

Cutaneous Immune Microenvironment Profiling as a Platform for Precision Dermatology: Lessons From Inflammatory and Malignant Skin Diseases

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Submitted: 29 May 2026 Revised: 13 July 2026 Accepted: 27 July 2026 Published: 23 October 2026

Precision medicine has transformed medical oncology and several systemic immune-mediated diseases; however, dermatology remains largely dependent on morphologic classification and empiric therapeutic selection. Thus, dermatologic disease management is increasingly challenging with the endless addition of immune modulatory treatments. The skin offers a uniquely accessible immune organ in which longitudinal sampling of the disease microenvironment is feasible through minimally invasive approaches. Recent advances in single-cell transcriptomics, spatial biology, circulating tumor and immune profiling, and non-invasive skin sampling technologies have accelerated efforts toward biomarker-driven precision dermatology. Inflammatory and malignant skin diseases share convergent immune pathways involving T-cell activation, cytokine dysregulation, tissue-resident immune populations, and stromal remodeling, suggesting that integrated immune microenvironment profiling may provide a unified framework for disease stratification and therapeutic selection. Psoriasis has emerged as a prototype disease demonstrating molecularly distinct immune endotypes associated with differential responses to biologic therapy. More recently, lichen planus and cutaneous T-cell lymphoma illustrate the expanding translational relevance of interferon signaling, Janus kinase–signal transducer and activator of transcription activation, and spatial immune architecture. Understanding the variability in these immune, stromal, and malignant cellular ecosystems likely facilitates improved therapeutic development and prediction of treatment response. Novel technologies including hydrocolloid micro-patch sampling, tape stripping, spatial transcriptomics, and circulating cell-free DNA analysis may enable serial, non-invasive monitoring of cutaneous disease activity and therapeutic response. This review discusses current and emerging platforms for immune microenvironment profiling in dermatology, highlights translational applications across inflammatory and malignant skin diseases, and proposes an integrated precision dermatology framework capable of transforming clinical decision-making and longitudinal disease monitoring.

Keywords: precision medicine; dermatology; psoriasis; lichen planus; cutaneous T-cell lymphoma; single-cell RNA sequencing; spatial transcriptomic; cytokine profiling

Introduction

Precision medicine seeks to individualize diagnosis, prognostication, and therapeutic selection to patients' molecular and immunologic characteristics rather than rely on clinical phenotype alone. Oncology has led this advancement through genomic and immune profiling technologies; however, dermatology has remained focused on clinicopathologic pattern recognition and empiric treatment algorithms. The increasing complexity of therapeutic options in inflammatory and malignant skin disease has exposed critical limitations in this paradigm, particularly in predicting a patient's treatment response and relapse risk.

The skin possesses unique opportunities for precision medicine advancement compared to other organ systems. It permits direct access to the tissue immune microenvironment and allows for repeated sampling over time. Se-

rial evaluation is often conducted using minimally invasive techniques that assess molecular and immunologic changes throughout disease progression and treatment. Recent advances in single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, multiplex imaging, circulating biomarker analysis, and non-invasive epidermal sampling technologies have accelerated the transition toward biomarker-guided dermatologic care [1,2,3].

Cutaneous diseases that would benefit from precision medicine frequently share overlapping immune mechanisms: T-cell dysregulation, cytokine signaling abnormalities, tissue-resident memory (TRM) cells, stromal interactions, and epithelial-immune crosstalk [4,5,6,7]. These shared pathways create opportunities for identifying disease-specific immune endotypes while simultaneously uncovering therapeutic vulnerabilities.

This review examines emerging approaches to immune microenvironment profiling and their applications across psoriasis, lichen planus (LP), and cutaneous T-cell lymphoma (CTCL). We discuss translational technologies enabling precision dermatology, highlight evolving biomarker paradigms, and propose a framework integrating longitudinal molecular monitoring into future dermatologic practice. This article aims to systematically summarize and propose implications of various immune profiling techniques as it pertains to psoriasis, LP and CTCL.

The Skin Immune Microenvironment as a Precision Medicine Platform

The skin is not simply a passive barrier, but a highly organized immune organ composed of epidermal, dermal, vascular, neural, stromal, and immune compartments. Its immune function is spatially compartmentalized: keratinocytes dominate the epidermis; Langerhans cells reside primarily in the epidermal compartment; dendritic cells, macrophages, mast cells, fibroblasts, endothelial cells, and lymphocytes populate the dermis; and TRM T cells occupy both epidermal and dermal niches. This architecture creates a uniquely accessible immune microenvironment in which disease biology can be repeatedly sampled, mapped, and therapeutically targeted [8]. While conventional microscopy remains diagnostically essential, it lacks the molecular resolution necessary to identify biologically distinct disease endotypes. Molecular profiling technologies now demonstrate that clinically similar dermatologic conditions may possess markedly different immune signatures (Table 1) associated with divergent therapeutic responses [9,10,11,12].

Keratinocytes are central immune regulators rather than passive targets of inflammation. They express pattern-recognition receptors and respond to microbial, cytokine, mechanical, and injury signals by producing cytokines, chemokines, antimicrobial peptides, and alarmins. These signals recruit neutrophils, dendritic cells, T helper 17 (Th17) and T cytotoxic 17 (Tc17) cells, Th1 cells, and other effector populations, thereby linking epidermal barrier disruption to adaptive immune activation [13,14,15]. This keratinocyte immune program is disease specific. In psoriasis, Interleukin (IL)-17A, IL-22, tumor necrosis factor (TNF), and IL-23 pathway activation drives keratinocyte hyperproliferation, impaired terminal differentiation, and production of C-C motif chemokine ligand 20 (CCL20), C-X-C motif chemokine ligand 1 (CXCL1), CXCL8, defensin beta 4A (DEFB4A), S100 calcium-binding protein A7 (S100A7), S100A8, and S100A9. CCL20 promotes recruitment of CCR6-positive Th17/Tc17 cells, while CXCL1 and CXCL8 support neutrophil trafficking and formation of Munro microabscesses. In contrast, type 2 inflammatory diseases such as atopic dermatitis are enriched for IL-4, IL-13, IL-31, thymic stromal lymphopoietin (TSLP),

