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Molecular Mechanisms of Early Renal Fibrosis: Integrating Multi-Omics Evidence for Translational Nephrology

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Abstract

Early renal fibrosis represents a critical and potentially reversible stage in the progression of chronic kidney disease, yet its complex molecular underpinnings remain incompletely understood. Traditional histopathological and single-pathway approaches have provided limited insight into the dynamic and heterogeneous processes driving fibrotic initiation. Recent advances in high-throughput omics technologies have enabled comprehensive interrogation of molecular alterations across multiple regulatory layers, offering new opportunities to elucidate early fibrogenic mechanisms. This comprehensive review synthesizes evidence from genomic, epigenomic, transcriptomic, proteomic, and metabolomic studies to define the molecular landscape of early renal fibrosis from a systems biology perspective. Integrated multi-omics analyses reveal that early fibrogenesis arises from coordinated dysregulation of profibrotic signaling pathways, metabolic reprogramming, inflammatory activation, and extracellular matrix remodeling rather than isolated molecular events. Single-cell and spatial transcriptomic studies further demonstrate that distinct cell-state transitions and spatially restricted interactions among epithelial, stromal, endothelial, and immune cells shape fibrotic niches prior to overt structural damage. Network-based integration identifies convergent molecular modules and key regulatory hubs that govern fibrosis initiation and progression, providing mechanistic insights with translational relevance. Collectively, these findings underscore the value of multi-omics integration for advancing early detection strategies, therapeutic target prioritization, and precision nephrology. While challenges remain, including limited longitudinal human datasets and technical barriers to data integration, multi-omics approaches are poised to transform understanding and management of early renal fibrosis by enabling mechanism-driven, individualized intervention strategies.

Keywords: early renal fibrosis; multi-omics integration; chronic kidney disease; systems biology; single-cell transcriptomics

1. Introduction

Chronic kidney disease (CKD) is a major and fast growing worldwide health problem that affects hundreds of millions of individuals worldwide and imposes a substantial amount of morbidity, mortality, and health care costs. Whatever the insult causes it, the same pathological pathway can lead ultimately to progressive renal fibrosis to cause irreversible impaired renal function, and end-stage renal disease [1]. Fibrosis is the foundation of the structural changes in the kidney that involves remodeling the kidney structure, which in turn causes decrease in glomerular filtration, tubular dysfunction and microvascular rarefaction, where fibrosis is the most vital of the determining factors of CKD progression [2].Renal fibrosis is not an end stage disease or dichotomous but insidious and starts at the initial stages of kidney damage. The early renal fibrosis is marked by minimal extracellular matrix deposition, metabolic restructuring, inflammatory surveillance, and maladaptive cell repair mechanisms that most often

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persists to manifest into the overt histopathological alterations [3]. The initial fibrosis is a suitable target of intervention because fibrotic remodelling is often dynamic and potentially reversible at this stage. Nevertheless, the molecular complexity and cellular heterogeneity of initial fibrotic reactions have hampered detecting them in time and therapically targeting them [4].Conventional methods of examining renal fibrosis have been based on the histopathological examination and the study of individual signalling pathways, specifically transforming growth factor-b (TGF-b)-regulated pathways. Although the above strategies have produced valuable information, they do not portray the multidimensional and systems-level aspect of fibrogenesis [1]. Fibrosis is a result of complex interactions between mesenchymal, epithelial, endothelial, immune and metabolic networks, that cannot be comprehensively studied in single-pathway or single-layer terms. In addition, histology does not have the sensitivity of detecting early molecular changes that occur before irreversible structural changes are caused [5].Recent developments in high-throughput omics technologies have changed the field of nephrology research because they now have the means to interrogate biological systems on a grand scale across a variety of molecular scales [6]. Genomic and epigenomic studies have identified genetic susceptibility sites, regulatory changes that are linked to the risk of fibrosis, whilst transcriptomic and single-cell tools have identified cell-type-specific fibrotic programs and intercellular communication circuits [7]. Proteomics, metabolomics and lipidomics have also shed more light on post-translational regulation, extracellular matrix remodelling and metabolic changes that are behind the initial fibrotic response [8]. It is important to note that multi-omics investigations have shown that metabolic dysregulation serves as the point of convergence between inflammation and fibrosis and place cellular metabolism as a dominant force behind the onset of disease in its early stages [9].

Multi-omics in renal fibrosis is an ever-growing field of information that is piecemeal on platforms, experimental models, and disease pillars. Single studies usually concentrate on one omics layer or biological process, which does not enable them to establish convergent molecular processes that determine fibrotic initiation. Integrative multi-omics synthesis is thus necessary to find common regulatory centers, molecular fingerprints of early fibrosis and translation targets of diagnosis and treatment. These integrative modes have already been promising in improving CKD classification, discovering new biomarkers, and providing knowledge on precision nephrology plans [3]. The comprehensive review aims to decipher the molecular landscape of early renal fibrosis through an integrative multi-omics perspective. This review will elucidate important molecular pathways, cellular drivers, and regulatory networks that regulate the onset of renal fibrosis by synthesizing evidence of genomics, epigenomics, transcriptomics, proteomics and metabolomics research. It puts the emphasis on systems level interpretation and translational relevance, and focuses on bettering early detection measures and guiding therapeutic advancement in future.

