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REVIEW

Application of Nanomaterial-Mediated Ferroptosis Regulation in Kidney Disease

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Abstract: Kidney diseases are a significant global cause of death and disability, resulting from the destruction of kidney structure and function due to an imbalance between the death of renal parenchymal cells and the proliferation or recruitment of maladaptive cells, caused by various pathogenic factors. Currently, therapies and their efficacy for kidney diseases are limited. Ferroptosis is a newly discovered iron-dependent regulated cell death. The imbalance of iron homeostasis and lipid metabolism affects the occurrence and progression of kidney diseases by triggering ferroptosis, which is considered an important target for the development of kidney disease drugs. However, in clinical practice, targeted ferroptosis therapy for kidney diseases faces obstacles such as poor drug solubility, low drug resistance, and imprecise targeting. With the rapid development of nanomaterials in the medical field, new opportunities have emerged for the precise regulation of ferroptosis in the treatment of kidney diseases. This article provides a detailed introduction to the regulatory mechanisms of ferroptosis, the properties of nanomaterials, and their application in the treatment of kidney diseases, with a focus on discussing the mechanisms of action and therapeutic potential of nanomaterials based on ferroptosis regulation in kidney diseases. The aim of this article is to provide new ideas and directions for future kidney disease treatments.

Keywords: nanomaterial, nanomedicine, ferroptosis, kidney disease

Introduction

Kidney disease is widely distributed in the world and seriously endangers human health. More than 850 million people worldwide suffer from chronic kidney disease (CKD), acute kidney injury (AKI) or Renal Cell Carcinoma (RCC).[1] Kidney diseases cause damage in many aspects. They lead to the retention of metabolic wastes, causing discomfort. They disrupt the water-salt balance, inducing edema and high blood pressure. They affect the urinary system and may even develop into renal failure, endangering life. With more than 5 million people dying each year from untreated kidney disease, this grim situation highlights the urgency of advanced prevention and control strategies, and its complex and diverse nature poses great challenges to the academic community.[2]

Ferroptosis, a distinct form of regulated cell death mediated by iron ions and reactive oxygen species (ROS), has gained recognition for its potential role in kidney disease management.[3] This process, characterized by lipid peroxidation, has been the focus of intensive research aimed at unraveling its regulatory mechanisms for therapeutic exploitation. The high metabolic activity of the kidney renders it particularly susceptible to oxidative stress and ferroptosis, positioning it as a promising target for therapeutic intervention.[4] The exploration and development of strategies that modulate ferroptosis hold significant promise for enhancing renal therapy efficacy. Although targeted ferroptosis therapies are promising, clinical translation is hampered by issues of stability, specificity, and effectiveness. The emergence of nanomaterials offers hope that their customizable, versatile and adaptable properties offer unique advantages for the precise regulation of ferroptosis.[5] The integration of nanomedicine approaches with drug delivery systems and combination therapies is expected to significantly advance this field.[6]

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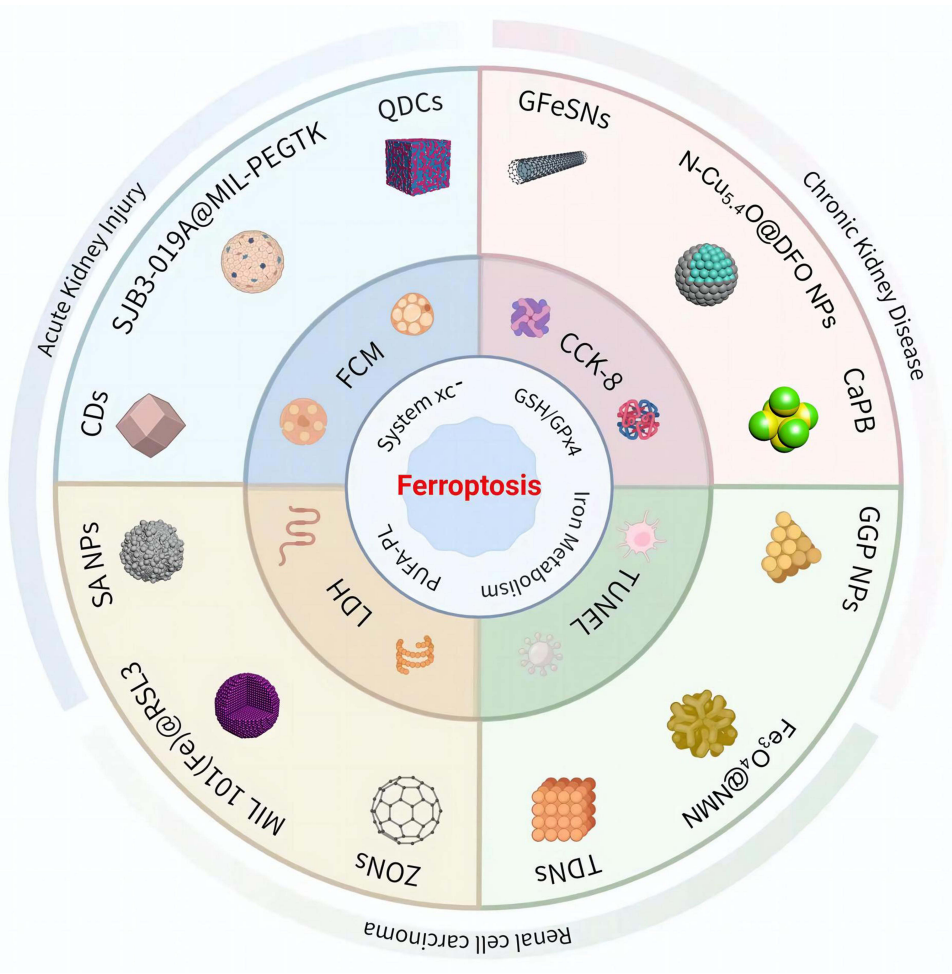
Graphical Abstract



The objective of this review is to explore the potential applications of nanomaterials in the context of ferroptosis and kidney diseases, highlighting the importance of this research in advancing therapeutic strategies. Understanding the interplay between nanomedicine and ferroptosis may lead to innovative treatments that not only target the underlying mechanisms of renal injury but also enhance the delivery and efficacy of therapeutic agents. This review provides an in-depth analysis of the physiological details of ferroptosis and the physicochemical properties of nanomaterials, summarizing the application of nanomaterials in kidney disease imaging and elucidating the role of nanomaterials in regulating ferroptosis in the context of kidney diseases. The significance of this research lies in its potential to improve patient outcomes and reduce the burden of kidney diseases, which are a leading cause of morbidity and mortality worldwide. By harnessing the unique properties of nanomaterials to influence ferroptosis pathways, we may pave the way for more effective and targeted therapies that address the complexities of kidney diseases.

Physiological Characteristics of Ferroptosis

The origin of ferroptosis as a unique iron-dependent and finely regulated cell death paradigm can be traced to the successful identification of RSL (RAS selective lethal) compounds in screening experiments aimed at finding novel cellular responses, since which the unique properties of ferroptosis have been clearly defined. The most significant characteristic of ferroptosis is the influence of inducers on glutathione peroxidase through multiple pathways.[4] These

inducers have the ability of directly or indirectly depleting the antioxidant defense system of cells, and then promote the gradual accumulation of lipid ROS, and eventually inevitably promote the cell to the outcome of oxidative death. From the perspective of morphology, biochemistry and genetics, this form of cell death is significantly different from traditional apoptosis, necrosis and autophagy, showing its unique characteristics and mechanisms.[7] As far as the current level of research is concerned, the regulatory mechanism of ferroptosis is mainly achieved by several specific metabolic pathways, including the cysteine/glutamate transporter (System xc^-), the antioxidant activity of glutathione peroxidase 4 (GPX4), the complex lipid metabolic pathways, and the related mechanisms of iron homeostasis. These elements are interwoven and synergistic, and together shape the unique cell biological phenomenon of ferroptosis.[8]

Ferroptosis Discovery Process

The journey toward understanding ferroptosis began prior to its formal classification, with the identification of eras tin as a compound selectively toxic to RAS-mutated tumor cells during a high-throughput small molecule screen in 2003.[9] Contrary to initial expectations, cells treated with eras tin did not exhibit characteristics of apoptosis.[10] The pivotal moment in the recognition of ferroptosis occurred in 2012, when Dixon et al delineated the unique iron-dependent, non-apoptotic cell death induced by eras tin, thereby solidifying the concept of ferroptosis.[11] Since its initial discovery and subsequent reporting in 2003,[12] ferroptosis has emerged as a critical player in a spectrum of pathophysiological events, including ischemic organ injury, stroke, cardiomyopathy, and neurodegenerative diseases. The functional significance and regulatory intricacies of ferroptosis have piqued the interest of the research community. Despite the ongoing quest to fully elucidate its physiological and pathological roles, the mechanistic understanding of ferroptosis has been progressively uncovered through dedicated research endeavors (Figure 1).

Ferroptosis Regulation Mechanism

The intricate regulation of ferroptosis is mediated through several key biological processes, encompassing the modulation of the System xc^-, the GSH/GPX4 antioxidant mechanism, lipid peroxidation-driven pathways, and iron metabolic pathways (Figure 2). The interplay among these mechanisms is crucial for determining cellular sensitivity to ferroptosis, which in turn has profound implications for overall health.

