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REVIEW ARTICLE

Spatial transcriptomics uncovers new dimensions of skin disease heterogeneity and their implications for therapeutic strategies

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Abstract

Spatial transcriptomics (ST) differs from traditional transcriptomic approaches by retaining tissue architecture and enabling the spatial mapping of gene expression. As a promising method, ST has been applied to skin diseases in recent years, such as psoriasis, atopic dermatitis, and skin tumors. This review provides a comprehensive overview of ST in skin diseases. We first summarize the mainstream ST technologies and the key factors influencing platform selection for skin disease research. We then outline recent advances in the application of ST in dermatology, highlighting its ability to systematically reveal in situ cellular interactions and regional heterogeneity. We also discuss how ST can guide therapeutic strategies for skin diseases through target discovery, response prediction, and the elucidation of spatially resolved mechanisms underlying treatment resistance. These spatial findings have also informed the development of novel targeted therapies and the optimization of existing treatment regimens for various skin disorders. In summary, ST offers new perspectives and powerful tools for understanding the regulatory mechanisms of skin physiology, thereby promoting the clinical translation of precision diagnostic and therapeutic strategies. A better understanding of ST applications in skin diseases will enable more effective treatments.

Keywords: Spatial transcriptomics, Skin disease heterogeneity, Skin cancer, Atopic dermatitis, Psoriasis

1 INTRODUCTION

Spatial transcriptomics (ST) preserves tissue structure and maps gene expression in physical space. Unlike bulk RNA-seq or scRNA-seq, ST keeps positional information [1, 2]. Because skin function depends directly on its layered architecture, it is a tissue for which dissociative transcriptomic approaches are inherently limited. The clinical and biological heterogeneity of skin diseases therefore makes the case for applying ST particularly strong.

ST captures transcriptomic information at the spot level or even at near-single-cell resolution directly in situ and links each measurement to a spatial coordinate, enabling the simultaneous interrogation of gene expression profiles and tissue spatial architecture. Current ST platforms fall into two categories: imaging-based and sequencing-based methods [3]. The skin contains diverse cell types and varies markedly across patients. ST connects morphology with molecular profiles. It can pinpoint the actual locations where disease-related interactions occur. This could offer a practical roadmap for targeted interventions [4].

Skin diseases are heterogeneous across multiple levels. In psoriasis and atopic dermatitis (AD), clinical manifestations and histopathological features differ markedly among patients. At the tissue and cellular levels, the epidermis, dermis, and skin appendages, such as hair follicles and sebaceous glands, are intricately stratified and comprise diverse cell types, including keratinocytes, fibroblasts, endothelial cells, and a wide range of

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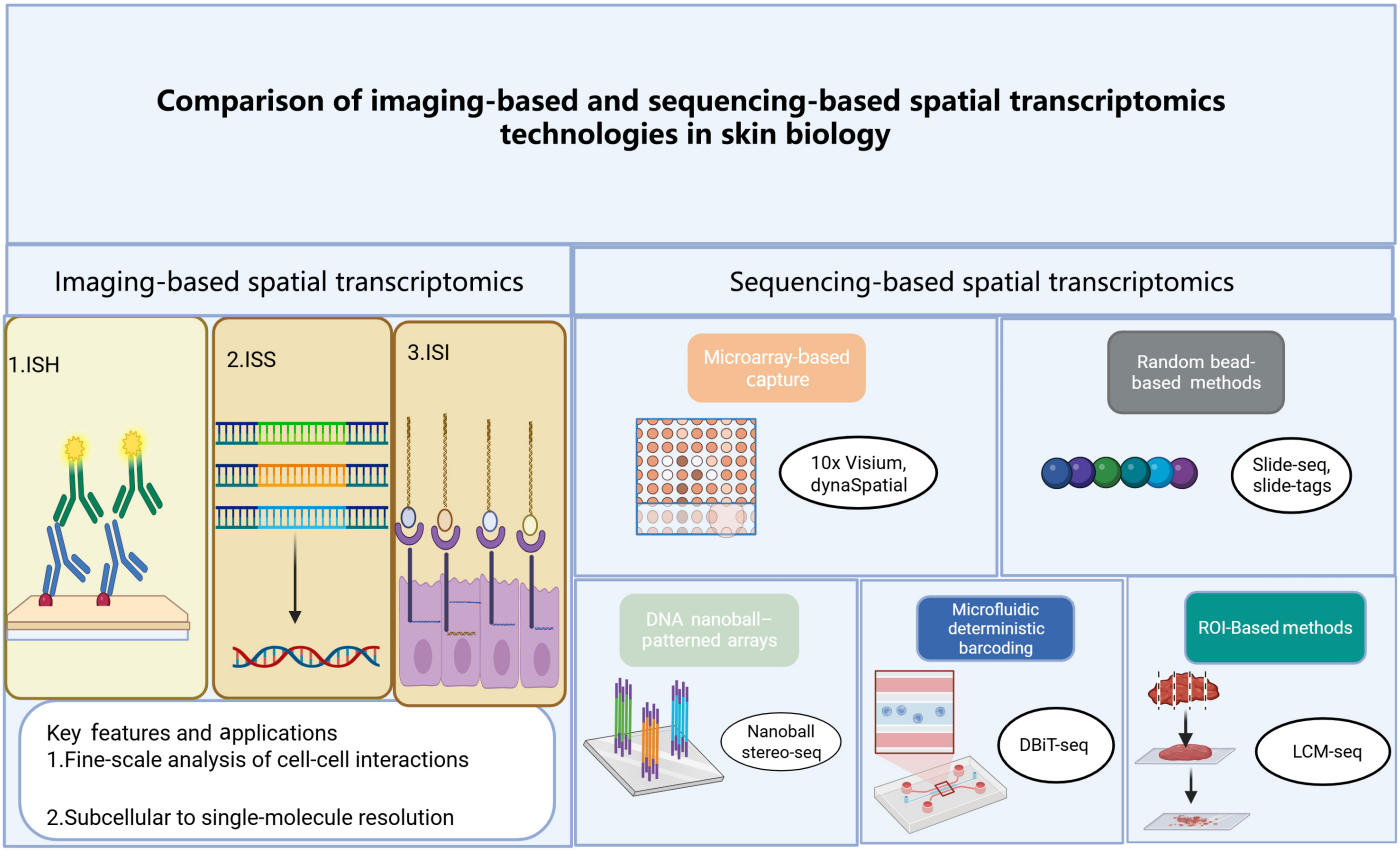

