• Review Article •

Targeting ferroptosis in ocular diseases: mechanisms, clinical implications, and therapeutic horizons

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Received: 2026-03-28 Accepted: 2026-06-02

Abstract

● Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, has been increasingly implicated in selected ocular diseases, although its causal relevance varies across disease entities. The retina and retinal pigment epithelium are biologically susceptible to ferroptosis-related injury because of their high oxygen demand, abundant polyunsaturated lipids, mitochondrial activity, light exposure, and tightly regulated iron handling. This review summarizes core mechanisms of ocular ferroptosis, including iron uptake and export, glutathione–glutathione peroxidase 4 (GPX4)-dependent antioxidant defense, lipid peroxidation, mitochondrial dysfunction, neuroinflammation, and blood–retina barrier disruption. We discuss evidence from major degenerative, vascular, ischemic, hereditary, infectious, and immune-mediated retinal diseases, with particular attention to glaucoma, age-related macular degeneration, diabetic retinopathy, ocular toxoplasmosis, uveitis, retinal vasculitis, and inflammatory chorioretinopathy. We also evaluate ferroptosis-targeted therapeutic strategies, proposed operational criteria for defining ferroptosis in retinal disease, and candidate structural, functional, biochemical, and imaging endpoints for future translational studies. Current evidence supports ferroptosis as a context-dependent contributor to retinal injury rather than a uniform pathogenic mechanism. Future studies should integrate cell-type-resolved biomarkers, lipidomic and imaging readouts, functional rescue experiments, and clinically meaningful visual outcomes to clarify when ferroptosis modulation may support vision preservation.

● **KEYWORDS:** ferroptosis; lipid peroxidation; retinal pigment epithelium; iron chelation; glaucoma; age-related macular degeneration; diabetic retinopathy; ischemic fundus disorders

DOI:10.18240/ijo.2026.09.21

Citation: Zhang NY, Kong HQ, Liao YQ, Pan YJ, Sun W, Xi L, Yu HH, Shi YH. Targeting ferroptosis in ocular diseases: mechanisms, clinical implications, and therapeutic horizons. *Int J Ophthalmol* 2026;19(9):1858-1877

INTRODUCTION

Historical Evolution of Iron and Cell-Death Concepts in Retinal Disease Degenerative and vascular fundus diseases have historically been interpreted through broad pathophysiological frameworks, including ischemia, oxidative stress, metabolic compromise, apoptosis, and nonspecific necrosis. However, the ocular relevance of iron toxicity has long been recognized. Clinical observations of ocular siderosis and retained intraocular iron foreign bodies provided early evidence that excess iron can damage the retina and retinal pigment epithelium (RPE)[1]. Later histopathological studies reported abnormal iron deposition in the macula, retinal pigment epithelial layer, optic nerve head, and degenerating retinal tissues[1-3]. For many years, such iron accumulation was generally interpreted as a secondary consequence of advanced degeneration rather than as part of a regulated cell-death program[1-3]. The identification of ferroptosis as an iron-dependent, lipid peroxidation-driven form of regulated cell death has expanded this framework by linking iron

dysregulation, glutathione–glutathione peroxidase 4 (GPX4) failure, and impaired lipid peroxide detoxification to retinal injury[4]. With evidence accumulating from experimental models indicating that manipulation of ferroptosis-related pathways can modify retinal damage, ferroptosis is increasingly viewed as a potential contributor or amplifier in selected fundus diseases, rather than a uniform primary mechanism across all disease contexts[2-4].

Understanding Natural Retinal Tissues and Their Intrinsic Susceptibility The neurosensory retina and RPE create a physiologically dependent unit that is extremely metabolically active, structurally specific, and subject to chronic oxidative stress due to its functions[5-6].

Photoreceptor cells replace their outer segment membrane that has been metabolically modified with polyunsaturated fatty acids (PUFA), continually operates at high oxygen concentrations, and need high-density mitochondrial networks to generate phototransduction signals[7-9].

For the RPE to function optimally, it must remove and recycle the discarded photoreceptor outer segments that are rich in visual chromophores, maintain ion and fluid transport across the photoreceptor-RPE interface, and protect the integrity of the outer blood-retina barrier[10-12]. Iron plays a critical role in maintaining the fine balance of this system since it acts as a cofactor for enzymes involved in oxidative phosphorylation, the visual cycle, and neurotransmitter synthesis[1].

Since the retinal functional dependency on iron creates significant structural vulnerability, this is directly related to the potential for ferroptosis to occur. There is considerable evidence that the combination of high levels of oxidation prone lipids, high levels of mitochondrial activity, and continuous generation of reactive oxygen species (ROS) through the photochemical reaction makes the retina uniquely vulnerable to disturbances in iron availability. Therefore, when there are disruptions in the ability to take up iron into the cell, store it, utilize it, or export it, labile iron pools increase and drive Fenton reactions which lead to sequential lipid peroxidation of retinal membranes. Thus, the retina possesses biological features that may predispose it to ferroptosis-related injury when iron homeostasis and redox balance are disrupted, although such changes should be interpreted in the context of overlapping oxidative, inflammatory, and regulated cell-death pathways[13-15].

