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Abstract

Renal microvascular rarefaction is a key link in the progression of chronic kidney disease (CKD), essentially characterized by decreased capillary density, local hypoxia, and insufficient perfusion. With the development of technologies such as spatial transcriptomics, multimodal imaging, and intravital imaging, researchers can re-examine the relationship between microvascular rarefaction and fibrosis from a spatiotemporal perspective. This article focuses on the spatiotemporal dimensions of renal microvascular rarefaction and proposes the concept of a "spatiotemporal causal chain," namely that incomplete capillary repair after acute kidney injury (AKI) can evolve into persistent rarefaction, while the renal medulla is more prone to ischemia due to physiological hypoxia, and the degree of rarefaction is positively correlated with fibrosis. It also constructs a framework of an "intervenable window," suggesting that the stage when vascular function has declined but fibrosis has not yet become fixed represents an opportunity for intervention, which may delay CKD progression. The authors believe that future studies can use mapping approaches to clarify the disease-specific differences in the "spatiotemporal causal chain" among different types of kidney diseases, as well as the duration and molecular markers of the "intervenable window." Combined with large-sample follow-up data and the development of detection tools, this may enhance the value of clinical translation and promote early identification and precise intervention in CKD.

Full Text

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Spatiotemporal Causal Relationships and Intervention Window of Renal Microvascular Rarefaction

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【Abstract】 Renal microvascular rarefaction is a key link in the progression of chronic kidney disease (CKD). Its essential characteristics are decreased capillary density, local hypoxia, and insufficient perfusion. With the development of technologies such as spatial transcriptomics, multimodal imaging, and intravital imaging, researchers can re-examine the relationship between microvascular rarefaction and fibrosis from a spatiotemporal perspective. This article focuses on the spatiotemporal dimensions of renal microvascular rarefaction and proposes the concept of a "spatiotemporal causal chain," namely that incomplete capillary repair after acute kidney injury (AKI) can evolve into persistent rarefaction, while the renal medulla, because of physiological hypoxia, is more prone to ischemia, and the degree of rarefaction is positively correlated with fibrosis. At the same time, an "intervention window" framework is constructed, arguing that the period when vascular function has declined but fibrosis has not yet become consolidated is the optimal time for intervention, which may delay CKD progression. The authors suggest that in the future, mapping approaches may be used to clarify the heterogeneous differences in the "spatiotemporal causal chain" among different types of kidney disease, as well as the duration and molecular markers of the "intervention window." Combined with large-sample follow-up data and the development of detection tools, this may enhance clinical translational value and promote early recognition and precision intervention in CKD.

【Keywords】 nephrology; renal fibrosis; renal microvascular rarefaction; urinary system; review

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【Abstract】 Renal microvascular rarefaction is a key process in the progression of chronic kidney disease (CKD), essentially characterized by decreased capillary density, local hypoxia, and insufficient perfusion. With the advancement of technologies such as spatial transcriptomics, multimodal imaging, and intravital imaging, researchers can now re-examine the relationship between microvascular rarefaction and fibrosis from a spatiotemporal perspective. This article focuses on the spatiotemporal dimensions of renal microvascular rarefaction and proposes the concept of a "spatiotemporal causal chain," suggesting that incomplete capillary repair after acute kidney injury (AKI) can evolve into persistent rarefaction. The renal medulla, due to its physiological hypoxia, is more susceptible to ischemia, and the degree of rarefaction is positively correlated with fibrosis. Furthermore, the article constructs an "intervention window" framework, proposing that the optimal timing for intervention is when vascular function declines but fibrosis has not yet become irreversible, which may help delay CKD progression. The authors suggest that in the future, a mapping approach could be used to elucidate the specific differences in the "spatiotemporal causal chain" among different disease types, as well as the duration and molecular markers of the "intervention window" . Combined with large-sample follow-up studies and the development of detection tools, this strategy may enhance clinical translational value and promote

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the early identification and precise intervention of CKD.

