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Ferroptosis in diabetic nephropathy: Mechanisms and therapeutic implications

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ABSTRACT

Diabetic Nephropathy (DN), the most common complication in diabetes mellitus, has been affecting the lives of people diabetic for a long time. Numerous studies have demonstrated the unbreakable connection between ferroptosis and kidney cell damage. Ferroptosis is a type of iron-dependent, non-apoptotic, regulated cell death, characterized by the buildup of intracellular lipid peroxides to lethal levels. Although the role of programmed cell deaths like apoptosis, autophagy, and necroptosis in the pathogenesis of DN has been demonstrated, the implication of ferroptosis in DN was least interrogated. Hence, the main aim of this review was to discuss the current understanding of ferroptosis focusing on its potential mechanisms, its involvement in DN, and emerging therapeutic opportunities.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia due to a defect in insulin action, secretion, or both [1]. It is one of the four prioritized non-communicable diseases targeted for action by the World Health Organization (WHO) since both its prevalence and number of cases have gradually increased over the last few decades [2]. According to the International Diabetic Federation (IDF) report, in 2017 it was estimated that about 451 million adult people living with DM worldwide, and predicted to rise to 693 million by 2045 [3]. DM is linked to a variety of chronic complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease [4]. Diabetic nephropathy (DN) is the most common microvascular complication, which is expected to affect approximately 40–60% of diabetic individuals [5]. DN, also known as Diabetic Kidney Disease (DKD), is the deprivation of kidney function in patients with type 1 and type 2 diabetes [6]. In the absence of other renal disorders, DN is distinguished by increased urine albumin excretion. Diabetic kidney disease is currently the major cause of kidney failure and the single leading cause of diabetic mortality [7]. Although vascular dysfunction

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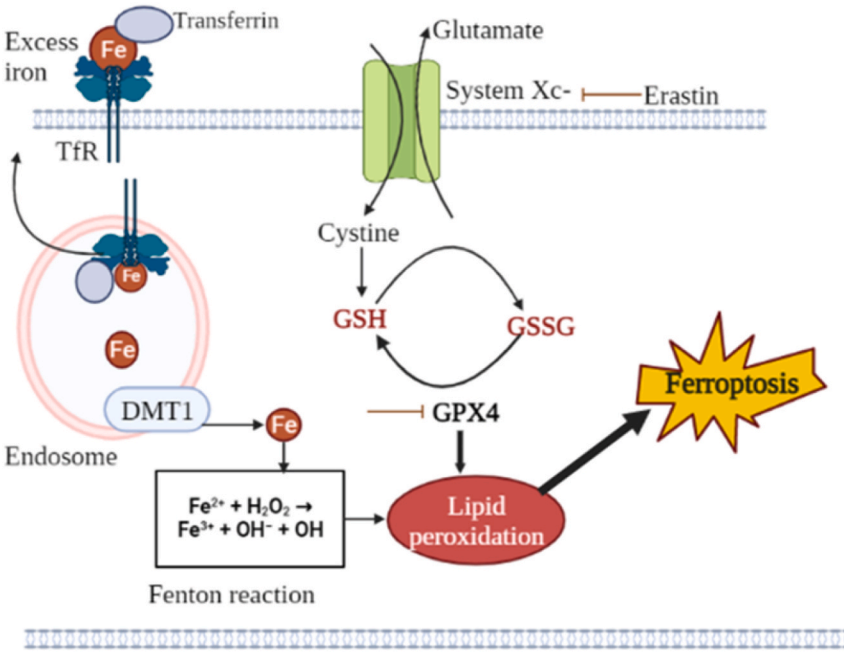

Fig. 1. Overview of key ferroptosis pathways. The primary trigger for ferroptosis is the inhibition of system Xc-activity. System Xc-inhibition decreases cysteine amino acid levels within cells, which decreases glutathione (GSH) levels. GSH depletion results in decreased GPX4 activity, which triggers lipid peroxidation. The execution of ferroptosis is also based on an excess of iron in the blood. Transferrin binds and transports excess iron (Fe) in the blood. Fe-transferrin is bound to the transferrin receptor (TfR) and endocytosed. In the endosome, Feis dissociated from transferrin-TfR. Then free Fe is exported to cytosol by divalent metal transporter-1 (DMT1) where it can then undergo the Fenton reaction with reactive oxygen species. In both cases, lipid peroxidation results in the activation of ferroptosis cell death.

brought on by hyperglycemia is the primary cause of DN, oxidative stress, inflammation, and fibrosis all play a role in the disease's progression [8].