Figure 1. Comparison of imaging-based and sequencing-based ST technologies in skin biology. Schematic overview of the two major categories of ST technologies used in skin research. The left panel shows imaging-based approaches, including ISH, ISS and ISI. These approaches enable fine-scale analysis of cell–cell interactions and can achieve subcellular or single-molecule resolution. Some imaging-based platforms are also compatible with FFPE samples. The right panel shows sequencing-based approaches classified according to their spatial capture or barcoding strategies, including microarray-based capture methods, such as 10x Visium and DynaSpatial; random bead-based methods, such as Slide-seq and Slide-tags; DNA nanoball–patterned arrays, such as Stereo-seq; microfluidic deterministic barcoding methods, such as DBiT-seq; and ROI-based methods, such as LCM-seq. Created by the authors using BioRender.com. ST, spatial transcriptomics; ISH, in situ hybridization; ISS, in situ sequencing; ISI, in situ imaging; FFPE, formalin-fixed, paraffin-embedded; DNA, deoxyribonucleic acid; Stereo-seq, SpaTial Enhanced REsolution Omics-sequencing; DBiT-seq, deterministic barcoding in tissue for spatial omics sequencing; ROI, region of interest; LCM-seq, laser capture microscopy coupled with full-length messenger RNA sequencing.

innate and adaptive immune cells [5]. Conventional "homogenization" approaches struggle to answer where inflammatory signals originate, which cells drive them, and how they are amplified and sustained within a given spatial architecture. The application of ST is therefore transforming our understanding of skin disease from a two-dimensional "cellular parts list" into a three-dimensional atlas of the spatial organization of cells [6].

This review focuses on using ST to investigate the pathogenesis and potential therapeutic targets of skin diseases. We first summarize mainstream ST technology routes and key considerations for platform selection. We then outline recent progress enabled by ST technologies in inflammatory skin diseases, autoimmune and fibrotic disorders, and skin tumors, highlighting newly defined spatial niches, cell–cell communication programs, and molecular subtypes. We also discuss how these insights can facilitate the identification of novel targets, the optimization of therapeutic regimens, and the development of strategies to overcome treatment resistance by remodeling pathogenic microenvironments.

2 STRENGTHS AND LIMITATIONS OF MAJOR ST APPROACHES

Based on their technical principles and implementation strategies, existing ST methods can be broadly categorized into imaging-based and sequencing-based approaches, as shown in **Figure 1**. Each category encompasses several techniques with distinct strengths and limitations, which must be carefully considered for their optimal application in skin disease research.

2.1 Imaging-based ST

Imaging-based ST methods, such as in situ hybridization (ISH), in situ sequencing (ISS) and in situ imaging (ISI), can detect RNA molecules directly in fixed tissue sections [7-9]. They achieve nanoscale or subcellular resolution and work well with formalin-fixed, paraffin-embedded samples [10]. They can even analyze fine structures such as hair follicle niches [11]. Thus, these methods are particularly well suited for analyzing complex anatomical regions. In skin research, high-resolution spatial data can show gene activity clearly in all skin layers. They can reveal clusters of immune cells near skin glands and hair follicles. They can also detect changes in skin cells. However, imaging-based methods can detect only a limited number of transcripts and are relatively costly. These limitations restrict the broader application of imaging-based ST [12].

2.2 Sequencing-based ST

High-definition array-based platforms such as 10x Visium have become widely used tools for spatial profiling [13]. Although Visium HD can achieve ~2 μm resolution, it demands considerable computational resources [2, 14, 15]. Standard 55–100 μm spots reduce the heavy computational burden but do not provide single-cell resolution [13, 16].

