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REVIEW

Mitochondrial Oxidative Stress and Vascular Remodeling in Uric Acid Nephropathy: Mechanistic Insights and Therapeutic Implications

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Abstract: Uric acid nephropathy (UAN), driven by sustained hyperuricemia, is an underrecognized but increasingly prevalent contributor to chronic kidney disease (CKD) progression. Mitochondrial oxidative stress and vascular remodeling are central to its pathogenesis. Excess mitochondrial reactive oxygen species (ROS) cause renal tubular injury, impair mitophagy, and activate pro-apoptotic signaling pathways. In parallel, ROS disrupt endothelial homeostasis, promote phenotypic switching of vascular smooth muscle cells, and induce pathological structural changes in the renal microvasculature. These processes are mutually reinforcing, thereby exacerbating inflammation, hypoxia, and fibrosis. This review synthesizes emerging mechanistic insights into the mitochondrial–vascular axis in UAN and discusses therapeutic strategies targeting mitochondrial dysfunction and vascular pathology. Particular emphasis is placed on mitochondria-targeted antioxidants and inhibitors of key signaling pathways as potential interventions to interrupt the ROS–remodeling cycle. We also highlight the need for biomarker development and clinical translation. A more comprehensive understanding of mitochondrial–vascular crosstalk may ultimately enable the development of effective strategies to slow or halt UAN progression.

Keywords: uric acid nephropathy, mitochondrial dysfunction, oxidative stress, vascular remodeling, reactive oxygen species, endothelial dysfunction, mitochondria-targeted therapy

Introduction

Uric acid nephropathy (UAN) is a renal disorder initiated by persistent hyperuricemia, primarily characterized by monosodium urate crystal deposition, tubular epithelial cell injury, and progressive chronic renal dysfunction.[1–3] With the increasing global prevalence of hyperuricemia, UAN has been recognized as a significant contributor to the development and progression of chronic kidney disease (CKD), which is emerging as a major public health concern worldwide.[4–7] Epidemiological investigations have demonstrated a sustained increase in the incidence of hyperuricemia in various populations. For instance, a nationwide health survey conducted in South Korea reported an age-standardized prevalence of 11.4%,[8] while a longitudinal cohort study in China documented a baseline prevalence of 18.4% and an incidence rate of 68.58 per 1,000 person-years.[9] Hyperuricemia is frequently observed in patients with CKD and is strongly associated with accelerated progression of CKD. In the United States, CKD affects approximately 13% of adults, and UAN is increasingly being acknowledged as a critical pathogenic contributor.[10,11] A cross-sectional study further revealed that 96.49% of patients with CKD exhibited hyperuricemia, with an inverse correlation between serum uric acid levels and CKD stage severity.[12]

Distinguishing UAN from gout nephropathy is important. Although both conditions are associated with hyperuricemia, their clinicopathologic manifestations differ. UAN primarily manifests as progressive renal dysfunction driven by urate crystal deposition, mitochondrial injury, and vascular remodeling, often in the absence of overt gouty arthritis.[13] By contrast, gout nephropathy typically arises in patients with long-standing gout and is characterized by deposition of urate

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tophi in the renal interstitium and tubules, frequently accompanied by a history of recurrent gout flares. This clinical distinction is essential for accurate diagnosis and for guiding targeted therapeutic strategies.[14,15]

Despite the growing recognition of UAN as a key etiological factor for CKD, therapeutic interventions remain limited and suboptimal. Clinical management of UAN presents multiple challenges, including the need for effective control of serum uric acid to prevent crystal formation, while avoiding overcorrection that may precipitate hypouricemia and associated risks.[16] Currently, no pharmacological agents that can directly dissolve or facilitate the removal of deposited urate crystals are available, rendering crystal clearance a critical therapeutic bottleneck.[17] Furthermore, current pharmacotherapies exhibit limited efficacy in modulating the complex interplay between mitochondrial oxidative stress and vascular remodeling, which is a recently recognized pathological cascade involved in the progression of UAN.

Mitochondrial dysfunction and the resultant overproduction of reactive oxygen species (ROS) are mechanistically proven to be core drivers of renal injury in UAN.[18–20] Converging evidence from doxorubicin (DOX) toxicity models further supports the central role of mitochondrial oxidative stress. In a rat model of DOX-induced nephrotoxicity, esculetin attenuated renal inflammation and injury by reversing DOX-driven dysregulation of inflammatory and apoptotic gene expression and by improving biochemical indices of renal function; in silico analyses supported direct interactions with key molecular targets.[21] Likewise, in a complementary rat model of DOX-induced hepatotoxicity, esculetin mitigated oxidative stress responses; downregulated Casp3 and Casp9, as well as Hspa1a, Hsp4a, and Hsp5a; and differentially modulated FOXO transcription factors—decreasing Foxo1 while increasing Foxo3—thereby highlighting the ROS-linked caspase–FOXO–heat-shock protein axes as actionable nodes.[22] Although these studies are not specific to UAN, collectively they reinforce the pathogenic primacy of mitochondrial ROS and downstream stress-response pathways, providing a mechanistic rationale for mitochondria-targeted interventions in UAN. Impairment of mitochondrial function leads to excessive ROS generation, which initiates oxidative stress cascades.[23] ROS originating from dysfunctional mitochondria not only provoke direct cytotoxicity to renal parenchymal cells and activate pro-inflammatory signaling pathways but also contribute significantly to vascular remodeling processes.[24–26] Vascular remodeling is a critical pathological feature of UAN. Previous studies have indicated that hyperuricemia may upregulate the expression of macrophage migration inhibitory factor (MIF), which promotes phenotypic switching of vascular smooth muscle cells (VSMCs), exacerbating inflammation and structural remodeling, and ultimately aggravating renal vascular injury.[27] Given the pivotal role of vascular remodeling in the pathogenesis of UAN, elucidating the underlying mechanisms remains essential.

Although the roles of mitochondrial oxidative stress and vascular remodeling in the UAN have been independently investigated, the mechanistic crosstalk between these two processes remains unclear. This review aims to consolidate current knowledge concerning the bidirectional interaction between mitochondrial dysfunction and vascular remodeling in the context of UAN. We also examined the contribution of ROS-driven vascular alterations to disease initiation and progression, and highlighted emerging mitochondrial-targeted therapeutic approaches. By focusing on the mitochondrial–vascular axis, this review seeks to provide novel insights into the mechanistic basis of UAN and inform the development of more effective treatment strategies to halt or reverse disease progression. A graphical overview of the conceptual framework in UAN is illustrated in Figure 1, highlighting the epidemiological burden of hyperuricemia and the mechanistic interplay between mitochondrial oxidative stress and vascular remodeling.

In preparing this narrative review, we conducted a structured literature search aligned with the PRISMA 2020 and PRISMA-S reporting guidelines to enhance transparency; no protocol was registered. We searched PubMed/MEDLINE, Embase, Web of Science, Scopus, the Cochrane Library, Google Scholar, China National Knowledge Infrastructure (CNKI), and Wanfang Data from database inception through July 31, 2025, and we hand-searched reference lists and forward citations. Search terms combined controlled vocabulary and free-text terms across three domains: (1) uric acid nephropathy and hyperuricemia with kidney outcomes; (2) mitochondrial and oxidative pathways, including reactive oxygen species, mitophagy, PINK1 and Parkin, mitochondrial DNA, and Drp1; and (3) vascular remodeling, including endothelial dysfunction, vascular smooth muscle cells, and the renal microvasculature. We included original in vitro, animal, and human studies published in English or Chinese that reported mitochondrial or vascular endpoints and mechanistic readouts of therapies, and we excluded non–full-text abstracts, editorials, narrative reviews without new data, case reports without mechanistic outcomes, and studies unrelated to renal outcomes.