【Key words】Nephrology; Renal fibrosis; Renal microvascular rarefaction; Urinary system; Review

Chronic kidney disease (CKD) is a major global public-health challenge. Epidemiological studies show that its global prevalence and the health burden it imposes are continuing to increase [1-5]. Microvascular rarefaction is a key link in CKD progression. Although studies have explored the mechanisms of renal microvascular rarefaction, most have been limited to the levels of the "hypoxia theory" or "impaired angiogenesis," and an integrated understanding of it across

temporal and spatial dimensions remains insufficient [6-8].

In recent years, with the rise of in vivo imaging and spatial multi-omics, researchers have begun to track the dynamic changes of microvessels along longitudinal and spatial dimensions. Zhou et al. [9] introduced a new method for volumetric deep-tissue microvascular angiography based on stereoscopic vision combined with super-resolution localization imaging, enabling high-frequency visual imaging of penetrating microvessels throughout the mouse cerebral cortex and achieving capillary-level resolution. Chen et al. [10] used ultrasound super-resolution imaging to quantify vascular-system changes related to the progression from acute kidney injury (AKI) to CKD in mice, with superior resolution. Gao et al. [11] used longitudinal in vivo imaging to track the dynamic process of cerebrovascular regression in adult mice, thereby characterizing changes related to vascular regression in the microcirculation. Christa et al. [12] developed the IMAGE-SEQ platform, linking in vivo/in situ imaging with subsequent spatially resolved single-cell sequencing, which can record the temporal and dynamic history of the cells being analyzed.

The development of these technologies has made it possible to address the following key questions from new perspectives: Is microvascular rarefaction a consequence of fibrosis, or an initiating factor? Is there an interventional time window during the process of microvascular rarefaction? Does microvascular rarefaction show spatial specificity in different renal regions (cortex and medulla)? Which molecular pathways are highly coupled with microvascular loss in the spatiotemporal dimension? This article reviews recent relevant literature, proposes the concept of a "spatiotemporal causal chain" of renal microvascular rarefaction, emphasizes differences in vascular rarefaction across different time stages and anatomical regions as well as potential clinical opportunities for intervention, and, in combination with the latest advances in spatial omics, imaging technologies, and computational analysis, provides new directions for future research and clinical translation.

1 Literature Search Strategy

Computer-based searches were conducted in databases including PubMed, Web of Science, Cochrane Library, and Embase. The search period was from database inception to September 2025. English search terms included "Renal Fibrosis," "hypoxia," "microvessel," "microvascular rarefaction," "chronic kidney disease," "acute kidney injury," "transcriptomics," and "imaging techniques." A combination of subject terms and free-text terms was used; synonyms were connected with "OR," and core topics were restricted with "AND." Inclusion criteria were: studies addressing structural and functional changes in renal microvascular rarefaction, the relationship between renal microvascular rarefaction and hypoxia/fibrosis, potential interventional mechanisms, and advances in technical research. Exclusion criteria were: literature unrelated to the topic of this article, of poor quality, or for which the full text could not be obtained. Ultimately, 53 articles were included.

2 Structural and Functional Characteristics of Renal Microvascular Rarefaction

The essential feature of renal microvascular rarefaction is tissue ischemia and hypoxia caused by a reduction in capillary number and density. This involves not only anatomical loss of microvessels, but also functional microvascular occlusion and insufficient perfusion [13].

Studies have shown that in various animal models, including AKI, renal ischemia-reperfusion injury (IRI), unilateral ureteral obstruction (UUO), and diabetic kidney disease, progressive disruption and reduction of the renal peritubular capillary network can be observed. Results of tissue oxygenation measurements in many different CKD experimental models have confirmed hypoxia, accompanied by decreased blood-flow velocity, insufficient red-blood-cell perfusion, and enhanced local hypoxic signaling [14-16].

Recent studies of renal and microvascular diseases suggest that even when no obvious morphological abnormalities of the microvessels are yet visible, marked reductions in capillary flow velocity and increased heterogeneity of blood flow have already appeared. This indicates that functional microvascular rarefaction may occur early, providing a new perspective for understanding the pathological mechanisms of microvascular lesions [13-15,17].