Bead-based methods provide an alternative. Slide-seq and Slide-tags use densely packed barcoded beads spaced 10–20 μm apart to achieve single-cell resolution. These methods can better resolve microenvironments and limit RNA diffusion [17-19].

Deterministic barcoding in tissue for spatial omics sequencing (DBiT-seq) and similar microfluidic deterministic barcoding methods offer another approach. Rather than prioritizing the highest spatial resolution, they enable the simultaneous analysis of RNA and protein expression [20, 21]. Because skin diseases often involve both the epidermis and dermis, this multimodal analysis can help identify intercellular interactions [22, 23].

Region-of-interest-based platforms such as NanoString GeoMx DSP represent another strategy. They focus on predefined regions, such as hair follicles or psoriatic plaques, rather than enabling continuous tissue-wide profiling. This targeted design is unsuitable for unbiased discovery [24].

However, selecting an appropriate platform is challenging because each technology has distinct strengths and limitations that can affect data interpretation. For example, although Visium HD provides the highest resolution among array-based methods, the resulting data volume can exceed the capacity of standard computational pipelines. More importantly, the 55-μm spots of conventional Visium arrays mix transcripts from multiple cells. Bead-based platforms partially address this limitation through finer spatial sampling. However, random bead placement does not guarantee true single-cell capture [24].

The choice of a suitable platform depends largely on the disease under investigation. In melanoma, array-based methods may be appropriate because the lesions often have clearly defined tissue boundaries. In psoriasis and acne, where pathological margins may be poorly defined, bead-based approaches can minimize signal crosstalk. DBiT-seq is suitable when simultaneous analysis of RNA and protein expression is required. For well-defined structures such as hair follicles, region-of-interest-based platforms may be appropriate. No single platform is suitable for all research settings. The best choice depends on the specific research question and tissue complexity [12].

3 APPLICATIONS OF ST IN SKIN DISEASE HETEROGENEITY

An overview of key spatially resolved mechanisms across major skin diseases is presented in **Figure 2**.

3.1 Inflammatory skin diseases

3.1.1 Psoriasis

Recent studies using ST have revealed complex cellular circuits that drive psoriasis. This approach has revealed an IL-36 inflammatory hub in the upper epidermis. Specific fibroblast subsets located in the papillary dermis are associated with lesion recurrence [25, 26]. Activated keratinocytes participate in the IL-36 loop to amplify local inflammation [25]. Basal keratinocytes exhibit a metabolically dominant state characterized by COX7B-driven oxidative phosphorylation combined with glycolytic lactate production. This metabolic state fuels their hyperproliferation and also promotes the expansion of neighboring γδT17 cells. This creates a pro-inflammatory feedback loop between epithelial and immune cells [27, 28]. A discrete AKR1B10$^+$/MT1G$^+$ spinous-layer keratinocyte subset has also been linked to disease severity and treatment resistance [29, 30]. Even clinically uninvolved skin in severe psoriasis patients exhibits molecular abnormalities. Keratinocytes in those regions appear pre-activated, with upregulation of FGFR3 and DGAT2. This might point to an underlying defect in barrier integrity [26]. Dermal fibroblasts are also actively involved in the inflammatory process. SFRP2$^+$ fibroblasts recruit monocytes and activated dendritic cells. CD8$^+$ T cells secrete CCL13, CCL19, and CXCL12 [25]. WNT5A$^+$/IL-24$^+$ fibroblasts promote matrix remodeling and angiogenesis [31, 32]. FAP$^+$ fibroblasts cluster with endothelial cells and antigen-presenting cells to form structures resembling tertiary lymphoid microdomains [33, 34].

Patients who respond poorly to IL-23 blockade exhibit persistent Th17 activation programs [35]. In contrast, a response to IL-17A blockade with agents such as secukinumab is associat-