Regulation Mechanism of Cystine/Glutamate Reverse Transporter (System Xc^-)

System xc^-, a ubiquitous amino acid antiporter in the phospholipid bilayer, is composed of two principal subunits: the light chain SLC7A11 and the heavy chain SLC3A2.[13] This transporter mediates the exchange of cystine and glutamate in a stoichiometric 1:1 ratio, a process integral to the cellular uptake of cystine,[14] within the cell, cystine is metabolized to cysteine, a precursor essential for the synthesis of glutathione (GSH), a paramount endogenous antioxidant.[15] GSH plays a critical role in neutralizing ROS and reactive nitrogen species through the catalytic action of glutathione peroxidases (GPXs). The proper functioning of System xc^- is paramount, as its inhibition can disrupt GSH synthesis by impeding

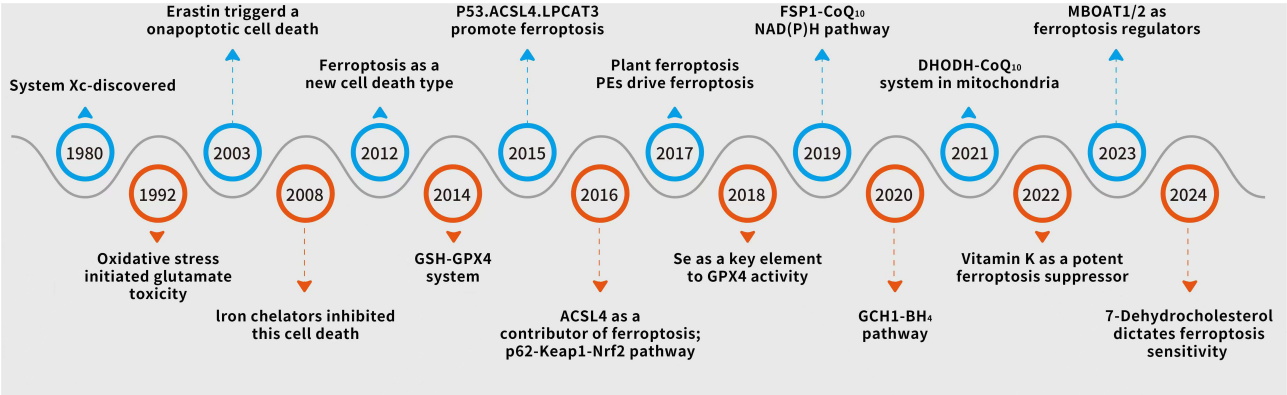


Figure 1 Time history of the development of ferroptosis. Time axis from the initial discovery of System xc^- to its explicit definition as ferroptosis and finally to the discovery and clarification of its mechanism.

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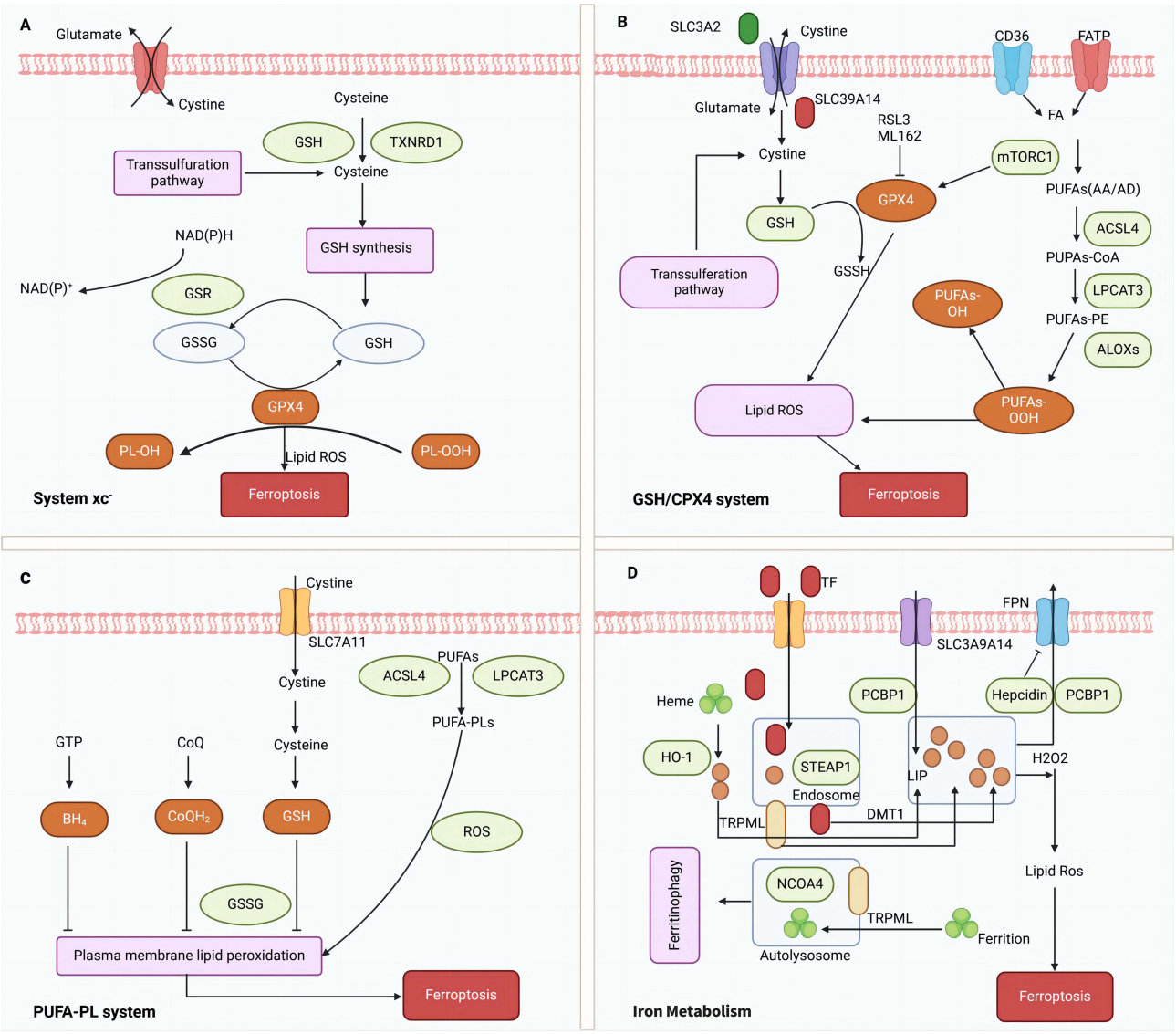

Figure 2 Ferroptosis regulation mechanism. Overview of metabolic pathways that regulate ferroptosis. (**A**) Regulation mechanism of System xc^-. (**B**) Regulation mechanism of GSH and GPX4. (**C**) Lipid metabolic pathways. (PUFA-PL synthesis and peroxidation regulation mechanism) (**D**) Iron metabolism regulation mechanism.

cystine uptake. This disruption can lead to a cascade of events, including diminished GPX activity, a reduction in cellular antioxidant defenses, and an accumulation of lipid ROS, culminating in oxidative damage and the onset of ferroptosis.[16] Furthermore, the tumor suppressor protein p53 can modulate cystine uptake by downregulating SLC7A11 expression, thereby influencing GPX4 activity and the cell's vulnerability to oxidative stress-induced ferroptosis.[17]

Regulation Mechanism of GSH and GPX4

GPX4 assumes a pivotal role as a regulator of ferroptosis, functioning as a central protein in the modulation of this form of cell death. It possesses the capability to break down a spectrum of small molecule peroxides and lipid peroxides, thereby inhibiting the pernicious cascade of lipid peroxidation. GPX4 enzymatic action as an antioxidant is instrumental in catalyzing the reduction of lipid peroxides, thereby indirectly modulating the Fenton reaction and maintaining intracellular hydrogen peroxide (H_2O_2) levels in a balanced state.[18] When cellular H_2O_2 levels rise, the resulting ROS can quickly oxidize fatty acids and arachidonic acid, forming harmful lipotoxic substances. GPX4 counters this oxidative assault by facilitating the conversion of glutathione to its disulfide form (GSSG) and neutralizing cytotoxic lipid hydroperoxides (L-OOH) into their corresponding, less harmful alcohols (L-OH).[19] The interplay between GSH and

its oxidized form, GSSG, is delicately managed by glutathione reductase and $NADPH/H^+$, ensuring the continuous availability of GSH to support GPX4 catalytic function.[20] The expression levels of GPX4 are a critical determinant of cellular susceptibility to ferroptosis; downregulation of GPX4 renders cells more vulnerable to this form of death.[21] Conversely, bolstering GPX4 activity can suppress ferroptosis. GSH contribution to the GPX4 reaction is multifaceted, not only as a reducing agent but also in the regeneration of GSSG back to GSH through the action of glutathione reductase (GR). This underscores the significance of glutathione in preserving GPX4 enzymatic activity and its broader implications in cellular redox homeostasis.

Regulation of Polyunsaturated Fatty Acid-Phospholipid (PUFA-PL) Synthesis and Peroxide Metabolism

Polyunsaturated fatty acids (PUFAs) are recognized as key instigators of lipid peroxidation, a critical process that contributes to the onset of ferroptosis.[22] These fatty acids serve as essential substrates in the synthesis of bioactive lipid mediators, including arachidonic acid (AA) and its derivatives.[23] The integration of free PUFAs into the cellular membrane phospholipids (PL) is facilitated by the enzyme Lys phosphatidylcholine acyltransferase 3 (LPCAT3), which is pivotal for the subsequent peroxidation events,[24] Once incorporated, these PUFA-enriched PLs are subject to catalysis by lipoxygenases (LOX), initiating a cascade of reactions that generate iron-dependent lipid peroxidation, a hallmark of ferroptosis.[25] The enzyme ACSL4 has emerged as a significant biomarker and contributor to ferroptosis, with its expression levels being positively correlated with the sensitivity of cells to this form of death.[26] The role of ACSL4 is further underscored by its requirement in the peroxidation process that occurs subsequent to GPX4 inhibition. Conversely, the loss of LPCAT3 has been shown to confer protection against ferroptosis, albeit to a lesser extent than the deletion of ACSL4, suggesting a nuanced role for LPCAT3 in modulating ferroptosis.[27] The susceptibility of PUFA-containing phosphatidylethanolamines (Pes), particularly those enriched with AA and adrenal acid (AdA), to peroxidation underscores their role in ferroptosis. Excessive lipid peroxidation can profoundly alter the structural integrity of the lipid bilayer, leading to cytotoxicity and, ultimately, the progression to irreversible cell death.