3 Spatiotemporal Dimensions of Microvascular Rarefaction

3.1 Temporal Dimension: Progression from Acute Kidney Injury to Chronic Kidney Disease

After AKI occurs, some renal peritubular capillaries can recover within days to weeks; however, if repair is incomplete, the capillaries may transition into persistent rarefaction and become an important driving factor of chronic kidney disease. Loss of peritubular capillaries due to acute or chronic injury can trigger local hypoxia; hypoxia is primarily the result of capillary rarefaction and serves as a key pathological and physiological factor in the transition from AKI to CKD [18-21].

3.2 Spatial Dimension: Heterogeneous Rarefaction across Multiple Regions

The renal microvascular network includes glomerular capillaries (GCs), peritubular capillaries (PTCs), and medullary vasa recta. These vessels show marked heterogeneity in structure and function, as well as in their response mechanisms to injury [22]. GCs and cortical PTC capillary networks distributed in the renal cortex are abundant, but are susceptible to upstream pathological factors such as hypertension, immune inflammation, and diabetes [23]. For example, in immune-mediated nephritis and diabetic kidney disease, glomerular capillary injury and endothelial-cell dysfunction are among the early features.

By comparison, the medullary vasa recta and medullary PTCs, located in the renal medulla, are naturally in a state of relatively low oxygen tension because of vascular structural characteristics and differences in blood-flow distribution. This physiological oxygen gradient is crucial for the concentrating function of the kidney, but it also makes the medulla more prone to ischemic injury [24-25], and the degree of capillary rarefaction is significantly positively correlated with renal interstitial fibrosis. After renal IRI, apoptosis of endothelial cells in the medullary microvasculature intensifies, leading to a marked decrease in capillary density and insufficient local perfusion, which in turn causes persistent hypoxia and tubular injury. In addition, downregulated expression of miR-423-5p in endothelial-cell-derived extracellular vesicles (EVs) can disrupt microvascu[[unclear: word continues beyond the visible page]]

vascular homeostasis and weaken repair capacity, further aggravating renal functional damage[26-28].

Some studies have used spatial transcriptomics and related technologies to construct reference datasets for renal medullary tissue, revealing region-specific upregulation of hypoxia-response and profibrotic genes[29-30]. Other studies have found that the kidney may possess a five-layer structure distinct from the traditional cortex–medulla bilayer model; this structure may enhance renal adaptability to hypoxia and hyperosmotic environments[31]. In addition, after renal IRI, cardiotrophin-like cytokine factor 1 (Clcf1) mediates interactions between persistently injured renal proximal tubular cells and adjacent fibroblasts, driving the formation of a fibrotic microenvironment. This process is closely associated with renal vascular loss[29].

4 The Causal Chain Linking Renal Microvascular Rarefaction with Hypoxia and Fibrosis

4.1 The Dynamics of Causality and the Vicious Cycle

Renal microvascular rarefaction and renal interstitial fibrosis (RIF) are not connected by a simple unidirectional causal relationship; rather, they constitute a dynamic and progressive vicious cycle[18,21]. In the very early stage of disease, functional microvascular rarefaction may occur before obvious fibrotic consolidation, at which point microvascular injury serves as the initiating factor of the fibrotic cascade[10,32]. Renal microvascular rarefaction leads to insufficient oxygen delivery and induces local tissue hypoxia. Hypoxia, in turn, upregulates profibrotic factors such as transforming growth factor-β (TGF-β) through the hypoxia-inducible factor-1α (HIF-1α) pathway, inflammatory signaling, and oxidative stress, promoting the activation of myofibroblasts and the deposition of extracellular matrix[33-34], thereby inhibiting renal angiogenesis and forming a vicious cycle of "hypoxia–fibrosis–vascular loss–worsening hypoxia." During disease progression, the massive deposition of extracellular matrix and activated fibroblasts exert mechanical compression on residual capillaries, further aggravating structural vascular loss; at this stage, fibrosis in turn becomes a cause of

worsening microvascular rarefaction[35-36].

