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REVIEW

Copper-Induced Cell Death in Renal Diseases: Molecular Mechanisms and Therapeutic Implications

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Abstract: Copper dyshomeostasis and the resulting induction of cuproptosis, a novel regulated cell death pathway driven by mitochondrial copper overload, play a critical role in renal pathophysiology. Cuproptosis is characterized by FDX1-mediated copper reduction, irreversible aggregation of lipoylated TCA cycle enzymes, such as dihydrolipoamide S-acetyltransferase, and destabilization of iron–sulfur cluster proteins, leading to proteotoxic mitochondrial collapse. The kidney's high vulnerability arises from its filtration and metabolic functions. This review consolidates evidence linking cuproptosis to various renal disorders, including acute kidney injury (eg, sepsis-induced, cisplatin-induced, and ischemia-reperfusion injury), diabetic nephropathy through mitochondrial dysfunction and immune dysregulation, and chronic kidney disease involving podocyte damage or context-dependent dysregulation in fibrosis and clear cell renal cell carcinoma. Notably, cuproptosis and ferroptosis interact synergistically through shared mechanisms, where glutathione depletion or iron overload exacerbates both pathways, while mitochondrial dysfunction and lipid peroxidation create a self-perpetuating injury cycle. Emerging diagnostic strategies utilize cuproptosis-related biomarkers for early detection, supported by various prediction models. In therapeutic contexts, copper chelators, transporter modulators, and dual-pathway inhibitors targeting both cuproptosis and ferroptosis mitigate renal damage in preclinical models. Dietary interventions that modulate copper bioavailability also hold promise. However, challenges remain, including identifying renal cell type-specific mechanisms, developing noninvasive biomarkers, optimizing kidney-targeted nanotherapeutics, and preventing iatrogenic copper deficiency. Future research may focus on translational applications and the physiological roles of cuproptosis in renal repair. Targeting cuproptosis offers a promising avenue for innovative diagnostics and treatments in nephrology.

Keywords: cuproptosis, kidney, mechanism, diagnosis, therapy

Introduction

Copper, an essential trace element, serves as a crucial catalytic cofactor in vital biological processes, including mitochondrial respiration, antioxidant defense, iron metabolism, and enzymatic reactions within the tricarboxylic acid (TCA) cycle.[1] Its redox activity is central to these physiological functions, yet dysregulation can lead to significant toxicity through the generation of reactive oxygen species (ROS) and disruption of cellular homeostasis.[2] The accumulation of intracellular copper exceeds the buffering capacity, triggering cuproptosis, a recently identified form of regulated cell death.[3] Cuproptosis is defined by copper-dependent aggregation of lipoylated TCA cycle enzymes, destabilization of iron–sulfur (Fe–S) cluster proteins, and irreversible mitochondrial proteotoxic stress.[3] Unlike apoptosis, ferroptosis, or necroptosis, cuproptosis results from direct copper binding to mitochondrial metabolic machinery.[3]

The kidney, particularly the metabolically active proximal tubules, is especially vulnerable to copper dysregulation due to its role in filtration, reabsorption, and exposure to circulating metals.[4] Disrupted copper homeostasis is linked to various renal pathologies, including acute kidney injury (AKI), diabetic nephropathy (DN), and chronic kidney disease (CKD).[5–8] This review consolidates current insights into copper metabolism, the molecular mechanisms of cuproptosis, its pathogenic contributions to kidney diseases, its interaction with ferroptosis, and emerging diagnostic and therapeutic approaches. The findings provide a foundation for targeting copper homeostasis in nephrology.

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Molecular Mechanisms of Cuproptosis

Copper Metabolism and Homeostasis

Intracellular copper primarily exists as reduced Cu^{+} and oxidized Cu^{2+} species. Copper uptake is tightly regulated by specific transporters: SLC31A1 imports Cu^{+} with high affinity after extracellular reduction of Cu^{2+} by metalloreductases such as STEAP proteins.[9,10] SLC11A2 facilitates direct Cu^{2+} uptake,[11] while CD44 mediates endocytosis of hyaluronic acid-bound copper.[12] Once inside the cell, cytosolic chaperones sequester copper to prevent toxicity: CCS delivers copper to SOD1,[13] ATOX1 transports copper to the trans-Golgi network for loading onto cuproenzymes like lysyl oxidase or for export,[14] and COX17 aids in mitochondrial copper delivery for cytochrome c oxidase assembly.[15] Excess copper is buffered by metallothioneins and glutathione.[2,16] Systemic copper homeostasis is maintained by P-type ATPase exporters ATP7A and ATP7B. Under basal conditions, these transporters localize to the trans-Golgi network but translocate to the plasma membrane or hepatocyte canalicular membranes during copper overload, facilitating biliary excretion, the primary elimination route.[17] Excessive intracellular copper triggers cuproptosis, a regulated cell death pathway. Dysregulation of this coordinated import-chaperone-export network is implicated in copper deficiency in Menkes disease, which can cause renal tubular dysfunction and impaired ammoniagenesis.[1,17,18] In contrast, pathological copper accumulation in Wilson's disease results in renal copper deposition, contributing to Fanconi syndrome, hypercalciuria, and nephrolithiasis.[19]

The Core Cuproptosis Pathway

Cuproptosis is a copper-dependent form of regulated cell death, initiated by excessive copper accumulation, which disrupts mitochondrial integrity. Copper ions enter cells and mitochondria via transporters like SLC11A2 and SLC31A1 or ionophores such as elesclomol. Within the mitochondria, ferredoxin 1 (FDX1) catalyzes the reduction of copper to its highly reactive cuprous form. Cuprous ions bind directly to lipoylated TCA cycle enzymes, particularly dihydrolipoamide S-acetyltransferase (DLAT), a process also facilitated by FDX1. This interaction triggers irreversible aggregation of DLAT, impairing TCA cycle and electron transport chain functions. Concurrently, FDX1-mediated copper accumulation destabilizes Fe–S cluster proteins in electron transport chain complexes I–III, inducing proteotoxic stress and mitochondrial collapse, marked by the release of damage-associated molecular patterns. Notably, cuproptosis is dependent on mitochondrial respiration, making cells with high oxidative phosphorylation activity particularly susceptible.[3] In addition, a mitochondria-independent mechanism involves copper-induced aggregation of cytoplasmic protein complexes like p97-NPL4, which impairs ubiquitin–proteasome function, exacerbating proteotoxicity.[20] A summary of the core cuproptosis pathways is depicted in Figure 1.