Regulation of Iron Metabolism in Ferroptosis

Iron, with its inherent redox activity, is a crucial catalyst in the generation of ROS, which are produced through both enzymatic and non-enzymatic reactions. This metal plays a pivotal role in the execution of ferroptosis. Typically, extracellular ferric ion(Fe^{3+}) initially complex with transferrin (TFR), subsequently being internalized by cells through the action of the transferrin receptor 1 (TFR1).[28] Within the cell, these ions are often sequestered within ferritin complexes, primarily composed of the ferritin light chain and the ferritin heavy chain 1 (FTH1). The intracellular reduction of Fe^{3+} to the more reactive ferrous ion (Fe^{2+}) is a critical step, with these ions being either utilized within the cell or, in excess, stored within ferritin. Dysregulation of iron metabolism can have profound effects, particularly when there is a reduction in FTH1 expression coupled with an overexpression of TFR1. Such an imbalance can lead to an excessive accumulation of iron, which in turn can trigger a surge in ROS production through the Fenton reaction. This heightened oxidative environment can ultimately precipitate ferroptosis in vulnerable cells.[29]

Detection Techniques for Ferroptosis

The accurate identification of ferroptosis stands as a critical objective for scientific research. To gain a comprehensive understanding of the regulatory mechanisms and the developmental process of ferroptosis, researchers have adopted a suite of detection methods that leverage the unique attributes of this form of cell death.[30] The CCK-8 assay is a standard technique employed to assess cell viability, thereby providing an indirect measure of the surviving cell population in the wake of ferroptosis events. Cytotoxicity, a hallmark indicator of ferroptosis, is quantified through the measurement of lactate dehydrogenase (LDH) released into the culture medium, which serves as a reflection of the extent of ferroptosis progression. Furthermore, the TUNEL assay is utilized to evaluate iron-mediated cell death, offering insights into the DNA damage characteristic of ferroptosis.[31] Complementing these methods, the flow cytometry-based C11-BODIPY fluorescent probe allows for the precise detection and quantification of intracellular ROS and lipid ROS, shedding light on the oxidative stress associated with ferroptosis.[32] To further elucidate the morphological changes that

accompany ferroptosis, transmission electron microscopy is employed, revealing ultrastructural alterations such as cell membrane rupture, vacuolation, and mitochondrial condensation.[33] Employed individually or in tandem, these assays provide a robust framework for monitoring the initiation and advancement of ferroptosis, as illustrated in Figure 3.

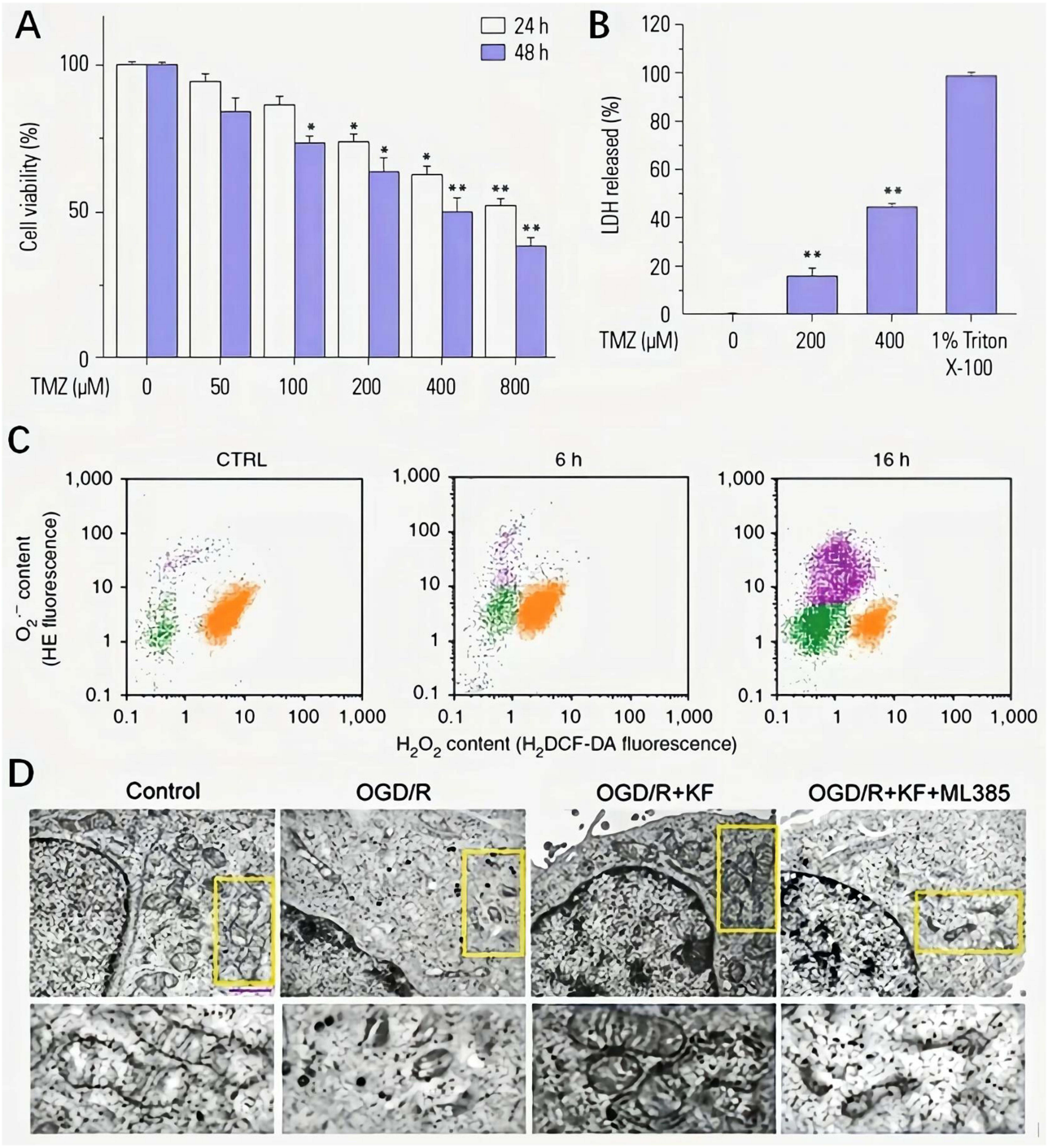

Figure 3 Detection techniques for ferroptosis.(**A**) Cell viability was measured by CCK8, and (**B**) LDH release was measured. **p*<0.05, ***p*<0.01 compared with the control group (*t* test). Adapted from Song Q, Peng S, Sun Z, Heng X, Zhu X. Temozolomide drives ferroptosis via a DMT1-dependent pathway in glioblastoma cells. *Yonsei Med J*. 2021;62(9):843–849. Creative Commons.[31] (**C**) Flow cytometric analysis of ROS and GSH in living cells. Adapted with permission from Cossarizza A, Ferraresi R, Troiano L, et al. Simultaneous analysis of reactive oxygen species and reduced glutathione content in living cells by polychromatic flow cytometry. *Nat Protoc*. 2009;4(12):1790-1797. Copyright ©2009, Springer Nature Limited.[34] (**D**) Mitochondrial morphology associated with ferroptosis was observed under transmission electron microscopy. Effect of kaempferol mitochondrial morphology in OGD/R-treated neurons. Neurons were treated as indicated in Mitochondrial morphology associated with ferroptosis was determined by transmission electron microscopy. The bottom panels display magnified images of the regions indicated by the yellow rectangles in the top panels. Scale bar, 1 μm. Adapted from Yuan Y, Zhai Y, Chen J, Xu X, Wang H. Kaempferol ameliorates oxygen-glucose deprivation/reoxygenation-induced neuronal ferroptosis by activating Nrf2/SLC7A11/GPX4 axis. *Biomolecules*. 2021;11(7):923. Creative Commons.[33]

Modulation of Ferroptosis by Inducers and Inhibitors

Ferroptosis can be triggered through both extrinsic and intrinsic mechanisms. Extrinsically, the process is often initiated by the modulation of transport proteins, notably the inhibition of the amino acid antiporter System xc^-. Intrinsically, it involves the suppression of the expression or functionality of endogenous antioxidant enzymes, such as GPX4. To elucidate the regulatory roles of ferroptosis inducers and inhibitors, we have systematically categorized compounds and drugs that influence ferroptosis into three groups based on their mechanisms of action: (1) those affecting the System xc^-, (2) those targeting GPX4, and (3) those impacting lipid peroxidation pathways (Table 1). This classification facilitates a comprehensive understanding of their potential applications in the modulation of ferroptosis.[35]

Application of Nanomaterials in Kidney Diseases

Overview of Nanomaterials

Nanomaterials, defined as particles with dimensions below 1 micrometer, are engineered from a spectrum of substances including polymers, lipids, and metals.[51] They exhibit a suite of remarkable characteristics: a high surface-area-to-volume ratio, augmented electrical conductivity, superparamagnetic properties, a spectral shift in light absorption, and distinctive fluorescence. These attributes have propelled their integration into medical applications, where they offer innovative solutions for disease diagnosis and treatment. In the medical sector, nanomaterials are categorized into organic and inorganic types, each with distinct properties and potential uses.[52] Organic nanomaterials, synthesized from lipids, proteins, polysaccharides, and functional polymers, are prized for their biocompatibility and biodegradability. They serve as versatile platforms for drug delivery systems and tissue engineering scaffolds.[53] Conversely, inorganic nanomaterials,

Table 1 Inducers and Inhibitors of Ferroptosis

Type	Drug	Target	Mechanism	References
Inducer	Erastin	System xc^-	Obstruct cystine uptake, increase LIP levels	[11]
	Piperazine erastin	System xc^-	Upregulated PTGS2, inhibited by vitamin E	[36]
	Imidazole ketone erastin	System xc^-	Obstruct cystine uptake, deplete glutathione	[37]
	Sulfasalazine	System xc^-	Obstruct cystine uptake, deplete glutathione	[38]
	Sorafenib	System xc^-	Increase ROS production and reduce GPX4 activity.	[39]
	Glutamate	System xc^-	Obstruct cystine uptake, deplete glutathione	[40]
	Altretamine	GPX4	Inhibit GPX4	[41]
	Withaferin A	GPX4	Inhibit GPX4	[42]
	FIN56	GPX4	Inhibit GPX4	[43]
	FINO2(1,2-dioxolane)	Lipid	Inhibit GPX4	[44]
	BAY 11–7085	Lipid	Increased HO-1	[45]
Inhibitor	Cycloheximide	System xc^-	Inhibit System xc^-	[46]
	Beta-mercaptothion	System xc^-	Inhibit System xc^-	[46]
	Dopamine	GPX4	Prevent GPX4 degradation	[47]
	Liproxstatins	Lipid	Inhibit lipid peroxidation	[48]
	Idebenone	Lipid	Target lipid peroxyl radicals	[49]
	Ferrostatins	Lipid	Inhibit lipid peroxidation	[11]
	CoenzymeQ10	Lipid	Inhibit lipid peroxidation	[50]

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predominantly made from mineral or metallic components, are valued for their robust mechanical stability and enhanced biocompatibility. They are capable of eliciting specific biological responses and modulating biological functions, making them ideal for applications such as imaging contrast agents and antimicrobial therapies.[54] The unique biological interactions of inorganic nanomaterials, combined with their inherent ability to maintain biological activity, contribute to their efficacy in targeted therapeutics. The comparative advantage of inorganic nanomaterials over their organic counterparts lies in their superior mechanical stability and higher biocompatibility, which supports their role in achieving precise and effective medical interventions. This distinction underscores the significant research potential of inorganic nanomaterials and their burgeoning application in the medical field.[55]

Renal Physiology

The kidneys are essential for the body's blood filtration and detoxification processes (Figure 4). They operate through the nephron, the cornerstone of renal function, which is responsible for the constant filtration, reabsorption, and secretion of substances. The nephron is a sophisticated assembly that includes the glomerulus, proximal convoluted tubules, medullary loops, distal convoluted tubules, collecting tubules, and peritubular capillaries.[56] The glomerulus, as the kidney's filtration sieve, is a network of capillaries supported by mesangial cells and bordered by Bowman's spaces. Its capillary walls, with their multilayered design, finely tune the blood filtration process. The kidneys not only filter out the body's waste but also are instrumental in preserving the balance of ions and fluids, through the reabsorption of vital components and the elimination of significant waste quantities from the blood.

