World Journal of Diabetes

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World J Diabetes 2025 September 15; 16(9): 107663

DOI: 10.4239/wjd.v16.i9.107663

ISSN 1948-9358 (online)

MINIREVIEWS

Spatial transcriptomics meets diabetic kidney disease: Illuminating the path to precision medicine

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Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade A, Grade A, Grade B, Grade B, Grade B

Novelty: Grade A, Grade B, Grade B, Grade C

Creativity or Innovation: Grade A, Grade B, Grade B, Grade C

Scientific Significance: Grade A, Grade A, Grade B, Grade B

P-Reviewer: Budaya TN, PhD, Indonesia; Cai L, United States; Chen S, PhD, China; Hwu CM, Taiwan

Received: March 28, 2025

Revised: May 23, 2025

Accepted: August 15, 2025

Published online: September 15, 2025

Processing time: 167 Days and 9.1 Hours

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Abstract

Diabetic kidney disease (DKD), a primary cause of end-stage renal disease, results from progressive tissue remodeling and loss of kidney function. While single-cell RNA sequencing has significantly accelerated our understanding of cellular diversity and dynamics in DKD, its lack of spatial resolution limits insights into tissue-specific dysregulation and the microenvironment. Spatial transcriptomics (ST) is an innovative technology that combines gene expression with spatial localization, offering a powerful approach to dissect the molecular mechanisms of DKD. This mini-review introduces how ST has transformed DKD research by enabling spatially resolved analysis of cell interactions and identifying localized molecular alterations in glomeruli and tubules. ST has revealed dynamic intercellular communication within the renal microenvironment, lesion-specific gene expression patterns, and immune infiltration profiles. For example, Slide-seqV2 has highlighted disease-specific cellular neighborhoods and associated signaling networks. Furthermore, ST has pinpointed key genes implicated in disease progression, such as fibrosis-related proteins and transcription factors in tubular damage. By integration of ST with computational tools such as machine learning and network-based analysis can help uncover gene regulatory mechanisms and potential therapeutic targets. However, challenges remain in limited spatial resolution, high data complexity, and computational demands. Addressing these limitations is essential for advancing precision medicine in DKD.

Key Words: Diabetic kidney disease; Spatial transcriptomics; Single-cell RNA sequencing; Renal microenvironment; Precision medicine; Computational biology

Core Tip: This mini-review highlights the emerging role of spatial transcriptomics (ST) in diabetic kidney disease (DKD) research. ST enables high-resolution mapping of gene expression within intact tissues, offering novel insights into cellular interactions, lesion-specific transcriptional changes, and immune infiltration. The mini-review further discusses the integration of ST with computational tools such as machine learning and network analysis, and its potential in precision diagnostics and therapy. Despite challenges in spatial resolution and data complexity, ST is poised to transform DKD research by bridging molecular discovery with clinical application.

Citation: Liu DD, Hu HY, Li FF, Hu QY, Liu MW, Hao YJ, Li B. Spatial transcriptomics meets diabetic kidney disease: Illuminating the path to precision medicine. *World J Diabetes* 2025; 16(9): 107663
URL: https://www.wjgnet.com/1948-9358/full/v16/i9/107663.htm
DOI: https://dx.doi.org/10.4239/wjd.v16.i9.107663

INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) worldwide[1,2]. Epidemiological data estimate that approximately 30%-40% individuals with type 1 diabetes and up to 50% of those with type 2 diabetes are at risk of developing to DKD[3]. Beyond the irreversible decline in renal function, DKD markedly increases the risk of cardiovascular events and overall mortality, posing a substantial burden on global healthcare systems[1]. According to the 2021 Global Burden of Disease Study, the disability-adjusted life years due to DKD have been on the rise, indicating the growing impact of DKD on public health and the challenges it poses to healthcare systems in terms of resource allocation and management[4].

