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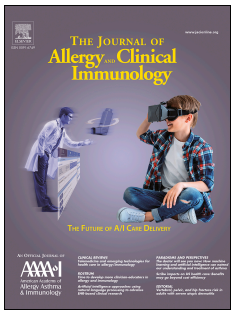

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T cells in the skin: lymphoma and inflammatory skin disease

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Conflict of interest

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Abstract

T cells are established contributors to the pathogenesis of atopic dermatitis (AD) and psoriasis, yet whether they are the key drivers or simply unwitting participants remains incompletely understood. Conversely, malignant T cells are the undisputed culprits of cutaneous T cell lymphoma (CTCL), a group of diseases that share key clinical, histopathological and molecular features with inflammatory skin disease (ISD). Here, we compare the pathogenesis of ISD and CTCL and discuss the resulting insights. Recurrent, skin-limited disease implicates skin-resident T cells (T_{RM}) in both ISD and CTCL. In CTCL, malignant T cells recruit benign T cells into inflammatory skin lesions, a disease-amplifying function also proposed for pathogenic T cells in ISD. Mechanistically, cytokines produced by malignant T cells in CTCL and by pathogenic T cells in ISD, respectively, are likely both necessary and sufficient to drive skin inflammation and pruritus, which in turn promotes skin barrier dysfunction and dysbiosis. Therapies for ISD target T cell effector functions but do not address the chronicity of disease while treatments for CTCL target malignant T cells but not primarily the symptoms of the disease. By integrating our understanding of ISD and CTCL, important insights into pathogenesis and therapy can be made which may improve the lives of sufferers of both disease groups.

1. What do we know?
   - *ISD and CTCL share key clinical and molecular features and T cells are at the heart of pathogenesis in both disease groups*
   - *ISD are increasingly well understood and amendable to targeted therapies whereas CTCL lacks efficient, let alone curative, therapeutic options.*
   - *Comparative analysis of ISD and CTCL provides insight into the pathogenesis of both disease groups*
2. What is still unknown?
   - *What is the role of T cell-derived cytokines in cutaneous manifestation and progression of CTCL? Can lessons from cytokine blockade in ISD be transferred to novel CTCL treatment approaches?*
   - *Curative approaches in CTCL aim at eradicating malignant (skin-resident) T cells. Can similar approaches be applied to ISD with the aim of curing, rather than suppressing disease?*
   - *In early stage CTCL, few clonal malignant T cells cause infiltration of large amounts of bystander T cells, which are necessary for clinical disease manifestation. Could a minor population of potentially auto-antigen-specific, pathogenic T cells cause disease in ISD via similar mechanisms as in CTCL?*
   - *The signals and pathways that govern (pathogenic) T cell activation in ISD remain incompletely understood. Can insights into oncogenic signaling in malignant CTCL cells be transferred to pathogenic T cells in ISD to open up new therapeutic targets and opportunities?*

Abbreviations

AD	Atopic dermatitis
AHR	Aryl hydrocarbon receptor
CTCL	Cutaneous T cell lymphoma
DC	Dendritic cell
EATL	Enteropathy-associated T cell lymphoma
ISD	Inflammatory skin disease
JAK	Janus kinase
MALT	Mucosa-associated lymphoid tissue lymphoma
MAPK	Mitogen-activated protein kinase
MF	Mycosis fungoides
MMAE	Monomethyl auristatin E
PUVA	Psoralen plus UVA
scRNA-seq	Single cell RNA sequencing
SOCS	Suppressor of cytokine signaling
SS	Sézary Syndrome
STAT	Signal transducer and activator of transcription proteins
T_{CM}	Central memory T cell
TCR	T cell receptor
T_H2	T helper type 2 cell
T_{RM}	Resident memory T cells
UVA	Ultraviolet light

Introduction

Chronic inflammatory skin diseases (ISDs) comprise a wide range of cutaneous disorders that clinically manifest in variable combinations of erythema, plaques, scaling, pruritus, and pain. ISDs also accompany a variety of histopathological features, including epidermal thickening, spongiosis, parakeratosis and, near universally, T cell infiltration. The two most common T cell driven-ISDs are atopic dermatitis (AD) and psoriasis and, for the purposes of this review, ISD will refer to AD and psoriasis unless otherwise specified. Cutaneous T cell lymphoma (CTCL) encompasses a similarly heterogeneous collection of T cell malignancies of the skin. Arguably the best understood variants of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS), which have distinct and overlapping phenotypes that are discussed in this review. ISD and CTCL demonstrate striking epidemiological, clinical, and molecular parallels and respond to similar treatments, despite being elicited by distinct causes. Drawing comprehensive parallels between ISDs and CTCL generates important insights into the pathogenesis of both disease groups that may both inform and inspire new therapeutic approaches.

Clinical, epidemiological, and genetic parallels between ISD and CTCL

Clinical parallels

ISD and CTCL, in particular MF, share many basic skin morphologies (Figure 1). Both may present as erythematous patches, papules, and plaques, whereas only CTCL may develop skin tumors(1-3). Secondary morphologies may be eczematous or papulosquamous in nature in both disease groups. Thus, AD and psoriasis are at the forefront of the clinical differential diagnosis of MF. Erythrodermic CTCL, mostly caused by SS, may resemble primary or secondary erythroderma, which can also be observed in both AD and psoriasis(4).

Certain clinical features are typical for CTCL and distinguish them from ISDs. For instance, CTCL patches may be hypopigmented or hyperpigmented. Postlesional hyper- or hypopigmentation also occurs in ISD, but typically only after the inflammatory component of the lesion has resolved. MF tends to occur in non-sun-exposed areas, which may help to distinguish it from typical AD lesions on the flexor surfaces and typical psoriasis lesions on the extensor aspects of the knees and elbows(1, 2). The clinical presentation of MF is generally more variable than that of chronic ISD and tends to change morphology more substantially over the course of the disease (e.g. development of tumors and ulcerations).

In terms of symptoms, lesions from both CTCL and ISDs, in particular AD and other forms of eczema, are often pruritic and pruritus is a key determinant of poor quality of life in both disease groups. Erythroderma in particular, either in SS or ISD, is associated with agonizing pruritus(1, 2).