CCL17, CCL22, and CCL26, illustrating how keratinocyte programs can define immune endotypes across visually overlapping inflammatory dermatoses [16]. In lichen planus, keratinocytes function as both targets and amplifiers of interface dermatitis. Interferon-gamma (IFN- γ) exposure induces keratinocyte expression of CXCL9, CXCL10, and CXCL11, promoting recruitment of C-X-C chemokine receptor 3 (CXCR3)-positive lymphocytes to the epithelial interface. In oral lichen planus, lesional tissue demonstrates increased IFN- γ , CXCR3, CXCL9/MIG, and CXCL10/interferon gamma-induced protein 10 (IP-10) transcripts, supporting an IFN- γ /CXCR3 chemokine axis in disease maintenance [17].

Dendritic cell and macrophage populations provide a second layer of immune control. These populations integrate antigen presentation with cytokine production and T-cell polarization. In psoriasis, single-cell analysis has identified cluster of differentiation 14 (CD14)-positive type 3 dendritic cells co-producing IL-1B and IL-23A, supporting a model in which antigen-presenting cells sustain the IL-23/Th17 axis rather than merely initiating inflammation [18]. In lichen planus, the antigen-presenting cell compartment likely supports cytotoxic interface inflammation through T-cell activation and local amplification of IFN-driven chemokine networks [17]. In CTCL, myeloid populations are increasingly recognized as active components of the tumor microenvironment. Single-cell RNA sequencing of advanced CTCL identified enrichment of CCL13-positive monocytes/macrophages and lysosomal associated membrane protein 3 (LAMP3)-positive conventional dendritic cells, with predicted inhibitory interactions involving CD47-signal regulatory protein alpha (SIRPA), macrophage migration inhibitory factor (MIF)-CD74, and CCR1-CCL18. These findings support a model in which myeloid cells shape an immunosuppressive CTCL niche and may contribute to malignant T-cell persistence [5].

Tissue-resident memory T cells are particularly important for precision dermatology because they provide a cellular explanation for chronicity, recurrence, and site-specific relapse. Skin TRM cells are commonly characterized by CD69, CD103, CD49a, CXCR6, and variable expression of cytokine programs including IL-17A, IL-22, IFN- γ , and cytotoxic mediators such as granzyme B and perforin. Epidermal CD8-positive CD103-positive TRM cells can persist in clinically resolved psoriasis and retain the capacity to produce IL-17A and IL-22 upon reactivation. This supports the concept that clinically normal-appearing skin may remain molecularly primed for recurrence [19]. More recent mechanistic work in oral LP implicates CD8⁺ tissue-resident memory T cells in erosive disease, supporting a model in which resident cytotoxic lymphocytes maintain localized mucosal inflammation [20].

The precision-medicine implication is that many inflammatory and malignant skin diseases should be classified not only by morphology, but by dominant

Table 1. Distinct molecular endotypes across psoriasis, lichen planus (LP), and cutaneous T-cell lymphoma (CTCL).

	Psoriasis	Lichen planus	CTCL
Dominant immune program	IL-17 & IL-23	IFN- γ & JAK-STAT	Th2 and tumor-associated programs
Key cellular features	Th17 cells, CD8 ⁺ TRM, neutrophils, activated keratinocytes, inflammatory fibroblasts, inflammatory dendritic cells	CXCR3 ⁺ CD8 ⁺ T cells, cytotoxic effectors, interface dendritic cells, activated keratinocytes	Malignant T cell clones, exhausted T cells, B cells, CCL13 ⁺ monocytes/macrophages, LAMP3 ⁺ dendritic cells, M2-like macrophages
Molecular signatures	IL-17A, IL-23, IL-22, TNF, CCL20, CXCL1/8, DEFB4A, S100A7/A8/A9, LCN2, TRM, and fibroblast activation signatures	IFN- γ , CXCL9/10/11, STAT1, ICAM1, granzyme B, perforin, JAK1/2 activation cytotoxic signature	PDCD1, TIGIT, TOX, IL-4/IL-13, CCR4, KIR3DL2 proliferation (MYC) or exhaustion signatures, EZH2, STAT3
Potential targeted therapy	IL-23, IL-17, TNF, JAK, TYK2, IL-36, fibroblast pathways	JAK1/2, IFN signaling, CXCR3 axis, cytotoxic pathways	CCR4, HDAC, PD-1, JAK-STAT, immune microenvironment modulators
Prognostication	HLA-Cw6	Unknown	TNMB stage, 17-gene signature
Potential disease monitoring	IL-17A, IL-22/23, β -defensin-2, S100A8/A9, lipocalin-2, IL-36 γ , S100, TRM reactivation	CXCL9/10/11	CCR4/30, KIR3DL2 blood tumor burden, ctDNA

IL, interleukin; IFN- γ , interferon-gamma; JAK-STAT, Janus kinase–signal transducer and activator of transcription; Th2, T helper 2; TRM, tissue-resident memory; CXCR3, C-X-C chemokine receptor 3; CCL20, C-C motif chemokine ligand 20; TNF, tumor necrosis factor; DEFB4A, defensin beta 4A; S100A7, S100 calcium-binding protein A7; LCN2, lipocalin-2; TYK2, tyrosine kinase 2; HLA-Cw6, human leukocyte antigen-Cw6; STAT, signal transducer and activator of transcription; CXCL, C-X-C motif chemokine ligand; ICAM1, intercellular adhesion molecule 1; LAMP3, lysosomal associated membrane protein 3; PDCD1, programmed cell death 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TOX, thymocyte selection associated high mobility group box; CCR4, C-C motif chemokine receptor 4; KIR3DL2, killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2; MYC, Myc oncogene; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; PD-1, programmed cell death protein 1; TNMB, tumor node marrow blood staging.