Morphological, Biochemical and Metabolic Hallmarks

Cells undergoing cuproptosis exhibit distinctive morphological changes, observable via transmission electron microscopy, including mitochondrial shrinkage with cristae dissolution, plasma membrane rupture, endoplasmic reticulum dilation, and chromatin fragmentation without nuclear condensation.[21,22] Biochemically, cuproptosis is characterized by DLAT oligomerization, detectable via nonreducing immunoblotting, depletion of Fe–S cluster assembly proteins such as lipoic acid synthetase (LIAS) and FDX1, and elevated HSP70 expression.[3] Upregulation of copper transporters or metalloreductases, including SLC11A2, SLC31A1, and STEAP family members, has also been observed under conditions inducing cuproptosis.[10,23,24] Metabolic profiling reveals characteristic perturbations, including decreased α-ketoglutarate, succinate, and fumarate, along with the accumulation of citrate and guanosine diphosphate.[3] These features collectively distinguish cuproptosis from caspase-driven apoptosis and lipid peroxidation-dependent ferroptosis, establishing a unique phenotypic signature.[3] Representative morphological, biochemical, and metabolic hallmarks of cuproptosis are summarized in Figure 2.

Pathological Roles of Cuproptosis in Kidney Diseases

Acute Kidney Injury (AKI)

In sepsis-induced AKI, pronounced activation of cuproptosis is observed, driven by mitochondrial copper overload and dysregulated copper homeostasis. In murine cecal ligation and puncture models, elevated urinary and renal copper levels,

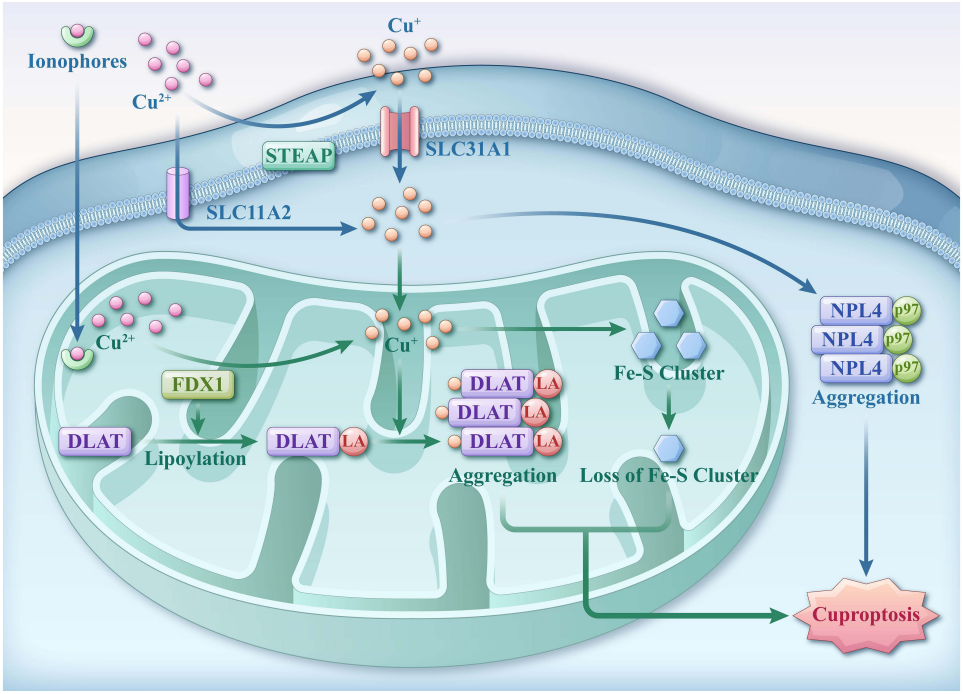

Figure 1 The core cuproptosis pathways.

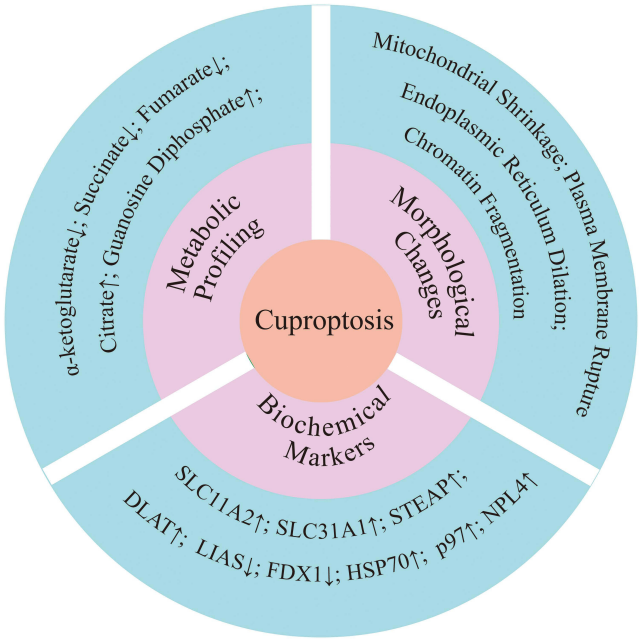

Figure 2 Representative morphological, biochemical and metabolic hallmarks of cuproptosis.
Note: Arrows indicate changes in expression levels (↑, upregulation/increase; ↓, downregulation/decrease).