Objectives

1. To synthesize and integrate multi-omics evidence defining the molecular mechanisms underlying the initiation of early renal fibrosis
2. To delineate key cellular drivers and signaling networks revealed by multi-omics analyses that govern early fibrotic remodeling and disease progression in chronic kidney disease
3. To evaluate the translational implications of multi-omics discoveries, including biomarker identification and therapeutic target prioritization for early intervention in renal fibrosis

2. Methodology

The comprehensive integrative review synthesized evidence on the molecular mechanisms of early renal fibrosis using a multi-omics framework. Major biomedical databases, including PubMed, Scopus, Web of Science, and EMBASE, were systematically searched to identify omics-based studies addressing early fibrotic processes in renal disease (Fig 1). Eligible studies included human, animal, and translational investigations employing genomic, epigenomic, transcriptomic, proteomic, or metabolomic approaches. Relevant molecular pathways, cell types, and regulatory networks were extracted and organized by omics layer. Findings were integrated using a narrative, systems-level approach to identify convergent mechanisms across datasets. Methodological heterogeneity and potential biases were critically considered during synthesis.

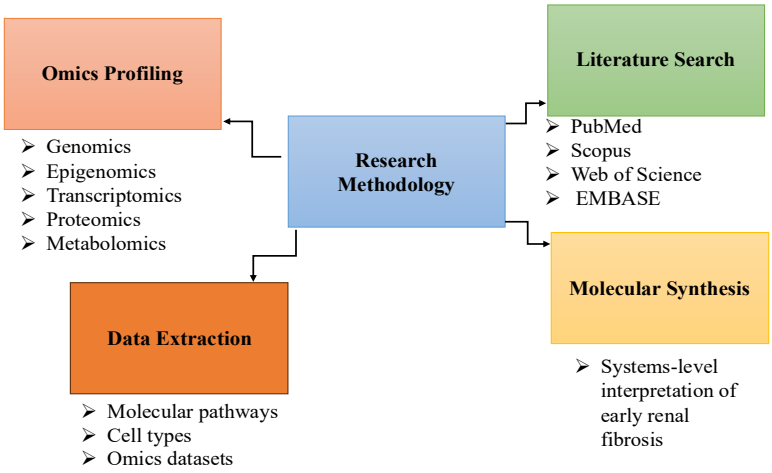

Fig 1: Methodological Framework for Integrative Multi-Omics Analysis of Early Renal Fibrosis

The schematic outlines the structured research methodology integrating systematic literature search, multi-omics profiling, data extraction, and molecular synthesis to enable systems-level interpretation of cellular pathways and regulatory mechanisms driving early renal fibrosis.

3. Results

3.1 Overview of Included Evidence

The literature review included a wide and rigorously methodological collection of omics-based investigations that covered the molecular pathways of molecular events involved in the pathogenesis of early renal fibrosis when evaluated in both experimental and clinical settings. The evidence included in this case was human, animal and translational studies that used high throughput molecular profiling to describe the early fibrotic remodeling before structural damage was done in an advanced way. Altogether, these investigations contributed to the complementary molecular data on the various layers of biological regulation involved in the development of renal fibrosis.

Omics was all-inclusive and transcriptomic technologies achieved the greatest presence in the most prevailing evidence base constituting the mainstay of early fibrotic gene expression programs and cell-type-specific reactions. Epigenomic and genomic studies helped to inform on genetic vulnerability, regulatory diversity and chromatin-scale regulation of profibrotic pathways. Proteomic measurements showed extra-cellular matrix-remodeling, changes in signalling proteins and post-translational controls and metabolic studies and lipidomic analyses revealed metabolic changes and bioenergetic changes during early fibogenesis.

Both human and experimental dataset were highly represented. The mechanistic understanding was mostly based on animal and in vitro models and this allowed one to interrogate molecular pathways and cellular interactions in a controlled manner. Multi-omics of tissues and non-invasive biomarker measurements were forms of human experimentation that provided clinical compelling evidence of relationships between molecular signature that is linked to an early fibrotic change in chronic kidney disease. A number of studies combined experimental and human data, enhancing the translational applicability and helping to cross-species confirm the identified molecular mechanisms.

The evidence provided is the overall and multidimensional omics landscape of early renal fibrosis, a variety of molecular layers, and biological systems. This richness of data furnished a solid basis of integrative analysis of convergent signaling networks, regulatory nodes and cellular drivers of initial fibrotic remodeling.

