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# Functional consequence of Iron dyshomeostasis and ferroptosis in systemic lupus erythematosus and lupus nephritis

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## Abstract

Systemic lupus erythematosus (SLE) and its renal manifestation Lupus nephritis (LN) are characterized by a dysregulated immune system, autoantibodies, and injury to the renal parenchyma. Iron accumulation and ferroptosis in the immune effectors and renal tubules are recently identified pathological features in SLE and LN. Ferroptosis is an iron dependent non-apoptotic form of regulated cell death and ferroptosis inhibitors have improved disease outcomes in murine models of SLE, identifying it as a novel druggable target. In this review, we discuss novel mechanisms by which iron accumulation and ferroptosis perpetuate immune cell mediated pathology in SLE/LN. We highlight intra-renal dysregulation of iron metabolism and ferroptosis as an underlying pathogenic mechanism of renal tubular injury. The basic concepts of iron biology and ferroptosis are also discussed to expose the links between iron, cell metabolism and ferroptosis, that identify intracellular proferroptotic enzymes and their protein conjugates as potential targets to improve SLE/LN outcomes.

### Keywords

SLE; Lupus nephritis; Iron; Ferroptosis

## 1. Introduction

Systemic lupus erythematosus (SLE) is the most prevalent form of lupus, an autoimmune disease characterized by the loss of tolerance to self-DNA, histones, and ribonucleoproteins [1,2]. The adaptive immune cells of individuals with SLE have limited ability to discern between self and non-self-antigens [3], which results in the production of autoantibodies that form circulating and in-situ immune complexes (IC) that induce multiple organ inflammation and pathology [2,4]. While the etiology of SLE is incompletely understood,

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a combination of genetic susceptibility, hormonal changes, and exogenous factors (e.g., allergens, infection, heavy metals) can trigger the onset [5]. Circulating and in situ IC disproportionately affect the highly vascular kidneys, resulting in lupus nephritis (LN). LN is the most severe end-organ complication of SLE that leads to end-stage kidney disease (ESKD) [6,7]. Since IC deposits are the dominant feature in LN patients, glomeruli are considered the initiating site of renal pathology. However, tubulointerstitial inflammation and pathology strongly correlate with renal dysfunction independent of the extent of glomerular damage and predict worse outcomes [8-11].

Our understanding of SLE has come a long way since the discovery of the disease by Cazenave and Biett in 1833 and Hebra in 1846 [12]. However, novel pathogenic mechanisms of human SLE and LN are continuously uncovered [13,14]. While these new challenges influence disease outcomes, they also provide novel opportunities for intervention [15,16]. A recent addition to this list is iron (Fe) metabolism [17,18] and ferroptosis, an iron-dependent form of regulated cell death [19,20].

In this review, we briefly introduce the fundamentals of iron metabolism and ferroptosis and discuss novel iron-centric mechanisms of immune effectors and parenchymal cells contributing to the pathogenesis of SLE/LN.

## 2. Fundamentals of iron biology and ferroptosis

Iron is essential for physiology, cell survival, and proliferation, and reducing intracellular iron induces cell cycle arrest and apoptosis [21]. Without iron, cells cannot proceed from the G1 to the S phase of the cell cycle [22]. Fe-containing proteins catalyze critical reactions involved in oxygen sensing [23,24], energy metabolism [25], and DNA synthesis (e.g., ribonucleotide reductase) [22]. Bioactive or labile Fe ($Fe^{2+}$) participates in the Fenton reaction and catalyzes the generation of reactive oxygen species (ROS), which induce oxidative stress and lipid oxidation [26,27]. Hence systemic and cellular iron metabolism is dynamic, tightly regulated, and a well-orchestrated symphony with evolutionary conserved pathways that control cellular iron levels [28]. The hepcidin-ferroportin axis primarily regulates systemic iron metabolism [29]. At a mechanistic level, the flow of iron out of the cells is controlled by hepcidin through two known mechanisms: occlusion of the open-outward conformation of ferroportin by hepcidin [30] and hepcidin-induced endocytosis and degradation of ferroportin [31]. In contrast, cellular iron metabolism is a complex and coordinated symphony involving multiple iron importers, chaperons, storage molecules, and iron export [32,33].

The role of iron regulation in immunometabolism and immune-related disease is documented [34] and in SLE, the pathological consequences of abnormal iron metabolism and consequent mitochondrial and cellular dysfunctions are reported [18,35,36]. We have previously reviewed the details of renal iron metabolism in context of LN [17]. Iron accumulation, oxidative stress, and lipid peroxidation, the major biochemical characteristics of ferroptosis [37], are observed in SLE/LN [38-40]. There is a recent spurt in the literature reporting the occurrence of ferroptosis in SLE/LN by multiple independent groups [40-45].

