks“; PUVA therapy was shown to dismantle these cell–cell interactions by inducing turnover of benign infiltrating T cells, a change that correlated with clinical improvement [5]. Remarkably, the infiltrate – which prior to therapy is enriched for Th2-associated chemokines – can shift toward a Th1-skewed profile after PUVA, with increased production of CXCL9, CXCL10 and CXCL11 [5]. This aligns with earlier findings that PUVA promotes a Th2 to Th1 immune rebalancing in lesions, potentially restoring antitumor immune function [7]. Phototherapy has

been shown to reduce the expression of IL-9 and STAT3/STAT5 in mycosis fungoides lesions. These pathways are involved in the survival of malignant T cells [26]. In addition, gene expression profiling and immunohistochemical analyses have shown that mycosis fungoides lesions exhibit a baseline deficiency in epidermal type I interferon production, which is restored by PUVA therapy [27].

Together, these observations support the concept that both, the direct effects of phototherapy on malignant T cells and its ability to reduce and reprogram the inflammatory infiltrate contribute to the therapeutic response observed with phototherapy, consistent with the broader model of "malignant inflammation".

2.3 Radiotherapy

Radiotherapy represents an established treatment modality for cutaneous T-cell lymphoma, particularly for localized lesions and, in selected patients with more extensive disease, total skin electron beam therapy (TSEBT). Given the high radiosensitivity of lymphocytes, even low doses of radiation can achieve effective local disease control with acceptable toxicity profiles [28, 29]. Electron beam therapy is widely used in MF/SS because electrons provide a favorable dose distribution for cutaneous disease, delivering the highest dose within the target tissue while minimizing radiation exposure of deeper structures. Photon-based approaches (e.g., X-rays) may be considered when greater penetration or specific anatomical coverage is required [28, 29].

Radiotherapy induces DNA damage, including DNA double-strand breaks, which can lead to micronuclei formation and cytosolic DNA accumulation. In other cancer models, these processes have been shown to activate the cGAS–STING pathway, resulting in type I interferon production and enhanced anti-tumor immune responses [30–32].

However, whether these immunostimulatory mechanisms contribute to therapeutic responses in MF/SS remains unclear.

Beyond direct cytotoxic effects, low-dose radiotherapy has been reported in other tumor entities (highly metastatic lung adenocarcinoma tumors) to exert immunomodulatory effects, including macrophage polarization, modulation of immune cell trafficking, and enhancement of immune effector functions [33]. The extent to which these mechanisms apply to MF/SS requires further investigation. In addition, radiotherapy may reduce the inflammatory infiltrate within lesions, potentially disrupting microenvironmental signals that support malignant T-cell persistence.

Together, these observations provide a rationale for investigating the potential role of radiotherapy-induced tumor microenvironment modulation in MF/SS, although direct evidence for such effects remains limited.

3.0 Interferon

Interferon-α is an established systemic treatment for MF/SS and is included in current treatment guidelines. As interferon-α represents one of the most frequently used combination partners for PUVA in MF, its impact on the tumor microenvironment deserves particular attention. Its immunomodulatory effects include activation of $CD8^+$ T cells and NK cells, upregulation of MHC class I expression on malignant lymphocytes, and attenuation of the Th2-skewed immune milieu [34].

In addition, Furudate et al. demonstrated that IFN-α modulates tumor-associated macrophages by reducing the production of CCL17 and CCL18 while increasing the Th1-associated chemokines CXCL10 and CXCL11, suggesting a shift toward a more antitumor immune microenvironment [35].

4.0 Retinoids

Besides interferon-α, retinoids – particularly bexarotene – represent another well-established combination partner for PUVA in the treatment of MF. Bexarotene is a third-generation, retinoid X receptor (RXR)-selective retinoid approved for the treatment of both early- and advanced-stage CTCL. While the clinical efficacy of this combination has long been recognized, recent evidence suggests that part of its therapeutic benefit may also be mediated through modulation of the tumor microenvironment.