3.2 Molecular Signaling Pathways Identified in Early Renal Fibrosis

3.2.1 Profibrotic Signaling Networks

In the literature review, the transformation of growth factor-B (TGF-B) signaling was identified as a key regulatory node in the development of early renal fibrosis. Activation of the canonical TGF-B/SMAD pathway was consistently found in the tubular epithelial cells, fibroblasts and pericytes in the early stages of fibrotic remodeling by omics-based analyses [10]. Transcriptomic and proteomic analyses revealed the up-regulation of TGF-B ligands and receptors and SMAD downstream transcriptional programs, related to extracellular matrix deposition, fibroblast activation, and maladaptive epithelial repair [11]. The findings were noted in various experimental models and human datasets that highlight the evolutionary nature of TGF-bb signaling in the initiation of fibrosis [12].

Besides canonical signaling, non- canonical profibrotic pathways were often also found to be involved in initial renal fibrosis. Phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK)-activation were reported to cause cell survival, metabolic reprogramming and fibroblast persistence. Multi-omics data demonstrated that these pathways act in an autoregulatory fashion in the absence of and in collaboration with TGF-b signaling that enhances profibrotic responses by SMAD-independent pathways [13]. Proteomic and phosphoproteomic studies identified dynamic control of kinase activity in these pathways in the early stages of the disease, and insinuated their role in the regulation of the intensity and duration of fibrotic signaling.

3.2.2 Developmental Pathway Reactivation

The reactivation of signaling pathways that regulate development was also a notable characteristic found during early renal fibrosis. Wnt/ β-Catenin signaling was confirmed in transcriptomic and proteomic literature, and Wnt ligands, receptors, and subsequent transcriptional targets showed elevation in fibrotic kidneys (Fig 2). Even though canonical Wnt signaling was dominant, there were also indications that non-canonical Wnt pathways also regulate cellular polarity, migration and cytoskeletal dynamics, the processes involved in fibroblast activation and epithelial plasticity [14].

Hedgehog and Notch signaling pathway was also repeatedly involved in an early fibrogenesis. Studies using omics showed Hedgehog ligands and downstream effectors upregulation in both fibroblast and epithelial compartments and crosstalking between Hedgehog, Wnt, and TGF-B signaling [15]. Components of notch signaling were also activated, especially in tubular epithelial cells and interstitial fibroblasts, in which they were linked to a prolonged profibrotic gene expression and defective tissue repair [16]. These pathways of developmental reactivation are coordinated, indicating that there is a common regulatory program governing early fibrotic remodeling (Table 1).

3.2.3 Inflammatory and Immune-Associated Pathways

Inflammatory and immune-associated signaling pathways were prominently represented in the reviewed omics studies of early renal fibrosis. Activation of nuclear factor-κB (NF-κB) signaling was consistently observed, with transcriptomic analyses revealing upregulation of pro-inflammatory cytokines, chemokines, and adhesion molecules in both renal parenchymal and immune cells. NF-κB activation was closely linked to sustained inflammatory signaling and the recruitment of immune cell populations that contribute to fibrotic progression [11].

Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling was also identified as a key immune-associated pathway in early fibrosis. Omics data revealed that there is an augmented activation of STAT transcription factor upon cytokine signaling that advances fibroblast stimulus and immune cell endurance in the renal interstitium [13]. Cross-signaling of immune cells and fibroblasts became a common motif, and data on the support of bidirectional loops of signaling to reinforce inflammation-dependent fibrogenesis were found. The applicability of NF-kB and JAK/STAT signaling to early fibrotic response is, in turn, further substantiated by similar regulatory principles outlined in case of chronic inflammatory states [17].

