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REVIEW

Inflammation: The Pathological Axis of Cisplatin-Induced Renal Injury

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Abstract: Acute kidney injury (AKI) is a common and serious dose-limiting complication of cisplatin chemotherapy. Cisplatin-induced AKI (CI-AKI) is initiated predominantly in proximal renal tubular epithelial cells (RTECs), where cisplatin enters through organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1). This accumulation drives mitochondrial dysfunction, reactive oxygen species (ROS) overproduction, and the release of damage-associated molecular patterns (DAMPs). These signals activate key innate immune pathways, including Toll-like receptor 4/myeloid differentiation primary response 88/nuclear factor kappa B (TLR4/MyD88/NF-κB) signaling and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, leading to a cytokine-driven inflammatory response. Macrophages are major infiltrating immune cells in CI-AKI: early M1 polarization amplifies tubular damage, whereas later M2-like macrophages support inflammation resolution and tissue repair. This review summarizes the mechanistic links between RTEC injury, innate immune activation, and RTEC–macrophage crosstalk, and highlights therapeutic opportunities such as TLR4/NF-κB blockade and modulation of macrophage polarization to reduce nephrotoxicity without compromising anticancer efficacy. Overall, an inflammation-centered view of RTEC–macrophage interactions may guide the development of effective renoprotective adjuncts for cisplatin-based regimens.

Keywords: cisplatin, AKI, RTECs, macrophages, inflammation

Introduction

Cisplatin is a broad-spectrum and highly effective chemotherapeutic agent, but its dose-limiting toxicity primarily manifests as kidney damage.[1] Clinically, cisplatin-induced AKI has a high incidence rate, affecting approximately one-fourth to one-third of patients. Even after just one standard dose of cisplatin treatment, evidence of renal function impairment appears in about 25–35% of patients.[2] The occurrence of cisplatin nephrotoxicity often compels physicians to reduce the dose or discontinue treatment, thereby impacting antitumor efficacy.[3] Beyond AKI, repeated renal insults may cumulatively lead to chronic kidney disease or even end-stage renal disease, imposing a severe burden on patients. Cisplatin-induced kidney injury often presents as acute necrosis of proximal RTECs, renal tubular dysfunction, electrolyte disturbances, etc. In severe cases, acute renal failure requiring dialysis may occur.[4] Due to the lack of specific preventive and therapeutic measures, current clinical management primarily relies on supportive strategies such as adequate hydration, reducing the cumulative cisplatin dose, and monitoring renal function to mitigate its nephrotoxicity.[5] The clinical reality of cisplatin nephrotoxicity necessitates a careful balance between antitumor efficacy and renal safety when administering this drug.

Numerous studies have demonstrated that the inflammatory response occupies a pivotal pathological hub position in cisplatin-induced kidney injury, driving and amplifying renal cell damage.[6] After cisplatin enters RTECs, it triggers cellular stress and injury signals, causing the local kidney to generate a significant inflammatory mediator response, including the cascade upregulation of pro-inflammatory cytokines and chemokines. For instance, in mouse models, cisplatin injection induces significant upregulation of the genes encoding various pro-inflammatory cytokines and chemokines, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Monocyte Chemoattractant Protein-1 (MCP-1), and Macrophage inflammatory protein-2 (MIP-2), in renal tissue.[7–10] These inflammatory mediators promote immune cell infiltration into the

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kidneys and cause further damage to the renal tubules. Blocking key inflammatory factors can markedly attenuate kidney injury. Existing research has proven that neutralizing TNF-α or genetic deficiency of TNF-α can suppress the cisplatin-induced renal inflammatory cascade, thereby protecting renal function from impairment.[11] Therefore, this review synthesizes evidence that sterile inflammation is the central pathological hub of cisplatin-induced AKI, initiated by transporter-driven cisplatin accumulation in proximal RTECs (OCT2/CTR1, with potential contributions from OAT1/3) and amplified by mitochondrial injury, ROS spillover, and metabolic activation. Building on this early intrarenal injury, we highlight how DAMP release, chemokine production, immune-cell recruitment, and tubule–endothelial–fibroblast crosstalk transform focal tubular damage into a whole-nephron inflammatory network that governs both acute tubular necrosis and the AKI-to-CKD transition. We outline the interconnected inflammation–cell death circuitry involving TLR4/MyD88/NF-κB, the CXCL1/CXCR2 chemokine axis, and NLRP3 inflammasome-linked pyroptosis/necroptosis, and further integrate emerging cross-cellular amplification mechanisms such as NLRP3–cGAS–STING cooperation, macrophage metabolic reprogramming, and tubule–endothelial inflammatory coupling. By aligning these mechanistic modules with the strengths and limitations of conventional anti-inflammatory approaches, the promise of targeted inhibitors, and next-generation modalities (natural products, gene and nano-delivery, extracellular vesicles), we aim to identify actionable therapeutic nodes and clinically relevant biomarker directions to better balance anticancer efficacy with renal safety and to curb the AKI-to-CKD transition.

Cisplatin's Renal Uptake, Metabolism and Early Inflammatory Activation

Transporter-Mediated Intracellular Accumulation via OCT2, CTR1, OATs

Cisplatin's selective toxicity to the kidneys is largely attributable to the high uptake and accumulation of cisplatin in renal tubular epithelium.[12] Proximal RTECs highly express OCT2 and CTR1 on their basolateral membrane, which serve as the primary channels for cisplatin entry into cells.[13,14] OCT2 is responsible for the uptake of cationic substances like cisplatin from the blood into tubular cells, while CTR1 can transport platinum-based compounds, including cisplatin. Evidence indicates that inhibiting or reducing these transporters significantly decreases cisplatin accumulation and toxicity within renal cells.[15] Downregulating CTR1 expression in vitro or pre-treating with copper ions to competitively inhibit CTR1 reduces intracellular cisplatin uptake and lowers cell mortality. Similarly, applying OCT2 inhibitors such as cimetidine or carbuterol can partially reduce renal cell uptake of cisplatin.[16] Simultaneous inhibition of CTR1 and OCT2 results in a more pronounced reduction in cisplatin uptake and cytotoxicity. At the whole-animal level, Organic Cation Transporter (OCT) 1/2 double-knockout mice also exhibit some tolerance to cisplatin nephrotoxicity, indicating the importance of OCT-mediated uptake in cisplatin-induced kidney injury.[12] Furthermore, recent studies suggest that organic anion transporters Organic Anion Transporter 1 (OAT1) and OAT3 may also participate in the uptake of cisplatin and its metabolites. Compared to wild-type mice, OAT1- or OAT3-deficient mice show significantly attenuated increases in serum creatinine and blood urea nitrogen, along with less severe tubular necrosis after receiving high-dose cisplatin,[17] This implies that beyond OCT2/CTR1, the OAT1/3-mediated transport pathway for cisplatin or its derivatives also contributes to cisplatin accumulation in the renal cortex and the induction of toxicity. In summary, the high uptake and retention of cisplatin by renal tubular epithelium form the basis of its nephrotoxicity: multiple membrane transporters (especially OCT2 and CTR1, and potentially OAT1/3) efficiently import cisplatin from the circulation into renal parenchymal cells, resulting in cisplatin concentrations in the renal cortex far exceeding those in other tissues. This lays the foundation for the subsequent cascade of cellular damage and inflammatory responses.

Existing studies suggest that after cisplatin enters RTECs mediated by OCT2 and CTR1, it not only directly induces cytotoxic damage but also triggers a local inflammatory response. In in vitro experiments, high expression of OCT2 leads to cisplatin accumulation within renal epithelial cells, subsequently causing increased intracellular ROS levels, aggravated DNA damage, and ultimately activating classical inflammatory pathways such as TLR4/MyD88/NF-κB.[18] In animal models, OCT1/2 double-knockout mice treated with cisplatin not only exhibit lower renal cisplatin content and reduced cellular necrosis but also show significantly decreased expression of inflammatory factors such as MCP-1 and TNF-α in the kidneys, further proving the link between cisplatin uptake and the activation of the inflammatory response.[19] Similarly, functional defects in CTR1 or its competitive inhibition by copper ions, besides reducing cisplatin accumulation in renal tissue, can also concurrently downregulate the expression of pro-inflammatory factors like IL-6

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and IL-1β in renal tissue.[20] This indicates that the high uptake of cisplatin mediated by OCT2 and CTR1 not only facilitates its direct toxicity but also serves as a crucial initiating step in provoking a local sterile inflammatory response in the kidneys. Furthermore, cisplatin-induced excessive ROS generation and mitochondrial dysfunction also provide signal amplification mechanisms for the inflammatory response. Therefore, OCT2 and CTR1 not only determine the level of cisplatin accumulation within renal tubular cells but also play a key role in the subsequent inflammatory pathological processes. Blocking or inhibiting the function of the OCT2 and CTR1 transporters can reduce cisplatin accumulation in the kidneys at its source, effectively preventing cisplatin-mediated cellular damage and secondary inflammatory responses, thereby achieving the goal of mitigating or blocking cisplatin nephrotoxic effects.

Mitochondrial Damage and ROS Spillover Trigger Inflammatory Signaling

Following cisplatin entry into RTECs, it first triggers a series of early events at the subcellular organelle level, among which mitochondrial damage and the generation of oxidative stress are particularly prominent.[21] Due to their positive charge, cisplatin and its metabolites preferentially accumulate in the negatively charged mitochondrial matrix, causing damage to mitochondrial DNA and membrane components.[22] Mitochondrial dysfunction subsequently ensues, manifesting as reduced activity of respiratory chain complexes, decreased ATP synthesis, and other impairments. These injuries lead to massive production of ROS by mitochondria and their release into the cytosol.[23] Experimental evidence confirms that cisplatin treatment causes a significant increase in mitochondrial ROS within proximal tubular cells and disrupts cellular redox homeostasis.[21] In cisplatin-induced kidney injury, excessive ROS not only directly damages cellular molecules but also acts as a "second messenger" for inflammatory activation. Studies have found that cisplatin induces substantial ROS production in RTECs; these ROS, via the erythropoietin receptor-associated JAK2/STAT1 pathway, induce alterations in genes such as SOCS1 and amplify the inflammatory response,[24] Furthermore, ROS are recognized as important activating signals for the NLRP3 inflammasome. Research in renal tissue reveals that cisplatin promotes NLRP3 assembly and caspase-1 activation through oxidative modifications, leading to IL-1β maturation and release.[25] On the other hand, damaged mitochondria themselves release pro-inflammatory signals. In cisplatin-induced AKI models, mitochondrial DNA fragments escaping into the cytosol act as damage-associated molecular patterns (DAMPs) that can be detected by intracellular DNA sensors such as Toll-like receptor 9 (TLR9) and cyclic GMP-AMP synthase (cGAS), further amplifying sterile inflammatory responses in the kidneys.[26] Beyond ROS-mediated signaling, cisplatin also undergoes glutathione (GSH) conjugation and enzymatic breakdown activation at the tubular luminal surface. Cisplatin-GSH conjugates formed during hepatic detoxification are reabsorbed by RTECs. Gamma-glutamyl transpeptidase (GGT) on the brush border membrane then cleaves these conjugates into cysteine-S-conjugates. This intermediate is converted by cysteine conjugate β-lyase into a highly reactive thiol, which rapidly depletes mitochondrial antioxidants and activates glucose-6-phosphate dehydrogenase, leading to an explosive overproduction of cellular ROS. This further stimulates canonical pro-inflammatory transcription programs, thereby reinforcing the vicious cycle of oxidative stress and inflammation.[27] In summary, mitochondrial accumulation and metabolic activation of cisplatin within renal cells initiate a cascade of ROS release and abnormal increase. These oxidative stress signals trigger inflammatory responses in renal cells early on, activating inflammatory pathways from the very initial stages of injury. These early events lay the foundation for subsequent immune cell recruitment and whole-kidney inflammation. Therefore, mitochondrial damage and ROS-mediated inflammatory activation constitute an integral component of cisplatin nephrotoxicity and represent a potential target for intervention.A summary of the above mechanisms is provided in Figure 1.