Current clinical interventions for DKD, such as glycemic control, blood pressure management, and renin-angiotensin-aldosterone system inhibitors, can delay disease progression to some degree, but their effectiveness remains limited. Many patients still advance to ESRD despite optimal medical management. This gap in therapeutic efficacy largely reflects the complexity of DKD pathophysiology, which involves a convergence of metabolic disturbance, chronic inflammation, oxidative stress, and hemodynamic changes within the kidney[3]. Compounding this challenge, the molecular regulatory network that drives disease progression remains incompletely understood, limiting our ability to predict clinical trajectories or develop targeted therapies.

The onset and progression of DKD involve multiple renal cell types and their complex dynamic changes. Previous studies have shown that glomerular cell, and glomerular endothelial cells, as well as renal tubulars cells, play a central role in the pathological process of DKD[1]. Podocyte loss disrupts the glomerular filtration barrier, while the epithelial-to-mesenchymal transition of tubular epithelial cells contributes to interstitial fibrosis. Meanwhile, aberrant immune cell infiltration and activation further exacerbate tissue damage[5,6]. Therefore, elucidating the cellular heterogeneity and temporal shifts in these populations is essential for advancing our understanding of DKD pathogenesis and identifying new therapeutic avenues.

In recent years, single-cell RNA sequencing (scRNA-seq) has brought significant advances to the study of DKD by enabling high-resolution transcriptomic profiling of individual renal cells[7], and has shed light on the transcriptional dynamics of podocytes, tubular cells, and infiltrating immune cells in the diabetic kidney[8]. However, a key limitation of scRNA-seq lies in the loss of spatial context during tissue dissociation, which obscures the native tissue architecture and the spatial relationships among cells[9]. These spatial cues are critical, particularly in organs like the kidney, where cell positioning and microenvironmental signals influence both structure and function[10].

The raise of spatial transcriptomics (ST) has addressed a major limitation of scRNA-seq, the loss of spatial context during tissue dissociation[11], as shown in Figure 1. By preserving spatial information while mapping gene expression, ST enables detailed interrogation of cell-cell interactions, region-specific gene activity, immune cell localization, and spatially defined signaling pathways within intact tissue sections[12,13]. Unlike scRNA-seq, which emphasizes cellular heterogeneity at single-cell resolution, ST provides complementary insights into the spatial organization of gene expression. A side-by-side comparison of their key features is provided in Table 1. The combination of ST with single-cell technologies has opened new possibilities for studying kidney disease at the level of cellular neighborhoods and local microenvironments[14].

In this mini-review, we summarize the recent applications of ST in DKD research. We focus on its contributions to elucidating spatial patterns of gene expression, immune infiltration, and intercellular communication, as well as its integration with computational tools for identifying key regulators of disease. We also discuss the implications of these findings for precision medicine in DKD and the challenges that remain for broader clinical translation.

ADVANCES IN DKD RESEARCH WITH ST

The rapid development of ST has opened new avenues for investigating DKD. With continuous technological improvements, ST now enables near single-cell resolution analysis of gene expression in kidney tissues, while preserving spatial context. This has significantly advanced our ability to study cellular interactions, lesion-specific gene expression, immune infiltration, local molecular changes, and disease-associated signaling pathways in situ. These major research

Table 1 The differences of single-cell RNA sequencing and spatial transcriptomics