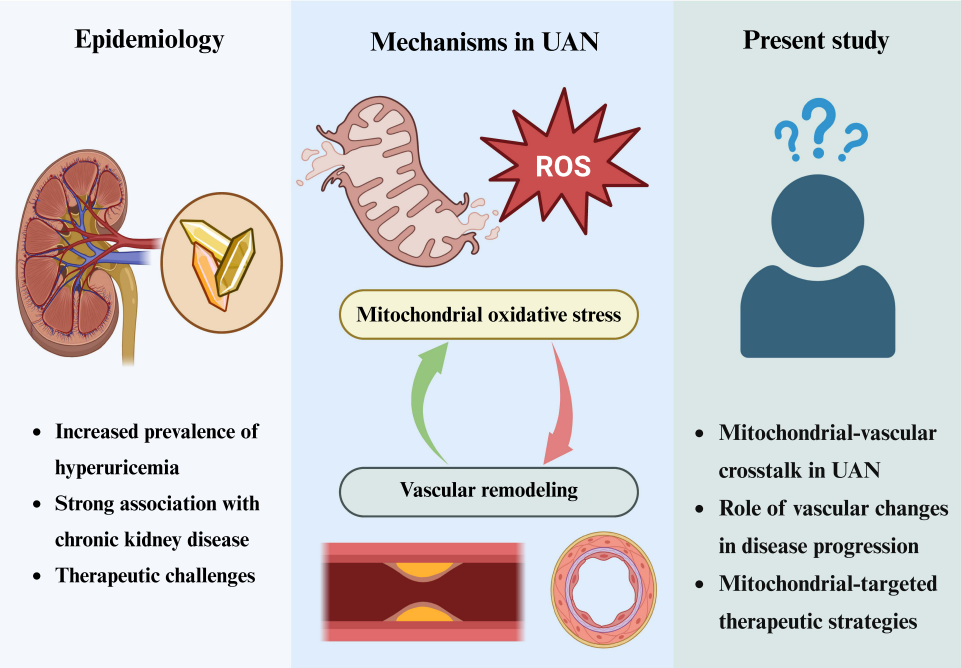

Figure 1 Conceptual framework of UAN, illustrating the epidemiological burden, mitochondrial oxidative stress, and vascular remodeling. Persistent hyperuricemia triggers excessive ROS production and vascular changes, which reinforce each other in a feedback loop that drives renal injury.

Mitochondrial Oxidative Stress and Dysfunction in Renal Cells

ROS Generation and Mitochondrial Dysfunction

Mitochondria are central bioenergetic organelles responsible for adenosine triphosphate (ATP) production via oxidative phosphorylation. Beyond ATP production, mitochondrial function is tightly coupled to cellular redox homeostasis. Dietary phenolic compounds exert a dual, dose-dependent influence on oxidative stress: within physiological ranges they can scavenge reactive species and upregulate endogenous defenses via Nrf2–ARE signaling, thereby supporting recovery and mitochondrial adaptations, whereas excessive supplementation may blunt adaptive ROS-mediated signaling, including pathways governing mitochondrial biogenesis.[28] At the vascular interface, human serum paraoxonase-1 (PON1)—an HDL-associated hydrolase with antiatherogenic properties—constitutes a key enzymatic barrier to lipid peroxidation and is pharmacologically modifiable; several antihypertensive agents inhibit PON1 with micromolar IC50 or Ki values and exhibit distinct mechanisms of inhibition—competitive for midodrine and nadolol, and noncompetitive for atenolol and pindolol.[29] In addition, small-molecule quinones (naphthoquinones, benzoquinones, anthraquinones) inhibit PON1 in vitro, with IC50 values of approximately 3.27–82.90 μM, underscoring that xenobiotics can attenuate enzymatic antioxidant capacity and thereby shift the redox set point.[30] Collectively, these observations highlight that systemic modifiers of redox biology—whether nutraceutical or pharmacologic—can indirectly shape mitochondrial oxidative tone and vascular risk, concepts relevant to hyperuricemia-related renal microvascular pathology. During this process, electrons are sequentially transferred through the mitochondrial electron transport chain (ETC) to molecular oxygen, generating the proton gradient required for ATP synthesis. However, partial electron leakage from the ETC inevitably leads to incomplete reduction of oxygen, resulting in the formation of ROS, including superoxide anions and hydrogen peroxide.[31–33]

Under physiological conditions, mitochondria sustain redox homeostasis by balancing ROS production and scavenging through endogenous antioxidant enzymes such as superoxide dismutase and glutathione peroxidase.[34–36] However, this equilibrium is disrupted in the context of sustained hyperuricemia. Mitochondrial membrane potential decreases, and ATP synthesis efficiency is impaired, leading to accelerated ROS generation.[37–40] Beyond these intrinsic mitochondrial events, pharmacologic and xenobiotic modulators of redox homeostasis provide convergent evidence. Aldose reductase (AR)—a polyol pathway enzyme that consumes NADPH and can exacerbate oxidative stress—is potently inhibited by

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newly designed 2-pyrazoline derivatives; the lead compound showed submicromolar potency (IC50 approximately 0.160 μM) with competitive inhibition (Ki approximately 0.019 μM) and outperformed epalrestat and quercetin in vitro, underscoring the tractability of ROS-generating nodes.[41] By contrast, attenuation of HDL-associated antioxidant defenses may shift the redox set point toward oxidative injury: human serum paraoxonase-1 (PON1), which limits lipoprotein oxidation, is inhibited in vitro by several sulfonamides (IC50 24–201 μM) with mixed competitive and noncompetitive mechanisms,[42] and by commonly used antiepileptic drugs, including valproic acid, gabapentin, primidone, phenytoin, and levetiracetam.[43] Although these studies are not specific to UAN, collectively they support a mechanistic link whereby systemic modifiers of antioxidant capacity propagate lipid peroxidation and ROS signaling, thereby exacerbating mitochondrial depolarization, bioenergetic failure, and downstream vascular injury relevant to UAN.

Excess ROS accumulation destabilizes the mitochondrial inner membrane, resulting in dissipation of membrane potential.[44,45] Mitochondrial dysfunction facilitates calcium ion overload within organelles, further impairing mitochondrial integrity. Elevated intramuscular calcium interferes with ATP synthase activity and promotes mitochondrial membrane permeabilization, thereby aggravating the cellular energy deficits. Furthermore, the collapse of the membrane potential induces the opening of the mitochondrial permeability transition pore (mPTP), permitting the leakage of calcium ions and ROS into the cytosol. This release not only amplifies cytoplasmic oxidative stress, but also activates apoptotic pathways, ultimately contributing to renal cell dysfunction and injury.[46]

mtDNA Damage and Apoptotic Signaling

Mitochondrial DNA (mtDNA), which lacks protective histone proteins and resides in close proximity to the ETC, is particularly susceptible to ROS-induced oxidative insult by ROS. In human dermal fibroblasts, age-related accumulation of mtDNA mutations has been strongly correlated with elevated levels of 8-hydroxy-2'-deoxyguanosine, with mutation rates estimated to be 10- to 20-fold higher than those found in nuclear DNA.[47] ROS oxidize guanine residues in mtDNA to 8-oxo-7,8-dihydroguanine (8-oxoG), and deficiency of β-hOGG1 impairs base excision repair, thereby increasing the mtDNA mutation burden.[48]

Damage to mtDNA directly compromises the function of the mitochondrial respiratory chain, leading to increased ROS production and establishment of a self-amplifying loop of mitochondrial dysfunction.[49–51] Critically, such damage results in the loss of the mitochondrial membrane potential and decreased ATP generation, which triggers the opening of the mPTP. This facilitates the release of pro-apoptotic factors, including cytochrome c, thereby initiating the caspase cascade and activating intrinsic apoptotic pathways.[52–54]