### 2.1. Ferroptosis

Ferroptosis was identified as a distinct iron-dependent, regulated form of cell death driven by excessive lipid peroxidation [37]. It is independent of other metals and is morphologically, biochemically, and genetically distinct from apoptosis and necrosis [37]. Ferroptosis is now appreciated as a widespread and evolutionary conserved form of cell death across species since ferroptosis-like cell death in plants, protozoa, and fungi has also been observed [46,47].

Ferroptosis-driven lipid peroxidation disrupts the thickness, permeability, and structure of membrane bilayers, which is lethal to the cells [48,49]. Lipid peroxidation can occur via the selective enzymatic or random non-enzymatic free radical chain reaction [50,51]. Both enzymatic and non-enzymatic lipid peroxidation involve abstraction of the bis-allylic hydrogen, rearrangement of the resonance radical structure, addition of the molecular oxygen that generates peroxyl radical to form hydroperoxy lipid [52]. Reaction rates of non-enzymatic peroxidation of poly-unsaturated fatty acids (PUFA) are proportional to the number of bis-allylic hydrogens [53]. In contrast to this random profile of free radical peroxidation, enzymatic lipid peroxidation by di-oxygenases (e.g., cyclooxygenases [COXs] and LOXs) is highly substrate-selective and product-specific [54].

The identification of the specific lipids and sites that drive ferroptosis and the enzymes that promote their generation and incorporation into cell membranes has been a critical discovery in ferroptosis research [55,56]. Ferroptosis is now defined as an organized oxidation of only one class of phospholipids, phosphatidylethanolamines (PEs), with a specificity toward two fatty acyls-arachidonoyl (AA) and adrenoyl (AdA) [55]. PUFA, a common component of phospholipids, have enhanced susceptibility to ferroptosis. The presence of multiple double bonds in PUFAs increases the propensity to form highly reactive peroxyl radicals that cause irreparable membrane damage [57]. Additionally, lipid peroxidation or ferroptosis breakdown products, including 4-hydroxynonenal (HNE) and malondialdehyde (MDA), are damaging to cellular processes because they form adducts with proteins and DNA [58,59]. Ferroptosis is inhibited by the canonical system $xc^{-}$-/GHS/GPX4 pathway and promoted by enzymes such as long-chain acyl-co-enzyme A (CoA) synthase 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), lipoxygenase (LOX), and cytochrome P450s (CYPs), or non-enzymatically by Fe-dependent free radical-induced peroxidation [60-62].

The canonical control of ferroptosis entails four key steps (Fig. 1): 1) uptake of cystine via the cystine-glutamate antiporter, system xc−; 2) reduction of cystine to cysteine; 3) synthesis and reduction of glutathione to reduced glutathione (GSH); and 4) GSH-dependent activation of the enzyme glutathione peroxidase 4 (GPX4), a selenoprotein that reduces toxic phospholipid hydroperoxides (PE-OOH) to corresponding non-toxic alcohols (PE-OH) [63-65].

The long-chain acyl-coenzyme A (CoA) synthase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) were the first proferroptotic identified gene products [55]. To initiate lipid peroxidation on cell membranes (Fig. 1), ACSL4 first catalyzes the conversion of arachidonic acid (AA) into AA-CoA, followed by the esterification of AA-CoA into

phosphatidylethanolamine (PE) to form AA-PE with the assistance of LPCAT3. Then, acid-15-lipoxygenase (ALOX15) catalyzes the oxidation of AA-PE to its toxic hydroperoxy form (PE-OOH) [55,66,67]. In addition, lipoxygenases (LOXs) catalyze the oxidation of excessive PUFA-CoA and contribute to ferroptosis [68].

In a non-enzymatic manner, intracellular $Fe^{2+}$ can promote lipid peroxidation and initiate ferroptosis via the Fenton reaction or by increasing the catalytic activity of ALOX15, which has an iron-binding site and produces ROS [69] (Fig. 1). By participating in the Fenton reaction, $Fe^{2+}$ can react with hydrogen peroxide to produce highly reactive free radicals such as OH·, OH−. Then, OH·, in the presence of oxygen, attacks the C═C double bonds of PUFAs and produces PE-OOH [70]. The oxidation state of iron is vital for its ability to contribute to ferroptosis: $Fe^{2+}$ promotes ferroptosis, whereas $Fe^{3+}$ is generally inert and stored in ferritin, except in the active site of lipoxygenases, where Fe (III) is the active form of the enzyme.