immune circuits. A practical framework would include: IL-23/IL-17/TNF-dominant inflammation in psoriasis; IL-4/IL-13/IL-31/TSLP-dominant inflammation in atopic dermatitis and pruritic type 2 disease; IFN- γ /CXCL9/CXCL10/CXCL11/Janus kinase–signal transducer and activator of transcription (JAK-STAT)-dominant inflammation in interface dermatitis such as lichen planus; and malignant T-cell clonality with variable Th2 skewing, exhaustion markers, and tumor-microenvironment remodeling in CTCL. This reframes dermatologic disease as a set of spatially organized immune programs that can be measured, monitored, and therapeutically interrupted [1].

The accessibility of skin tissue further enables longitudinal profiling strategies that are difficult to achieve in other organ systems. Serial assessment of cytokines, transcriptomic changes, and immune cell populations may ultimately facilitate real-time therapeutic optimization analogous to adaptive treatment paradigms in oncology.

Emerging Technologies Enabling Precision Dermatology

Single-Cell RNA Sequencing

Single-cell RNA sequencing has transformed the understanding of cutaneous immune heterogeneity by permitting transcriptional characterization of individual cellular populations within lesional skin. Unlike bulk RNA sequencing, scRNA-seq identifies rare immune subsets, lineage trajectories, and dynamic cellular states that may drive disease pathogenesis [1,21].

In psoriasis, scRNA-seq studies have demonstrated expanded IL-17A producing T-cell populations, activated dendritic cell subsets, and inflammatory fibroblast programs associated with lesional persistence [1]. Recent single-cell and spatial transcriptomic studies in oral lichen planus identified expanded CD8⁺ tissue-resident memory T-cell populations enriched within erosive lesions, with increased IFN- γ , TNF, and IL-17 expression and activation of CXCL9/CXCL10 inflammatory signaling networks involving keratinocytes, stromal cells, and cytotoxic lymphocytes localized along the epithelial interface, supporting a model in which localized TRM-driven cytokine circuits contribute to chronic mucosal inflammation and re-

current epithelial injury [20,22]. In CTCL, single-cell approaches have identified transcriptionally distinct malignant T-cell populations expressing exhaustion markers, altered metabolic pathways, and variable cytokine programs associated with progression risk [23].

Despite its transformative potential, widespread clinical implementation of scRNA-seq remains limited by cost, technical complexity, tissue processing requirements, and bioinformatic infrastructure needs.

Spatial Transcriptomics and Multiplex Imaging

Spatial transcriptomic technologies preserve tissue architecture while simultaneously mapping gene expression patterns across the cutaneous microenvironment. These approaches address an important limitation of dissociative single-cell methods by maintaining spatial relationships between immune and stromal populations [24].

Spatial profiling has demonstrated compartmentalized inflammatory niches within psoriasis plaques and revealed complex tumor-immune interactions in squamous cell carcinoma, melanoma, and CTCL [2,25,26,27]. Multiplex imaging techniques, including imaging mass cytometry and multiplex immunofluorescence, further enable simultaneous visualization of numerous cellular markers within intact skin tissue sections as a complementary method to spatial transcriptomics [28].

These technologies may ultimately identify spatial biomarkers predictive of treatment response, relapse risk, or malignant transformation.

Non-Invasive Epidermal Sampling

One of the most promising advances in precision dermatology involves development of minimally invasive sampling approaches capable of longitudinal disease monitoring without repeated biopsies. Tape stripping and hydrocolloid micro-patch technologies permit collection of epidermal proteins, cytokines, nucleic acids, and cellular debris from lesional skin [29].

Tape stripping provides a minimally invasive method for sampling stratum corneum RNA and proteins and has been used to characterize inflammatory skin endotypes, distinguish psoriasis from atopic dermatitis using IL-36 γ , and monitor biomarker changes during targeted therapy [30,31]. Emerging hydrocolloid micro-patch systems may further enable serial cytokine profiling with improved patient tolerability and broader applicability in chronic disease monitoring [32].

Non-invasive sampling strategies are particularly attractive for CTCL and chronic inflammatory disorders requiring repeated disease assessment over time. Such approaches may reduce procedural morbidity while facilitating more granular longitudinal molecular analysis.

Circulating Biomarkers and Cell-Free DNA

Circulating biomarkers offer an additional minimally invasive approach to disease monitoring. Serum cytokines, circulating immune populations, and cell-free DNA (cfDNA) analysis have gained increasing attention across inflammatory and malignant dermatologic disease. cfDNA refers to fragmented extracellular DNA released into circulation through apoptosis, necrosis, NETosis, active secretion, and tissue injury. In dermatology, cfDNA is attractive because it offers a minimally invasive blood-based biomarker that may capture inflammatory burden, tissue damage, tumor burden, and treatment response over time. However, cfDNA should be described carefully: in inflammatory skin disease, most studies evaluate total cfDNA concentration or disease-associated DNA fragments, whereas in malignancy, the clinically relevant fraction is usually ctDNA, a tumor-derived subset of total cfDNA [33].

In inflammatory dermatoses such as psoriasis, circulating cfDNA levels are elevated during active disease and may correlate with inflammatory burden and disease severity. More targeted approaches have identified psoriasis-associated inflammatory genes, including TNF- α , S100A7, and S100A15, within circulating cfDNA, suggesting that cfDNA may reflect disease-specific immune activation in addition to generalized tissue injury [34]. In cutaneous malignancy, ctDNA has shown greater translational maturity. In melanoma, ctDNA can detect tumor-associated mutations and may assist with prognostication, treatment monitoring, minimal residual disease detection, and identification of therapeutic resistance. Although clinical implementation remains limited by assay sensitivity and tumor burden, ctDNA is increasingly recognized as a promising liquid biopsy platform in melanoma management [35].