Cisplatin-Triggered Inflammation–Cell Death Network

TLR4/MyD88/NF-κB Axis

Sterile tissue injury can activate innate immune pathways through pattern recognition receptors (PRRs). In cisplatin-induced AKI, DAMPs are released and activate the Toll-like receptor 4 (TLR4) signaling pathway.[28] Damaged or necrotic RTECs release DAMP molecules such as high-mobility group box 1 (HMGB1). HMGB1 is recognized by and binds to TLR4, initiating downstream inflammatory responses.[29] TLR4 primarily signals via the MyD88-dependent pathway, activating the transcription factor NF-κB, which leads to the upregulation of transcription for various pro-

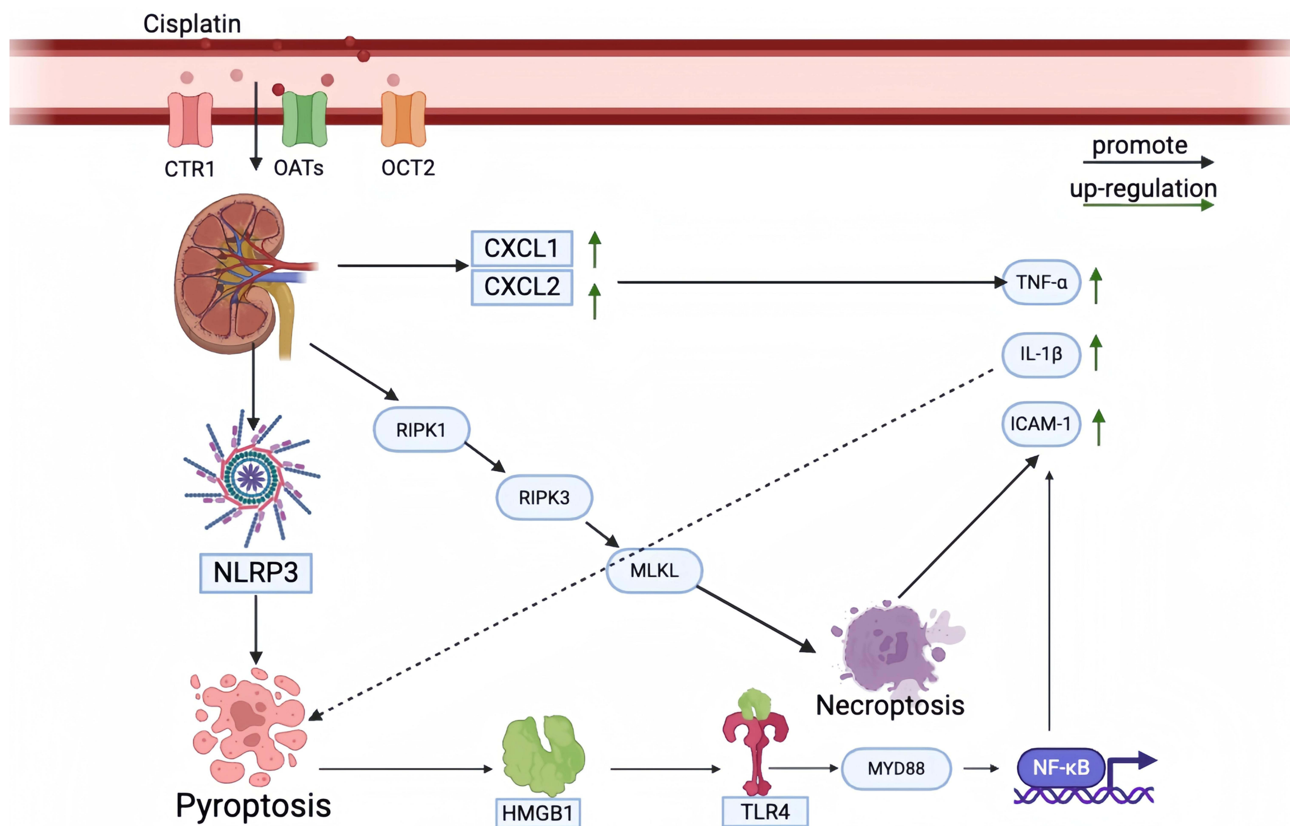

Figure 1 Cisplatin uptake via renal tubular transporters (CTR1, OATs, OCT2) initiates a cascade of inflammatory and cell death signaling. It induces the release of chemokines CXCL1 and CXCL2, promoting neutrophil infiltration and the expression of pro-inflammatory cytokines such as TNF-a and IL-1ß, along with adhesion molecule ICAM-1. Simultaneously, cisplatin activates the NLRP3 inflammasome and the RIPK1-RIPK3-MLKL axis, triggering necroptosis in tubular cells. This process leads to the extracellular release of HMGB 1 and other DAMPs, which engage the TLR4-MYD88-NF-kB pathway in immune cells, forming a positive feedback loop that further amplifies renal inflammation. This integrated network links chemokine signaling, regulated necrosis, and innate immune activation, contributing to cisplatin-induced nephrotoxicity.

inflammatory genes, including TNF-α, IL-1β, and ICAM-1.[30] Experimental evidence supports the critical role of TLR4 in cisplatin nephrotoxicity inflammation: TLR4-deficient mice exhibit significantly attenuated renal functional impairment after cisplatin administration compared to wild-type mice, along with lower levels of pro-inflammatory cytokines and chemokines in the kidneys.[31] Similarly, pharmacological inhibition of TLR4 signaling (eg, using TLR4 inhibitors) has been shown to alleviate cisplatin-induced renal dysfunction and histological damage in mice.[32] Furthermore, NF-κB, as a key node in the TLR4-MyD88 pathway, is hyperactivated in cisplatin kidney injury. Its target genes, such as TNF-α mRNA, show a marked increase early in the injury process.[33] Therefore, the TLR4/MyD88/NF-κB axis constitutes the main pathway for cisplatin-induced sterile inflammation: DAMPs released from injured renal cells activate TLR4, triggering an NF-κB-mediated pro-inflammatory transcriptional program that accelerates the initiation and progression of renal inflammatory injury.

CXCL1/CXCR2 and Other Chemokines

The Chemokine Network Plays a Pivotal Role in Cisplatin-Induced Inflammatory Cell Infiltration. Among these, the axis formed by CXCL1 and its receptor (C-X-C motif chemokine receptor 2) CXCR2 is particularly crucial. CXCL1 is a neutrophil chemokine produced by injured/stressed renal tubular cells and endothelial cells, with interleukin-8 (IL-8/CXCL8) being its human homolog.[34] Animal studies show that the expression of CXCL1 and CXCR2 in renal tissue significantly increases after cisplatin treatment, coinciding with massive neutrophil infiltration into the renal parenchyma during the peak injury period. Knocking out CXCL1 or CXCR2, or applying CXCR2 antagonists (such as Repertaxin), significantly reduces neutrophil infiltration into the kidneys of cisplatin-treated mice, lowers pro-inflammatory cytokine expression, and improves renal function and histopathological damage.[7] This indicates that the CXCL1/CXCR2

chemotactic axis plays a key role in recruiting neutrophils and amplifying the inflammatory response, making it an important pro-inflammatory pathway in cisplatin nephrotoxicity. Beyond neutrophils, the recruitment of monocyte-macrophages and T lymphocytes is also mediated by other chemokines. For example, monocyte chemoattractant protein-1 (MCP-1/CCL2) attracts monocytes/macrophages into renal tissue via the CCR2 receptor, while chemokines such as RANTES (CCL5) and CX3CL1 can mediate T-cell and monocyte adhesion and migration. In cisplatin kidney injury models, the gene expression of these chemokines is upregulated.[35] In summary, the chemokine network, exemplified by CXCL1/CXCR2, drives the directional migration of inflammatory cells to the kidneys and is a core component mediating cisplatin-induced immune cell infiltration and inflammatory propagation. Blocking these pathways holds promise for reducing the inflammatory burden, thereby protecting renal tissue from excessive damage.

NLRP3 Inflammasome and Pyroptosis/Necroptosis

The Innate Immune Sensor NLRP3 Inflammasome Also Plays a Significant Role in Cisplatin-Induced Inflammatory Cell Death. When renal cells are stimulated by cisplatin-induced oxidative stress, ATP leakage, ion imbalance, and other insults, the NLRP3 inflammasome can be activated, triggering a downstream caspase-1-mediated inflammatory cell death process known as pyroptosis.[36] Pyroptosis characteristically causes plasma membrane pore formation and the release of mediators, such as mature IL-1β and IL-18. These inflammatory mediators amplify systemic and local inflammatory responses.[37] Studies show that in chronic kidney injury models induced by repeated cisplatin administration, the NLRP3 inflammasome is significantly activated in renal tissue, accompanied by pyroptosis of RTECs and progression of fibrosis. Using the specific NLRP3 inhibitor MCC950 or knocking out the NLRP3 gene significantly reduces cisplatin-induced inflammation and tissue fibrosis while protecting renal function.[38] This demonstrates that NLRP3 inflammasome-driven pyroptosis contributes to the pathogenesis of cisplatin nephrotoxicity. It is also noteworthy that cisplatin can induce another form of programmed necroptosis.[39] Necroptosis is mediated by the eceptor-interacting protein kinase (RIPK) 1/3/ mixed lineage kinase domain-like protein (MLKL) pathway and results in cell death in a necrotic-like manner, releasing DAMPs.[40] Research has proven that mice deficient in RIPK3 or MLKL are protected against cisplatin kidney injury, exhibiting reduced tubular damage and lower levels of pro-inflammatory factors.[41] This suggests a positive feedback loop of inflammatory cell death exists in cisplatin nephrotoxicity: inflammation induces pyroptosis and necroptosis, and the cellular contents released by these death processes (such as ATP, HMGB1, and other DAMPs) further stimulate inflammation. In summary, NLRP3 inflammasome-mediated pyroptosis and RIPK3/MLKL-mediated necroptosis together constitute the network of inflammatory cell death in cisplatin-induced kidney injury. These pathways lead to cell membrane rupture and the release of inflammatory mediators, amplifying the inflammatory damage to renal tissue.A summary of the above mechanisms is provided in Figure 2.

Cross-Cellular Amplification and Interaction Network of Inflammatory Signaling

Cisplatin-induced renal inflammation is not confined to intracellular signaling alterations within a single cell; rather, it generates a trans-cellular amplification effect through intercellular communication. Within the microenvironment of AKI, diverse cell types (such as tubular epithelial cells, macrophages, endothelial cells) propagate inflammatory signals and establish positive-feedback amplification via the release of damage-associated molecular patterns (DAMPs), cytokines, and extracellular vesicles.[42,43] This interactive network converts a localized initial stimulus into a whole-nephron inflammatory response. The following subsections will dissect several pivotal trans-cellular amplification mechanisms, including the coordinated activation of innate immune DNA-sensing pathways and inflammasomes, metabolic reprogramming of macrophages and paracrine loops, and the inflammatory coupling between renal tubules and microvascular endothelium.

NLRP3-cGAS-STING Synergy: DNA Sensing and Intercellular Communication

In cisplatin-induced renal cell injury, substantial mitochondrial DNA or nuclear DNA fragments leak into the cytosol and become potent innate-immune activating signals. Among these, the cGAS-STING pathway serves as the principal

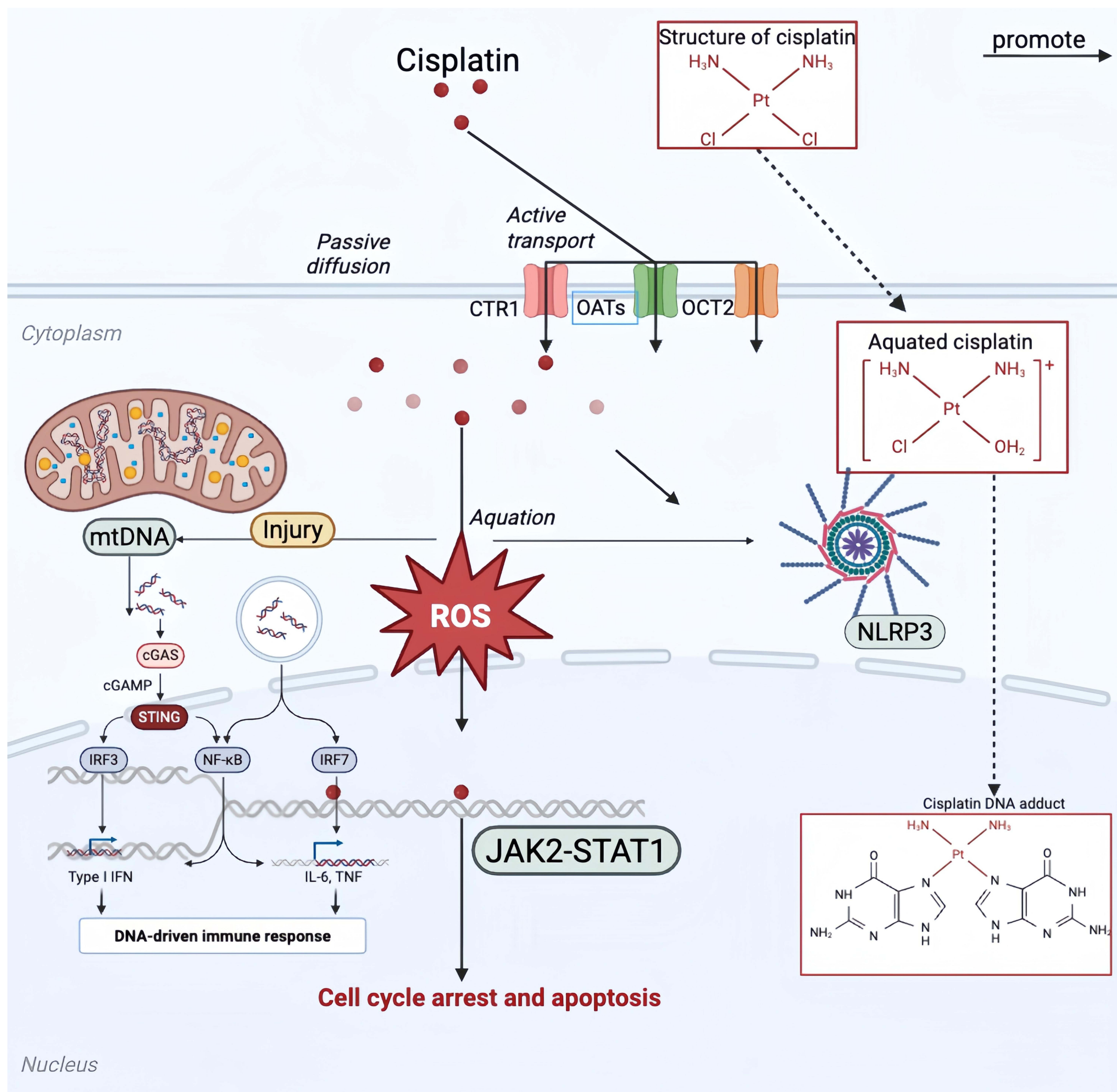

Figure 2 Cisplatin enters renal tubular epithelial cells through multiple transporters, including CTR1, organic anion transporters (OATs), and OCT2. Inside the cell, cisplatin undergoes aquation, forming reactive aquated species that cause mitochondrial injury and generation of reactive oxygen species (ROS). Mitochondrial damage results in the release of mitochondrial DNA (mDNA), which activates the cGAS-STING pathway, leading to NF-kB and IRF3/IRF7 signaling and subsequent expression of type I interferons (IFN), IL-6, and TNF. These pathways collectively mediate a DNA-driven immune response. In parallel, ROS promotes JAK2-STAT1 signaling, resulting in cell cycle arrest and apoptosis. Aquated cisplatin also activates NLRP3 inflammasome and forms DNA adducts, contributing to cytotoxicity and inflammation. This integrative model illustrates the multifaceted mechanisms of cisplatin nephrotoxicity involving DNA damage, innate immunity, and cell death.

