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Ferroptosis and Tubular Injury: Molecular Drivers of Renal Damage, Maladaptive Repair, and Disease Progression.

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ABSTRACT

Ferroptosis has been shown to be a significant regulated cell death mechanism that associates renal tubular injury with maladaptive repair and progressive renal dysfunction. This review will discuss the molecular mechanism of ferroptosis in tubular epithelial cells and the role of ferroptosis in both acute and chronic renal damage. Collectively, iron dysregulation, lipid peroxidation, depletion of glutathione, impairment of GPX4, ferroptinophagy, and disruption of NRF2 signaling all contribute to the susceptibility of the tubules to ferroptotic injury. On-going ferroptotic stress can disrupt epithelial regeneration, induce cell cycle arrest, further enhance inflammatory and profibrotic signals, and lead to tubulointerstitial fibrosis. These mechanisms link acute kidney injury, inadequate tubular recovery, the transition from acute to chronic kidney disease, diabetic kidney disease, and the loss of nephrons. Therapeutics based on iron homeostasis, lipid peroxidation, GSH–GPX4 axis, and other alternative antioxidant pathways hold promise for the prevention of renal damage associated with ferroptosis. There is a need for validated ferroptosis-specific biomarkers, better patient stratification, clinically representative models, and well-defined therapeutic windows to translate insights into mechanisms into effective renal intervention in the future.

Keywords: Ferroptosis, Kidney disease, Lipid peroxidation, Maladaptive repair, Tubular injury

1. Introduction

Pathological mechanism of renal tubular injury is the key in the onset and development of various renal diseases. The tubular epithelial cells are performing crucial roles in reabsorbing solutes, regulating electrolytes, maintaining metabolic homeostasis and maintaining the renal microenvironment, but they have a very high energy requirement and are very vulnerable to ischemic, toxic, inflammatory, and metabolic insults. If tubular damage is severe or persistent, it can result in disruption of the integrity of the epithelium, function of the nephrons and trigger responses that go beyond the damage itself. The tubular necrosis and loss of nephrons are important factors in determining both acute functional impairment and subsequent structural decline of the kidney [1]. The mechanisms are executed in a complex pathophysiological setting that is heterogeneous, including vascular dysfunction, inflammation, mitochondrial dysfunction, oxidative stress, and various types of regulated forms of cell death in acute kidney injury (AKI).

Despite high regenerative capacity of renal tubular epithelial cells, complete recovery, when injured, is not always achieved [2,3]. Healed cells can proliferate and promote restoration of tubular structure while persistent cellular stress can direct this response towards maladaptive repair. Maladaptation is defined by incomplete epithelial recovery, persistent inflammatory signaling, cell-cycle changes, microvascular dysfunction and fibrogenic pathway activation. These processes give a mechanism for the transition from an acute insult to chronic structural damage [4]. Thus the AKI-to-CKD spectrum is now considered a dynamic biological process rather than a static CKD. Injured tubules may be repaired successfully or may become fibrotic and chronically dysfunctional, depending on the molecular changes that occur during this repair process [5].

Ferroptosis has garnered significant attention as a regulated cell death process linked with iron metabolism, oxidative stress and membrane lipid damage, and is one of the mechanisms of tubular injury regulated pathways. Unlike other mechanisms of cell death such as apoptosis, the hallmark features of ferroptosis are the accumulation of phospholipid peroxides and a lack of cell antioxidant defenses, which is dependent on iron. It is of special biological significance in the kidney, where renal tubular cells are subject to significant metabolic and oxidative stress. Ferroptosis may also be connected with a network of cellular damage that includes apoptosis, pyroptosis, and cuproptosis [6]. This overall concept is significant in understanding why single inhibition of death mechanism

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may not be sufficient to maintain tubular viability.

Ferroptosis is regulated by a molecular machine that offers several entry points to tubular fate. Iron overload due to disturbed intracellular iron handling can lead to an increase in the availability of redox-active iron, and oxidation of polyunsaturated phospholipids can cause damaging effects to the membranes. Meanwhile, low levels of glutathione or dysfunction of the protective enzyme, glutathione peroxidase 4, reduce one of the defenses against lipid peroxidation. Mitochondrial dysfunction may also exacerbate oxidative stress and affect tubular metabolic adaptation in AKI [7]. Importantly, ferroptotic activity may achieve beyond the acute phase of cell loss. Recent studies strongly suggest that cells that escape ferroptosis may change their phenotype, affecting the subsequent tissue repair, inflammatory and remodeling responses, and that ferroptosis is associated with the biological quality of renal recovery [8].

This association is especially important in the progression from AKI to CKD. Recurrent or un-resolved ferroptotic stress may sustain tubular dysfunction, enhance inflammatory and profibrotic signaling and exacerbate the interstitial fibrosis and nephron loss. Ferroptosis is thus a potential molecular link between acute epithelial injury and chronic renal injury [8,9]. Injury to the tubules is not just a feature of AKI. Continued metabolic stress, oxidative imbalance, mitochondrial abnormalities, inflammation, and tubular epithelial dysfunction play significant roles in driving progressive renal damage in DKD [10]. These observations expand the relevance of ferroptosis beyond an acute injury mechanism to a potential shared contributor to the progression of kidney disease.