Characteristics	Single-cell RNA sequencing	Spatial transcriptomics
Resolution	Single-cell level	From near single-cell to tens of micrometers (most current ST platforms have a resolution of 50-100 μm)
Spatial information	Lost during tissue dissociation	Preserved, enabling in situ analysis of gene expression within tissue sections
Data complexity	High, requiring processing of large numbers of single-cell data and cell type identification	Very high, as data include gene expression matrices, spatial coordinates, and metadata related to tissue morphology and cell identity
Technical workflow	Tissue is dissociated into a single-cell suspension followed by sequencing	Tissue section processing, capturing gene expression information while preserving spatial location through specific technologies (*e.g.*, Slide-seqV2)
Key advantages	Enables high-resolution profiling of individual cell transcriptomes and reveals cellular heterogeneity	Combines gene expression with spatial location, allowing analysis of cell-cell interactions, region-specific gene expression, and immune cell localization
Limitations	Loss of spatial context and inability to study the impact of tissue structure on function	Current resolution is insufficient for analyzing fine anatomical structures (*e.g.*, glomeruli and tubules). ST also has high demands for sample preparation (*e.g.*, tissue section thickness, integrity, and RNA quality)
Applications	Illuminates transcriptional dynamics of podocytes, tubular cells, and infiltrating immune cells in diabetic kidneys	Used in diabetic kidney disease research to analyze spatial interactions of cells in the renal microenvironment, lesion-specific gene expression patterns, immune infiltration, localized molecular alterations, and disease-associated pathway changes
Data analysis	Requires single-cell-specific tools (*e.g.*, Seurat, Scanpy) for cell clustering and marker gene identification	Requires spatial analysis tools (*e.g.*, SpaTrack, STlearn) for spatial clustering, gene pattern recognition, and cell-cell interaction modeling. Integration with machine learning and deep learning methods can enhance analytical capabilities
Typical output	Cell clusters, cell type-specific marker genes	Spatial cellular atlases, cell neighborhoods, spatially restricted gene expression patterns, disease-related pathway alterations

ST: Spatial transcriptomics.

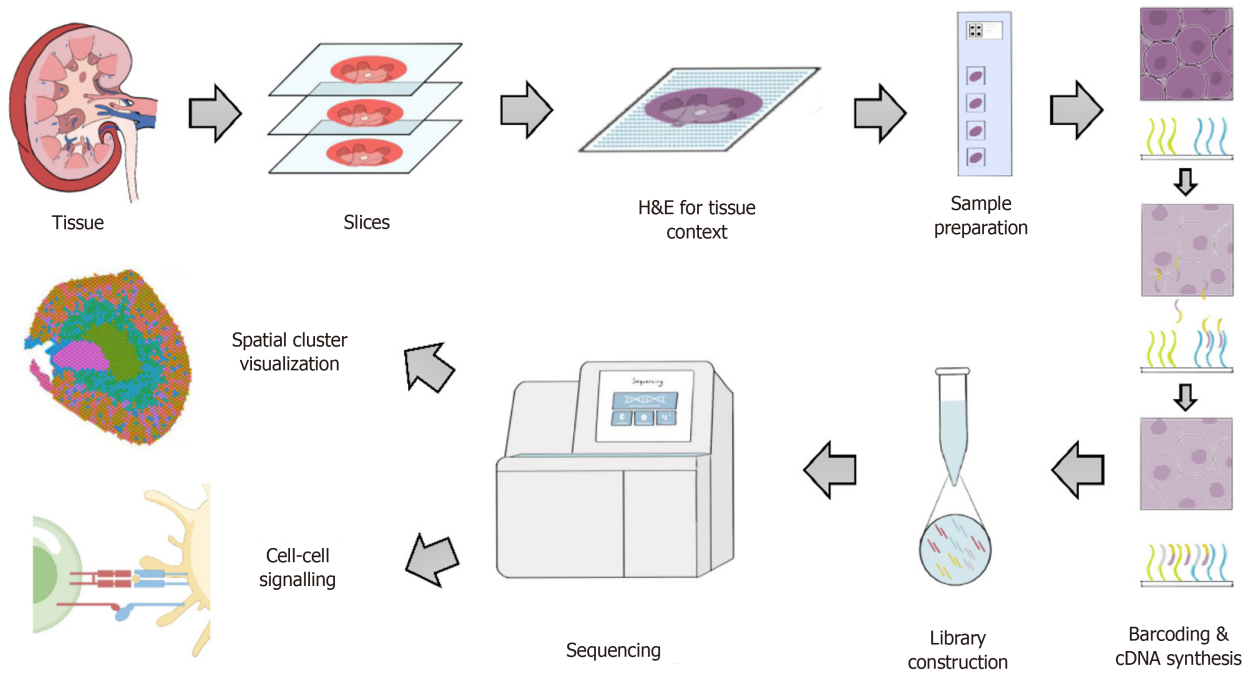

Figure 1 The experimental workflow of spatial transcriptomics in diabetic kidney disease. Kidney tissue is first sectioned and stained with hematoxylin and eosin to retain histological context. Prepared slides undergo spatial barcoding and cDNA synthesis, followed by library construction and sequencing. The resulting data are used to reconstruct spatial gene expression patterns, identify cellular neighborhoods, and infer cell–cell interactions within intact renal tissue.

directions and applications of ST in DKD are illustrated in Figure 2.