Epidemiological and genetic parallels between ISD and CTCL

Patients with a history of ISD have an increased risk of developing CTCL(5). Psoriasis patients in particular have a strongly increased hazard ratio (up to HR >6)(6), but also severe AD is associated with non-Hodgkin-lymphoma, including CTCL(7, 8).Especially early stage CTCL can be misdiagnosed as ISD, given its clinical and histological similarities, and this might explain

part of the epidemiological connection. However, even when taking this bias into account, the epidemiological link remains strong and prompts the search for additional explanations. These include common genetic background, chronic inflammatory environment in the skin, and long-term side effects of ISD treatment, as discussed below.

The genetic background of both ISD and CTCL is increasingly well understood. Risk loci predisposing for psoriasis or AD are enriched for genes related to keratinocyte differentiation, innate immune signaling, cytokine mediated signaling, and T cell activation and differentiation(1, 9-11). Genetic alterations in CTCL comprise of copy number variations and single-nucleotide variants that affect similar pathways, particularly T cell receptor (TCR) signaling and the nuclear factor kappa B (NF-κB) pathway, the MAP kinase pathway, and JAK–STAT signaling(3, 12). At the single gene level, CTCL shares genetic alterations with both psoriasis and AD in the STAT3 gene (Figure 2). STAT3 is a key mediator of T cell responses to interleukins(13), underscoring the importance of cytokines in the pathogenesis of both disease groups.

Another putative mechanistic link between ISD and CTCL is chronic inflammation. Chronic inflammation can act as promotor of tumor development(14). Many cancers arise at sites of chronic infection or chronic inflammation(15), wherein inflammatory cells are thought to establish a microenvironment that drives the neoplastic process. Interestingly, in some murine models of CTCL, skin tumors only form in the setting of skin inflammation(16). Although the role of inflammation in driving CTCL in humans remains incompletely understood, links have been more firmly established in other types of lymphoma. Specifically, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, an indolent B-cell NHL arising in lymphoid infiltrates from H. pylori gastroduodenitis(17), and enteropathy-associated T cell lymphoma (EATL), a peripheral T cell lymphoma (PTCL) derived from intestinal intraepithelial lymphocytes of patients with longstanding celiac disease(18). In EATL, ongoing T cell activation and the inflammatory milieu in the intestinal epithelium causes the accumulation of genetic alterations in pathways related to lymphoma development. These include genes involved in cytokine signaling (*JAK1, JAK3, STAT3, STAT5B, SOCS1*), MAPK signaling (*BRAF, KRAS*), and chromatin modification (*CREBBP*), all of which are genetic vulnerabilities also found in CTCL. As in the case of ISD and CTCL, EATL shares a genetic background with its underlying inflammatory disease, celiac disease (e.g. variants in *TNFAIP3*)(18). Taken together, it is likely that ISD is linked to CTCL pathogenesis by shared underlying genetics and chronic T cell-driven skin inflammation(17).

Pathogenetic parallels between CTCL and ISD

T cells as major culprits in CTCL and ISD

T cells are, by definition, the cause of cutaneous pathology in CTCL but they also play a central role in ISD(1-3). Indeed, the capacity of malignant CTCL clones to recapitulate the full clinical picture and symptoms of eczema or psoriasis underscores the remarkable pathogenic potential of dysregulated T cells in skin inflammation. Further evidence for a critical involvement of T cells in ISD includes the efficacy of cyclosporine in its treatment(19-21) and the HLA-association of disease(22, 23). Further, T cells make up a substantial part of the inflammatory infiltrate, their presence correlates with disease severity(24) and targeting T cell-derived proinflammatory cytokines efficiently restores skin homeostasis in AD and psoriasis(1, 2). Critically, a large body of animal research have demonstrated the sufficiency of T cells to drive AD- and psoriasis-like

phenotypes in mice and established cytokines as central to T cell effector function in inflammatory disease(25, 26). Thus, T cells may be proposed as the critical node of ISD, regardless of underlying genetics and other pathogenetic factors such as damage to the epithelium or skin dysbiosis(1-3).

Skin resident T cells in CTCL and ISD

Adult human skin harbors billions of nonrecirculating resident memory T (T_{RM}) cells(27, 28). Most T_{RM} in human skin are dermal CD4+ T helper cells, while the epidermis contains both CD4+ and CD8+ T_{RM}. T_{RM} are generated as a consequence of local skin infection, may persist in the absence of antigen, and provide rapid immune protection against local reinfection(29). Both CD4+ and CD8+ T_{RM} are intricately linked to pathogenesis of both CTCL and ISD.

Translational studies in CTCL patients have led to a model in which malignant T cells in MF express a T_{RM} phenotype and a skin-homing central memory (T_{CM}) phenotype in Sézary syndrome, respectively(28, 30). This model provides an elegant explanation for key clinical observations. The skin-sessile T_{RM} phenotype of malignant MF cells explains why most patients have skin-limited disease with well-demarcated, stable inflammatory skin lesions that resolve under topical therapy but recur at the same location if treatment is stopped(28). Conversely, the T_{CM} phenotype of malignant T cells in SS allows them to recirculate between the blood and skin, enter lymph nodes, and cause diffuse erythema of the skin, thus explaining the clinical hallmarks of SS (i.e. diffuse erythema, blood and lymph node involvement). The T_{RM}-T_{CM} model further explains why MF is primarily treated with skin-directed therapies whereas SS requires systemic treatment(31). However, this model does not account for the extensive diversity and plasticity of malignant T cells in CTCL with respect to their surface marker expression, maturation status, and function(32-34). Further, single cell analysis in MF patients suggest that malignant clones from skin may switch from a T_{RM} phenotype to a T_{CM} phenotype when they leave the skin and enter lymph nodes or blood(35). This indicates that malignant T cells are highly plastic and strongly respond to their microenvironment, a still understudied phenomenon in human skin immunology. Translational studies in CTCL patients hold the potential to address this phenomenon and to generate insights also applicable to ISD(35-37).