Integration of circulating biomarkers with tissue-based and spatial profiling technologies may ultimately provide a comprehensive systems-level understanding of cutaneous disease biology.

Psoriasis as a Prototype Precision Dermatology Disease

Psoriasis has emerged as the clearest example of successful translational immunology in dermatology and serves as a model for biomarker-driven therapeutic development [36]. The evolution from broad immunosuppressive therapy toward targeted biologics was enabled through progressive elucidation of the IL-23/Th17 inflammatory axis and the complex cellular interactions within the psoriatic immune microenvironment [18]. Despite the availability of highly effective biologic therapies, therapeutic selection remains largely empirical, underscoring the need for molecular stratification approaches capable of predicting response, resistance, and relapse.

Early transcriptomic studies demonstrated that psoriasis lesions contain robust upregulation of IL-17A, IL-23A, TNF, IFN- γ , CXCL1, CXCL8, and S100 family genes relative to normal skin [37,38]. Subsequent work revealed that these inflammatory signatures are not uniform across patients, suggesting the existence of biologically distinct inflammatory endotypes [1,9,39]. Swindell et al. [40] demonstrated significant heterogeneity in lesional cytokine programs, with subsets of patients exhibiting differential enrichment of IL-17, TNF, and interferon-driven pathways. These findings challenged the concept of psoriasis as a singular inflammatory entity and instead supported a multidimensional immune classification model.

ScRNA-seq has substantially expanded understanding of this heterogeneity. Recent studies have identified multiple pathogenic T-cell populations within psoriatic plaques, including IL-17A-producing CD8⁺ TRM T cells, activated Th17 cells, inflammatory dendritic cell populations, and disease-associated fibroblast subsets. Reynolds et al. [1] used integrated single-cell analysis to demonstrate that psoriasis lesions contain expanded populations of inflammatory fibroblasts expressing CCL19, IL-6, and CXCL8 that participate directly in leukocyte recruitment and maintenance of chronic inflammation. These findings further established psoriasis as a multicellular stromal-immune disease rather than an isolated T-cell disorder. Advanced single cell analyses additionally revealed substantial keratinocyte heterogeneity within lesional skin. A recent integrated single-cell and spatial transcriptomic study identified a proliferative ubiquitin conjugating enzyme E2 T (UBE2T)-positive keratinocyte subpopulation localized predominantly within the stratum spinosum of psoriatic epidermis. These cells demonstrated enrichment of IL6-JAK-STAT3, TNF-nuclear factor Kappa-light-chain enhancer of activated B cells (NF- κ B), hypoxia, and inflammatory signaling pathways while exhibiting enhanced interactions with IL-17-secreting CD8⁺ T-cell populations through CXCL14, MIF, and CD58 signaling networks. Importantly, UBE2T overexpression increased IL-23A expression and keratinocyte proliferation *in vitro*, suggesting that keratinocytes may actively perpetuate the inflammatory microenvironment rather than merely serving as downstream targets of immune activation [41].

Spatial transcriptomics has further refined understanding of psoriasis microanatomy by preserving tissue architecture during molecular analysis. Unlike dissociative single-cell methods, spatial profiling permits identification of organized inflammatory niches within lesional skin, allowing for assessment of spatial communications. Recent spatial analyses demonstrated compartmentalized immune programs involving epidermal IL-17-rich regions adjacent to stromal fibroblast populations enriched for chemokine signaling and angiogenic pathways, including CXCL12, CCL19, VEGFA, and TNF superfamily (TNFSF) family mediators [42]. Emerging evidence additionally sug-

gests that disease memory in psoriasis localizes to discrete epidermal-dermal immune niches enriched for tissue-resident memory T cells, activated dendritic cells, and persistent inflammatory stromal programs, potentially contributing to site-specific relapse following clinical resolution [43,44]. Cheuk et al. [45] identified epidermal CD8⁺ TRM populations expressing CD103 and IL-17A within clinically resolved lesions following treatment. These populations persisted despite clinical clearance and rapidly re-activated upon disease recurrence, suggesting that durable remission may require elimination or functional suppression of pathogenic TRM populations [45]. This finding has important therapeutic implications, particularly regarding biologic discontinuation strategies and development of curative approaches.

Biomarker-guided therapeutic stratification remains an active area of investigation in psoriasis as increasing molecular heterogeneity is recognized among patients with clinically similar disease. HLA-C*06:02 positivity has consistently demonstrated association with enhanced response to ustekinumab and may also influence responsiveness to IL-23-targeted therapy, supporting the concept that genetic background contributes to biologic selection [46,47,48]. Beyond germline genetics, transcriptomic profiling studies have identified distinct inflammatory endotypes characterized by variable enrichment of IL-17, TNF, interferon, and keratinocyte activation signatures [49]. Patients with stronger IL-17-dominant transcriptional programs appear more likely to respond to IL-17 blockade, whereas elevated baseline interferon-response signatures and persistent myeloid inflammatory pathways have been associated with diminished TNF inhibitor responsiveness in some cohorts [50,51]. However, reproducibility across biomarker studies remains inconsistent because of disease heterogeneity, variable sampling methods, evolving treatment exposure, and the complexity of integrating multidimensional immune datasets into clinically actionable therapeutic algorithms.