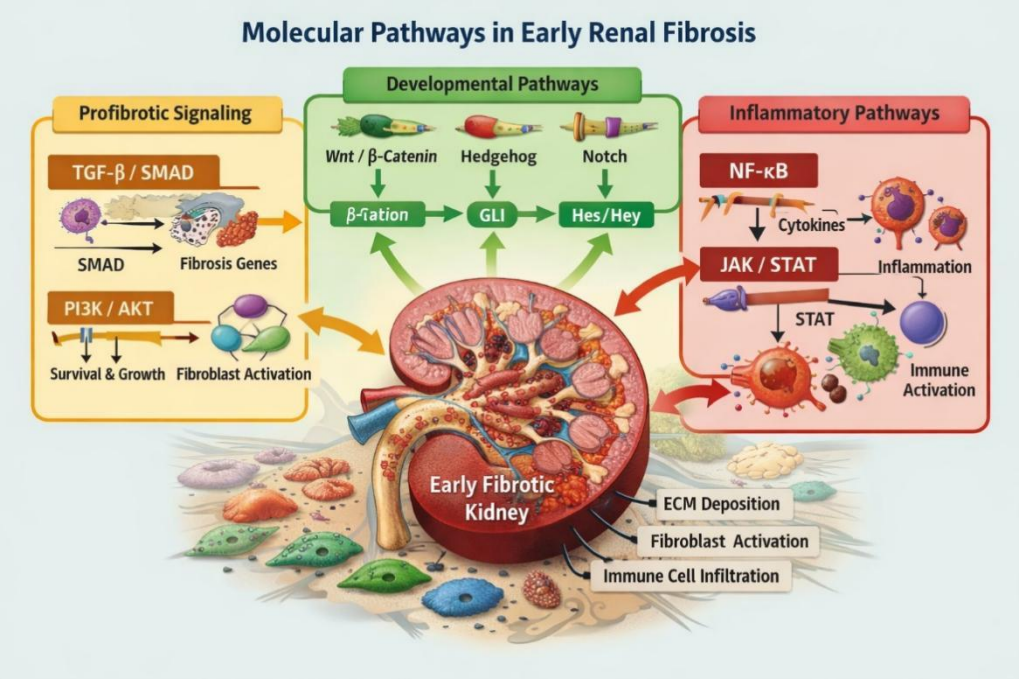

Fig 2: Integrated Signaling Networks Driving Early Renal Fibrosis

The schematic illustrates the convergence of profibrotic, developmental, and inflammatory signaling pathways in early renal fibrosis, highlighting crosstalk among TGF-β, Wnt, Hedgehog, Notch, and immune pathways that collectively drive fibroblast activation, inflammation, and extracellular matrix deposition.

Table 1. Major Signaling Pathways Implicated in Early Renal Fibrosis Identified Through Multi-Omics Studies

Signaling Pathway	Key Molecular Components	Primary Cell Types Involved	Major Fibrotic Effects	Evidence from Multi-Omics Studies	Key References
TGF-β/SMAD (Canonical)	TGF-β1, TGFBR1/2, SMAD2/3/4	Tubular epithelial cells, fibroblasts, pericytes	ECM deposition, fibroblast activation, maladaptive repair	Transcriptomics, proteomics, phosphoproteomics	Yu et al. [10]; Zhang et al.[11]
TGF-β (Non-Canonical)	PI3K, AKT, MAPK (ERK, p38)	Fibroblasts, epithelial cells	Cell survival, metabolic reprogramming, fibroblast persistence	Proteomics, kinase activity profiling	Zhang et al. [11]; Niculae et al. [12]
Wnt/β-Catenin (Canonical)	Wnt ligands, Frizzled, β-catenin	Tubular epithelial cells, fibroblasts	Fibroblast activation, epithelial plasticity	Transcriptomics, single-cell RNA-seq	Zhang et al. [11]
Wnt (Non-Canonical)	Wnt5a, PCP signaling components	Fibroblasts, migrating epithelial cells	Cell polarity, migration, cytoskeletal remodeling	Transcriptomics, functional pathway analyses	Lojk & Marc, [14]
Hedgehog	Shh, Ptch, Gli transcription factors	Fibroblasts, epithelial cells	Fibroblast proliferation, pathway crosstalk	Transcriptomics, network analyses	Sreeshma et al. [16]
Notch	Notch receptors, Jagged, Hes/Hey	Tubular epithelial cells, fibroblasts	Sustained profibrotic signaling, impaired regeneration	Transcriptomics, proteomics	Gao et al. [15]
NF-κB	IKK complex, p65/p50	Immune cells, tubular cells	Pro-inflammatory cytokine production, immune recruitment	Transcriptomics, cytokine profiling	Zhang et al. [11]; Niculae et al. [12]
JAK/STAT	JAKs, STAT1/3	Immune cells, fibroblasts	Cytokine-driven fibroblast activation, immune persistence	Transcriptomics, phosphoproteomics	Geng et al. [13]; Ageeva et al. [17]

3.3 Cellular and Spatial Insights from Transcriptomics

Transcriptomic analyses have given important insights into cellular heterogeneity and spatial organization of the initial renal fibrotic remodeling. A combination of bulk, single-cell, and spatial transcriptomic studies demonstrated coordinated but cell type specific programs of transcription that occur prior to the onset of overt structural fibrosis emphasizing complex interactions among epithelial, mesenchymal, and endothelial and immune compartments (Fig 3).

3.3.1 Tubular Epithelial Cell Maladaptive Repair Programs

Early fibrotic responses were found to be mediated by renal tubular epithelial cells. Transcriptomic studies have repeatedly shown that after injury, tubular epithelial cells undergo maladaptive repair programs, including sustained stress signaling, partial epithelial dedifferentiation, and changes in metabolic state, which puts tubular epithelium as an active rather than a passive participant in fibrogenesis [18]. These observations were further narrowed down to specific epithelial subpopulations with injury-induced transcriptional states that are associated with fibrotic progression by single-cell RNA sequencing [19].

3.3.2 Fibroblast and Pericyte Heterogeneity

Transcriptomic profiling showed there was substantial heterogeneity in the fibroblasts and pericytes populations in early stages of renal fibrosis. Single-cell experiments revealed that there were several fibroblast subsets that showed divergent transcriptional signatures indicating variations in their activation status, extracellular matrix production and sensitivity to profibrotic signaling. The expression patterns of pericytes were demonstrated to be transitional with the indications of mesenchymal activation, and their role in increasing fibroblast pool was endorsed. These results emphasize that fibrogenic cells are a continuum of phenotypes and not a homogenous group, and this suggests the possibility of selective targeting of pathogenic subsets [20].