Spatial resolution of cellular interactions in renal microenvironment

ST provides a powerful tool for mapping spatial interactions between renal cell types during the progression of DKD. By constructing spatial cellular atlases of glomeruli and tubules, researchers have uncovered dynamic intercellular

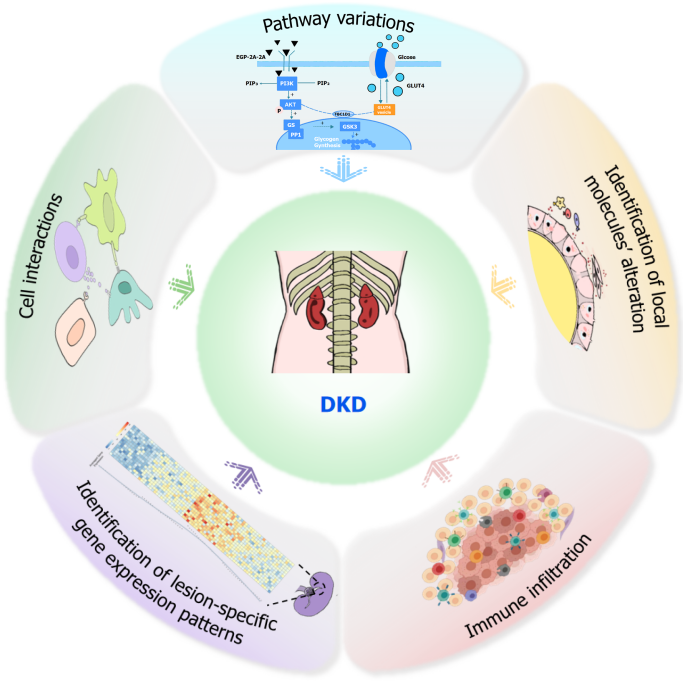

Figure 2 Applications of spatial transcriptomics in diabetic kidney disease. Spatial transcriptomics (ST) has been applied to diabetic kidney disease to investigate a range of spatially resolved pathological features. The representative examples include the analysis of cell-cell interactions within the renal microenvironment, the identification of region-specific gene expression signatures, and the characterization of immune infiltration in glomerular lesions-particularly involving M2 macrophages and mast cells. In addition, ST enables the detection of localized molecular alterations, such as lipid accumulation and mitochondrial damage in tubular epithelial cells, as well as spatial variation in signaling activity, including alterations in the phosphoinositol-3 kinase pathway. DKD: Diabetic kidney disease.

interactions that contribute to disease development. For instance, Slide-seqV2 technology has been used to delineate disease-specific cellular neighborhoods in DKD kidneys, revealing co-localization patterns of multiple cell types and their associated signaling networks[15]. Moreover, integrating scRNA-seq with ST has helped define the trans-differentiation of tubular epithelial cells and their complex interactions with neighboring cells (Table 2)[15-22]. These findings highlight the importance of spatially defined cell-cell communication in DKD pathogenesis.

Lesion-specific gene expression patterns in DKD

ST enables the identification of region-specific gene expression changes within DKD lesion, offering important clues for disease procession and biomarker discovery. In a study analyzing human DKD kidney tissue, 700 differentially expressed genes were identified-342 upregulated and 358 downregulated-many of which were spatially restricted to diseased regions[17]. Furthermore, deep learning-based spatial analysis of renal tubule nuclei revealed disease-associated transcription factors, further refining our understanding of lesion-specific gene regulation in DKD[23].

