Research progress in single-cell omics technologies for kidney disease (Review)

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Abstract. The kidney is a vital organ for maintaining metabolic balance within the body and facilitating excretion. Its complex tissue structure comprises diverse cell types, including glomerular, tubular, interstitial and immune cells. The highly differentiated nature of these cells presents challenges for investigating kidney disease mechanisms. In recent years, the rapid advancement of single-cell omics technologies has provided novel perspectives for renal research. These techniques have revealed the diversity and heterogeneity of renal cells, enabling precise identification of multiple immune cell types within the kidney. These findings further elucidate the dynamic changes in renal immune cells during disease progression and their interactions with other renal cells, laying a foundation for in-depth analysis of renal disease pathogenesis. The present review aims to summarize the current applications of single-cell omics technologies in renal ageing and kidney diseases, providing crucial insights for deciphering disease mechanisms and identifying therapeutic targets.

Contents

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1. Introduction

Kidney disease refers to structural or functional impairment of the kidney caused by various factors and is the seventh leading cause of death globally. It has been indicated that ~850 million individuals worldwide suffer from kidney disease, with projections suggesting that 5.4 million individuals will require renal replacement therapy by 2030. Furthermore, 15-20% of patients succumb within 12 months of initiating dialysis, posing a severe threat to human health and imposing a substantial economic burden (1). Currently, the precise mechanisms underlying kidney disease remain unclear, and specific therapeutic approaches are lacking. Therefore, exploring renal physiological and pathological mechanisms and developing novel treatment strategies are urgently needed. However, the complex and highly differentiated cellular composition of the kidney poses challenges for investigating the molecular mechanisms of kidney disease.

In recent years, the advancement of single-cell omics technologies has enabled the study of kidney disease mechanisms at the cellular level. Through high-throughput sequencing and high-precision analysis at the single-cell level, this technology has revealed distinct cell subpopulations and functional alterations in kidney diseases, mapping the renal cell landscape. These findings provide novel perspectives for investigating kidney cell development, ageing, and patterns of change under disease conditions (2-4). Accordingly, the present review summarizes the application of single-cell omics technologies in acute kidney injury (AKI), diabetic nephropathy (DN), IgA nephropathy (IgAN) and lupus nephritis (LN). The aim of the present study was to provide novel insights for elucidating the mechanisms of kidney diseases and identifying therapeutic targets.

2. Overview of single-cell omics technologies

Single-cell omics technologies collectively refer to a class of techniques capable of performing multidimensional molecular analysis on individual cells. They primarily encompass single-cell transcriptomics, single-cell proteomics (SCP), single-cell metabolomics (SCMET) and single-cell spatial transcriptomics. Over the past decade, these technologies have undergone continuous updates and iterations, enabling

rapid and precise acquisition of multidimensional molecular information from tens of thousands of cells. They have thus become among the most influential technologies in the field of life sciences research. In kidney research, these technologies are not applied in isolation but form an integrated technical framework characterized by 'interconnectedness, complementary validation and synergistic empowerment'. By integrating transcriptional, proteomic, metabolic and spatial localization information from individual cells, they collectively advance the identification of kidney cell identities, spatial organization analysis, and functional output clarification. This provides an unprecedented high-precision perspective for elucidating kidney physiological functions and disease mechanisms and identifying therapeutic targets (Fig. 1).

Single-cell transcriptomics. Single-cell RNA sequencing (scRNA-seq), as a cutting-edge branch of transcriptomics, focuses on the types, quantities, structures and functions of all transcript products (mRNA and non-coding RNA) within an organism at the single-cell level under specific time points and conditions. Its core advantage lies in overcoming the 'averaging' limitations of traditional bulk transcriptomics, enabling precise analysis of expression patterns across diverse cell types within complex renal tissue. This makes scRNA-seq a foundational platform for cell identity identification and heterogeneity analysis in kidney research, providing essential molecular clues for subsequent exploration of cellular regulatory potential, tracking cell fate trajectories, and deciphering intercellular interactions (5,6).

The primary workflow of scRNA-seq includes sample collection and processing, single-cell suspension preparation and isolation, RNA extraction and reverse transcription, library construction, sequencing and data analysis (7). Among these steps, the preparation and isolation of single-cell suspensions are critical for enhancing efficiency and throughput. Iterations of this technology have significantly advanced kidney research: Early microscopy or laser capture methods allowed the analysis of only a few cells, failing to capture kidney cell diversity; subsequent FACS and MACS technologies enabled preliminary enrichment of kidney cell subpopulations through automated sorting; and in October 2016, the 10x Genomics Chromium platform emerged. Leveraging microfluidic chips, barcoding, and unique molecular identifier (UMI) technology has enabled high-throughput, efficient, and cost-effective sequencing of kidney cells. The 10x Genomics Chromium platform has been widely applied in constructing kidney single-cell atlases, mapping cellular developmental trajectories, studying rare cells, and exploring immune mechanisms (8) and has become the mainstream commercial platform for kidney single-cell research (9-11). In 2024, the scGRO-seq technology developed by Mahat *et al* (12) employed click chemistry to capture nascent RNA, enabling precise analysis of real-time gene expression regulation in kidney cells. This addresses the limitations of scRNA-seq in studying cellular transcriptional dynamics, providing a new tool for elucidating transient regulatory mechanisms in kidney cell function.

SCP. SCP, an innovative branch of proteomics, involves the systematic investigation of the expression levels, post-translational modifications, interaction networks, and functional mechanisms of proteins expressed in individual cells, tissues, or organisms under specific temporal and conditional circumstances. It serves as a pivotal tool for deciphering the molecular foundations of biological activities. Its core value lies in validating transcriptional regulatory features identified by scRNA-seq, revealing the functional implementation of cellular regulatory potential, bridging the 'transcription-translation disconnect' gap between transcriptomes and proteomes, and simultaneously enabling the discovery of kidney cell-specific protein biomarkers and the elucidation of protein interaction networks. This provides direct evidence for elucidating kidney cell functional outputs (13,14). Iterative advancements in SCP technology have further enhanced its applicability in renal research. In 2018, Budnik *et al* (15) developed SCP by mass spectrometry (MS), which integrates isotope labelling and carrier proteomics to achieve quantitative analysis of more than 1,000 proteins in mouse embryonic stem cells, laying the technical foundation for renal cell proteomics research. In 2025, Ye *et al* (16) introduced the innovative SCP technology Chip-Tip. By integrating a novel chip with a liquid chromatography system, it unified cell sample preparation, protein extraction and MS analysis. This approach increased the number of identifiable proteins in a single kidney cell from ~2,000 to 5,000-6,500, significantly enhancing the detection sensitivity for protein profiles in rare kidney cell subpopulations. Subsequently, the team developed single-cell pulsed stable isotope labelling, which for the first time enabled precise analysis of protein turnover rates in individual kidney cells. This breakthrough provides a novel tool for investigating dynamic protein regulatory mechanisms during renal cell damage repair, such as the synthesis and degradation of proteins involved in tubular epithelial cell repair, which represents a major advance in SCP.