Evolution of Ferroptosis and Biomimetic Voncepts in Ocular Science Ferroptosis was first recognized through oncologic and neurodegenerative studies when researchers identified that there existed a specific form of iron-dependent lipid damage which led to what appeared to be an atypical form of cell death—one that did not fit the known mechanisms of cell death (apoptosis, necrosis)[16]. It became apparent after the researchers transitioned their focus from those areas of study into the field of ophthalmology that several of the key characteristics of ferroptosis (iron overload, phospholipid oxidation, disruption of the glutathione pathway) were also found in previously documented forms of retinal degeneration. The researchers observed the presence of these characteristics of ferroptosis by utilizing *in vitro* and *in vivo* models of photoreceptor damage, RPE toxicity, glaucoma optic neuropathy, and ischemic/reperfusion injury, all of which exhibited evidence of iron overload, oxidative lipid damage, and sensitivity to ferroptosis inhibitors[17-19].

As the preclinical data were emerging regarding the potential use of Biomimetic & Bio-Inspired approaches to regulate ferroptosis in the retina, the development of antioxidant nanocarriers, enzyme-mimetic nanoparticles, gene-based therapeutic technologies that mimic endogenous protective mechanisms (GPX4, ferroportin, ceruloplasmin, transferrin *etc*.) were being utilized to enhance ocular endogenous defenses against ferroptosis. Induced pluripotent stem cell-derived RPE culture systems and retinal organoid models have been established and provide significant experimental controls over the biological system being studied while providing models of ferroptosis-related injury in a controlled, biomimetic environment. As a result of these advances, ferroptosis has become an increasingly investigated pathway in ocular science and may provide one molecular framework for linking iron-dependent lipid damage to tissue-level degenerative processes[20-22].

Current Applications and Clinical Significance in Fundus Diseases Ferroptosis has clinical relevance in a wide range of diseases affecting the fundus. Research on glaucoma indicates that iron deposition, lipid peroxidation, oxidative stress, and impaired antioxidant defense are associated with retinal ganglion cell loss and optic nerve injury, in addition to elevated intraocular pressure (IOP), suggesting that ferroptosis-related pathways may represent complementary therapeutic targets alongside IOP-lowering strategies[23-24]. The evidence from studies of age-related macular degeneration (AMD), specifically the atrophic form, indicates that the RPE experiences abnormal regulation of iron, accumulates lipid peroxides, and demonstrates diminished ability to counteract oxidative stress consistent with a ferroptosis-related mechanism of macular injury[2,25].

Chronic metabolic disturbances, along with microvascular defects and retinal tissue hypoxia associated with diabetic retinopathy and ischemic fundus disease, collectively result in unstable redox and iron homeostatic states. Redox instability, microvascular dysfunction, and tissue hypoxia may create conditions in which ferroptosis-related pathways contribute to the link between vascular pathology, neuronal

injury, and blood-retina barrier disruption. Rapid increases in oxidative stress and redox-active iron after acute insults, such as retinal detachment, trauma, or ischemia-reperfusion, may trigger ferroptosis-related injury in photoreceptors and inner retinal neurons under susceptible conditions[26-28]. Additionally, hereditary and inflammatory retinopathies have been identified in which genetic defects, immune activation, or infection-driven inflammation may converge on mitochondrial dysfunction, lipid metabolic disturbance, and altered iron regulatory protein function, all of which are consistent with ferroptosis-related vulnerability. In particular, ocular toxoplasmosis has recently emerged as an infectious retinochoroiditis model in which disrupted iron handling, lipid peroxidation, reduced GPX4-dependent antioxidant defense, and photoreceptor injury are mechanistically linked to retinal inflammation. More broadly, immune-mediated posterior segment inflammation, including autoimmune uveitis, retinal vasculitis, and inflammatory chorioretinopathy, provides clinically relevant settings in which iron metabolism, lipid oxidation, innate immune activation, and retinal tissue injury may interact dynamically.

Rationale and Objectives of the Present Review While there has been an explosion of scientific literature surrounding ferroptosis; the understanding of ferroptosis at the current time is still highly compartmentalized among subdomains, disease states, and experimental systems. A high proportion of studies report findings from single disease states, molecular targets, or experimental systems; therefore, it remains challenging for clinicians and researchers to determine when ferroptosis acts as a primary driver, secondary amplifier, or associated stress response in fundus pathology. Therefore, what is needed is a synthetic approach that integrates the mechanistic basis of ferroptosis with its manifestation(s) in glaucoma, AMD, diabetic retinopathy, ischemia, retinal detachment/trauma, hereditary retinal degeneration, and infectious or immune-mediated inflammatory fundus diseases, including ocular toxoplasmosis; as well as a critical assessment of the translational potential of therapies directed against ferroptosis. Importantly, throughout this review, ferroptosis is considered as a context-dependent contributor to retinal injury rather than a uniform or exclusive cause of fundus disease.

This review addresses this gap by curating clinical and experimental studies to create a balanced narrative that connects ferroptosis-related mechanisms with retinal pathobiology while acknowledging differences in evidence strength across disease contexts. Throughout the disease-specific sections, we distinguish findings supported by direct functional evidence from those inferred from associated iron dysregulation, lipid peroxidation, or antioxidant failure. This review aims to provide an overview of the core molecular mechanisms involved in ferroptosis in ocular tissue, to examine how ferroptosis-related processes may contribute to the pathogenesis or progression of major fundus diseases under specific conditions, and to evaluate emerging strategies for modulating ferroptosis-related injury as potential therapeutic interventions. As such, this review will also highlight gaps in methodology, areas of uncertainty in concept, and highest priorities for future research with the long-term goal of providing evidence-based rationale for the development of ferroptosis-targeted interventions aimed at preserving vision in patients with retinal/fundus disorders.