upregulation of the copper importer SLC31A1, depletion of Fe–S cluster proteins (including FDX1 and ACO2), and increased HSP70 expression—hallmarks of cuproptosis-driven tubular injury—are noted. Administration of reduced glutathione alleviates AKI by suppressing SLC31A1-mediated copper accumulation, restoring FDX1/ACO2 expression, and mitigating mitochondrial proteotoxicity, highlighting cuproptosis as a key pathogenic mechanism and underscoring the therapeutic potential of targeting copper homeostasis.[5] Following cisplatin exposure, the transcription factor ELF3

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upregulates SLC31A1, disrupting copper homeostasis and triggering mitochondrial dysfunction through cuproptosis. Knockdown of SLC31A1 reduces renal injury in vivo, confirming its role in the pathogenesis and its potential as a therapeutic target.[23] The flavonoid quercetin offers renoprotection in cisplatin-AKI models by simultaneously suppressing ferroptosis through restoration of the SLC7A11/GPX4 axis and inhibiting cuproptosis via upregulation of ATP7B and activation of glutaminase. This dual inhibition reduces copper accumulation and lipid peroxidation while improving renal function.[25] Renal ischemia–reperfusion injury (RIRI), a major cause of AKI, also activates cuproptosis. Xu et al[26] identified 18 genes associated with cuproptosis, including genes linked to downregulated mitochondrial components such as SDHB and NDUFB6. Bioinformatics and experimental validation confirmed that RIRI induces copper overload, disrupts mitochondrial function through aggregation of TCA cycle enzymes—particularly SDHB/NDUFB6—and triggers apoptosis. Notably, the copper chelator D-penicillamine mitigates renal damage, reduces apoptosis, and restores SDHB/NDUFB6 expression both in vivo and in vitro, demonstrating cuproptosis as a central pathological mechanism. Furthermore, iron overload exacerbates RIRI by promoting tubular cuproptosis through disruption of LIAS function and iron–sulfur cluster homeostasis, a process alleviated by the iron chelator deferoxamine.[27] Clinical evidence from diabetic patients undergoing cardiopulmonary bypass reveals significant increases in serum and urinary copper, DLAT, and HSP70, alongside depletion of renal Fe–S cluster proteins (LIAS, ACO2, and SDHB) and mitochondrial damage, confirming that cuproptosis is a key driver of cardiopulmonary bypass-associated AKI. Diabetes significantly amplifies this effect.[28] Collectively, these findings establish cuproptosis as a conserved pathological mechanism across diverse AKI etiologies, including sepsis, drug toxicity, and ischemia–reperfusion injury. Therapeutic strategies targeting copper transporters or dual-pathway inhibition show substantial translational promise.

Diabetic Nephropathy (DN)

Cuproptosis is implicated in immune dysregulation in diabetic tubulopathy. Chen et al[6] identified 33 cuproptosis-related differentially expressed genes (DEGs) in DN tubules, enriched in stress response and mitochondrial pathways. An intersection with immune-related modules from weighted gene co-expression network analysis (WGCNA) revealed FSTL1, CX3CR1, and AGR2 as hub genes linking cuproptosis, immunity, and tubular injury. These genes were upregulated in both the human DN cohort and the STZ-induced and db/db mouse models, with negative correlations to glomerular filtration rate. Single-nucleus RNA sequencing localized FSTL1 to podocytes/mesangial cells and AGR2 to the loop of Henle, a site of high mitochondrial activity, suggesting that cuproptosis contributes to mitochondrial dysfunction during DN progression. Lan et al[29] further implicated cuproptosis in DN pathogenesis through dysregulated ceRNA networks and immune crosstalk. In a rat DN model induced by uninephrectomy, high-fat diet, and streptozotocin, RNA sequencing identified 73 cuproptosis-related genes enriched in inflammatory pathways. A core ceRNA network centered on miR-34a-3p and its targets revealed that the lncRNA USR0000B2476D is a key regulator. Immune profiling showed increased infiltration of resting dendritic cells and NK cells, along with a reduction in regulatory T cells in DN kidneys. Hub cuproptosis-related DEGs, such as CYCS, EGR1, FOS, and IGF1, were significantly correlated with regulatory T-cell depletion, linking cuproptosis to immune dysfunction in DN. Luo et al[30] stratified DN glomerular samples into distinct immune-metabolic phenotypes via cuproptosis gene clustering. Cluster C1 exhibited low expression of cuproptosis genes (FDX1, LIAS, DLAT, DBT) but high immune infiltration, whereas Cluster C2 showed the opposite, with metabolic pathway enrichment. Key cuproptosis regulators NLRP3 and CDKN2A were positively correlated with immune scores, while NFE2L2, LIAS, LIPT1, and DLD exhibited immunosuppressive effects. The protective genes DCXR and HRSP12, validated in high-glucose HK-2 cells, were downregulated in DN and negatively correlated with immune activation, suggesting their nephroprotective roles. Liu et al[31] integrated multiomics and experimental validation, revealing that FDX1 and LIAS, key regulators of cuproptosis, were upregulated in the kidneys of diabetic mice and localized to tubular segments with high mitochondrial activity. Elevated urinary copper levels in patients with DN and decreased monomeric DLAT in db/db mice indicated cuproptosis activation. This study further supports the role of copper-induced cell death in DN. These findings collectively suggest that cuproptosis contributes to DN pathogenesis through mitochondrial dysfunction and immune dysregulation, as demonstrated by integrated bioinformatics and experimental validation in both human and rodent models.

