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Single-Cell Multi-Omics in Chronic Kidney Disease: Mechanistic Insights into Renal Fibrosis, Inflammatory Remodeling, and Precision Therapeutics

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Abstract

Chronic kidney disease (CKD) represents a progressive and multifactorial disorder characterized by persistent renal injury, inflammatory remodeling, fibrosis, and irreversible decline in kidney function. Despite substantial advances in nephrology, the molecular complexity and cellular heterogeneity underlying CKD progression remain incompletely understood, thereby limiting the development of effective targeted therapies. Recent innovations in single-cell multi-omics technologies have transformed the understanding of renal pathophysiology by enabling high-resolution characterization of transcriptional, epigenomic, proteomic, metabolomic, and spatial alterations within individual kidney cell populations. These approaches have uncovered dynamic interactions among tubular epithelial cells, fibroblasts, endothelial cells, immune populations, and stromal compartments that collectively drive fibrosis and chronic inflammation. Single-cell analyses further reveal profound cellular plasticity, maladaptive repair mechanisms, metabolic reprogramming, and immune dysregulation contributing to progressive renal injury. Importantly, integrative multi-omics approaches have facilitated the identification of novel biomarkers, pathogenic signaling pathways, and therapeutic vulnerabilities suitable for precision nephrology strategies. Emerging computational platforms, artificial intelligence-assisted analyses, and spatial transcriptomic technologies are additionally enhancing understanding of intrarenal cellular communication and disease heterogeneity. This review discusses the current landscape of single-cell multi-omics in CKD, emphasizing mechanistic insights into renal fibrosis, inflammatory remodeling, cellular heterogeneity, and emerging translational opportunities for personalized therapeutic intervention.

1. Introduction

Chronic kidney disease (CKD) constitutes a major global health burden affecting approximately 10% of the worldwide population and represents one of the leading causes of morbidity and mortality [1]. CKD is characterized by progressive deterioration

of renal function accompanied by glomerulosclerosis, tubular atrophy, vascular injury, inflammatory remodeling, and interstitial fibrosis [2]. Regardless of the initiating cause, progressive fibrosis and chronic inflammation ultimately converge toward irreversible nephron loss and end-stage renal disease (ESRD), necessitating dialysis or kidney transplantation [3]. The pathogenesis of CKD is remarkably complex and involves intricate interactions among multiple renal cell populations, immune compartments, metabolic pathways, and extracellular matrix remodeling processes [4]. Conventional bulk transcriptomic and histopathological approaches have provided substantial insights into renal disease mechanisms; however, these methodologies fail to adequately capture the extensive cellular heterogeneity and dynamic intercellular communication occurring within diseased kidneys [5]. Consequently, many critical molecular mechanisms underlying CKD progression and therapeutic resistance have remained incompletely understood.

Recent advances in single-cell sequencing technologies have fundamentally transformed nephrology research by enabling high-resolution analysis of individual cellular populations within complex renal tissues [6]. Single-cell transcriptomics, epigenomics, proteomics, metabolomics, and spatial omics approaches collectively allow comprehensive characterization of cellular diversity, lineage plasticity, inflammatory states, and signaling networks involved in CKD progression [7]. These technologies have uncovered previously unrecognized renal cell subtypes, transitional cellular states, and maladaptive repair programs contributing to fibrosis and inflammation. Renal fibrosis represents the final common pathological pathway in CKD progression irrespective of disease etiology [8]. Fibrotic remodeling involves excessive extracellular matrix deposition, fibroblast activation, tubular epithelial injury, endothelial dysfunction, and chronic inflammatory infiltration [9]. Single-cell analyses have revealed substantial heterogeneity among fibroblast populations and identified specific profibrotic cell subsets associated with collagen production, transforming growth factor-beta (TGF-β) signaling, and myofibroblast differentiation [10]. These findings challenge traditional concepts regarding the origins and functional diversity of renal fibroblasts.