Moreover, apoptosis-inducing factor may translocate from the mitochondria to the nucleus, where it enhances apoptotic signaling by inducing chromatin condensation and large-scale DNA fragmentation.[55–57] ROS-mediated mtDNA damage also activates the tumor suppressor protein p53, increasing apoptotic activity and aggravating renal injury, particularly in the renal tubular epithelial cells. This mechanism further drives the pathophysiological progression of UAN.[58–60]

Impaired Mitophagy and Mitochondrial Homeostasis Disruption

Mitophagy is a pivotal quality-control mechanism that mediates the selective degradation of dysfunctional mitochondria, thereby maintaining cellular homeostasis.[61,62] Under physiological conditions, mitochondrial impairment caused by the accumulation of ROS activates the PINK1–Parkin signaling pathway. Specifically, PTEN-induced kinase 1 (PINK1) accumulates on the outer membrane of damaged mitochondria and serves as a molecular signal to recruit E3 ubiquitin ligase Parkin. Parkin subsequently ubiquitinates outer mitochondrial membrane proteins, targeting the compromised organelles for clearance through the autophagic system.[63–65]

This degradation pathway is essential for preserving mitochondrial integrity and preventing the intracellular buildup of ROS-producing organelles. However, in the context of UAN, mitophagy is dysregulated, resulting in the impaired clearance of dysfunctional mitochondria.[20,66] Consequently, these damaged mitochondria accumulate within cells, sustaining elevated levels of ROS and exacerbating oxidative stress. The inability to effectively eliminate dysfunctional mitochondria perpetuates a deleterious feedback loop, in which oxidative damage and mitochondrial dysfunction reinforce each other. Ultimately, this cycle amplifies renal cellular injury and promotes disease progression in UAN patients.

Antioxidant System Impairment

In UAN, the activity of key antioxidant enzymes is markedly suppressed, resulting in diminished capacity to neutralize ROS.[67] Concurrently, the hyperuricemic milieu promotes excessive ROS production by activating nicotinamide adenine dinucleotide phosphate oxidases, particularly NOX4, thereby exacerbating oxidative stress and compromising the antioxidant defence system.[68] This redox imbalance intensifies mitochondrial and cellular injury as sustained ROS accumulation amplifies oxidative damage. Dysfunction of the antioxidant network further destabilizes redox homeostasis, propagating cellular stress and organelle impairment.[69,70]

Under conditions of prolonged hyperuricemia, renal tubular epithelial cells exhibit impaired capacity to preserve physiological function due to chronic oxidative insult. Notably, stimulation by uric acid (UA) activates the RhoA/Rho-associated coiled-coil protein kinase (ROCK) signaling pathway, which drives intracellular ROS overproduction in tubular epithelial cells, thereby promoting renal oxidative injury.[71] Disruption of the redox equilibrium contributes significantly to the aggravation of renal damage and disease progression.

Collectively, the aforementioned mechanisms, including excessive ROS production, mtDNA damage, defective mitophagy, and weakened antioxidant defenses, form a self-perpetuating cycle that accelerates mitochondrial dysfunction and cellular injury in UAN. Persistent ROS accumulation aggravates structural and functional mitochondrial deterioration leading to increased oxidative stress, apoptosis, and progressive renal impairment. Failure of mitophagy to clear damaged mitochondria, compounded by an insufficient antioxidant system, further exacerbates vascular remodeling and renal pathology. The mechanistic links between mitochondrial injury, ROS production, and vascular remodeling are depicted in Figure 2.

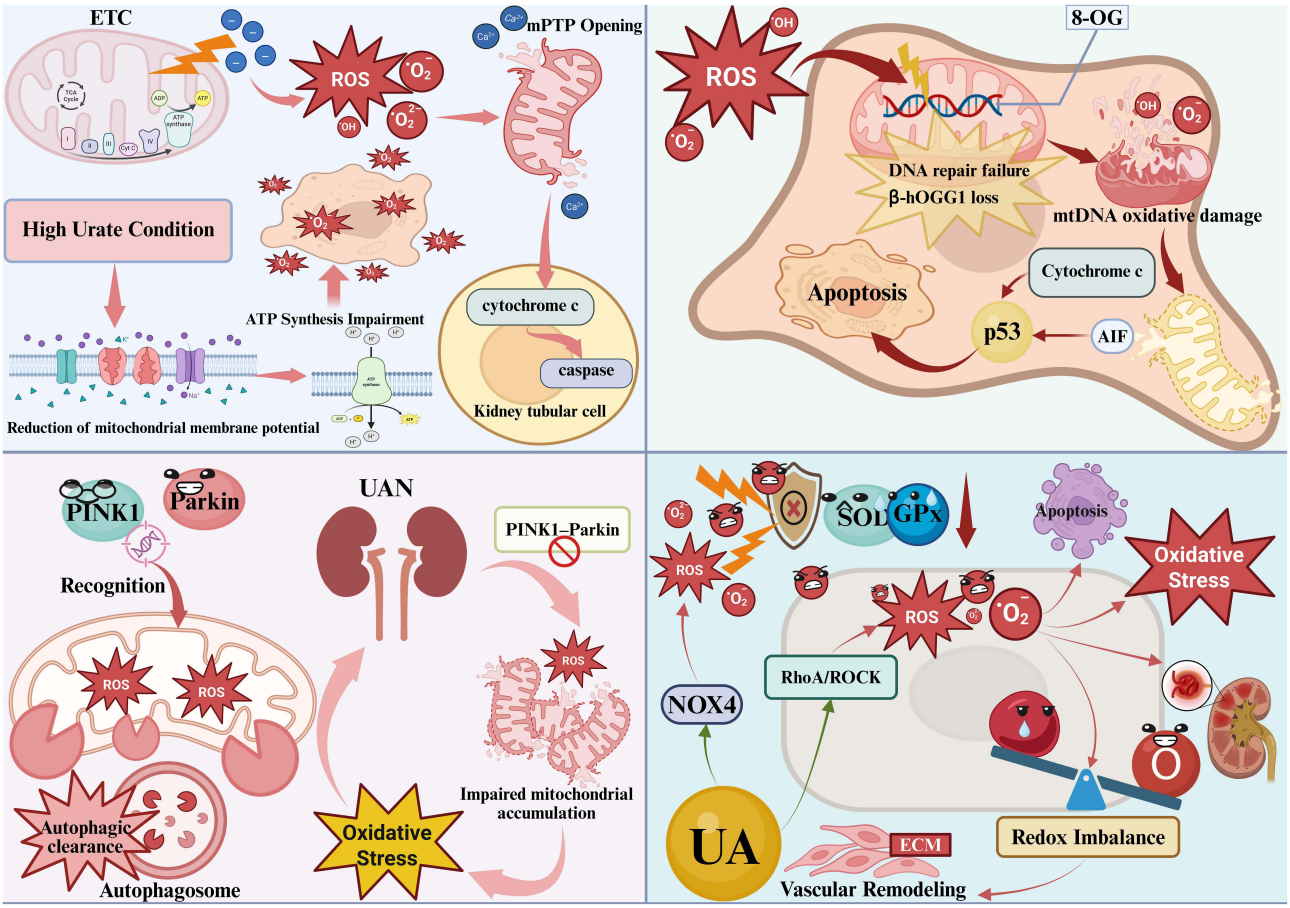

Figure 2 Pathogenic mechanisms of mitochondrial oxidative stress in UAN. Hyperuricemia impairs mitochondrial function, leading to excess ROS generation, mtDNA damage, defective mitophagy, and redox imbalance. These processes trigger tubular injury, apoptosis, and vascular remodeling, creating a feedback loop that exacerbates renal injury.