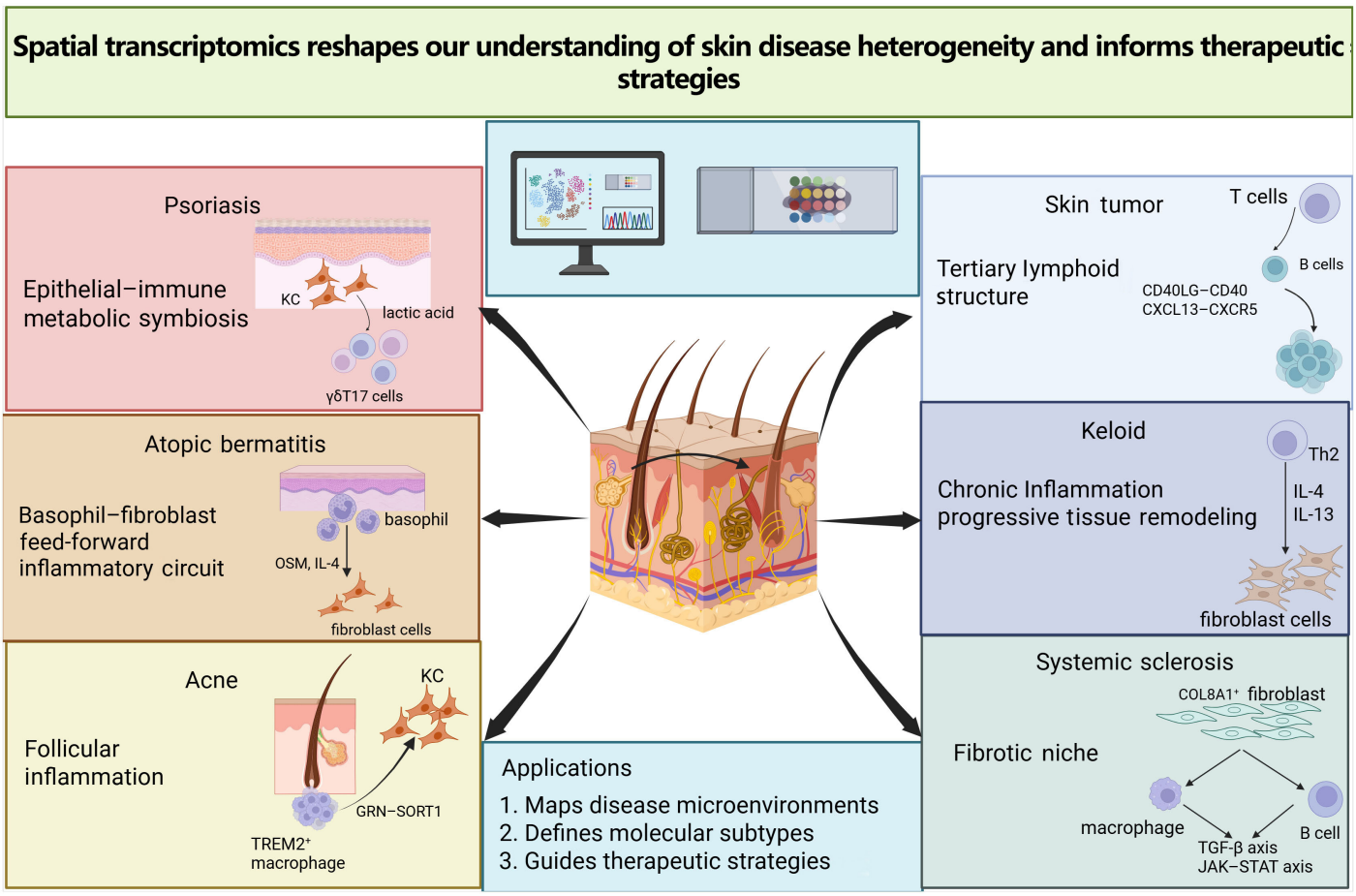

Figure 2. ST reshapes our understanding of skin disease heterogeneity and informs therapeutic strategies. This figure summarizes key findings from ST studies of six major skin diseases. In psoriasis, metabolic symbiosis links keratinocytes with γδ T17 cells. In atopic dermatitis, ST reveals a basophil–fibroblast feed-forward inflammatory circuit mediated by OSM and IL-4, and keratinocytes. Acne is characterized by follicular inflammation associated with TREM2$^+$ macrophages and the GRN-SORT1 axis. In skin tumors, ST reveals T-cell–B-cell interactions within tertiary lymphoid structures (TLSs) through CD40LG–CD40 and CXCL13–CXCR5 signaling. In keloids, ST identifies chronic inflammation and progressive tissue remodeling involving Th2 cells, IL-4, IL-13, and fibroblasts. In systemic sclerosis, ST reveals a fibrotic niche comprising COL8A1$^+$ fibroblasts, macrophages, and B cells, with involvement of the TGF-β and JAK–STAT pathways. Together, these examples illustrate how ST identifies cellular crosstalk, niche-specific pathways, and disease heterogeneity to inform targeted therapeutic strategies. Created by the authors using BioRender.com. ST, spatial transcriptomics; KC, keratinocyte; γδ T17 cell, gamma delta T17 cell; Th2 cell, T helper 2 cell; OSM, oncostatin M; IL-4, interleukin 4; IL-13, interleukin 13; TREM2, triggering receptor expressed on myeloid cells 2; GRN, granulin precursor; SORT1, sortilin 1; CD40LG, CD40 ligand; CD40, CD40 molecule; CXCL13, C-X-C motif chemokine ligand 13; CXCR5, C-X-C motif chemokine receptor 5; COL8A1, collagen type VIII alpha 1 chain; TGF-β, transforming growth factor beta; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

ed with the downregulation of hypoxia-related pathways involving genes such as RHCG [36]. Although treatments such as secukinumab and Dead Sea climatotherapy can achieve similar clinical effects, they leave distinct molecular scars. These molecular imprints differ in their transcriptomic profiles, with 479 genes, including SERPINB4, IL36G, and AKR1B10, being differentially expressed between the treatment groups. The treatments also produce distinct proteomic changes in key microenvironments, such as CD103$^+$ cell niches and the dermis. Such treatment-specific molecular scars may influence disease memory and relapse patterns [37]. Moreover, obesity and resistance to biologic therapy are associated with persistently high expression of epidermal innate immune signals, such as S100A8/A9, IL-36, and TNFSF10/TRAIL. This pattern suggests an innate immunity- and metabolism-driven subtype that is independent of classical Th17 pathways [38]. Together, these findings from ST define a spatially organized inflammatory circuit. This circuit spans epidermal amplifiers, metabolically primed keratinocytes, and heterogeneous fibroblast hubs.