cytosolic DNA-sensing machinery and is rapidly activated[44] cGAS recognizes aberrantly present double-stranded DNA and synthesizes the second messenger cGAMP, which binds to and activates the endoplasmic-reticulum-resident STING protein, triggering downstream IRF3 and NF-κB signaling that promotes type I interferon and inflammatory mediator production.[45] Notably, STING activation not only elicits the classical antiviral-like response but also cooperates with the inflammasome pathway through direct interaction with NLRP3, generating a synergistic amplification effect. In models of inflammatory AKI, STING physically associates with the NLRP3 inflammasome, facilitating NLRP3 localization to the endoplasmic reticulum and relieving its ubiquitin-mediated inhibition, thereby accelerating inflammasome assembly and caspase-1–dependent maturation of IL-1β.[46] Activation of cGAS-STING further causes lysosomal damage and

cytosolic Ca2+ efflux, an ionic imbalance that constitutes one of the key secondary signals for NLRP3 activation.[47] Consequently, within injured tubular epithelial cells, the cGAS-STING pathway markedly amplifies NLRP3 inflammasome activity through these multiple mechanisms, resulting in a substantial increase in IL-1β and other inflammatory factors.

Beyond intracellular synergy, the DNA-sensing–inflammasome axis also propagates inflammation via intercellular communication. On one hand, cisplatin-damaged cells undergoing pyroptosis release intracellular DAMPs—including DNA fragments—into the tubular microenvironment through Gasdermin-D pores formed by NLRP3 activation. These extracellular DNA species are taken up by adjacent macrophages, triggering their internal cGAS-STING pathway and AIM2 and other DNA inflammasomes, thereby spatially disseminating inflammatory signals.[40] On the other hand, the cGAMP molecule itself can be transferred between cells via gap junctions or extracellular vesicles. Upon reception of cGAMP, neighboring undamaged cells activate their own STING, and—akin to the spread of a "viral infection signal"—produce interferons and chemokines, amplifying the overall inflammatory response.[48] Collectively, the cGAS-STING and NLRP3 innate-immune pathways form a cooperative network in AKI: DNA leakage serves as the common trigger, and via intracellular collaboration and intercellular propagation, they ignite an enormous inflammatory cascade. In AKI mice, exogenous oxidized DNA simultaneously activates STING and NLRP3, yet STING blockade alone fails to substantially reverse injury, whereas inhibition of NLRP3-mediated pyroptosis markedly improves outcomes,[49] indicating that the NLRP3 inflammasome may be the more critical effector in DNA-driven inflammation, whereas STING functions predominantly as an amplifier and coordinator. It is worth noting that intrinsic negative-feedback mechanisms also regulate this axis: for example, the E3 ubiquitin ligase A20 has been reported to interact with NLRP3, restrict its assembly, and temper DNA-induced STING–NLRP3 inflammation, thereby protecting the kidney from excessive inflammatory damage.[50] In summary, the synergistic activation of the NLRP3–cGAS–STING pathway represents a key mechanism underlying trans-cellular amplification of cisplatin nephrotoxicity, involving DNA-sensing-driven reciprocal activation of injured cells and their neighbors, and it lays the foundation for inflammatory cascade amplification at the earliest stages of AKI. Parallel to pyroptosis and necroptosis, cisplatin-induced oxidative stress also predisposes tubular cells to ferroptotic lipid peroxidation, and these death programs intersect to reinforce inflammatory signaling and promote the AKI-to-CKD transition.

Macrophage Metabolic Reprogramming and Paracrine Amplification Loop

Macrophages function as "signal amplifiers" in renal inflammation amplification. Cisplatin-induced initial tubular injury releases chemokines that recruit circulating monocytes into renal tissue and drives macrophage activation toward an M1 inflammatory phenotype.[51] M1-polarized macrophages undergo pronounced metabolic reprogramming to support massive inflammatory mediator production: energy metabolism switches from oxidative phosphorylation to high-level aerobic glycolysis, accompanied by accumulation of tricarboxylic acid cycle intermediates such as succinate.[52] Succinate accumulation inhibits prolyl hydroxylase and stabilizes inducible HIF-1α, a transcription factor that drives expression of a suite of pro-inflammatory genes, including the gene encoding IL-1β.[53] Thus, metabolic signals become directly coupled to inflammatory signals: HIF-1α not only up-regulates glycolytic enzymes to fuel M1 macrophages but also induces effector molecules such as IL-1β, establishing a "metabolism–inflammation" positive-feedback loop. Correspondingly, HIF-1α activity in macrophages is indispensable for the full expression of the classical pro-inflammatory phenotype; conditional deletion of HIF-1α in macrophages attenuates the expression of inflammatory factors INOS and IL-1β and reduces tissue injury.[54] In contrast, anti-inflammatory M2 macrophages rely primarily on fatty-acid oxidation and an intact tricarboxylic acid cycle for energy, prefer oxidative phosphorylation, and channel arginine metabolism toward the arginase pathway to generate active products that promote tissue repair.[55] Therefore, metabolic conditions within the injured kidney microenvironment—such as local hypoxia and substrate availability—dictate macrophage polarization and the resulting functional product spectrum.

In cisplatin-induced AKI, macrophage metabolic reprogramming is accompanied by altered secretory capacity that generates abundant paracrine factors amplifying the inflammatory response. Classical pro-inflammatory cytokines released by M1 macrophages—including TNF-α, IL-1β, IL-6, and CCL2—not only act directly on tubular epithelial cells to exacerbate injury and death but also stimulate epithelial and endothelial cells to express additional chemokines and adhesion molecules, recruiting further immune-cell infiltration and creating an amplification loop.[56] For example,

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studies have observed that TNF-α and CCL2 secreted by kidney-infiltrating macrophages promote inflammatory injury and apoptosis in surviving neighboring tubular cells, intensifying tubulointerstitial inflammation.[57] Concurrently, damaged tubular epithelial cells emit signals that sustain the M1 state in macrophages: under hypoxic stress, tubular epithelia release extracellular vesicles containing miR-23a, which are taken up by macrophages and initiate an HIF-1α-dependent pro-inflammatory gene program that drives M1 polarization.[58] This bidirectional communication establishes an inflammatory paracrine circuit between macrophages and tubular cells—when tubular epithelial cells are injured, macrophages secrete more inflammatory factors, which in turn act on the epithelial cells to generate additional damage signals that further activate macrophage inflammasomes, perpetually amplifying inflammation.

Extracellular vesicle (EV) exchange between macrophages and other cells also plays a pivotal role in the amplification loop. EVs released from RTECs subjected to cisplatin injury or lipid toxicity are enriched in pro-inflammatory/pro-fibrotic proteins such as leucine-rich α-2-glycoprotein (LRG1).[59] Upon uptake of LRG1-laden EVs, macrophages are activated via the TGF-β receptor pathway and subsequently secrete EVs carrying tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). These TRAIL-bearing EVs act on tubular cells through DR5 receptor engagement, inducing apoptosis.[60] This process vividly illustrates how, in a chronically inflamed milieu, injured epithelia and activated macrophages can exchange "death signals" via EVs, establishing a self-perpetuating vicious cycle.Beyond protein cargo, metabolically disturbed macrophages also influence neighboring cells through secreted metabolites. M1 macrophages generate high levels of lactate and reactive oxygen species (ROS) that diffuse locally, provoking oxidative stress and inflammatory responses in adjacent, previously uninjured cells and thereby expanding the zone of damage.[61] It is noteworthy that these paracrine amplification effects are most vigorous during the early phase of cisplatin AKI; later, macrophages convert toward an M2 phenotype that participates in tissue repair.[62] Therapeutically, targeting macrophage metabolism to modulate polarization and thereby restrain the inflammatory cascade has been proposed. Administration of glycolytic inhibitors—such as LDHA inhibitors—attenuates the pro-inflammatory macrophage phenotype and reduces renal injury in murine AKI models.[63] In summary, through metabolic reprogramming macrophages acquire potent inflammatory amplification capacity and disseminate inflammatory signals across diverse renal cell types via multiple paracrine routes. This process enables focal cisplatin cytotoxicity to evolve into a global, sterile renal inflammatory response, exacerbating AKI severity and laying the groundwork for subsequent chronic alterations.

Renal Tubule–Endothelial Inflammatory Coupling

The tubular epithelium and the peritubular microvascular endothelium constitute an anatomical and functional "twin unit" of the nephron: their close topographical apposition and interdependent activities make them a single pathophysiological entity.[64] Cisplatin-induced tubular injury is almost invariably accompanied by microcirculatory failure and endothelial activation, and the two cell types engage in a cross-talk that locks them into a mutually reinforcing inflammatory coupling. In the very first hours of acute injury, damaged tubular epithelial cells release a burst of inflammatory mediators and chemokines that diffuse across the narrow interstitium and impinge on the abluminal surface of adjacent capillaries, forcing an immediate phenotypic switch in the endothelium. First, endothelial cells exposed to IL-1β rapidly up-regulate adhesion molecules—ICAM-1, VCAM-1—and chemokines, prominently CCL2, thereby enhancing leukocyte tethering and emigration.[65] Neutrophils and monocytes adhere to the activated endothelium, transmigrate, and amplify the interstitial inflammatory infiltrate. Second, tubular ATP and other DAMPs act on endothelial P2X7 receptors or additional pattern-recognition receptors, provoking endothelial production of IL-6, IL-8 and other soluble mediators that feed back onto neighboring epithelial cells and perpetuate the loop.[66] This bidirectional positive feedback continuously escalates inflammation within the tubulo-endothelial unit. In both ischemia-reperfusion and cisplatin AKI models, renal microvascular endothelial cells secrete Angiopoietin-2; plasma levels rise in parallel with inflammation and capillary rarefaction.[67,68] Ang-2 acts in an autocrine manner on endothelial Tie-2 receptors to drive further CCL2 expression, sustaining macrophage recruitment and chronic inflammation.[69] Neutralizing Ang-2 antibody reduces post-AKI capillary loss and fibrosis,[70] underscoring the pathogenic importance of endothelial–epithelial crosstalk. Conversely, endothelial dysfunction feeds back on epithelial fate. Cisplatin toxicity injures the dense cortical capillary network, reducing nutritive blood flow,[67] Diminished endothelial nitric oxide (NO) and increased endothelin-1 provoke vasoconstriction, compounding local ischemia.[71] Tubular segments—especially the outer-cortical S3 segment—

are exquisitely hypoxia-sensitive; reduced oxygen delivery evokes ATP depletion, oxidative stress, and further DAMP release.[72] Thus, an "ischemia–inflammation" cycle is established: tubular damage triggers endothelial inflammation and vascular insufficiency, while ischemia forces the tubule to emit additional inflammatory signals. This coupling becomes particularly prominent and persistent during the AKI-to-CKD transition.[73] Direct physical contact also mediates signaling. Renal medullary resident macrophages extend filopodia that traverse the endothelium to contact the epithelium, "scanning" urinary contents for early detection of injury or infection.[74] Although this represents an immunosurveillance function, the same anatomical intimacy guarantees reciprocal influence under inflammatory conditions. Intrinsic counter-regulatory mechanisms exist to prevent runaway tubulo-endothelial inflammation. Perivascular CD169+ resident macrophages have been shown to down-regulate endothelial ICAM-1 expression via direct cell contact, limiting neutrophil accumulation and mitigating the post-ischemic inflammatory cascade.[75] Likewise, macrophage-derived IL-1 receptor antagonist (IL-1Ra) antagonizes IL-1 signaling on endothelial cells, attenuating IL-6 production and curbing systemic amplification.[76] In cisplatin AKI, however, the magnitude of initial damage and signal strength often shifts the balance toward positive feedback, entrapping both epithelial and endothelial cells in sustained inflammatory activation.[77] In summary, tubular epithelial and endothelial cells are locked in a soluble-factor and contact-mediated inflammatory embrace. Injury or activation in either compartment is instantaneously transmitted to the other, jointly driving leukocyte infiltration and tissue damage. This coupling explains why cisplatin nephrotoxicity is accompanied by overt microvascular pathology, tissue hypoxia, and rapid spread of inflammation throughout the kidney. A precise understanding of this intercellular dialogue is essential for timely intervention in early AKI events and for preventing uncontrolled inflammation.