3.3.3 Endothelial Dysfunction and Immune Infiltration

Transcriptomic changes in endothelial cells showed evidence of early dysfunction, such as a decrease in the expression of genes of vascular stability and an increase in the number of pro-inflammatory signals. These transformations were followed by increased expression of adhesion receptors and chemokines which enable the recruitment of immune cells. At the same time, immune cell populations had transcriptional programs that matched that of sustained activation and crosstalk with resident renal cells. Combined comparisons and

contrasts showed that spatial proximity of activated immune cells and fibrotic niches is proximate to a coordinated contribution of endothelial dysfunction and immune infiltration to augmenting early fibrotic remodeling [21].

3.3.4 Contributions of Single-Cell and Spatial Transcriptomic Analyses

The single-cell and spatial transcriptomic technologies provided significant progress in solving the cellular and spatial associations in initial renal fibrosis. Single-cell RNA sequencing made it possible to accurately identify rare and transitional cell states which are blurred in bulk cells, whereas spatial transcriptomics maintained tissue architecture, which made it possible to localize transcriptional programs in specific microenvironments [18]. Combined with these strategies localized epithelial-immune and fibroblast-vascular interactions in the fibrotic regions to give a spatially resolved molecular map of initial fibrogenesis [22]. The combination of these methodologies provided complementary information on the dynamics of the cell-state and intercellular communication networks that induce early renal fibrosis.

3.4 Genomic and Epigenomic Regulators

Genomic and epigenomic analyses have identified regulatory mechanisms that shape susceptibility to early fibrotic activation and influence the persistence of profibrotic transcriptional programs. Not as direct pathogenic drivers, genetic variants seem to be modulators of fibrosis risk by increasing cell-state responsiveness and injury-induced transcriptional dynamism instead of increasing cells-state risk further than by heterogeneous inflammatory and regenerative endothelial subpopulations with different regulatory profiles, revealed through single-cell resolved genomic studies [23]. The epigenomic studies also suggested DNA methylation and histone modification patterns as key regulators of fibrotic genes expression, where changes in methylation and histone acetylation or methylation states allow persistent chromatin access of fibrotic and inflammatory loci [24]. Complex disease models have demonstrated integrated genomic-epigenomic schemes of dynamic epigenetic remodelling that can result in overt pathology and stabilize maladaptive transcriptional programmes, which may also play a comparable role in early renal fibrogenesis [25]. Also, long non-coding RNAs have been identified as a fundamental player in epigenetic priming, organizing relations between regions of the genome and chromatin-modifying complexes to enhance profibrotic signaling in response to repeated or sustained injury signals [26]. Together, these results suggest that early renal fibrosis is under the control of both genetic predisposition and epigenetic memory controls that restrict the responsiveness of cells, transcriptional persistence, and heterogeneity of fibrotic development.

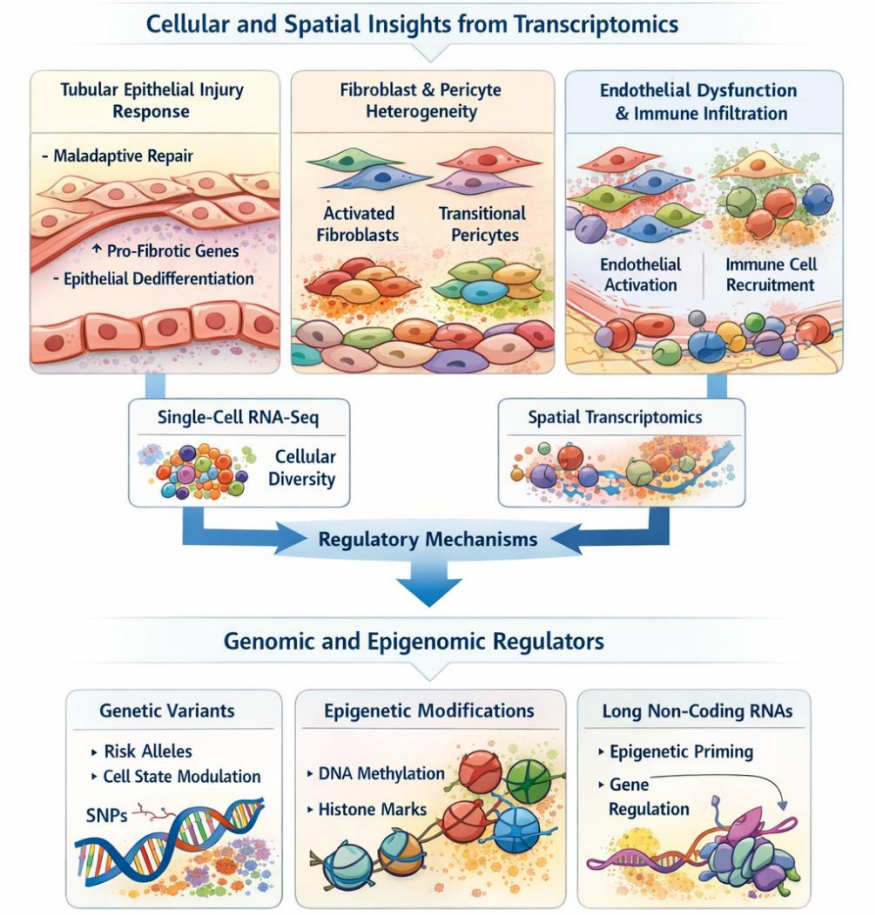

Fig 3: Integrated Cellular, Spatial, and Epigenomic Regulation of Early Renal Fibrosis

The schematic illustrates how transcriptomic heterogeneity across epithelial, fibroblast, endothelial, and immune compartments integrates with genomic and epigenomic regulators to drive maladaptive repair, cellular crosstalk, and molecular priming during the initiation of early renal fibrosis.