Recent studies have increasingly evaluated circulating biomarkers as tools for longitudinal disease monitoring and therapeutic response assessment in psoriasis. Elevated serum IL-17A, IL-23, β -defensin-2, S100A8/A9 (calprotectin), lipocalin-2, and human beta-defensin-2 levels correlate with disease severity in multiple cohorts and often decline following successful biologic therapy, suggesting that circulating inflammatory mediators may provide dynamic readouts of systemic immune activation [52,53,54,55]. Several studies additionally identified circulating microRNAs—including miR-21, miR-146a, miR-155, and miR-210—as potential biomarkers associated with keratinocyte activation, Th17 signaling, and treatment response, although reproducibility and disease specificity remain inconsistent across platforms [56,57]. Extracellular vesicles and exosome-associated inflammatory proteins have also emerged as candidate biomarkers capable of re-

flecting immune-cell and keratinocyte communication during active disease [58,59]. Integration of circulating immune biomarkers with spatial transcriptomics, single-cell sequencing, and non-invasive epidermal sampling may ultimately provide a more comprehensive systems-level approach to disease stratification and longitudinal monitoring.

Single-cell and spatial technologies have also begun to clarify mechanisms underlying therapeutic resistance and disease recurrence in psoriasis. Persistent IL-17-producing tissue-resident memory T-cell populations remain detectable within clinically resolved lesions and may rapidly reactivate inflammatory pathways following treatment withdrawal [6,43]. In parallel, inflammatory fibroblast subsets, metabolically adapted keratinocyte states, and IL-1B/IL-23A-producing dendritic cell populations appear capable of sustaining alternative inflammatory circuits despite pharmacologic suppression of dominant cytokine pathways [1,18,42]. Recent single-cell analyses additionally demonstrate dynamic transcriptional remodeling during biologic therapy, including shifts in stromal signaling, interferon-response programs, and myeloid inflammatory states that may contribute to secondary treatment failure [18,25,42,60]. These findings suggest that biologic resistance may reflect adaptive multicellular network behavior rather than isolated cytokine escape and support future therapeutic strategies targeting interconnected immune-stromal compartments rather than single inflammatory mediators alone.

Collectively, psoriasis illustrates both the promise and current limitations of precision dermatology. While biologic development successfully translated mechanistic immunology into highly effective therapies, treatment selection remains insufficiently individualized. Integration of spatial transcriptomics, single-cell analysis, circulating biomarkers, and longitudinal non-invasive sampling may ultimately permit true biomarker-guided management strategies capable of predicting response, relapse, and resistance prior to clinical deterioration.

Lichen Planus: Interferon Signaling, JAK-STAT Activation, and Emerging Precision Immunology

Lichen planus (LP) is a chronic inflammatory interface dermatitis characterized by dense lichenoid lymphocytic infiltrates, basal keratinocyte apoptosis, and variable mucocutaneous and hair follicle involvement [61]. Historically regarded as a nonspecific T-cell mediated disorder, recent molecular studies increasingly support classification of LP as an interferon-driven inflammatory disease with substantial translational implications [17,62,63].

The immunopathogenesis of LP involves IFN- γ driven inflammatory disorders directed against basal keratinocytes expressing altered self-antigens or stress-induced immune signals [61,64]. The primary sources of IFN- γ include cytotoxic CD8⁺ T cells, γ - Δ T cells and a recently identified novel subset of CXCL13+CD8⁺ T cells particularly in cu-

taneous and mucosal LP [65,66]. Lesional tissue demonstrates elevated expression of IFN- γ , CXCL9, CXCL10, CXCL11, granzyme B, perforin, and multiple JAK-STAT pathway mediators [17,20,67]. These findings position interferon signaling as a central driver of disease activity and provide mechanistic rationale for emerging targeted therapies [68].

Transcriptomic analyses have demonstrated substantial overlap between LP and other interface dermatitis/interferon-associated disorders, including cutaneous lupus erythematosus and graft-versus-host disease [62,63,69,70]. Spatial and single-cell investigations further suggest compartmentalized inflammatory niches involving activated keratinocytes, interferon-responsive stromal cells, and cytotoxic lymphocyte aggregates concentrated near the epithelial interface [20,22,71]. Although IL-17 involvement has been reported in LP pathogenesis, most studies are focused on oral LP, particularly the chronic erosive subtype, suggesting that IL-17 may play differential roles in pathophysiology [72]. To date, the principal pathogenic mediators of LP are thought to be IFN primed T cell-mediated immune disorders.

Keratinocytes in LP are increasingly recognized as active immunologic participants rather than passive injury targets. IFN- γ stimulation primes keratinocytes for cytotoxic T-cell-mediated injury through JAK2/STAT1-dependent induction of major histocompatibility complex (MHC) class I and inflammatory signaling [67]. LP keratinocytes and fibroblasts can secrete CXCL9, CXCL10, and CCL19, amplifying recruitment of T lymphocytes into lesional skin [22]. This feed-forward inflammatory loop may contribute to chronicity and therapeutic resistance. Additionally, lesional keratinocytes exhibit enhanced STAT1 pathway activation, further implicating interferon/JAK-STAT signaling in disease persistence [22,67,68].

These mechanistic insights have generated substantial interest in JAK inhibition as a therapeutic strategy [68,73]. Multiple case reports and small series have demonstrated clinical improvement using tofacitinib, baricitinib, and upadacitinib in refractory cutaneous, oral, erosive vulvovaginal, nail, hypertrophic, and follicular LP variants [68,73,74,75,76]. Hwang et al. [65] reported an early and sustained clinical response in 12 patients with cutaneous and mucosal LP to Baricitinib, and demonstrated a correlation between reductions in CXCL13+CD8⁺ T cells and clinical improvement. Similar responses have been described in lichen planopilaris and erosive mucosal disease, particularly among patients refractory to corticosteroids and conventional immunosuppressants [68,73,77,78]. These reports suggested that JAK inhibition may protect keratinocytes from IFN-induced cytotoxic injury.