Tubular epithelial cells also play central roles in CKD progression beyond their conventional physiological functions [11]. Following injury, tubular epithelial cells undergo profound transcriptional and metabolic reprogramming characterized by dedifferentiation, epithelial-to-mesenchymal transition-like phenotypes, inflammatory signaling activation, and cellular senescence [12]. Single-cell transcriptomic studies demonstrate that maladaptive tubular repair contributes significantly to persistent inflammation and fibrotic progression within diseased kidneys. Inflammation constitutes another fundamental driver of CKD progression [13]. Activated macrophages, dendritic cells, T lymphocytes, neutrophils, and innate immune pathways collectively promote chronic inflammatory remodeling and extracellular matrix accumulation [14]. Recent single-cell immune profiling studies have revealed substantial heterogeneity among renal immune populations, including pro-inflammatory, profibrotic, reparative, and immunoregulatory cellular states [15]. Importantly, these immune populations dynamically interact with stromal and epithelial compartments through cytokines, chemokines, and growth factor signaling networks.

Metabolic dysregulation additionally contributes substantially to CKD pathogenesis. Renal tubular cells possess exceptionally high metabolic demands and rely heavily upon mitochondrial oxidative phosphorylation for energy production [16]. CKD progression is frequently accompanied by mitochondrial dysfunction, oxidative stress, fatty acid oxidation impairment, and altered cellular metabolism [17]. Single-cell metabolomic approaches now permit detailed characterization of metabolic heterogeneity and adaptive stress responses within individual renal cell populations. Spatial transcriptomics and imaging-based multi-omics technologies are further expanding understanding of CKD biology by preserving tissue architecture and cellular localization information [18]. These approaches enable mapping of cell-cell interactions, inflammatory niches, fibrotic microenvironments, and vascular remodeling within diseased kidneys. Integration of spatial and single-cell omics data is therefore facilitating unprecedented insights into intrarenal signaling networks and disease evolution.

Artificial intelligence and machine learning algorithms are increasingly applied to analyze large-scale multi-omics datasets generated from CKD studies [19]. These computational approaches enable identification of novel biomarkers, disease trajectories, therapeutic targets, and predictive molecular signatures associated with renal decline and treatment response. Precision nephrology

strategies integrating molecular profiling with clinical phenotyping may ultimately improve patient stratification and individualized therapeutic intervention.

Importantly, single-cell multi-omics technologies have also accelerated identification of therapeutic vulnerabilities in CKD. Novel pathways involving fibroblast activation, inflammatory signaling, epigenetic remodeling, metabolic dysfunction, and cellular senescence are emerging as promising targets for therapeutic development [20]. Continued integration of multi-omics technologies with translational nephrology is therefore expected to substantially reshape future CKD diagnosis and treatment paradigms. This review discusses the current landscape of single-cell multi-omics in chronic kidney disease, emphasizing mechanistic insights into renal fibrosis, inflammatory remodeling, cellular heterogeneity, and emerging precision therapeutic strategies (Figure 1).