3.1.2 AD

The combination of ST and single-cell RNA sequencing has revealed cellular circuits involved in AD [39]. These techniques

localize disease-associated cellular interactions to specific regions of the skin, thereby helping to guide therapies targeting specific tissue regions [40-42].

Keratinocyte hyperproliferation contributes directly to two key features of AD: epidermal thickening (acanthosis) and dysregulated keratinization. ST enables the localization of disease-associated changes to specific tissue regions. Activated keratinocytes produce large amounts of chemokines such as CCL17 and CCL22 and cytokines like TSLP and IL-33. These mediators recruit and activate immune cells, thereby sustaining inflammation in AD [43]. Barrier dysfunction is shown at the molecular level. At the same time, IL-4 and IL-13 derived from Th2 cells directly downregulate key barrier-related genes, such as FLG, which encodes filaggrin. Additionally, IL-22 secreted by Th22 cells acts synergistically with Th2 cytokines to induce spongiosis and differentiation defects characteristic of AD [44, 45].

In the dermis, fibroblasts serve as key amplifiers and form active signaling networks with multiple immune cell populations. In leukocyte-infiltrated regions, COL18A1-expressing activated fibroblasts co-localize with CCR7-expressing dendritic cells, CCL13/CCL18-expressing M2 macrophages, and T cells, establishing stable communication networks via ligand–receptor pairs such as CCL19–CCR7 [42]. Deeper mechanisms have been revealed in mouse models. Basophils can initiate a potent basophil–fibroblast feed-forward inflammatory circuit by secreting oncostatin M and IL-4. This circuit provides potential targets for disrupting pathogenic intercellular communication [43, 46].

ST has revealed extensive remodeling of immune cell compartments in AD lesions. Macrophages and dendritic cells increase markedly in abundance and serve as bridges between innate and adaptive immunity. Their infiltration is a hallmark of immune activation, and these cells serve as major sources of inflammatory mediators, secreting cytokines such as TNF-α and IL-23 that amplify inflammation and may promote distinct inflammatory endotypes, such as Th17- and Th22-associated endotypes. As terminal effectors, Th2, Th22, and Th1 subsets produce IL-4, IL-13, IL-22, and IFN-γ to directly mediate itch, barrier disruption, and epidermal hyperplasia—consistent with AD being fundamentally a T-cell-mediated immune disease [43]. Sebaceous glands are also being redefined as active regulators in disease. ST indicates that sebaceous glands in AD lesions undergo Th2 inflammation-associated lipid metabolic reprogramming, characterized by altered expression of genes such as CCL17 and HSD3B1, suggesting that they may participate in disease-specific local immune modulation [47].

In-depth analysis of multi-omic data has identified new candidate regulators and endotype markers. At least three core AD subtypes have been resolved: (i) a barrier-defect/metabolic-dysregulation subtype characterized by downregulation of UGT3A2 and impaired barrier repair; (ii) an immune-imbalance "endogenous" subtype associated with high CHRM4 expression and low IgE levels, suggesting atypical Th2 activation; and (iii) a cytokine-driven inflammatory activation subtype featuring high expression of IL-36A, IL-4R, and other key factors that drive strong local inflammation. These subtypes point to distinct targets for precision intervention—barrier repair, innate immune modulation, and targeted anti-cytokine therapy—providing a scientific basis for moving from a single clinical diagnosis toward stratified therapy guided by molecular subtyping [43]. These insights have profound implications for treatment strategy. The limitations of strategies that target only the Th2 axis, such as treatment with anti-IL-4Rα antibodies, may be explained by their limited effects on parallel pathways, such as the IL-22 pathway [45]. Therefore, multipathway strategies, such as dual targeting of the AhR and JAK pathways or interventions targeting specific intercellular circuits such as the basophil–fibroblast axis, appear more promising [41, 43, 45, 46]. Collectively, these spatial and single-cell insights are transforming our understanding of the complexity of AD. They reveal distinct disease subtypes and multicellular interaction networks that pave the way for subtype-specific, multitarget precision therapies.

3.1.3 Acne

Sebaceous glands are dynamic and heterogeneous functional units. ST is updating our understanding of their role in acne. By combining single-cell sequencing with ST, studies have distinguished keratinocyte subpopulations across different anatomical regions at the molecular and spatial levels. These studies have also mapped the full differentiation trajectory of human sebaceous lineage cells from proliferation and lipid synthesis to terminal rupture, and defined stage-specific marker genes [48, 49]. These findings enable the precise localization of disease-associated changes.