Tanita et al. demonstrated that bexarotene suppresses the production of CCL22 by M2-polarized tumor-associated macrophages, thereby reducing the recruitment of $CCR4^+$ malignant T cells, regulatory T cells, and Th2 cells to lesional skin. These findings indicate that, beyond its direct effects on malignant T cells, bexarotene may contribute to a less immunosuppressive and more antitumor immune microenvironment [36].

5.0 Local and systemic chemotherapy

Topical and systemic chemotherapeutic approaches have long been part of the therapeutic armamentarium for cutaneous T-cell lymphoma, although their role differs substantially according to disease stage and treatment setting.

Chlormethine (2-chloro-N-(2-chloroethyl)-N-methylethan-1-amine, mechlorethamine) is an alkylating agent with potent antiproliferative activity, and its use in mycosis fungoides was first described in 1959 [37, 38]. As a topical formulation, chlormethine gel is currently recommended as a first-line treatment for early-stage disease (stages IA–IIA) [13]. Its cytotoxic effects are mediated by DNA alkylation, which induces DNA damage and ultimately leads to cell death [38, 39]. Notably, contact dermatitis occurs in more than 50% of treated patients [13]. An association between the development of contact dermatitis and treatment response has been reported, suggesting that this reaction may serve as a clinical predictor of response [40].

This may be mechanistically relevant because MF lesions are shaped by close interactions among keratinocytes, Langerhans cells, and malignant T cells. Specifically, a chlormethine-induced delayed-type hypersensitivity reaction can shift the local immune milieu from a Th2- toward a Th1-dominated response. This shift promotes the apoptosis of malignant T cells, thereby driving disease regression [38].

To contextualize the clinical value of such skin-directed approaches, it is important to note the limitations of systemic alternatives. In fact, systemic chemotherapy, whether administered as a single agent or in combination, has generally shown only limited durability of disease control in MF. It is therefore usually reserved for advanced disease or for patients in whom other therapeutic options have been exhausted [13, 41, 42]. This notable contrast underscores the critical need for effective and durable topical treatments like chlormethine in early-stage disease to delay or avoid the necessity of systemic interventions.

6.0 Antibiotic therapy

The rationale for antibiotic therapy in MF or SS is supported by increasing evidence that *Staphylococcus aureus* colonization contributes to disease progression**.** Colonization and infection with *Staphylococcus aureus* are common in patients with MF or SS [43, 44]. Notably, patients with Sézary syndrome exhibit higher rates of *S. aureus* colonization compared with patients with non-erythrodermic mycosis fungoides [43].

For several decades, enterotoxin-producing *S. aureus* has been suspected to play a key role in the pathogenesis [45–47]. This hypothesis was further supported by observations demonstrating that antibiotic therapy not only suppressed clinical disease activity but also reduced the proportion of malignant T cells in skin lesions colonized by enterotoxin-producing *S. aureus* in patients with advanced MF/SS [48].

Additional evidence from mouse models strengthens this concept, showing that animals living in a germ-free environment failed to develop fulminant malignant disease [49]. In another murine model, topical triple antibiotic treatment significantly delayed tumor onset and growth and prolonged survival [50].

Several studies have begun to elucidate the mechanisms by which *Staphylococcus aureus* and its enterotoxins contribute to malignant T-cell expansion in MF or SS.

Woetmann et al. showed that non-malignant T cells enhance proliferation of the malignant cells in a staphylococcal enterotoxin- and MHC class II–dependent manner [51].

Willerslev-Olsen et al. demonstrated that Staphylococcal enterotoxin A (SEA) activates signal transducer and activator of transcription 3 (STAT3) and induces interleukin-17 expression in malignant T cells when co-cultured with non-malignant T cells [52]. He further showed that *Staphylococcus aureus* and its enterotoxins enhance the expression of the oncogenic microRNA (miRNA) 155 (miR-155) [53].

Zeng et al. demonstrated that upon exposure to patient-derived *S. aureus* and its enterotoxin, keratinocytes stimulate IL-2Rγ/JAK3-dependent proliferation of malignant and nonmalignant T cells in an environment with nonmalignant T cells [54].