T_{RM} are also intricately linked to pathology in ISD, a prototypical example being psoriasis. Pathogenic T_{RM} cells exist in lesional, non-lesional and post-lesional skin of psoriasis patients, and their aberrant activation causes disease(38, 39). Other ISD in which T_{RM} play a key role include fixed drug eruption(40), allergic contact dermatitis(41), and AD(42, 43). As in the case of MF, disease-causing T_{RM} would help explain why many skin lesions of ISD resolve with therapy but reoccur in the same location once therapy is discontinued(29) or why patch-test reactions to contact allergens may flare-up in response to systemic allergen exposure(44).

Therapeutic strategies aiming at curing rather than suppressing CTCL and ISD, respectively, will thus have to address the longevity of pathogenic T_{RM} in the skin. Unless this population can be eradicated or fundamentally reprogrammed, disease will likely relapse(45). A better understanding of the cell of origin of malignant T cells in CTCL and their response to environmental cues will provide important insights into basic human T cell biology and spark new therapeutic developments in ISD.

Pathogenic and bystander T cells in CTCL and ISD

A key unanswered question in ISD is the cause and nature of TCR activation. Both AD and psoriasis have been proposed to be autoimmune diseases, but the identification of T cell autoantigens has proven challenging(46-48). It remains unclear whether autoreactive T cells found in psoriasis and AD are the primary cause of disease or a secondary autoimmune phenomenon as observed in other chronic inflammatory conditions(46, 49). T cells may also be responding to exogenous antigens, particularly in AD, where T cell reactivity to bacterial antigens and allergens have been reported(46, 48). Alternatively, disease-driving T cells in ISD might be activated without cognate antigens, an "innate" immune process known as bystander T cell activation. Bystander T cell activation relies on cytokines and other nonspecific, T cell-extrinsic factors and plays an important part in physiological immune responses, but also contributes to immunopathology(50, 51). Supportive of a bystander-driven process are TCR repertoire studies of ISD patients that have repeatedly found more polyclonal T cells in lesional AD and psoriatic skin compared to clinically resolved skin(42, 52, 53). Conversely, other studies have observed a more restricted, oligoclonal TCR repertoire, particularly in psoriasis, suggestive of antigen-driven T cell activation(52, 54). However, the lack of a consistent and dominant signature TCR repertoire across multiple patients and studies in ISD points to a relevant role of bystander T cells in mediating skin inflammation in ISD.

To study bystander T cell activation in skin inflammation, the interplay between malignant T cell clones and benign T cells in CTCL may provide additional insight. Of note, it has been established that clinically visible inflammation in CTCL is dependent on activation of benign T cells, and that clinical improvement post therapy is linked to changes in the benign T cell compartment, but not to malignant T cell reduction(55). This is additionally supported by recent scRNA-seq data demonstrating the presence of phenotypically distinct CTCL clones in normal-appearing skin of patients with advanced-stage MF(37). Thus, clinical manifestations of CTCL appear to be mostly mediated by bystander-activated T cells, as may be the case in ISD(42, 52, 53). In CTCL, benign T cells are activated either by malignant T cell-derived cytokines or via immunological synapses involving dendritic cells (DCs) and OX40-OX40L interactions(55, 56). DCs and OX40 signaling also contributes to T cell activation in AD and psoriasis where therapeutics targeting of DC-T cell interactions are under clinical investigation(1, 57). Whether in turn such immunological synapses provide survival signals to malignant T cells in CTCL or autoreactive T cell in ISD, respectively, remains to be investigated.

In light of these recent insights, it may be time to revisit a major outstanding question remains regarding plasticity of CTCL, particularly during disease progression. Historically, the differential detection of type 2 cytokines at different stages led to the notion that a shift towards "type 2" was associated with malignancy(58). However, this theory is confounded by the evidence that early CTCL is controlled, at least in part, by cytotoxic T cells as part of an immune surveillance, which is diminished in later stages of disease(59). As such, the cytokine milieu changes with advancing CTCL can alternatively be seen from the perspective of the bystander T cells, from an initial cytotoxic response that, as it becomes exhausted, "unmasks" the intrinsic type 2 cytokine-driving nature of these cells. These competing hypotheses will be assessed/resolved through detailed and longitudinal assessments of bystander and malignant T cells within the same patient at different stages of disease.

If indeed a minor population of pathogenic T cells amplifies its effects via bystander T cell activation in both ISD and CTCL, these cells and their products would be prime targets for therapeutic intervention. Such a view is reminiscent of the concept of "pathogenic" versus "conventional" Th cell subsets, which posits that human inflammatory disease is caused by distinct subpopulations of allergen- or autoantigen-specific pathogenic Th cells(60, 61). Both pathogenic T_H17 (pT_H17) and pathogenic T_H2 cells (variably abbreviated pT_H2, T_H2A, T_Hpath2) have been described and are distinguished from their conventional counterparts by unique differentiation requirements, surface phenotypes, and functional attributes(62-65). Applying this concept to CTCL, malignant CD4+ T cells in MF might emulate pT_H2 cells and act as orchestrators of skin inflammation. In fact, there is an intriguing phenotypic overlap between malignant T cells, skin-resident T_{RM} from healthy skin, and pT_H2 cells(28, 30, 60, 66) (Table 1). These populations share expression of distinct cytokines (*IL13, IL22*), chemokine receptors (*CCR4*), co-inhibitory receptors (*TIGIT, LGALS3*) and transcription factors (*TOX*)(35, 37, 60, 66, 67). Noteworthy, skin T_{RM} with a T_H2 phenotype remain elevated in formerly lesional skin of treated AD patients, consisent with a "pathogenic T cell" designation(36). While the importance of this similarity remains to be elucidated, it suggests that CTCL cells, CD4+ T_{RM} and pT_H2 cells share a tissue-differentiation program. This program is likely the result of the skin microenvironment(60, 64) and its disruption might prove a valuable therapeutic approach in both ISD and CTCL.