MECHANISTIC FOUNDATIONS OF FERROPTOSIS IN OCULAR TISSUES

Ferroptosis is an iron-dependent form of regulated cell death characterized by lipid peroxidation and failure of lipid peroxide detoxification systems, particularly the glutathione–GPX4 axis, ultimately compromising membrane integrity[21]. The development of this process in the eye involves the highly specialized environments of the neurosensory retina and RPE. These two locations have a high demand for iron, a large amount of polyunsaturated fats, and, therefore, a continuous exposure to oxidative stress. Therefore, understanding the intersections between iron homeostasis, fatty acid metabolism, and redox control in ocular tissues is essential for evaluating when and how ferroptosis-related processes may contribute to fundus disease.

It is important to emphasize that iron dysregulation, lipid peroxidation, and oxidative stress are not specific to ferroptosis. These biochemical features may overlap with apoptosis, necroptosis, pyroptosis, autophagy-related cell death, and nonspecific oxidative injury in complex retinal tissues. Therefore, in this review, ferroptosis is discussed as part of a broader and interconnected cell-death landscape rather than as a solitary execution pathway. The relative contribution of ferroptosis is likely to vary according to disease type, disease stage, cell type, and the nature of the initiating stress.

In addition to its role as a regulated cell-death pathway, ferroptosis-related lipid peroxidation may also influence retinal inflammation. Oxidized lipid mediators and damaged-cell signals generated during ferroptosis can potentially activate microglia, recruit macrophages, modulate complement-related responses, and aggravate vascular inflammatory injury. This immunogenic and inflammation-amplifying dimension is particularly relevant in infectious and immune-mediated retinal diseases, where cell death, innate immune activation, and barrier disruption may reinforce one another.

Iron Handling and Redox-Active Pools in the Retina The retina requires iron to perform normally. Iron is needed by mitochondria located within retinal ganglion cells and photoreceptors to enable oxidative phosphorylation; by the

key enzymes of the visual cycle present in the RPE; and by those of the neurotransmitters found in the neurons of the inner retina. The iron that is present in the eye at physiological levels is regulated very tightly and is carried *via* the bloodstream to the ocular tissues bound to transferrin. It then crosses the blood-retinal barrier, is stored in a safe form within ferritin, and is transported out of the retina using an iron transporter called ferroportin. Under normal physiological conditions the size of the labile iron pool in the eye is maintained at a small size and is under tight control[26].

Ferroptosis-related vulnerability may increase when iron homeostasis in the eye is disrupted. Retinal and RPE cells may show ferroptosis-related changes under conditions such as aging, metabolic stress, hypoxia, inflammation, and mutations affecting iron regulatory proteins. All of these disruptions have caused an increase in the size of the redox-active iron pool in retinal and RPE cells. When the level of ferrous iron exceeds a certain threshold, it will participate in Fenton type reactions which convert mild ROS into highly reactive radicals. The radicals produced from Fenton type reactions react with the membrane lipids surrounding them causing peroxidation of the membranes. When antioxidant buffering capacity is insufficient, iron-driven lipid damage may propagate and increase the likelihood of ferroptosis, although overlapping forms of oxidative and inflammatory cell death may coexist in diseased retinal tissue[13,25-26].

Polyunsaturated Lipids and Lipid Peroxidation Cascades The retina has high levels of PUFA which can be found in the outer segment of photoreceptors and apical membrane of RPE. PUFAs contribute to the fluidity and biochemistry necessary for the efficiency of phototransduction; however, they are also prone to peroxidation[7-8,29]. In the ferroptotic cascade, the peroxidation of PUFA containing phospholipids begins with their enzymatic incorporation into membrane phospholipids by Acyl-CoA synthetase long chain family member 4 or similar enzymes and subsequent oxidation *via* iron-dependent pathways[9,30-31].

In addition to enzymatically initiated peroxidation, lipoxygenases and other oxidases insert oxygen into the PUFA chains of the acyl groups. Simultaneously, non-enzymatic free radical mechanisms involving iron and ROS initiate and propagate lipid peroxidation across the membrane[32]. The resultant phospholipid hydroperoxide fragments into reactive aldehydes that cross link proteins, disrupt the structural organization of the membrane and compromise the structural integrity of the organelles. Because retinal and RPE cells contain abundant oxidation-prone lipids and undergo continuous membrane renewal, lipid peroxidation may exceed local antioxidant capacity and increase susceptibility to ferroptosis-related injury[13,27,33].