Cellular/Tissue-Level Inflammatory Effects

Proximal Tubular Epithelial Cells: Source of Cytokines

Proximal tubular epithelial cells are not only the primary direct target of cisplatin toxicity but also a major source of inflammatory mediators.[77] Upon cisplatin exposure, these cells mount a stress response that actively drives the secretion of multiple pro-inflammatory cytokines and chemokines.[2] For instance, after cisplatin challenge, tubular cell expression of TNF-α rises markedly.[78] TNF-α is a potent pro-inflammatory cytokine that acts on neighboring cells and infiltrating immune cells to trigger cascading inflammatory amplification.[79] In cisplatin nephrotoxicity models, neutralization of TNF-α or use of TNF-α-deficient mice significantly attenuates the up-regulation of multiple cytokines and chemokines—such as IL-1β, MCP-1, and MIP-2—and lessens renal functional impairment.[80] This demonstrates that tubular-cell-derived TNF-α occupies a central node in the inflammatory network, driving kidney inflammation through autocrine and paracrine routes. Beyond TNF-α, damaged tubular cells have been shown to be a source for additional inflammatory mediators, including IL-6, TGF-β, MCP-1, and RANTES, all of which are elevated in cisplatin-induced injury.[81] Tubular cells also up-regulate intercellular adhesion molecule-1 (ICAM-1) and other adhesion molecules, promoting immune cell adhesion to renal tubules and thereby intensifying local inflammation. It is worth emphasizing that DAMPs released from injured or necrotic tubular cells—such as HMGB1 and ATP—activate surrounding healthy cells and recruit immune cells, further expanding the inflammatory territory.[82] Thus, in cisplatin nephrotoxicity, proximal tubular epithelial cells function as "inflammatory signal generators": while enduring toxic injury, they actively convert damage signals into inflammatory cues by releasing cytokines, chemokines, and DAMPs, thereby initiating and propelling the kidney's inflammatory injury process. Clinically, several of these tubular injury and inflammation-associated molecules, including KIM-1, IL-18 and MCP-1, are being developed as urinary or plasma biomarkers to enable earlier prediction and risk stratification of cisplatin-induced AKI than serum creatinine alone.[83–85]

Immune Cell Infiltration – Neutrophils, Macrophages, T Cells

Release of inflammatory mediators recruits multiple immune cell subsets into injured renal tissue; among them, neutrophils, macrophages, and T lymphocytes constitute the dominant infiltrating populations observed in cisplatin nephrotoxicity. Neutrophils are the first to arrive, appearing around tubules within hours and peaking within the first day after cisplatin exposure.[86] They carry myeloperoxidase (MPO), elastase, and reactive oxygen species that directly injure tubular epithelial

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and vascular endothelial cells, aggravating tissue damage.[87] Interventional studies support their pathogenic role: anti-neutrophil monoclonal antibody treatment or genetic ablation of neutrophil-related molecules markedly reduces renal neutrophil counts and MPO levels, improves renal function indices, and lessens histological injury.[88]

Monocytes/macrophages infiltrate the interstitium slightly later, reaching peak numbers 1–3 days after injury.[89] These cells display dual roles. Early-stage M1-dominant macrophages secrete TNF-α, IL-1β, and nitric oxide, promoting inflammation and apoptosis, thereby intensifying acute damage. Subsequently, local cues can shift macrophages toward an M2 phenotype that releases IL-10, TGF-β, and growth factors, facilitating debris clearance and tissue repair. Experimental macrophage depletion—using pharmacologic or genetic strategies—yields divergent results depending on the model: some studies show attenuated injury,[90] whereas others report delayed repair.[91] Collectively, macrophages can exacerbate inflammation acutely and aid reconstruction during recovery, with stage-dependent effects.

T lymphocytes, particularly CD4+ T cells, also participate in immune modulation. Activated CD4+ T cells infiltrate the kidney early after cisplatin, produce TNF-α, and express Fas ligand (FasL), inducing tubular cell apoptosis.[92] CD4+ T-cell depletion in some experiments mitigates injury, but outcomes vary, partly because protective regulatory T cells (Treg) are simultaneously removed.[93] Indeed, Treg cells have been shown to protect against AKI, and their absence worsens damage.[94] Thus, T-cell subsets display complex roles: effector T cells may drive inflammation and cell death, whereas regulatory subsets such as Treg restrain excessive inflammation and foster recovery. In summary, the sequential infiltration and interaction of neutrophils, macrophages, and T cells determine the magnitude and outcome of the inflammatory response in cisplatin nephrotoxicity. Modulating the recruitment and polarization of these immune cells represents a promising strategy to attenuate renal injury.

Cross-Talk of Vascular Endothelium and Interstitial Fibroblasts

The renal microvasculature is also a component affected in cisplatin nephrotoxicity, and there is a close interplay between inflammation and microcirculatory dysfunction. Vascular endothelial cells are highly sensitive to cisplatin, which can directly kill endothelial cells and cause significant microvascular dysfunction.[95] Cisplatin induces a reduction in cortical and outer medullary capillary density and blood flow, manifested as decreased renal medullary blood flow and strong constriction of small vessels, thereby exacerbating local acute ischemia and worsening tubular injury.[96] Under normal conditions, the kidney responds to ischemia with self-regulatory vasodilation to maintain perfusion; however, in cisplatin nephrotoxicity, an abnormal vasoconstrictor response is observed, further aggravating hypoxic injury.[97] Along with hemodynamic changes, cisplatin also induces endothelial cell apoptosis and necrosis: in vitro studies show that low concentrations of cisplatin trigger mitochondrial pathway apoptosis in endothelial cells, whereas high concentrations lead to ATP depletion and calcium overload, causing necrosis mediated by both caspases and calpains.[98] Endothelial cell damage often occurs before clinical signs of renal dysfunction; for example, circulating endothelial injury marker vWF rises early after cisplatin administration, with its peak preceding the rise in serum creatinine.[95] Injured endothelial cells influence inflammatory progression through several mechanisms: first, endothelial damage increases capillary permeability, allowing more pro-inflammatory substances to enter the renal interstitium; second, endothelial ICAM-1 and VCAM-1 are further up-regulated in an inflammatory environment, promoting adhesion and transmigration of neutrophils and monocytes into renal tissue, amplifying neuropathologic inflammation; third, endothelial dysfunction reduces vasodilatory factors such as NO and increases vasoconstrictors such as endothelin, aggravating local ischemia and hypoxia, which are activating stimuli for pro-fibrotic factors like HIF-1α.

Interstitial fibroblasts are important cells involved in tissue remodeling and chronic injury progression during the late phase of inflammation. During the acute injury stage, inflammatory mediators (eg, TGF-β1, IL-1) activate quiescent renal interstitial fibroblasts into myofibroblasts, which exhibit proliferation and produce large amounts of extracellular matrix (collagen, fibronectin).[99] If inflammation is not effectively controlled, persistent inflammatory signals drive these activated fibroblasts to deposit excessive collagen, leading to renal interstitial fibrosis.[100] There is also interaction between renal microvasculature and fibroblasts: pericytes surrounding capillaries can differentiate into fibroblasts under persistent inflammation and hypoxia, providing one source of renal fibrosis;[101] conversely, fibroblast-secreted matrix metalloproteinases and growth factors may disrupt capillary basement membranes and inhibit angiogenesis, causing capillary rarefaction and further worsening oxygen and nutrient supply to renal tissue.[102] Studies have indicated

that inhibiting inflammation and cell death can reduce late fibrotic changes in cisplatin nephrotoxicity,[103] emphasizing the role of the inflammation–endothelium–fibroblast axis in AKI-to-CKD progression. In summary, in cisplatin nephrotoxicity, vascular endothelial injury and inflammation are inseparable: inflammation not only damages endothelial function but also induces hemodynamic and permeability changes via endothelial cells; in turn, microcirculatory disturbance and hypoxia drive further inflammation and activate fibroblasts. If the persistent inflammatory–ischemic state is not reversed, it may ultimately evolve into chronic renal interstitial fibrosis, resulting in irreversible loss of kidney function.

Anti-Inflammatory Regulatory Strategies

Conventional Small Molecules-Glucocorticoids, Indomethacin, etc. -Limitations and Insights

Because inflammation plays a central role in cisplatin nephrotoxicity, strategies aimed at reducing inflammation have attracted considerable attention. Classical broad-spectrum anti-inflammatory agents such as glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) have been tested for alleviating cisplatin-induced kidney injury, but their efficacy and applicability are limited. Glucocorticoids possess potent inhibitory effects on the production of inflammatory mediators and immune cell activity. In theory, steroids could attenuate renal injury by broadly suppressing pro-inflammatory signaling and thereby reducing cytokine storms[80] In practice, however, glucocorticoids have not been widely adopted for prevention of cisplatin nephrotoxicity, partly because long-term high-dose steroid use in cancer patients carries severe side effects (increased infection risk, elevated blood glucose and blood pressure, etc).,[104] and because definitive clinical trial evidence demonstrating a significant reduction in the incidence of cisplatin nephrotoxicity by steroids is lacking. Moreover, animal studies show that glucocorticoids can modulate cisplatin-induced inflammation but do not completely block kidney injury, indicating the need for more targeted interventions owing to the complexity of inflammatory pathways.[105] NSAIDs have been shown in both in vivo and in vitro studies to confer protection against cisplatin-induced nephrotoxicity.[106] From an anti-inflammatory perspective, some NSAIDs reduce the release of cisplatin-induced renal inflammatory mediators such as PGE_2 and TXA_2.[107] However, exceptions exist: indomethacin, for example, may aggravate injury. Prostaglandins in the kidney promote afferent arteriolar dilation to maintain hemodynamic stability,[108] whereas cisplatin has been found to down-regulate renal COX-2 and vasodilatory prostaglandins, leading to vasoconstriction and ischemia.[109] Under these circumstances, additional NSAID-mediated prostaglandin inhibition could worsen renal ischemia and further deteriorate renal function. Thus, indomethacin and similar NSAIDs are unsuitable for preventing cisplatin nephrotoxicity and may even pose potential risks. Indeed, some protective-strategy studies against cisplatin nephrotoxicity emphasize avoiding NSAIDs to prevent interference with renal autoregulation. Although classical anti-inflammatory drugs have limitations in cisplatin nephrotoxicity, the insights gained highlight that simple broad-spectrum anti-inflammation is insufficient to abolish cisplatin nephrotoxicity, reflecting the multifactorial complexity of inflammatory responses involved. This suggests that more specific anti-inflammatory interventions targeting key inflammatory pathways—such as TNF-α or particular chemokines—are required, rather than broad immunosuppression. Lessons from classic drugs also inform new therapeutic approaches: for instance, TNF-α inhibitors and leukotriene-pathway antagonists are being explored as more precise anti-inflammatory agents to mitigate cisplatin nephrotoxicity.[110,111] In summary, the limitations of traditional anti-inflammatory drugs in preventing cisplatin nephrotoxicity prompt a shift toward precise molecular-targeted therapy, while underscoring the importance of combination regimens and comprehensive supportive care for renal protection.