Despite recent progress, there are still several questions to answer about the exact role ferroptosis plays in the different stages of renal injury. The significance of tubular ferroptosis can differ depending on severity of the injury, tubular segments, disease setting, and time course. In addition, Ferroptosis and other cell death mechanisms and stress responses can co-occur, making it difficult to distinguish Ferroptosis from the other cell-death and stress-induced mechanisms. Molecular endotypes and injury phases can be identified by biomarkers, which may aid in mechanistic interpretation and precise timing of therapeutic interventions [11]. Combination of mechanistic studies with biomarkers and clinically relevant models is therefore required to define the role of ferroptosis as a causal driver, as a part of the broader cellular stress or as a therapeutically actionable pathway. The development of biomarkers is also important to learn how acute injury progresses to chronic disease and to identify patients who are at higher risk for suboptimal recovery [12].

Therefore, this review will focus on ferroptosis as a mechanistical connection between tubular epithelial injury, maladaptive repair and progressive renal dysfunction. Special attention is given to molecular regulators of ferroptotic susceptibility, their role in acute and chronic tubular injury, and importance in potential therapeutics. The objectives of this study are as follows:

1. To characterize the molecular mechanisms governing ferroptosis and susceptibility of renal tubular epithelial cells to injury
2. To examine how ferroptotic tubular damage contributes to maladaptive repair, fibrosis, and kidney disease progression
3. To evaluate ferroptosis-targeted therapeutic strategies, translational barriers, biomarkers, and priorities for future renal research

2. Molecular Framework of Ferroptosis

2.1 Defining Features of Ferroptotic Cell Death

Ferroptosis is a type of regulated cell death, defined by iron-dependent lipid peroxidation and progressive loss of membrane integrity. It is not primarily mediated by caspase activation or classical apoptotic morphology as in apoptosis. Molecular phenotype is characterized by an imbalance between oxidative lipid damage and cellular antioxidant capacity, particularly in phospholipid membranes [13]. Ferroptosis has become an increasingly significant process in the kidney, as tubular epithelial cells are very vulnerable to oxidative and metabolic stress. Ferroptosis is a critical therapeutic target of acute and chronic kidney injury because of its unique biochemical features.

2.2 Iron Homeostasis and Labile Iron Accumulation

Iron homeostasis is a major factor determining susceptibility to ferroptosis as excess intracellular ferrous iron promotes the generation of highly reactive free radicals. Changes in iron uptake, storage, utilization and export can increase the labile iron pool, thus increasing oxidative stress in tubular epithelial cells [14]. Under pathological conditions, the degradation of ferritin can release stored iron and enhance ferroptotic signaling. Disturbance of these regulatory mechanisms in kidney diseases promotes lipid oxidation and cellular injury. Therefore, iron availability modulation and restoration of intracellular iron homeostasis may be potential strategies to limit ferroptosis-associated renal damage.

2.3 Lipid Peroxidation and Membrane Oxidative Damage

Lipid peroxidation is the main execution mechanism of ferroptosis . Polyunsaturated fatty acids in membrane phospholipids are particularly prone to oxidation, leading to the formation of lipid hydroperoxides that progressively damage membrane structure and function. Oxidative membrane injury becomes irreversible and leads to ferroptotic death when their formation exceeds the detoxification capacity of the cell [15]. Excessive accumulation of lipid hydroperoxides in renal tubular epithelial cells may also modulate signaling pathways involved in tissue remodeling. The reduction of TGF-β/Smad signaling and the mitigation of renal interstitial fibrosis are linked to the inhibition of tubular ferroptosis and lipid hydroperoxides.

2.4 System Xc^{-}–GSH–GPX4 Defense Axis

The System Xc^{-}–GSH–GPX4 axis is a central antioxidant pathway that protects cells from ferroptosis. System Xc^- imports cystine in exchange for intracellular glutamate, and provides cysteine required for glutathione synthesis. Reduced glutathione is then an important cofactor for glutathione peroxidase 4 (GPX4), which reduces damaging phospholipid hydroperoxides to less reactive lipid alcohols. Any disruption at this level of the pathway diminishes antioxidant protection and promotes ferroptotic injury [16]. Thus, preservation or pharmacological enhancement of this defense network

has been recognized as an important approach to reduce ferroptosis-associated tubular damage in kidney diseases.

2.5 GPX4-Independent Ferroptosis Defense Mechanisms

GPX4 is not the only protein mediating resistance to ferroptosis, because other antioxidant systems are also able to limit lipid peroxidation and preserve cell viability. Other important GPX4-independent mechanisms include ferroptosis suppressor protein 1-mediated reduction of coenzyme Q and other metabolic pathways that maintain the antioxidant capacity of the membrane. These parallel defenses offer additional protection when the canonical GSH-GPX4 system is compromised and could lead to differences in the ferroptotic susceptibility of renal cells. The knowledge of these compensatory mechanisms is relevant to renal injury, where oxidative stress and repair responses often co-exist and determine whether tubular epithelial cells recover or suffer a progressive damage [17] (Table 1) (Figure 1).