Antioxidant and Anti-Ferroptotic Defense Systems Cells also have specific defenses against ferroptosis through an array of lipid antioxidants and free radical scavengers. However, these defenses are limited by the availability of cofactors (*i.e.*, vitamin E) and, therefore, depend on dietary intake. The primary defense mechanism in this case involves the reduction of the oxidized form of glutathione, glutathione disulfide (GSSG), back to its reduced state, reduced glutathione (GSH), *via* nicotinamide adenine dinucleotide phosphate (NADPH)[34-36]. This process is necessary to maintain adequate amounts of GSH for use in detoxifying the lipid peroxide products formed during oxidative damage. A second defense mechanism involves the reduction of hydroperoxides formed from fatty acids, such as arachidonic acid, to less harmful forms. This is accomplished through the action of the enzyme GPX4. GPX4 utilizes GSH to reduce the lipid peroxide to its alcohol form. This mechanism is essential in preventing the accumulation of lipid hydroperoxides within cellular membranes and the subsequent disruption of membrane structure and function[37-39].

A number of studies have demonstrated that the retina and RPE utilize this GPX4/glutathione pathway to prevent lipid peroxidation and oxidative damage associated with aging and disease. For example, when GPX4 is inhibited by certain compounds, the formation of lipid peroxides increases dramatically, leading to the rapid degeneration of the retina[40]. Similarly, when glutathione is depleted due to increased demands placed upon the glutathione system by oxidative stress, lipid peroxides accumulate rapidly and cause significant damage to the retina and RPE. The loss of glutathione has also been shown to inhibit the ability of the retina to remove damaged mitochondria, further contributing to oxidative damage[41-42].

There are several additional defense systems in the retina and RPE that help to regulate ferroptotic sensitivity. These include coenzyme Q-dependent lipid antioxidant pathways, NADPH-generating enzymes, and other redox couples. While much remains to be learned about the role of these pathways in the eye, growing evidence suggests that ferroptosis may emerge when multiple layers of lipid antioxidant defense are insufficient, particularly in cells already exposed to iron dysregulation and oxidative stress.

Table 1[43-48] summarizes key ferroptosis-related regulators in ocular tissues, their core functions, and illustrative evidence from specific retinal cell types or disease models where available.

Organelle-Specific Contributions: Mitochondria, Lysosomes, and Endoplasmic Reticulum Ferroptosis is generally thought of as being initiated at the plasma membrane, but each of the many different cellular organelles has unique

Table 1 Key ferroptosis-related regulators and their illustrative relevance in retinal cell types and disease models

Regulator or pathway	Core function in ferroptosis	Illustrative relevance in the eye
Labile iron pool, transferrin, ferritin, ferroportin[43]	Control uptake, storage, and export of redox-active iron and thereby determine the magnitude of iron-catalysed radical formation	Implicated in RPE iron handling, photoreceptor/RPE injury, optic nerve head stress, ischemic retinal injury, and ocular toxoplasmosis models; altered iron storage or export may increase ferroptosis-related vulnerability in RPE cells, retinal ganglion cells, and photoreceptors
PUFA metabolism (including ACSL4 and related enzymes)[44]	Incorporate PUFA into membrane phospholipids, creating substrates for peroxidation	Highly relevant to photoreceptor outer segments and RPE membranes, where PUFA-rich lipids are abundant; supports susceptibility in AMD-like RPE stress, light-induced injury, and photoreceptor degeneration models
Lipoxygenases and other oxidases[45]	Catalyse enzymatic oxygenation of PUFA-containing phospholipids, generating phospholipid hydroperoxides	May contribute to lipid peroxide accumulation in RPE cells, photoreceptors, and ischemic or light-stressed retina; some mechanistic details remain partly extrapolated from non-ocular ferroptosis systems
Cystine–glutamate antiporter (system Xc^-)[46]	Imports cystine required for glutathione synthesis and maintains intracellular reducing capacity	Relevant to RPE and retinal neuronal models in which cystine uptake or GSH synthesis is impaired; altered SLC7A11 activity may sensitize retinal cells to lipid peroxidation and ferroptosis-related injury
Glutathione and glutathione peroxidase 4[47]	Detoxify phospholipid hydroperoxides and protect membrane integrity	Directly relevant to RPE cells, photoreceptors, and retinal ganglion cells; GPX4/GSH impairment is a common readout in retinal degeneration, oxidative injury, ischemia-reperfusion, and ocular toxoplasmosis models
Mitochondrial metabolism and redox handling[48]	Regulate production of reactive oxygen species and iron–sulfur cluster turnover	Particularly relevant to photoreceptors, RPE cells, and retinal ganglion cells because of their high mitochondrial demand; direct retinal evidence exists, but some organelle-level mechanisms remain extrapolated from non-ocular systems

RPE: Retinal pigment epithelium; PUFA: Polyunsaturated fatty acid; ACSL4: Acyl-CoA synthetase long-chain family member 4; AMD: Age-related macular degeneration; SLC7A11: Solute carrier family 7 member 11; GPX4: Glutathione peroxidase 4; GSH: Reduced glutathione.

and complementary functions that shape ferroptotic sensitivity. For example, mitochondria are large producers of ROS and sites where iron-sulfur clusters are metabolized; because of their high concentration of mitochondria, when disruptions occur to either electron transport or mitochondrial dynamics in photoreceptor and RPE cells, they generate higher levels of ROS as a result of increased electron leakage and feed into an iron catalyzed peroxidation system[49-50].