Ferroptosis is a type of iron-dependent, non-apoptotic, regulated cell death that is characterized by the buildup of intracellular lipid peroxides to lethal levels. Recent studies have revealed that ferroptosis affects various kidney diseases, including DN. The onset and development of DN are extremely complex [9]. Numerous cells and molecular mechanisms linked to the development of DN have been identified. Inflammation, hemodynamic abnormalities, oxidative stress, genes, and a disorder of glucose metabolism all play a role in the pathogenesis of DN. The aforementioned are significant factors in the development of DN as well [10]. Cell death is thought to play a role in the gradual depletion of renal cells in DN [11]. Recent studies indicate that the development of DN is linked to a type of cell death known as ferroptosis. Ferroptosis is a relatively new type of cell death that is primarily accompanied by iron accumulation and is characterized by lipid peroxidation [12]. While the contributions of programmed cell deaths, such as apoptosis, autophagy, and necroptosis, to the development of diabetic nephropathy have been well-established, the relevance of ferroptosis in this context remains insufficiently explored [13]. Thus, the primary objective of this review is to provide an overview of the current knowledge on ferroptosis, with a particular emphasis on its potential mechanisms, its role in the pathogenesis of diabetic nephropathy, and the prospects for emerging therapeutic interventions.

2. Ferroptosis: A specialized type of cell death

Ferroptosis is a form of regulatory cell death (RCD) that was coined in 2012 by Brent Stockwell [14]. It is an oxidative, iron-dependent form of cell death that differs from apoptosis, classic necrosis, autophagy, and other types of cell death [15]. Ferroptosis exhibits different biochemical and morphological features, such as shrinking mitochondria, increased mitochondrial membrane density, excessive accumulation of lipid peroxides and reactive oxygen species (ROS), and reduced antioxidant capacity [16]. As illustrated in Fig. 1, iron accumulation, increased lipid peroxidation, and an inability to efficiently reduce lipid peroxide are the three main pathological pillars that underlie the ferroptosis mode of cell death [17]. The metabolism of amino acids (especially cysteine), lipids and iron regulates the initiation and execution of ferroptosis [18].

Cysteine metabolism plays a critical role in the initiation of ferroptosis. The small molecule erastin induces ferroptosis by inhibiting cystine import, resulting in glutathione (GSH) depletion and inactivation of the phospholipid peroxidase glutathione-peroxidase 4 (GPX4) [19]. During erastin-induced ferroptosis, glutamate-cysteine antiporter (xc^-) is the most common target of erastin. System xc^- is a cell membrane amino acid transporter that imports cystine and exports glutamate, resulting in GSH synthesis. GSH is a well-known antioxidant tripeptide that also functions as a cofactor for the GPX4 enzyme. System xc^- inhibition depletes cellular cysteine, making it unavailable for GSH synthesis and inactivation of GPX4. These results in the accumulation of lipid-peroxide and ROS subsequently ferroptosis cell death [20,21]. Despite its critical role in life, too much iron is harmful due to its capacity to produce reactive ROS. Although the precise mechanisms of iron in ferroptosis remain unknown, there is abundant evidence that iron metabolism plays a critical part in the process of ferroptosis. For instance, iron chelators inhibit ferroptosis cell death *in vitro* and *in vivo* [22], increased cellular labile iron is commonly detected during ferroptosis induction [23], and exogenous iron supplementation increases cell sensitivity to ferroptosis [24]. Hence, the key metabolic event that triggers ferroptosis is iron-mediated lipid peroxidation (the process of oxidative destruction of lipids by free radicals). As a result, an increase in free radical production, fatty acid supply, and lipid peroxidation by certain enzymes is critical for ferroptosis [25]. In general, either the extrinsic or the intrinsic pathway can activate it. Regulating transporters (for example, inhibiting the amino acid antiporter system or activating the iron transporters transferrin and lacto-transferrin) activate the extrinsic pathway, also called transporter dependent pathway. Whereas the intrinsic pathway, also called enzyme regulated pathway is primarily activated by inhibiting the expression or activity of intracellular antioxidant enzymes such as GPX4 [26,27].

3. Ferroptosis in diabetic nephropathy

DN is a serious diabetic complication characterized by proteinuria and reduced glomerular filtration rate. In DM, hyperglycemia-induced iron overload, lipid peroxidation, oxidative stress, inflammation, and fibrosis in renal cells, all of which are involved in the pathogenesis of DKD [28]. In addition to several kinds of programmed cell death, such as autophagy, apoptosis, and necrosis, studies have shown that ferroptosis

Table 1
Summary of studies on new molecules and their key method of modulating ferroptosis to attenuate DN.