Integrating research involving metabolism, iron regulation, and ROS biology has yielded insights into distinct aspects of ferroptosis. For example, metabolism explains how the critical substrates of ferroptosis are generated and remodeled; iron regulation indicates how the availability of $Fe^{2+}$ is controlled and compartmentalized; and ROS biology shows how endogenous defenses against lipid peroxidation function. The dysregulation of these three pillars of ferroptosis is also a salient feature in SLE/LN [17,71-74]. For example, in SLE, metabolic reprogramming alters the CD4+ T and B cell responses and their effector functions [75-78]. Iron accumulation in immune cells drives their cytokine production and differentiation into pathogenic effectors in SLE [79-81]. Additionally, improper iron sequestration and accumulation in the renal tubules promotes ferroptosis in LN [42]. Finally, ROS-induced pathology in different organelles as well as the role of lipid mediators in SLE and LN have also been documented [40,82,83]. These observations support an inherent role of ferroptosis in SLE and LN.

Below, we focus on literature that has identified dysregulated iron metabolism and the occurrence of ferroptosis in neutrophils, T cells, B cells, and the proximal tubular epithelial cells (PTEC) of the kidneys, the critical effectors in the pathogenesis of SLE/LN.

### 2.2. Neutrophils, iron and ferroptosis

Neutrophils are the most numerous white blood cells in the body and are primarily studied in settings of innate responses following acute injury. Neutrophils secrete lipocalin-2 to limit bacteria from scavenging host iron from the bloodstream [84,85]. They also secrete myeloperoxidase (MPO), a hemoprotein whose $Fe^{3+}/Fe^{2+}$ redox states are critical to its anti-microbial effects [86]. In addition, neutrophils produce large amounts of lactoferrin to scavenge iron, inhibiting bacterial proliferation [87]. By binding its cognate receptor, lactoferrin promotes the maturation, migration, and cell proliferation of macrophages and monocytes [88]. As such, neutrophils present an active iron metabolism as a part of their normal immunological response. The role of neutrophils in SLE/LN is increasingly appreciated [89-91]. LN kidneys have an elevated α-defensin gene transcript, a neutrophil product associated with neutrophil extracellular traps (NETS) and co-relates positively with local IFN-I expression [92]. In SLE patients, neutrophils exhibit an increased tendency to

undergo apoptosis, which positively correlates with anti-dsDNA antibody titers and disease activity [93,94]. Increased MPO (iron-containing hemoprotein)-DNA complexes in SLE patients are observed [95]. Neutrophils of SLE patients also demonstrate an increased propensity to undergo netosis and release neutrophil extracellular traps (NETs), the fibrous strands composed of self-antigens including dsDNA, histones, chromatin, granule proteins, and mitochondrial DNA (mtDNA) [96,97]. Dysfunctional or reduced DNase due to genetic factors leads to impaired degradation of NETS and is associated with worse outcomes of LN [98,99]. This mechanism is now considered a key source of self-antigens in SLE.

The pathogenic role of neutrophil ferroptosis in SLE was first reported by a collaborative effort between P. Lipsky, G. Tsokos, and X. Zhang groups [45]. Using sera and neutrophils from SLE patients as well as murine models, they demonstrated that autoantibodies and IFN-α contained in SLE serum induce neutrophil ferroptosis [45]. Mechanistically, autoantibodies and type I IFNs cooperatively promote the nuclear translocation of cAMP response element modulator (CREMα) and its binding to the *Gpx4* promoter in neutrophils, suppressing neutrophil GPX4 expression, promoting their ferroptosis and worsening disease outcomes. The authors found a conserved cAMP response element (CRE) upstream of the human *Gpx4* promoter. SLE serum, or normal serum supplemented with SLE IgG or IFN-α recapitulated this effect in healthy donor neutrophils. The importance of GPX4 in neutrophil health was demonstrated by neutrophil specific *Gpx4* haploinsufficiency, which led to lipid peroxidation and ferroptosis, and recapitulated key clinical features of human SLE in mice. Finally, Liproxstatin-1, a ferroptosis inhibitor that traps lipid-derived free radicals to inhibit the propagation of nonenzymatic lipid peroxidation [100], ameliorated disease outcomes in MRL/lpr lupus-prone mice. Thus, these studies provided a novel proof of concept that neutrophil ferroptosis is a source of self-antigens that may be presented to the T cells to perpetuate SLE.

### 2.3. T cells, iron, and ferroptosis

Pioneering work by the Tsokos group has shown that the aberrant and heightened T cell receptor (TCR) signaling in SLE T cells is due to the substitution of CD3ζ protein in the TCR–CD3 complex by the Fc receptor common gamma subunit chain (FcRγ) [101,102]. FcRγ recruits Syk instead of ZAP-70, resulting in the higher calcium influx and activation of T cells [103]. Auto-reactive $CD4^+$ T cells are expanded in active SLE, produce effector cytokines, and invade the kidneys [104]. These intrarenal $CD4^+$ T cells are oligoclonal, indicating local accumulation of antigen-specific T cells in inflamed kidneys [105].