Lysosomes also contribute to this process by controlling the rate of degradation of ferritin *via* ferritinophagy. By degrading ferritin, the iron stored in the ferritin is released back into the cytoplasm and increases the size of the labile iron pool. Therefore, under conditions of high rates of autophagy or lysosomal stress, this process can be one of the major contributors to ferroptotic sensitivity[51-53]. The endoplasmic reticulum acts as a central site for protein folding and stress signaling. Endoplasmic reticulum stress responses regulate the expression of transporters, antioxidant enzymes and redox regulatory genes, such as those involved with cystine uptake and glutathione biosynthesis[54-55]. In diabetes, hypoxia, or inflammation, combined mitochondrial, lysosomal, and endoplasmic reticulum stress may increase ferroptosis-related vulnerability in retinal cells, although the relative contribution of each organelle remains incompletely defined in ocular tissues. Some organelle-specific mechanisms discussed here are supported directly in retinal or RPE models, whereas others remain extrapolated from cancer, systemic neurodegeneration, or other non-ocular ferroptosis systems. Future retinal studies should determine whether these organelle-level mechanisms operate similarly across photoreceptors, RPE cells, retinal ganglion cells, glia, endothelial cells, and pericytes. A schematic representation of these mechanistic interactions is shown in Figure 1, which illustrates the relationships between iron regulation, lipid peroxidation, and antioxidant defenses within a typical retinal cell[56].

Cell Type–Specific Vulnerability in Ocular Ferroptosis

Photoreceptors, which have an extremely high metabolic rate, contain many mitochondria, and contain many poly-unsaturated lipids, all of which are exposed to light, are particularly susceptible to ferroptosis. This susceptibility will be compounded by any abnormality in either iron metabolism or antioxidant defense in these cells. Similarly, the RPE may be particularly susceptible to ferroptosis-related stress because it continuously phagocytoses and digests highly oxidizable photoreceptor outer segments. Although normally a healthy and normal process, if the RPE has reduced antioxidant capacity or if there is a problem with regulating iron, then the RPE will have a high propensity for undergoing ferroptosis-related injury.

Glaucomatous disease causes chronic mechanical, metabolic and oxidative stress to retinal ganglion cells at the optic nerve head. In addition to the above stresses, mechanical strain caused by increased IOP and impaired axonal transport also contribute to increased susceptibility to ferroptosis in these cells[57-59]. Experimental evidence indicates that, under certain circumstances, ferroptosis may occur in ganglion cells, due to increased levels of iron, lipid peroxidation and loss of antioxidant defenses.

In both diabetic and ischemic retinopathy, the microvascular endothelial cells and pericytes are subjected to hyperglycemia,