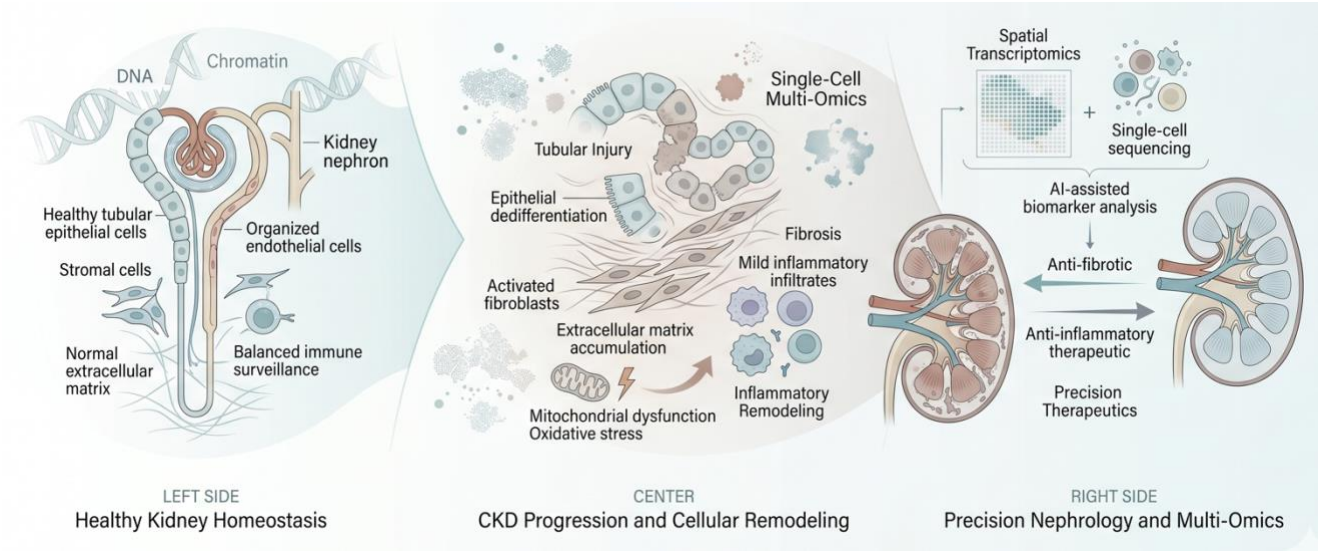

Figure 1: Overview of the molecular and cellular landscape underlying chronic kidney disease progression and the emerging role of single-cell multi-omics technologies in precision nephrology. The figure illustrates the transition from physiological renal homeostasis toward tubular injury, fibroblast activation, inflammatory remodeling, mitochondrial dysfunction, and extracellular matrix accumulation during CKD progression. Integration of single-cell sequencing, spatial transcriptomics, and AI-assisted biomarker analysis enables identification of disease-associated cellular heterogeneity and therapeutic targets for anti-fibrotic and anti-inflammatory precision interventions.

2. Methodology

This review was conducted through a comprehensive literature search of peer-reviewed publications indexed in PubMed, Scopus, Web of Science, and Google Scholar databases. Relevant studies published primarily between 2005 and 2026 were identified using combinations of keywords including "chronic kidney disease", "single-cell RNA sequencing", "single-cell multi-omics", "renal fibrosis", "inflammation", "spatial transcriptomics", "kidney injury", "fibroblasts", "immune remodeling", and "precision nephrology". Original research articles, systematic reviews, meta-analyses, and landmark mechanistic studies were prioritized. Particular emphasis was placed on investigations involving single-cell transcriptomics, epigenomics, proteomics, metabolomics, and spatial omics technologies in CKD and renal fibrosis models. Additional studies focusing on translational applications, biomarker discovery, computational biology, and emerging therapeutic strategies were also included. References cited within selected articles were manually screened to ensure scientific relevance and comprehensive coverage of the topic.

3. Cellular Heterogeneity, Tubular Injury, and Fibroblast Plasticity Revealed by Single-Cell Multi-Omics in Chronic Kidney Disease

The kidney is among the most structurally and functionally heterogeneous organs in the human body, consisting of highly specialized epithelial, endothelial, stromal, and immune cell populations that cooperate to maintain fluid balance, electrolyte homeostasis, filtration, and metabolic regulation [21]. During chronic kidney disease progression, this intricate cellular architecture undergoes profound remodeling characterized by maladaptive repair responses, inflammatory activation, fibroblast expansion, vascular dysfunction, and extracellular matrix accumulation [22]. Traditional bulk transcriptomic analyses have historically masked the remarkable cellular diversity underlying these

pathological processes. However, recent advances in single-cell multi-omics technologies have transformed understanding of renal cellular heterogeneity and disease-associated transcriptional plasticity.

Single-cell RNA sequencing (scRNA-seq) studies have identified previously unrecognized renal epithelial cell states associated with CKD progression [23]. Injured proximal tubular epithelial cells exhibit dedifferentiation signatures involving activation of developmental pathways, inflammatory mediators, senescence-associated genes, and profibrotic signaling networks [24]. These maladaptive epithelial states display elevated expression of transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and extracellular matrix-associated genes that collectively promote fibrosis and inflammatory remodeling.