3.5 Proteomic and Metabolomic Remodeling

Proteomic and metabolomic studies have given essential information on the post-transcriptional regulation and metabolic changes that accompany early renal fibrotic remodelling. Multi-omics analyses that combine proteomic and metabolic layers always revealed that fibrogenesis cannot be governed by transcriptional regulations but is highly controlled by protein-level regulation, post-translational modification, and cellular energy metabolism changes [27]. The use of integrative network based techniques has been especially useful in the discovery of coordinated molecular modules between extra-cellular matrix reorganization, signaling stimulation, and metabolic dysregulation across disease states [28].

The proteomic profiling showed strong changes in extracellular matrix (ECM)-related proteins in early fibrosis that involve elevation of collagens, fibronectin, laminins, and matrix-modifying enzymes. These modifications indicate dynamic remodelling of the interstitial microenvironment and lead to the change in the tissue stiffness and cell-matrix signalling [29]. It was shown through network-based multi-omics integration methodologies that the components of the ECM are organized in highly interconnected protein modules that connect to inflammatory and profibrotic signaling pathways and thus play a key role in the formation of fibrotic niches [30].

In addition to protein abundance, post-translational regulation turned out to play a significant role in fibrotic signaling activity. The phosphoproteomic and proteomic analysis revealed the dynamic control of kinase-regulated pathways by phosphorylation, acetylation, and other forms of modifications that regulate the levels and duration of signaling. These regulation strata allow quick amplification or dampening of profibrotic cues regardless of alterations in the expression of genes, and they help to maintain pathway stimulation at early disease phases. The integrative multi-omics models have demonstrated that such post-translational processes are fundamental in the coordination of signaling networks in complex pathological states [31].

Metabolomic studies also revealed that metabolic reprogramming and mitochondrial dysfunction were among the features of early fibrotic remodelling. A change in the energy-related metabolites, lipid intermediates, and oxidative stress marker profiles reflected a change in the oxidative metabolism to less efficient bioenergetic states [29]. These metabolic responses were well associated with mitochondrial enzyme and metabolic regulation proteomic changes, which might imply concerted metabolic network remodelling. According to the multi-omics integration strategies, metabolic dysregulation interacts with signaling and ECM mechanisms to enhance fibrotic progression, indicating that metabolism is a constituent of fibrogenic networks and not a by-product of tissue injury [31].

Proteomic and metabolomic data has supported the role of post-transcriptional control and remodelling of the metabolic network in early renal fibrosis. The molecular layers give complimentary information to genomic and transcriptomic observations and lead to systems-level comprehension of fibrotic initiation and maintenance (Table 2).

Table 2. Proteomic and Metabolomic Remodeling in Early Renal Fibrosis Identified Through Multi-Omics Studies

Molecular Layer	Key Components	Biological Processes Affected	Functional Implications in Early Fibrosis	Multi-Omics Evidence Type	References
Proteomics – ECM Remodeling	Collagens, fibronectin, laminins, matrix metalloproteinases	Extracellular matrix turnover, tissue stiffness	Formation of fibrotic niche, altered cell–matrix signaling	Proteomics, network integration	Zhao et al. [30]
Proteomics – Signaling Regulation	Kinases, phosphatases, adaptor proteins	Profibrotic signaling amplification	Sustained pathway activation independent of transcription	Proteomics, phosphoproteomics	Blaser et al. [28]
Post-Translational Modifications	Phosphorylation, acetylation, ubiquitination	Signal transduction dynamics	Modulation of signaling intensity and duration	Phosphoproteomics, integrative modeling	Blaser et al. [28]
Metabolomics – Energy Metabolism	TCA cycle intermediates, glycolytic metabolites	Bioenergetic remodeling	Shift toward inefficient energy utilization	Metabolomics, proteomics correlation	Pinero et al. [31]

Metabolomics – Lipid Remodeling	Lipid intermediates, fatty acid metabolites	Lipid signaling and lipotoxicity	Promotion of inflammatory and fibrotic signaling	Metabolomics, network analysis	Blaser et al. [28]
Mitochondrial Dysfunction	Mitochondrial enzymes, oxidative stress markers	Redox imbalance, ROS production	Reinforcement of fibrotic signaling loops	Proteomics–metabolomics integration	Blaser et al. [28]
Integrated Network Modules	ECM–metabolism–signaling hubs	Systems-level coordination	Identification of regulatory nodes driving fibrosis	Multi-omics network fusion	Chierici et al. [27]