T cell-derived cytokines as key mediators in CTCL and ISD

Cytokines play a central pathogenic role in ISD, as evidenced by the impressive effect of cytokine blockade in psoriasis and AD(1, 2). Most of these pathogenic cytokines are either produced directly by T cells (i.e. IL-13 and IL-31 in AD; IL-17A and IL-17F in psoriasis) or act "upstream" and regulate pathogenic function via binding to receptors on T cells (i.e. IL-23 in psoriasis). The cytokine(s) acting "upstream" of T_H2 cells in AD, presuming they exist, have yet to be identified. Proposed cytokines include IL-33, IL-25, TSLP, IL-1a and IL-18 (Figure 2) (68-72). T cells of varying subsets express receptors for these cytokines, all of which can be produced in the skin(69), and trials blocking each of these cytokines in AD are ongoing. Collectively, these observations firmly place T-cell-activating and T-cell-derived cytokines as central drivers of ISD.

Several questions regarding the involvement of cytokines in ISD remain. First, due to the transient nature of cytokine expression in T cells and detection limitations, it is difficult to investigate the expression patterns and hence the involvement of certain T cell-derived cytokines such as IL-2 or IL-4(73). Thus, their role must be inferred, primarily from clinical response to cytokine blockade. For example, the apparently comparable Phase 3 response of AD to dupilumab(74) and lebrikizumab (NCT04146363; NCT04178967) suggests that IL-13 is predominant over IL-4 in driving AD, but in the absence of head-to-head trials this remains speculative. Moreover, the absence of IL-4 from AD skin, as observed in tissue transcriptomics studies(75), does not rule out a role for this cytokine within secondary lymphoid organs, which may be promoting the expansion of disease-driving T cells in ISD or of malignant clones in CTCL over the long-term. Second, questions remain as to whether different cytokines act in additive, complementary or synergistic fashion. For example, do IL-13 and IL-31 act together to drive AD and IL-17A with IL-17F to drive psoriasis? Or there are different endotypes of ISD, in which one cytokine predominates over the other depending on the individual? Finally, additional T cell-derived cytokines of largely unknown function have been identified in ISD, including GM-CSF, IL-24, IL-26 and IL-32(36, 75-78), but their contribution to disease remains largely

unexplored. While understanding the role of cytokines in ISD requires more investigation, current data collectively shows that pathogenic T cells are the central drivers of ISD, and T cell-derived cytokines are likely both necessary and sufficient for disease.

In CTCL, evidence suggests that malignant T cells use cytokines to foster an inflammatory and tumorigenic milieu that mediate the clinical manifestation of CTCL(3, 79). Both early but especially advanced stages of CTCL are characterized by a T_H2 bias, which is thought to be intrinsic to malignant T cells and then imposed on non-clonal benign T cells via T_H2 cytokines(56). The concept of a T_H2 bias in CTCL helps explain several pathological and clinical hallmarks of CTCL, including impairment of skin barrier function, dysbiosis, propensity for infections, eczematous skin lesions, itch and eosinophilia(3, 79). The central role of cytokines in mediating ISD further supports this notion and opens up new therapeutic avenues for CTCL treatment. In particular, targeting of T_H2 cytokines such as IL-4, IL-13, and IL-31 appears promising. However, clinical outcomes in CTCL patients treated with dupilumab are controversial. A number of case reports show progression of disease under dupilumab(80-83), while others show control of itch and reversal of T_H2 bias(84-86). Further research is necessary to better understand which cytokines should be targeted in CTCL and under which conditions. In addition to T_H2 cytokines, cytokines such as IL-15(87, 88), IL-21(35), IL-22(89), IL-26(88), and IL-32(35, 88) might also serve as targets in CTCL. Howsoever, cytokine blockade appears as an understudied opportunity in CTCL therapy, given the pivotal role of cytokines in mediating signs and symptoms of skin disease, in shaping the tumor microenvironment, and in controlling T cell biology.

The skin microbiome in ISD and CTCL

The skin microbiome in ISD and CTCL shows considerable abnormalities and contributes to skin inflammation and clinical burden in both. For instance, colonization with *Staphylococcus aureus* in lesional skin is associated with disease severity and flares in both ISD and CTCL(1, 90, 91). Conversely, antiseptic or antibiotic treatments can improve clinical signs and symptoms of AD and CTCL, respectively(92-95), strongly suggesting that the microbiome participates in driving or amplifying skin inflammation. Shared host-microbiome interactions might thus be at play in ISD and CTCL. However, whether these microbiotal abnormalities are secondary to epidermal barrier defects or secondary to skin inflammation remains unknown. In AD, skin dysbiosis has been attributed to epithelial barrier defects caused by genetic deficiencies in structural proteins such as filaggrin(96). However, genetic defects in skin barrier genes are unlikely the reason for dysbiosis in CTCL, as germline mutations in skin barrier proteins are not enriched in CTCL patients(3) (Figure 1). Furthermore, the prevalence of atopy - a proxy for genetic predisposition for epithelial barrier defects - in CTCL is comparable to that of the general population(97). Thus, microbiotal dysbiosis in CTCL might be the direct consequence of malignant T cell-driven skin inflammation and a dysregulated cutaneous T cell compartment appears to be sufficient to cause barrier dysfunction and consequent dysbiosis in both CTCL and ISD. Indeed, lesional psoriasis skin shows similar downregulation as AD of key barrier proteins such as *FLG*, and *LOR*, despite a lack of genetic association with these genes(98, 99) and topical steroids alone are capable of reducing *S. aureus* colonization in lesional AD skin(100). In addition to inflammation, cutaneous immune deficiency caused by dysregulated T cells might also contribute to dysbiosis, as patients with primary immunodeficiency commonly suffer from

skin disease, including AD, and this has been linked to microbial skin dysbiosis(101, 102). Overall, these observations in ISD and CTCL underscore the central role of skin T cells in regulating epithelial barrier integrity and the skin microbiome.

T cell-driven pruritus in ISD and CTCL

The mechanisms of T cell-driven itch are incompletely understood, particularly in humans, but itch is largely considered to be histamine-independent in ISD. Whether T cells produce classic ligands for direct activation of neurons (i.e. via ion channels or GPCRs) has not been well explored, but the role of T cell-derived cytokines in driving itch has been firmly established(103). In particular, IL-13 and IL-17 are clearly itch-drivers in AD and psoriasis, respectively, evidenced by the early reduction of itch with anti-IL-4/13R and anti-IL-13 in AD and IL-17 blockade in psoriasis(104, 105). Of these, IL-13 would appear to be the most potent mediator of itch, based on the higher intensity of itch in AD compared to psoriasis. Notably, dupilumab can also be very effective at alleviating itch in CTCL(84). Collectively, these data strongly implicate T cell-derived IL-13 as a key mediator of itch in CTCL and ISD.