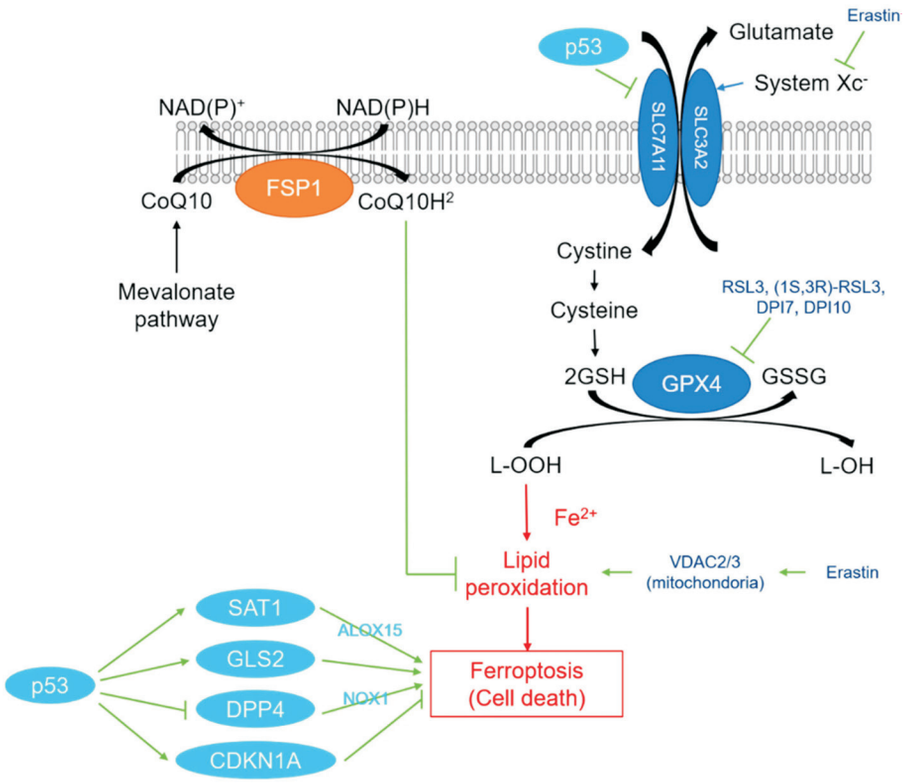

Figure 1 Schematic diagram of the ferroptosis signaling pathway Adapted from reference[56]. Ferroptosis is driven by iron-dependent lipid peroxidation and failure of lipid peroxide detoxification systems. Glutathione peroxidase 4 (GPX4) reduces lipid hydroperoxides (L-OOH) to non-toxic lipid alcohols (L-OH) using reduced glutathione (GSH) as a cofactor; in this process, GSH is oxidized to glutathione disulfide (GSSG), which is regenerated by glutathione reductase (GR). GSH synthesis depends on cysteine availability, which is supported by the cystine–glutamate antiporter system Xc^-, whose light-chain component is solute carrier family 7 member 11 (SLC7A11). Ferroptosis suppressor protein 1 (FSP1) regenerates ubiquinol from ubiquinone independently of GPX4 and acts as a membrane-associated radical-trapping system. Oxidative phosphorylation (OXPHOS) and the tricarboxylic acid (TCA) cycle can contribute to ferroptosis sensitivity by regulating mitochondrial metabolism, redox balance, and lipid peroxide accumulation. p53 may either promote or suppress ferroptosis depending on cellular context through targets such as spermidine/spermine N1-acetyltransferase 1 (SAT1), glutaminase 2 (GLS2), cyclin-dependent kinase inhibitor 1A (CDKN1A/p21), dipeptidyl peptidase 4 (DPP4), and SLC7A11. $NAD(P)^+$: Oxidized nicotinamide adenine dinucleotide phosphate; NAD(P)H: Reduced nicotinamide adenine dinucleotide phosphate; CoQ10: Coenzyme Q10; $CoQ10H^2$: Ubiquinol; RSL3: A glutathione peroxidase 4 inhibitor; DPI7 and DPI10: Diarylpyrazole ferroptosis inducers; VDAC2/3: Voltage-dependent anion channels 2 and 3; ALOX15: Arachidonate 15-lipoxygenase; NOX1: NADPH oxidase 1.

fluctuations in oxygen availability, and inflammatory mediators. For the maintenance of the integrity of the blood-retinal barrier, the endothelial cells must maintain their membrane structure and tight junctions[60-62]. Therefore, ferroptosis-related injury in these cells may contribute to blood-retinal barrier disruption and capillary dropout, although these vascular changes are also shaped by inflammation, metabolic stress, and other forms of cell death. Microvascular endothelial cells can influence the function of glial cells (Müller cells and microglia) through glutamate buffering, redistribution of iron, and signaling for immune response. However, once lipid mediators associated with ferroptosis have activated the glial cells, the glial cells can produce cytokines that can promote additional ferroptosis-related injury, thus forming a feedback loop between lipid injury mediated by iron and inflammation[63].

FERROPTOSIS IN GLAUCOMA

The traditional conceptualization of glaucoma as an ongoing optic nerve disease process, with increased IOP, vascular problems and individual risk factors combining to damage retinal ganglion cell bodies and axons, has been supported by the primary explanatory models for decades; mechanical deformation of retinal ganglion cells at the lamina cribrosa, impaired axoplasmic transport of nutrients, and a multitude of apoptotic and necrotic cell death mechanisms. However, with the increasing body of knowledge on the molecular basis of ferroptosis, it has become apparent that there is a new way of looking at how iron dependent lipid peroxidation and failure of cellular defenses against oxidative stress contribute to the degeneration of neurons in glaucoma. In this context, IOP and vascular abnormalities may be viewed as upstream stresses that

disturb iron metabolism, redox equilibrium, and mitochondrial function within retinal ganglion cells, thereby increasing susceptibility to ferroptosis-related injury[14,64-65].

Iron Dysregulation and Oxidative Microenvironment in Glaucomatous Tissues The optic nerve head and peripapillary retina represent locations with high levels of metabolic need as well as unique biomechanical stresses. Ganglion cell bodies require uninterrupted axoplasmic transport across the lamina cribrosa; consistent mitochondrial adenosine triphosphate production; and precise redox balance to ensure continuous signal transmission along the visual pathway[66]. In glaucoma, elevated IOPs; changed translaminar pressure gradients; and compromised microvasculature alter this state of balance. This results in increased mechanical and oxidative stress on axons and glial cells and an increase in the amount of ROS produced locally in response to the oxidative stress caused by the compromised functioning of mitochondria (which are already overburdened in terms of producing the high amounts of energy required by ganglion cells).

In this environment of increased oxidative stress, maintaining a balance of iron homeostasis is difficult. Mechanical and ischemic stress may result in impaired gene expression or protein translocation for iron transporters, disrupted ferritin iron storage and ferroportin mediated iron export, and damaged blood-retina and blood-optic nerve barrier. Activated microglia and continued low-grade inflammation also contribute to alterations in iron distribution *via* the release of cytokines that regulate proteins involved in iron metabolism. Increased accumulation of labile iron within axons, somas, and glial cells may create a localized redox environment that supports Fenton chemistry and increases the formation of highly reactive free radicals, thereby predisposing retinal ganglion cells to ferroptosis-related injury[14,23].

Retinal Ganglion Cell Vulnerability to Ferroptosis-Related Stress The retinal ganglion cells have an extraordinary location in relation to ferroptosis due to their large and unmyelinated axons inside the eye and in front of the optic nerve, with their dense mitochondrial clusters for the constant activity and in which they are subject to several different stresses (mechanical, metabolic, and oxidative). The biochemical changes associated with ferroptosis have been found in retinal ganglion cells from animal models of glaucoma, including high levels of labile iron, high levels of lipid peroxidation, and disruption of the glutathione/GPX4 redox system[24,65,67].