Chronic Kidney Disease (CKD)

Excessive copper accumulation triggers cuproptosis, which directly leads to the destruction of the podocyte cytoskeleton and subsequent injury in CKD models. Both high copper exposure and adriamycin-induced nephropathy cause intracellular copper overload, resulting in downregulation of key cuproptosis proteins such as FDX1, LIAS, and DLAT. This disruption leads to mitochondrial dysfunction, characterized by decreased ATP synthesis, increased ROS, and depolarization of the mitochondrial membrane potential, ultimately impairing essential cytoskeletal components like NMMII-A, ACTN4, SYNPO, and nephrin. Notably, interventions targeting copper accumulation—such as using the copper chelator D-penicillamine, overexpressing ATP7B, or silencing the upstream regulator chemokine CXCL5—attenuate cuproptosis, restore mitochondrial function, and mitigate cytoskeletal damage. These findings identify CXCL5-mediated cuproptosis as a pathogenic mechanism and potential therapeutic target.[7] In comparison with these findings, Shi et al[8] demonstrated suppression of cuproptosis pathways in unilateral ureteral obstruction (UUO)-induced renal fibrosis, a model of progressive CKD. Gene set variation analysis revealed significantly lower enrichment scores for cuproptosis-related pathways compared to controls, along with downregulation of key executors (ATP7, DBT, DLAT, DLD, DLST, FDX1). These results contrast with an increase in disulfidptosis, suggesting that cuproptosis inhibition may contribute to tubular injury pathogenesis in conjunction with immune dysregulation in CKD fibrosis, revealing a novel imbalance in cell death mechanisms specific to the disease. Collectively, these studies demonstrate that cuproptosis plays a role in CKD pathogenesis, either through activation or suppression, depending on the disease context, highlighting its complex role in the pathophysiological continuum of renal fibrosis.

Renal Neoplasms

Clear cell renal cell carcinoma (ccRCC, KIRC) is the predominant subtype of renal cell carcinoma (RCC) and a major contributor to kidney cancer mortality.[32,33] Copper ionophores can trigger cuproptosis in KIRC cells: in Caki-1 cells, elesclomol suppresses proliferation and migration while upregulating FDX1 and depleting Fe–S cluster proteins, providing experimental support for therapeutic strategies targeting copper toxicity in RCC.[34] Notably, recent ccRCC data link cuproptosis programs with the tumor microenvironment, suggesting that copper-modulating strategies may be viable treatment options. Given the VHL/HIF-dominant biology of ccRCC, genotype-informed testing of copper-targeted approaches is warranted.[35] Translationally, both copper ionophores (eg, disulfiram, elesclomol) and copper-depleting strategies are under investigation. Historical data in patients with advanced kidney cancer have shown that tetrathiomolybdate may achieve disease stabilization in a subset of patients, accompanied by shifts in antiangiogenic biomarkers, highlighting its clinical plausibility and the need for modern, biology-guided trials.[36,37]

Other Kidney Diseases

Oxidized low-density lipoprotein (oxLDL) induces tubular cuproptosis by suppressing ATP7B and causing copper overload. Clinical data show that elevated serum and urinary copper levels correlate inversely with estimated glomerular filtration rate in patients with kidney disease, with pathognomonic copper deposits observed in the renal tubules of those with obesity-related nephropathy. High-fat diet-fed mice and oxLDL-treated tubular cells replicate these findings, exhibiting mitochondrial dysfunction, depletion of Fe–S cluster proteins (LIAS, SDHB), and reduced lipoylated DLAT/DLST. Notably, oxLDL downregulates the copper exporter ATP7B, while ATP7B overexpression restores mitochondrial membrane potential and suppresses cuproptosis, establishing a mechanistic link between dyslipidemia and copper-driven tubular injury.[38] Obesity induced by a high-fat diet increases renal copper accumulation and upregulates cuproptosis executors (FDX1, DLAT), alongside suppression of antioxidant enzymes (SOD, GPX, GR). Quercetin and caloric restriction attenuate these effects by reducing copper overload, FDX1/DLAT expression, and mitochondrial stress. When combined, these interventions synergistically protect against obesity-induced cuproptosis.[39]

The role of cuproptosis in kidney diseases is summarized in Table 1.