Filtration of Nanomaterials in the Kidney

The glomerular filtration barrier (GFB) is the sentinel within the glomeruli, positioned strategically between the glomerular capillaries and the Bowman's space, and is essential for the selective filtration of ingested nanomaterials. It is a multilayered structure comprising the glomerular capillary endothelium, the underlying glomerular basement membrane, and the epithelial cells with foot processes.[57] The GFB's filtration mechanism is integral to the kidney's regulatory functions, with nanomaterial size being a key influence on their filtration within the kidney, due to the GFB's size-selective nature.[58] Investigations have determined that the GFB's permeability threshold for nanoparticles is around 8–10 nm, with the majority of particles below this threshold being filtered out.[59] The filtration of larger nanomaterials in the kidney is additionally governed by their shape and form (Figure 5).

Once nanomaterials enter the systemic circulation, they will be filtered by the glomerulus as part of the blood. Current research indicates that though these nanoparticles are small enough for kidney filtration, the charge selectivity of kidney

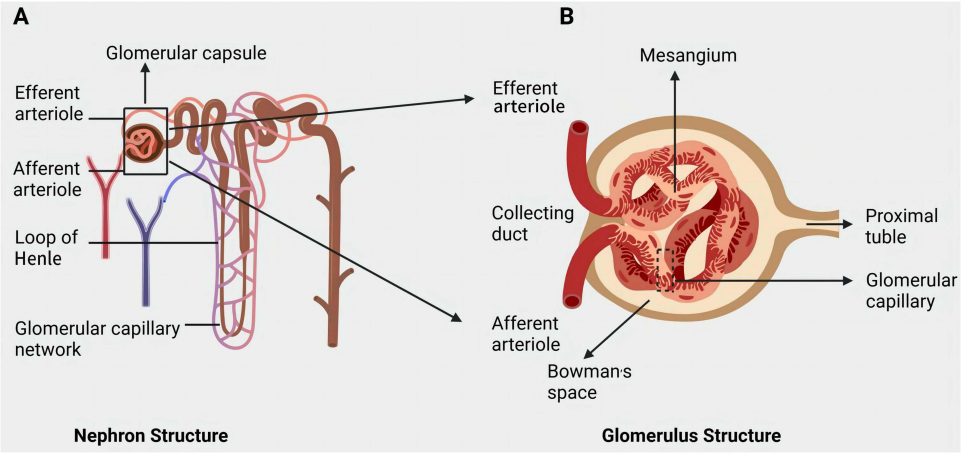

Figure 4 Renal physiology. (**A**) Nephron Structure. (**B**) Glomerulus Structure. The nephron consists of the renal corpuscle and the renal tubule. The renal corpuscle contains the glomerulus (where the afferent arteriole branches into a network of capillaries and then converges into the efferent arteriole. The walls of the capillaries are composed of endothelial cells, basement membrane and podocytes) and the double-layered cup-shaped renal capsule that wraps around the glomerulus. Both of them participate in the formation of the primary urine. The renal tubule is divided into the proximal convoluted tubule, the loop of Henle and the distal convoluted tubule, which are responsible for reabsorption and secretion functions.

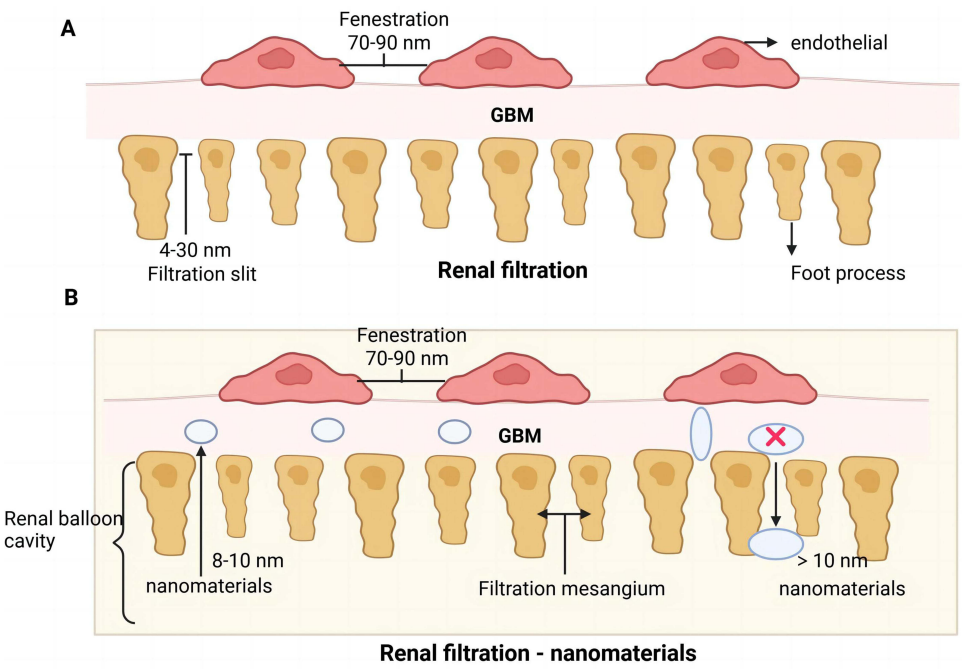

Figure 5 Normal kidney filtration versus nanomaterial filtration in the kidney. (**A**) Normal renal filtration. (**B**) Filtration of nanomaterials in the kidney. Normal renal filtration. Filtration of nanomaterials in the kidney. (Nanomaterials with a diameter of 8–10 nm can be filtered through the glomerulus, and the 10 nm size critical threshold is affected by the overall shape of the nanomaterial and applies to the smallest size dimension).

filtration affects their interaction with differently charged ones.[60] Positively charged nanoparticles are more likely to pass through kidney filtration due to electrostatic repulsion. Moreover, as nanoparticles are made of different materials, their material properties influence kidney accumulation.[61] Research shows that when the material density is low, the kidney targeting ability is low while the kidney clearance rate is high (Table 2), which can be attributed to the density-dependent circulation rate of low-density nanoparticles in the bloodstream.[62]

Application of Nanomaterials in Imaging Examination of Kidney Diseases

Nanomaterials, upon entering the body, are filtered through the glomeruli along with the blood. Current research has discovered that the filtration of nanomaterials in the kidney can be precisely controlled by adjusting their size, shape, and material composition. Understanding the impact of various nanomaterials on the kidney is crucial for enhancing the targeting of kidney diseases and mitigating the potential harm of nanomaterials to the body.[71] The exploration of

Table 2 Filtration of Different Nanomaterials in Kidney

Nanomaterials	Size (nm)	Renal Clearance	References
Silicon nanoparticle	2.4 nm	100% ID	[63]
Gold nanoparticle	3.1 nm	42% ID	[64]
Gold nanoparticle	2–3 nm	75% ID	[65]
Gold nanoparticle	2.4 nm	53% ID	[66]
Gold nanoparticle	2.5 nm	50% ID	[67]
Nanodot	5.6 nm	95% ID	[68]
CdSe/ZnS	4.4 nm	75% ID	[69]
Silica nanoparticle	3.3 nm	98% ID	[70]

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nanomaterials in detecting early kidney pathological changes has emerged as a key area of research. Nanomaterials, as a means of molecular imaging, cover optical imaging, nuclear imaging (with radioisotope imaging), and magnetic resonance imaging (MRI).[72] They facilitate the early diagnosis of kidney diseases by employing tracers to acquire real-time information on renal metabolism,[73] which is vital for detecting early renal damage (Figure 6). Consequently, the study of inorganic nanomaterials with multifunctionality and renal clearance has emerged as a highly promising research direction in nanomedicine.[74]

Optical Imaging

Optical imaging has emerged as a pivotal diagnostic tool in the medical field, particularly for the early detection of kidney diseases.[72] Since 2007, it has been extensively utilized for the tracking of nanoparticles cleared by the kidneys.[65] This modality offers superior spatial-temporal resolution and remarkable sensitivity compared to other imaging techniques such as SPECT, CE-CT, MRI, and ultrasound imaging. It achieves this by leveraging molecular probes to detect subtle variations in biomarker concentrations at the site of disease.[77] Jiaguo Huang et al have made significant strides in this domain by developing a series of molecular renal probes (MRPs) designed for the rapid detection of renal excretory function. These probes are instrumental in the optical imaging of cisplatin-induced AKI. Comprising cyclodextrins for renal clearance, a biomarker response component, and a fluorescent signal component, MRPs offer a multifaceted approach to monitoring the earliest alterations in renal filtration and the onset of kidney damage. Notably, these probes have demonstrated the ability to detect kidney damage 36 hours earlier than conventional medical imaging methods.[75] This advancement signifies the potential of optical imaging strategies in facilitating the early diagnosis of AKI.