Immune infiltration in DKD

ST has proven valuable for dissecting immune infiltration patterns in DKD. For instance, increased numbers of M2 macrophages and resting mast cells have been observed in the glomeruli of DKD patients[18]. These changes are closely linked to inflammation and represent key drivers of disease progression. ST also facilitates the identification of genes and pathways associated with immune infiltration, providing important insights for the development of immune-targeted therapies[19].

Identification of local molecular changes in DKD

ST and proteomics allow researchers to track localized molecular alterations across DKD stages, including changes in protein expression and metabolite synthesis. For example, spatial proteomic profiling has revealed fibrosis-related protein signatures in advanced DKD[24]. Chung *et al*'s study[20] showed that interleukin (IL)-32 is significantly upregulated in the renal tubules of DKD patients and contributes to tubular damage by modulating mitochondrial ROS production and apoptosis pathways. These findings underscore the role of local molecular changes in disease progression and point to new therapeutic targets.

Pathway alterations in DKD

Combining ST with multi-omics approaches enables the identification of signaling pathways involved in DKD, providing new directions for strategies such as early diagnosis and treatment of the disease. For instance, genes such as *c-jun* and *SLC4A4*-implicated in renal fibrosis-have been shown to interact with the phosphoinositol-3 kinase/protein kinase B signaling pathway[21]. ST has also uncovered spatial alterations in inflammatory and apoptotic signaling, which may

Table 2 Top studies utilizing spatial transcriptomics in diabetic kidney disease

Number	Research topic	Application of ST and key issues resolved	Findings	Ref.
1	Discovery of disease-specific cell neighborhoods and signaling pathways	Used Slide-seqV2 technology to build cell-neighborhood maps and uncovered cell localization patterns and signaling networks	Revealed the cell interactions and signaling pathways in diabetic nephropathy	Marshall *et al* [15], Chen *et al* [16]
2	Epithelial-mesenchymal transition and interactions of renal tubular cells in DKD	Combined single-cell RNA sequencing with spatial transcriptomics to define the epithelial-mesenchymal transition of renal tubular epithelial cells and their interactions	Gained an in-depth understanding of the dynamic changes and mechanisms of renal tubular epithelial cells	Wang *et al*[17]
3	Immune cell infiltration patterns in DKD	Utilized spatial transcriptomic analysis to observe increases in specific immune cells in glomeruli	Clarified the role of immune cell infiltration in disease progression	Zhang *et al*[18]
4	Fibrosis-related protein biomarkers in DKD	Conducted spatial proteomic analysis to reveal late-stage fibrosis-related protein biomarkers	Provided potential diagnostic and therapeutic biomarkers	Hu *et al*[19]
5	Molecular mechanisms of renal tubular injury in DKD	Integrated spatial transcriptomic and proteomic analyses to find IL-32 upregulation and its mechanisms	Uncovered the key role of IL-32 in renal tubular injury	Chung *et al*[20]
6	Pathway alterations in DKD	Combined ST with multi-omics approaches to identify signaling pathways involved in DKD	Uncovered spatial alterations in inflammatory and apoptotic signaling pathways	Delrue and Speeckaert[21]
7	Involvement of AEBP1 in DKD	Spatial transcriptomic analysis of kidney biopsies from DKD patients	AEBP1 is notably upregulated and associated with fibrosis and inflammation	Tao *et al*[22]

DKD: Diabetic kidney disease; IL: Interleukin; ST: Spatial transcriptomics.

drive disease progression. Moreover, AEBP1 is notably upregulated in kidney biopsies from DKD patients[22] and is thought to be involved in fibrosis and inflammation. Together, these findings demonstrate how spatial gene expression analysis can deepen our understanding of DKD pathophysiology and support the development of early diagnostic tools and targeted treatments.

INTEGRATION OF ST WITH COMPUTATIONAL TOOLS

Machine learning and spatial transcriptome data analysis

The integration of ST with machine learning offers a powerful research paradigm for analyzing gene regulatory networks (GRNs) and extracting meaningful biological patterns from high-dimensional data. By leveraging machine learning algorithms, researchers can gain a deeper understanding of spatial gene regulation and improve the interpretation of complex transcriptomic landscapes. Various statistical machine learning methods are widely applied in ST data analysis. These approaches help not only in identifying spatial gene expression patterns but also in extracting contextual information from histological images, which is particularly valuable in disease diagnosis and tissue classification[25].