Author (s)	Compound (s)	Feature of the compound (s)	Animal model	Mechanism of action	Author (s) Conclusion
Quanwei Li et al. [47]	N-acetylcysteine (NAC)	NAC is sulfhydryl-containing compound, which is the acetylated form ofl-cysteine	large mammal (beagle) DN model	By increasing mitochondrial GSH activity, NAC reduced mitochondrial oxidative damage and ferroptosis	NAC could be a promising candidate for the treatment of DN
Lo, Yi-Hsin et al. [48]	Nobiletin (Nob)	a critical active flavonoid of citrus fruits	Ureteral obstructive mouse model	Nob reduced kidney fibrosis, oxidative stress, and ferroptosis-associated damage, as well as the inflammatory response in mice kidneys	Nob could be a promising therapeutic choice for the treatment of progressive CKD
Tan H et al. [44]	Glabridin (Glab)	A bioactive component of licorice herb	STZ-induced DN rat	Glab prevents kidney damage and dysfunction through mitigating ferroptosis	Glab could have a protective effect on the progression of DN in DM
Huang Bin et al. [49]	Dapagliflozin (DAPA)	DAPA is one of the clinically used hypoglycemic agents for diabetic treatment	STZ-induced T2 DM mice	DAPA ameliorates renal tubular ferroptosis in DM through stabilization of iron export protein in mammals called SLC40A1	Ferroptosis inhibitory effects of DAPA could be employed in the treatment of DKD
Wang, Yunguang et al. [50]	Germacrone	The major bioactive constituent of Rhizoma curcuma (Chinese medicine with anti-inflammatory and antioxidant effects)	T1 DM mouse	Germacrone prevented podocyte ferroptosis by protecting against mitochondrial damage, limiting ROS buildup, and restoring GPX activity and GPX4 protein expression	Germacrone could be an effective therapeutic option for DN in T1 DM
Biyu, Hou et al. [51]	Puerarin (PUR)	PUR is an isoflavone extracted from the dry-root of the legume Pueraria lobate	T2 DM rat model	**PUR reduced excessive ECM accumulation in DN by preventing glomerular mesangial cell ferroptosis, while PUR therapy reduced iron overload and lipid peroxidation in DN kidneys**	A new mechanism of PUR could be a potential therapy site for DN

Abbreviations: CKD = chronic kidney disease; DKD = diabetic kidney disease; DN = diabetic nephropathy; ECM = extra cellular matrix; GSH = reduced glutathione; SLC40A1 = solute carrier family 40 member 1; STZ = streptozocin.

plays a critical role in the development of DN. Ferroptosis-related molecules are elevated in DN kidney biopsy tissues compared to non-DN patients, and the involvement of ferroptosis has also been confirmed in DN animal models. In addition, ferroptosis indicators, such as serum ferritin and lactate dehydrogenase release, are elevated in DKD patients [29]. For instance, a recent retrospective study revealed that renal tubular epithelial cells from DN patients showed higher iron deposition and transferrin expression when compared to the healthy control group. The important point is that intracellular iron deposition is the key factor causing ferroptosis [30].

Transforming growth factor-β1 (TGF-β1) is recognized to contribute to DN, as was previously stated. Intracellular glutathione concentration was decreased and lipid peroxidation was increased in TGF-β1-stimulated tubular cells of DM patients, both of which are linked to ferroptosis-related cell death [31]. Ferroptosis was found to be involved in the progression of tubular cell death in DN, as evidenced by increased expression levels of acyl-CoA synthetase, decreased expression levels of GPX4, increased lipid peroxidation, and iron content in both *in vivo* and *in vitro* studies on animal models [32]. Renal hypoxia and increased oxidative stress are symptoms of DN. The hypoxia response is the method by which kidneys adapt to oxygen deficiency. The major mediators of metabolic hypoxia are hypoxia-inducible factors (HIFs), and their aberrant activity appears to play an important role in the pathogenesis of diseases such as nephropathy [33]. Ferroptosis exacerbated DN and damaged renal tubules in an animal model study via the hypoxia-inducible factor (HIF)-1/heme oxygenase (HO)-1 pathway. Increased heme decomposition causes iron to build up in the renal tubules, which in turn leads to a rise in ROS production and an accumulation of lipid peroxidation [34]. On the contrary, however, some studies have demonstrated that HO-1 protects renal epithelial cells from oxidative stress in a significant way. Consequently, it is still unclear how HO-1 controls ferroptosis [35]. As previously stated, iron accumulation and aberrant expression of iron, transporters are implicated in ferroptosis. ZRT/IRT-like protein 14 (ZIP14) was elevated and ferrous iron levels were enhanced in both *in vivo* and *in vitro* studies in DN rat models and human kidney tubular cell line models. Together with this, the expression of GPX4 and GSH levels were reduced, consistent with ferroptosis, demonstrating the unique role of ZIP14 in DM kidney injury mediated by ferroptosis. ZIP14 is a transporter protein that can mediate iron uptake [36].