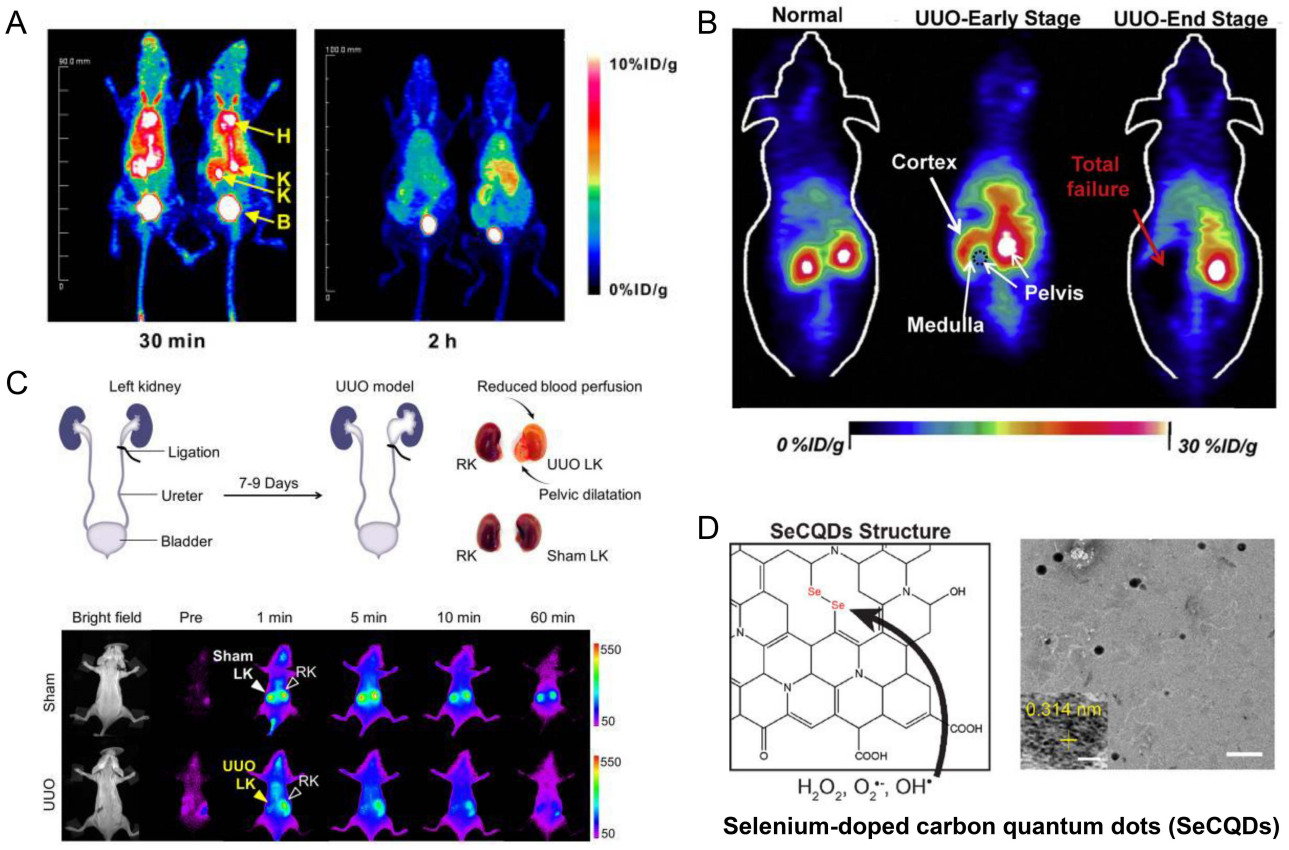

Figure 6 Imaging of nanomaterials in kidney disease.[75,76] (**A** and **B**) PET imaging of POM clusters in healthy mice and mice with early or end stage of UUO. (**C**) Optical imaging of renal insufficiency and renal clearance AuNPs assessed renal function in UUO mouse models by optical imaging. Adapted from Jiang D, Rosenkrans ZT, Ni D, Lin J, Huang P, Cai W. Nanomedicines for renal management: from imaging to treatment. *Acc Chem Res*. 2020;53(9):1869–1880. Copyright @2020, American Chemical Society.[75] (**D**) Specific renal localization of SeCQDs at 40 nm. Adapted from Rosenkrans ZT, Sun T, Jiang D, et al. Selenium-doped carbon quantum dots act as broad-spectrum antioxidants for acute kidney injury management. *Advanced Science*. 2020;7(12):2000420. © 2020 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[76]

Nuclear Imaging

Nuclear imaging, encompassing both Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), harnesses minute quantities of radioactive isotopes for the noninvasive tracking of biological processes.[78] This modality is distinguished from optical imaging by its profound depth of penetration, affording it an extensive array of diagnostic insights and solidifying its prevalence in clinical settings. Unlike rapidly eliminated small radiolabeled molecules, nanomedicine-based tracers exhibit superior renal specificity and imaging efficacy in the evaluation of renal function, A multitude of radiolabeled nanomaterials have thus been repurposed for renal imaging.[79] In a pioneering 2016 study, Lovell, Cai, et al engineered a porphyrin-PEG construct with inherent[80] Cu labeling for the imaging of renal function. The fluorescence imaging of porphyrin suggested systemic AKI subsequent to rhabdomyolysis.[81] Moreover, dynamic PET imaging can discern the delayed excretion indicative of renal impairment, facilitating potential clinical stratification. Subsequent research by Dawei Jiang and associates revealed that by modulating the PEG chain length attached to individual porphyrin molecules, an optimal equilibrium between cardiac circulation and renal clearance could be achieved.[82] This underscores the potential of nanomaterials designed for radiolabeling to synchronize imaging requirements and renal clearance within an appropriate temporal framework.

X-Rays and Magnetic Resonance Imaging (MRI)

X-ray imaging, with its exceptional depth of penetration and spatial resolution, is instrumental in the precise pinpointing of renal damage sites.[83] In a seminal 2018 study, Yu et al revealed the renal clearance capability of gold nanoparticles (AuNPs) using non-invasive X-ray imaging, applicable to both normal and nephrotic kidneys. Through a meticulous quantification of AuNPs' transport dynamics across the renal cortex, medulla, and pelvis, the research uncovered that ureteral obstruction impedes not only the ureteral excretion of nanomaterials but also significantly retards their medullary-to-pelvic transit, concurrently amplifying cellular uptake.[84] Moreover, the study established a precise correlation between the transport dynamics of nanomaterials and the anatomical and pathological features of the kidney, thereby introducing a novel method for non-invasive imaging of renal dysfunction and anatomical-level damage.

MRI, celebrated for its high-resolution anatomical imaging and surpassing the capabilities of traditional CT, has been adeptly utilized by Brown, O'Brien, et al in the development of superparamagnetic iron oxide nanoparticles (SPIONs) for MRI-guided targeted renal drug delivery. SPIONs, composed of a crystalline iron oxide core, a singular oleic acid alkyl chain, and an outer phospholipid monolayer, can be conjugated with a diverse array of biomolecules for MRI targeting. The employment of anti-MHC Class II antibodies (RT1) for renal medullary inflammation imaging underscored the high efficiency of renal targeting.[85] The superior binding affinity of RT1-SPIONs over non-specific SPIONs indicates a pronounced specificity for the renal medulla, highlighting their potential in disease detection and targeted drug delivery.[86]

Application of Nanomaterials to Regulate Ferroptosis in Kidney Disease

In recent years, the involvement of ferroptosis in a myriad of pathological conditions, including cancer and neurodegenerative diseases, has been well-documented.[87] Recognized as a promising therapeutic target, the modulation of ferroptosis presents new opportunities for disease intervention. Globally, CKD afflicts an estimated 850 million individuals with its etiology being multifaceted, involving complex interplays among various key elements and pathways. Notably, cell death-induced renal damage is a significant factor propelling the progression of diverse kidney disorders. The application of nanomaterials in renal medicine has been a subject of extensive research.[88] A detailed review of the potential therapeutic roles of novel nanomaterials in AKI, CKD, and RCC through targeted intervention in ferroptosis has been conducted, highlighting disease-specific strategies (Table 3).

Acute Kidney Injury

Harm and Pathogenic Mechanism of AKI

AKI stands as a significant public health issue, leading to an estimated 1.7 million fatalities globally each year.[80] It not only escalates the duration of hospital stays but also incurs substantial economic burdens. The underlying pathophysiological mechanisms of AKI remain elusive; however, they are predominantly linked to oxidative stress, inflammation,

Table 3 Targeted Regulation of Renal Ferroptosis by Novel Nanomaterials

Type	Nanomaterials	Animal Model	Regulation of Ferroptosis	References
AKI	SA NPs	DDP-induced AKI mouse model	Inhibit glutathione and GPX4	[89]
	TDNs	DDP-induced AKI mouse model	Restore the activity of GPX4	[90]
	QDCs	DDP-induced AKI mouse model	Reduce ROS generation	[91]
	SeCD	DDP-induced AKI mouse model	Reduce ROS generation	[92]
	TMNPs	I/R-induced AKI mouse model	Reduce ROS generation	[93]
	N-$Cu_{5.4}O$@DFO NPs	I/R-induced AKI rat model	Reduce ROS generation	[94]
	GGP NPs	I/R-induced AKI rat model	Inhibit glutathione and GPX4	[95]
	Fe_3O_4@NMN	I/R-induced AKI rat model	Enhance iron ion activity	[96]
	SeNPs	I/R-induced AKI rat model	Inhibit ferritinophagy	[97]
CKD	SJB3-019A@MIL-PEGTK	HD-induced CKD rat model	Reduce oxidative stress	[98]
RCC	ZONs	Tumorigenicity mouse model	Inhibition of GPX4	[99]
	MIL101(Fe)@RSL3	LPO-induced RCC rat model	Increased ROS	[100]

mitochondrial dysfunction, and hypoxia.[101] Clinically, AKI is characterized by a sudden plummet in the glomerular filtration rate (GFR),[102] reflecting the kidney's diminished capacity to filter waste and excess fluids. The etiology of AKI is intricate, encompassing ischemia-reperfusion injury (IRI), sepsis, and the toxic effects of certain drugs,[103] These factors are equally contributory and can inflict varying degrees of physical and psychological harm on patients. Consequently, there is an urgent need for the advancement of preventive and therapeutic strategies to combat AKI.