Table 1. Core Molecular Components of Ferroptosis

Component	Primary role	Ferroptotic consequence	Reference
Labile Fe^{2+}	Drives iron-dependent oxidation	Promotes oxidative damage	[13]
PUFA-phospholipids	Oxidizable membrane substrates	Promote lipid peroxidation	[14]
System Xc^-	Supports cystine uptake	Maintains GSH synthesis	[15]
GSH	Antioxidant cofactor	Restrains lipid oxidation	[15]
GPX4	Detoxifies lipid hydroperoxides	Suppresses ferroptosis	[16]
GPX4-independent defenses	Alternative antioxidant protection	Increase ferroptosis resistance	[17]

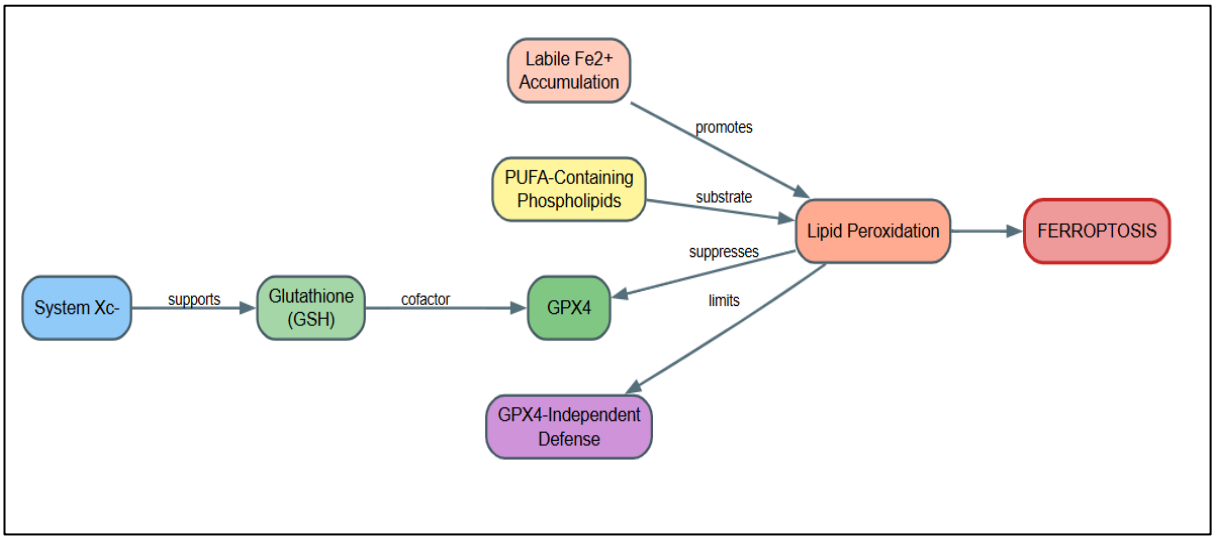

Figure 1. Core molecular framework of ferroptosis showing iron accumulation, lipid peroxidation, and major antioxidant defense systems

3. Renal Tubular Susceptibility to Ferroptosis

3.1 Metabolic Characteristics of Renal Tubular Epithelial Cells

Renal tubular epithelial cells are metabolically active because active solute transport and reabsorption require continuous energy production. The high density of mitochondria and oxygen consumption support these functions but also make them more vulnerable to metabolic and oxidative disturbances [18]. Disturbance of cellular energetics in acute kidney injury may impair tubular transport, modify metabolic adaptation and induce epithelial cell damage. Injured tubular cells may then develop maladaptive phenotypes that contribute toward persistent renal dysfunction or undergo adaptive recovery . Such metabolic features generate a cellular niche that is particularly susceptible to ferroptotic stress.

3.2 Tubular Iron Handling and Oxidative Burden

Renal tubular cells actively participate in iron handling by uptake associated with filtration, intracellular storage, recycling and transport processes. Disruption of this balance may increase intracellular redox-active iron leading to reactive oxygen species generation and oxidative injury [19]. Excess oxidative burden leads to lipid peroxidation and impairment of cell antioxidant defenses, creating a permissive environment for ferroptosis. Chronic generation of reactive oxygen species can also activate inflammatory and fibrogenic pathways that perpetuate tubular damage beyond the initial insult. Thus, the dysregulation of iron-dependent oxidative stress may serve as a link between acute epithelial injury, progressive fibrosis and chronic kidney dysfunction.