Studies have also explored the injury mechanism of ferroptosis in mesangial cells, podocytes, and other parts of the kidney. A transcription factor involved in DNA recombination and repair is called High Mobility Group Box-1 (HMGB1) [37]. It has been demonstrated that DN can be prevented by blocking the interaction between HMGB1 and its receptor [38]. On the other hand, HMGB1 controls glucose-induced ferroptosis in mesangial cells via the nuclear factor E2-related factor 2 (Nrf2) pathway, including its downstream targets [39]. Furthermore, p53 signaling is active in DM, and p53 transcriptionally suppresses the xc-transporter in endothelial cells. Downregulation of xc^- inhibits cystine uptake and diminishes GSH synthesis, which is implicated in activating ferroptosis in endothelial cells and ultimately leads to endothelial dysfunction [40]. Evidence suggests that diabetes-induced renal endothelial dysfunction is a critical and potential contributor to the progression of DN. Hence, ferroptosis is involved in endothelial dysfunction followed by DN [41].

4. Potential therapeutic implications targeting ferroptosis for DN

The link between ferroptosis and the pathophysiology of DN suggests that ferroptosis modulators could be used as therapeutic agents. Recently, ongoing studies are being carried out to develop molecules that can mitigate the effect of ferroptosis in DN. For instance, it has been demonstrated that up-regulation of peroxiredoxin 6 (Prdx6) expression, one of the key players in the pathogenesis of DN prevents podocyte injury through the mitigation of oxidative stress and ferroptosis [42]. The transcription factor high-mobility group box-1 (HMGB1) is involved in chromatin remodeling as well as DNA recombination and repair. Extracellular HMGB1 can activate NF-κB, leading to the production of pro-inflammatory cytokines [43]. It was discovered that in high glucose-treated mesangial cells, HMGB1 is translocated from the nucleus to the cytoplasm and acts as a positive regulator of ferroptosis, suggesting that innovative therapeutic strategies targeting HMGB1 and ferroptosis in diabetic kidney disease are needed [39]. It has been shown that HO-1 plays a significant role in the protection of renal damage. Hemin, an HO-1 inducer, and anti-porphyria medication may have a promising effect against contrast-induced nephropathy (CIN), although its effect on DN has not been investigated [35]. Furthermore, bioactive substances are being researched for their ability to reduce DN by

preventing ferroptosis. For instance, in a streptozotocin-induced diabetic rat model, glabridin, a bioactive component of licorice, reduces DN by regulating ferroptosis [44]. Calycosin, the main bioactive component in Astragali Radix dry root extract, protects against diabetic kidney damage by regulating ferroptosis [45]. As previously indicated, GPX4 is an important regulator in ferroptosis. Inhibiting GPX4 function increases lipid ROS production and lipid peroxidation, resulting in ferroptosis. Platycodin D, isolated from the dry root of Platycodon grandiflorum, regulates high glucose-induced ferroptosis by increasing the expression of GPX4 in the human renal proximal tubule epithelial cell line [46]. Table 1 also illustrates other molecules that have a regulatory effect on ferroptosis to prevent DN.

5. Conclusion

Ferroptosis is a pro-inflammatory form of regulated necrosis characterized by lipid peroxidation. There is evidence that ferroptosis occurs during DN and that it contributes to the pathogenesis of DN via a variety of signaling pathways in podocytes, mesangial cells, and tubule cells. Drugs and medicinal substances that target these pathways may reduce ferroptosis-associated DN in patients with DM. Ferroptosis is a worthwhile target for the treatment of DN in general, but rigorous clinical trials are needed to understand its mechanism and the full effect of medicinal substances.

Authors contribution

MM (correspondence author) developed the concept of the review. All authors have participated in manuscript drafting and revision. All authors have approved the final version of the manuscript to be published.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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