Importantly, molecular heterogeneity likely exists within LP despite relatively uniform histopathology. Some lesions demonstrate dominant IFN- γ /CXCR3 chemokine signaling, whereas others show contributions from TNF,

IL-17, cytotoxic effector programs, or TRM-associated cytokine networks [17,20,22,71]. Immune–epithelial cell cross-talk likely differs among distinct subclinical subtypes of lichen planus, potentially contributing to variations in disease phenotype, progression and response to therapy. At present, however, validated biomarkers capable of stratifying patients according to dominant inflammatory pathways remain lacking.

Recent work has additionally explored immune checkpoint pathways in LP pathogenesis. PD-1/PD-L1 pathway expression has been evaluated in LP lesional tissue, and lichenoid eruptions are well-described immune-related adverse events during PD-1/PD-L1 checkpoint blockade, supporting biologic overlap between antitumor immune activation and interface dermatitis [79,80]. However, PD-1/PD-L1 findings in idiopathic LP are not fully consistent across studies, so checkpoint biology should be framed as an emerging area rather than an established biomarker platform [79,80,81].

Single-cell technologies remain comparatively underutilized in LP relative to psoriasis and CTCL but represent a major future opportunity. Recent single-cell and spatial transcriptomic work in erosive oral LP identified CD8⁺ tissue-resident memory T-cell populations producing IFN- γ , TNF, and IL-17, supporting a model in which localized TRM-driven cytokine networks contribute to chronic mucosal inflammation and epithelial injury [20]. Recently, Jiang et al. [66], using single-cell and spatial profiling approaches, identified a role of IL-15 produced by cDC2A cells in close proximity to CXCL13+CD8⁺ T cells in cutaneous and mucosal LP. In this study, *TNFRSF9* (4-1BB) was found to be a vital effector molecule and a potential therapeutic target for LP. However, the absence of reliable biomarkers remains a major clinical limitation in LP management. Disease severity, chronicity, treatment responsiveness, and malignant transformation risk — particularly in oral LP — are currently difficult to predict using conventional histopathology alone [82,83]. Molecular profiling approaches incorporating interferon signatures, cytotoxic effector markers, T-cell recruitment chemokines, T-cell receptor clonality, cytokine gradients, and spatial immune architecture may eventually provide more accurate prognostic and therapeutic stratification tools.

Therefore, LP represents an emerging frontier for precision dermatology. Although therapeutic development and selection remain less advanced than psoriasis, the expanding understanding of interferon biology, cytotoxic epithelial injury, chemokine-mediated T-cell recruitment, and JAK-STAT activation has rapidly transformed the translational landscape. Future integration of spatial transcriptomics, single-cell profiling, and longitudinal biomarker monitoring may ultimately enable pathway-directed treatment selection and more individualized management strategies. However, unlike psoriasis, currently validated treatment algorithms are not readily available for LP.

Cutaneous T-Cell Lymphoma and Longitudinal Immune Monitoring

Cutaneous T-cell lymphoma (CTCL) represents one of the most complex examples of cutaneous immune dysregulation and highlights the challenges of distinguishing chronic inflammation from malignant immune evolution. Mycosis fungoides (MF) and Sézary syndrome, the most common CTCL subtypes, demonstrate substantial clinical, histopathologic, immunophenotypic, and molecular heterogeneity that complicates diagnosis, prognostication, and therapeutic selection [84,85,86]. Distinction of tumor cell characteristics as it pertains to different stages of CTCL is especially important in understanding clinical treatment responses, given the overall variability in clinical manifestations, progression, and prognostication of the CTCL spectrum. Early-stage MF frequently mimics benign inflammatory dermatoses both clinically and histologically, often delaying diagnosis for years [84]. Conventional histopathology lacks sufficient sensitivity and specificity in early disease, creating significant interest in molecular biomarkers capable of improving diagnostic accuracy. Transcriptomic studies have identified differential expression of CXCL13, thymocyte selection associated high mobility group box (TOX), programmed cell death 1 (PDCD1), killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2 (KIR3DL2), GATA binding protein 3 (GATA3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), and cell adhesion molecule 1 (CADM1) in malignant T-cell populations relative to inflammatory dermatoses, although no single biomarker has demonstrated adequate standalone diagnostic performance [87,88,89,90,91].

ScRNA-seq has substantially expanded understanding of CTCL heterogeneity by revealing transcriptionally diverse malignant T-cell states within individual lesions. Gaydosik et al. [10] identified malignant populations exhibiting variable proliferative, exhausted, interferon-responsive, and cytokine-associated programs, while Liu et al. [3] demonstrated that malignant clones coexist with reactive inflammatory T cells, macrophages, dendritic cells, fibroblasts, and endothelial populations within complex tumor immune ecosystems [5]. Additional studies revealed substantial interpatient heterogeneity involving Th2-skewed cytokine programs, Myc-associated proliferative signatures, interferon signaling states, and immune exhaustion phenotypes characterized by PD1, TIGIT, CTLA4, lymphocyte activation gene 3 (LAG3), and TOX expression [3,5,10,23]. These findings suggest that CTCL progression reflects dynamic tumor–microenvironment interactions rather than isolated malignant T-cell expansion alone.

Spatial transcriptomic approaches have further refined understanding of CTCL architecture by preserving tissue organization during molecular analysis. Recent multimodal

studies integrating spatial transcriptomics, single-cell RNA sequencing, and T-cell receptor sequencing demonstrated that malignant T cells localize within compartmentalized microenvironments enriched for stromal remodeling, altered metabolic programs, dendritic cell interactions, and immunosuppressive cytokine signaling [5,27]. Li and colleagues [27] recently identified malignant Th2-skewed CTCL populations supported by B-cell-rich tumor microenvironments, suggesting that organized immune niches may contribute to disease persistence and therapeutic resistance. Spatial analyses additionally demonstrate that malignant T-cell populations distribute heterogeneously across lesions, resembling spatially organized tumor ecosystems observed in solid tumor oncology [5,27].