3.3 Mitochondrial Dysfunction and Redox Imbalance

Mitochondria are critical for tubular energy metabolism and redox regulation, and mitochondrial dysfunction is an important contributor to susceptibility to ferroptosis. Cellular injury can inhibit mitochondrial respiration and ATP production, and increase the generation of reactive oxygen species, leading to an intracellular oxidative stress environment. Damage to lipids and membranes can be exacerbated when the antioxidant systems are not able to neutralize these reactive intermediates sufficiently

[20]. Such redox imbalance also interacts with regulated cell death pathways involved in renal fibrosis. Thus, mitochondrial and oxidative disturbances may continuously promote tubular injury and contribute to pathological remodeling during the progression of kidney disease.

3.4 Segment-Specific Vulnerability of the Renal Tubule

The sensitivity of tubular segments to ferroptotic injury differs depending on the transport activity, metabolic demand and mitochondrial dependence and exposure to injurious substances of epithelial populations. Such metabolically active tubular areas may be under greater oxidative pressure if oxygen delivery or cellular energetics are compromised. Thus, segmental disparities may determine the degree and impact of ferroptotic damage in acute and chronic renal injury. Furthermore, ferroptosis may crosstalk with other regulated death processes including necroptosis that may accelerate epithelial loss and inflammatory responses in susceptible tubular compartments, and promote disease progression [21,22] (Table 2) (Figure 2).

Table 2. Factors Determining Renal Tubular Susceptibility to Ferroptosis

Susceptibility factor	Tubular alteration	Ferroptotic implication	Reference
High metabolic demand	Increased energy requirement	Greater stress sensitivity	[18]
Iron dysregulation	Increased redox-active iron	Promotes lipid oxidation	[18]
ROS accumulation	Increased oxidative burden	Enhances membrane damage	[19]
Mitochondrial dysfunction	Impaired ATP/redox regulation	Increases cellular vulnerability	[20]
Segmental heterogeneity	Variable metabolic characteristics	Differential injury susceptibility	[21]
Death-pathway crosstalk	Ferroptosis–necroptosis interaction	Amplifies tubular injury	[22]

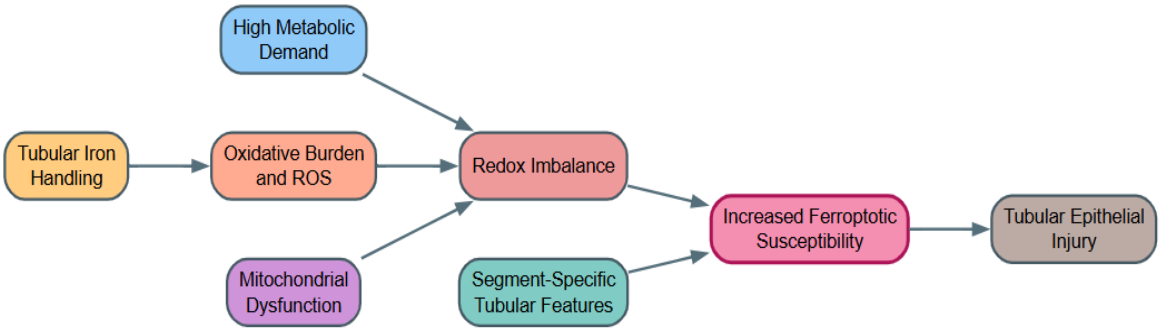

Figure 2. Major determinants of renal tubular susceptibility to ferroptosis

4. Molecular Drivers of Ferroptosis-Mediated Tubular Injury

The iron metabolic and lipid oxidation defects, the antioxidant defense, and the cellular stress response are interconnected and contribute to ferroptosis-mediated tubular injury. Iron overload and disturbed iron homeostasis widen the labile intracellular pool of iron which promotes the production of iron dependent Reactive Oxygen Species (ROS) and promote the environment for oxidative membrane injury. Excess or inadequate iron uptake, storage, use, or release from renal tubular epithelial cells (RTEC) can, therefore, increase ferroptotic susceptibility.Increased or decreased iron uptake, storage, usage or release from renal tubular epithelial cells (RTEC) can, therefore, increase ferroptotic susceptibility. Another important mechanism is lipid remodeling, which is mediated by ACSL4 and allows the incorporation of PUFAs into membrane phospholipids, providing substrates for lipid peroxidation. The sulfonic acid in phospho-lipid hydro-peroxides gradually damages the integrity of membranes and promotes tubular cell death and renal fibrotic responses [23]. The depletion of glutathione and the dysfunction of GPX4 also promote ferroptotic susceptibility. In GPX4-mediated detoxification of lipid hydroperoxides, reduced glutathione is essential, and its disruption allows for unchecked lipid oxidation, worsening tubular damage. Changes in the stability of proteins or regulatory pathways can also affect the antioxidant and cell-death responses in the kidney during injury [24]. Ferritinophagy regulated by NCOA4 is an important link between intracellular iron storage and ferroptosis. When ferritinophagy is excessive, it can lead to a rise in the amount of iron available for the redox reactions in the cell, potentially contributing to the amplification of lipid peroxidation.Excessive ferritinophagy can result in the release of stored iron from ferritin, which can contribute to an increase in the amount of iron available for redox reactions in the cell, potentially leading to the amplification of lipid peroxidation. In contrast, the antioxidant control by NRF2 represents a protective counter balance acting through the coordination of genes related to glutathione metabolism, iron handling and oxidative defense. The failure of these protective mechanisms may lead to sustaining oxidative damage and promote the molecular shift from acute kidney damage to chronic renal damage [25]. Ferroptosis also is not the only pathway affected by