Importantly, single-cell analyses reveal that tubular epithelial injury is not merely a passive consequence of renal dysfunction but rather an active driver of fibrogenesis [25]. Injured epithelial populations secrete cytokines, chemokines, and growth factors that recruit immune cells and activate fibroblasts within the renal interstitium. Persistent epithelial stress additionally induces mitochondrial dysfunction, oxidative injury, metabolic reprogramming, and cellular senescence, further amplifying inflammatory and fibrotic cascades [26]. Fibroblast heterogeneity has emerged as another major discovery arising from single-cell multi-omics studies in CKD. Historically, fibroblasts were regarded as relatively uniform matrix-producing cells. However, recent investigations demonstrate the existence of multiple fibroblast subpopulations possessing distinct transcriptional programs, inflammatory phenotypes, and profibrotic functions [27]. Specific fibroblast subsets exhibit enhanced collagen synthesis, extracellular matrix deposition, TGF-β responsiveness, and myofibroblast differentiation capacity.

Myofibroblasts represent principal effector cells responsible for pathological matrix accumulation during CKD progression [28]. Single-cell analyses indicate that myofibroblasts may originate from multiple cellular sources including resident fibroblasts, pericytes, endothelial cells, and injured epithelial populations [29]. These findings highlight the remarkable plasticity of renal stromal compartments and underscore the complexity of fibrotic remodeling. Spatial transcriptomic approaches have further revealed distinct fibrotic microenvironments within diseased kidneys [30]. Profibrotic fibroblast populations frequently localize adjacent to injured tubular segments and inflammatory infiltrates, suggesting the existence of highly organized intercellular communication networks driving disease progression. Ligand-receptor interaction analyses additionally demonstrate extensive signaling crosstalk involving TGF-β, PDGF, WNT, NOTCH, and inflammatory cytokine pathways among epithelial, stromal, and immune compartments.

Epigenetic remodeling also contributes substantially to fibroblast activation and persistence during CKD. Single-cell epigenomic studies demonstrate altered chromatin accessibility and enhancer landscapes in profibrotic fibroblast populations [31]. Histone modification imbalance, DNA methylation changes, and chromatin remodeling abnormalities collectively sustain persistent activation of fibrogenic transcriptional programs. Such epigenetic plasticity may explain the chronic and self-perpetuating nature of renal fibrosis. Endothelial dysfunction represents another critical component of CKD progression uncovered through single-cell analyses [32]. Injured endothelial populations display inflammatory activation, impaired angiogenic signaling, oxidative stress responses, and vascular rarefaction-associated transcriptional programs. Endothelial dysfunction contributes substantially to hypoxia, inflammatory cell recruitment, and fibrotic remodeling within diseased kidneys. Collectively, single-cell multi-omics technologies reveal that CKD progression involves highly dynamic and heterogeneous cellular interactions rather than uniform pathological processes. Understanding these complex cellular ecosystems is essential for development of targeted therapeutic strategies capable of interrupting maladaptive repair responses and fibrotic progression.

4. Immune Remodeling, Inflammatory Microenvironments, and Metabolic Reprogramming in Chronic Kidney Disease

Inflammation represents a central pathogenic mechanism driving chronic kidney disease progression and fibrosis [33]. Persistent immune activation contributes to tubular injury, fibroblast activation, vascular dysfunction, oxidative stress, and extracellular matrix deposition across diverse CKD etiologies. Recent single-cell immune profiling studies have substantially expanded understanding of the remarkable heterogeneity and functional plasticity of renal immune populations during chronic inflammatory remodeling. Macrophages constitute among the most abundant immune cell

populations within diseased kidneys [34]. Single-cell transcriptomic analyses reveal multiple macrophage subsets exhibiting distinct inflammatory, reparative, profibrotic, and immunoregulatory transcriptional states. Pro-inflammatory macrophages express elevated levels of IL-1β, TNF-α, NF-ϰB-associated genes, and chemokines that promote leukocyte recruitment and tubular injury [35]. Conversely, profibrotic macrophage populations secrete TGF-β, platelet-derived growth factor (PDGF), and matrix remodeling enzymes that facilitate fibroblast activation and extracellular matrix accumulation (Figure 2).