Recent studies have also explored the use of deep learning in both single-cell and ST. Deep learning models can integrate multi-omics data, uncover hidden gene expression patterns through generative models and align multiple modalities such as transcriptomic and imaging data[26]. For example, THItoGene, a newly developed tool, combines deep learning with histological image analysis, enabling more accurate prediction of the spatial distribution of gene expression, thus providing new insights for interpreting ST data[27]. Similarly, unsupervised convolutional neural networks such as CoSTA, have been used to detect spatial gene expression patterns without relying on pre-labeled data, opening new possibilities for exploratory analysis of spatial heterogeneity[28]. These foresaid machine learning approaches enable automated analysis of high-dimensional datasets, reveal spatially resolved biological features, and enhance the potential of ST in biomedical research.

Identification of key genes in DKD based on network analysis

Biological networks, such as GRNs and protein-protein interaction networks, are essential tools for identifying functional gene modules and pathways involved in the progression of DKD. By constructing GRNs, researchers can investigate complex gene interactions and identify transcriptional programs associated with disease states[29]. One widely used method, weighted gene co-expression network analysis[30], has been applied to predict gene modules related to disease progression and uncover key genes and pathways involved in DKD. In addition, the tools such as SCENIC, which integrate single-cell and ST data, help dissect cell-type-specific regulatory networks, offering insights into cellular heterogeneity and disease mechanisms[31].

The spatial dimension offered by ST further enhances network-based analyses. By providing spatial localization of gene activity, ST allows researchers to investigate how gene regulatory mechanisms vary across different tissue regions. This can reveal spatially restricted signaling pathways and localized pathogenic processes relevant to DKD[32]. For

instance, spatially resolved network analysis can pinpoint key genes that are specifically active in fibrotic regions or areas of immune infiltration, offering new targets for intervention[33]. Furthermore, combining ST data with causal inference frameworks-such as deep learning-based causal network models-can help explore directional relationships between genes and identify upstream regulators that drive disease progression[29]. This integrative approach provides a more comprehensive understanding of the molecular basis of DKD and may facilitate the development of targeted therapies [29].

CHALLENGES IN ST FOR DKD

Limitations of spatial resolution

ST technology enables the capture of gene expression within its native spatial context, offering a new dimension for studying tissue organization and cellular heterogeneity. However, the current spatial resolution of most ST platforms-typically ranging from 50 μm to 100 μm-remains insufficient to resolve fine anatomical structures. In the context of DKD, this limitation may hinder the precise analysis of complex microstructures such as glomeruli and renal tubules. Although computational methods like soScope can improve spatial resolution through data augmentation, their effectiveness still relies on the quality and granularity of the original data source[34].

Data complexity and computational requirements

ST data are inherently high-dimensional and complex, comprising not only gene expression matrices but also spatial coordinates and metadata related to tissue morphology and cell identity. Analyzing such data requires sophisticated computational methods for spatial clustering, gene pattern recognition, and cell–cell interaction modeling[35]. These tasks are further complicated when integrating multi-modal datasets-such as transcriptomics, proteomics, and metabolomics-which increases both the computational load and analytical complexity. While standardized data formats and tools (*e.g.*, Pysddb) have made data preprocessing more accessible, effective analysis still demands a substantial level of computational proficiency[36].

Challenges in omics data integration

A key step toward comprehensive understanding of DKD is the integration of ST with other omics layers. However, differences in data structure, scale, and noise present significant barriers. Effective integration requires novel computational frameworks capable of aligning diverse data types in a spatially coherent manner. For example, SpatialGlue is a dual-attention neural network model designed to integrate multi-modal omics data while preserving spatial relationships [37], and it enhances the ability to infer histological structures from transcriptomic and proteomic data[38]. Nonetheless, the success of such models depends not only on algorithmic performance but also on their biological interpretability-a critical consideration when translating computational insights into clinical relevance[39].