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A deeper understanding of these interconnected mechanisms is essential for the identification of novel therapeutic targets. Interventions aimed at correcting mitochondrial dysfunction and mitigating oxidative stress may offer promising avenues for disrupting this pathogenic cycle, ultimately contributing to the development of effective strategies for the prevention and management of UAN.

Mechanisms of Vascular Remodeling in UAN

Pathological Mechanisms Underlying Vascular Remodeling

Vascular remodeling is a critical pathological hallmark of the progression of UAN. Accumulating evidence suggests that UA upregulates macrophage MIF expression in the renal tubular epithelium. In turn, MIF facilitates the phenotypic transition of VSMCs from a contractile to a synthetic state, an event intimately linked to vascular inflammation and structural remodeling. In murine models of chronic hyperuricemia, sustained UA exposure results in increased circulating and tissue levels of MIF accompanied by enhanced vascular inflammation, VSMC dedifferentiation, and remodeling. Notably, pharmacological inhibition or genetic silencing of MIF markedly suppressed UA-induced VSMC phenotypic switching, thereby ameliorating vascular dysfunction and remodeling.[27]

The proliferation and migration of VSMCs are pivotal steps in the pathophysiological cascade of vascular remodeling. p21-activated kinase 1 (PAK1) is a critical mediator of angiotensin II- and platelet-derived growth factor (PDGF)-induced activation of VSMCs. Inhibition of PAK1 through the expression of a dominant-negative construct delivered via adenoviral vectors significantly attenuated neointimal hyperplasia.[72] Similarly, suramin suppresses PDGF-BB-driven VSMC proliferation, migration, and dedifferentiation by targeting the TGFBR1/Smad2/3 signaling axis, thereby attenuating vascular remodeling.[73]

ROS serve as important upstream signals that exacerbate VSMC activation. Under oxidative stress, VSMCs exhibit enhanced proliferation, increased migratory behavior toward injury sites, and augmented deposition of extracellular matrix (ECM) components.[74–77] These pathological changes culminate in vascular wall thickening and luminal narrowing, ultimately reducing the renal perfusion. Excessive accumulation of ECM and the associated vascular architectural disruptions impair microcirculatory flow, intensifying renal hypoxia and injury. Vascular remodeling has emerged as a key mechanistic driver of UAN, linking metabolic disturbances with structural deterioration that culminates in CKD progression.

Role of Endothelial Dysfunction

ROS exert direct cytotoxic effects on vascular endothelial cells, thereby initiating endothelial dysfunction, a pivotal contributor to the progression of UAN.[78–81] Under physiological conditions, endothelial cells maintain vascular tone and renal microcirculation largely through the synthesis and release of nitric oxide (NO), a potent vasodilator.[82,83] However, excessive accumulation of ROS impairs endothelial nitric oxide synthase activity and promotes NO degradation, resulting in diminished NO bioavailability and subsequent vasoconstriction and vasospasm.[84–86] This dysregulation of vascular tone contributes not only to elevated blood pressure but also to the amplification of intravascular inflammatory responses.[87]

Simultaneously, ROS-mediated endothelial apoptosis disrupts the structural and functional integrity of the endothelial barrier, further compromising vascular stability.[88,89] The deterioration of endothelial integrity accelerates vascular remodeling and fosters the progression of renal injury.[90–92] Collectively, endothelial dysfunction, characterized by oxidative injury, impaired vasodilatory capacity, and structural compromise, represents a central pathological event in UAN that disrupts microvascular perfusion and amplifies both the systemic and local inflammatory cascades.

Hemodynamic Changes and Hypoxia-Driven Injury

In the UAN, structural abnormalities within the renal vasculature result in compromised perfusion, thereby precipitating tissue hypoxia.[93,94] The ensuing reduction in oxygen delivery markedly diminishes renal tissue oxygenation and establishes a hypoxic microenvironment.[95] In response, the hypoxia-inducible factor 1 alpha (HIF-1α) pathway, a key transcriptional regulator of cellular adaptation to low oxygen tension, is activated.[96,97] Upon stabilization, HIF-1α upregulates the expression of vascular endothelial growth factor (VEGF) and other angiogenic mediators, initiating

neovascularization and remodeling programs aimed at restoring oxygen homeostasis.[98,99] However, prolonged or excessive activation of this pathway may paradoxically promote vascular instability, inflammation, and interstitial fibrosis, thereby exacerbating renal injury.[99–101]

The persistent interplay between impaired perfusion, sustained hypoxia, and maladaptive vascular remodeling establishes a vicious cycle that accelerates the structural and functional deterioration of the kidney. Importantly, vascular alterations in UAN are not merely reactive events secondary to tubulointerstitial damage, but constitute an intrinsic and parallel pathological axis active throughout disease progression. This observation supports the conceptualization of UAN as a multifactorial disorder driven by coordinated injury across the "metabolic–mitochondrial–vascular–nephron" axis. Within this framework, vascular remodeling and endothelial dysfunction should be recognized as co-primary drivers, rather than merely downstream consequences of UAN. These processes act synergistically with mitochondrial oxidative stress and apoptosis to accelerate the disease progression. Mechanisms of uric acid–induced vascular remodeling and hypoxia-driven renal injury are illustrated in Figure 3.

Mitochondria to Vascular Crosstalk: Mechanistic Integration

ROS-Triggered NF-κB/NLRP3 Inflammatory Activation

ROS are central mediators of endothelial injury and have been increasingly recognized as critical drivers of UAN pathogenesis.[102–104] The pathological accumulation of ROS results in extensive oxidative damage to endothelial cells, thereby impairing their physiological function and disrupting the structural integrity of the endothelial barrier.[105,106] This oxidative insult initiates a cascade of inflammatory responses, prominently involving the activation of the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling axis[107] and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome pathway.[106,108]

Activation of the NF-κB pathway induces the transcription of a range of pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-6, and interleukin-1 beta (IL-1β), which collectively exacerbate endothelial dysfunction