Table 1 The Role of Cuproptosis in Kidney Diseases

Disease Model	Intervention Strategy	Representative Agent/Method	Mechanism of Action	Reference
Sepsis-induced Acute Kidney Injury (AKI)	Reduced glutathione administration	Reduced glutathione	Suppresses SLC31A1-mediated copper uptake; restores Fe-S cluster proteins (FDX1, ACO2); attenuates mitochondrial proteotoxic stress; reduces renal copper overload	[5]
Cisplatin-induced AKI	Genetic inhibition of SLC31A1	shSLC31A1 lentivirus	Suppresses the cisplatin-induced, ELF3-mediated transcription of SLC31A1; reduces copper overload, mitochondrial dysfunction, and lipoylated TCA enzyme aggregation	[23]
Cisplatin-induced AKI	Dual inhibition of ferroptosis and cuproptosis	Quercetin (orally administered)	Upregulates ferroptosis suppressor SLC7A11/GPX4 axis; enhances cuproptosis regulator ATP7B expression and glutaminase activity; reduces renal copper accumulation and lipid peroxidation	[25]
Renal Ischemia–Reperfusion Injury (RIRI)	Copper chelation therapy	D-Penicillamine (intravenous)	Chelates Cu^{2}+; inhibits copper-dependent aggregation of lipoylated TCA enzymes (eg, DLAT); restores Fe-S cluster proteins (SDHB, NDUFB6); attenuates mitochondrial proteotoxicity and apoptosis	[26]
RIRI	Iron chelation; Overexpression of [4Fe–4S] assembly proteins	Deferoxamine; AAV-mediated ISCA1/2 overexpression	Iron overload disrupts [4Fe–4S] cluster biogenesis, leading to LIAS destabilization, defective protein lipoylation, and enhanced cuproptosis; Iron chelation or Fe-S cluster restoration attenuates both cuproptosis and ferroptosis.	[27]
Cardiopulmonary bypass-associated AKI in diabetes	Copper chelation therapy	Not tested; chelation proposed based on mechanistic rationale	Confirmed cuproptosis activation: Elevated serum/urinary Cu^{2}+, DLAT, HSP-70; depleted renal Fe–S proteins (LIAS, ACO2, SDHB); mitochondrial damage. Diabetes exacerbates effect.	[28]
Diabetic Nephropathy (DN) (STZ-induced & db/db mice)	Diagnostic biomarker validation	RT–qPCR of kidney cortex	Confirmed upregulation of cuproptosis-immunity hub genes FSTL1, CX3CR1, AGR2; validated correlation with mitochondrial dysfunction, immune dysregulation, and renal functional decline.	[6]
DN (STZ-induced rat model)	Diagnostic/ Mechanistic study	RNA-seq + bioinformatic analysis	Identified a cuproptosis-related ceRNA network (eg, USR0000B2476D/miR-34a-3p/MMP9) and 18 hub DE-CRGs (eg, CYCS, EGR1, FOS, IGF1); Hub DE-CRGs were enriched in immune and inflammatory pathways; Correlated with immune infiltration dysregulation.	[29]
DN	Genetic modulation of key cuproptosis regulators	shDCXR and shHRSP12	Identified as nephroprotective genes via cuproptosis-based clustering/machine learning; inversely correlated with immune score; shDCXR/shHRSP12 increased high-glucose HK-2 proliferation.	[30]
DN (db/db mice)	Multiomics analysis and experimental validation	Bulk/single-cell/spatial transcriptomics + IHC/WB	Reveals upregulation of FDX1/LIAS in tubular segments; links urinary copper elevation and decreased monomeric DLAT to cuproptosis activation in DN.	[31]
Chronic Kidney Disease (Adriamycin-induced podocyte injury)	Copper chelation and ATP7B upregulation	D-Penicillamine/ ATP7B-OE plasmid	Reduces intracellular copper accumulation; Inhibits cuproptosis (restores FDX1/LIAS/DLAT); Attenuates mitochondrial dysfunction; Suppresses CXCL5-mediated cuproptosis signaling	[7]

(*Continued*)

Table 1 (Continued).

Disease Model	Intervention Strategy	Representative Agent/Method	Mechanism of Action	Reference
Renal Fibrosis (UUO mouse model)	Diagnostic biomarker quantification	RT–qPCR of renal tissue	Enables early detection of fibrosis via elevated Bcl2a1b, Clec4n, and Col1a1; identifies suppressed cuproptosis pathways (ATP7, DBT, DLAT, DLD, DLST, FDX1) for risk stratification and therapeutic targeting	[8]
Clear cell renal cell carcinoma (ccRCC)	Copper ionophore treatment	Elesclomol	Elesclomol binds FDX1 and impairs Fe–S cluster biosynthesis, leading to FDX1-dependent mitochondrial cuproptosis; upregulates FDX1 with concomitant Fe–S depletion and suppresses proliferation and migration of Caki-1 KIRC cells.	[34]
ccRCC	Genetic knockdown of cuproptosis-related genes	shFDX1 and shPDHB	Knockdown of FDX1 and PDHB reduces proliferation and migration of ccRCC cells, suggesting a context-dependent role of cuproptosis regulators in tumor growth.	[35]
Advanced Kidney Cancer (Phase II trial)	Copper chelation therapy	Tetrathiomolybdate (oral)	Depletes bioavailable copper; reduces serum proangiogenic factors (VEGF, IL-6, IL-8, bFGF); achieves disease stabilization in a subset of patients	[37]
Lipid-Related Kidney Injury (HFD-fed mice and ox-LDL-treated tubular cells)	Genetic enhancement of copper exporter expression	ATP7B overexpression plasmid transfection (OE-ATP7B)	Restores copper efflux capacity; Attenuates mitochondrial lipoylated protein (DLAT/DLST) aggregation and Fe-S cluster protein (LIAS, SDHB, etc.) destabilization; Improves mitochondrial membrane potential and respiratory chain activity.	[38]
Nutritional obesity-related kidney injury (HFD-fed mice)	Antioxidant therapy combined with dietary modification	Quercetin + Calorie Restriction	Reduced renal copper overload; Downregulated cuproptosis executors (FDX1, DLAT); Enhanced antioxidant enzymes (SOD, GPX, GR); Synergistically attenuated mitochondrial proteotoxic stress.	[39]