The mechanism of cytokine-driven itch remains underexplored. One possibility is that inflammatory cytokines reduce the threshold of activation of itch neurons. This has been demonstrated in mice for type 2 cytokine signaling, in which IL-4 potentiated a clinical response to a normally subclinical dose of histamine(106). But additional mechanistic explanations exist, and the propensity of transgenic mice over-expressing cytokines to drive pruritus extends beyond IL-4 and IL-13(107, 108) to include IL-22(109), IL-31(110), TSLP(111) and IL-18(112). How these cytokines elicit itch is not entirely clear. For IL-13, IL-31, IL-17 and TSLP, the receptors are expressed by itch neurons, and a direct effect can be envisaged. Conversely, IL-18 and IL-23 likely cause itch indirectly via activation of T cells. How IL-22 overexpression leads to itch in mice remains even less clear, since the IL-22 receptors are primarily expressed by keratinocytes. This observation, along with the partial response to anti-IL-22 in AD patients(113), suggests a capacity of epidermal keratinocytes to directly drive itch. This is consistent with other mouse models in which epidermally-confined genetic dysregulation that also evoke AD-like phenotypes(114-116), and is indirectly supported by the GWAS associations of AD with epidermally-expressed genes(22). Collectively, these data raise the prospect that T cell-derived cytokine-driven itch in ISD is not necessarily acting directly via itch neurons but may additionally (or predominantly) act via keratinocytes and potentially other cells, including antigen presenting cells. These observations also raise the prospect that other T cell- and CTCL-derived members of the IL-20 family may play a role in itch via the keratinocyte, particularly IL-24 and IL-26.

Tissue and serum biomarkers of ISD and CTCL

Biomarkers serve important functions in clinical and research settings, informing prognosis and management at the patient level as well as disease understanding in research and in clinical trials. Today, biomarkers are not mainstay tools in the management of ISD or CTCL, but hold huge potential for better management of both. As biomarkers in ISD have been comprehensively reviewed elsewhere(117, 118), we focus here on selected biomarkers and potential learnings from CTCL.

Tissue biomarkers. In ISD, tissue biopsies are not routinely stained for markers, although biopsies are regularly taken to confirm diagnosis. In contrast, CTCL biopsies are stained for various molecules of interest, including CD3, CD4, CD30, Ki67 and TIA1. These biomarkers are not yet relevant for management of ISD but may inform research endeavors. For example, CD30 is a maker of T cell activation, and shown to be elevated on pT_H2 cells in AD(60), meaning that it could be integrated into CITE-sequencing(119) or spatial sequencing(120) experiments to identify activated T cells vs bystander T cells in ISD. Similarly, TIA1 is a likely marker of activated CD8 T cells, is upregulated in psoriasis(121) and lichen planus(122), and may help delineate CD8 involvement in ISD and CD8+ MF.

Systemic biomarkers. The most validated blood biomarkers in ISD are molecules which are produced in large quantities in response to inflammatory cytokines, such that they are sufficiently abundant to diffuse from the skin to the blood. In the context of clinical trials ISD, two of the most validated biomarkers are CCL17 (TARC) in AD and beta-defensin 2 (BD-2; DEFB4B) in psoriasis, which serve as simultaneous biomarkers of cytokine signaling (type 2 and type 17, respectively) and disease burden(123, 124). CCL17 is also elevated in CTCL(125), consistent with the T_H2 bias in CTCL, and might serve to monitor therapy success and repolarization of the tumor microenvironment towards an anti-tumor type 1 milieu.

In CTCL, systemic biomarker endeavors focus on identifying the malignant clones using flow cytometry, an approach greatly aided by the advancements in multiparametric flow cytometry(126). Future assessments in ISD may similarly focus on the pathogenic T cells, particularly if the therapeutic intervention is aimed at reducing or eliminating them.. Multiparametric flow cytometry in PBMCs from ISD patients identified specific T cell subsets changes unique to AD relative to healthy volunteers and psoriasis patients, which highlight potential assays for monitoring disease response(127).

Endotyping. On the premise that the better defined the patient, the more effectively one can treat their disease, there are ongoing endeavors to identify the different endotypes of disease and their distinct response to treatment. While plaque psoriasis is relatively homogeneous disease with high response rates to blockade of a single cytokine (e.g. IL-17 or IL-23), the subgrouping of AD patients into clinically meaningful endotypes has remained elusive. Historically, AD has been grouped into “extrinsic” (presence of allergy) and “intrinsic” (no atopy), with serum IgE serving as the molecular arbiter of the two(128). Later, molecular markers such as the presence of a FLG mutation have been introduced. , however no clear relationship to therapy response has been found so far. More recently, there have been efforts to endotype AD biochemically(129, 130), with one group reporting 4 AD subgroups based on serum proteins(131). Yet, how all these endotypes relate to treatment response remains largely unknown(132, 133). The question remains whether non-responders to a targeted therapy (e.g. cytokine blockade) comprise a definable subgroup or whether they merely sit at the more severe end of a spectrum of disease, possibly driven by quantitative variations in cytokine levels but otherwise clinically indistinguishable. Further research in ISD endotyping is needed and will likely lead to a deeper cellular and molecular understanding of the pathogenic T cells, both in the circulation and within the skin. From this, lessons may be transferrable to clinical subtyping and biomarker development in CTCL.