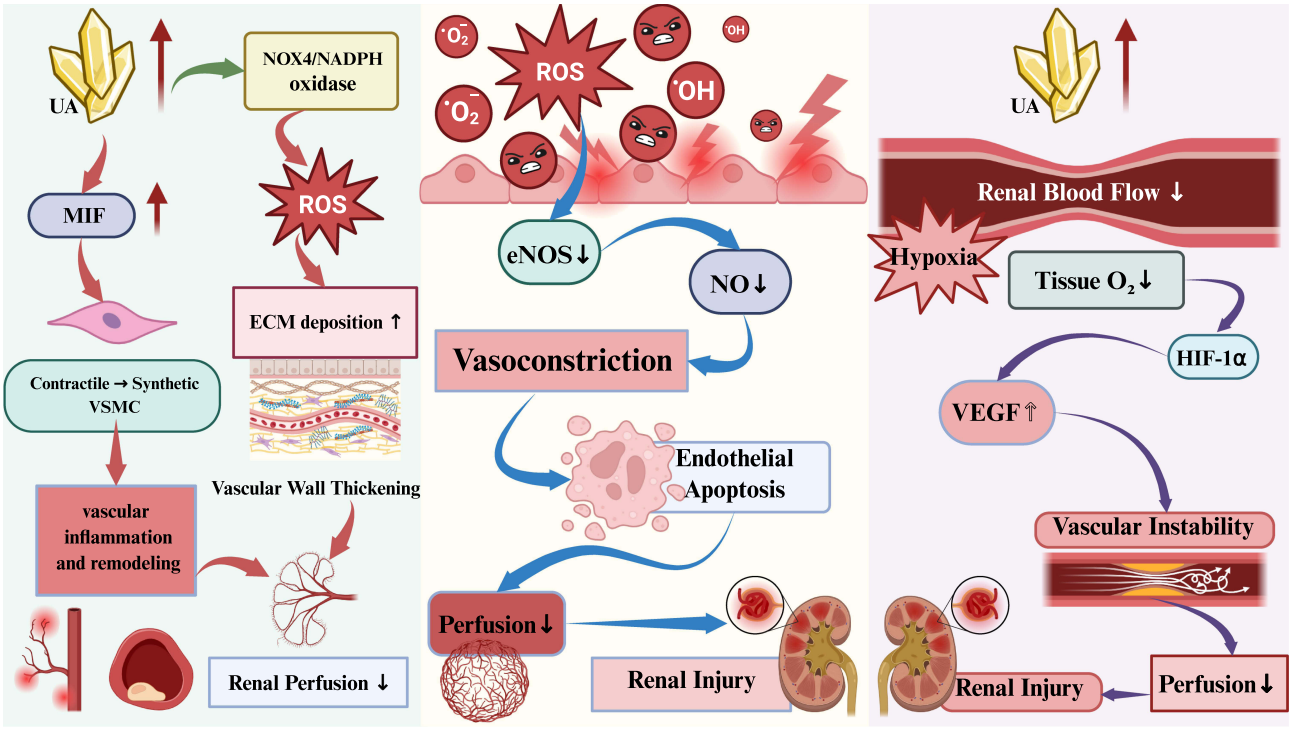

Figure 3 Uric acid–induced vascular remodeling and hypoxia in UAN. Excess ROS promote VSMC phenotypic switching, ECM deposition, and endothelial dysfunction, leading to vascular remodeling and reduced renal perfusion. Sustained hypoxia stabilizes HIF-1α and alters VEGF signaling, further aggravating renal injury.

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and perpetuate vascular inflammation.[109,110] Concurrently, ROS-induced damage activates NLRP3 inflammasome, facilitating caspase-1–mediated maturation and release of IL-1β, thereby amplifying local inflammatory responses.[111–113]

These two pathways converge to aggravate endothelial injury, promote ECM deposition, and accelerate vascular remodeling and fibrosis. The persistent crosstalk between oxidative stress and inflammation establishes a self-reinforcing pathological loop that drives UAN progression and contributes to a sustained renal functional decline.

mtDNA Release and cGAS–STING Activation

ROS critically mediate the cytosolic release of mtDNA, serving as a key trigger for the activation of innate immune signaling. Beyond direct mitochondrial damage, perturbations of enzymatic antioxidant and detoxification systems can further intensify ROS signaling and thereby favor release of mtDNA into the cytosol. Chalcones inhibit human glutathione S-transferase (GST) in vitro, with Ki values of approximately 7.8–41.9 μM and both competitive and noncompetitive mechanisms of inhibition, potentially constraining GSH-dependent detoxification and redox buffering.[114] Likewise, several widely used pesticides suppress hepatic GST purified from Van Lake fish, with Ki values of approximately 0.025–3.72 mM; λ-cyhalothrin acts competitively, consistent with xenobiotic-driven reduction of GST activity.[115] In addition, the HDL-associated antioxidant enzyme paraoxonase-1 (PON1) is inhibited by indazole derivatives (Ki approximately 26–111 μM; competitive), and molecular docking supports active-site binding, implying a reduced capacity to hydrolyze lipid peroxides.[116] Although these studies are not specific to UAN, collectively they support a model in which xenobiotic or pharmacologic suppression of GST or PON1 lowers antioxidant resilience, amplifies oxidative stress, and creates a milieu conducive to cytosolic mtDNA release and downstream innate immune activation in susceptible renal tissues. Mitochondrial dysfunction induced by excessive ROS accumulation results in oxidative damage to mtDNA, which subsequently escapes to the cytoplasm. Cytosolic mtDNA is recognized by cyclic GMP–AMP synthase (cGAS), leading to the activation of the cGAS–stimulator of interferon genes (STING) signaling axis.[117,118]

Once activated, the cGAS–STING pathway promotes the transcription of type I interferons and a range of proinflammatory cytokines, thereby initiating a potent inflammatory response.[119,120] Although this mechanism plays a crucial role in maintaining immune vigilance under physiological stress, sustained ROS generation and continuous mtDNA leakage provoke persistent activation of the pathway, aggravating inflammation and contributing to cellular and tissue damage.[121–123]

In the pathological setting of UAN, ROS-mediated mtDNA release perpetuates aberrant activation of the cGAS–STING pathway, driving chronic renal inflammation and fibrotic remodeling.[121,123] This self-reinforcing loop, involving oxidative stress, mtDNA damage, and innate immune activation, represents a fundamental mechanism that accelerates UAN progression and exacerbates renal functional decline.

Drp1-Mediated Fission and Vascular Remodeling

Mitochondrial dysfunction triggered by excessive ROS accumulation induces the activation of dynamin-related protein 1 (Drp1), a GTPase that governs mitochondrial fission and is essential for maintaining mitochondrial dynamics.[124–126] Drp1-mediated fission leads to fragmentation of the mitochondrial network, destabilization of mitochondrial membranes, and amplification of intracellular stress responses.[127–129]

In VSMCs, excessive Drp1 activation facilitates mitochondrial fragmentation and enhances cellular proliferation and migration.[130] These processes contribute to pathological vascular remodeling by promoting VSMC migration to sites of vascular injury and deposition of ECM proteins, ultimately resulting in vascular wall thickening and luminal stenosis.[131–133]

Maladaptive proliferation and migration of VSMCs, driven by persistent ROS generation and mitochondrial fragmentation, contributes to a vicious feedback loop between oxidative stress and structural remodeling. This loop accelerates vascular dysfunction and aggravates the renal injury. Collectively, mitochondrial fragmentation and aberrant Drp1 activation have emerged as pivotal molecular mechanisms orchestrating vascular remodeling in the UAN.

Disrupted Mitophagy Drives ECM Remodeling

Impairment of mitophagy leads to the accumulation of dysfunctional mitochondria within cells, resulting in persistent ROS overproduction, deleterious cycle of oxidative stress, and mitochondrial injury.[134–136] This persistent oxidative state

activates a spectrum of pathological signaling pathways, particularly those implicated in pro-inflammatory and profibrotic responses.[137,138]

A major downstream effect is the excessive deposition of ECM components such as collagen, which represents a hallmark of vascular remodeling.[138–140] Aberrant ECM accumulation thickens the vascular wall and narrows the lumen, consequently disrupting renal microcirculation and impairing oxygen delivery to nephron units.[141]

ROS-driven ECM remodeling, exacerbated by defective mitophagy, significantly promotes renal fibrosis and compromises vascular integrity. As a result, progressive structural deterioration of the renal vasculature constitutes a critical pathogenic event in UAN progression.

Calcium Overload and Mitochondrial Fragmentation Promote Vasoconstriction

Excessive accumulation of ROS is intimately linked to intracellular calcium (Ca^{2+}) overload, which activates a range of Ca^{2+}-dependent enzymatic pathways and initiates a cascade of deleterious cellular responses including VSMC contraction and vasospasm.[142–145] Mitochondrial fragmentation, a hallmark feature of mitochondrial dysfunction, further exacerbates calcium imbalance by promoting the release of Ca^{2+} from intracellular stores such as the endoplasmic reticulum and mitochondria.[146]

Elevated cytosolic Ca^{2+} activates key downstream effectors, including calcium/calmodulin-dependent protein kinase II and phospholipase A2, both of which enhance VSMC contractility and contribute to luminal narrowing of blood vessels.[147–149] These pathological changes result in pronounced vasoconstriction, reduced renal perfusion, and elevated vascular resistance, thereby impairing the renal microcirculation.