inflammation and other cellular stress pathways. Inflammatory conditions can exacerbate redox and iron homeostasis, whereas lipid peroxidation, oxidative metabolites and injured tubular cells can amplify inflammatory signaling. An additional layer is added by mitochondrial dysfunction that hampers energy production, disrupts metabolic adaptation and raises oxidative stress in tubular cells [26, 27] These mechanisms contribute to a vicious cycle of tubular iron accumulation, ACSL4-mediated lipid remodeling, reduced activity of GSH–GPX4, ferritinophagy, vulnerable NRF2 protection, and inflammatory-metabolic stress, which are responsible for tubular ferroptotic injury and progression toward chronic renal damage (Table 3) (Figure 3).

Table 3. Core Molecular Regulators of Ferroptosis in Renal Tubular Injury

Molecular factor	Main function	Effect on tubular ferroptosis	Reference
Labile Fe^{2+}	Promotes oxidative reactions	Increases lipid oxidation	[23]
ACSL4	Remodels PUFA-containing phospholipids	Increases ferroptotic sensitivity	[24]
GSH	Supports antioxidant defense	Depletion promotes ferroptosis	[25]
GPX4	Detoxifies lipid hydroperoxides	Suppresses ferroptosis	[26]
NCOA4	Mediates ferritinophagy	Increases available intracellular iron	[26]
NRF2	Regulates antioxidant responses	Restrains ferroptotic stress	[27]