3.6 Integrative Multi-Omics Findings

Integrative multi-omics analyses provided a systems-level view of early renal fibrogenesis by enabling simultaneous interrogation of molecular alterations across genomic, transcriptomic, proteomic, and metabolomic layers. Network-based integration approaches consistently demonstrated that fibrotic initiation is characterized by convergence of signaling, metabolic, and extracellular matrix–associated pathways rather than isolated molecular events. By fusing multi-layered datasets, these studies identified coordinated molecular modules that captured the complexity and interdependence of fibrotic regulatory mechanisms [27]

A recurrent finding across integrative analyses was the convergence of profibrotic pathways across omics layers. The activation of pathways was supported by irreducible changes in transcriptome signature maps, proteomic, and metabolomic changes, which suggests multi-level control of important fibrotic processes. Convergence of such signaling cascades associated with extracellular matrix remodeling, inflammatory activation, and metabolic reprogramming was observed, and these observations implicate tight coupling between molecular networks, but no longer hierarchies of signaling [30].

Integrative network modeling also allowed the disclosure of important regulatory nodes which have disproportionate effects on fibrotic networks. These hubs frequently were cross roads of several biological processes as signaling mediators, metabolic regulators, and transcriptional modulators. The network centrality measurements also indicated that perturbation of these hubs might affect several downstream pathways at once, and that they may play an important role in regulating fibrosis initiation and progression [31]. It was shown by similar integrative schemes used in other complex diseases that multi-omics integration is useful in ranking causal regulators in highly interacting molecular networks.

Also, network-based methods provided information on the temporal and causal structure of fibrosis initiation. Combination of omics data into network models allowed studies to predict directional interactions and regulatory interactions between molecular entities which identify early network perturbations that are antecedents of subsequent fibrotic remodelling [29]. These analyses suggested that early renal fibrosis arises from coordinated dysregulation of interconnected molecular modules, rather than from isolated gene or protein alterations. Collectively, integrative multi-omics findings underscore the value of systems biology approaches for elucidating the complex molecular architecture of early renal fibrosis and for identifying regulatory frameworks that may inform future translational strategies.

4. Discussion

Early renal fibrosis is a biologically complex and dynamically controlled process that cannot be described by linear and single-pathway models. The synthesis of evidence at the levels of genomic, transcriptomic, proteomic, metabolomic, and spatial data is in support of a paradigm where the initiation of fibrosis is due to the coordinated perturbation of multiple layers of the molecules, cell types, and tissue microenvironment. Instead of a late and passive consequence of chronic injury, fibrosis seems to be programmed in early disease stages in interacting networks with epithelial responses to stress, immune activation, metabolic reprogramming and extracellular matrix remodelling. This is supported by systems-level studies in fibrotic diseases which show that fibrogenesis is an expression of emergent behavior of interconnected molecular circuits but not stochastic expression of individual signaling cascades, including attributes of specialized immune polarization states that actively modulate the fibrotic niche [32].

The main finding that can be made by integrative studies is that signaling pathways, metabolism, and inflammation are closely interlinked during early fibrotic remodeling. Such profibrotic signaling pathways as TGF- β, Wnt, and inflammatory cascades are not isolated activities but functionally integrated with the metabolic condition and the redox signaling [33]. Reactive oxygen species, i.e., are important signaling intermediates that connect mitochondrial dysfunction to the activation of inflammatory and fibrotic mammalian pathways, which enhance maladaptive repair reactions [34]. Genetic interaction studies also suggest that lipid metabolism and inflammatory signalling intersect to regulate disease susceptibility and progression as metabolic dysregulation is not just an end product of fibrosis, but rather an initiator that prepares renal cells to sustained profibrotic activation [35]. This overlap suggests that epithelial, stromal and immune cells are predisposed to profibrotic signals by early metabolic and inflammatory disturbances and then maintained in that state by epigenetic and post-translational processes.

The main purpose of using multi-omics data is to help improve the knowledge of how these processes work, as they allow cross-validation of molecular signals across regulatory layers. The changes in transcriptomes are not sufficient to understand the fibrotic biology because gene expression does not necessarily correspond to

protein concentration, activity of the signaling pathway, or metabolic rate. Combining multi-omics data can indicate which pathways are universally dysregulated in different molecule states and give more confidence in their biological significance. This convergence is a characteristic of core fibrotic drivers as opposed to secondary or context-dependent alterations and minimizes the risk of false-positive associations inherent in single-omics research [36]. Systems biology Fibrosis is a network disease which can be said to have highly connected modules as opposed to discrete molecular events and that analytical frameworks are required which can capture non-linear interactions and feedback loops.

Single-cell and spatial transcriptomic technologies, which unravel heterogeneity and spatial structure of cellular fibrotic tissue. Such methods have shown that earlier fibrosis is a state of particular cell populations and not of homogenous populations with epithelial, fibroblast, endothelial, and immune subpopulations making different contributions to disease onset. Spatially resolved mapping studies have revealed that fibrotic signaling is frequently concentrated around specific microenvironments in which immune cells, fibroblasts and injured epithelial cells coexist in a close interaction, maintaining local inflammatory and profibrotic signaling positive loops [37]. This information of the space context is significant since bulk analyses may overlook pathogenic interactions which occur in discrete niches. In combination, single-cell and spatial technologies of molecular profiling and tissue architecture can give a more physiologically relevant image of early fibrogenesis.