Furthermore, the sustained interaction between Ca^{2+} overload and ROS accumulation establishes a self-perpetuating feedback loop that reinforces vascular smooth muscle contraction and promotes progressive vascular remodeling. This vicious cycle plays a central role in exacerbating renal injury and accelerating the progression of UAN. The crosstalk between mitochondrial oxidative stress and vascular remodeling is illustrated in Figure 4, highlighting key signaling pathways such as NF-κB, NLRP3, cGAS–STING, and Drp1 that contribute to inflammation, vascular dysfunction, and renal fibrosis.

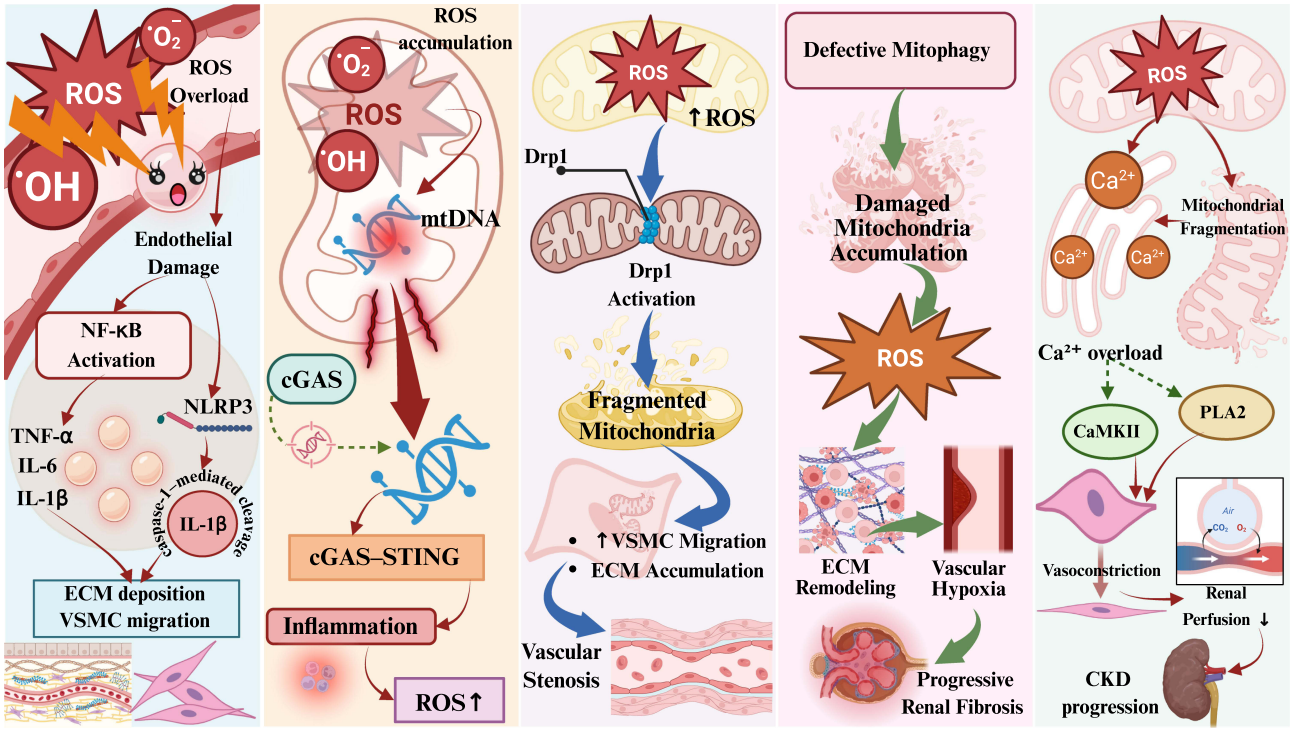

Figure 4 Crosstalk between mitochondrial oxidative stress and vascular remodeling in UAN. Excess ROS drive inflammation, mtDNA leakage, mitochondrial fission, and impaired mitophagy, leading to endothelial dysfunction, VSMC activation, and ECM remodeling. These processes interact in a feedback loop that promotes vascular stenosis, hypoxia, and renal fibrosis.

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Experimental and Clinical Evidence

In vitro and in vivo Experimental Studies

The inference that mitochondrial oxidative stress causally contributes to urate crystal–induced kidney injury is supported primarily by preclinical data from cell and animal models, whereas human evidence remains largely associative; mechanistic claims are therefore framed cautiously pending prospective clinical validation. Accumulating evidence from both in vitro and in vivo studies supports a mechanistic link between mitochondrial dysfunction and vascular remodeling in the pathogenesis of UAN. Elevated levels of uric acid have been shown to disrupt mitochondrial homeostasis, thereby enhancing the production of ROS, which initiate oxidative stress, impair endothelial function, and promote pathological vascular remodeling.[150–152]

Mitochondria-targeted antioxidants, such as MitoQ, have demonstrated significant efficacy in reducing mitochondrial ROS levels and mitigating oxidative damage in various experimental models.[153,154] In a bilateral renal ischemia–reperfusion mouse model, intravenous MitoQ (4 mg/kg) administered 15 min before ischemia significantly reduced 24-h plasma creatinine compared with vehicle and lowered renal protein carbonyls and mtDNA damage (one-way ANOVA; $p \leq 0.01$ across endpoints), indicating on-target mitochondrial protection.[155] Similarly, in a rat ischemia–reperfusion model, the mitochondria-targeted peptide SS-31 (0.5–5 mg/kg, s.c). decreased tubular necrosis scores in a dose-dependent manner (ANOVA; $p < 0.0001$), reduced TUNEL-positive tubular cells, accelerated ATP recovery, and lessened medullary vascular congestion at 24 h.[156] In a model of metabolic kidney injury, elamipretide in *db/db* mice suppressed albuminuria and urinary H_2O_2, reduced mesangial matrix expansion by approximately 50%, and restored renal superoxide levels.[157]

MitoQ selectively accumulates within the mitochondria owing to its lipophilic triphenylphosphonium moiety, enabling direct scavenging of ROS and restoration of mitochondrial membrane potential. Consequently, MitoQ preserves mitochondrial bioenergetics, suppresses ROS-triggered cellular injury, and inhibits a cascade of events leading to vascular and renal pathologies.[158–161]

Collectively, these findings provide compelling preclinical evidence for the therapeutic utility of mitochondria-targeted strategies in alleviating uric acid–induced endothelial dysfunction and vascular remodeling. These findings provide a mechanistic foundation for future translational studies and for the development of targeted interventions aimed at halting the progression of UAN.

Clinical Correlations and Biomarker Potential

Clinical evidence increasingly supports a strong correlation between elevated ROS levels, renal function decline, and vascular abnormalities in patients with UAN.[162,163] Notably, increased ROS production is inversely associated with the estimated glomerular filtration rate (eGFR), a principal clinical marker of renal function, and positively associated with indicators of endothelial dysfunction and vascular remodeling, both of which are hallmark structural alterations of the renal vasculature.[164,165] At the population level, a meta-analysis of 15 cohort datasets reported that each 1 mg/dL increase in serum urate was associated with a 22% higher risk of incident CKD, with stronger associations observed in younger cohorts.[166]

Moreover, endothelial dysfunction and vascular remodeling are strongly implicated in the pathophysiology of UAN, and are exacerbated by persistent oxidative stress.[167,168] Randomized trial data on vascular function are mixed. In stage 3 CKD, 12 weeks of allopurinol reduced serum urate by approximately 3.24 ± 1.35 mg/dL but did not significantly change brachial artery flow-mediated dilation (FMD) overall; among nondiabetic participants, FMD showed a nonsignificant trend toward greater improvement.[169] Regarding renoprotection, two large RCTs—CKD-FIX and PERL—did not demonstrate a benefit of urate lowering on the estimated glomerular filtration rate (eGFR) slope: CKD-FIX reported −3.33 vs −3.23 mL/min/1.73 m² per year for allopurinol versus placebo, and PERL similarly found no clinically meaningful benefit on iohexol-measured GFR after 3 years of treatment plus washout.[170,171]

These findings collectively highlight the potential of ROS not only as a mechanistic driver of disease progression but also as a candidate biomarker for clinical monitoring and risk stratification in UAN.