Proliferation and effector functions of immune cells are energy-expensive processes. T cells require iron for many metabolic and redox reactions as well as heme- and Fe-S-containing enzymes essential for cell division, metabolism, and cytokine production [106,107]. Human studies showed that iron deficiency reduced the number of circulating T lymphocytes and their blastogenic response to mitogens [108,109]. CD71 (TfR1: transferrin receptor-1) mediated uptake of transferrin-bound iron and albumin-heme complex is the principal mechanism of cellular iron import [110], and its expression on T lymphocytes increases within the first few minutes of TCR/CD3 engagement [111]. In line with this observation, downregulation of TfR1 is associated with the induction of T cell anergy, a process

whereby an activated T cell becomes tolerant and functionally inactive [112]. Furthermore, hematopoietic-specific deletion of the ferritin heavy chain gene *Fth1,* which encodes for the intracellular iron sequestering protein FtH, reduced the numbers of lymphocytes while other immune cell types such as granulocytes and monocytes are unaffected [113]. The proposed mechanism entails increased free intracellular $Fe^{2+}$ levels, leading to oxidative stress and cell death [113]. However, upon stimulation, FtH-deficient $CD4^+$ T cells proliferated more before ultimately dying, highlighting an obligatory function of iron in cell proliferation. Given that proliferating $CD4^+$ T cells import high levels of iron, it is not surprising that GPX4 is essential for their survival and expansion, highlighting the importance of preventing lipid peroxidation and iron dysregulation in proliferating $CD4^+$ T cells [114].

Iron contributes to activation-induced T-cell expansion by positively regulating IL-2R signaling and mitochondrial function [115]. Iron deposits have been observed in the brains of patients with multiple sclerosis, an autoimmune, $CD4^+$ T cell-driven disease, and iron-deficient mice fail to develop autoimmune encephalomyelitis [116]. At a mechanistic level, iron promoted GM-CSF and IL-2 production in $CD4^+$ T cells by stabilizing the RNA-binding protein PCBP1, and iron deficiency in T cells improved outcomes [117].

In the context of SLE, Zhao et al. demonstrated for the first time a pathological consequence of iron accumulation in the $CD4^+$ T cells from patients [79]. This novel study identified a reduced expression of 3-hydroxy butyrate dehydrogenase 2 (BDH2), a modulator of intracellular iron homeostasis in the $CD4^+$ T cells of SLE patients. BDH2 is a member of the short-chain dehydrogenase family of reductases, and it catalyzes a rate-limiting step in the biogenesis of the mammalian siderophore [118]. Loss of BDH2 impaired intracellular iron sequestration and increased the availability of $Fe^{2+}$. Excess iron elevated global DNA hydroxymethylation levels, corresponding to a reduced DNA methylation levels in SLE $CD4^+$ T cells as compared to healthy controls [79], leading to overexpression of immune-related genes. The same group has recently identified BDH2 deficiency-driven labile iron accumulation in SLE $CD4^+$ T cells as promoting the demethylation and hence upregulation of the *BCL6* gene, and thereby promoting T follicular helper (Tfh) cell differentiation [80,81]. Tfh cells are a key effector subset in SLE with a frequency that correlates with disease activity [119]. This work identified a functional role for iron in $CD4^+$ T cell biology and the development into pathogenic effectors in SLE. Lipid peroxidation leading to ferroptosis in Tfh cells is not surprising, given that these cells have excess labile iron. Tfh cells show intensified lipid peroxidation and altered mitochondrial morphology, resembling the features of ferroptosis that is kept in check by the seleno-enzyme GPX4, which is necessary for Tfh cell survival [120]. The deletion of GPX4 in T cells selectively abrogated Tfh cells and germinal center responses in immunized mice, and selenium supplementation enhanced GPX4 expression in T cells, increased Tfh cell numbers and promoted antibody responses [120].

Collectively, these studies highlight that activated $CD4^+$ T cells immediately turn on their iron import machinery for proliferative and metabolic requirements. In the context of autoimmunity, iron can act as a chaperon to stabilize cytokine mRNA or induce epigenetic modifications to polarize into specialized effectors. Hence, $CD4^+$ T effector cells have defense mechanisms to counter iron-mediated pathology like ferroptosis.