SCMET. Metabolomics, a vital branch of systems biology, involves the quantitative analysis of the dynamic changes in all small-molecule metabolites (such as amino acids, carbohydrates, lipids and nucleotides) within an organism. This approach reveals the comprehensive metabolic network landscape under specific physiological or pathological conditions, elucidating the regulatory mechanisms of life activities (17,18). SCMET, an innovative branch of metabolomics, primarily employs MS, nuclear magnetic resonance, combined with microfluidics, laser capture microdissection, and other techniques to isolate and extract small-molecule metabolites from individual cells. Its core advantage lies in capturing metabolic heterogeneity among renal cells, deciphering the metabolic phenotypes ultimately resulting from cellular regulatory potential, elucidating the functional output characteristics of renal cells at the metabolic level, and providing a microscopic perspective for studying renal physiological metabolic mechanisms and disease-related metabolic disorders (19,20).

MS, with its high sensitivity, rapid speed and label-free nature, serves as the core technology for SCMET. Among these methods, matrix-assisted laser desorption/ionization MS (MALDI-MS) is the most effective tissue imaging technique and has been widely applied in renal tissue metabolic imaging studies (21,22). Previous innovations in SCMET technology have further expanded its applications in renal research: Wang *et al* (23) innovatively combined isotope labelling

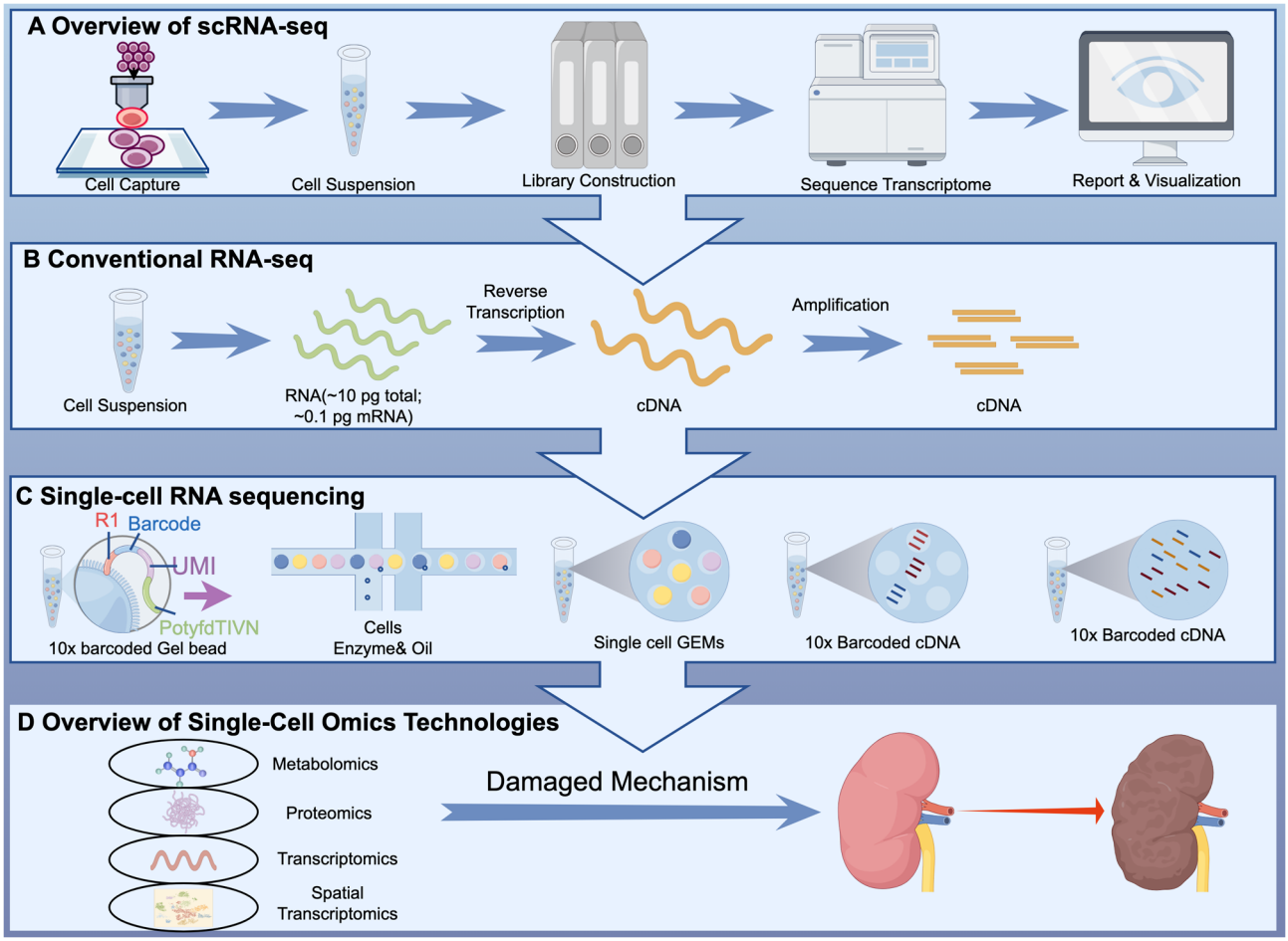

Figure 1. Development and applications of single-cell omics technologies. (A) The single-cell sequencing workflow includes cell capture, preparation and separation of single-cell suspensions, library construction, sequencing and data analysis. (B) Traditional sequencing technologies involve sequencing pooled RNA from a population of cells, followed by batch analysis to obtain average information about the cell population. (C) Single-cell transcriptomics utilizes microfluidic chips to encapsulate individual cells alongside gel beads bearing unique barcodes and UMIs within oil droplets. Within these droplets, mRNA released from lysed cells binds to primers on the gel beads, triggering reverse transcription to generate barcode- and UMI-labelled cDNA, which is subsequently amplified and sequenced. (D) Metabolomics, proteomics, transcriptomics and spatial omics technologies are collectively used to advance the exploration of kidney disease mechanisms. UMIs, unique molecular identifiers.

with MALDI-MS, overcoming the limitations of traditional techniques in capturing dynamic metabolic processes. They successfully traced the metabolic transition from glycolysis to fatty acid β-oxidation during the differentiation of renal vesicles into proximal tubules, revealing for the first time the functional transformation mechanism during renal cell development at the single-cell metabolic level. In 2024, Qin *et al* (24) developed the in-depth organic MS flow cytometry technique. By optimizing lysis strategies and extending the analysis time, more than 600 metabolites were successfully identified within individual renal cells. This achieved precise single-cell metabolite identification and isomer quantification based on secondary MS, enabling accurate differentiation of metabolic differences between distinct renal cell subpopulations (for example, proximal vs. distal convoluted tubule cells). In 2025, the team integrated organic MS flow cytometry with stable isotope tracing to establish a high-throughput, label-free, dynamic SCMET platform. This platform was successfully applied to identify the polarization subtypes of tumour-associated macrophages and is equally applicable for studying the metabolic phenotypes of renal immune cells, providing a novel tool for deciphering the metabolic regulatory mechanisms of immune cells during renal inflammation (2).