Cuproptosis-Ferroptosis Crosstalk in the Kidney

Ferroptosis is an iron-dependent process of phospholipid peroxidation driven by labile iron and the failure of the GSH/GPX4 system, with backup mechanisms from FSP1-CoQ10 and mitochondrial DHODH systems. Shared hubs, such as glutathione depletion and mitochondrial/TCA cycle activity, explain why ferroptosis inducers can potentiate cell death triggered by copper ionophores. Phenotypes linked to other ions, such as "calcicoptosis" and "zincoptosis/lysozincrosis," remain provisional and may be described descriptively until consensus criteria are established. The interplay between cuproptosis and ferroptosis converges on glutathione depletion and mitochondrial dysfunction. Glutathione depletion disrupts copper chelation, promoting cuproptosis via FDX1-mediated copper toxicity, while simultaneously inactivating GPX4 to induce ferroptosis.[3,40] Mitochondrial metabolism, particularly the TCA cycle, serves as a shared node: cuproptosis-triggered aggregation of lipoylated enzymes like DLAT impairs mitochondrial respiration, amplifies oxidative stress, and sensitizes cells to ferroptosis.[41] Additionally, iron overload can directly potentiate cuproptosis by disrupting the biogenesis of Fe–S clusters, crucial for lipoylation of TCA cycle enzymes, thus perpetuating a vicious cycle of metabolic failure.[27] Pharmacological agents, including erastin and sorafenib, alongside engineered nanoparticles, induce both death pathways by depleting glutathione, overloading iron/copper, and exacerbating lipid peroxidation.[42,43]

In CKD, copper–iron crosstalk exacerbates tubular injury through interconnected mechanisms. Copper overload upregulates hepcidin via MTF1, inhibiting ferroportin and causing iron retention.[44,45] This process synergizes with HO-1-mediated heme degradation, increasing labile iron levels and fueling ferroptosis through Fenton reactions.[46,47] Simultaneously, copper-induced DLAT aggregation disrupts mitochondrial metabolism, depleting ATP and generating

ROS that inactivate renal antioxidant defenses, particularly SOD1 and GPX4.[48] Diabetic models confirm that advanced glycation end products increase copper import via SLC31A1, triggering cuproptosis and impairing Fe–S clusters,[49] while TGF-β1/Smad3-driven fibrosis in DN and CKD is further exacerbated by ferroptosis inducers.[50,51]

Therapeutic strategies utilizing copper chelators, such as trientine, reduce renal damage by correcting copper overload, attenuating oxidative stress, and mitigating fibrosis.[50] Therefore, the synergistic activation of cuproptosis and ferroptosis establishes a self-amplifying loop of metabolic collapse and oxidative injury, driving progressive renal damage in patients with CKD and DN. A summary of shared and distinct features across cuproptosis, ferroptosis, and other ion-linked phenotypes is provided in Table 2.

Diagnostic and Therapeutic Strategies

Biomarkers and Diagnostic Approaches

AKI: Li et al[52] identified six differentially expressed cuproptosis-related genes (FDX1, DLD, DLAT, DBT, PDHA1, ATP7A) that effectively distinguished patients with AKI from controls. A diagnostic model incorporating these genes demonstrated high accuracy. Immune infiltration analysis revealed a correlation between the expression of cuproptosis-related genes and macrophage polarization, highlighting their dual role as both diagnostic biomarkers and mechanistic regulators. In RIRI: Xu et al[26] developed machine learning-based diagnostic models, integrating four key cuproptosis marker genes—LIPA, LIPT1, SDHB, and NDUFB6—with good AUC values. Additionally, a five-hub-gene support vector machine model (MOAP1, PPP2CA, SYL2, ZZZ3, and SFRS2) demonstrated strong diagnostic potential.

DN: Lan et al[29] constructed a cuproptosis-specific ceRNA diagnostic network, identifying the USR0000B2476D/miR-34a-3p axis and eight target mRNAs (MMP9, PIK3C3, PROM1, SNTA1, SLC51B, NTRK3, SNCA, and EGF) associated with immune dysregulation. Chen et al[6] established a diagnostic model integrating cuproptosis-immunity crosstalk and identified a three-gene signature—FSTL1, CX3CR1, and AGR2—that achieved excellent AUC values and correlated with clinical renal function markers.

Renal Fibrosis: Shi et al[8] identified and validated BCL2A1B, CLEC4N, and COL1A1 as potential diagnostic biomarkers for renal fibrosis in patients with UUO, confirmed by qRT-PCR. Gene set variation analysis showed reduced enrichment of the cuproptosis pathway, with downregulation of key copper metabolism genes.

Table 2 Comparative Features of Cuproptosis, Ferroptosis and Other Metal Ion–Linked Cell Death Phenotypes

Feature	Cuproptosis	Ferroptosis	Other Ion-Linked (Provisional)
Trigger	Mitochondrial Cu overload; FDX1→Cu+ binds lipoylated TCA enzymes (eg, DLAT); Fe–S loss; proteotoxic mitochondrial collapse	Labile-iron–driven phospholipid peroxidation when GSH/GPX4 and FSP1–CoQ10/DHODH defenses fail	Zn/Ca overload phenotypes (eg, "lysozincrosis", "calcicoptosis"); frequently overlap with ferroptosis
Core machinery	LIAS/LIPT1/DLAT/DBT, Fe–S proteins; active OXPHOS/TCA	SLC7A11–GSH–GPX4, ACSL4/LPCAT3; FSP1–CoQ10 and mitochondrial DHODH backups	Context dependent; nomenclature not standardized
Readouts	DLAT oligomers (nonreducing WB); Fe–S protein loss; mitochondrial cristae collapse	Lipid-ROS (BODIPY-C11), MDA/4-HNE; GPX4 loss; iron probes	Zn: lysosomal dysfunction/mitochondrial impairment; Ca: sustained Ca^{2+} overload
Pharmacology	Copper chelators; limit copper import via SLC31A1; enhance copper export via ATP7B; elesclomol–Cu models	Ferrostatin-1/Liproxstatin-1; iron chelators; ACSL4/ALOX inhibition; bolster GSH/CoQ/FSP1	Often partially mitigated by ferroptosis blockers
Crosstalk	Sensitized by GSH depletion and high TCA flux; Iron overload disrupts Fe–S biogenesis; Fe–S fragility	Shares GSH/mitochondria hubs; ferroptosis inducers can potentiate cuproptosis	Terminology and criteria still evolving