Application of Nanomaterials to Regulate Ferroptosis in AKI

The application of nanomaterials in the modulation of ferroptosis for AKI presents a burgeoning frontier in nanomedical research. Cisplatin, a widely utilized chemotherapeutic agent, is notorious for its renal toxicity, which is partly attributed to the induction of ferroptosis-a form of cell death governed by iron and lipid peroxidation.[104] Liping Deng et al have ingeniously designed selenium nanoparticles (Se/Albumin NPs, SA NPs) with exceptional antioxidant properties (Figure 7).[89] These nanoparticles have demonstrated the capacity to significantly upregulate anti-ferroptosis proteins GPX4 and FPN1 by modulating ferroptosis-related genes, thereby inhibiting the transferrin and ACSL4 proteins and reversing cisplatin-induced ferroptosis-associated molecular imbalances, as confirmed by PCR experiments.[105] Additionally, Jiaying Li's research has delved into tetrahedral DNA nanostructures (TDNs), showcasing their protective role against cisplatin-induced renal tubular cell death.[106] TDNs have been observed to mitigate lipid ROS production and restore the downregulation of GPX4, thus inhibiting cell death induced by the ferroptosis inducer RSL3. Furthermore, TDNs can reverse the downregulation of GPX4 or diminish the cleavage of poly (ADP-ribose) polymerase (PARP), reducing cisplatin-induced cell death.[107] In a pioneering study, Zhu et al developed a renal avengeable quantum dot-drug conjugate (QDCs), integrating carbon quantum dots (CDs), deferoxamine (DFO), and polyethylene glycol (PEG), specifically for the treatment of chemotherapy-induced AKI.[108] The QDCs's CDs component endows DFO with a high renal targeting ability, effectively reducing unstable iron in the kidney and thereby blocking the source of ROS production. Concurrently, it exerts robust antioxidant activity to clear ROS and prevent oxidative kidney damage.[91] Similarly, Jiahuan Li and his team developed a new type of selenium nanomaterial, polyacrylic acid-coated selenium-doped carbon dots (SeCD), which has high biocompatibility. It can accumulate specifically in the kidney. SeCD can effectively clear broad-spectrum ROS and significantly promote GPX4 expression through the release of selenium, thus significantly alleviating ferroptosis and cisplatin-related AKI in renal tubular epithelial cells without affecting the efficacy

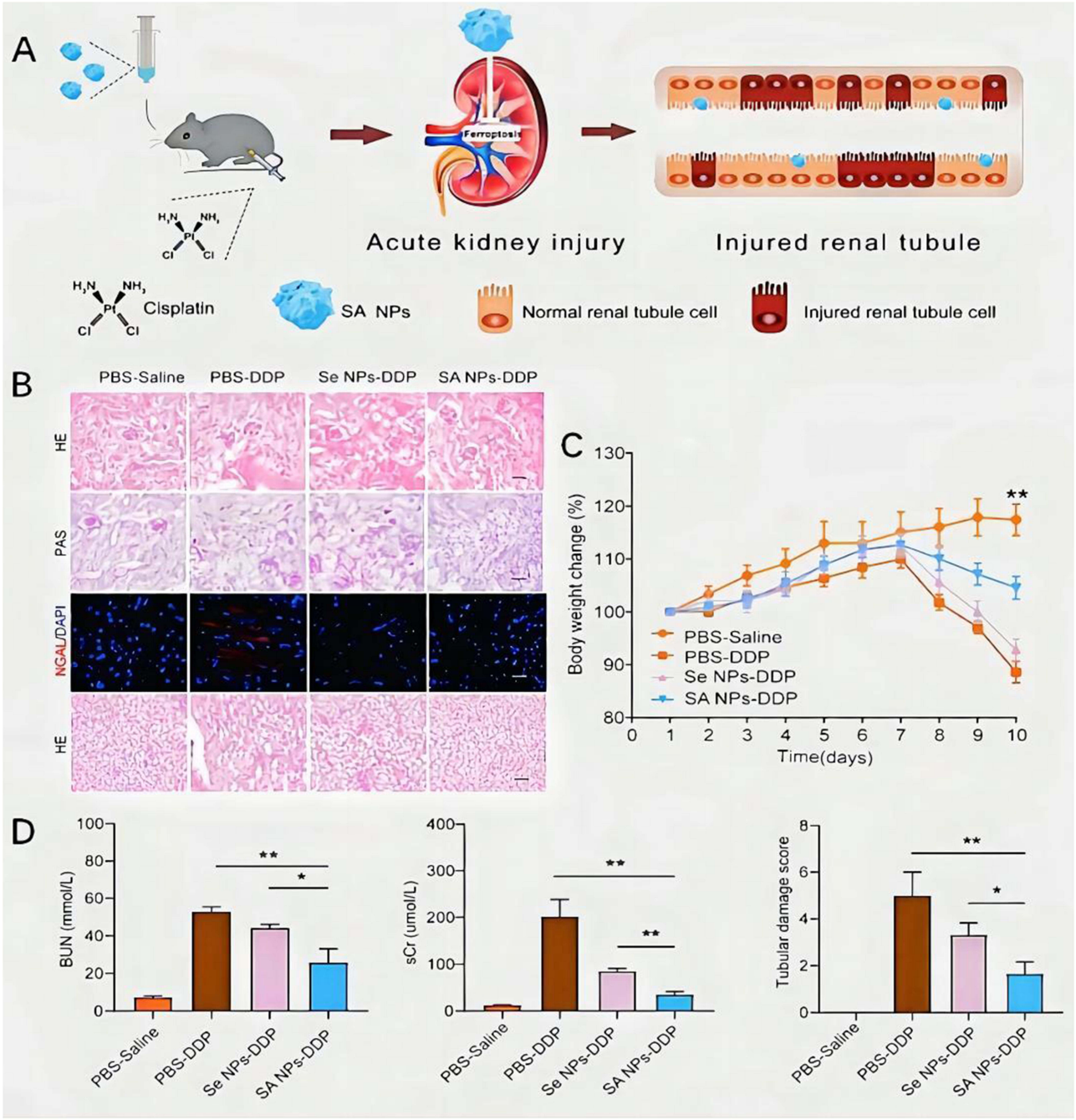

Figure 7 SA NPs improves DP-AKI. (**A**) AKI models and diagrams showing the administration patterns and details of each group of mice. (**B**) histopathological analysis. (**C**) Weight change after medication. (**D**) SCR and BUN concentrations. Scale bar: 100 μm (n = 6; *$p < 0.05$; and **$p < 0.01$). Adapted with permission from Deng L, Xiao M, Wu A, et al. Se/albumin nanoparticles for inhibition of ferroptosis in tubular epithelial cells during acute kidney injury. *ACS Appl Nano Mater.* 2022;5(1):227–236. Copyright ©2022, American Chemical Society.[89]

of cisplatin chemotherapy. This study highlights a new and promising treatment approach for clinical prevention of AKI in cancer patients receiving cisplatin chemotherapy.[92]

The pathological analysis of AKI indicates that ROS can initiate oxidative stress and inflammation, inflicting damage on lipids, nucleic acids, and proteins, which are intimately linked to the onset of AKI.[109] Excessive ROS accumulation in the kidney can lead to cellular oxidative stress damage and exacerbate kidney disease.[110] Hence, the effective clearance of ROS may be pivotal in the prevention and treatment of AKI. Zhuobin Xu synthesized mackinawite nanomesas (GFeSNs) from GSH and Fe^{3+}, employing them as ROS scavengers for ROS-associated AKI treatment. GFeSNs have exhibited a broad-spectrum ROS

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scavenging capability through the synergistic action of multiple enzyme-like activities and polysulfide release properties. Both in vitro and in vivo experiments have demonstrated that even very low doses of GFeSNs provide a significant cytoprotective effect on ROS-induced kidney injury, markedly enhancing the therapeutic efficacy of AKI.[111] Therefore, GFeSNs hold immense potential in the treatment of and other ROS-related diseases, attributed to their high biocompatibility and potent reactive oxygen scavenging capabilities.[112] Cellular redox balance is intricately maintained by a suite of endogenous antioxidant systems, including superoxide dismutase (SOD), catalase (CAT), and GPx.[113] Jiawei Liu and team have explored the catalytic prowess of a GPx-mimetic nanas, utilizing selenium-free carbon dots (CDs) that exhibit robust GPx-like activity in vitro. The phenolic moieties on these CDs demonstrate a significantly lower bond dissociation energy compared to the selenocysteine in natural GPx, favoring peroxide formation and initiating a GPx-like reaction. Their renal targeting and intracellular antioxidant capabilities are instrumental in mitigating cisplatin-induced AKI in vivo by curbing oxidative stress-driven ferroptosis.[114] This work paves the way for the development of efficient, metal-free carbon-based nanomaterials to combat ROS-related pathologies. In a parallel advancement, Keyi Wang et al have engineered an ultra-small nanoparticle, $KCa(H_2O)_2[Fe^{III}(CN)_6]\cdot H_2O$, known as CaPB nanas, a multi-enzyme analog designed to effectively scavenge ROS and further inhibit ferroptosis, In vitro studies have established CaPB's comprehensive cytoprotective effects, particularly its proficiency in inhibiting iron-mediated oxidation and modulating inflammatory responses. In vivo studies reveal that CaPB nanas rapidly accumulates in the kidney, exhibiting high renal clearance and biocompatibility. Notably, the CaPB nanas not only ameliorates renal function and diminishes renal tubular damage but also exhibits anti-apoptotic, cell-proliferative, and antioxidant properties. Furthermore, CaPB nanas acts as a potent inhibitor of ferroptosis, significantly upregulating the expression of the ferroptosis regulator GPX4 and alleviating ferroptosis effects.[115] The CaPB nanomesas, with their exceptional ROS scavenging, advanced iron inhibition, and biocompatibility, emerge as a unique antioxidant modality for the amelioration of AKI and other oxidative stress-induced conditions[116.] Xin Wang's team constructed a novel self-assembled peptide nanoparticle with specific p38 inhibitory activity that connects the functional domain of p38, mitogen-activated protein kinase 3b (MKK3b), to the cell-penetrating TAT sequence. Finally, TAT-MKK3b nanoparticles (TMNPs) were self-assembled by tyrosinase oxidation.[93] The findings suggest that multifunctional TMNPs, with its ability to target kidneys, ROS clearance and alleviate iron poisoning, may be a promising therapeutic agent for the treatment of AKI and its progression to CKD.