Targeted Molecular Inhibitors: PARP-1, JAK/STAT, TLR4 Antagonists

In-depth mechanistic studies of cisplatin nephrotoxicity have revealed numerous molecular pathways amenable to targeted intervention, and in recent years several more selective molecular inhibitors have demonstrated excellent renoprotective potential in experimental models. Poly(ADP-ribose) polymerase-1 (PARP-1) is a key enzyme in the DNA-damage response; cisplatin-induced DNA damage leads to excessive PARP-1 activation, which depletes cellular NAD^+ and ATP and precipitates an energy-crisis form of cell death.[112] In addition, hyperactive PARP promotes inflammation—for example, by PAR polymer–mediated release of HMGB1.[113] Consequently, PARP-1 has emerged as an attractive target. Genetic deletion or pharmacologic inhibition of PARP-1 markedly attenuates CI-AKI. In one tumor-bearing mouse study, the FDA-approved PARP inhibitor niraparib reduced tubular cell death and tissue damage, preserved renal

function, and suppressed cisplatin-triggered renal inflammation and interstitial fibrosis without compromising anticancer efficacy.[114] Suggesting that PARP-1 inhibitors could mitigate cisplatin nephrotoxicity. The JAK/STAT pathway is another focal point for anti-inflammatory intervention. After cisplatin injury, multiple cytokines (eg, IL-6, IFN-γ) activate Janus kinases (JAK) and downstream signal transducer and activator of transcription (STAT) family members. In cisplatin AKI models, STAT3 phosphorylation is elevated, accompanied by increased expression of pro-apoptotic and pro-ferroptotic genes; JAK/STAT inhibitors reverse these deleterious processes and reduce apoptosis and ferroptosis.[115] Moreover, the AMPK activator AICAR up-regulates SOCS1 (suppressor of cytokine signaling-1) to provide negative feedback on the JAK/STAT pathway and counteract cisplatin nephrotoxicity.[24] Thus, direct targeting of JAK2 or STAT3—using FDA-approved JAK inhibitors such as tofacitinib, already employed for rheumatologic disease—holds theoretical promise and awaits further validation.

Regarding TLR4 antagonists, as described earlier TLR4 plays a pivotal role in cisplatin sterile inflammation; therefore, TLR4 inhibition represents a highly promising strategy. The small-molecule TLR4 antagonist TAK-242 (Resatorvid) has been used in experimental inflammatory diseases. In renal injury models (eg, endotoxemia, contrast-induced nephropathy), TAK-242 suppresses inflammasome activation and reduces ROS generation.[116] Although specific data in cisplatin nephrotoxicity models remain limited, the renoprotection observed with TLR4 deletion or inhibition in cisplatin AKI, implies that TLR4 antagonists could dampen cisplatin-driven pro-inflammatory cascades. Beyond these targets, numerous other anti-inflammatory pathway inhibitors are under investigation: p38 MAPK inhibitors decrease production of cytokines such as TNF-α,[117] CCR2 antagonists block monocyte infiltration, and caspase-1 inhibitors reduce pyroptosis. Combined use of these targeted anti-inflammatory agents holds the potential for comprehensive suppression of key inflammatory drivers in cisplatin nephrotoxicity, thereby providing more potent renoprotection with fewer side effects than traditional anti-inflammatory drugs.

Natural Products and Dietary Supplements (Umbelliferone, Dihydromyricetin, Sulfides/H_2S Donors)

Beyond traditional pharmacology, many natural products and dietary supplements have been investigated for their renoprotective potential against cisplatin nephrotoxicity because of their antioxidant and anti-inflammatory properties. Several plant-derived compounds have shown remarkable renal protective effects in animal models. Umbelliferone (7-hydroxycoumarin), a coumarin isolated from plants of the Apiaceae family, possesses well-documented antioxidant and anti-inflammatory activities. In a murine model of cisplatin nephrotoxicity, umbelliferone significantly lowered serum creatinine and blood urea nitrogen, ameliorated tubular histopathological damage, and up-regulated the key intracellular antioxidant factor NRF2. By activating the NRF2 pathway, umbelliferone enhanced expression of antioxidant enzymes such as HO-1 and SOD, reduced ROS accumulation and lipid peroxidation in renal tissue, and simultaneously inhibited NF-κB–mediated inflammatory signaling and production of multiple pro-inflammatory cytokines. Thus, the renoprotective effect of umbelliferone is achieved through its potent dual antioxidant and anti-inflammatory actions.[118] Dihydromyricetin (DHM), a flavonoid found mainly in the medicinal vine tea Ampelopsis grossedentata and in fruits such as bayberry, is known for scavenging free radicals and modulating cell signaling pathways. In cisplatin injury models, DHM markedly attenuated oxidative stress and inflammatory damage: mice treated with DHM exhibited lower renal MDA levels and higher glutathione content, while expression of pro-inflammatory cytokines and apoptotic molecules was reduced and tubular architecture was preserved. Mechanistically, DHM modulates the EGFR/HSP27/STAT3 pathway, thereby decreasing apoptosis and maintaining mitochondrial function.[118,119] Collectively, these actions confer significant renal protection, suggesting that DHM as a dietary supplement could help prevent cisplatin nephrotoxicity. Sulfides and H_2S donors constitute another class of promising protective agents. The endogenous gasotransmitter hydrogen sulfide (H_2S) exerts antioxidant, anti-inflammatory, and vasodilatory effects; in renal pathology, it is regarded as a "double-edged sword," yet moderate elevation of H_2S is generally beneficial in AKI. Investigators have employed sulfide compounds (eg, diallyl trisulfide abundant in garlic) and slow-release H_2S donors (eg, GYY4137) and found that they markedly improved cisplatin nephrotoxicity outcomes. In mice treated with polysulfides or H_2S donors, renal transcription and protein levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 were significantly reduced, and infiltration of neutrophils and macrophages was diminished. Mechanistic studies revealed that H_2S persulfidates critical

inflammatory signaling molecules such as STAT3 and IKKβ, thereby inhibiting STAT3 phosphorylation and activation of the IκB kinase complex and blocking NF-κB–dependent inflammatory gene expression.[120] These effects endow H_2S donors with potent anti-inflammatory and anti-apoptotic activity in cisplatin AKI models. In conclusion, naturally derived antioxidant and anti-inflammatory molecules provide valuable leads for preventing cisplatin nephrotoxicity. Umbelliferone, dihydromyricetin, and H_2S donors attenuate oxidative stress and inflammation, protect mitochondrial function, and act at multiple steps in the pathogenesis of cisplatin nephrotoxicity. With relatively low toxicity, these natural products can serve as dietary supplements or as starting points for drug development, offering promising strategies to reduce cisplatin nephrotoxicity in the clinic.

Prospective Therapies: Gene Delivery, Nano-Delivery, and Extracellular Vesicles

As mechanistic insights into cisplatin nephrotoxicity deepen, several innovative therapeutic strategies are emerging that aim to protect the kidney with greater precision while preserving cisplatin's anticancer efficacy. Gene therapy represents a leading frontier, leveraging gene delivery to reinforce intrinsic renal protective mechanisms or to suppress deleterious pathways. For example, transferring anti-inflammatory cytokine genes (such as IL-10) or pro-survival genes (such as Klotho or HO-1) into tubular cells could enhance their tolerance to cisplatin injury. Animal studies have already demonstrated that IL-10 overexpression attenuates inflammation and improves outcomes in ischemic AKI,[121] and a similar concept can be applied to cisplatin-induced AKI. However, renal gene therapy faces challenges in delivery efficiency and specificity. Recent advances include the use of kidney-targeted vectors—such as tubular-epithelial-tropic viral vectors or peptides—to direct therapeutic genes to the kidney, thereby minimizing systemic adverse effects and maximizing local concentration. In addition, short hairpin RNA (shRNA) or CRISPR-based interventions can silence key mediator genes of cisplatin nephrotoxicity (eg, TNF-α, TLR4), and experimental work has shown that such approaches suppress inflammation and lessen renal injury.[122] Continued refinement of gene-editing and delivery systems positions gene therapy as a future personalized tool for preventing cisplatin nephrotoxicity.

Nanoparticle delivery systems constitute another highly anticipated innovation, employing nano-carriers for targeted drug delivery and controlled release. Nanotechnology has already been explored to reduce systemic toxicity of chemotherapeutics; for instance, encapsulating cisplatin in specialized nanoparticles (such as liposomal cisplatin "Lipoplatin") alters its biodistribution, enriching the drug in tumors while sparing the kidneys, thereby lowering nephrotoxicity. Clinical trials of certain nano-cisplatin formulations have reported lower incidences of renal dysfunction compared with conventional cisplatin, inspiring further research into nano-carrier–based kidney protection.[123] A complementary approach involves nanoparticle delivery of renoprotective agents—for example, loading antioxidants or anti-inflammatory drugs onto kidney-targeted nanoparticles for high-concentration local release in the kidney, thereby mitigating cisplatin's intrarenal toxicity without systemic side effects. Investigators have used polymer nanoparticles bearing AP-conjugated peptides to deliver anti-apoptotic molecules to renal tubules, reducing drug-induced kidney injury in animals.[123] Advances in materials science continue to refine nanoparticle size, surface modification, and targeting ligands, promising high renal selectivity and making nano-delivery a viable strategy for toxicity reduction and efficacy enhancement.

Extracellular vesicles (EVs) represent an emerging cell-derived therapeutic modality beyond cell therapy itself. Stem-cell–derived exosomes and microvesicles are rich in microRNAs, proteins, and lipids capable of conferring stem cell-like tissue repair without direct cell transplantation. In multiple AKI models, EVs from mesenchymal stem cells have repeatedly demonstrated significant renoprotective effects, including in cisplatin AKI. For example, intrarenal infusion of human umbilical cord MSC–derived exosomes into cisplatin-injured rats improved renal function, lowered inflammation and apoptosis, and activated cell-survival pathways such as autophagy.[124] EV efficacy stems partly from their cargo of stem-cell–derived beneficial signals: certain EVs carry miRNAs (eg, miR-146b) that down-regulate inflammatory pathways such as NF-κB, reducing inflammation and apoptosis;[125] others are enriched in pro-regenerative proteins that stimulate local cell proliferation and epithelial repair.[126] Importantly, EV therapy avoids potential immunological rejection or tumorigenic risks associated with cell therapy and can be administered intravenously or via direct renal perfusion, demonstrating convenience and effectiveness in animal models.[127] Future efforts to engineer EVs—by enhancing renal targeting or loading specific renoprotective factors—are expected to further improve therapeutic outcomes. In summary, gene therapy, nano-drug delivery, and extracellular vesicle therapy represent cutting-edge directions for preventing cisplatin nephrotoxicity. These strategies hold the potential to deliver precise interventions targeting the

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molecular basis of cisplatin renal toxicity, significantly reducing kidney-related adverse effects while preserving anticancer efficacy, and thereby opening new avenues for the safe clinical use of cisplatin.

Knowledge Gaps and Future Directions

Although research on cisplatin-induced kidney injury has made substantial progress, several key aspects of the inflammatory cascade and its integration with other injury pathways remain incompletely understood and warrant deeper exploration.First, the temporal sequence of the inflammatory–ferroptotic–fibrotic continuum has not been fully elucidated. How acute inflammation and cell death evolve into chronic fibrosis is a central question in the AKI-to-CKD transition. In models employing repeated cisplatin dosing, the causal relationships among inflammatory mediators, modes of cell death (apoptosis, necroptosis, ferroptosis), and fibroblast activation across different time windows require finer spatiotemporal resolution. Future studies should leverage single-cell sequencing and lineage-tracing technologies to construct a cellular-fate atlas of cisplatin nephrotoxicity from acute inflammation to chronic fibrosis, identifying the critical decision points that dictate disease trajectory. Second, the clinical-translational potential of inflammatory biomarkers and their value as predictive tools in patients deserves focused attention. Serum creatinine, the current clinical standard, is a lagging indicator that cannot detect early injury. Inflammatory markers identified in murine models—such as elevated CXCL1/KC—hold promise for translation into human urine or plasma biomarkers for early prediction, risk stratification and dynamic monitoring of cisplatin nephrotoxicity. Prospective clinical studies are needed to measure levels of CXCL1, IL-18, KIM-1, and other inflammatory or injury molecules in urine and blood of cisplatin-treated patients and to correlate these levels with AKI incidence, thereby validating reliable biomarkers. Third, the design of individualized cisplatin dosing combined with pathway-specific anti-inflammatory strategies represents a pivotal next step toward clinical implementation. Because cisplatin nephrotoxicity is influenced by multiple factors (genetic background, comorbidities, dosing regimen), future strategies may tailor cisplatin dosing according to individual risk—eg, adjusting dose or schedule based on OCT2 or other transporter polymorphisms. In high-risk patients, adjunctive anti-inflammatory or antioxidant therapy could be tested: for example, combining cisplatin with a safe anti-inflammatory agent (low-dose tacrolimus to inhibit NF-κB, or a TNF inhibitor confirmed to lack tumor-protective effects) to determine whether AKI incidence can be reduced. Such combination trials must be meticulously designed, with close monitoring of anticancer efficacy to ensure no compromise in tumor response. Tumor-bearing animal models are essential for pre-clinical validation prior to human studies. Anti-inflammatory and renoprotective strategies for cisplatin-induced nephrotoxicity are summarized in Table 1.

Table 1 Anti-Inflammatory and Renoprotective Strategies for Cisplatin-Induced Nephrotoxicity

Intervention/ Strategy	Mechanism of Action	Key Molecular Target(s)	Evidence (Pre-Clinical/ Clinical)	Refs.
Glucocorticoids	Broad NF-κB suppression resulting in decreased production of pro-inflammatory cytokines	NF-κB, multiple cytokines	Rodent studies: lower BUN/Cr and milder tubular injury; no definitive clinical benefit due to side-effects	[101–103]
NSAIDs (eg Indomethacin)	Cyclooxygenase inhibition leading to reduced PGE_2 and TXA_2; may worsen renal vasoconstriction when protective prostaglandins are already down-regulated	COX-1/2	Some NSAIDs mildly protective, but Indomethacin aggravates cisplatin AKI; generally avoided clinically	[80,104–106]
TNF-α inhibitors (eg Etanercept)	Neutralisation of TNF-α dampening the early inflammatory cascade	TNF-α/ TNFR1-2	Blockade reduces tubular damage and cytokine surge in mice	[107]

(*Continued*)

Table 1 (Continued).