Gluud et al. demonstrated that SE-producing *S. aureus* promotes skin barrier impairment in CTCL through cytokine-driven, JAK-dependent repression of structural proteins in keratinocytes [55].

Staphylococcus aureus enterotoxins can further induce drug resistance in primary malignant T cells. Using multimodal single-cell sequencing, they identified activation of T-cell receptor (TCR), NF-κB, and JAK/STAT signaling pathways, which have been associated with therapeutic resistance, as potential mediators of enterotoxin-induced drug resistance [56]. It has been demonstrated that treatment with NB-UVB in MF patients is associated with a significant post-treatment reduction of *Staphylococcus aureus* in lesional skin [57].

Furthermore, the findings of a murine model suggest that combining phototherapy with targeted antimicrobial strategies could provide twofold benefits: direct tumor cell cytotoxicity and disruption of bacterial-mediated resistance mechanisms [50].The importance of the skin microbiome is further supported by observations that therapeutic interventions other than antibiotics may also modulate bacterial dysbiosis. Complementing these findings, Chrisman et al. showed that radiation therapy not only eliminates lesions through induction of apoptosis, but also promotes restoration of the skin barrier and recolonization with bacterial taxa associated with a healthy skin microbiome [58].

Taken together, the data underscore a central role for *Staphylococcus aureus*–driven immune modulation in MF and SS pathogenesis and support microbial targeting as an integral component of effective therapeutic strategies.

Indeed, various clinical studies have indicated that, under certain conditions, treatment with antibiotics ameliorates skin symptoms, particularly in patients with Sézary syndrome or erythrodermic mycosis fungoides [43, 45, 47, 48, 59].

7.0 Emerging immunomodulatory strategies target inflammatory signaling

Building on the concept that the pathogenesis of MF/SS is driven by inflammation, emerging therapies such as Janus kinase (JAK) inhibitors and agents that target the OX40/OX40L pathway aim to disrupt cytokine-driven survival signals and T-cell activation more selectively within the tumor microenvironment. These approaches may complement established therapies.

7.1 OX40/OX40L blockade

OX40 (CD134) is a costimulatory receptor of the TNF receptor superfamily that is upregulated on activated $CD4^+$ and $CD8^+$ T cells. Its ligand, OX40L (CD252), is mainly expressed by antigen-presenting cells, including dendritic cells, B cells, and macrophages. Engagement of OX40 by OX40L enhances T-cell proliferation, survival, and effector functions such as cytokine production [60–62]. In MF/SS, both OX40 and OX40L are expressed in an aberrant manner on both malignant and reactive T cells within the tumor microenvironment. This suggests that this axis may contribute to disease progression by promoting pathogenic T-cell activation. Guglielmo et al. recently reviewed this concept in detail [63].

Kawana et al. demonstrated the active involvement of OX40–OX40L axis in the pathophysiology of MF and SS [64]. They analyzed the mRNA expression of both molecules and observed markedly higher levels in lesional skin than in the healthy controls. OX40 expression was associated with poorer disease-specific survival. They also observed that CTCL cell lines expressed both molecules on their surface and that proliferation could be reduced by blocking either OX40 or OX40L with neutralizing antibodies. Furthermore, in a xenograft mouse model, treatment with either antibody significantly slowed tumor growth. Taken together, these observations suggest that interfering with OX40–OX40L interactions could provide a new therapeutic strategy for MF/SS.

Therapeutically, OX40-targeting strategies are already being explored in inflammatory skin diseases such as atopic dermatitis, where OX40-blocking antibodies—including rocatinlimab [65] and amlitelimab [66] have demonstrated reductions in pathogenic T-cell activation and improvements in inflammatory biomarkers in early clinical trials [63]. These developments highlight the potential relevance of OX40 pathway modulation for MF/SS and support ongoing interest in evaluating this axis as a future therapeutic target.