Technical challenges in sample preparation for ST in DKD

The preparation of high-quality tissue sections for spatial transcriptomic analysis poses significant technical challenges in DKD research. For instance, the intricate architecture of the kidney necessitates precise manipulation to preserve tissue integrity throughout the sectioning process. Furthermore, RNA degradation in diseased tissue samples can markedly compromise data quality. Meeting the stringent technical specifications of ST platforms-such as tissue section thickness, integrity, and RNA quality-represents a formidable barrier to successful spatial profiling[40]. These technical hurdles emphasize the need for rigorous protocols to minimize variability and enhance reproducibility in experiments.

FUTURE DIRECTIONS AND POTENTIAL OF ST IN DKD RESEARCH

Enhancing spatial resolution for detailed renal microenvironment analysis

Though ST has significantly improved our ability to resolve tissue organization, the spatial resolution of most current technologies still falls short of the single-cell or subcellular level-particularly in the analysis of intricate structures like glomeruli, renal tubules, and capillaries[41]. Future advancements in high-resolution imaging platforms, such as MERFISH and seqFISH+, are expected to bridge this gap by enabling gene expression profiling at finer spatial scales. This will allow more precise mapping of cell populations and their molecular states in DKD. In parallel, deep learning-based super-resolution modeling holds promise for computationally enhancing ST resolution, facilitating the reconstruction of small-scale GRNs with improved fidelity.

Integrating single-cell and multi-omics data for system-level network construction

DKD is driven by complex interactions among diverse cell types, molecular pathways, and regulatory circuits, making it difficult for a single omics approach to capture the full landscape of disease progression. In the coming years, ST will likely be increasingly integrated with scRNA-seq, spatial proteomics, metabolomics, and other omics platforms to build multi-layered networks connecting genes, cells, and molecular functions[42]. For example, integrating spatial proteomics with ST data will allow dynamic analysis of post-translational modifications and their roles in disease-associated signaling pathways. Similarly, incorporating spatial metabolomics will help elucidate metabolic reprogramming within the renal microenvironment, providing insights into the functional consequences of transcriptional alterations.

Advancing ST data analysis through artificial intelligence and computational methods

The high dimensionality and complexity of ST data necessitate robust computational frameworks. Artificial intelligence (AI) and machine learning are poised to become indispensable in addressing these analytical challenges. Deep neural networks, graph convolutional networks, and generative adversarial networks are among the tools being developed to enhance imputation of missing data, infer gene expression in unmeasured regions, and reconstruct spatial gene maps[43]. Additionally, AI algorithms can automate key steps such as cell-type annotation, spatial domain identification, and regulatory network reconstruction-streamlining the ST analysis pipeline and improving biomarker discovery in DKD.

Bridging basic research and clinical translation for precise medicine in DKD

Beyond basic research, ST is increasingly relevant to clinical applications, including early diagnosis, biomarker discovery, and personalized therapy. For instance, integrating ST data into clinical workflows could enable more accurate classification of DKD subtypes and identification of region-specific biomarkers from biopsy samples-ultimately improving diagnostic accuracy and informing individualized treatment strategies[44]. Building on these findings, ongoing pilot efforts are translating ST defined fibrotic (COL1A1+/AEBP1+) and inflammatory (IL-32+/CD68+) signatures into routine biopsy-based patient stratification, merging these spatial features with clinical variables in machine-learning risk models for eGFR decline, and embedding ST quantified fibrotic burden as early surrogate endpoint in adaptive clinical trials.

DATA EXTRACTION AND VALIDATION

To identify relevant studies for data extraction, we conducted a comprehensive search using the following search strategy: ("diabetic kidney disease" OR "diabetic nephropathy" OR “DKD”) AND ("spatial transcriptomics" OR "single-cell RNA-seq" OR "single-cell sequencing" OR "multi-omics" OR "omics").

In this study, two independent reviewers carried out the data extraction process to guarantee the data's accuracy and credibility. Both reviewers had undergone specialized training and adhered to a unified set of standard operating procedures for data extraction. The data extracted covered all the essential information fields. Upon completion of the extraction, the two reviewers exchanged their data files to conduct cross-verification, ensuring the data's integrity and consistency.