Therapeutic consequences

Following the success of cytokine blockade in ISD, dozens of drugs are being evaluated as potential therapeutics in ISD, the most progressed of which are anti-cytokine antibodies and JAK inhibitors(1, 2). Psoriasis has seen the advancement of particularly efficacious therapies in the form of anti-IL-17 and anti-IL-23 antibodies and our therapeutic armamentarium is even further expanded with the advent of oral allosteric TYK2 inhibitors (e.g. deucravacitinib)(2). In contrast, in AD, there has yet to be an antibody that demonstrates superiority over dupilumab, and the (conventional, non-allosteric) JAK inhibitors, while effective, accompany safety concerns. Additional, early-stage therapeutics in AD seek to interfere with T cell re-circulation (e.g sphingosine-1-phosphate receptor 1 modulators; NCT04162769; NCT04684485), skin homing (CCR4 inhibitor; NCT04271514), or T cell activation, either directly (anti-OX40L-antibody; NCT05131477) or via Treg expansion (IL-2 conjugate; NCT04081350). Nevertheless, none of these ISD therapies are expected to eliminate the pathogenic T cells. The following ISD therapies might conceptually be applied to CTCL:

JAK inhibitors: Based on the genetic alterations in CTCL, JAK inhibition appears promising. In malignant T cells, the JAK-STAT pathway is constitutively active regardless of whether its constituents are affected by mutations(134). Inhibition of the JAK-STAT pathway leads to apoptosis of CTCL cells *in vitro*(135, 136) and to sensitization to other drugs such as histone deacetylase inhibitors.(137) Yet, it is difficult to predict the clinical efficacy and long-term effects of JAK inhibitors in CTCL, as they are likely to impact the anti-tumor immune response and may trigger escape mutations. Topical JAK inhibitors(138) may potentially impact skin T_{RM} survival and thus malignant T cell survival in MF, based on the potentially critical role for common gamma chain signaling in maintenance of memory T cells(139).

Aryl hydrocarbon receptor (AHR) modulators(140, 141): Topical AHR modulators may potentially impact T_{RM} survival in the skin, based on their effects on human and murine T cells *in vitro*(142).

Anti-OX40L-antibody: In CTCL, T cell activation via immunological synapses involving DCs and OX40-OX40L have been proposed to provide tumorigenic signals(55, 56). Thus, the anti-OX40L monoclonal Antibody (KY1005) being developed in AD might prove beneficial in CTCL as well.

CCR4 inhibitor: RPT193 is an oral small molecule CCR4 antagonist under clinical trials in AD. It is thought to block recruitment of T_H2 cells into and retention of T_{RM} in skin. Given the important expression of CCR4 on malignant T cells(28) and the solid clinical efficacy of the anti-CCR4 antibody mogamulizumab in CTCL, application of CCR4 inhibitors in CTCL appears promising.

In contrast to therapies in ISD, therapies for CTCL ultimately aim at eliminating the cancerous T cells, particularly in later stages of disease. A wide variety of topical, physical, and systemic therapies are used in CTCL, the vast majority of which lack curative potential(3). Some insights from CTCL therapy studies are, however, of interest for therapeutic development in ISD as well.

PUVA: In psoralen plus ultraviolet A (UVA) light (PUVA) therapy, patients ingest or topically apply 8-methoxypsoralen and then are exposed to UVA light. PUVA is an effective treatment for MF and for ISDs including psoriasis and AD, albeit with the risk of inducing non-melanoma skin cancer(143). Interestingly, PUVA is capable of eradicated malignant T cells in low-

burden MF patients(55), suggesting that chemo-phototherapy regimens might be adapted for curative approaches in ISD, aiming to deplete the pathogenic T cells in lesional skin.

Anti-CD52 (alemtuzumab): T cell-depleting antibody that is effective but accompany significant risk of infection, autoimmune reactions and other side effects.

Anti-CD30 (Brentuximab vedotin): An antibody-drug conjugate, in which anti-CD30 has been linked to Monomethyl auristatin E (MMAE), a potent anti-mitotic compound, for the depletion of CD30+ T cell lymphoma cells, including CTCL(144). MMAE has been conjugated to other antibodies for the treatment of pancreatic, breast, ovarian and urothelial cancers, as well as B cell malignancies, and is often associated with toxicities (most notably peripheral neuropathy) irrespective of the antibody it is conjugated to(145).

Anti-CCR4 (mogamulizumab): An afucosylated monoclonal antibody for enhanced antibody-dependent cellular cytotoxicity of CTCL cells in both MF and SS(146). The afucosylation may overcome the challenge of tissue-level depletion of T cells reported in alemtuzumab-treated patients(28). Clinical response is likely augmented by the concomitant depletion of CCR4+ regulatory T cells (i.e. an immuno-oncology-mediated effect), which accompanies toxicity (most frequently skin rashes)(147).

Currently, there is a dichotomy between therapies for ISD that aim to suppress T cell-driven inflammation versus therapies for CTCL that seek to eliminate the cause of disease. However, both disease spheres might profit from one another, with cross-fertilization of pathogenetic concepts and therapeutic approaches becoming more and more relevant as our understanding of the diseases grows. Although the toxicity profile of current, broad-acting anti-T cell antibodies makes them poorly suited for ISD, they nevertheless demonstrate the feasibility of T cell elimination as a therapeutic option, which can be expected to evolve with time. Additional potential strategies for directly targeting T cells include radioligand therapy(148), antibody-siRNA conjugates(149), CD3 bi-specific antibodies(150), CAR T cells(151), drugs targeting T cell metabolism(152) and transcription factor inhibition, including novel STAT3-degraders(153). As our capacity to target malignant and pathogenic T cells become safer and more refined, they will raise the inexorable question: Instead of merely treating CTCL and ISD, can we cure it?