### 2.4. B cells, iron, and ferroptosis

We have a limited understanding of whether iron and ferroptosis in B cells play a role in SLE. In lupus, the aberrant activation of TLR7 by self-nucleic acids leads to a break in tolerance and perpetuation of the autoimmune feed-forward loop [121]. Additionally, RNA-associated autoantigens activate B cells by combining B cell antigen receptor and TLR7 engagement [122]. Since B cell intrinsic TLR7 signaling plays a critical role in viral infections [123-125] and iron plays an essential role in B cell anti-viral and immunization responses [125], we may draw parallels to gain insights on the role of iron in B cell effector function during the evolution of SLE.

B cells that receive the appropriate activation signals in the presence or absence of T cells initiate an energy-intensive differentiation program to develop into highly proliferative, antibody-secreting plasma cells [126]. During this process, B cells utilize iron in different forms and cellular compartments. Patients with a Tyr20His substitution in the *TFRC* gene encoding for TfR1, the principal receptor for uptake of transferrin-bound iron, have significantly reduced numbers of memory B cells, impaired B cell proliferation, and impaired IgE production [127]. Iron is essential for B cell proliferation as iron deficiency suppresses cyclin E1 induction and S phase entry in activated B cells [128]. Iron-dependent histone 3 lysine 9 demethylation controls B cell proliferation, and iron-deficient individuals and mice exhibit a significantly reduced antibody response to the measles vaccine compared to iron-normal control [128]. Activated B cells also utilize iron-sulfur (Fe—S) clusters as cofactors for the activity of DNA polymerases, helicases, and glycosylases [128]. These Fe—S cluster proteins are synthesized in the mitochondria, and the Fe-S-glutathione intermediate is exported to the cytoplasm for maturation by the mitochondrial transporter ABCB7 [129,130]. Conditional deletion of ABCB7 in B cells blocked bone marrow B cell development at the pro-B cell stage. Surprisingly though, the loss of ABCB7 in pro-B cells increased intracellular iron and replication-induced DNA damage but did not increase cellular or mitochondrial ROS, ferroptosis, or apoptosis. Why ABCB7-mediated export of Fe—S intermediates are required for bone marrow B cell development, proliferation, and class switch recombination but dispensable for peripheral B cell homeostasis in mice remains unanswered [128]. The importance of interaction between secreted iron binding proteins and B cell function was showcased by a study that showed that the HIV-1 accessory protein Nef induces the production and secretion of ferritin, an iron-sequestration protein, in infected macrophages in a NF-κB-dependent manner [131], which then induces B-cell hyperactivation and exhaustion. This study identified soluble ferritin heavy and light chains as the essential soluble factor secreted by infected macrophages responsible for B-cell proliferation. B cells express T cell immunoglobulin-domain and mucin-domain 2 (TIM2) [132], and TfR1 [133]; the receptors for soluble ferritin. In vitro exposure to the supernatant from cultures of Nef-expressing or HIV-1-infected macrophages led to B cells proliferation and differentiation into memory B cells and plasma cells. Exogenous ferritin induced B-cell proliferation and the expression of the activation markers, which were suppressed when ferritin was immunodepleted from the supernatants, demonstrating a causal effect of ferritin on B cells.

Ferritin is uptaken via the TIM-2 receptor-mediated endocytosis and, eventually, transits through the lysosomal compartment, distinguishing it from the transferrin-based mechanism, the classical vehicle for cellular iron delivery [134]. Secreted serum ferritin levels mirror the degree of acute and chronic inflammation, independent of iron status [135,136]. Serum ferritin levels are increased in SLE/LN patients and correlate with disease activity [137,138]. Hepcidin, present at high levels in SLE [139,140] can degrade ferroportin and attenuate systemic iron availability [29]. Whether secreted ferritin acts as a non-classical source of iron to support B cell function remains to be evaluated.

Within B cell subsets, B1 and marginal zone (MZ) B cells display increased sensitivity to lipid peroxidation and ferroptosis compared to follicular B cells [141]. Increased metabolic requirements and differences in lipid metabolism between B1/MZ and follicular B cells dictates the requirement of GPX4 to scavenge lipid ROS and inhibit ferroptosis. Fat uptake and active breakdown of lipid droplets fuel the mitochondrial Krebs cycle to generate ATP, which is critical for B1 cells to sustain mitochondrial oxidative phosphorylation [142]. ACSL-mediated activation of fatty acids is required for lipid-droplet formation [143]. Mechanistically, ACSL4 promotes the intracellular lipogenesis and lipid droplets accumulation to enhance fatty acid oxidation (FAO) and adenosine triphosphate production by upregulating the FAO rate-limiting enzyme CPT1A (carnitine palmitoyltransferase 1 isoform A) [144]. However, ACSL4 also enriches cellular membranes with long polyunsaturated omega-6 fatty acids and is essential for ferroptosis execution. Thus, activation of ACSL4 during lipid-droplet formation and lipolysis may collaterally facilitate ferroptosis in *Gpx4*-deficient B1 and MZ B cells. Moreover, since high intracellular free fatty acids levels also cause oxidative stress [145], B1/MZ B cells may require GPX4 to prevent accentuated ROS and ferroptosis. Consequently, GPX4 is dispensable for the development and maintenance of follicular B cells, antibody responses, and germinal center reactions, whereas B1 and MZ B cells die by ferroptosis in the absence of GPX4 [141]. These data shed light on the complex interplay between subset-dependent-B cell metabolism, their redox biology and ferroptosis.