Intervention/ Strategy	Mechanism of Action	Key Molecular Target(s)	Evidence (Pre-Clinical/ Clinical)	Refs.
Leukotriene-BLT1 blockade	Inhibition of LTB_4 signalling which diminishes neutrophil chemotaxis	LTA4H, BLT1	BLT1-knockout or antagonists lower neutrophil influx and creatinine rise in cisplatin AKI	[108]
PARP-1 inhibitors (eg Niraparib)	Prevention of NAD^+ and ATP depletion and reduced HMGB1 release following DNA damage	PARP-1	Niraparib preserves renal function and limits fibrosis in tumour-bearing mice	[109–111]
JAK/STAT inhibitors	Blockade of cytokine-driven JAK2 and STAT3 activation, thereby lowering pro-apoptotic and ferroptosis-related gene expression	JAK2, STAT3	Inhibitors or AMPK-SOCS1 up-regulation protect rat kidneys	[112,113]
TLR4 antagonist (TAK-242)	Interference with DAMP sensing by TLR4 which decreases NF-κB activation and inflammasome activity	TLR4, MyD88 pathway	TLR4-knockout and TAK-242 protect against AKI; cisplatin-specific data emerging	[31,32,114]
p38 MAPK inhibitor	Suppression of stress-activated p38 MAPK thereby reducing TNF-α and IL-1β production	p38 MAPK	Lowers cytokine load and tubular injury in cisplatin AKI	[115]
Umbelliferone	Activation of the Nrf2 antioxidant pathway combined with inhibition of NF-κB	Nrf2/HO-1, NF-κB	Decreases ROS and lipid peroxidation, increases HO-1/ SOD, improves renal indices in mice	[24]
Dihydromyricetin	Provision of antioxidant effects and suppression of the EGFR–HSP27–STAT3 signalling axis	EGFR, HSP27, STAT3	Lowers MDA, boosts GSH, inhibits apoptosis; protects mouse kidneys	[116]
H_2S donors (eg GYY4137, DATS)	Persulfidation of STAT3 and IKKβ resulting in NF-κB blockade together with vasodilation and ROS scavenging	STAT3, IKKβ	Donors decrease TNF-α, IL-1β, IL-6, lessen necrosis and creatinine rise in mice	[117]
Gene therapy (IL-10, Klotho, HO-1; shRNA/CRISPR)	Expression of cytoprotective genes or silencing of injurious genes to reinforce endogenous defence pathways	IL-10, Klotho, HO-1; TNF-α, TLR4	Targeted delivery reduces inflammation and tubular death in AKI models	[118,119]
Nano-delivery systems	Alteration of drug biodistribution: tumour-targeted liposomal cisplatin lowers renal uptake, whereas kidney-targeted nanoparticles deliver protectants locally	Liposomes, polymeric nanoparticles	Lipoplatin shows 0% grade ≥ 3 nephrotoxicity in Phase II; kidney-directed nanoparticles reduce CKD in mice	[122–124]
Stem-cell extracellular vesicles	Transfer of protective miRNAs and proteins that inhibit NF-κB and promote tubular repair	NF-κB, PI3K/ Akt, mTOR–ATG	MSC-derived EVs improve creatinine, reduce apoptosis and inflammation in rodent cisplatin AKI	[116,124,126,127]

Conclusion

Cisplatin-induced nephrotoxicity is best viewed as a sterile inflammatory syndrome, initiated by tubular cisplatin uptake and oxidative stress and propagated through coordinated tubular, immune and vascular responses. This integrated perspective underscores the limitations of non-specific anti-inflammatory drugs and supports the development of pathway-focused interventions that modulate key inflammatory nodes without compromising antitumor efficacy. In parallel,

inflammatory and injury biomarkers that mirror this cascade should be refined and clinically validated to enable earlier risk prediction and more precise protection of renal function in patients receiving cisplatin.

Data Sharing Statement

No Data associated in the manuscript.

Ethics Approval

This article is an observational study and does not require ethical approval.

Consent for Publication

All authors agreed to publish.

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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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References

1. Fang C-Y, Lou D-Y, Zhou L-Q, et al. Natural products: potential treatments for cisplatin-induced nephrotoxicity. *Acta Pharmacol Sin*. 2021;42 (12):1951–1969. doi:10.1038/s41401-021-00620-9
2. McSweeney KR, Gadanec LK, Qaradakhi T, Ali BA, Zulli A, Apostolopoulos V. Mechanisms of cisplatin-induced acute kidney injury: pathological mechanisms, pharmacological interventions, and genetic mitigations. *Cancers*. 2021;13(7):1572. doi:10.3390/cancers13071572
3. Gupta S, Glezerman IG, Hirsch JS, et al. Derivation and external validation of a simple risk score for predicting severe acute kidney injury after intravenous cisplatin: cohort study. *BMJ*. 2024;384:e077169. doi:10.1136/bmj-2023-077169
4. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders H-J. Acute kidney injury. *Nat Rev Dis Primers*. 2021;7(1):52. doi:10.1038/s41572-021-00284-z
5. Alassaf N, Attia H. Autophagy and necroptosis in cisplatin-induced acute kidney injury: recent advances regarding their role and therapeutic potential. *Front Pharmacol*. 2023;14:1103062. doi:10.3389/fphar.2023.1103062
6. Chen X, Wei W, Li Y, Huang J, Ci X. Hesperetin relieves cisplatin-induced acute kidney injury by mitigating oxidative stress, inflammation and apoptosis. *Chem Biol Interact*. 2019;308:269–278. doi:10.1016/j.cbi.2019.05.040
7. Liu P, Li X, Lv W, Xu Z. Inhibition of CXCL1-CXCR2 axis ameliorates cisplatin-induced acute kidney injury by mediating inflammatory response. *Biomed Pharmacother*. 2020;122:109693. doi:10.1016/j.biopha.2019.109693
8. Tripathi P, Alshahrani S. Mitigation of IL-1β, IL-6, TNF-α, and markers of apoptosis by ursolic acid against cisplatin-induced oxidative stress and nephrotoxicity in rats. *Hum Exp Toxicol*. 2021;40(12_suppl):S397–S405. doi:10.1177/09603271211045953
9. Cheng J, Li M, Li C, et al. Protective Effect of Mangiferin on Cisplatin Induced Acute Kidney Injury in Vivo. *Nat Prod Commun*. 2025;20 (3):1934578X251325035. doi:10.1177/1934578X251325035
10. Wada Y, Iyoda M, Matsumoto K, et al. Reno-protective effect of IL-34 inhibition on cisplatin-induced nephrotoxicity in mice. *PLoS One*. 2021;16(1):e0245340. doi:10.1371/journal.pone.0245340

11. Loren P, Saavedra N, Saavedra K, Zambrano T, Moriel P, Salazar LA. Epigenetic mechanisms involved in cisplatin-induced nephrotoxicity: an update. *Pharmaceuticals*. 2021;14(6):491. doi:10.3390/ph14060491
12. Pabla N, Murphy RF, Liu K, Dong Z. The copper transporter Ctr1 contributes to cisplatin uptake by renal tubular cells during cisplatin nephrotoxicity. *Am J Physiol Renal Physiol*. 2009;296(3):F505–11. doi:10.1152/ajprenal.90545.2008
13. Ailabouni A, Prasad B. Organic cation transporters 2 (OCT2): structure, regulation, functions, and clinical implications. *Drug Metab Dispos*. 2025;53(3):100044. doi:10.1016/j.dmd.2025.100044
14. Su Y, Zhang X, Li S, Xie W, Guo J. Emerging roles of the copper–CTR1 Axis in tumorigenesis. *Mol Cancer Res*. 2022;20(9):1339–1353. doi:10.1158/1541-7786.MCR-22-0056
15. Schoeberl A, Gutmann M, Theiner S, et al. The copper transporter CTR1 and cisplatin accumulation at the single-cell level by LA-ICP-TOFMS. *Front Mol Biosci*. 2022;9:1055356. doi:10.3389/fmolb.2022.1055356
16. Wu H, Ning Y, Sun Z, et al. Both carvedilol and cimetidine alleviate cisplatin-induced nephrotoxicity via downregulating OCT2. *Biochim Biophys Acta Mol Basis Dis*. 2025;1871(5):167754. doi:10.1016/j.bbadis.2025.167754
17. Hu S, Leblanc A, Gibson A, et al. Identification of OAT1/OAT3 as contributors to cisplatin toxicity. *Clin Transl Sci*. 2017;10(5):412–420. doi:10.1111/cts.12480
18. Ciarimboli G, Deuster D, Knief A, et al. Organic cation transporter 2 mediates cisplatin-induced oto-and nephrotoxicity and is a target for protective interventions. *Am J Pathol*. 2010;176(3):1169–1180. doi:10.2353/ajpath.2010.090610
19. Filipski KK, Mathijssen RH, Mikkelsen TS, Schinkel AH, Sparreboom A. Contribution of organic cation transporter 2 (OCT2) to cisplatin-induced nephrotoxicity. *Clin Pharmacol Ther*. 2009;86(4):396–402. doi:10.1038/clpt.2009.139
20. Ishida S, Lee J, Thiele DJ, Herskowitz I. Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals. *Proc Natl Acad Sci*. 2002;99(22):14298–14302. doi:10.1073/pnas.162491399
21. Mapuskar KA, Steinbach EJ, Zaher A, et al. Mitochondrial superoxide dismutase in cisplatin-induced kidney injury. *Antioxidants*. 2021;10(9):1329. doi:10.3390/antiox10091329
22. Cocetta V, Ragazzi E, Montopoli M. Mitochondrial involvement in cisplatin resistance. *Int J Mol Sci*. 2019;20(14):3384. doi:10.3390/ijms20143384
23. Kleih M, Böpple K, Dong M, et al. Direct impact of cisplatin on mitochondria induces ROS production that dictates cell fate of ovarian cancer cells. *Cell Death Dis*. 2019;10(11):851. doi:10.1038/s41419-019-2081-4
24. Tsogbadrakh B, Ryu H, Ju KD, et al. AICAR, an AMPK activator, protects against cisplatin-induced acute kidney injury through the JAK/STAT/SOCS pathway. *Biochem Biophys Res Commun*. 2019;509(3):680–686. doi:10.1016/j.bbrc.2018.12.159
25. Jiang S, Zhang H, Li X, et al. Vitamin D/VDR attenuate cisplatin-induced AKI by down-regulating NLRP3/Caspase-1/GSDMD pyroptosis pathway. *J Steroid Biochem Mol Biol*. 2021;206:105789.
26. Maekawa H, Inagi R, Nangaku M, Inoue T, Inoue R, Nishi H. SUN-155 mitochondrial DNA leakage causes inflammation via the cGAS-STING axis in cisplatin-induced acute kidney injury. *Kidney Int Rep*. 2019;4(7):S222. doi:10.1016/j.ekir.2019.05.556
27. Salama SA, Abd-Allah GM, Mohamadin AM, Elshafey MM, Gad HS. Ergothioneine mitigates cisplatin-evoked nephrotoxicity via targeting Nrf2, NF-κB, and apoptotic signaling and inhibiting γ-glutamyl transpeptidase. *Life Sci*. 2021;278:119572. doi:10.1016/j.lfs.2021.119572
28. Andrade-Silva M, Cenedeze MA, Perandini LA, et al. TLR2 and TLR4 play opposite role in autophagy associated with cisplatin-induced acute kidney injury. *Clin Sci*. 2018;132(16):1725–1739. doi:10.1042/CS20170262
29. Michel HE, Menze ET. Tetramethylpyrazine guards against cisplatin-induced nephrotoxicity in rats through inhibiting HMGB1/TLR4/NF-κB and activating Nrf2 and PPAR-γ signaling pathways. *Eur J Pharmacol*. 2019;857:172422. doi:10.1016/j.ejphar.2019.172422
30. Fu Y, Xiang Y, Wang Y, et al. The STAT1/HMGB1/NF-κB pathway in chronic inflammation and kidney injury after cisplatin exposure. *Theranostics*. 2023;13(9):2757. doi:10.7150/thno.81406
31. Zhang B, Ramesh G, Uematsu S, Akira S, Reeves WB. TLR4 signaling mediates inflammation and tissue injury in nephrotoxicity. *J Am Soc Nephrol*. 2008;19(5):923–932. doi:10.1681/ASN.2007090982
32. Gao H, Wang X, Qu X, et al. Omeprazole attenuates cisplatin-induced kidney injury through suppression of the TLR4/NF-κB/NLRP3 signaling pathway. *Toxicology*. 2020;440:152487. doi:10.1016/j.tox.2020.152487
33. Wang X, Zhou J, Yang J, Wang S, Yang L. Role of TLR4/MyD88/NF-κB signaling in the contrast-induced injury of renal tubular epithelial cells. *Exp Ther Med*. 2020;20(5):115. doi:10.3892/etm.2020.9243
34. Korbecki J, Barczak K, Gutowska I, Chlubek D, Baranowska-Bosiacka I. CXCL1: gene, promoter, regulation of expression, mRNA stability, regulation of activity in the intercellular space. *Int J Mol Sci*. 2022;23(2):792. doi:10.3390/ijms23020792
35. Zarate-Peñata EDC, Fiorillo-Moreno O, Meza-Torres C, Navarro-Quiroz E. Cytokines, chemokines, inflammasomes, myokines and complement-related factors in acute kidney injury. In: *Organ Crosstalk in Acute Kidney Injury: Basic Concepts and Clinical Practices*. Springer; 2023:59–81.
36. Lee DW, Faubel S, Edelstein CL. A pan caspase inhibitor decreases caspase-1, IL-1 α and IL-1 β, and protects against necrosis of cisplatin-treated freshly isolated proximal tubules. *Renal Failure*. 2015;37(1):144–150. doi:10.3109/0886022X.2014.970194
37. Vasudevan SO, Behl B, Rathinam VA. Pyroptosis-induced inflammation and tissue damage. *Semin Immunopathol*. 2023;69:101781. doi:10.1016/j.smim.2023.101781
38. Li S, Lin Q, Shao X, et al. NLRP3 inflammasome inhibition attenuates cisplatin-induced renal fibrosis by decreasing oxidative stress and inflammation. *Exp Cell Res*. 2019;383(1):111488. doi:10.1016/j.yexcr.2019.07.001
39. Xu Y, Ma H, Shao J, et al. A role for tubular necroptosis in cisplatin-induced AKI. *J Am Soc Nephrol*. 2015;26(11):2647–2658.
40. Guerrero-Mauvecin J, Villar-Gómez N, Rayego-Mateos S, et al. Regulated necrosis role in inflammation and repair in acute kidney injury. *Front Immunol*. 2023;14:1324996. doi:10.3389/fimmu.2023.1324996
41. Meng X-M, Li H-D, Wu W-F, et al. Wogonin protects against cisplatin-induced acute kidney injury by targeting RIPK1-mediated necroptosis. *Lab Invest*. 2018;98(1):79–94. doi:10.1038/labinvest.2017.115
42. Preissner KT, Fischer S, Deindl E. Extracellular RNA as a versatile DAMP and alarm signal that influences leukocyte recruitment in inflammation and infection. *Front Cell Develop Biol*. 2020;8:619221. doi:10.3389/fcell.2020.619221
43. Tan S-Y, Weninger W. Neutrophil migration in inflammation: intercellular signal relay and crosstalk. *Curr Opin Immunol*. 2017;44:34–42. doi:10.1016/j.coi.2016.11.002