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789 Table 1: Genes commonly expressed by pathogenic T_H2, T_{RM}, and malignant CTCL cells

Category	Gene	Name	Role in type 2 inflammation	Putative role in CTCL
Cytokine receptor	IL9R	Interleukin 9 receptor (CD129)	- IL-9R signaling promotes survival, proliferation and cytokine production in T_H2 cells(63, 154, 155)	- May promote tumor cell growth(156, 157) - May inhibit anti-tumor immunity(156, 157)
Surface receptors	TIGIT	T cell immunoreceptor with Ig and ITIM domains	- Inhibitory receptor on T cells(158, 159) - Ligation enhances Th2 function(160)	- May promote Th2 bias in malignant T cells while suppressing anti-tumor immunity(161)
	LGALS3	Galectin 3	- Induces keratinocyte hyperproliferation(162) - May promote long-term survival of $T_{RM(163)}$	- May participates in epithelial barrier disruption(162) - May promote chemoresistance to genotoxic agents(164)
Chemokine receptor	CCR4	CC chemokine receptor 4	- Ligand for CCL17 and critical for skin-homing and skin-residency of T cells(165) - Highly expressed on Th2 and Treg cells(166)	- CCL17-CCR4 interactions may promote epidermotropism of malignant T cells(166) - CCR4+ Treg cells may suppress cancer immunity
	CCR8	CC chemokine receptor 8	- $CCR8^+$ T_H2 cells express high levels of cytokines and are pathogenic in models of type 2 skin inflammation(167) - CCL18 (ligand of CCR8) is highly upregulated in AD(75, 168)	- CCL18 expression correlates with disease severity in CTCL(169) - CCR8-CCL18 interactions recruit Th2 cells into CTCL lesions(55)
Cytokines	IL9	Interleukin 9	- Autocrine/paracrine growth and activation factor for Th2 cells(63, 154) - Induces secretion of proinflammatory mediators by mast cells(154)	- Promotes tumor cell growth(156, 157) - Inhibits anti-tumor immunity(156, 157)
	IL13	Interleukin 13	- promotes skin barrier disruption, immune cell recruitment, itch, and tissue remodeling(170)	- promotes skin barrier disruption, immune cell recruitment, itch, and tissue remodeling - may function as autocrine/paracrine growth factor in malignant T cells(171)
	IL22	Interleukin 22	- inhibits epidermal differentiation(172) - promotes recruitment of immune cells(172) - promotes tissue remodeling(173)	- Promotes epidermal hyperplasia and migration of CCR6+ cells such as Langerhans cells into lesional skin(89) - May promote tissue remodeling(173)
Transcriptional regulator	TOX	Thymocyte selection associated high mobility group box	- Induces transcriptional program associated with T cell exhaustion(174) - Prevents TCR overstimulation of T cells and activation-induced cell(175) - Highly expressed in skin T_{RM}	- may promote TCR-signal independent survival and prevent apoptosis in malignant T cells(176) - may promote malignant T cell metabolism via mTORC1 activation(177)

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793 **FIGURE LEGEND**
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795 **Figure 1: Clinical presentation of selected cases of cutaneous T cell lymphoma, atopic dermatitis, and**
796 **psoriasis.**
797 **Overlapping clinical features between CTCL, psoriasis, and atopic dermatitis**
798 (A, B) Plaque psoriasis. (C, D) Plaque-type mycosis fungoides. (E) Atopic dermatitis. (F) Allergic contact eczema
799 (G, H) Patch- and plaque-type mycosis fungoides. (I) Eczematous plaque of mycosis fungoides

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801
802 **Figure 2: Genetic alterations in CTCL and susceptibility loci associated with atopic dermatitis or psoriasis.**

803 Venn diagram intersecting genes found to be mutated in CTCL(3) (blue) with genes associated with psoriasis[9-11]
804 (green) and atopic dermatitis(1) (red) by GWAS.

805

806 **Figure 3: Signaling pathways that regulate inflammatory cytokine production by pathogenic and malignant T**
807 **cells in ISD and CTCL.**

808 Cytokine expression is controlled by signaling through NF-kB inducers (magenta), the JAK-STAT pathways (red),
809 and via TCR signaling (light blue). In CTCL, mutations within these pathways bypass the requirement for external
810 signals.

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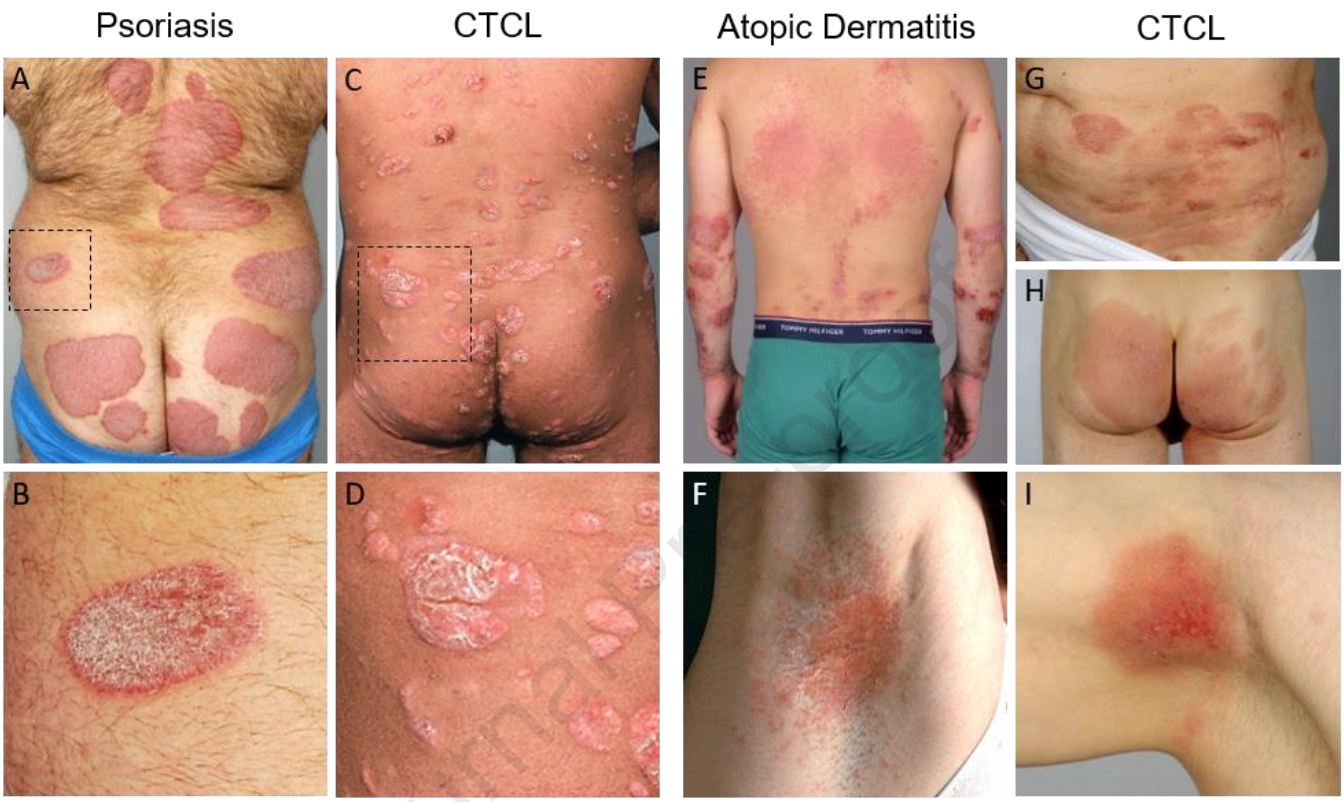