B cell ferroptosis was very recently reported in human and murine SLE [44]. Single-cell RNA sequencing and gene set enrichment analysis of B cell subsets revealed a significant enrichment of genes associated with pathways related to cell death, iron metabolism, iron ion binding, and response to oxidative stress in SLE patients. The expression of GPX4was reduced in both naive and memory B cells from SLE patients, and ultrastructural analysis of B cells from SLE patients showed mitochondrial condensation, swelling, with reduced or absent crista, features associated with ferroptosis. These features were recapitulated in B cells isolated from the MRL/lpr mice, and Liproxstatin-1 reversed lipid peroxidation in purified human B cells exposed to SLE serum, thus confirming B cell ferroptosis across species in settings of SLE/LN. We had earlier reported anomalous iron deposits in the splenic white pulp of nephritic MRL/lpr mice [38], and by identifying the occurrence of B cell ferroptosis in aged MRL/lpr mice, Chen et al. [44] mechanistically furthered our observations.

### 2.5. Renal iron handling: a potential clue to increased susceptibility of renal tubules to iron mediated pathology

Iron accumulation in renal tubular epithelial cells of LN patients and lupus-prone mice has been documented [38,146]. In the kidneys, the proximal tubular epithelial cells (PTECs) are the most metabolically active, and as such, they contain more mitochondria than any other cells in the kidney [147]. Mitochondria, the primary source of ROS [148,149], produce highly reactive and toxic hydroxyl radicals (OH) via metal-dependent breakdown using cellular transition metals, most notably iron [148,150]. Little is known about iron handling by the glomerular cells, and most of our understanding of renal iron handling is based on studies on the tubular compartment [17,151]. The distal renal tubules express proteins associated with iron import. The expression of light and heavy chain ferritin mediated iron storage is low, and the iron exporter ferroportin is not detected in distal tubules [146]. The lack of expression of ferroportin and lower expression of ferritin might render the distal tubules susceptible to iron-mediated damage. However, majority of literature dwelling on iron-induced pathology in renal tubules reports PTEC pathology and we know little about iron mediated injury in distal tubules [152-155]. This may be because, unlike the distal renal tubules, PTECs express receptors for iron import, high levels of light and heavy chain ferritin, as well as ferroportin [146]. Hence, PTECs, but not the distal renal tubules, are more likely to participate in iron recycling [146]. Under physiological conditions, a fraction of transferrin-bound Iron (TBI) is filtered by the glomerulus into the renal tubular lumen and almost entirely reabsorbed by renal tubular epithelial cells [156,157]. TBI is imported from the apical surface of the PTEC via TfR1 and megalin-cubulin endocytic complex [158,159], whereas non-transferrin bound iron (NTBI) is imported by ZIP8 and/or ZIP14 [160], such that iron loss in the urine is minimal. We have previously discussed the details of PTEC iron transport in health and LN [17].

The injury to the glomerular structure increases the permeability of all proteins, including transferrin and albumin. Unlike TfR1, the receptor for transferrin, which is post-transcriptionally downregulated in cells that accumulate excess iron [161], the expression of the megalin-cubulin endocytic complex, ZIP8, and ZIP14 is not regulated by the iron content of the cells [162]. Furthermore, PTECs also reabsorb albumin [163,164], which is a heme- and iron-carrier protein [165-167], whose excessive uptake can increase the iron content of the tubular cells. Consequently, following the breakdown of the glomerular filtration barrier, iron can be taken up by PTECs in a disproportionate manner. Thus, the combination of excessive filtered iron uptake due to a compromised glomerular function in LN and a high mitochondrial content render the PTECs susceptible to iron-catalyzed, ROS-mediated injury and ferroptosis.

### 2.6. Renal tubules, iron, and ferroptosis

Reports of the beneficial effects of modulating iron metabolism in SLE/LN are limited. Non-heme iron levels in the kidneys of (New Zealand Black X New Zealand White) F1 (NZB/W) mice are increased compared with healthy New Zealand White (NZW) mice in an age- and strain-dependent manner [36]. The expression of TfR1 is attenuated in tubules from NZB/W compared to NZW mice, and ferritin expression increased, consistent with increased iron accumulation and compensatory downregulation of uptake pathways.