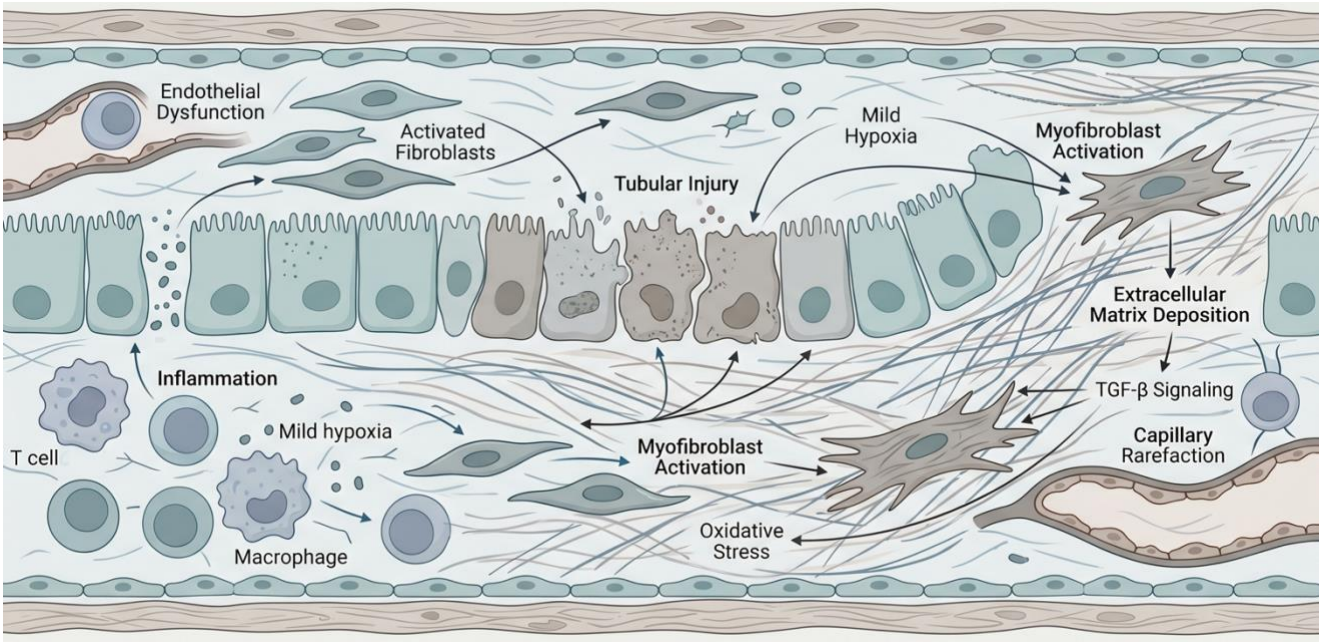

Figure 2: Schematic illustration of inflammatory and fibrotic remodeling during chronic kidney disease progression. Tubular epithelial injury, endothelial dysfunction, hypoxia, oxidative stress, and immune cell infiltration collectively promote fibroblast-to-myofibroblast transition, extracellular matrix deposition, and TGF-β-mediated renal fibrosis. Persistent inflammatory signaling and capillary rarefaction further amplify maladaptive tissue remodeling and progressive renal dysfunction.

Importantly, macrophage phenotypes display substantial plasticity and dynamically adapt to local microenvironmental signals [36]. Spatial transcriptomic analyses demonstrate that profibrotic macrophages frequently localize near injured tubular segments and activated fibroblast clusters, suggesting coordinated inflammatory-fibrotic signaling niches within diseased kidneys. These cellular interactions establish self-perpetuating inflammatory circuits that accelerate disease progression. T lymphocytes also contribute substantially to CKD-associated inflammatory remodeling [37]. Single-cell immune analyses identify activated CD4+ helper T cells, cytotoxic CD8+ T cells, regulatory T cells, and exhausted T-cell populations within fibrotic kidneys. Chronic antigen exposure, inflammatory cytokines, and metabolic stress collectively influence T-cell differentiation and functional states during CKD progression.