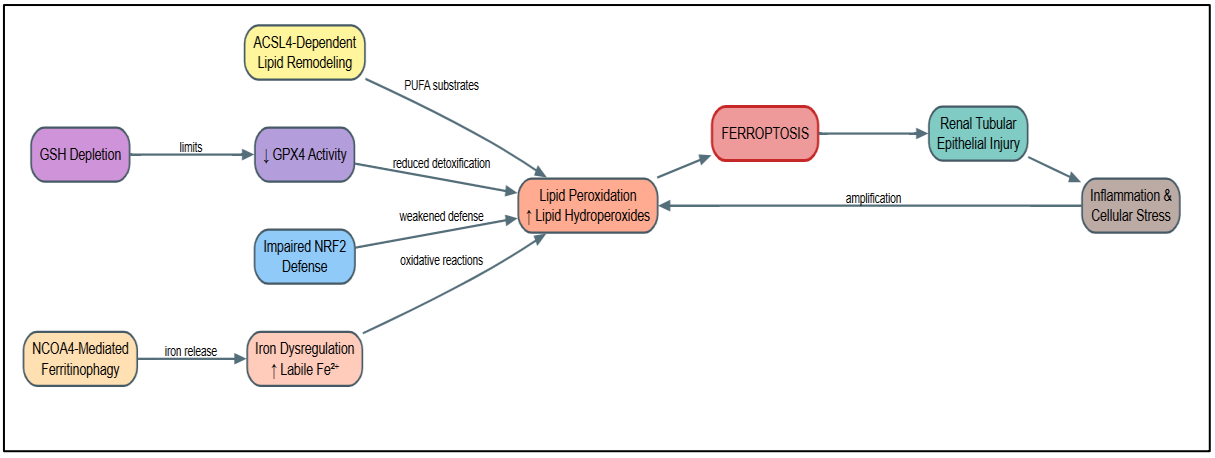

Figure 3. Molecular Mechanism of Ferroptosis-Mediated Renal Tubular Injury

5. Ferroptosis in Acute Tubular Injury

Ferroptosis is now recognized as a key player in acute tubular injuries, such as those seen in ischemic conditions, nephrotoxic agents, and acute systemic inflammation. Ischemia reperfusion injury results in substantial oxidative stress, mitochondrial disturbances, iron dysregulation, and lipid peroxidation in tubular epithelial cells. These events can trigger ferroptotic and other regulated necrotic pathways, exacerbating epithelial damage and local inflammatory processes in acute kidney injury (AKI) [28]. The mechanisms of injury in tubular damage due to drugs and nephrotoxins also involve stress pathways that affect mitochondrial function, antioxidant defense, and membrane stability. Ferroptosis can occur alongside other regulated pathways of cell death, such as apoptosis, necroptosis, and other forms, suggesting that tubular damage is likely a consequence of multiple pathways, not single ones [29]. This idea has been further elaborated, and other mechanisms of cell death, such as those mediated by metals and metabolism, have been identified to intersect with oxidative stress and mitochondrial dysfunction in kidney diseases [30]. The combination of systemic inflammation, microcirculatory abnormalities, oxidative stress and metabolic reprogramming associated with sepsis-associated acute kidney injury makes it a very special and complex setting to which tubular damage is subjected. Ferroptosis is involved in a network of cell death that is tightly coupled and can amplify epithelial damage and weaken renal repair [31]. Iron poisoning tubular injury effects are more than epithelial cell kill. Long-lasting injury may interfere with tubular reabsorption, disrupt the integrity of the epithelial barrier, induce inflammatory signaling, and interfere with proper tissue regeneration. How much and how long these changes occur will dictate the nature of whether renal function returns to baseline or progresses towards incomplete recovery. Severe acute injury can lead to surviving tubular cells that initiate maladaptive repair pathways with persistent activation of stress signaling pathways and abnormal regeneration responses, which establishes a mechanistic link between acute injury and subsequent chronic injury. Experimental targeting of molecular pathways that mediate maladaptive tubular repair has shown promise of reducing AKI to CKD progression, highlighting the importance of events after the initial cell-death phase on long-term renal outcomes [32] Therefore, ferroptosis in AKI should be viewed as part of a spectrum that includes acute tubular cell death, renal functional impairment, and progressive renal functional loss (Table 4) (Figure 4).

Table 4. Ferroptosis in Major Forms of Acute Tubular Injury

AKI context	Major mechanism	Tubular consequence	Reference
Ischemia–reperfusion	Oxidative and regulated necrotic injury	Tubular epithelial loss	[28]
Nephrotoxic injury	Oxidative stress and antioxidant failure	Tubular cell death	[29]
Sepsis-associated AKI	Integrated cell-death signaling	Tubular dysfunction	[30]
Metal-dependent stress	Metabolic and redox disruption	Regulated cell death	[31]
Persistent tubular injury	Incomplete cellular recovery	Maladaptive repair	[32]

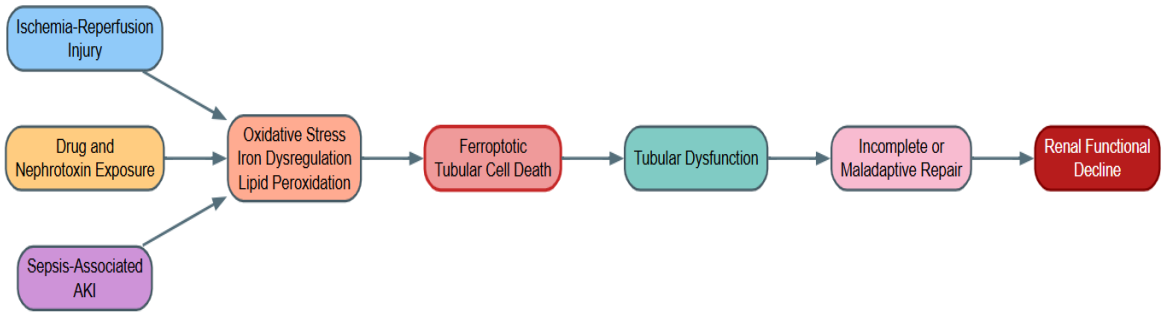

Figure 4. Major acute kidney injury contexts that converge on ferroptotic tubular damage and impaired renal function

6. Ferroptosis and Maladaptive Tubular Repair

6.1 Tubular Regeneration Following Acute Injury

Surviving tubular epithelial cells after acute kidney injury initiate coordinated repair responses to restore epithelial integrity and nephron function. These responses include cellular dedifferentiation, proliferation, migration, and subsequent redifferentiation to replace damaged epithelial populations. Extent of injury, preservation of viable tubular cells, and proper regulation of local signaling pathways determine successful regeneration. If these mechanisms work well, tubular architecture can recover substantially [33]. However, severe or repetitive injury may compromise regenerative programs and skew tissue responses toward maladaptive repair and progressive kidney dysfunction.

6.2 Persistent Ferroptotic Stress and Failed Tubular Recovery

Continued ferroptotic stress may compromise tubular recovery by perpetuating iron-dependent oxidative injury and lipid peroxidation following the initial renal insult. Persistent imbalance between pro-ferroptotic signals and antioxidant defenses limits epithelial survival and may not permit the full recovery of tubular structure and function [34]. Oxidative injury, inflammation and progressive loss of functional renal cells in chronic kidney disease have been associated with ferroptosis. Thus, unresolved ferroptotic stress may convert potentially reversible tubular injury to irreversible dysfunction, providing a basis for chronic kidney injury.

6.3 Cell-Cycle Arrest and Maladaptive Tubular Phenotypes

Tubular epithelial cells that survive severe injury may fail to complete normal regenerative programs and acquire maladaptive phenotypes. Prolonged cellular stress can lead to cell-cycle arrest, altered secretory activity, incomplete epithelial differentiation, and impair successful tubular repair. Hypoxic signaling is of special interest because hypoxia affects metabolic adaptation, cell survival, inflammation, and repair following acute kidney injury [35]. Dysregulated hypoxia-inducible signaling may thus create an environment where incomplete epithelial recovery and maladaptive cellular states are maintained, predisposing to subsequent fibrotic remodeling and chronic kidney dysfunction.