Treating these mice with deferiprone, an FDA-approved iron chelator, delayed the onset of albuminuria even though anti-dsDNA IgG levels were comparable to the vehicle-treated group. We have shown the beneficial effect of exogenous hepcidin in reducing renal iron accumulation, labile iron content, and glomerular and tubular injury in MRL/lpr mice [38]. As in the NZB/W mice, hepcidin treatment did not reduce renal IC deposits and serum autoantibodies, but it mitigated intrarenal cytokine production, immune cell infiltration, and tubular injury without worsening lupus-associated anemia. Hepcidin was protective even when administered to mice with existing proteinuria, highlighting its therapeutic potential. Our study challenges the existing paradigm that suggests that inhibition of ferroportin-induced iron export should worsen iron-mediated injury [168]. We observed that intermittent administration of exogenous hepcidin more than doubled the expression of renal FtH, a cytoprotective molecule [38]. The protective role of FtH in a rodent model of thymocyte antigen-1-induced glomerulonephritis was previously highlighted by Cheng et al. who showed that reduced expression of FtH accelerated mesangial cell death [169]. Furthermore, forced expression of wild-type FtH made the cells more resistant to ROS-mediated injury, and this salutary effect was not observed in FtH mutants that lost the capacity for iron storage and ferroxidase activity [169].

A common theme in the reno-protective effect of iron chelator or hepcidin was the lack of difference in circulating autoantibodies and glomerular IC deposits between vehicle and drug-treated animals, suggesting a direct effect on renal parenchyma. Thus, these data support the ongoing hypothesis that approaches to increase renal parenchymal cell resistance may mitigate progression to renal disease in SLE.

Since most iron resorption and accumulation occurs in the tubular compartment of the kidneys, it is not surprising that ferroptosis predominantly occurs in this segment of the nephron. Ferroptosis-related differentially expressed genes were identified in the glomeruli and tubulointerstitium in kidney biopsies of healthy controls and LN patients [20,170]. These studies identified genes associated with antioxidant system inhibitors and ferroptosis suppressors significantly altered in LN. Expression of some of these genes was positively correlated with immune cell infiltration in glomeruli [20,170]. However, most of the data in these reports is based on transcriptomics, which has not been validated by animal studies that can open avenues for mechanistic and therapeutic queries.

We have recently described the occurrence of intra-renal ferroptosis in LN patients and in female MRL/lpr and male (NZW X BXSB) F1 mice, two spontaneous models of murine LN using protein, gene, and lipidomic analyses [42]. Our study, for the first time, showed that the protein expression of 4-hydroxynonenal (4-HNE), a marker for lipid peroxidation [171], and ACSL4 are increased in the iron accumulating tubular segments of the nephron in both human and murine LN kidneys. In line with an active ferroptosis program, we reported that SLC7A11 (cystine importer), the glutathione synthesis pathway, and GPX4 was attenuated in the nephritic kidneys. GPX4 is a glutathione-dependent enzyme, and glutathione synthesis requires adequate cystine supply. As pièce de resistance, we observed a significant increase in the esterification of the sn-2 chain of PE with adrenic acid (C22:4) (P-18:0/22:4), the preferred substrate for lipid peroxidation [172] in the nephritic kidneys [42]. To highlight the importance of labile iron $Fe^{2+}$ sequestration in the tubular

compartment during the evolution of LN, we showed that FtH deficiency selectively in PTECs exacerbated tubular injury and ferroptosis in a model of nephrotoxic serum-induced immune complex glomerulonephritis [42]. This observation further validated our previous study [38], which showed that hepcidin-induced increase in intrarenal FtH is associated with amelioration of LN. LN patients' serum induced ferroptosis in human PTECs, which was reversed by Liproxstatin-2, a novel next-generation ferroptosis inhibitor, in a prophylactic and therapeutic approach, identifying ferroptosis as a druggable target to mitigate tubular injury in LN.

### 2.7. Conclusion

The studies highlighted in this review suggest that a finely tuned iron metabolism supports cellular bioenergetic, but when dysregulated, can cause ferroptosis, contributing to immune and tubular cell pathology in SLE and LN. We have highlighted articles that focus on the dysregulation of iron metabolism in immune and parenchymal cells involved in the pathogenesis of SLE/LN. During the evolution of SLE and its progression to LN, innate and adaptive immune cells use iron for varying functions. Novel approaches have revealed the Janus face of iron in immune cells, wherein it transcends its obligatory physiological functions to drive pathology and, consequently, the outcomes of SLE/LN.