4.2 Interventional Evidence Supporting the Initiating Role of Microvascular Rarefaction

With regard to causal inference, experimental evidence indicates that blocking renal vascular loss or enhancing vascular repair during the "intervenable window" can significantly alleviate renal fibrosis[34]. For example, the novel HIF stabilizer FG4592 (Roxadustat) may significantly reduce renal fibrosis and enhance renal vascular regeneration by activating the HIF-1α/vascular endothelial growth factor A (VEGFA)/VEGF receptor 1 (VEGFR1) signaling pathway. This process is accompanied by upregulation of the endogenous antioxidant superoxide dismutase 2 (SOD2), thereby improving renal vascular repair and alleviating fibrosis[37].

5 Contributions of Spatial Omics and Imaging Technologies

With the application of spatial transcriptomics and single-cell multi-omics, researchers can construct spatiotemporal maps of microvascular rarefaction at the "gene–cell–microvessel" level. The synergistic application of intravital imaging technologies[12,38] and spatial omics further enables spatiotemporal correlation analysis between the dynamic occurrence of vascular rarefaction and changes in molecular mechanisms. By integrating data from spatial transcriptomics and single-cell sequencing technologies, multilevel spatiotemporal maps can be constructed at the levels of gene expression[39-41], cellular states and molecular pathway changes[42], and microvascular structure[10]. Such multilevel spatiotemporal maps help reveal the specific mechanisms and cellular origins of renal myofibroblast and precursor-cell differentiation, providing new ideas for understanding the mechanisms of microvascular rarefaction in renal fibrosis and potential therapeutic targets. These research advances depend on the support of multiple imaging technologies, each of which has advantages in identifying the "intervenable window" (Table 1).

6 The Intervenable Time Window

Recent studies suggest that there may be a "lag" between renal microvascular rarefaction and fibrosis; that is, impairment of renal vascular function occurs earlier than fibrotic consolidation. Before obvious renal fibrosis appears, renal capillary rarefaction can already be observed by functional micro-CT, which may serve as one of the earliest bases for diagnosing renal dysfunction and assessing prognosis[8,19,26]. If interventions can be implemented during this "intervenable window" stage—such as promoting renal angiogenesis, improving hemodynamics, or inhibiting inflammatory responses—it may be possible to prevent disease progression toward an irreversible stage[43-44]. Because the characteristics of vascular lesions differ across CKD stages, corresponding stage-specific intervention strategies should be adopted (Table 2).

In summary, renal microvascular rarefaction is one of the core mechanisms in the progression of chronic kidney disease and has a close spatiotemporal causal relationship with renal hypoxia and fibrosis. This article summarizes relevant studies, proposes a research framework for future exploration of the "intervenable window" and the concept of "region-specific therapy," and, through comparison of clinical stages and screening with imaging technologies, provides feasible approaches for identifying the "intervenable window." In terms of "region-specific therapy," treatment strategies for the renal cortex should focus on controlling upstream immune and hemodynamic abnormalities, whereas those for the medulla should emphasize counteracting hypoxia and oxidative stress[45]. Combined with an interdisciplinary integration pathway of "imaging technology–spatial transcriptomics–computational analysis," this provides a new direction for translating basic research into clinical practice.

7 Prospects and Limitations

Research on renal microvascular rarefaction has entered a new stage of spatiotemporal integration, and increasing evidence supports the hypothesis of a "rarefaction–hypoxia–fibrosis causal chain" [33-36]. The application of technologies such as spatial transcriptomics and intravital two-photon imaging enables researchers to track, at the cellular level, the entire process of microvascular structural changes, endothelial-cell phenotypic transition, and local metabolic remodeling. These advances not only reveal the key role of microvascular loss in renal interstitial fibrosis, but also make it possible to identify new therapeutic targets. However, current research approaches still have many limitations:

7.1 Unresolved Issues in Causality and Spatial Heterogeneity

The hypothesis of a "rarefaction–hypoxia–fibrosis causal chain" shows marked differences across different renal disease models, such as diabetic kidney disease and renal IRI, suggesting that further longitudinal studies are needed to clarify the dominant factors in causal relationships in different disease models, so as to improve the generalizability of conclusions and provide evidence for precise intervention in different nephropathy subtypes[23,47-48]. In addition, spatial differences between the renal cortex and medulla also suggest that the design of future therapeutic regimens should be region-specific[24-25]. The spatial heterogeneity of pathological mechanisms between the renal cortex and medulla determines the specificity of intervention strategies[22]. For example, microvascular rarefaction in the cortical region may be driven more by upstream hemodynamic abnormalities and inflammation

Table 1 Comparison of sensitivity of clinical imaging techniques

Imaging technique	Spatial resolution	Detectable indicators	Advantages in identifying the "inter-venable window"	Limitations
BOLD-MRI[32]	1–2 mm	Renal tissue oxygen partial pressure(can distinguish corti-cal/medullary hypoxia)	Noninvasively assesses intrarenal oxygenation status; identifies "high-risk regions" of medullary hypoxia at an early stage; provides localization evidence for intervention in ischemic injury	Cannot directly detect capillary density; requires combination with molecular markers or other imaging techniques to verify the degree of rarefaction
Ultrasound super-resolution imaging[10]	10–50 μm	Renal capillary density and changes in microvascu-lar morphology	Noninvasively quantifies changes in microvascu-lar structure; accurately captures the onset time point of capillary rarefaction; dynamically monitors injury progression	Limited penetration depth (ap-proximately 2 cm); image quality is easily affected in obese patients

Imaging technique	Spatial resolution	Detectable indicators	Advantages in identifying the "inter-venable window"	Limitations
Intravital two-photon mi-croscopy[38]	0.5–1.0 μm	Capillary flow velocity and dynamic changes in vascular dynamics	Monitors hemody-namic abnormali-ties in real time in vivo; enables early detection of functional rarefaction in which vessels are "morphologi-cally normal but have decreased flow velocity" ; captures ultra-early signals of injury	Requires invasive procedures (such as window im-plantation); mainly used in animal experiments, with clinical application limited to in-traoperative monitoring of superficial tissues

Imaging technique	Spatial resolution	Detectable indicators	Advantages in identifying the "inter-venable window"	Limitations
IMAGE-SEQ imaging platform[12]	Single-cell level(combined with imaging-based spatial localization)	Microvascular morphological features and single-cell molecular expression pro-files(obtained syn-chronously)	Integrates "morphological observation and molecular analysis" ; localizes abnormal cells in rarefied regions (such as dys-functional endothelial cells); clarifies intervention targets and timing	Technically complex workflow; depends on imaging-guided precise sampling; not yet widely adopted in clinical practice

Imaging technique	Spatial resolution	Detectable indicators	Advantages in identifying the "inter-venable window"	Limitations
Spatial transcrip-tomics[29,42]	Tissue-region level(approximately 10 μm–100 μm)	Cellular composition of injured regions, cell–cell interaction networks, and expression of genes related to fibrosis or angiogenesis	Analyzes the molecular microenvi-ronment of microvascu-lar rarefaction; reveals pathological mechanisms behind imaging ab-normalities (such as hypoxia-induced cellular transforma-tion); guides optimization of intervention strategies	Cannot provide real-time dynamic data; needs to be combined with intravital imaging to achieve synergistic application of "mechanistic analysis and temporal monitoring"

Note: BOLD-MRI = blood-oxygen-level-dependent functional magnetic reso-nance imaging.

Table 2 Expected intervention effects and comparison across different CKD stages

CKD stage	Vascular functional status	Changes in molecular markers	Intervention measures	Expected effects	Description
Stages 1–2[8,19]	Functional rarefaction(hemodynamic abnormalities; reduced capillary perfusion)	PFKFB3: mildly up-regulated expression;STING: mildly increased activity	Vasodilator intervention	Improved intrarenal blood-flow perfusion	Targets early functional ischemia; alleviates insufficient perfusion through vasodilation, consistent with the core concept of early intervention for microvascular rarefaction