When discrepancies emerged in the extraction results, the two reviewers first engaged in a discussion to resolve the differences. If consensus couldn't be reached through discussion, a senior third researcher was brought in for arbitration.

To ensure the reliability and quality of the cited studies, we assessed the quality of the included studies using the Newcastle-Ottawa Scale (Table 3)[1,15,16,18,22-24]. The results indicate that, despite methodological differences across studies, the overall quality is high, providing a solid foundation for subsequent analyses.

CONCLUSION

ST has introduced a new dimension to DKD research by enabling the spatially resolved analysis of gene expression within the native tissue context. This technology has proven invaluable for uncovering cellular interactions, lesion-specific gene signatures, immune infiltration patterns, and alterations in disease-related signaling pathways. Its application has not only deepened our understanding of DKD pathophysiology but has also facilitated advances in early diagnosis, biomarker discovery, and precision medicine. However, certain risk factors' prominence in disease progression warrants further discussion. Metabolic disturbances like hyperglycemia can spark inflammation and oxidative stress, varying across populations. Our findings bear significant clinical and public health implications, potentially informing therapeutic strategies and shaping evidence-based policies to enhance disease prevention and population health. ST can sharpen early DKD diagnosis *via* biomarkers and guide personalized treatment. They also inform screening protocols and stress the need for diabetes management campaigns. But limitations exist. Heterogeneity in studies, often retrospective, with inconsistent DKD definitions and possible publication bias, can affect result reliability. The inconsistent definitions of DKD across studies further complicate the interpretation and comparison of results. Looking ahead, improvements in spatial resolution, advances in high-throughput imaging, and the development of more robust computational frameworks will help to fully realize the potential of ST. As ST is increasingly combined with single-cell technologies, AI, and spatially resolved multi-omics, it is poised to become a key driver in the development of personalized strategies for the diagnosis and treatment of DKD. These ongoing innovations hold promise for improving clinical outcomes and delivering more precise and effective care to patients living with DKD. Looking forward, the integration of ST with drug discovery, disease modeling, and clinical trial design is expected to drive the translation of spatial molecular insights into precision medicine solutions for DKD. For instance, fibrosis or immune specific spatial signatures could stratify patients by progression risk, enrich trial cohorts with high-expression subgroups, and serves as early response biomarkers.

Table 3 Newcastle-Ottawa Scale quality assessment of included studies

Ref.	Selection				Comparability		Exposure			Sources
	A representative and well-defined study population	Method of sample selection	Non-response rate of study subjects	Additional confirmation of study subjects	Matching of study and control groups based on specific factors	Adjustment of study and control groups based on specific factors	Method of determining study outcomes	Blinded assessment of outcomes	Follow-up time and adequacy	
Lay *et al* [1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Marshall *et al*[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Chen *et al*[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Winfree *et al*[23]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	6
Zhang *et al*[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Kondo *et al*[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Tao *et al* [22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7

Marshall *et al*[15] scored 9/9, indicating very high quality with a highly rigorous study design and implementation. The remaining six studies scored 7/9, indicating good quality but with some unclear details, such as the blinding assessment and follow-up time.

FOOTNOTES

Author contributions: Liu DD drafted the original manuscript; Liu DD and Liu MW handled resources and visualization; Liu DD, Hao YJ, and Li B were responsible for conceptualization and data curation; Hu HY, Li FF, and Hu QY provided the critical review and editorial input; Hao YJ and Li B supervised this project and secured funding; all authors reviewed and approved the final version of this manuscript.

Supported by Science and Technology Research Program of Chongqing Municipal Education Commission, No. KJQN202100538; and Talent Innovation Project in Life Sciences of Chongqing Normal University, No. CSSK2023-04.

Conflict-of-interest statement: All the Authors have no conflict of interest related to this manuscript.

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S-Editor: Luo ML
L-Editor: A
P-Editor: Xu ZH

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