Nonetheless, the translation of ROS into reliable clinical biomarkers presents a significant challenge. Among these are the limited specificity of ROS indicators and current lack of validation in large-scale prospective patient cohorts. Therefore, future clinical investigations are essential to elucidate the prognostic value of ROS levels, refine their

relationship with eGFR and vascular pathology, and to determine their potential role in guiding personalized therapeutic strategies for UAN.

Research Gaps

Despite substantial progress in elucidating the molecular mechanisms underlying UAN, current knowledge is predominantly derived from animal models and in vitro systems. A critical limitation of the field is the absence of long-term, large-scale clinical cohort studies that can validate experimental findings in human populations. In particular, the lack of prospective clinical datasets and mitochondria-specific biomarkers poses a major barrier for accurately monitoring mitochondrial dysfunction and oxidative stress dynamics throughout the course of UAN.

This gap significantly impedes efforts to delineate the temporal evolution of mitochondrial damage and its correlation with renal pathology. Moreover, the paucity of validated biomarkers limits their ability to assess therapeutic responses and hinders the integration of mechanistic insights into clinical practice.

To address these challenges, future research must prioritize the identification and validation of sensitive and specific mitochondrial biomarkers capable of reflecting early stage dysfunction. The design and execution of robust, large-scale, longitudinal clinical trials to evaluate the diagnostic and prognostic values of these biomarkers are equally important. Such efforts are essential for enabling early detection, refining risk stratification, and guiding the development of personalized treatment strategies for UAN.

Therapeutic Implications

Antioxidants Targeting Mitochondria

Mitochondria-targeted antioxidants, such as MitoQ, SkQ1, and SS-31, have emerged as promising therapeutic candidates for alleviating mitochondrial dysfunction and mitigating vascular remodeling in the UAN. These agents are structurally designed to selectively accumulate within the mitochondria, where they neutralize ROS, restore redox homeostasis, and preserve the mitochondrial integrity.

Among these, MitoQ has demonstrated notable protective effects in experimental models of oxidative injury. In a PM2.5-induced aortic fibrosis model, MitoQ effectively attenuated mitochondrial ROS overproduction, restored mitochondrial membrane potential and ATP synthesis, and downregulated the expression of the mitochondrial fission mediator, Drp1, thereby ameliorating mitochondrial fragmentation and dysfunction. Furthermore, MitoQ modulated the PINK1/Parkin-dependent mitophagy pathway, contributing to the clearance of damaged mitochondria and suppression of VSMC phenotypic switching and collagen deposition.[153]

Similarly, SkQ1[172] and SS-31[173] confer mitochondrial protection via distinct yet complementary mechanisms. Both agents inhibit mitochondrial dysfunction, reduce inflammatory responses, and suppress fibrotic remodeling, which are the hallmark processes that contribute to the pathogenesis of UAN. By directly targeting mitochondrial oxidative stress, these mitochondria-directed antioxidants offer a novel therapeutic paradigm that addresses the central pathogenic axis in UAN, with the potential to delay disease progression and preserve renal function.

Current clinical development status and safety profiles are summarized as follows. In a randomized, placebo-controlled pilot trial in stage 3–4 CKD (n = 18), 4 weeks of oral MitoQ 20 mg daily improved brachial artery flow-mediated dilation compared with placebo and was well tolerated.[174] A registered CKD trial (NCT02364648) also evaluated MitoQ in a double-blind design.[175] In healthy adults, an acute high-dose randomized crossover study found that MitoQ did not increase urinary kidney injury biomarkers, supporting short-term renal safety.[176] For SS-31 (elamipretide), a Phase 2a randomized, placebo-controlled trial in patients with atherosclerotic renal artery stenosis undergoing angioplasty/stenting showed reduced postprocedural renal hypoxia on BOLD-MRI at 24 h and higher renal blood flow at 3 months; overall tolerability was acceptable, with injection-site reactions as the principal adverse events.[177] For SkQ1, no CKD trials have been conducted to date; however, ophthalmic Phase II/III randomized trials in dry eye disease have demonstrated clinical efficacy and good tolerability of SkQ1 eye drops.[178,179]

Inhibitors of Vascular Remodeling

Pharmacological inhibition of the transforming growth factor-β (TGF-β) signaling pathway and the ROCK cascade has demonstrated considerable therapeutic potential in attenuating VSMC proliferation and migration, two pivotal processes in the pathogenesis of vascular remodeling.[180,181] The TGF-β pathway plays a central role in modulating ECM production and in regulating the phenotypic transition of VSMCs from a contractile to a synthetic state. Inhibition of this pathway has been shown to reduce ECM deposition and ameliorate pathological vascular structural changes.[182–184]

Accumulating evidence indicates that targeting TGF-β signaling effectively suppresses VSMC proliferation and migration, which are fundamental drivers of vascular wall thickening and luminal narrowing, both of which are hallmarks of advanced vascular remodeling.[185,186] In parallel, ROCK inhibitors such as Y-27632 act on the Rho/ROCK signaling axis, a critical regulator of actin cytoskeleton organization and cellular contractility.[187–189] By blocking ROCK activity, these agents not only inhibit VSMC motility but also downregulate ECM synthesis, thereby mitigating fibrotic vascular remodeling.[190,191]

Taken together, combinatorial strategies employing TGF-β and ROCK pathway inhibitors offer a rational and mechanistically grounded approach to counteract pathological vascular remodeling. Such interventions have significant therapeutic potential for halting or slowing the progression of UAN, wherein excessive vascular remodeling constitutes the core pathogenic mechanism.

Combined Therapies

The integration of uric acid-lowering agents, such as xanthine oxidase inhibitors (XOIs), with mitochondria-targeted protectants represents an emerging therapeutic paradigm that may enhance efficacy while minimizing treatment-related adverse effects, particularly in the management of UAN. XOIs, including allopurinol and febuxostat, lower serum uric acid levels by inhibiting xanthine oxidase, an enzyme that catalyses the conversion of hypoxanthine to uric acid.[192,193]

Nonetheless, despite effective urate-lowering, long-term administration of XOIs may not fully mitigate oxidative stress, as persistent hyperuricemia or urate fluctuations can still induce mitochondrial dysfunction and promote ROS.[194] In this context, concomitant administration of mitochondrial protectants, such as MitoQ and SS-31, represents a rational adjunctive strategy. These agents specifically target mitochondrial oxidative stress, restore mitochondrial membrane integrity, reduce ROS generation, and ultimately inhibit downstream processes involved in vascular remodeling.

Importantly, such a combination strategy is anticipated to exert additive or even synergistic effects, not only enhancing therapeutic efficacy but also potentially reducing the dosage or duration of XOIs required, thereby limiting associated adverse events. By simultaneously addressing both the systemic urate burden and mitochondrial redox imbalance, this dual-targeted approach provides a comprehensive framework for the treatment of UAN and may help delay or prevent the progression to irreversible renal injury.

Clinical Challenges and Prospects for Translation

Despite recent advances, several critical challenges hinder the clinical translation of therapeutic strategies for UAN, particularly those targeting mitochondrial dysfunction and vascular remodeling. The key to this is the development of efficient and precise drug delivery systems, particularly mitochondria-targeted antioxidants. The therapeutic efficacy of such agents depends on their ability to selectively accumulate within the mitochondrial matrix, while sparing other cellular compartments. Inadequate targeting not only limits pharmacological potency but also increases the risk of off-target effects and systemic toxicity.