In acne, immune cells gather at specific microanatomical sites, forming organized clusters that amplify local inflammation. ST reveals that early lesions feature $TREM2^+$ macrophages activated by lipid signals. These cells form a key hub for the initiation of inflammation [50]. Spatial co-localization further suggests direct macrophage–keratinocyte communication through axes such as GRN–SORT1, promoting keratinocyte hyperproliferation and hyperkeratinization and thereby providing a spatial explanation for the cellular origin of follicular hyperkeratosis and comedone formation [51, 52]. ST identifies a scar-associated niche in which profibrotic $SPP1^+$ macrophages coexist with $POSTN^+$ fibroblasts and cooperate through SPP1 signaling to drive abnormal collagen deposition [53].

Based on these mechanistic insights, $TREM2^+$ macrophages and downstream molecules such as SORT1 and SPP1 have emerged as potential therapeutic targets to interrupt acne inflammation and fibrotic progression [50, 53]. Equally impor-

tant, ST provides a powerful framework to evaluate how existing therapies remodel the spatial ecology of lesions.

3.2 Skin tumors

3.2.1 Cutaneous squamous cell carcinoma (cSCC)

The pathogenesis of cSCC is driven by genetic mutations, tumor heterogeneity, and remodeling of the immune microenvironment. Spatial omics reveals that driver mutations in TP53 and NOTCH1 initiate the transition from precancerous states to invasive carcinoma, challenging conventional linear progression models [54]. Tumor heterogeneity in skin cancers is largely attributable to keratinocyte plasticity. Keratinocyte differentiation programs depend on signals from the surrounding tissue [6, 55, 56]. Cancer-associated fibroblasts (CAFs), for instance, promote tumor invasiveness via the MDK–ITGA6 signaling axis. Certain tumor clones also recruit regulatory T cells through CXCL16/CXCR6 chemokine signaling to build an immunosuppressive microenvironment [57, 58]. To target the tumor microenvironment in cSCC, researchers recently developed a modified chlorin e6 derivative called Shengtaibufen. Shengtaibufen induces STING-mediated PANoptosis, when combined with lymphocyte-activation gene 3 blockade, enables a synergistic photodynamic therapy–immunotherapy strategy that reshapes the tumor immune microenvironment [59]. Together, these findings link cSCC progression to spatially coordinated interactions among genetic mutations, stromal cells, and immune populations.

3.2.2 Melanoma

Melanoma heterogeneity is not randomly distributed. An early ST study of lymph node melanoma metastases revealed that distinct tumor subclones occupy separate spatial domains within a single lesion, with MITF-low and MITF-high transcriptional programs intermixed [60].

For example, in melanomas arising from congenital melanocytic nevi, deeper tumor invasion is associated with higher expression of immunosuppressive genes, stronger T-cell inhibitory signatures, and greater M2 macrophage polarization. Metastatic lesions also upregulate additional immune evasion genes like AXL, EPHA2, and BST2. A stress-like cancer cell state characterized by FOS/JUN pathway activation and heat-shock protein expression has also been confirmed in both zebrafish and human melanoma models. This state, which has been observed in multiple cancer types, may contribute to drug resistance [61].

Integrative lineage tracing and ST have established a hierarchical melanoma growth model with tumorigenic competence confined to a perivascular niche and mesenchymal-like cells identified as metastasis-initiating cells [62]. In melanoma brain metastases, multi-omic analyses revealed chromosomal instability, a neuronal-like state, and enrichment of dysfunctional TOX^+ $CD8^+$ T cells and monocyte-derived macrophages [63].

A conserved "interface" cell state at tumor boundaries was identified in zebrafish models, marked by coordinated cilia gene upregulation [64]. In acral melanoma, MYC^+ melanoma cells and $FGFBP2^+$ natural killer T cells were linked to lymph node metastasis through MITF-induced fatty acid oxidation, a targetable dependency [65]. Together, these studies highlight the power of ST to resolve melanoma's cellular heterogeneity, immune remodeling, and therapeutic vulnerabilities.

3.2.3 Basal cell carcinoma (BCC)

Recent advances in single-cell RNA sequencing and ST have provided high-resolution insights into the cellular heterogeneity and spatial organization of skin cancers, particularly BCC [66]. Integrated analyses of human BCC have revealed that tumor cells within the invasive niche adopt collective migration phenotypes characterized by increased expression of cell–cell junction-related genes, whereas spatially adjacent CAFs exhibit extracellular matrix-remodeling features and respond to tumor-derived activin A signaling [67]. A distinct CAF subset (C01_TNC) enriched in peritumoral regions has been identified. It may promote tumor progression through matrix remodeling and spatial colocalization with regulatory T cells, contributing to an immunosuppressive barrier [68]. In Gorlin syndrome, BCCs shift from a basal to a squamous phenotype. PCYT2 and ETNK1 in the phosphatidylethanolamine biosynthesis pathway appear to suppress this phenotypic transition [69]. On the diagnostic side, chromogenic in situ hybridization for GLI1 RNA achieves high specificity (98%) and sensitivity (95%), outperforming conventional hematoxylin and eosin staining and other BCC markers [70]. In a phase 2 trial of cemiplimab for locally advanced BCC (n=84), the objective response rate was 31% (95% confidence interval, 21%–42%), including five complete responses [71]. ST reveals that a CAF/macrophage niche at the tumor front excludes $CD8^+$ T cells, driving resistance to cemiplimab. In short, from diagnosis to treatment resistance, spatial context matters in BCC.