Immune exhaustion has emerged as a particularly important feature of CTCL biology. Malignant T cells frequently express PD1, TIGIT, LAG3, CTLA4, and TOX, suggesting chronic antigenic stimulation and dysfunctional immune states [10,23,88]. Reactive immune populations within the tumor microenvironment may simultaneously exhibit exhaustion phenotypes, potentially impairing anti-tumor surveillance and facilitating disease progression [3,23]. These findings have generated interest in checkpoint-directed therapies, although responses to PD1 blockade in CTCL remain variable and occasionally paradoxical, with reports of both clinical responses and disease acceleration [92,93].

Circulating biomarkers are particularly relevant in CTCL because advanced disease frequently demonstrates systemic involvement. High-throughput T-cell receptor sequencing, ctDNA, and peripheral blood clonality assays increasingly demonstrate utility for monitoring tumor burden, minimal residual disease, and clonal evolution [33,94,95]. De Masson et al. [95] demonstrated that peripheral blood T-cell receptor sequencing sensitively identified malignant clones and correlated with disease burden across CTCL stages. Additional studies suggest that ctDNA-based approaches may ultimately permit earlier detection of progression or relapse prior to overt clinical deterioration [94]. Cytokine profiling further demonstrates dynamic immunologic evolution during disease progression, with early MF often exhibiting relative Th1-associated inflammation and advanced disease transitioning toward Th2 polarization characterized by elevated IL-4, IL-5, IL-10, and IL-13 expression [96,97]. This Th2 shift contributes to impaired anti-tumor immunity, increased infection susceptibility, and worse clinical outcomes [96,97].

Similarly, direct evaluation of circulating tumor cells of advanced stage CTCL or Sézary syndrome may offer an additional non-invasive opportunity for disease monitoring. Understanding the hematologic dissemination and genetic transformations of malignant cells demonstrates potential prognostication and treatment responsiveness of various metastatic solid organ tumors [98].

Non-invasive longitudinal monitoring represents one of the most promising translational opportunities in CTCL. Repeated biopsies are limited by sampling variability, lesion heterogeneity, procedural burden, and poor suitability for serial disease monitoring. Emerging tape-strip, microneedle, and hydrogel-based sampling approaches may permit minimally invasive longitudinal collection of cytokines, nucleic acids, and tumor-associated biomarkers directly from lesional skin [29,32,99]. Although these technologies remain investigational in CTCL, they may ultimately facilitate dynamic monitoring of treatment response, molecular progression, and therapeutic resistance while reducing reliance on repeated invasive biopsies. [29,32,99].

Integration of multimodal datasets may ultimately define future CTCL management, but current guidelines are limited. Previous reviews have highlighted that understanding tumor microenvironment and metabolic reprogramming of tumor cells may have important therapeutic implications for treatment refractory malignancies [100,101,102]. Recently, Dorando et al. [103] preformed a comprehensive multiomics assessment to understand the genomic associations of CTCL disease progression. It was found that disease progression was associated with recurrent mutations in the epigenetic modifier enhancer of zeste homolog 2 (EZH2) and also identified gain-of-function STAT3 mutations that enhance binding of Ras homolog guanosine triphosphatase (Rho GTPase) pathways [103]. Although, further studies are needed to understand the implications on treatment refractory disease.

Combining spatial immune architecture, malignant clone characterization, circulating tumor biomarkers, cytokine profiling, single-cell transcriptomics, and longitudinal non-invasive sampling could generate individualized disease signatures capable of guiding therapeutic selection and adaptive treatment strategies. CTCL therefore represents a uniquely informative model at the intersection of inflammatory immunology and cutaneous oncology, and continued advances in spatial biology, single-cell profiling, and longitudinal biomarker monitoring may ultimately transform CTCL into a truly precision-guided malignancy.

Challenges and Barriers to Clinical Implementation

Despite rapid advances in spatial biology, single-cell sequencing, and circulating biomarker technologies, several barriers continue to limit implementation of precision dermatology in routine clinical practice. A major challenge is the marked biologic heterogeneity that exists both within and between lesions, particularly in inflammatory disorders such as psoriasis and lichen planus and in highly heterogeneous malignancies such as CTCL [1,3,10]. Single-lesion biopsies may inadequately capture regional immune variation, stromal organization, or clonal diversity, raising concerns regarding sampling bias and reproducibility of molecular signatures [25,27].

Technical standardization remains another major limitation. Differences in tissue handling, dissociation methods, sequencing platforms, spatial transcriptomic pipelines, and bioinformatic processing can substantially alter downstream results and complicate cross-study validation [24,104,105]. Integration of multimodal datasets—including transcriptomics, proteomics, imaging, clonality analysis, and circulating biomarkers—further requires advanced computational infrastructure that is not yet broadly available in clinical dermatology settings [24,104].

An additional challenge involves translation of high-dimensional molecular data into clinically actionable algorithms. Although numerous candidate biomarkers have been associated with disease severity, therapeutic responsiveness, or relapse risk, few have demonstrated sufficient sensitivity, specificity, prospective validation, or reproducibility for routine clinical implementation [1,33,46]. Many reported biomarkers also reflect generalized immune activation rather than disease-specific biology, limiting their utility for individualized treatment selection [33].

Economic and logistical barriers also remain substantial. Single-cell and spatial technologies are expensive, labor-intensive, and dependent on specialized technical expertise [106]. While costs continue to decline, widespread adoption will likely require development of simplified clinically scalable assays, standardized analytic frameworks, and reimbursement models supporting molecular diagnostics in dermatology [106,107]. Additionally, the large volume and complexity of genomic and spatial data raise important issues related to data storage, interpretation, interoperability, and clinical reporting [24,107].