6.4 Inflammatory and Profibrotic Signaling During Maladaptive Repair

Maladaptive tubular repair is associated with ongoing communication between injured epithelial cells, inflammatory cells, fibroblasts, and other components of the renal microenvironment. Ongoing injury to tubular cells can release cytokines, chemokines, growth factors and profibrotic mediators that perpetuate inflammation and stimulate extracellular matrix production. These responses gradually transform repair from regeneration to pathological remodeling. Identification of the molecular signals distinguishing adaptive from maladaptive recovery is thus important for therapeutic development [36]. Mechanistic characterization of injury and repair pathways may reveal points of intervention that can preserve tubular recovery and prevent chronic fibrotic progression.

6.5 Ferroptosis-Associated Tubulointerstitial Fibrosis

Ferroptosis may contribute to promoting tubulointerstitial fibrosis through persistent epithelial injury, oxidative stress, inflammation, and profibrotic signaling in the renal interstitium. Repeated ferroptotic damage results in loss of viable tubular populations and creates molecular conditions that activate fibroblasts and promote extracellular matrix deposition. This association raises the possibility that ferroptosis might mechanistically contribute to ongoing tubular injury and renal scarring [37]. The progression of fibrosis leads to structural distortion and nephron loss and impairs renal recovery, thereby cementing the transition from acute injury to chronic kidney disease and narrowing the window for effective therapeutic intervention [38] (Table 5).

Table 5. Ferroptosis in Maladaptive Tubular Repair

Repair stage/process	Major alteration	Pathological consequence	Reference
Tubular regeneration	Epithelial proliferation and redifferentiation	Functional recovery	[33]
Persistent ferroptosis	Continued oxidative lipid damage	Failed recovery	[34]
Hypoxic stress	Altered cellular adaptation	Maladaptive phenotype	[35]
Persistent inflammation	Cytokine/profibrotic signaling	Pathological remodeling	[36]
Fibroblast activation	Increased matrix production	Interstitial fibrosis	[37]
Progressive fibrosis	Structural remodeling	AKI-to-CKD progression	[38]

7. Ferroptosis in Kidney Disease Progression

It is becoming clear that ferroptosis is involved in the progression of structural and functional damage in kidney disease and is linked with recurrent tubular injury. Tubular epithelial damage may persist following the acute phase of AKI-to-CKD, as a direct consequence of incomplete resolution of iron dysregulation, lipid peroxidation, mitochondrial injury and oxidative stress. The sustained mitochondrial redox imbalance can also trigger regulated cell death processes, which can hinder recovery and promote chronic remodeling [39] Long-term hyperglycemic and metabolic stress may disrupt endoplasmic reticulum homeostasis and antioxidant defenses in diabetic kidney disease, and endoplasmic reticulum stress may lead to the aggravation of lipid oxidative damage and tubular dysfunction through ferroptosis. This intermodulation is a useful mechanism that can promote the progression of metabolic injury in diabetic renal disease [40]. Chronic tubulointerstitial injury is another condition in which ferroptosis also plays a role: repeated epithelial stress may help to keep the microenvironment in the tubules oxidative and inflammatory. Mutations in mitochondria lead to enhanced production of ROS and decrease the cell's energy supply, while ferroptotic signaling will further impair tubular viability. They interact with each other and can amplify profibrotic responses and lead to ongoing interstitial remodeling in chronic kidney disease [41]. The continued injury leads to progressive fibrosis, which results in the loss of nephron function and alteration of the tubular and interstitial architecture and ultimately leads to irreversible nephron loss. This process may be exacerbated by oxidative stress and mitochondrial dysfunction, which can lead to an impairment of energy metabolism, redox imbalance, and activation of molecular pathways that promote cellular injury and fibrogenesis [42]. The long-term effect is a gradual progressive loss of renal function, with ongoing tubular loss and failure of repair continually reducing functional nephron reserve. Ferroptosis might thus act not only as a single cell-death process but as a self-propagating pathological network comprised of metabolic dysfunction, oxidative damage, mitochondrial abnormalities, inflammation and fibrosis. This activity, spanning from the acute-to-chronic transition period to diabetic kidney disease and established CKD, suggests its potential relevance as a mechanism that drives kidney disease and a therapeutic target for slowing the continued progression of renal disease (Table 6) (Figure 5).