Ischemia-reperfusion (I/R) injury, another principal etiology of AKI, is characterized by perturbed energy metabolism, tubular necrosis, inflammation, oxidative stress, and progressive renal dysfunction.[117] Recent findings underscore the pivotal role of ferroptosis in I/R-induced AKI. To address this, Chenguang Ding has reported the development of Cup-based nanoparticles (N-$Cu_{5.4}O$@DFO NPs) coated with a neutrophil cell membrane for targeted I/R kidney injury intervention. These nanoparticles, with their ultra-small size, extensive ROS scavenging capacity, and high biocompatibility, enhance drug solubility and circulation time in the bloodstream, effectively modulating cell death events,[118] Encapsulation within neutrophil cell membranes endows these nanoparticles with the ability to inhibit oxidative damage and neutralize pro-inflammatory cytokines, significantly amassing in inflamed kidneys to attenuate oxidative and inflammatory responses, culminating in synergistic renal I/R injury treatment.[94] Additionally, Xie and team have synthesized gallate-gallium polyvinyl pyrrolidone nanoparticles (GGP NPs), which, as potential iron scavengers with excellent biocompatibility in renal epithelial cells, inhibit ferroptosis pathways by reducing intracellular free iron and mitochondrial dysfunction, thereby significantly ameliorate renal injury induced by I/R.[119] Building on the unique properties of Fe_3O_4 nanoparticles for magnetic resonance imaging enhancement and surface chemistry, Rui Xue Duan et al have designed the Fe_3O_4@NMN nanomagnet, leveraging the ultra-small Fe_3O_4 nanoparticles as carriers for the NAD^+ precursor nicotinamide mononucleotide (NMN). This design, capitalizing on the structural similarity between NMN and nicotinamide riboside upon phosphate group attachment to the Fe_3O_4 nanoparticle, facilitates the delivery of the NAD^+ precursor to kidney cells via nicotinamide riboside kinase 1 on the cell membrane.[95] Subsequently, the research team led by Rui Xue Duan harnessed the superior magnetic resonance imaging (MRI) enhancement capabilities and distinctive surface chemistry of Fe_3O_4 nanoparticles to develop a novel nanocarrier for the NAD^+ precursor, nicotinamide mononucleotide (NMN). The innovative Fe_3O_4@NMN nanomagnet was crafted for targeted delivery of NMN to kidneys affected by IRI, offering a promising therapeutic approach. A key feature of this design is the attachment of NMN to the Fe_3O_4 nanoparticle surface via its phosphate group, which structurally resembles nicotinamide riboside. This resemblance facilitates the transport of the NAD^+ precursor into kidney cells via the nicotinamide riboside

kinase 1 (NRK1) enzyme located on the cell membrane.[96] The study demonstrated that the Fe_3O_4@NMN nanomagnet not only repaired the damaged renal structure and restored renal filtration function but also effectively reversed AKI caused by I/R.[120] Zhen ying Zuo, found that SeNPs also protected C57BL/6 mice from I/R-induced inflammation and iron sinking. Technologically, lysosomal iron accumulation and ferroptosis are associated with over-activation of NCOA4-mediated ferritin autophagy, which is alleviated by SeNPs by upregulating X-box-binding protein 1 (XBP1).[97] Down-regulation of XBP1 promoted the autophagy of ferritin and partially offset the protective effect of SeNPs on ferroptosis inhibition. Overall, Zhen ying Zuo's findings reveal a novel role for SeNPs in regulating ferritin phagocytosis, thereby improving lysosome function and alleviating ferroptosis of inhibit ferritinophagy in I/R-AKI.[97]

Chronic Kidney Disease

Harm and Pathogenic Mechanism of Chronic Kidney Disease

CKD, characterized by persistent alterations in renal function and/or morphology, has emerged as a pivotal issue of global health concern. In 2016, CKD was identified as the 13th leading cause of mortality on a global scale, and it is anticipated to escalate to the fifth most common cause of death attributable to kidney-related disorders by 2040.[121] The condition is marked by a gradual and relentless deterioration of renal capacity, compounded by diminished renal regenerative potential, which precipitates microvascular injury, metabolic disturbances, oxidative stress, and inflammatory responses, culminating in renal fibrosis.[122]

Application of Nanomaterials to Regulate Ferroptosis in Chronic Kidney Disease

Hypertensive nephropathy, a prevalent etiology of CKD, has been increasingly linked to the influence of Angiotensin II (Ang II) in its pathogenesis.[123] Studies indicate that elevated levels of Ang II can trigger podocyte damage, thereby accelerating the progression of CKD, Furthermore, Ang II is implicated in exacerbating renal pathology by elevating the lipid peroxidation indicator malondialdehyde (MDA) and diminishing the antioxidant enzyme glutathione peroxidase (GSH-Px), thereby triggering ROS and an oxidative stress cascade.[69] Building upon these findings, Fang Yi Hao's research group developed an Ang II–induced renal cell model and utilized quantitative RT-PCR and Western blot to analyze the impact of Ang II on the expression of ubiquitin-specific peptidase1 (USP1) in human kidney (HK-2) cells (Figure 8).[98] Their findings suggest that modulating USP1 expression can counteract the oxidative stress and ferroptosis induced by Ang II, with USP1 overexpression intensifying these effects. To optimize the therapeutic potential of USP1 inhibition,[124] the USP1 inhibitor SJB3-019A was encapsulated within MIL-100 and PEGTK to form the novel nanocomposite SJB3-019A@MIL-PEGTK. This nanomaterial was shown to effectively mitigate Ang II–induced oxidative stress and ferroptosis by targeting USP1. The study confirms that the SJB3-019A@MIL-PEGTK nanoparticles possess significant potential in alleviating hypertension-induced renal cell ferroptosis, offering a promising avenue for the treatment of kidney diseases.

Renal Cell Carcinoma

Harm and Pathogenic Mechanism of RCC

RCC is a common urinary system malignancy, causes hematuria, low back pain, and abdominal masses. In advanced stages, it metastasizes, severely threatening life. Its complex pathogenesis involves gene mutations, epigenetic changes, and abnormal cell signaling pathway activation, which prompt renal cell abnormal proliferation, angiogenesis, and immune surveillance escape, thus advancing the tumor.

Application of Nanomaterials to Regulate Ferroptosis in Renal Cell Carcinoma

The burgeoning research in recent years has progressively unveiled the influential role of ferroptosis in the progression of RCC, highlighting its potential as an emergent therapeutic target. Notably, the Hippo signaling effector, TAZ, has been identified as a pivotal regulator of ferroptosis in RCC.[125] Despite these insights, the detailed regulatory mechanisms underpinning RCC progression are not yet fully elucidated. Zinc oxide nanoparticles (ZONs) represent a class of nanomaterials that have demonstrated clinical utility in homing in on a spectrum of cancer cell types and cancer stem cells.[126] A study led by Xing yuan Wang has substantiated the significant role of ZONs in the induction of ferroptosis in RCC cells through the modulation of the miR-27a-3p/YAP axis (Figure 9).[99] Findings indicate that ZONs suppress the

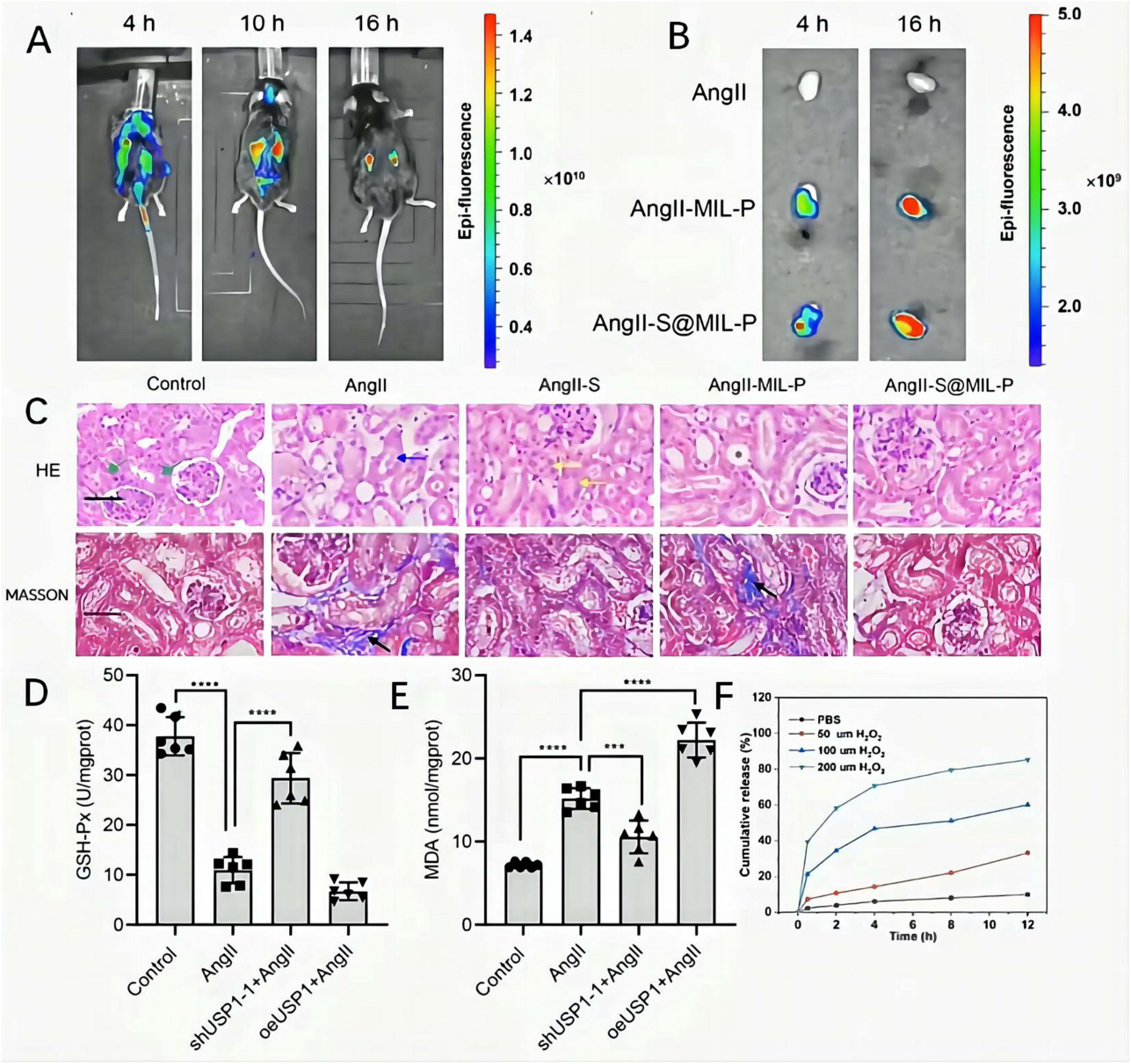

Figure 8 S@MIL-P alleviates hypertensive nephropathy in vivo. (**A** and **B**) Representative fluorescence imaging (red) at 4, 10, and 16 h after intravenous injection of 5 mg/kg S@MIL-P. In vitro fluorescence images of mouse kidney treated with Ang II at different time points. (**C**) Images of HE and Masson staining sections of mice kidney (scale bars, 50 μm). HE staining identifies normal proximal tubules with narrow and irregular lumen, unclear cell boundary, and presence of brush border structure (green arrow) and abnormal proximal tubules with tubular dilatation, atrophy (yellow arrow), and loss of brush border integrity (blue arrow). The black arrows indicate Masson-positive area. (**D**) GSH-Px and MDA (**E**) levels in mice. (**F**) Effects of different concentrations of H_2O_2 on the release of SJB3-019A at S@MIL-P in vitro. ***p <0.001, ****p < 0.0001. Adapted from *Eur J Pharmaceut Biopharmaceut*. Volume 193, Hao F, Li Y, Zhang Y, et al. Inhibition of USP1 ameliorates hypertensive nephropathy through regulating oxidative stress and ferroptosis: a precise treatment via SJB3-019A nanodelivery. 187–197, Copyright © 2023, with permission from Elsevier B.V. All rights reserved.[98]

expression of er GPX4 and solute carrier family 7 member 11 (SLC7A11), leading to an enhancement in ROS aggregation and a rise in intracellular iron levels within RCC cells. Erastian, recognized as an activator of ferroptosis, curtails the viability of RCC cells, an effect that is further intensified by ZONs. Additionally, ZONs have been observed to impede RCC cell invasion, migration, and in vitro survival. The yes-associated protein (YAP), a key effector within the Hippo signaling pathway, has been shown to foster the transcription of genes that stimulate growth and concurrently suppress those involved in apoptosis,[127] The microRNA miR-27a is known to directly target YAP1 expression. ZONs were found to downregulate YAP expression by upregulating miR-27a-3p. Interestingly, the overexpression of YAP and the inhibition of miR-27a-3p have been demonstrated to counteract the inhibitory effects of ZONs on RCC cell survival