Spatial transcriptomics. In 2016, the collaborative efforts of Ståhl *et al* (25) first introduced the concept of 'Spatial Transcriptomics (ST)'. The core breakthrough of this technology lies in preserving the spatial structural integrity of kidney tissue and addressing the limitations of scRNA-seq, SCP and SCMET by preserving the spatial integrity of kidney tissue. This enables simultaneous analysis of 'gene expression and spatial localization', providing a novel tool for investigating intercellular interactions, spatial organization patterns, and the spatial regulatory mechanisms underlying cellular functional outputs in the kidney (26,27). It serves as a critical bridge connecting single-cell molecular characteristics with kidney tissue function.

ST technology integrates high-throughput sequencing with spatial imaging, simultaneously capturing gene expression data while preserving the spatial positioning of renal cells. This precisely reveals the spatial distribution patterns of genes within renal tissue, providing robust support for

investigating dynamic changes in the cellular microenvironment associated with kidney diseases and elucidating disease mechanisms (12,28-30). Currently employed approaches primarily fall into three categories: Microarray-based techniques, bead-based techniques and microfluidic-based techniques. In microarray-based techniques, spatially barcoded oligonucleotide primers are fixed onto slides. After kidney tissue sections are combined with the array, mRNA is captured via poly(A) tails or probe hybridization, reverse-transcribed into spatially tagged cDNA, and sequenced to obtain spatial expression data (31,32). In bead-based techniques, including slide-seq (26) and HDST (27), beads with unique DNA barcodes are randomly distributed across kidney tissue sections. By combining mRNA sequencing with bead localization, these methods can be used to reconstruct spatial coordinates of gene expression, enabling higher-resolution spatial mapping of renal cells. In microfluidic-based techniques, microfluidic chips are utilized to generate microchannels on the surface of kidney tissue. Barcoded reagents are injected into specific regions, enabling precise capture and sequencing of localized mRNA to increase spatial resolution. In 2020, Liu *et al* (33) developed DBiT-seq technology, which uses microfluidic channels to precisely position spatially deterministic barcodes onto RNA and proteins. This technique successfully mapped the fine structures of the retinal pigment epithelium and microvascular endothelium in mouse embryos, validating its high-resolution advantage (34). This technology can be further applied to perform detailed spatial transcriptomics analysis of distinct regions within kidney tissue, including glomeruli, tubules and interstitial spaces, thereby deciphering the molecular characteristics of kidney cell spatial organization.

In summary, single-cell omics represents a frontier branch of systems biology. scRNA-seq can be employed to identify kidney cell identities and reveal regulatory potential at the transcriptional level; SCP can be used to validate regulatory features at the protein level, bridging transcription and function; SCMET can be used to decipher metabolic phenotypes, clarifying the metabolic basis of functional outputs; and ST can be used to supplement spatial information, elucidating cellular spatial organization patterns and spatially specific interactions. These four interconnected and complementary technical platforms integrate multidimensional molecular information from individual cells, collectively advancing a comprehensive and in-depth understanding of renal cell identity, regulatory potential, spatial organization and functional outputs. This propels kidney research from the 'cell population level' to the 'single-cell precision level,' aiding in the elucidation of renal physiological functions, disease mechanism studies, and the identification of therapeutic targets. This drives the paradigm shift in kidney disease diagnosis and treatment from 'empirical medicine' to 'molecular medicine'. In recent years, these approaches have demonstrated significant application value in studies of kidney cell proliferation, development, ageing and disease states (Fig. 2).

3. Applications of single-cell omics technologies in basic renal research

The rapid advancement of single-cell omics technology has provided revolutionary tools for deeply analysing the cellular composition and molecular mechanisms of the kidney. High-resolution kidney cell atlases have been successfully constructed, offering precise insights into renal physiological functions and disease development. More importantly, this technology has been extensively applied to study physiological and pathological processes such as renal ageing, revealing dynamic changes in the immune microenvironment during ageing and laying a solid theoretical foundation for the prevention and treatment of kidney diseases.

Application of single-cell omics technology in constructing a renal cell atlas. The rapid growth of single-cell omics technology has propelled the identification, localization and functional characterization of renal cell types, leading to the successful construction of a renal cell atlas. This technology holds profound significance for deepening the understanding of renal physiology and disease mechanisms and advancing precision medicine. In 2018, Park *et al* (35) performed single-cell sequencing on kidney cells from healthy mice, identifying 16 cell types and establishing the first mouse kidney cell atlas. They discovered a novel transitional cell type in the collecting duct expressing both principal cell and intercalated cell marker genes. Abedini *et al* (36) employed single-cell multi-omics analysis of 81 human kidney tissue samples from 58 participants. They precisely defined 44 major cell types and their subpopulations, including glomeruli, tubules at various segments, collecting ducts, endothelial cells and stromal cells, at the molecular level, generating a comprehensive, spatially resolved single-cell atlas of the human kidney. Li *et al* (37) combined single-cell transcriptomics with spatial metabolomics to reveal distinct transcriptional, epigenetic and metabolic signatures of the same tubular cell type across cortical, medullary and papillary regions, establishing a foundation for kidney disease research.