ccRCC/KIRC: Across various cohorts, the core cuproptosis mediator FDX1 is downregulated in KIRC tumors compared to adjacent kidney tissue, with higher FDX1 expression correlating with improved survival and distinct immune features, supporting its role as a favorable prognostic marker.[53] In line with these findings, Luo et al[54] derived a six-gene cuproptosis-related ferroptosis (CRFG) signature (TRIB3, SLC2A3, PML, CD44, CDKN2A, MIOX) from TCGA-KIRC data, which successfully stratified patient prognosis and demonstrated differential immune checkpoint expression and drug sensitivity patterns in KIRC. In addition to single genes, a four-lncRNA cuproptosis-related signature (LINC01605, AGAP2-AS1, FOXD2-AS1, and LINC02195) has been shown to delineate immune-inflamed phenotypes with higher tumor-immune microenvironment scores and potential for drug-response stratification.[55]

Collectively, these cuproptosis-associated molecular signatures—including gene panels, RNA regulatory axes, and pathway enrichment profiles—offer promising tools for the early detection and stratification of various renal pathologies.

The diagnostic value of these biomarkers in kidney diseases is summarized in Table 3.

Therapeutic Interventions

Copper Chelators: Copper chelators demonstrate significant renoprotective efficacy. D-Penicillamine alleviates mitochondrial copper overload and restores Fe–S cluster proteins in models of RIRI and CKD.[7,26] Tetrathiomolybdate, a copper chelator that reduces bioavailable copper, counters pathological copper accumulation in obesity-related nephropathy and has achieved prolonged disease stabilization in a subset of patients with advanced kidney cancer in a phase II trial, supporting copper depletion as an anti-angiogenic strategy in RCC.[36–38] Additionally, the iron chelator deferoxamine has been shown to provide protective effects in RIRI by concurrently attenuating both ferroptosis and cuproptosis.[27]

Modulation of Copper Transporters: Inhibiting the copper importer SLC31A1 offers protection against tubular injury in cisplatin-induced and septic AKI.[5,23] Pharmacologically upregulating the copper exporter ATP7B using agents such as quercetin alleviates copper retention in obesity-related nephropathy and cisplatin toxicity.[25,38] Quercetin provides a polypharmacological advantage, suppressing both ferroptosis and cuproptosis simultaneously.[25]

Copper Ionophores: Ionophores like elesclomol effectively induce FDX1-dependent mitochondrial cuproptosis in malignancies,[56] but their role in renal pathologies remains underexplored. Interestingly, cuproptosis may be suppressed

Table 3 Cuproptosis-Related Biomarkers and Their Diagnostic Utility in Kidney Diseases

Disease	Biomarkers	Sample Source	Diagnostic Efficacy	Reference
AKI	FDX1↓, DLD↓, DLAT↓, DBT↓, PDHA1↓, ATP7A↓	Renal tissue	AUC = 0.917 (Training cohort: GSE139061)	[52]
RIRI	Cuproptosis Marker Gene Model: LIPA↓, LIPT1↑, SDHB↓, NDUFB6↓; 5-Hub-Gene SVM Model: MOAP1, PPP2CA, SYL2, ZZZ3, SFRS2 (Direction N/A)	Renal tissue	CMGM: AUC = 0.741–0.834 (External validation: GSE30718/GSE139061) SHoSM: AUC = 0.909 (Training), AUC = 0.750 (GSE30718), AUC = 0.591 (GSE139061)	[26]
DN	Core ceRNA network: USR0000B2476D (lncRNA↓), miR-34a-3p↑, target mRNAs (MMP9↓, PIK3C3↓, PROM1↓, SNTA1↓, SLC51B↓, NTRK3↓, SNCA↓, EGF↓)	Renal tissue	Significantly discriminates DN from controls; correlates with immune dysregulation (Treg depletion, dendritic/NK cell infiltration)	[29]
DN	FSTL1↑, CX3CR1↑, AGR2↑	Renal tubulointerstitial tissue	Individual AUCs: 0.911 (FSTL1), 0.935 (CX3CR1), 0.922 (AGR2); Combined AUC: 0.946	[6]
Renal Fibrosis (UUO)	BCL2A1B↑, CLEC4N↑, COL1A1↑	Renal tissue	Significantly discriminates fibrotic from normal tissue (qRT–PCR validation); Associated with suppressed cuproptosis pathways	[8]
ccRCC/KIRC	FDX1↓	Renal tissue	Three-gene prognostic model AUC: 1-year = 0.667, 3-year = 0.657, 5-year = 0.676; correlates with immune infiltration and checkpoint expression	[53]
ccRCC/KIRC	CRFG signature: TRIB3↑, SLC2A3↑, PML↑, CD44↑, CDKN2A↑, MIOX↓	Renal tissue	AUC for OS: 1-year = 0.750, 3-year = 0.675, 5-year = 0.654; high-risk group associated with poor survival and distinct immune infiltration	[54]
ccRCC/KIRC	CRGscore signature: LINC01605↑, AGAP2-AS1↑, FOXD2-AS1↑, LINC02195↑	Renal tissue	Training cohort: AUC at 1-year = 0.814, 3-year = 0.709, 5-year = 0.701; Overall cohort: AUC at 1-year = 0.764, 3-year = 0.681, 5-year = 0.670	[55]

Note: Arrows indicate changes in expression levels (↑, upregulation/increase; ↓, downregulation/decrease).

during renal fibrosis progression.[8] Empirical evidence supporting the use of copper ionophores in kidney disease models is limited, necessitating further mechanistic and therapeutic investigations.