B-cell populations and tertiary lymphoid structures have additionally been identified in chronic inflammatory kidney diseases [38]. These immune aggregates contribute to sustained local cytokine production, autoantibody generation, and adaptive immune activation. Recent evidence suggests that epigenetic remodeling and metabolic reprogramming strongly influence immune cell differentiation and inflammatory responsiveness within CKD microenvironments. Metabolic dysregulation represents another major hallmark of CKD progression. Renal tubular epithelial cells possess exceptionally high metabolic demands and depend heavily upon mitochondrial oxidative phosphorylation for ATP generation [39]. Single-cell metabolomic and transcriptomic analyses reveal profound metabolic reprogramming during CKD characterized by impaired fatty acid oxidation, glycolytic shifts, mitochondrial dysfunction, and oxidative stress accumulation.

Mitochondrial dysfunction contributes substantially to epithelial injury and inflammatory activation [40]. Injured tubular cells display reduced mitochondrial biogenesis, impaired electron transport chain activity, and excessive reactive oxygen species generation. Oxidative stress further amplifies inflammatory signaling, DNA damage, cellular senescence, and profibrotic transcriptional

programs. Hypoxia also exerts profound influence over CKD progression. Vascular rarefaction and impaired oxygen delivery create chronically hypoxic microenvironments within fibrotic kidneys [41]. Hypoxia-inducible factor (HIF) signaling induces transcriptional adaptation programs involving angiogenesis, glycolysis, inflammation, and extracellular matrix remodeling. Single-cell analyses demonstrate substantial heterogeneity in hypoxic responses among renal epithelial, stromal, and immune populations.

Cellular senescence has emerged as another critical driver of chronic inflammatory remodeling in CKD [42]. Senescent tubular cells, fibroblasts, endothelial cells, and immune populations accumulate within diseased kidneys and secrete pro-inflammatory mediators collectively termed the senescence-associated secretory phenotype (SASP). SASP factors amplify fibrosis, inflammation, and tissue dysfunction through persistent cytokine and growth factor signaling. Single-cell multi-omics studies further reveal extensive intercellular communication networks linking inflammation, fibrosis, metabolism, and senescence during CKD progression [43]. Ligand-receptor analyses identify coordinated signaling pathways involving TGF-β, IL-6, TNF-α, WNT, CXCL chemokines, and VEGF networks across multiple cellular compartments. These findings highlight the systems-level complexity of CKD biology and emphasize the importance of targeting intercellular signaling interactions in future therapeutic strategies.

5. Spatial Transcriptomics, Artificial Intelligence, and Emerging Precision Therapeutic Strategies in Chronic Kidney Disease

Recent advances in spatial omics technologies are revolutionizing nephrology research by enabling simultaneous characterization of molecular profiles and tissue architecture within diseased kidneys [44]. Unlike conventional single-cell sequencing approaches that require tissue dissociation, spatial transcriptomics preserves anatomical context and permits mapping of cell-cell interactions, inflammatory niches, vascular remodeling, and fibrotic microenvironments at high resolution. Spatial transcriptomic analyses have identified highly organized inflammatory-fibrotic niches within CKD tissues involving coordinated interactions among injured tubular cells, fibroblasts, macrophages, endothelial cells, and adaptive immune populations [45]. These studies reveal substantial regional heterogeneity in cytokine signaling, metabolic stress responses, extracellular matrix remodeling, and immune activation across diseased kidneys. Importantly, such spatial heterogeneity may significantly influence therapeutic responsiveness and disease progression rates among patients.