Application of single-cell omics technologies in renal ageing mechanistic research. The vicious cycle of chronic inflammation triggered by the accumulation of cellular senescence and immune cell ageing represents a core mechanism exacerbating renal ageing and inflammatory injury (38,39). Single-cell omics technologies (centred on scRNA-Seq) serve as critical research tools in this field, enabling the precise identification of abnormal cell subtypes during renal ageing and the identification of key regulatory factors. These technologies provide essential technical support for elucidating the mechanisms underlying renal ageing.

scRNA-Seq plays an irreplaceable role in studying the vicious 'inflammation-ageing' cycle in the kidney. Lymphocyte proliferation and tertiary lymphoid tissue (TLT) expansion are closely linked to senescence-associated T cells and age-associated B cells (40). By analysing renal cells from aged mice with unilateral ischaemic-reperfusion injury, scRNA-seq revealed that senescence-associated T cells secrete factors that induce age-associated B-cell generation. This process, coupled with CD153/CD30 signalling, drives TLT expansion and exacerbates renal inflammation (41). Furthermore, scRNA-seq aided in identifying GZMK as a key biomarker of renal ageing (42) and elucidated the enrichment pattern of $GZMK^{+}CD8^{+}$ T cells in aged mouse kidneys, along with their mechanism of accelerating renal cell

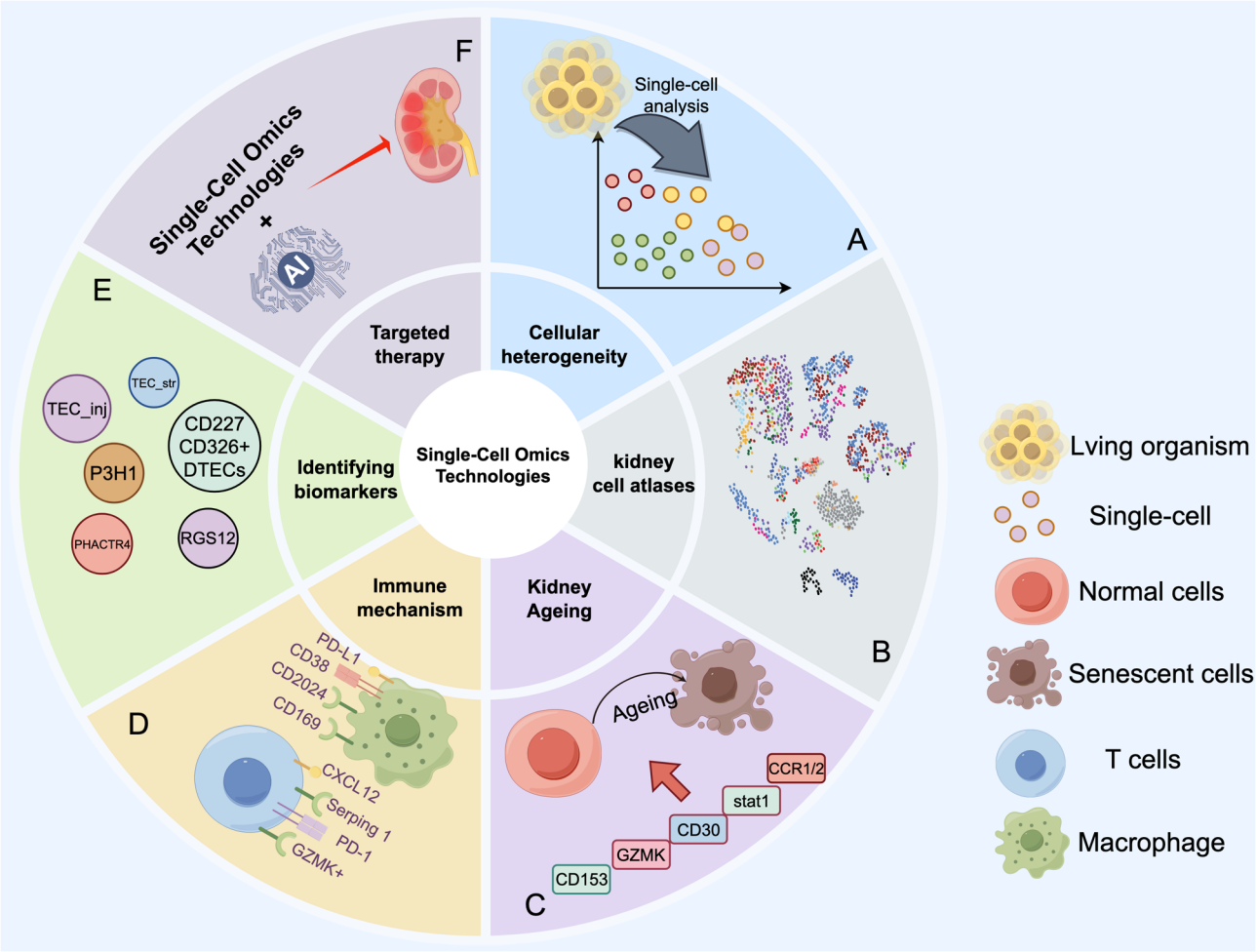

Figure 2. Applications of single-cell omics technologies in kidney research. (A) Analysis of cellular heterogeneity within complex kidney tissues. (B) Mapping of kidney cell atlases. (C) Elucidation of the mechanisms of kidney cell senescence. (D) Exploration of immune mechanisms in kidney diseases. (E) Identification of non-invasive biomarkers. (F) Identification of clinical therapeutic targets.

ageing through IFN-γ secretion (43). In macrophage-related studies, scRNA-seq further revealed bidirectional regulation between macrophages and renal ageing (44). Single-cell data from the kidneys of mice of different ages and aged mice with nephrotoxic serum nephritis (NTN) revealed that Stat1 upregulation in aged macrophages suppressed Pcbp1 transcription, activated ferroptosis, and promoted proinflammatory factor secretion, thereby accelerating renal interstitial fibrosis (45). Moreover, abnormal expression of CCR1, CCR2 and Fcγ receptor family members in the kidneys of aged NTN mice led to renal immune dysregulation and exacerbated renal injury (46,47). Additionally, scRNA-seq analysis of clinical data revealed that p21high macrophages mitigate transplant rejection in aged mice by upregulating Zfp36 expression and downregulating IL-27 expression, offering novel insights for kidney transplantation research (48).

In summary, using single-cell omics technologies to construct renal cell atlases, precisely identify abnormal cell subpopulations, and reveal key regulatory factors and molecular biomarkers not only provides core technical support for elucidating the pathogenesis of renal ageing and related diseases but also lays the foundation for early disease diagnosis, target screening and therapeutic optimization.

4. Applications of single-cell omics technologies in kidney diseases

Leveraging single-cell resolution as its core advantage, single-cell omics technologies enable precise analysis of cellular heterogeneity in kidney tissue, mapping of intercellular interaction networks, tracking of cellular fate trajectories, and identification of core regulatory programs. This technology overcomes the limitations of traditional bulk sequencing, which cannot capture individual cellular molecular characteristics. It provides unprecedented technical support for studying the mechanisms of kidney diseases, discovering novel non-invasive biomarkers, and screening potential therapeutic targets. This lays the theoretical foundation for personalized treatment and accelerates its clinical translation process (Table I).