Although these changes occur throughout the length of the axon, the highest concentrations were found in areas where the mechanical and metabolic stresses on the cells are greatest, particularly at the pre-laminar and laminar sections of the optic nerve. At these locations there are significant disruptions of the normal structure and function of the extracellular matrix and astrocytes surrounding the axons resulting in disrupted axonal transport of damaged mitochondria and accumulated iron. In addition, the ganglion cells are chronically exposed to excitotoxic glutamate, variable perfusion and pro-inflammatory mediators all of which can be expected to impair the ability of the ganglion cells to maintain their antioxidants systems. It has been proposed that once a sufficient amount of iron catalyzed lipid damage has occurred, then the ferroptotic pathway will become self-sustaining: phospholipid hydroperoxides will continue to accumulate, the membrane integrity will continue to deteriorate, and the cell will become irreversibly committed to death. This will typically occur in the absence of apoptosis like morphological changes[68-69].

Contribution of Glia, Vasculature, and Immune Signaling Retinal ganglion cells are the principal neuronal population injured in glaucoma; however, surrounding glial and vascular cells may influence their susceptibility to ferroptosis-related injury. Both astrocytes and Müller cells play a role in regulating the levels of glutamate, potassium and water outside of ganglion cell bodies; in addition, both types of cells provide buffers for, and redistribute, iron. Chronic increased pressure and/or inflammation can result in glial cells undergoing changes in their phenotype which may reduce their ability to protect ganglion cells and potentially contribute to toxicity in the case of certain conditions. The upregulation of nitric oxide (NO), cytokines, and ROS produced by activated glia, will produce additional oxidative stress on adjacent ganglion cells[23,64,69].

As the resident macrophages of the retina and optic nerve head, microglia serve as key components in the interface between inflammation and ferroptosis. Microglial activation leads to alterations in how iron is managed by the microglia, stimulation of the release of pro-inflammatory mediators, and regulation of the expression of antioxidant genes in nearby neurons and glia[70-71]. Products of lipid peroxidation that occur early in the ferroptotic process can act as danger signals and activate microglia further, creating positive feedback loops that enhance both inflammation and the effects of iron-induced damage.

Finally, the microvasculature adds another level of complexity to this system. Rarefaction of capillaries, disruption of autoregulatory mechanisms, and transient episodes of hypoxia compromise delivery of oxygen and nutrients to the optic nerve head, leading to increased mitochondrial stress and ROS formation. Disruption of normal vascular barriers allows for the abnormal entry of iron into neural tissue[72]. Collectively, these glial, vascular, and immune factors create an environment in which the initial stress could have been reversed but instead becomes a source of sustained neurodegenerative change through ferroptosis.

Intersection of Ferroptosis with Pressure-Dependent and Pressure-Independent Mechanisms The ferroptosis model has significant potential to provide an integrated explanation for both pressure-dependent and independent mechanisms of glaucomatous damage. As a major force driving damage, increased IOP generates mechanical and ischemic stress (disrupting perfusion at the optic nerve head) that reduces axonal transport and distorts the lamina cribrosa which disrupts the transport processes within ganglion cells[73]. Both types of stress lead to disturbances in the regulation of cellular iron homeostasis and the function of endogenous antioxidants, making ganglion cells more vulnerable to ferroptosis.

However, not all patients with glaucoma have significantly elevated IOP, and some individuals with high IOP do not develop comparable optic nerve damage. As a hypothesis-generating interpretation, variability in "normal-tension" or "pressure-resistant" glaucoma may be partially related to differences in mitochondrial resilience, antioxidant capacity, iron handling, lipid metabolism, or glial support. Genetic variants affecting iron transport, antioxidant enzymes, or lipid metabolism could modify susceptibility to ferroptosis-related stress at lower levels of mechanical or vascular insult, but this possibility remains speculative and requires validation in patient-stratified studies.

Thus, ferroptosis may represent one of several downstream injury pathways, alongside apoptosis, necroptosis, and nonspecific oxidative injury, through which mechanical stress, vascular dysregulation, metabolic insufficiency, and inflammatory insults contribute to retinal ganglion cell vulnerability. It should not be interpreted as a universal final endpoint shared by all forms of glaucomatous injury[23].

Considering ferroptosis as a potential contributor to glaucomatous neurodegeneration has several translational implications. The first implication is that successful treatment of glaucoma will require addressing the metabolic and redox vulnerabilities of retinal ganglion cells and their environment, in addition to lowering IOP. Iron chelators, lipophilic antioxidants, and small molecules that inhibit ferroptosis could be developed as adjunctive therapeutic agents to be administered systemically, intravitreally, or through slow-release implant devices positioned near the optic nerve head.

The second implication is that ferroptosis provides a theoretical basis for developing biomarkers. Non-invasive imaging methods or markers in ocular fluids to assess iron accumulation, lipid peroxidation products, and alterations in glutathione metabolism in the retina, optic nerve, or ocular tissues may identify those patients that are particularly susceptible to ferroptotic damage. Biomarkers such as these may improve the identification of patients who would benefit from neuroprotective interventions, serve as pharmacodynamic measures in clinical trials of ferroptosis modulating agents, and improve risk stratification.