44. Maekawa H, Inoue T, Ouchi H, et al. Mitochondrial damage causes inflammation via cGAS-STING signaling in acute kidney injury. *Cell Rep*. 2019;29(5):1261–1273.e6. doi:10.1016/j.celrep.2019.09.050
45. Qi X, Wang J, Fei F, et al. Myricetin-loaded nanomicelles protect against cisplatin-induced acute kidney injury by inhibiting the DNA damage-cGAS–STING signaling pathway. *Mol Pharmaceut*. 2022;20(1):136–146. doi:10.1021/acs.molpharmaceut.2c00520
46. Cao Y, Chen X, Zhu Z, et al. STING contributes to lipopolysaccharide-induced tubular cell inflammation and pyroptosis by activating endoplasmic reticulum stress in acute kidney injury. *Cell Death Dis*. 2024;15(3):217. doi:10.1038/s41419-024-06600-1
47. Li S, Kong L, Meng Y, et al. Cytosolic DNA sensing by cGAS/STING promotes TRPV2-mediated Ca2+ release to protect stressed replication forks. *Mol Cell*. 2023;83(4):556–573.e7. doi:10.1016/j.molcel.2022.12.034
48. Xu D, Jiang J, Liu Y, et al. TIMP2 protects against sepsis-associated acute kidney injury by cAMP/NLRP3 axis-mediated pyroptosis. *Am J Physiol Cell Physiol*. 2024;326(5):C1353–C1366. doi:10.1152/ajpcell.00577.2023
49. Luo X, Zhao Y, Luo Y, et al. Cytosolic mtDNA–cGAS–STING axis contributes to sepsis-induced acute kidney injury via activating the NLRP3 inflammasome. *Clin Exp Nephrol*. 2024;28(5):375–390. doi:10.1007/s10157-023-02448-5
50. Li H, Wu Y, Xiang L, et al. A20 attenuates oxidized self-DNA-mediated inflammation in acute kidney injury. *Signal Transduct Target Ther*. 2025;10(1):154. doi:10.1038/s41392-025-02194-y
51. Tan R-Z, Liu J, Zhang -Y-Y, et al. Curcumin relieved cisplatin-induced kidney inflammation through inhibiting Mincle-maintained M1 macrophage phenotype. *Phytomedicine*. 2019;52:284–294. doi:10.1016/j.phymed.2018.09.210
52. Yang Y, Cui -B-B, Li J, et al. Tricarboxylic acid cycle metabolites: new players in macrophage. *Inflammation Res*. 2024;73(4):531–539. doi:10.1007/s00011-024-01853-0
53. Tannahill G, Curtis A, Adamik J, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature*. 2013;496 (7444):238–242. doi:10.1038/nature11986
54. Malkov MI, Lee CT, Taylor CT. Regulation of the hypoxia-inducible factor (HIF) by pro-inflammatory cytokines. *Cells*. 2021;10(9):2340. doi:10.3390/cells10092340
55. Wang X, Chen J, Xu J, Xie J, Harris DC, Zheng G. The role of macrophages in kidney fibrosis. *Front Physiol*. 2021;12:705838. doi:10.3389/fphys.2021.705838
56. Batra R, Suh MK, Carson JS, et al. IL-1β (interleukin-1β) and TNF-α (tumor necrosis factor-α) impact abdominal aortic aneurysm formation by differential effects on macrophage polarization. *Arterioscleros Thrombos Vasc Biol*. 2018;38(2):457–463. doi:10.1161/ATVBAHA.117.310333
57. Hou C, Mei Q, Song X, et al. Mono-macrophage-derived MANF protects against lipopolysaccharide-induced acute kidney injury via inhibiting inflammation and renal M1 macrophages. *Inflammation*. 2021;44(2):693–703. doi:10.1007/s10753-020-01368-w
58. Jeon JS, Kim E, Bae Y-U, et al. microRNA in extracellular vesicles released by damaged podocytes promote apoptosis of renal tubular epithelial cells. *Cells*. 2020;9(6):1409. doi:10.3390/cells9061409
59. Yuc CCJZT, Jiad HFJLY. LRG1 contributes to the pathogenesis of multiple kidney diseases: a comprehensive review; 2024.
60. Hong Q, Zhang L, Fu J, et al. LRG1 promotes diabetic kidney disease progression by enhancing TGF-β–induced angiogenesis. *J Am Soc Nephrol*. 2019;30(4):546–562.
61. Xue C, Tian J, Cui Z, et al. Reactive oxygen species (ROS)-mediated M1 macrophage-dependent nanomedicine remodels inflammatory microenvironment for osteoarthritis recession. *Bioact Mater*. 2024;33:545–561. doi:10.1016/j.bioactmat.2023.10.032
62. Han HI, Skvarca LB, Espiritu EB, Davidson AJ, Hukriede NA. The role of macrophages during acute kidney injury: destruction and repair. *Pediatr Nephrol*. 2019;34(4):561–569. doi:10.1007/s00467-017-3883-1
63. Wei J, Chen X-Y, Wang Z-J, et al. Galloflavin mitigates acute kidney injury by suppressing LDHA-dependent macrophage glycolysis. *Int Immunopharmacol*. 2025;150:114265. doi:10.1016/j.intimp.2025.114265
64. Maringer K, Sims-Lucas S. The multifaceted role of the renal microvasculature during acute kidney injury. *Pediatr Nephrol*. 2016;31 (8):1231–1240. doi:10.1007/s00467-015-3231-2
65. Bui TM, Wiesolek HL, Sumagin R. ICAM-1: a master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. *J Leukoc Biol*. 2020;108(3):787–799. doi:10.1002/jlb.2mr0220-549r
66. Qian Y, Qian C, Xie K, et al. P2X7 receptor signaling promotes inflammation in renal parenchymal cells suffering from ischemia-reperfusion injury. *Cell Death Dis*. 2021;12(1):132. doi:10.1038/s41419-020-03384-y
67. Menshikh A, Scarfe L, Delgado R, et al. Capillary rarefaction is more closely associated with CKD progression after cisplatin, rhabdomyolysis, and ischemia-reperfusion-induced AKI than renal fibrosis. *Am J Physiol Renal Physiol*. 2019;317(5):F1383–f1397. doi:10.1152/ajprenal.00366.2019
68. Yu W-K, McNeil JB, Wickersham NE, Shaver CM, Bastarache JA, Ware LB. Angiopoietin-2 outperforms other endothelial biomarkers associated with severe acute kidney injury in patients with severe sepsis and respiratory failure. *Critical Care*. 2021;25(1):48. doi:10.1186/s13054-021-03474-z
69. Reikvam H, Hatfield KJ, Lassalle P, Olsnes Kittang A, Ersvaer E, Bruserud Ø. Targeting the angiopoietin (Ang)/Tie-2 pathway in the crosstalk between acute myeloid leukaemia and endothelial cells: studies of Tie-2 blocking antibodies, exogenous Ang-2 and inhibition of constitutive agonistic Ang-1 release. *Expert Opin Invest Drugs*. 2010;19(2):169–183. doi:10.1517/13543780903485659
70. Chang FC, Liu CH, Luo AJ, et al. Angiopoietin-2 inhibition attenuates kidney fibrosis by hindering chemokine C-C motif ligand 2 expression and apoptosis of endothelial cells. *Kidney Int*. 2022;102(4):780–797. doi:10.1016/j.kint.2022.06.026
71. Hannemann J, Böger R. Dysregulation of the nitric oxide/Dimethylarginine pathway in hypoxic pulmonary vasoconstriction—molecular mechanisms and clinical significance. *Front Med*. 2022;9:835481. doi:10.3389/fmed.2022.835481
72. Giuliani KTK, Grivei A, Nag P, et al. Hypoxic human proximal tubular epithelial cells undergo ferroptosis and elicit an NLRP3 inflammasome response in CD1c+ dendritic cells. *Cell Death Dis*. 2022;13(8):739. doi:10.1038/s41419-022-05191-z
73. Sato Y, Takahashi M, Yanagita M. Pathophysiology of AKI to CKD progression. *Semin Nephrol*. 2020;40(2):206–215. doi:10.1016/j.semnephrol.2020.01.011
74. He J, Cao Y, Zhu Q, et al. Renal macrophages monitor and remove particles from urine to prevent tubule obstruction. *Immunity*. 2024;57 (1):106–123.e7. doi:10.1016/j.immuni.2023.12.003
75. Karasawa K, Asano K, Moriyama S, et al. Vascular-resident CD169-positive monocytes and macrophages control neutrophil accumulation in the kidney with ischemia-reperfusion injury. *J Am Soc Nephrol*. 2015;26(4):896–906. doi:10.1681/asn.2014020195