Research advances in single-cell omics for AKI diagnosis and treatment. AKI is a clinically complex syndrome with high mortality rates. Its intricate pathogenesis and cellular heterogeneity significantly impede therapeutic progress (49,50). Single-cell omics technologies precisely capture novel cellular states and regulatory features during AKI progression and are pivotal for resolving diagnostic and therapeutic challenges.

Table I. Research on kidney diseases based on single-cell omics technologies.

Author/s, year	Types of disease	Research subjects	Research methods	Research findings	(Refs.)
Hasegawa, 2022	AKI	AKI mice	scRNA-seq	Between days 6 and 10 following AKI onset, there was a significant increase in the number of tubular cells expressing inflammatory markers.	(52)
Klocke *et al*, 2022		Urine samples from 32 AKI patients	scRNA-seq	TEC_inj and TEC_str, which are associated with injury, significantly increased during the mid-stage of the disease course (6-10 days).	(51)
Wagner *et al*, 2025		Urine of patients with AKI	scRNA-seq	The ratio of CD227/CD326^{+} DTECs correlated with the acute estimated glomerular filtration rate in patients with AKI.	(53)
Li *et al*, 2025		AKI mice	scRNA-seq	In AKI mice, lactate inhibition of aldehyde dehydrogenase in proximal tubular epithelial cells suppressed mitochondrial autophagy, exacerbated mitochondrial dysfunction, and consequently worsened renal injury.	(54)
Polonsky *et al*, 2024; Cui *et al*, 2024		AKI mice	scRNA-seq, spatial transcriptomics	Crlf1, Timp1, Npr3, ISG15, and TGF-βR1 expression was significantly upregulated in proximal tubule cells and surrounding fibroblasts. Among these, ISG15 promoted TGF-βR1 ISGylation and inhibited its ubiquitination, thereby exacerbating renal ibrosis.	(55,56)
Cai *et al*, 2025		AKI mice	scRNA-seq	Differential expression of S100A8/A9 proteins in renal tubular epithelial cells promoted renal macrophage polarization and activated the TNF signalling pathway.	(58)
Zhang *et al*, 2024		AKI mice	scRNA-seq and spatial transcriptomics	Mapping the Dynamic Profile and Spatial Distribution Characteristics of Renal Macrophages in the AKI-to-CKD Transition Model.	(57)
Yao *et al*, 2022		AKI mice	scRNA-seq	Significant upregulation of S100A8/A9 expression occurred in the S100a9hiLy6chiIMs subpopulation of renal macrophages, where high expression of Ccl2 and Ccl3 genes mediated early inflammation in AKI.	(59)
Qi *et al*, 2017	DKD	Patients with DKD	Single-cell proteomics	The PKM2 activator TEPP-46 increased glycolytic flux and upregulated Opa1 expression, thereby reversing high-glucose-induced toxic glucose metabolite accumulation and mitochondrial dysfunction, ultimately alleviating renal injury.	(64)
Jiang *et al*, 2025		Patients with DKD	scRNA-seq	LRPPRC exhibited low expression levels in damaged glomerular and tubular regions, with its expression levels negatively correlated with serum creatinine levels and proteinuria incidence.	(65)
Fu *et al*, 2022; Wang *et al*, 2025		Patients with DKD	scRNA-seq	Upregulating PPARα expression effectively reduced M1 macrophage infiltration and delayed the progression of DKD by inhibiting necrotic apoptosis via the RIP1/RIP3/MLKL pathway in renal tubular cells.	(67,68)

Table I. Continued.

Author/s, year	Types of disease	Research subjects	Research methods	Research findings	(Refs.)
Ji *et al*, 2024		Patients with DKD	scRNA-seq	The TGF-β1^{+}Arg1^{+} macrophage subpopulation promoted DKD renal fibrosis by activating the TGF-β1/Smad2/3/YAP signalling pathway, thereby promoting fibroblast activation and extracellular matrix deposition.	(69)
Chen *et al*, 2024		DKD mouse	scRNA-seq and proteomics technologies	RA reduced the recruitment of S100a4-positive macrophages, decreased oxidative stress in NK cells, and alleviated damage to glomerular epithelial cells.	(70)
Park *et al*, 2025		Type 2 diabetic nephropathy mice	scRNA-seq	CXCL12 secreted by proximal convoluted tubule cells interacted with glomeruli to jointly promote T-cell recruitment, thereby driving localized inflammatory responses in the kidney.	(71)
Zheng *et al*, 2020	IgA	Patients with IgAN	scRNA-seq	High expression of J CHAIN in mesangial cells of IgAN patients promoted IgA1 dimerization and deposition, and enhanced interactions between mesangial cells and endothelial cells, macrophages, and T cells.	(74)
Zhang *et al*, 2025		IgAN	scRNA-seq Luminex multiplex immunoassay technology	CX3CR1^{+} monocytes/macrophages induced mesangial cell injury through interaction with macrophage migration inhibitory factor and its receptor CD74 and activated the PI3K/AKT pathway, further exacerbating mesangial cell damage.	(75)
Zambrano *et al*, 2022		gddY mouse	SMART-seq2	Genes associated with endothelial dysfunction, such as Edn1, F8, and Nostrin, along with MHC I genes mediating endothelial cell immune responses, showed significantly upregulated expression. Their corresponding receptors were also overexpressed in PTCs, where binding promotes the release of inflammatory cytokines and exacerbates the extent of damage in PTCs during the early stages of IgAN.	(76)
Hasegawa *et al*, 2025; Chen *et al*, 2024		Patients and mice with IgAN	scRNA-seq spatial transcriptomics	Glomerular endothelial cells express CCL2, CXCL2, and EDNRB, and interact with macrophages via CXCL12/CXCR4.	(77,78)
Li *et al*, 2024	LN	Urine samples from patients with LN	Urine Proximity Extension Assay proteomics and scRNA-seq	Among patients with LN, urinary ICAM-2, FABP4, FASLG, IGFBP-2, SELE and TNFSF13B/BAFF protein levels showed the strongest correlation with clinical disease activity.	(84)

Table I. Continued.