7.2 JAK/STAT inhibition

The JAK/STAT signaling pathway plays a key role in regulating immune responses and inflammation and its dysregulation is a well-recognized feature

of cutaneous T-cell lymphomas. Somatic mutations in JAK1, JAK3, STAT3 and STAT5B, as well as copy-number gains affecting JAK2, STAT3 and STAT5B, lead to constitutive activation of downstream proliferative and anti-apoptotic signaling in malignant T cells [67]. An integrative review of MF/SS highlights persistent STAT3 and STAT5 activation as key molecular features associated with disease progression and therapeutic response [68].

These findings highlight the dependence of malignant T cells on JAK/STAT-mediated survival signaling. This signaling is further amplified by cytokines produced within the tumor microenvironment.

An analysis of leukemic CTCL showed frequent copy number gains and hyperactivation of STAT3 and STAT5. It has been demonstrated that pharmacological inhibition of upstream kinases, particularly p21-activated kinase (PAK), which promotes STAT3/5 activation, as well as direct targeting of STAT3/5 signaling reduced proliferation and induced apoptosis of malignant T cells. In an intradermal xenograft model, PAK inhibition significantly decreased tumor growth, supporting STAT3/5-dependent signaling as a potential therapeutic target in advanced disease [69].

Dey et al. investigated IQDMA, a small-molecule inhibitor targeting the CDC42–PAK2 signaling axis, as a novel targeted agent in CTCL and showed that it disrupts STAT3/5 signaling through collapse of the CDC42–PAK2–STAT nuclear transport axis, thereby suppressing tumor growth [70].

Other preclinical studies demonstrate that the JAK1/2 inhibitor ruxolitinib effectively suppresses STAT phosphorylation, reduces proliferation, and induces apoptosis in CTCL cell lines [71]. These findings provided a basis for clinical testing.

In a biomarker-driven phase 2 study of ruxolitinib in relapsed/refractory T-cell lymphomas, limited activity was observed in MF, with only one response among seven MF patients, whereas more durable responses occurred in tumors harboring JAK/STAT pathway mutations or phosphorylated STAT3 [72].

A recent systematic review summarizing thirteen published reports on JAK inhibitors in CTCL found response rates ranging from 11–35% in clinical studies, with 14–45% in MF. The review also described rare cases of *de novo* or relapsed CTCL occurring in patients receiving JAK inhibitors for autoimmune diseases, indicating that JAK/STAT pathway inhibition may exert both therapeutic and potentially disease-promoting effects depending on the clinical and biological context [67].

A recent multicentre real-world study by Amitay-Laish et al. evaluated systemic JAK inhibitor use in 20 patients with MF/SS across different clinical settings, none of whom had received treatment primarily for lymphoma-directed therapy. The heterogeneous outcomes, including reports of disease progression, highlight the need for careful patient selection and further prospective evaluation of JAK inhibitors in MF/SS [73].

In their narrative review, Packer and Brunner concluded that although JAK inhibitors are established therapies in inflammatory and hematologic diseases, their use in CTCL remains investigational and will require biomarker-guided studies to identify patients whose tumors are truly dependent on JAK/STAT signaling [74].

7.3 Checkpoint inhibitors

The increasingly immunosuppressive tumor microenvironment in MF during disease progression is characterized by high PD-L1 expression and accumulation

of PD-1-expressing exhausted T cells. PD-1 blockade aims to restore T-cell activation and cytotoxic function, thereby enhancing antitumor immune surveillance. However, because PD-1 is also expressed by regulatory T cells and, in some cases, by the malignant T-cell clone itself, checkpoint inhibition may exert complex and potentially opposing effects within the tumor microenvironment, which may contribute to the comparatively lower clinical efficacy observed in CTCL compared with other malignancies [75].

A recent systematic review including 66 patients with refractory mycosis fungoides and Sézary syndrome suggests that immune checkpoint inhibitors, particularly pembrolizumab, may provide meaningful clinical benefit in selected patients. Overall, complete and partial responses were observed in 20% and 33% of patients, respectively, while treatment-related discontinuation due to adverse events was uncommon [76].