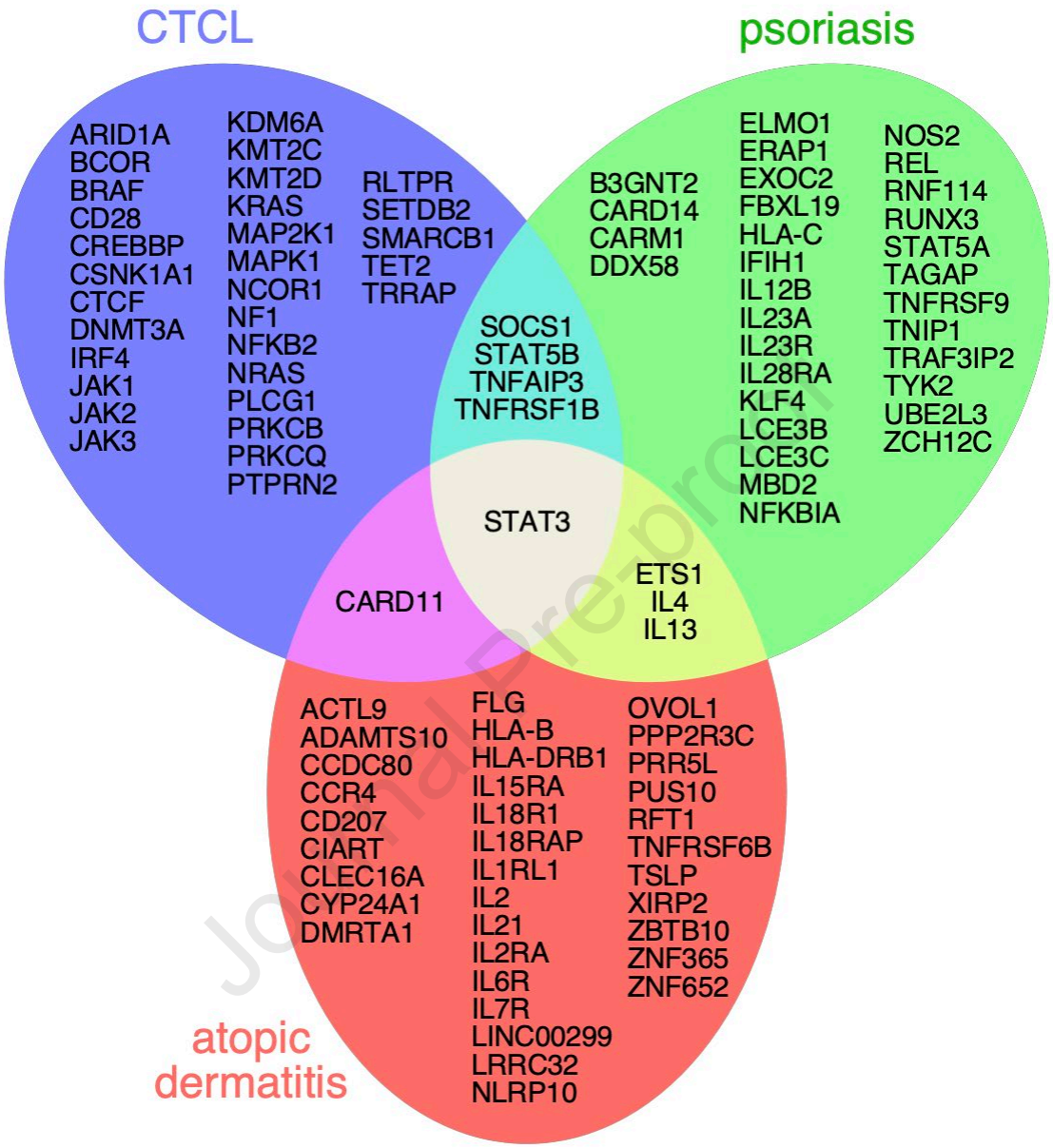
CTCL
psoriasis
atopic dermatitis
ARID1A
BCOR
BRAF
CD28
CREBBP
CSNK1A1
CTCF
DNMT3A
IRF4
JAK1
JAK2
JAK3
KDM6A
KMT2C
KMT2D
KRAS
MAP2K1
MAPK1
NCOR1
NF1
NFKB2
NRAS
PLCG1
PRKCB
PRKCQ
PTPRN2
RLTPR
SETDB2
SMARCB1
TET2
TRRAP
B3GNT2
CARD14
CARM1
DDX58
ELMO1
ERAP1
EXOC2
FBXL19
HLA-C
IFIH1
IL12B
IL23A
IL23R
IL28RA
KLF4
LCE3B
LCE3C
MBD2
NFKBIA
NOS2
REL
RNF114
RUNX3
STAT5A
TAGAP
TNFRSF9
TNIP1
TRAF3IP2
TYK2
UBE2L3
ZCH12C
SOCS1
STAT5B
TNFAIP3
TNFRSF1B
STAT3
CARD11
ETS1
IL4
IL13
ACTL9
ADAMTS10
CCDC80
CCR4
CD207
CIART
CLEC16A
CYP24A1
DMRTA1
FLG
HLA-B
HLA-DRB1
IL15RA
IL18R1
IL18RAP
IL1RL1
IL2
IL21
IL2RA
IL6R
IL7R
LINC00299
LRRC32
NLRP10
OVOL1
PPP2R3C
PRR5L
PUS10
RFT1
TNFRSF6B
TSLP
XIRP2
ZBTB10
ZNF365
ZNF652