Author/s, year	Types of disease	Research subjects	Research methods	Research findings	(Refs.)
Su *et al*, 2025		Patients with proliferative LN	scRNA-seq immunohisto-chemical analysis	The presence of $CD68^+$ macrophages in glomeruli of patients with proliferative LN increased the clinical response rate by 7.92-fold, serving as a significant predictor of treatment response.	(85)
Tang *et al*, 2022		Patients with LN	scRNA-seq immunopro teomics	ICx such as prolyl 3-hydroxylase 1, phosphatase and actin regulator 4, and G protein signal regulator 12 were significantly present in patients with LN.	(86)
Zhang *et al*, 2022		Patients with LN	Metabolomics based on UPLC-MS/MS	SM d34:2, DG (18:3 (9Z, 12Z, 15Z)/20:5 (5Z, 8Z, 11Z, 14Z, 17Z)/0:0), nervonic acid, Cer-NS d27:4, and PC (18:3 (6Z, 9Z, 12Z)/18:3 (6Z, 9Z, 12Z)) were significantly enriched.	(87)
Danaher *et al*, 2024		cLN		Precise identification of 11 immune cell types, clarifying the subpopulation composition and transcriptomic characteristics of each immune cell category.	(88)
Richoz *et al*, 2022		LN mice	Spatial transcriptomics	In LN mouse kidneys, the MoMac subset highly expressed FcγR receptors, internalized circulating ICs, and presented antigens. These cells activated the NF-κB and STAT3 pathways, leading to the secretion of the proinflammatory factors TNF-α/IL-1β. The TrMac subset secreted monocyte chemotactic factors and expressed B-cell survival factor BAFF, recruiting B cells and plasma cells to produce autoantibodies.	(90)
Chen *et al*, 2024		Patients with LN	scRNA-seq	iPTEC significantly enriched $CD163^+$ dendritic cells, which activated MHC-II molecules and upregulated the expression of proinflammatory cytokines (TNF, IL-1β) and T-cell-associated chemokines (CCL17, CCL22). This resulted in a highly proinflammatory microenvironment, exacerbating renal injury.	(91)
Gartshteyn *et al*, 2024		Patients with LN	scRNA-seq dataset	SLAM-related protein expression was significantly elevated in $CD4^+$ T cells. Upon binding to molecules within the lymphocyte activation molecule family, they jointly regulated TFH and TPH function, promoting TPH-dependent B-cell differentiation into plasma cells and thereby driving autoantibody production.	(92)
Wu *et al*, 2025		scRNA-seq	Patients with LN	$GZMK^+CD8^+$ T cells promoted ABC differentiation and antibody class switching by secreting IFN-γ and IL-21, thereby accelerating renal inflammatory responses.	(93)
Yamaguchi *et al*, 2024		scRNA-seq	LN mice	Podocyte-specific PI3Kα inhibitors not only suppressed activation of the AKT/mTOR pathway in LN mouse podocytes but also impaired B-cell and T-cell function, reducing production of inflammatory cytokines and autoantibodies.	(94)

AKI, acute kidney injury; DKD, diabetic kidney disease; LN, lupus nephritis; scRNA-seq, single-cell RNA sequencing; IgAN, IgA nephropathy.

They offer novel approaches for early diagnosis and targeted treatment, establishing themselves as core technical support in AKI research.

Single-cell omics facilitates AKI biomarker discovery. Single-cell omics technologies enable high-throughput sequencing of non-invasive samples to decipher single-cell molecular characteristics, overcoming the limitations of traditional biomarkers and establishing non-invasive diagnostic systems. Klocke *et al* (51) analysed urine samples from 32 patients with AKI via scRNA-seq and identified four novel damage-associated states in tubular epithelial cells (TECs). The urinary TEC transcriptome profile was highly concordant with that of renal biopsy tissue, confirming its ability to dynamically reflect renal injury. The study was the first to demonstrate that urinary single-cell sequencing can replace invasive biopsy. Hasegawa (52) pioneered scRNA-seq to demonstrate that the number of inflammation-associated tubular cells in urine from mice with AKI is correlated with injury severity. Wagner *et al* (53) identified a CD227/CD326^{+} DTEC subpopulation whose abundance was correlated with the glomerular filtration rate, positioning it as a novel non-invasive AKI biomarker. These studies, centred on single-cell technology, provide a series of highly specific and sensitive biomarkers for early diagnosis, disease monitoring and prognosis' assessment.

Single-cell omics advances AKI mechanistic research. Investigations into the mechanisms of tubular epithelial cell injury using single-cell omics analyses have revealed specific core regulatory programs and cellular state changes associated with injury, confirming the pivotal role of mitochondrial dysfunction. Li *et al* (54) utilized scRNA-seq to first identify a specific regulatory program of ALDH2 lactylation modification in the proximal tubular epithelial cells of mice with AKI, which suppressed mitochondrial autophagy, exacerbated mitochondrial dysfunction, and subsequently drove cellular injury. Researchers further combined spatial transcriptomics to localize and identify differentially expressed genes in the proximal convoluted tubules and surrounding fibroblasts, confirming that ISG15 regulates TGF-βR1 modification status and participates in the transition from tubular injury to renal fibrosis (55,56).

In studies of immune-inflammatory-mediated kidney injury, single-cell omics technologies have clearly resolved macrophage heterogeneity, core regulatory mechanisms and intercellular interaction networks for the first time. Zhang *et al* (57) employed combined scRNA-seq and spatial transcriptomics to map the dynamic profiles and spatial distribution characteristics of renal macrophages in an AKI-to-CKD progression model. They identified functional differences between resident and monocyte-derived macrophages and characterized a novel extracellular matrix (ECM)-remodelling macrophage subpopulation. This subset communicates with fibroblasts via the IGF signalling pathway. Spatial transcriptomics further clarified the spatial distribution patterns of macrophages across different stages of AKI. Through scRNA-seq, Cai *et al* (58) revealed that abnormal overexpression of S100A8/A9 in renal tubular epithelial cells paracentrally regulates macrophage polarization, activating TNF signalling to amplify inflammatory responses. Yao *et al* (59) identified S100a9hiLy6chi-infiltrating macrophages as a distinct proinflammatory subset via scRNA-seq, whose early infiltration was associated with tubular apoptosis. The application of single-cell omics technologies has fundamentally reshaped the understanding of the role of macrophages in AKI, providing novel therapeutic targets for preventing and treating AKI and chronic transition. This fully demonstrates their core value in renal immune-inflammatory research.

Research advances the diagnosis and treatment of diabetic kidney disease (DKD) using single-cell omics. DKD is a form of glomerulosclerosis triggered by metabolic abnormalities in patients with diabetes and is a major cause of end-stage renal disease. Previous studies indicated that 30-40% of diabetic patients worldwide develop DKD, with more than 50% of patients with DKD ultimately requiring end-stage renal replacement therapy, posing a significant threat to human health (60,61). Single-cell omics technology overcomes traditional research limitations by providing single-cell resolution. It revolutionizes DKD research by elucidating the dynamic states of cell types, core regulatory programs, and intercellular interaction patterns during DKD progression, offering core technical support for exploring its pathogenesis and identifying therapeutic targets (62).