Finally, prospective longitudinal studies remain limited across many dermatologic diseases. Most available datasets are cross-sectional and generated from relatively small cohorts, restricting understanding of dynamic immune evolution during treatment, relapse, and disease progression [25,46]. Future efforts integrating serial tissue sampling, non-invasive monitoring platforms, circulating biomarkers, and spatially resolved molecular profiling will be essential for translating precision dermatology from a predominantly investigational framework into clinically actionable practice.

Discussion and Future Directions: Toward Integrated Precision Dermatology

The integration of precision medicine in dermatology will likely require significant adjustments to current clinical frameworks. Utilization of spatial biology, longitudinal immune monitoring, and computational analysis are approaches that may achieve this change. Emerging data from psoriasis, lichen planus, and CTCL demonstrate that clinically similar lesions contain distinct immune and malignant cellular processes. This suggests that molecular endotyping, not morphology, ultimately proves more

predictive of therapeutic responsiveness [1,3,20,42]. Integration of single-cell transcriptomics, spatial transcriptomics, circulating biomarkers, and non-invasive skin sampling would enable more precise disease stratification and dynamic monitoring compared to traditional management methods [33,99].

Ongoing advancements in spatial and single-cell technologies are reshaping the current understanding of therapeutic resistance and disease relapse. Persistent tissue-resident memory T-cell populations, inflammatory fibroblast niches, altered myeloid signaling states, and tumor-supportive microenvironments appear to contribute to chronic disease persistence despite apparent clinical resolution [3,42,43]. These observations suggest that future therapeutic strategies may require targeting interconnected immune-stromal circuits rather than isolated cytokine pathways alone, particularly in heterogeneous diseases such as CTCL [3,27].

Longitudinal non-invasive monitoring platforms represent another major step towards precision dermatology. Tape stripping, microneedle sampling, hydrogel-based biomarker collection systems, and circulating cfDNA/ctDNA analysis may permit serial assessment of cytokines, nucleic acids, and treatment-response signatures [27,32,33]. Such approaches could negate the need for repeated biopsies and facilitate earlier identification of therapeutic resistance or relapse. This reduction in procedural burden would prove beneficial not only in CTCL management, but across various inflammatory diseases.

Despite these biotechnological advances, substantial barriers restrict widespread clinical implementation. Overcoming these obstacles will require standardized sampling protocols, scalable biomarker assays, prospective longitudinal validation studies, and computational frameworks capable of integrating high-dimensional spatial and transcriptomic datasets into clinically interpretable algorithms [24,104].

Although there are considerable logistical and cost prohibitive barriers to routine incorporation of the various immune microenvironment profiling tools in management of psoriasis, LP, and CTCL, the authors propose that the utilization of such may be valuable in several clinical scenarios. If biopsy is needed to aid in diagnosis, molecular characterizations with single-cell or spatial transcriptomics of sampled tissue can help identify dominant inflammatory pathways and aid in initial treatment selection. Additionally, failure of more than several first line treatment modalities may provide a second avenue to where precision dermatology techniques can be beneficial. In these cases, the authors suggest that the use of non-invasive sampling tools or circulating biomarkers may be more appropriate as they facilitate longitudinal disease monitoring while minimizing patient burden.

Conclusion

Precision medicine has increasingly gained understanding and value when managing complex disease states. Compared to other disease processes, the skin offers unique accessibility of tissue to determine the pathogenic immune microenvironments. Psoriasis has become a model for understanding the factors which drive disease, and LP and CTCL have demonstrated a similar potential. The rapid evolution of single-cell RNA sequencing, spatial transcriptomics, non-Invasive epidermal sampling tools, or circulating biomarkers/cell-free DNA position dermatology to emerge as a leading model for precision medicine across chronic inflammatory and malignant diseases.

Abbreviations

scRNA-seq, single-cell RNA sequencing; TRM, tissue-resident memory; Th17, T helper 17; Tc17, T cytotoxic 17; IL, Interleukin; TNF, tumor necrosis factor; CCL20, C-C motif chemokine ligand 20; CXCL1, C-X-C motif chemokine ligand 1; DEFB4A, defensin beta 4A; S100A7, S100 calcium-binding protein A7; CCR6, C-C motif chemokine receptor 6; TSLP, thymic stromal lymphopoietin; IFN- γ , Interferon-gamma; CXCR3, C-X-C chemokine receptor 3; MIG, monokine induced by gamma interferon; IP-10, interferon gamma-induced protein 10; CD14, cluster of differentiation 14; LAMP3, lysosomal associated membrane protein 3; SIRPA, signal regulatory protein alpha; MIF, macrophage migration inhibitory factor; JAK-STAT, Janus kinase–signal transducer and activator of transcription; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; UBE2T, ubiquitin conjugating enzyme E2 T; NF- κ B, nuclear factor Kappa-light-chain enhancer of activated B cells; VEGFA, vascular endothelial growth factor A; TNFSF, TNF superfamily; HLA, human leukocyte antigen; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TOX, thymocyte selection associated high mobility group box; PDCD1, programmed cell death 1; KIR3DL2, killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2; GATA3, GATA binding protein 3; TIGIT, T cell immunoreceptor with Ig and ITIM domains; CADM1, cell adhesion molecule 1; CTLA4, cytotoxic T-lymphocyte associated protein 4; LAG3, lymphocyte activation gene 3; EZH2, enhancer of zeste homolog 2; STAT3, signal transducer and activator of transcription 3; Rho GTPase, Ras homolog guanosine triphosphatase.

Availability of Data and Materials

Not applicable.

Author Contributions

LR, RH, TW and AJP contributed to conceptualization, investigation, data curation, writing-original draft, writing-review & editing. TW also contributed to supervision. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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