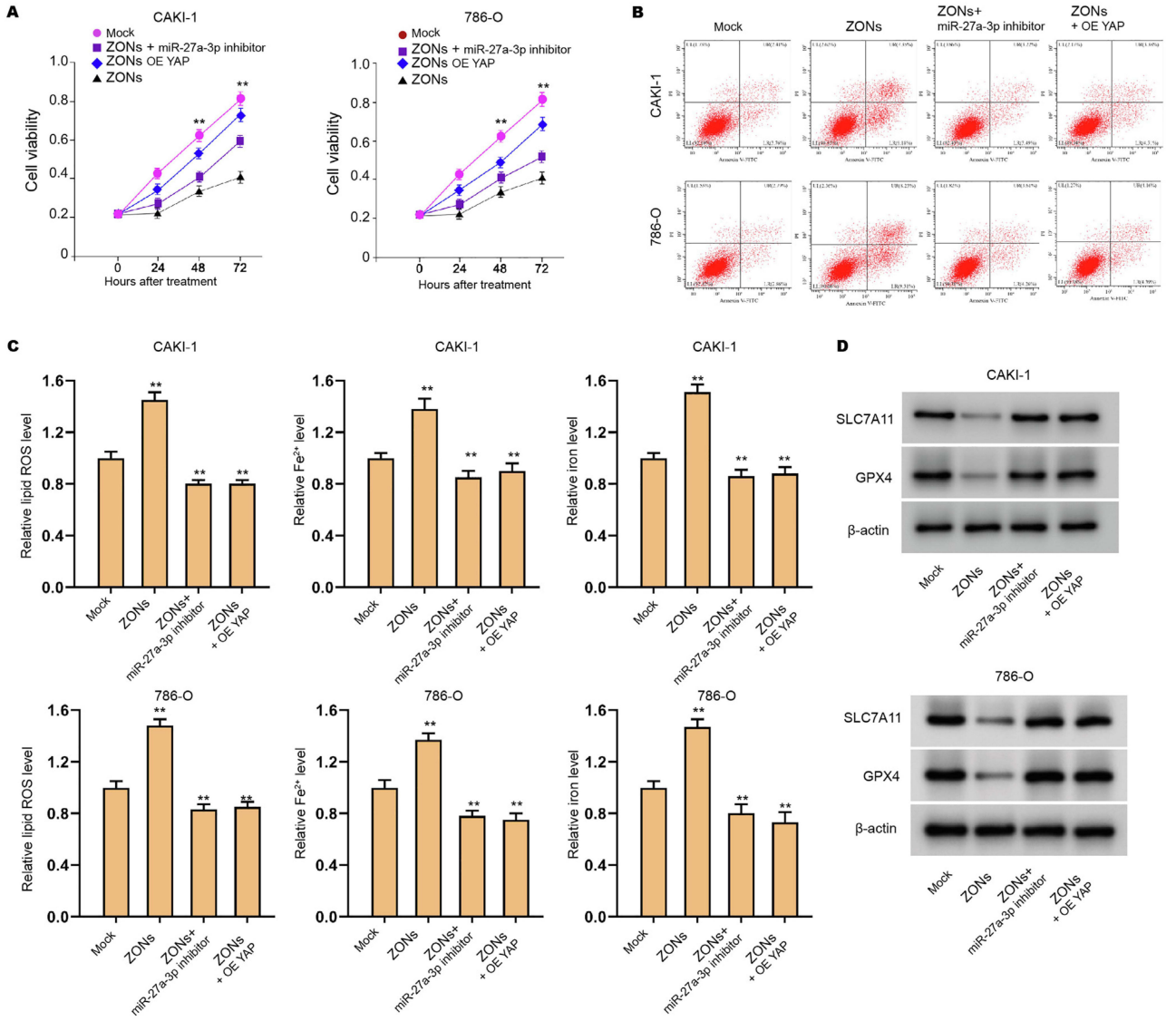

Figure 9 Zinc oxide nanoparticles promote ferroptosis and inhibit cancer cell survival by targeting the miR-27a-3p/YAP axis in renal cell carcinoma. (**A-C**) The CAKI-1 and 786-O cells were treated with ZONs, or co-treated with miR-27a-3p inhibitor or YAP overexpressing plasmids. The MTT assay (**A**) and Flow cytometry analysis (**B**) were carried out. The ROS analysis and iron/Fe^{2+} analysis (**C**) were conducted. (**D**) Western blot analysis of GPX4 and SLC7A11. N =3, mean ± SD: ** p<0.01.Reprinted from *Arab J Chem*. Volume 15(6), Wang X, Li D, Xia Z, et al. Zinc oxide nanoparticles promotes ferroptosis to repress cancer cell survival and inhibits invasion and migration by targeting miR-27a-3p/YAP axis in renal cell carcinoma. 103753, Copyright © 2022, with permission from Elsevier.[99]

in vitro.[128] Clear cell renal cell carcinoma (ccRCC) accounts for more than 75% of RCC cases,[129] The pathological changes of ccRCC mainly lie in the occurrence of ferroptosis, which is characterized by the accumulation of iron-dependent ROS and lipid peroxides (LPO) leading to cell death.[130] However, ccRCC has the characteristics of relatively hidden development and easy transfer,[129] Usually not sensitive to cytotoxic chemotherapy.[131] The study found that the rich PUFAs content in advanced ccRCC was sensitive to the treatment of ferroptosis. In response to this report, Wenjun Ni et al used MIL-101(Fe) nanoparticles to load RSL3 and form a new ferroptosis agonist (MIL101(Fe)@RSL3). MIL-101(Fe) released RSL3 and Fe^{3+} in the acidic tumor environment and degraded them. Fe^{3+}, as a degradation product, can be reduced to Fe^{2+} by reducing molecules such as iron reductase in cells, resulting in "iron overload".[132] In cancer cells, Fe^{2+} catalyzes self-non-toxic H_2O_2 to produce highly active •OH through Fenton reaction, attacking PUFAs to produce L-OOH, resulting in ferroptosis. Secondly, RSL3 further induces L-OOH distortion accumulation through GPX4, which aggravates the occurrence of ferroptosis. Subsequently, Fe^{2+} continues to catalyze L-OOH to produce the highly reactive

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lipid alkoxy radical (L-O•), which aggravates cell death based on iron poisoning.[100] In the treatment of disease occurrence, MIL-101(Fe)@RSL3 is therefore expected to have new potential for clear cell renal carcinoma.

Conclusion

The high incidence and refractory nature of kidney diseases have long plagued human life. Since 2012, significant progress has been made in exploring the therapeutic potential of ferroptosis in the treatment of kidney diseases. However, in clinical applications, drugs based on the regulation of ferroptosis are hindered by issues such as low drug resistance and inaccurate targeting, affecting their efficacy. Nanomaterials have been developed to address the occurrence and development of kidney diseases.[58] Due to their unique physical and chemical properties, nanomaterials can achieve more efficient targeted delivery and imaging within living organisms. Nanoparticles can penetrate the biological barriers of the kidney, enter kidney cells, and bind to specific targets, thereby enabling early detection and monitoring of kidney diseases. Nanomaterials, with their designability, multifunctionality, and precise targeting, have a significant advantage in the nanoscale regulation of ferroptosis. They can affect the occurrence of ferroptosis by precisely targeting and regulating the release of iron ions, thereby influencing intracellular iron homeostasis. This characteristic provides new ideas for the treatment of kidney diseases, especially in pathological states such as chronic kidney disease and acute kidney injury, where iron overload often exacerbates cellular damage. Through the application of nanomaterials, the toxicity of iron can be effectively reduced, and the survival rate of kidney cells can be improved.

However, there are still limitations to the research. First, the accuracy of the activation and drug release of kidney-targeting nanomaterials is crucial, and their sensitivity and synthesis need further clarification. Second, nanomaterials have complex interactions, and ensuring their biocompatibility with the human body is essential, requiring appropriate solutions. Lastly, there has been insufficient research on the treatment of kidney diseases with nanomaterials targeting ferroptosis, especially the potential safety risks of long-term application of nanomaterials.[133]

Prospects

With ongoing in-depth research into ferroptosis and nanomaterials, there is hope to overcome the existing challenges in the diagnosis and treatment of kidney diseases. However, several key issues deserve attention in future research. First, developing nanomaterials that can selectively target renal cells while minimizing off-target effects remains a significant challenge. Strategies to enhance the specificity and bioavailability of these nanocarriers will be crucial. Second, a deeper investigation into the precise molecular mechanisms by which nanomaterials affect ferroptosis, especially in renal cells, is needed. Understanding these mechanisms will aid in the design of more effective nanocarriers that can selectively target renal tissue to regulate ferroptosis. In addition, advancements in nanomaterial-based ferroptosis imaging techniques and biomarker identification will enhance our ability to monitor treatment responses in real-time, thereby allowing for the improvement of treatment strategies based on the needs of individual patients with kidney diseases. Lastly, large-scale clinical trials are essential for assessing the safety and efficacy of nanomaterial therapies in humans. In summary, the intersection of nanomaterials and ferroptosis regulation offers an exciting frontier for the treatment of kidney diseases. Based on current research and the accumulation of experience, along with improved design, nanomaterials that regulate ferroptosis are poised to shine in the field of kidney treatment, bringing revolutionary changes and new hope for the prevention, diagnosis, and treatment of kidney diseases.

Data Sharing Statement

Data will be made available on request.

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Disclosure

No potential conflict of interest was reported by the authors.

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