Application of single-cell omics in decoding DKD metabolic mechanisms. Metabolic abnormalities serve as key drivers of DKD progression. Renal metabolic dysregulation triggers oxidative stress and inflammatory responses that impair renal structure and function, exacerbate fibrosis, and accelerate disease progression (63). Single-cell omics precisely deciphers metabolism-related cellular regulatory programs and fate trajectories in DKD.

Qi *et al* (64) employed SCP to analyse glomeruli from patients with DKD at single-cell resolution. They identified pyruvate kinase M2 as a core protective factor in DKD, whose expression and activity were significantly reduced in patients and negatively correlated with renal injury severity. Jiang *et al* (65) employed spatial transcriptomics to reveal low LRPPRC expression in the damaged glomeruli and tubules of patients with DKD, which was negatively correlated with serum creatinine levels and proteinuria incidence, impairing the regulation of mitochondrial energy metabolism. By combining these findings with those of pseudo-time trajectory analysis, researchers first revealed that LOH and CT undergo abnormal differentiation towards podocytes as DKD progresses. These findings confirm that tubular energy metabolism disorders can progressively damage glomerular podocytes by regulating cellular fate trajectories, thereby exacerbating renal injury and driving disease progression. This approach refines the metabolic pathogenic mechanism of DKD from the ‘metabolic regulation-cell trajectory-spatial localization’ dimension.

Application of single-cell omics in elucidating DKD immunological mechanisms. Abnormal immune cell function significantly contributes to worsening renal injury in patients with DKD. Single-cell omics technologies provide critical support for identifying DKD immunotherapy strategies and improving patient outcomes by enabling the elucidation of immune cell heterogeneity, core regulatory programs and intercellular interaction networks (66).

Researchers have employed scRNA-seq to analyse kidneys of mice with DKD and revealed for the first time that compared with that in the kidneys of normal mice,

the proportion of M2 macrophages in the kidneys of DKD mice decreased to 3.8%, while the proportion of proinflammatory M1 macrophages increased to 65.3%, confirming the dominance of proinflammatory macrophages in DKD (67,68). Ji *et al* (69) employed scRNA-seq to identify a novel TGF-β1^{+}Arg1^{+} macrophage subset in kidneys of mice with DKD. This subset was shown to exacerbate renal fibrosis by activating the TGF-β1/Smad2/3/YAP pathway, promoting fibroblast activation and ECM deposition. Chen *et al* (70) combined scRNA-seq with proteomics to reveal that rosmarinic acid mitigates DKD renal injury by synergistically reducing inflammatory responses and glomerular epithelial cell damage. This occurs because of the suppression of S100a4-positive macrophage recruitment and the alleviation of NK cell oxidative stress, offering a novel immunomodulatory therapeutic approach for DKD. Furthermore, Park *et al* (71) employed single-cell omics to identify significantly elevated proportions of NK and T cells in the renal tissues of mice with type 2 DN. They demonstrated that CXCL12 secreted by proximal tubule cells forms spatial interactions with glomerular cells, jointly promoting T-cell recruitment and driving local renal inflammation. This discovery provides novel therapeutic targets for restoring renal immune homeostasis in patients with DKD. These studies, which focused on single-cell omics technology, comprehensively elucidate the core mechanisms of immune dysregulation in DKD, fully demonstrating the pivotal value of this technology in DKD immunology research.

Advances in single-cell omics for IgAN diagnosis and treatment. IgAN is the most common primary glomerular disease (72,73). Single-cell omics technology has revealed core cellular interactions and regulatory programs, driving breakthroughs in mechanistic research. Key findings include the following:

Application of single-cell omics in exploring the immunological mechanisms of IgAN. IgAN is characterized by IgA immune complex deposition, and single-cell omics technologies have elucidated its core immunological mechanisms. Zheng *et al* (74) identified a J CHAIN-upregulated regulatory program in the mesangial cells of patients with IgAN via scRNA-seq. This program promotes IgA1 deposition and intercellular crosstalk, confirming the central regulatory role of mesangial cells. Zhang *et al* (75) combined scRNA-seq with Luminex technology to identify elevated CX3CL1 and CX3CR1 expression in mesangial cells and monocytes/macrophages. These molecules interact via MIF/CD74 to induce mesangial cell injury and activate the PI3K/AKT pathway. Zambrano *et al* (76) employed SMART-seq2 to identify the greatest number of genes that are differentially expressed in glomerular endothelial cells (GECs) during early IgAN progression, revealing their inflammatory effects through multiple molecular interactions with immune cells. Through combined scRNA-seq and spatial transcriptomics (77,78), researchers have further revealed that GECs spatially interact with macrophages via axes such as CXCL12/CXCR4 and that the overexpression of these genes exacerbates PTC damage. This clarifies the crucial role of 'GEC-PTC' interactions, offering new insights for early intervention.

LN. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, and LN represents one of its most severe complications (79). Studies indicate that ~50% of SLE patients develop LN, with 10-30% of patients progressing to end-stage kidney disease within 10 years of onset (80-83). The core pathogenesis of LN remains unclear, and its high degree of heterogeneity not only complicates disease classification but also poses significant challenges for clinical diagnosis, treatment selection and prognosis assessment (80). Single-cell omics technology, leveraging its core advantage of single-cell resolution, has emerged as a pivotal tool for the thorough exploration of LN heterogeneity, the elucidation of its pathogenesis, and the development of novel diagnostic and therapeutic strategies.

Single-cell omics technology facilitates the identification of LN biomarkers. Non-invasive diagnosis, disease activity monitoring and treatment response prediction for LN are critical for improving patient outcomes. Traditional biomarkers suffer from limitations such as low specificity and difficulty in distinguishing disease subtypes and stages. By integration with multi-omics technologies, single-cell omics can be used to precisely identify the cellular origins of differentially expressed molecules and decipher their regulatory mechanisms, thereby screening for highly specific and sensitive non-invasive biomarkers. In a recent study, researchers innovatively combined urine Proximity Extension Assay proteomics with renal single-cell transcriptomics to precisely trace the renal cellular origins of differentially expressed urinary proteins. They identified six proteins most strongly correlated with LN activity, establishing novel molecular markers to distinguish active from patients with inactive LN. Single-cell technology further elucidated their regulatory mechanisms, enhancing the clinical reliability of these biomarkers (84). Su *et al* (85) further addressed the gap in biomarkers for predicting treatment response in patients with LN. Using scRNA-seq combined with immunostaining, they reported that the incorporation of the proportion of CD68^{+} macrophages significantly enhanced the prediction efficacy of a model for the treatment response of patients with proliferative LN, outperforming traditional models and providing novel cellular markers for precise prognostic assessment. Tang *et al* (86) focused on identifying biomarkers for early LN diagnosis. Through combined scRNA-seq and immunoproteomic analysis, they discovered three novel circulating immune complexes, P3H1, PHACTR4 and RGS12, that serve as potential markers for early diagnosis and disease monitoring in LN. Building upon single-cell technology research, Zhang *et al* (87) further integrated ultrahigh-performance liquid chromatography-tandem MS metabolomics to identify five serum metabolites specifically enriched in LN. These metabolites efficiently distinguish SLE from LN, filling a gap in biomarkers for differentiating between SLE and LN and providing theoretical support for their clinical application. These studies demonstrate that single-cell omics technologies, when integrated with proteomics and metabolomics, can be used to precisely identify a series of biomarkers suitable for non-invasive diagnosis, disease monitoring, treatment response prediction, and differential diagnosis of SLE-LN. The resolution advantages of single-cell technologies enable the further clarification of cellular origins, expression