Another significant concern is the clinical safety profile of mitochondria-targeted compounds. Given the novelty of these therapeutics and their prolonged intracellular retention, their long-term administration raises questions regarding their potential mitochondrial toxicity and cumulative adverse effects. Thus, rigorous preclinical toxicological assessments and long-term safety monitoring in clinical settings are imperative, particularly for patients requiring chronic treatment.

Moreover, the long-term efficacy of combination therapy that integrates xanthine oxidase inhibitors with mitochondrial protectants has yet to be conclusively demonstrated. Although preclinical data are encouraging, randomized

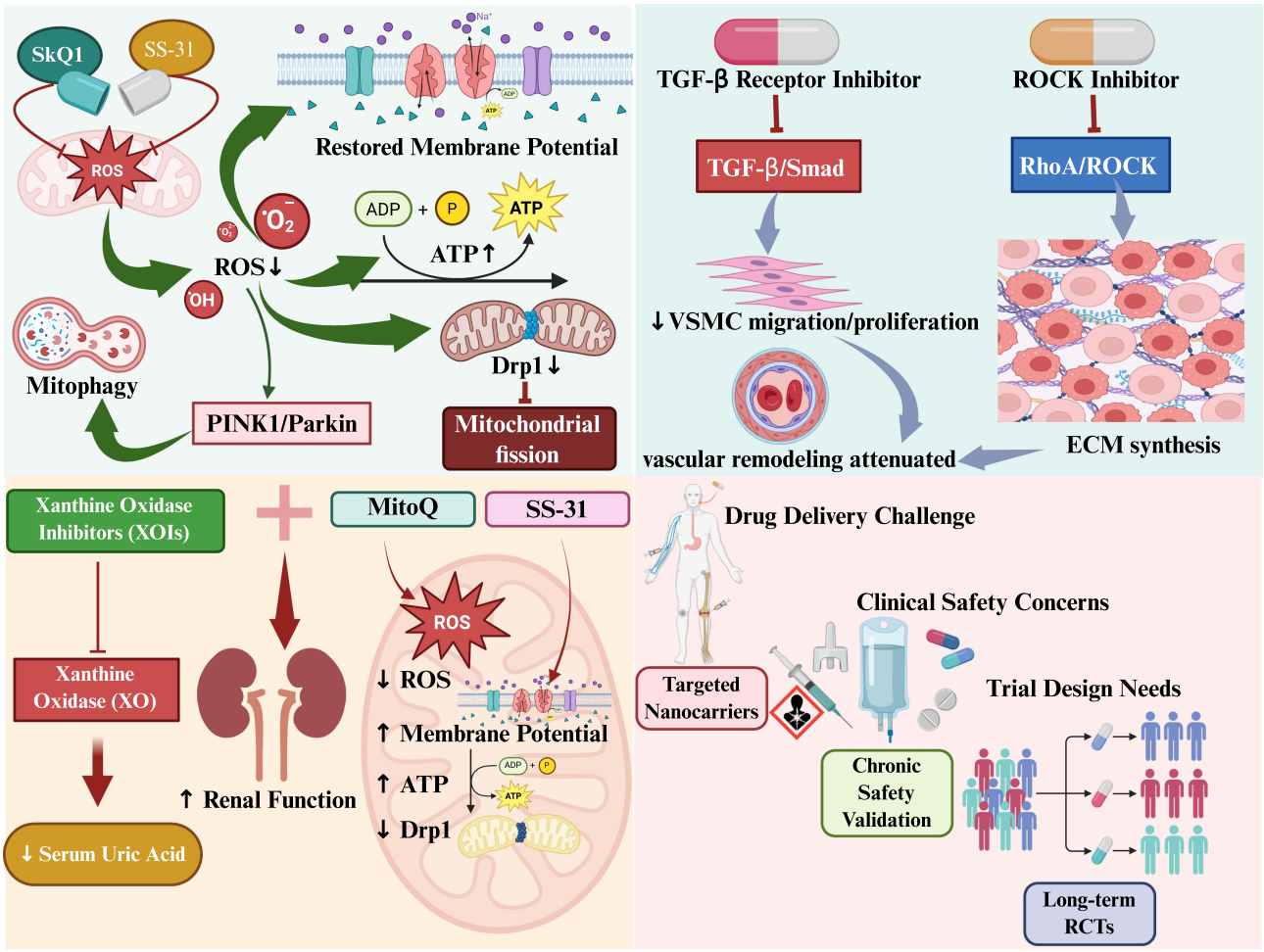

Figure 5 Therapeutic strategies targeting mitochondrial oxidative stress and vascular remodeling in UAN. Mitochondria-targeted antioxidants, xanthine oxidase inhibitors, and signaling pathway modulators help preserve mitochondrial function and attenuate vascular remodeling. Key challenges for clinical translation include targeted delivery, long-term safety, and validation in randomized controlled trials.

controlled trials evaluating the durability of renal function preservation, impact on disease progression, and overall benefit to patient outcomes are lacking.

Future clinical investigations should prioritize several objectives: (i) the design of advanced delivery platforms with mitochondrial-targeting capabilities; (ii) comprehensive evaluation of safety across diverse patient populations and dosing regimens; and (iii) longitudinal studies assessing therapeutic durability and clinical endpoints. These efforts are essential for translating mechanistic insights into practical interventions for effectively modifying the course of UAN. Figure 5 summarizes therapeutic strategies targeting mitochondrial oxidative stress and vascular remodeling in UAN, including mitochondria-targeted antioxidants, xanthine oxidase inhibitors, and signaling pathway modulators, as well as current translational challenges.

Conclusion and Perspectives

In conclusion, the bidirectional interplay between oxidative stress and vascular remodeling constitutes a fundamental pathogenic mechanism in UAN. Oxidative stress, primarily driven by mitochondrial dysfunction, leads to the overproduction of ROS, which not only aggravates vascular injury, but also promotes pathological remodeling of the vasculature. Conversely, vascular abnormalities such as endothelial dysfunction and VSMC proliferation further amplify oxidative stress, creating a self-reinforcing feedback loop that accelerates renal damage. Unraveling the mechanistic

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underpinnings of the mitochondria in the vasculature axis is essential for identifying novel therapeutic targets and improving clinical intervention strategies.

Despite the recent progress, several critical scientific issues remain unresolved and require further investigation. The identification of reliable mitochondria-specific biomarkers that can accurately predict UAN progression and reflect early mitochondrial dysfunction and ROS accumulation is essential to improve early diagnosis, dynamic disease monitoring, therapeutic assessment, and personalized treatment planning. Furthermore, the development of effective strategies to disrupt the ROS–vascular remodeling feedback loop at an early stage is of paramount importance given the role of this cycle as a principal driver of disease advancement. Interventions during the reversible phase may present a key opportunity to prevent irreversible vascular and renal injuries. Elucidating the molecular crosstalk between oxidative stress and vascular signaling pathways remains a research priority.

Equally important is the identification of a well-defined therapeutic window, as initiating treatment within this period may significantly improve the long-term clinical outcomes. Looking ahead, the integration of advanced technologies, such as multi-omics profiling, organoid-based disease modeling, and artificial intelligence-driven mechanistic analysis, holds transformative potential for advancing our understanding of UAN pathophysiology. Multi-omics platforms, including genomics, transcriptomics, proteomics, and metabolomics, enable comprehensive mapping of disease-associated networks. Organoid models that closely replicate the structural and functional characteristics of renal tissues provide physiologically relevant systems for mechanistic investigations and therapeutic screening. In parallel, AI-based analytical frameworks can synthesize multidimensional datasets to predict disease progression, stratify patient risks, and guide personalized treatment strategies.

Collectively, these technological innovations, combined with sustained translational and clinical efforts, hold significant promise for transforming the diagnosis, monitoring, and treatment of UAN, and for improving the precision and effectiveness of nephrological care.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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