Artificial intelligence (AI) and machine learning algorithms are increasingly integrated with single-cell and spatial omics datasets to improve disease classification, biomarker discovery, and therapeutic prediction [46]. Deep learning models capable of integrating transcriptomic, epigenomic, proteomic, imaging, and clinical data may identify molecular trajectories associated with fibrosis progression and renal decline. Such computational approaches are expected to significantly enhance precision nephrology implementation. Single-cell multi-omics technologies are also accelerating identification of novel therapeutic vulnerabilities in CKD. TGF-β signaling remains among the most extensively investigated profibrotic pathways [47]. However, recent multi-omics analyses demonstrate that fibrosis involves complex signaling networks extending beyond isolated cytokine pathways. WNT signaling, NOTCH activation, YAP/TAZ transcriptional programs, inflammasome signaling, and epigenetic remodeling collectively contribute to persistent fibroblast activation and maladaptive repair.

Epigenetic-targeted therapies are emerging as promising interventions for CKD and renal fibrosis [48]. Histone deacetylase inhibitors, bromodomain inhibitors, DNA methyltransferase modulators, and chromatin remodeling-targeted compounds demonstrate anti-fibrotic and anti-inflammatory effects in preclinical models. Importantly, epigenetic interventions may reverse maladaptive transcriptional programs without permanently altering genomic sequences. Senolytic therapies targeting senescent renal cells additionally possess significant therapeutic potential [49]. Experimental elimination of senescent tubular and stromal populations reduces inflammatory signaling, extracellular matrix accumulation, and renal dysfunction in animal models. Similarly, mitochondrial-targeted therapies aimed at restoring oxidative metabolism and reducing oxidative stress may improve tubular resilience and attenuate CKD progression.

Immune-targeted therapies are also being actively explored. Modulation of macrophage polarization, inflammasome signaling, cytokine pathways, and adaptive immune activation may mitigate chronic inflammatory remodeling within diseased kidneys

[50]. Integration of immune profiling with multi-omics analyses is expected to facilitate individualized immunomodulatory therapeutic strategies. Despite these advances, multiple challenges remain regarding clinical translation of single-cell multi-omics technologies. Tissue acquisition limitations, technical variability, computational complexity, and cost remain important obstacles to widespread clinical implementation [51]. Additionally, substantial interpatient heterogeneity necessitates large-scale longitudinal studies to validate predictive biomarkers and therapeutic targets. Future precision nephrology approaches will likely integrate single-cell sequencing, spatial transcriptomics, artificial intelligence, digital pathology, and longitudinal biomarker monitoring to improve diagnosis and therapeutic stratification [52]. Continued technological innovation and translational integration are therefore expected to profoundly reshape the future landscape of CKD management.

6. Conclusion

Chronic kidney disease is increasingly recognized as a highly heterogeneous and dynamically evolving disorder driven by complex interactions among epithelial, stromal, endothelial, immune, and metabolic pathways. Recent advances in single-cell multi-omics technologies have fundamentally transformed understanding of renal cellular heterogeneity, inflammatory remodeling, fibrotic progression, and maladaptive repair mechanisms underlying CKD pathogenesis. Single-cell transcriptomics, epigenomics, proteomics, metabolomics, and spatial omics approaches collectively reveal remarkable diversity among tubular epithelial cells, fibroblasts, immune populations, and vascular compartments during disease progression. These technologies have uncovered novel cellular states, profibrotic signaling niches, metabolic adaptation programs, and inflammatory communication networks that were previously obscured by conventional bulk analyses. Importantly, integrative multi-omics strategies are facilitating identification of molecular biomarkers, pathogenic pathways, and therapeutic vulnerabilities suitable for precision nephrology applications. Emerging therapeutic approaches involving epigenetic modulation, senolytic interventions, mitochondrial restoration, anti-inflammatory targeting, and AI-guided biomarker stratification possess substantial translational potential for improving CKD outcomes. Continued integration of single-cell technologies, computational biology, spatial transcriptomics, and translational nephrology will therefore remain essential for advancing personalized therapeutic strategies capable of mitigating fibrosis, preserving renal function, and reducing the global burden of chronic kidney disease.

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