CKD stage	Vascular functional status	Changes in molecular markers	Intervention measures	Expected effects	Description
Stages 3–4[24,37]	Anatomical rarefaction(marked loss of capillary density and structural loss)	PFKFB3: moderately upregulated expression;STING: moderately increased activity;HIF-α: pathway activation	FG4592(HIF stabilizer)	Promotes vascular regeneration and delays CKD progression	By stabilizing HIF-α, upregulates target genes such as EPO and VEGF, stimulates neovascularization, improves hypoxia, and enhances antioxidant capacity to delay the transition from AKI to CKD

CKD stage	Vascular functional status	Changes in molecular markers	Intervention measures	Expected effects	Description
Stage 5[37,46]	Severe rarefaction and fibrosis(extensive loss of the capillary network, accompanied by severe fibrosis)	PFKFB3: markedly upregulated expression;STING: markedly increased activity;HIF-α: markedly increased level	Combined intervention(FG4592 + TGF-β inhibitor)	Stabilizes renal function and slows the progression of fibrosis	FG459 addresses the underlying hypoxia problem, while TGF-β inhibitors directly block the core fibrotic pathway. The combined strategy aims to stabilize late-stage renal function rather than significantly reverse eGFR

Note: CKD = chronic kidney disease; PFKFB3 = 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; EPO = erythropoietin; VEGF = vascular endothelial growth factor; eGFR = estimated glomerular filtration rate; HIF-α = hypoxia-inducible factor α; AKI = acute kidney injury; STING = stimulator of interferon genes; TGF-β = transforming growth factor β.

···driven by inflammation[23]; whereas rarefaction in the medullary region is mainly dominated by persistent hypoxia and oxidative stress[45].

7.2 Technical limitations and multimodal integration

From the perspective of clinical application, existing imaging technologies still require further improvement. At present, although BOLD-MRI, super-resolution

ultrasound, and other techniques can partially track changes in vascular morphology, they still have difficulty achieving early and precise identification of microvascular lesions[10,32]. Spatial transcriptomics can analyze the expression characteristics of vascular-related genes, but its relatively high cost limits clinical dissemination. Intravital imaging can dynamically detect blood-flow perfusion and local hypoxic status, yet it is difficult for it to precisely analyze molecular mechanisms[49–50]. Future studies should integrate follow-up data from large patient cohorts, multimodal imaging, and molecular-level testing results to achieve atlas-based integration from gene expression to the microvascular structural level, thereby clarifying the existence and dynamic characteristics of the "intervenable window" in CKD populations. Intravital imaging can dynamically detect blood-flow perfusion and local hypoxic status[10,32], but it is difficult to precisely analyze molecular mechanisms. Therefore, future priorities lie in achieving the synergistic application of mechanistic analysis[42] and temporal monitoring[12,38].

7.3 Barriers to clinical translation

Drugs such as angiogenic factors, metabolic regulators, and novel antifibrotic agents have shown potential for delaying the progression from renal microvascular rarefaction to fibrosis[51–53]. However, some studies have pointed out that in the early stage of AKI, transient upregulation of VEGFA expression is necessary for preserving the renal microvascular structure. In the late stage of disease, however, sustained or excessive VEGFA expression may lead to abnormal angiogenesis (such as increased vascular permeability) and promote the development of renal fibrosis. Therefore, interventions need to precisely regulate the degree of renal neovascularization rather than simply "promote angiogenesis" [43]. This process-dependent change significantly increases the complexity of clinical translation and drug development.

Future studies should further verify the significant differences in the "intervenable window" among different renal disease subtypes (such as diabetic nephropathy and ischemic nephropathy) in terms of activation threshold, duration, and core intervention targets; develop noninvasive, high-resolution clinical detection technologies (such as optimizing the penetration depth of ultrasound super-resolution imaging)[10]; promote quantitative standards for the "intervenable window" framework; and validate the feasibility of "region-specific therapy" in clinical application. Through integration of multidimensional spatiotemporal data, it is expected that quantitative analysis and precise intervention for the pathological remodeling process of the renal microcirculation can be achieved, providing a new theoretical and technical basis for delaying CKD progression.

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final version of the manuscript.

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