76. Kim Y-M, Lee K-S, Kim W-M, et al. Hydrochloric acid-treated Bacillus subtilis ghosts induce IL-1 beta, IL-6, and TNF-alpha in murine macrophage. *Mol Cell Toxicol*. 2022;18(2):267–276. doi:10.1007/s13273-022-00221-5
77. Ozkok A, Edelstein CL. Pathophysiology of cisplatin-induced acute kidney injury. *Biomed Res Int*. 2014;2014(1):967826. doi:10.1155/2014/967826
78. Zhou X, Jiang K, Luo H, Wu C, Yu W, Cheng F. Novel lncRNA XLOC_032768 alleviates cisplatin-induced apoptosis and inflammatory response of renal tubular epithelial cells through TNF-α. *Int Immunopharmacol*. 2020;83:106472. doi:10.1016/j.intimp.2020.106472
79. Jang DI, Lee AH, Shin HY, et al. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. *Int J Mol Sci*. 2021;22(5):2719. doi:10.3390/ijms22052719
80. Lyrio RMC, Rocha BRA, Corrêa ALRM, et al. Chemotherapy-induced acute kidney injury: epidemiology, pathophysiology, and therapeutic approaches. *Front Nephrol*. 2024;4:1436896. doi:10.3389/fneph.2024.1436896
81. Faubel S, Lewis EC, Reznikov L, et al. Cisplatin-induced acute renal failure is associated with an increase in the cytokines interleukin (IL)-1beta, IL-18, IL-6, and neutrophil infiltration in the kidney. *J Pharmacol Exp Ther*. 2007;322(1):8–15. doi:10.1124/jpet.107.119792
82. DeWolf SE, Kasimsetty SG, Hawkes AA, Stocks LM, Kurian SM, McKay DB. DAMPs released from injured renal tubular epithelial cells activate innate immune signals in healthy renal tubular epithelial cells. *Transplantation*. 2022;106(8):1589–1599. doi:10.1097/TP.0000000000004038
83. Karmakova T, Sergeeva N, Kanukoev KY, Alekseev BY, Kaprin A. Kidney injury molecule 1 (KIM-1): a multifunctional glycoprotein and biological marker. *Современные технологии в медицине*. 2021;13(3 (eng)):64–78. doi:10.17691/stm2021.13.3.08
84. Tanase DM, Gosav EM, Radu S, et al. The predictive role of the biomarker kidney molecule-1 (KIM-1) in acute kidney injury (AKI) cisplatin-induced nephrotoxicity. *Int J Mol Sci*. 2019;20(20):5238. doi:10.3390/ijms20205238
85. Chen TK, Coca SG, Thiessen-Philbrook HR, et al. Urinary biomarkers of tubular health and risk for kidney function decline or mortality in diabetes. *Am J Nephrol*. 2023;53(11–12):775–785. doi:10.1159/000528918
86. Park I, Kim S, Um YW, et al. Intravital imaging of peritubular microcirculation impairment in cisplatin-induced acute kidney injury. *JCI Insight*. 2025;10(9). doi:10.1172/jci.insight.178689
87. Ganguly A, Chetty S, Primavera R, et al. Time-course analysis of cisplatin induced AKI in preclinical models: implications for testing different sources of MSCs. *J Transl Med*. 2024;22(1):789. doi:10.1186/s12967-024-05439-6
88. Chen H-C, Hou H-Y, Sung J-M, Shieh -C-C. Deletion of NADPH oxidase 2 attenuates cisplatin-induced acute kidney injury through reducing ROS-induced proximal tubular cell injury and inflammation. *Front Med*. 2023;10:1097671. doi:10.3389/fmed.2023.1097671
89. Yuan Y, Yuan L, Yang J, et al. Autophagy-deficient macrophages exacerbate cisplatin-induced mitochondrial dysfunction and kidney injury via miR-195a-5p-SIRT3 axis. *Nat Commun*. 2024;15(1):4383. doi:10.1038/s41467-024-47842-z
90. Sung CYW, Hayase N, Yuen PS, et al. Macrophage depletion protects against cisplatin-induced ototoxicity and nephrotoxicity. *Sci Adv*. 2024;10(30):eadk9878. doi:10.1126/sciadv.adk9878
91. Xu L. The role of myeloid cells in acute kidney injury and kidney repair. *Kidney360*. 2021;2(11):1852–1864. doi:10.34067/KID.0000672021
92. Gong J, Noel S, Hsu J, et al. TCR(+)CD4(-)CD8(-) (double negative) T cells protect from cisplatin-induced renal epithelial cell apoptosis and acute kidney injury. *Am J Physiol Renal Physiol*. 2020;318(6):F1500–f1512. doi:10.1152/ajprenal.00033.2020
93. Sears SM, Sharp CN, Krueger A, et al. C57BL/6 mice require a higher dose of cisplatin to induce renal fibrosis and CCL2 correlates with cisplatin-induced kidney injury. *Am J Physiol Renal Physiol*. 2020;319(4):F674–F685. doi:10.1152/ajprenal.00196.2020
94. Lee H, Keum D, Lee Y, et al. Attenuation effects of CD4+ CD25+ regulatory T cells on cisplatin induced nephrotoxicity in mice (40.24). *J Immunol*. 2009;182(1_Supplement):40.24. doi:10.4049/jimmunol.182.Supp.40.24
95. Cameron AC, McMahon K, Hall M, et al. Comprehensive characterization of the vascular effects of cisplatin-based chemotherapy in patients with testicular cancer. *JACC CardioOncol*. 2020;2(3):443–455. doi:10.1016/j.jaccao.2020.06.004
96. Koh ES, Chung S. Recent update on acute kidney injury-to-chronic kidney disease transition. *Yonsei Med J*. 2024;65(5):247. doi:10.3349/ymj.2023.0306
97. Gales A, Monteiro-Pai S, Hyndman KA. Endothelin system expression in the kidney following cisplatin-induced acute kidney injury in male and female mice. *Can J Physiol Pharmacol*. 2022;100(9):868–879. doi:10.1139/cjpp-2022-0126
98. Katanić Stanković JS, Selaković D, Rosić G. Oxidative damage as a fundament of systemic toxicities induced by cisplatin-the crucial limitation or potential therapeutic target? *Int J Mol Sci*. 2023;24(19):14574. doi:10.3390/ijms241914574
99. Huang R, Fu P, Ma L. Kidney fibrosis: from mechanisms to therapeutic medicines. *Signal Transduct Target Ther*. 2023;8(1):129. doi:10.1038/s41392-023-01379-7
100. Yu JB, Lee DS, Padanilam BJ, Kim J. Repeated administration of cisplatin transforms kidney fibroblasts through G2/M arrest and cellular senescence. *Cells*. 2022;11(21):3472. doi:10.3390/cells11213472
101. Li L, Fu H, Liu Y. The fibrogenic niche in kidney fibrosis: components and mechanisms. *Nat Rev Nephrol*. 2022;18(9):545–557. doi:10.1038/s41581-022-00590-z
102. Rodríguez-Sánchez E, Navarro-García JA, Aceves-Ripoll J, et al. Asociación entre disminución de la función renal y actividad metaloproteinasa-9 en el paciente hipertenso. [Association between renal dysfunction and metalloproteinase (MMP)-9 activity in hypertensive patients]. *Nefrologia*. 2019;39(2):184–191. doi:10.1016/j.nefro.2018.08.009
103. Chen XC, Huang LF, Tang JX, et al. Asiatic acid alleviates cisplatin-induced renal fibrosis in tumor-bearing mice by improving the TFEB-mediated autophagy-lysosome pathway. *Biomed Pharmacother*. 2023;165:115122. doi:10.1016/j.biopha.2023.115122
104. Kim KN, LaRiviere M, Macduffie E, et al. Use of glucocorticoids in patients with cancer: potential benefits, harms, and practical considerations for clinical practice. *Pract Radiation Oncol*. 2023;13(1):28–40. doi:10.1016/j.prro.2022.07.003
105. Motwani SS, Sandhu SK, Kitchlu A. Cisplatin nephrotoxicity: novel insights into mechanisms and preventative strategies. *Semin Nephrol*. 2022;42(6):151341. doi:10.1016/j.semnephrol.2023.151341
106. Okamoto K, Saito Y, Narumi K, Furugen A, Iseki K, Kobayashi M. Comparison of the nephroprotective effects of non-steroidal anti-inflammatory drugs on cisplatin-induced nephrotoxicity in vitro and in vivo. *Eur J Pharmacol*. 2020;884:173339. doi:10.1016/j.ejphar.2020.173339
107. Matsunuma S, Handa S, Kamei D, Yamamoto H, Okuyama K, Kato Y. Oxaliplatin induces prostaglandin E2 release in vascular endothelial cells. *Cancer Chemother Pharmacol*. 2019;84(2):345–350. doi:10.1007/s00280-019-03901-7

108. Ren Y, D'Ambrosio MA, Garvin JL, Wang H, Carretero OA. Prostaglandin E2 mediates connecting tubule glomerular feedback. *Hypertension*. 2013;62(6):1123–1128. doi:10.1161/hypertensionaha.113.02040
109. Tusgaard B, Nørregaard R, Jensen AM, et al. Cisplatin decreases renal cyclooxygenase-2 expression and activity in rats. *Acta Physiol*. 2011;202 (1):79–90. doi:10.1111/j.1748-1716.2011.02257.x
110. Pavitrakar V, Mody R, Ravindran S. Amelioration of cisplatin-induced renal inflammation by recombinant human golimumab in mice. *Curr Pharm Biotechnol*. 2022;23(7):970–977. doi:10.2174/1389201022666210810141139
111. Al-Kuraishy HM, Al-Gareeb AI, Almulaiky YQ, Cruz-Martins N, El-Saber Batiha G. Role of leukotriene pathway and montelukast in pulmonary and extrapulmonary manifestations of Covid-19: the enigmatic entity. *Eur J Pharmacol*. 2021;904:174196. doi:10.1016/j.ejphar.2021.174196
112. Kim J, Long KE, Tang K, Padanilam BJ. Poly(ADP-ribose) polymerase 1 activation is required for cisplatin nephrotoxicity. *Kidney Int*. 2012;82 (2):193–203. doi:10.1038/ki.2012.64
113. Kim J. Poly(ADP-ribose) polymerase activation induces high mobility group box 1 release from proximal tubular cells during cisplatin nephrotoxicity. *Physiol Res*. 2016;65(2):333–340. doi:10.33549/physiolres.932948
114. Noh M, Kannan A, Padanilam BJ. Niraparib, an FDA-approved poly-(ADP-Ribose) polymerase (PARP) inhibitor is renoprotective against cisplatin nephrotoxicity in ovarian tumor-bearing mice: TH-PO1116. *J Am Soc Nephrol*. 2024;35(10S). doi:10.1681/ASN.2024k2n8z778
115. Zhang L, Lu P, Guo X, Liu T, Luo X, Zhu YT. Inhibition of JAK2/STAT3 signaling pathway protects mice from the DDP-induced acute kidney injury in lung cancer. *Inflamm Res*. 2019;68(9):751–760. doi:10.1007/s00011-019-01258-4
116. Mohammad BI, Raheem AK, Hadi NR, Jamil DA, Al-Aubaidy HA. Reno-protective effects of TAK-242 on acute kidney injury in a rat model. *Biochem Biophys Res Commun*. 2018;503(1):304–308. doi:10.1016/j.bbrc.2018.06.020
117. Francescato HD, Costa RS, da Silva CG, Coimbra TM. Treatment with a p38 MAPK inhibitor attenuates cisplatin nephrotoxicity starting after the beginning of renal damage. *Life Sci*. 2009;84(17–18):590–597. doi:10.1016/j.lfs.2009.02.004
118. Yang Z, Ning R, Liu Q, Zang R, Liu S, Sun S. Umbelliferone attenuates cisplatin-induced acute kidney injury by inhibiting oxidative stress and inflammation via NRF2. *Physiol Rep*. 2023;11(23):e15879. doi:10.14814/phy2.15879
119. Xu Z, Zhang M, Zhang X, et al. Dihydromyricetin protects against cisplatin-induced renal injury and mitochondria-mediated apoptosis via the EGFR/HSP27/STAT3 signaling pathway. *Ren Fail*. 2025;47(1):2490202. doi:10.1080/0886022x.2025.2490202
120. Sun HJ, Leng B, Wu ZY, Bian JS. Polysulfide and hydrogen sulfide ameliorate cisplatin-induced nephrotoxicity and renal inflammation through persulfidating STAT3 and IKKβ. *Int J Mol Sci*. 2020;21(20):7805. doi:10.3390/ijms21207805
121. Soranno DE, Rodell CB, Altmann C, et al. Delivery of interleukin-10 via injectable hydrogels improves renal outcomes and reduces systemic inflammation following ischemic acute kidney injury in mice. *Am J Physiol Renal Physiol*. 2016;311(2):F362–72. doi:10.1152/ajprenal.00579.2015
122. Chu Y, Wei M, Cao Z, et al. Integrative analysis based on CRISPR screen identifies apilimod as a potential therapeutic agent for cisplatin-induced acute kidney injury treatment. *Sci China Life Sci*. 2025;68(6):1770–1785. doi:10.1007/s11427-025-2874-8
123. Aydin E, Cebeci A, Lekesizcan A. Prevention of cisplatin-induced nephrotoxicity by kidney-targeted siRNA delivery. *Int J Pharm*. 2022;628:122268. doi:10.1016/j.ijpharm.2022.122268
124. Jin C, Wu P, Wu W, et al. Therapeutic role of hucMSC-sEV-enriched miR-13896 in cisplatin-induced acute kidney injury through M2 macrophage polarization. *Cell Biol Toxicol*. 2025;41(1):50. doi:10.1007/s10565-025-09998-2
125. Zhang R, Zhu Y, Li Y, et al. Human umbilical cord mesenchymal stem cell exosomes alleviate sepsis-associated acute kidney injury via regulating microRNA-146b expression. *Biotechnol Lett*. 2020;42(4):669–679. doi:10.1007/s10529-020-02831-2
126. Wang J, Jia H, Zhang B, et al. HucMSC exosome-transported 14-3-3ζ prevents the injury of cisplatin to HK-2 cells by inducing autophagy in vitro. *Cytotherapy*. 2018;20(1):29–44. doi:10.1016/j.jcyt.2017.08.002
127. Wu P, Tang Y, Jin C, et al. Neutrophil membrane engineered HucMSC sEVs alleviate cisplatin-induced AKI by enhancing cellular uptake and targeting. *J Nanobiotechnol*. 2022;20(1):353. doi:10.1186/s12951-022-01574-8

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