3.3 Others

3.3.1 Keloid

Keloid formation depends on coordinated crosstalk among multiple cell types. Among these, fibroblasts act as the primary effector population. These cells are highly heterogeneous and scar-specific, making them particularly difficult to target therapeutically. Several pro-fibrotic fibroblast subsets have been identified in keloids. $POSTN^+$ mesenchymal fibroblasts drive tissue stiffness and progressive growth [53, 72, 73]. Mechanosensitive subsets facilitate invasive outward expansion [74]. $PRRX1^+$ subsets control phenotypic transitions, whereas pro-inflammatory subsets amplify inflammatory signaling [75, 76].

Clinical interventions change this fibroblast compartment. Standard therapy using triamcinolone combined with 5-fluorouracil reduces differentiation into pro-fibrotic states but may select for cells with enhanced self-renewal and multipotency. This could contribute to treatment resistance or later recurrence [77]. In contrast, IGFBP2$^+$ fibroblasts are abundant in normal skin and do not respond strongly to pro-fibrotic signals. They might protect against fibrosis and could be a target for pro-regenerative strategies [73]. Immune cells help initiate and sustain chronic inflammation in keloids. Macrophages shift toward M2 phenotypes [78]. SPP1$^+$ myeloid cells form a critical pro-fibrotic axis [53]. Th17 cells directly promote fibrosis by producing IL-17A. Th2 cells participate in a positive feedback loop with fibroblasts via IL-4 and IL-13 signaling [72, 79]. Endothelial cells actively contribute to structural and functional abnormalities. They support abnormal vascular networks. They undergo endothelial-to-mesenchymal transition. They directly convert into fibroblast-like effector cells and shift from passive conduits to active drivers of fibrosis [62]. Keratinocytes also participate in the process. They show epithelial–mesenchymal transition-like alterations that may disrupt the epidermal-dermal barrier and transmit pro-fibrotic signals into the dermis [74, 80]. Epigenetic and metabolic reprogramming probably underlies keloid persistence and treatment resistance. Upregulation of FERMT3 supports the increased energy and biosynthetic demands of continuously activated fibroblasts, sustaining scar formation [81]. Thus, keloid formation relies on an integrated multicellular network of fibroblast subsets, immune amplifiers, and mesenchymal-transitioning compartments that must be targeted coordinately.

3.3.2 Vitiligo

ST has clarified the central role of melanocytes in vitiligo. It provides multidimensional insights into upstream triggers. Oxidative stress is a key factor. It drives immunogenic melanocyte death through two parallel pathways [82]. First, genetic evidence has identified cathepsin S (CTSS) as a key target. Oxidative stress activates the transcription factor IRF1, which upregulates CTSS expression. Elevated CTSS promotes the release of damage-associated molecular patterns and enhances melanocyte antigenicity, making melanocytes more recognizable to the immune system. Second, ST reveals that oxidative stress disrupts melanocyte metabolism. This leads to abnormal accumulation of uridine diphosphate glucose (UDP-G). UDP-G is a danger signal released from injured melanocytes. It activates P2RY14 on nearby dendritic cells. It triggers pro-inflammatory gene programs and recruits immune cells. In the melanocyte microenvironment, CTSS increases antigenicity. Meanwhile, UDP-G promotes inflammation and activates dendritic cells. Together, these pathways promote CD8$^+$ T-cell-mediated melanocyte killing and clearance [83]. A spatial perspective further uncovers the spatiotemporal dynamics of immune activation and cooperation in vitiligo lesions. Neuro–immune crosstalk is crucial. Calcitonin gene-related peptide (CGRP) released by nociceptive sensory neurons can enhance type 1 conventional dendritic cell (cDC1) function and promote antigen presentation to CD8$^+$ T cells. This enhanced antigen presentation directly drives autoimmune attack [84]. These findings inspire new strategies. Upstream interventions targeting CTSS or neuroimmune regulators such as CGRP may block immune initiation or amplification [83, 84]. Overall, these advances imply a conceptual shift from broad immunosuppression toward precise restoration of local spatial homeostasis.

3.3.3 Systemic sclerosis

Systemic sclerosis is a prototypical autoimmune connective tissue disease. It reflects long-term remodeling of a fibrotic niche in the skin. Spatial multi-omics indicates that fibroblast subsets are spatially segregated within the dermis. COL8A1$^+$ fibroblasts act as major extracellular matrix deposition effectors and form stable interaction networks with macrophages and B cells. Macrophage–fibroblast crosstalk establishes profibrotic signaling hubs through the TGF-β, JAK–STAT, and ACKR3–CXCL12 axes [85]. Despite its value in dissecting the fibrotic niche, the application of ST in systemic sclerosis remains limited. As sequencing resolution and multi-omic compatibility improve, ST is poised to identify targets for antifibrotic intervention.