Translational perspective This realization has unimaginable consequences on the diagnosis and early intervention treatment. The biomarkers obtained with the help of multi-omics can potentially identify fibrotic activity before the structural damage in the nephrology major underutilized unmet need [38]. Combining molecular signals in integrated biomarker panels across some or all omics layers could be more advantageous than single-analytic biomarkers because it can be shown to signal on many dimensions of disease biology as seen in oncology and cardiovascular studies [39]. Moreover, network-based analyses can be used to prioritize regulatory hubs that have disproportionate control on fibrotic networks, which offer a reasonable therapeutic target whose manipulation can have the benefit of simultaneously impacting various pathogenic pathways. This is especially in fibrosis, where specific signaling molecules have provided a low response rate to therapy because of pathway redundancy and compensation.

Further improvement of the translational potential of multi-omics data is provided by the development of computational modeling methods and interpretable machine-learning methods. It is possible to integrate high-dimensional data using graph-based and network-oriented models, which maintain biological interpretability, support the discovery of biomarkers, the stratification of patients, and the identification of therapeutic targets [40]. These methods facilitated a transition to focus on precision nephrology where frontline clinical parameters are supplemented with molecular profiles to allow the personalization of risk assessment and treatment plans based on underlying disease mechanisms.

Irrespective of such progress, there are a number of limitations to the existing evidence base. The first problem is the lack of longitudinal human multi-omics data that would measure the initiation and progress of the disease over time. The majority of accessible literature consists of cross-sectional studies and does not allow establishing a causal relationship or drawing up a sequence of molecular events in time. Models Experimental models can be useful in understanding the mechanics of human disease, but do not necessarily capture the complexity and heterogeneity of human disease and introduce biases which are model-specific making translation difficult. Moreover, technical issues are still significant, such as heterogeneity of data across platforms, batch effects, missing support of all layers of molecules, and a lack of standardization of analytical pipelines. These have a detrimental effect on reproducibility and comparability between studies and are a critical impediment to clinical implementation [41].

The next steps will rely on the organized activities aimed at producing longitudinal, spatially resolved multi-omics data that will be combined with imaging, digital pathology, and clinical phenotyping. Such an integrative frameworks can be able to monitor fibrotic activity and therapeutic response in real time to bridge the gap between molecular changes and the structural and functional outcome. The application of multi-omics biomarkers in designing of clinical trials may also increase patient stratification and endpoint selection as well as treatment response particularly in early stages of the disease since interventions have the best chance to alter the course of the disease. The future of multi-omics in the analysis of early renal fibrosis is in the re-conceptualization of the perception, diagnosis and treatment of this disease, which would turn the field into a practical systems based precision-driven nephrology paradigm as analysis tools and data integration strategies continue to become mature.

5. Conclusion

Early renal fibrosis is a critical and possibly reversible period in the pathogenesis of chronic kidney disease, but due to its biological complexity, it has been overlooked in diagnosis and timely therapeutic response. This systematic review is a multi-omics-based integration of evidence to define the molecular architecture of the initiation of fibrosis in the renal environment, proving that early fibogenesis does not occur as a result of deregulation of specific signaling pathways but arises due to the concerted deregulation of genomic, epigenomic, transcriptomic, proteomic, and metabolomic layers. Integration of profibrotic signaling, metabolic reprogramming, inflammatory activation, and extracellular matrix remodeling highlight the fact that fibrosis is a systemic process which is the result of dynamic interactions amongst the epithelial, stromal, endothelial, and immune cell populations. Further developments of the single-cell and spatial transcriptomic methods provide an enhanced version of

this model in which the cell-type-specific programs and spatially limited molecular interactions in individual fibrotic niches were identified before the transformation of the structure itself. Notably, integrative network-based studies establish the critical regulatory nodes and molecular modules that have a disproportionate role in fibrotic initiation, which cannot be achieved in reductionist methods. Translationalally, the results imply the opportunities of multi-omics integration to provide a superior opportunity to detect fibrotic activity earlier and more accurately by the means of composite biomarker signatures and predict the priorities of therapeutic targets and patient-based stratification in the context of a precision nephrology paradigm. There are still major issues such as the fact that longitudinal human multi-omics datasets are still scarce, models tend to be biased, and technical and analytic barriers to strong data integration and standardization. Clinical translation will be necessary to address these limitations by undertaking longitudinal, multi-omics studies, with coordinated and spatially resolved multi-omics combined with clinical phenotyping and digital pathology. With further developments in analytical technologies and systems biology paradigms, multi-omics techniques are set to cause paradigm shifts in the concept of understanding, diagnosis, and management of early renal fibrosis with a shift in paradigm towards mechanism-based and personalized interventions capable of altering disease pathways and enhancing long-term renal outcomes.

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