regulatory mechanisms, and associations of these biomarkers with pathological processes. Single-cell technologies are highly promising tools for the precise clinical management of LN and have enabled the discovery of LN biomarkers.

Single-cell omics technologies and advances in research on the immunological mechanisms of LN. Immune-inflammatory responses serve as the core driver of renal injury in patients with LN. LN kidney tissue exhibits extensive immune cell infiltration and abnormal activation. Complex interactions among diverse immune cells and renal resident cells collectively constitute the local proinflammatory microenvironment in LN kidneys, promoting the progression of renal damage. Single-cell omics technologies have improved the understanding of the immune pathogenesis of LN at the single-cell and spatial levels, providing core evidence for the development of targeted immunomodulatory therapeutic strategies. Research by Danaher *et al* (88) laid a crucial foundation for studying LN immune cell heterogeneity and spatial distribution. Utilizing scRNA-seq technology, researchers performed single-cell resolution analysis of renal tissue from patients with paediatric LN, precisely identifying 11 immune cell types and clarifying the subpopulation composition and transcriptomic characteristics of each immune cell type. Further integration with spatial transcriptomics revealed for the first time the functional localization specificity of various immune cells within LN kidney tissue. Myeloid cells (for example, macrophages) predominantly enriched in the glomerular region exhibited significantly upregulated expression of genes associated with antigen uptake, lipid metabolism and inflammatory pathways, directly contributing to glomerular inflammatory injury. Lymphocytes (for example, B cells and T cells) predominantly cluster in the tubulointerstitial region, forming a dense network of cellular interactions with myeloid dendritic cells and macrophages to jointly alleviate the dysregulation of the local immune microenvironment in LN kidneys. The aforementioned study systematically revealed the distribution patterns and functional characteristics of renal immune cells in patients with LN through a three-dimensional approach of 'cellular heterogeneity-spatial localization-functional association', fully demonstrating the unique advantages of combining single-cell and spatial transcriptomics in deciphering immune mechanisms in patients with LN.

Single-cell omics technology serves as a core tool for analysing the functions of myeloid and lymphoid cells in LN pathogenesis. Myeloid cells serve as central regulators of renal immune inflammation in LN. IgG immune complexes in the LN renal mesangium activate myeloid cells, exacerbating renal injury. Single-cell omics precisely revealed their subpopulation heterogeneity and interaction mechanisms, confirming that macrophages are core regulators capable of amplifying inflammation (89). Notably, Richoz *et al* (90) employed combined scRNA-seq and spatial transcriptomics to first identify two macrophage subpopulations, TrMac and MoMac, elucidating their regulatory programs and synergistic pathogenic roles, thereby providing novel targets for immune-directed therapies. Abnormal activation of lymphocyte subsets lies at the core of LN immune dysregulation. Single-cell omics confirmed that the proportion of renal T and B cells in patients with LN is positively correlated with disease severity (91). Gartshteyn *et al* (92) revealed via scRNA-seq that SAP, which is highly expressed in $CD4^+$ T cells, regulates TFH/TPH function, elucidating the mechanism underlying the regulation of T-cell imbalance. Wu *et al* (93) used scRNA-seq to demonstrate that $GZMK^+CD8^+$ T cells promote B-cell activation and antibody production, clarifying the mechanism of abnormal renal B cells. Furthermore, scRNA-seq confirmed that PIK3CA-mutated podocytes regulate lymphocyte function (94), broadening the understanding of LN pathogenesis.

In summary, single-cell technologies have revealed novel therapeutic targets and immunomodulatory strategies, providing core support for the precision treatment of LN. Furthermore, the integration of single-cell omics with multi-omics approaches has refined the LN biomarker system, offering innovative tools for non-invasive diagnosis, disease monitoring, and treatment response prediction. These findings provide crucial foundations for subsequent mechanistic studies and clinical translation in LN.

5. Summary and outlook

In recent years, rapid advancements in single-cell omics technologies have opened new perspectives for kidney disease research, demonstrating unique advantages in revealing cellular heterogeneity and elucidating disease mechanisms. However, this technology faces numerous challenges, including inherent technical errors, insufficient sensitivity for detecting low-abundance molecules in rare kidney cells, complex data processing, inconsistent standards and difficulties in capturing dynamic cellular changes; moreover, spatial information cannot be preserved, making deciphering the relationship between cell-cell interactions and disease progression difficult. The emergence of multi-omics technologies has effectively addressed the limitations of single-cell omics through the systematic integration of multilevel biological information such as transcriptomics and proteomics. This enables a shift from single-molecule analysis to multidimensional collaborative interpretation, further refining the understanding of renal disease pathogenesis and laying a solid foundation for personalized medicine. However, its application still faces the following bottlenecks: Inefficient data integration strategies, a lack of standardized research protocols, and a pronounced disconnect between basic research and clinical translation. Moving forwards, efforts should focus on advancing the high-quality development and clinical application of single-cell and multi-omics technologies in kidney disease research. Technologically, this involves optimizing kidney single-cell suspension preparation, promoting high-sensitivity sequencing, and integrating single cells with spatial transcriptomics to address gaps in detection and spatial information. For data processing and analysis, kidney-specific standardized protocols should be established, artificial intelligence should be leveraged for efficient data handling, and disease biomarkers and targets should be deeply mined. In application translation, multidisciplinary collaboration should drive the conversion of omics discoveries into clinical diagnostic and therapeutic tools. As technologies mature and multidisciplinary integration advances, these approaches hold promise for overcoming limitations, usher in new breakthroughs for kidney disease prevention and treatment and propel research towards precision and individualization.

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Authors' contributions

JX wrote the original manuscript, revised and edited the draft, and completed the creation of tables and figures. ZC, SL, XW reviewed and edited the manuscript. MC participated in topic selection, manuscript review, paper revision, and finalization. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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