4 HOW NEW SPATIAL DISCOVERIES RESHAPE THERAPEUTIC STRATEGIES

4.1 Psoriasis

Spatial mapping resolves IL-36 activity into two epidermal compartments and explains why conventional assays misjudge pathway activity. Terminally differentiated keratinocytes in the upper spinous and granular layers serve as the primary source of IL-36γ, while basal and lower spinous keratinocytes express the IL-36 receptor and respond to this signal [25, 27]. This layered organization means that bulk biopsies or single-cell RNA-seq alone cannot capture the directional flow of IL-36 signaling from the upper epidermis downward.

Consistent with ST-derived insights into generalized pustular psoriasis (GPP), the rapid clinical responses observed with IL-36 blockade provide clinical support for this therapeutic strategy. In the Effisayil™ 1 trial (NCT03782792), the anti-IL-36 receptor antibody spesolimab resulted in a higher rate of pustule clearance, accompanied by reductions in IL-8 and S100A8/A9 [86]. Recibokibart (HB0034), a novel anti-IL-36R monoclonal antibody, demonstrated rapid onset of action in a Phase 1b open-label trial for acute GPP, with 77.8% of patients achieving complete or near-complete pustular clearance by week 1; however, the interpretation of these results is constrained by the single-arm, uncontrolled design and a small sample size of only nine patients [87].

4.2 Vitiligo

ST and imaging have uncovered an unexpected spatial relationship in vitiligo lesions. $CGRP^+$ nociceptive nerve fibers lie in close proximity to $CALCRL^+$ dermal cDC1s. In mouse models, ablation of $Trpv1^+$ sensory neurons or cDC1-specific deletion of the CGRP receptor abolished autoreactive $CD8^+$ T-cell responses. Exogenous CGRP restored these responses after sensory neuron ablation. This spatial finding directly inspired a drug repurposing pilot trial. For instance, rimegepant showed preliminary evidence of disease stabilization in an open-label pilot study (n=12). This work shifts vitiligo therapy from nonspecific immunosuppression toward targeting an upstream neuro-immune checkpoint [84].

4.3 Skin tumors

In cSCC, pretreatment spatial patterns predicted response to PD-1/PD-L1 inhibitors. Responders showed co-localization of $CD8^+$ T cells, $CD68^+$ macrophages, and CAFs within a 100-μm radius, with granzyme B^+ $CD8^+$ T cells adjacent to MHC-II^+ antigen-presenting cells. Non-responders instead exhibited a physical barrier of TNC^+ CAFs that excluded T cells from tumor islets [88]. Clinically, this raises the possibility of using pretreatment spatial signatures as companion diagnostics to guide patient selection for immunotherapy in cSCC.

In Merkel cell carcinoma, the viral antigen of Merkel cell polyomavirus is persistently expressed [89]. ST reveals that Merkel cell polyomavirus-specific $CD8^+$ T cells are already present at the tumor margin prior to treatment. But they are restrained by an immunosuppressive barrier. Clinically, response rates to anti-PD-1 therapy reach 50–60%, substantially higher than those reported in other skin cancers [90].

In locally advanced or metastatic BCC, the objective response rate to cemiplimab is 31% [71]. ST analysis shows that TLS with $CD4^+$ T follicular helper (Tfh) cells and B cells at their core are present in responders [67]. These TLS are located at the invasive tumor front. Tfh cells activate B cells via CD40LG-CD40 signaling. B cells further differentiate into plasma cells that produce tumor-specific antibodies [68]. This finding implies that the efficacy of PD-1 blockade in BCC may derive from the reversal of T cell exhaustion and the restoration of Tfh–B cell-mediated anti-tumor humoral immunity [67, 71].

5 DISCUSSION

Here, we outline major ST platforms and their uses in skin research, synthesize key mechanistic findings across inflammatory and neoplastic skin disorders, and highlight spatial niches and cell–cell interactions that point to new therapeutic opportunities. We also provide a framework for translating spatial multi-omics into clinical dermatology. ST moves beyond simple cell-type cataloging to reveal how spatial positioning shapes cellular function. These spatially resolved insights are already reshaping how we identify drug targets and develop biomarkers in skin disease.

Although ST fills long-standing gaps left by conventional single-cell or bulk sequencing, its real value in dermatology will not come from higher resolution or larger datasets. Instead, its impact will depend on clinical translation, including the prospective validation of spatial signatures as predictive biomarkers and direct testing of the functions of disease-associated niches using spatially targeted methods. Without such steps, ST will remain a research tool rather than a guide for clinical care.

6 CONCLUSION

ST is a valuable tool in dermatology. By revealing the spatial architecture of disease, it can inform clinical decision-making and treatment strategies. However, challenges such as high costs and a lack of standardization must be addressed through cost reduction, standardized protocols, and prospective clinical trials to realize the full clinical potential of ST. As standards improve and costs decrease, ST may transition from research settings to routine clinical practice.

DECLARATIONS

Author contributions

Mingyi Li wrote the original draft. Wenbo Zhou, Xinhong Dai, and Chennan Zuo performed the validation. Qingyu Zeng and Xiuli Wang contributed to the conceptualization and supervision of the study. All authors approved the final version of the manuscript.

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Data availability

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the manuscript for publication.

Competing interests

The authors declare that they have no competing interests.

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