Ferroptosis is most likely integral to lupus immune and parenchymal cell dysfunction, inflammation, and tissue damage. A continuum of publications indicates that ferroptosis is not only a novel therapeutic target in SLE/LN but understanding why cells progress to ferroptosis may shed light on fundamentals of cellular biology. For example, infections are common in SLE [173], and neutrophils release large amounts of ROS and undergo netosis during infections [174]. Since the hepcidin-ferroportin axis actively sequesters iron in neutrophils [175], whether its chronic activation impacts neutrophil ferroptosis to provide additional autoantigens remains to be investigated. Additionally, the understanding of the crosstalk between metabolism and ferroptosis is limited. The metabolic needs of proliferative and autoreactive B cells that drive a preference for fatty acid uptake and active breakdown of lipid droplets to generate ATP also generate intermediate metabolites essential for ferroptosis. How cells utilize iron for enhanced metabolic need, while putting a brake on ferroptosis may help identify novel cellular mechanisms in the pathogenesis of SLE. Thus, new generation ferroptosis inhibitors like FerroLOXINs that block enzyme-protein complexes [176], unlike archetype ferroptosis inhibitors like Liproxstatin-1 (that suppress nonenzymatic lipid peroxidation-induced ferroptosis by trapping the lipid derived free radicals) [100] hold promise as adjunct therapy to reduce dose and dependency of toxic immunosuppressants.

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## Data availability

No data was used for the research described in the article.

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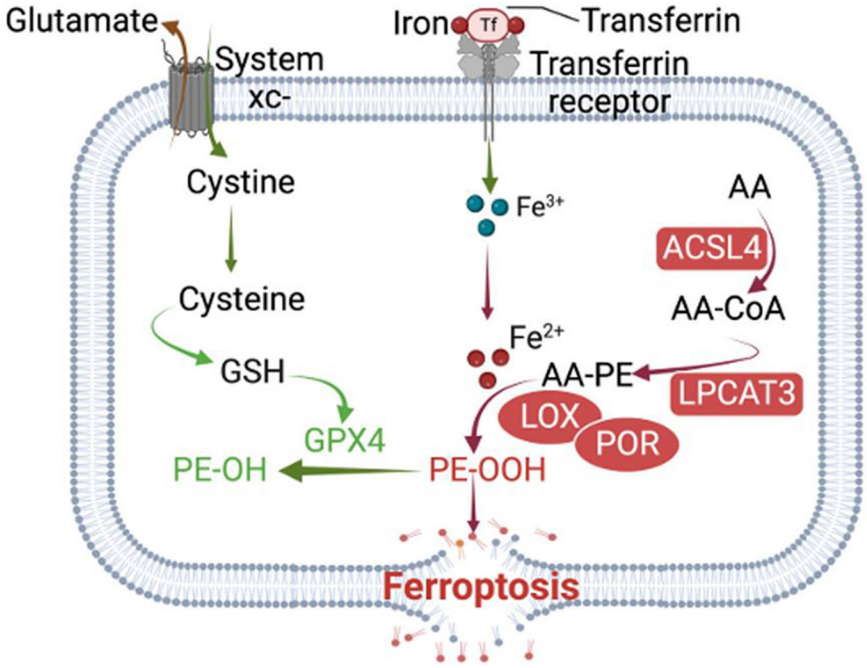


**Fig. 1.**

Adequate availability of cysteine via the cystine-glutamate antiporter, system xc – prevents the dynamic lipid-induced toxicity under physiological conditions and in pathology. Cysteine is essential for GSH synthesis, which in turn is required for the activity of GPX4 to convert toxic lipid hydroperoxides (PE-OOH) into inert lipid alcohols (PE-OH). The long-chain acyl-coenzyme A (CoA) synthase 4 (ACSL4) in conjunction with lysophosphatidylcholine acyltransferase 3 (LPCAT3) converts poly unsaturated fatty acid (PUFA) like Arachidonic acid (AA) into AA-CoA intermediate that is ultimately esterified into phosphatidylethanolamine (PE). Then, acid-15-lipoxygenase (ALOX15) catalyzes the oxidation of these esterified-PE and excessive AA-CoA to its PE-OOH, thus promoting ferroptosis. Intracellular $Fe^{2+}$ promotes lipid peroxidation and ferroptosis by increasing the catalytic activity of ALOX15 to exacerbate ROS. Additionally, $Fe^{2+}$ promotes the non-enzymatic arm of ferroptosis by participating, in the Fenton reaction to catalyze the generation of reactive free radicals, which target unsaturated phospholipids and convert them to toxic phospholipids hydroperoxides.

System xc−, GPX4: Attenuate ferroptosis; Iron, ACSL4, LPCAT3; Promote ferroptosis.