Table 6. Role of Ferroptosis in Kidney Disease Progression

Disease context	Ferroptosis-associated mechanism	Major outcome	Reference
AKI-to-CKD transition	Persistent mitochondrial redox imbalance	Incomplete recovery	[39]
Diabetic kidney disease	ER stress–ferroptosis crosstalk	Progressive tubular damage	[40]
CKD	Oxidative and mitochondrial dysfunction	Persistent cellular injury	[41]
Renal fibrosis	Mitochondria–ferroptosis crosstalk	Fibrotic remodeling	[41]
Progressive kidney disease	Tubular loss and failed repair	Nephron loss	[42]
Advanced CKD	Sustained injury and fibrosis	Renal functional decline	[42]

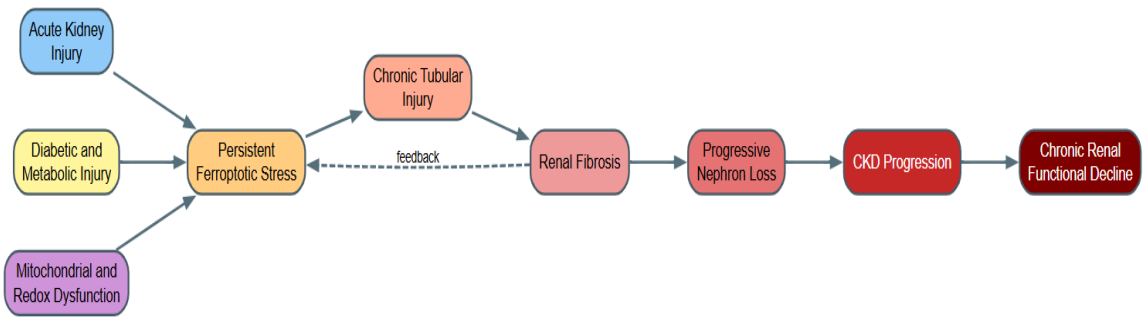

Figure 5. Role of ferroptosis in the progression from acute tubular injury to chronic kidney disease, fibrosis, and renal functional decline

8. Therapeutic Targeting and Future Perspectives

There are several therapeutic opportunities to protect renal tubular cells and to stop or slow the progression of kidney disease by therapeutic modulation of ferroptosis. Iron chelation and restoration of Fe homeostasis may make the labile Fe less available and limit Fe-dependent oxidative reactions that cause ferroptotic injury. Another approach is the inhibition of lipid peroxidation, where ferroptosis inhibitors and radical trapping antioxidants both can control the oxidation of phospholipids, thereby maintaining membrane integrity. Maintenance of glutathione availability or GPX4 activity may enhance GSH–GPX4 defense system and further improve the tubular resistance to oxidative damage. Canonical defenses may be ineffective, and activation of NRF2 and alternative ferroptosis defense pathways, such as GPX4-independent antioxidant mechanisms, could provide complementary protection. Increasingly, the therapeutic strategies are aimed at multiple ferroptosis-controlling processes, such as iron metabolism, lipid remodeling, mitochondrial redox state, ferritinophagy and cellular stress signaling. Yet, for clinical translation to be effective, there is a need for reliable biomarkers of ferroptosis that can distinguish ferroptosis-induced injury from similar regulated cell deaths and identify those patients who would most benefit from targeted intervention. Kidney disease etiology, severity of tubular injury, disease stage and temporal changes in ferroptotic activity should also be taken into account for patient stratification. Pathway redundancy is a major translational challenge, as is the uncertainty of optimal time of treatment as well as differences between experimental models and human disease, and potential for off-target effects. The development of validated kidney-specific markers, representative and clinically relevant models, pharmacokinetics and safety assessment, and the definition of therapeutic windows for the various stages should therefore be a priority in the future. Whole-transcriptome and molecular profiling in combination with longitudinal clinical information might ultimately enable precision strategies aimed at tackling ferroptosis at the molecular level based on the underlying mechanisms of each disease and facilitate the maintenance of tubular integrity and renal function.

9. Conclusion

The interaction of iron dysregulation, lipid peroxidation, decreased antioxidant defenses, and oxidative stress has led to the identification of ferroptosis as a key molecular mechanism in renal tubular injury. Tubular epithelial cells are more susceptible to ferroptotic injury because of their metabolic properties, especially in the case of acute, toxic, inflammatory, and metabolic injury. Most importantly, the effects of ferroptosis go beyond just the loss of cells. Other conditions such as persistent ferroptotic stress can disrupt tubular regeneration, support maladaptive epithelial phenotypes, maintain inflammatory and profibrotic signaling, and lead to tubulointerstitial fibrosis. These processes link together the mechanisms of acute tubular injury, incomplete repair, and progressive loss of nephrons. Ferroptosis could thus play a role in the AKI-to-CKD transition and in chronic deterioration in various chronic conditions like diabetic kidney disease and persistent tubulointerstitial injury. Modulation of iron homeostasis, lipid peroxidation, GSH–GPX4 axis, NRF2 signaling, and alternative antioxidant pathways are therapeutic targets that could help maintain tubular viability and limit progressive renal damage. Nevertheless, there is a need for valid and reliable ferroptosis-specific biomarkers, optimal timing for therapy, and more in vivo validation in clinically representative models. Ferroptosis is overall mechanistically relevant bridge between tubular damage, maladaptive repair, fibrosis and renal functional decline, and should be further explored as a potential mechanism-based therapeutic target in kidney disease.

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