8.0 Tumor-directed therapies targeting the malignant clone

In parallel, several approved systemic therapies directly target malignant T cells. Brentuximab vedotin, an anti-CD30 antibody–drug conjugate, induces selective cytotoxicity in CD30-expressing cells and has demonstrated significant clinical efficacy in advanced disease [77, 78]. Mogamulizumab, a defucosylated anti-CCR4 monoclonal antibody, eliminates malignant CCR4-positive T cells through antibody-dependent cellular cytotoxicity while simultaneously depleting CCR4-expressing regulatory T cells, thereby reshaping the tumor microenvironment and potentially enhancing antitumor immune responses [79, 80].

Thus, whereas brentuximab vedotin primarily mediates direct cytotoxicity against the malignant clone, mogamulizumab combines direct antitumor activity with immunomodulatory effects on the tumor microenvironment. An overview of the principal therapeutic targets and mechanisms of action discussed above is provided in Fig. 1.

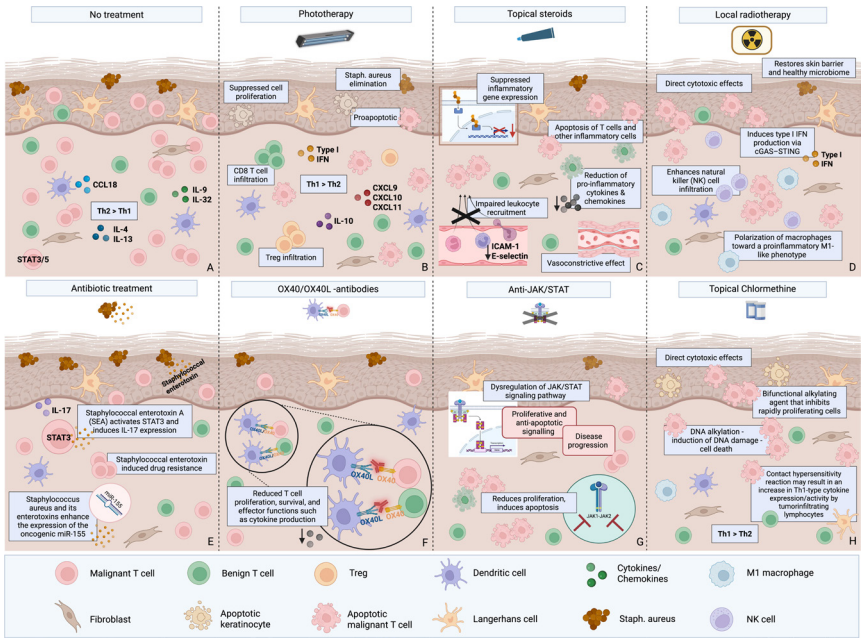

Figure 1. Overview of therapeutic targets and mechanisms of action affecting malignant cells and the inflammatory microenvironment in MF/SS (Created in https://BioRender.com).

9.0 Conclusion

The concept of malignant inflammation provides a framework for understanding cutaneous T-cell lymphoma as a disease sustained not only by malignant T cells but also by dynamic interactions with the surrounding immune microenvironment.

Increasing evidence indicates that cytokines and direct cell-cell interactions contribute to the persistence of malignant T cells and shape disease progression.

This perspective recognizes the tumor microenvironment as an active determinant of MF/SS pathogenesis, contributing to malignant T-cell persistence, immune dysregulation, and disease progression.

While current therapies target either malignant T cells or components of the inflammatory milieu, the extent to which simultaneous modulation of both compartments translates into improved clinical outcomes remains to be determined. Future studies should further define the reciprocal interactions between malignant and benign immune cells, identify biomarkers reflecting microenvironmental activity, and evaluate whether therapeutic strategies addressing both the malignant clone and its supportive microenvironment provide additional clinical benefit.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
Regarding the use of AI in the preparation of this manuscript, the authors declare the following: GPT.
Used for: Language, style and writing.
During the preparation of this work the authors used ChatGPT in order to enhance readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Data availability

All of the data that support the findings of this study are available in the main text.