Emerging Nanomedicine: Nanomedicine platforms derived from oncology offer opportunities for kidney-specific delivery. pH-responsive nanocarriers enable spatially controlled copper release, while siRNA-loaded systems can silence pathogenic mediators associated with cuproptosis.[57]

The clinical translation of these therapeutic strategies faces several critical challenges. Defining safe therapeutic windows for copper chelators and modulators is crucial to avoid iatrogenic copper deficiency. Clinically validated biomarkers are urgently needed to stratify patients who would benefit from cuproptosis-targeted therapies. Furthermore, designing combinatorial regimens targeting cuproptosis–ferroptosis crosstalk requires caution to prevent exacerbation of renal injury. Future innovations should focus on developing kidney-optimized nanotherapeutics for localized delivery to minimize systemic side effects. Currently, the promising approaches involve strategic inhibition of copper import via targets like SLC31A1, enhancement of copper export mechanisms through ATP7B upregulation, and advancing renal-specific nanointerventions.

Dietary Considerations

Dietary copper intake plays a critical role in regulating systemic copper homeostasis. Rich sources of copper include shellfish, organ meats, nuts, seeds, and dark chocolate. Copper from animal-based foods is typically more bioavailable than that from plant-based sources, owing to its lower phytate content.[58] Nutrient interactions significantly affect copper balance: high-dose zinc supplementation promotes the synthesis of intestinal metallothionein, which sequesters copper and impairs its absorption, while excessive iron competes with copper for SLC11A2-mediated uptake.[59–61] Diets high in fructose reduce duodenal SLC31A1 expression and enhance hepatic ATP7B-mediated biliary excretion, collectively decreasing copper retention.[47] Ascorbic acid aids in the reduction of Cu^{2+} to Cu^{+} for absorption but may exacerbate oxidative stress when coadministered with copper.[62,63] Therapeutic nutrients, such as α-lipoic acid and curcumin, have been shown to alleviate copper overload.[64,65] Notably, high-fat diets can redistribute copper to the kidneys, increasing the risk of nephrotoxicity in individuals with obesity and diabetes.[66] Clinical monitoring of serum ceruloplasmin may be helpful for high-risk populations to guide personalized dietary interventions.[67]

Challenges and Future Perspectives

Current Challenges and Knowledge Gaps

The clinical translation of cuproptosis research in renal pathologies faces several significant challenges. Key mechanistic uncertainties remain, particularly regarding the precise molecular triggers of mitochondrial rupture and the complex interactions between cuproptosis and other regulated cell death pathways during renal injury. Moreover, the lack of specific biomarkers remains a critical issue. Morphological features such as mitochondrial shrinkage overlap substantially with apoptosis, and metabolic signatures like depleted α-ketoglutarate lack the diagnostic specificity needed to distinguish cuproptosis in vivo. Thus, the development of reliable, renal-specific cuproptosis biomarkers is urgently needed. Additionally, the physiological relevance of cuproptosis in normal renal homeostasis, including its role in processes such as embryonic development, tissue repair, and aging, remains largely unexplored. From a therapeutic standpoint, challenges include the risk of inducing systemic copper deficiency with conventional chelators like D-penicillamine, the potential nephrotoxicity of copper ionophores, which are poorly characterized in kidney disease contexts, the limited renal biodistribution of current copper-modulating agents, and the technical difficulties in targeting genetic regulators of this pathway in vivo. These limitations hinder the effective application of promising nanomedicine strategies.

Future Research Directions

Future investigations should focus on several key areas to overcome current challenges and fully exploit the therapeutic potential of targeting cuproptosis. Understanding renal cell type-specific mechanisms is critical; employing CRISPR-based genetic screens in renal intrinsic cells will help define the unique molecular pathways that govern cuproptosis susceptibility and execution within distinct nephron segments. Simultaneously, efforts could be dedicated to developing and validating noninvasive biomarkers, such as urinary Fe–S cluster proteins, DLAT oligomers, or specific metabolic signatures detectable in biofluids. These biomarkers will

facilitate early detection and stratification of cuproptosis-driven renal injury, particularly in urgent clinical settings like AKI. Overcoming delivery challenges requires the engineering of advanced kidney-targeted nanotherapeutics. Strategies such as megalin ligand conjugation or pH-responsive carriers could enable precise spatial delivery of copper modulators, siRNA constructs, or genetic regulators to the proximal tubule. Additionally, the physiological roles of cuproptosis deserve further exploration. Using inducible lineage tracing models will clarify its potential involvement in renal development, adaptive repair after injury, and aging processes in the kidney. The validation of combinatorial therapeutic regimens that exploit the crosstalk between cell death pathways, such as combining cuproptosis inhibitors with immune checkpoint blockers or ferroptosis modulators, holds significant promise and should be rigorously tested in preclinical models representing various kidney disease etiologies. The integration of single-cell and spatial multiomics will enable precise mapping of cell-type-specific cuproptosis and copper-handling states, as well as the identification of urine biomarkers. Additionally, kidney organoids, tubuloids, and organ-on-chip platforms offer flow-based systems for mechanistic testing and rapid screening of copper-modulating therapies.

Conclusion

Dysregulated copper homeostasis and the newly identified cell death pathway of cuproptosis, driven by mitochondrial copper overload and aggregation of lipoylated TCA cycle enzymes, play significant roles in renal injury across various kidney diseases. Emerging diagnostic biomarkers and therapeutic strategies targeting copper transport or chelation show considerable promise. Future efforts may prioritize the development of renal-specific biomarkers and targeted delivery systems while deepening mechanistic understanding to successfully translate cuproptosis modulation into clinical practice.

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Disclosure

The authors declare that they have no conflicts of interest.

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