Finally, the ferroptosis framework may provide insight into why there is so much variability in disease progression among individuals with glaucoma. Individuals with identical IOP's experience vastly different rates of visual field loss and structural thinning of the optic nerve. Eventually, incorporating genetic or biochemical assessments of ferroptotic susceptibility in clinical evaluation may assist in understanding why some optic nerves are more resilient than others and facilitate the use of tailored combinations of pressure control and metabolic support based upon the specific needs of each patient.

This interpretation remains hypothesis-generating. Most evidence linking ferroptosis to glaucoma currently derives from experimental models, acute or subacute retinal ganglion cell stress, optic nerve injury paradigms, or biomarker associations. These models are valuable for defining molecular vulnerability, but they do not fully recapitulate the slow, chronic, and multifactorial progression of human glaucomatous optic neuropathy. Direct human evidence demonstrating ferroptosis as a final common pathway in glaucoma is not yet available. Therefore, ferroptosis should be interpreted as a potential contributor to glaucomatous neurodegeneration rather than as a proven final common pathway in human glaucoma.

FERROPTOSIS IN AGE-RELATED MACULAR DEGENERATION

Ferroptosis-related mechanisms are particularly relevant to AMD, a disease in which long-term oxidative stress, iron handling, lipid metabolism, and macular vulnerability intersect[74]. AMD provides a biologically plausible context for studying ferroptosis-related injury because RPE cells and overlying photoreceptors are closely coupled and are both involved in iron trafficking, lipid handling, and photooxidative stress. Ferroptosis-related pathways may help connect several features of macular degeneration, including iron deposition within macular tissue, progressive RPE dysfunction, photoreceptor loss, drusen-associated lipid and inflammatory changes, and progression toward geographic atrophy or neovascular complications[75].

The RPE-Bruch's-Choriocapillaris Unit as a Site of Ferroptosis-Related Vulnerability The outer retina's structure is a functional unit made up of RPE cells, Bruch's membrane and the choriocapillaris. These three structures interact to form an RPE cell/Bruch's membrane/choriocapillaris functional unit that supports the outer retina and may be particularly vulnerable to ferroptosis-related stress under conditions of iron dysregulation, lipid retention, and impaired antioxidant defense. RPE cells have several functions. Together, these functions create a microenvironment in which ferroptosis-related vulnerability may emerge when

lipid handling, iron transport, and antioxidant defenses become impaired[76]. One of their main functions is the phagocytic removal and degradation of photoreceptor outer segments that contain large amounts of polyunsaturated lipids. Another major function is the recycling of visual pigments (chromophores) from photoreceptors. A third function is regulating the movement of iron into photoreceptors and out of photoreceptors into the choroid; finally, RPE cells regulate the outer blood-retinal barrier. As such, all of the functions of RPE cells are highly dependent on energy, create high density networks of mitochondria, and create continuous oxidative by-product[77].

As individuals age, Bruch's membrane becomes thicker with increasing amounts of lipid, advanced glycation end products and complement components that increasingly inhibit the unidirectional exchange of nutrients, waste products, and lipoproteins between photoreceptors and the choroid. The choriocapillaris also exhibits focal dropout and changes in its perfusion pattern. In this compromised microenvironment, RPE cells experience a prolonged imbalance in the rate of substrate availability versus substrate utilization that results in a less-than-optimal removal of oxidized lipids and iron containing cellular debris. Eventually, the RPE-Bruch's-choriocapillaris unit will undergo a gradual decline in both the labile iron pool and in lysosome and mitochondrial function; in addition, the antioxidant system will be under constant stress[78]. These conditions may render the RPE-Bruch's membrane-choriocapillaris unit particularly susceptible to ferroptosis-related stress.

Iron Gradients, Lipoprotein Traffic, and Drusen Ecology The most distinctive microscopic feature of AMD is the formation of "drusen" which are extracellular accumulations of material between the RPE and Bruch's membrane. The deposits themselves are not inert; they have formed a complex "ecosystem" containing lipoproteins, complement proteins, lipofuscin and its metabolites, and trace metals such as iron. From a ferroptosis-informed perspective, drusen may reflect impaired handling of lipids, complement components, and metal-associated stress. This interpretation is supported indirectly by studies showing increased chelatable iron in AMD-affected RPE and Bruch's membrane[79], as well as proteomic evidence that drusen and Bruch's membrane contain oxidation-related lipid adducts such as carboxyethylpyrrole-modified proteins[80]. Nevertheless, direct spatial evidence that drusen composition drives ferroptosis in adjacent RPE cells remains incomplete. The RPE cells, overwhelmed by the quantity and oxidative status of the phagocytosed outer segment remnants, form basolateral lipoprotein-like particles packaging lipids and proteins, which would normally cross the barrier at Bruch's membrane and enter the choroid space. The barrier properties of Bruch's membrane become increasingly hydrophobic and structurally compromised with increasing age, reducing the efflux of these particles, resulting in the localized retention of lipids capable of oxidation and metal binding proteins[81].

It is reasonable to assume that there are significant iron gradients across the RPE cell-Bruch's membrane-choriocapillaris interface. Iron is imported by RPE cells from the choroid and the photoreceptor layer where it is stored in ferritin and exported into the choroid by ferroportin and other mechanisms. When export into the choroid is prevented due to alterations in the structure of Bruch's membrane and loss of the choriocapillaris, iron may accumulate both in the cytoplasm of RPE cells and in the immediately adjacent extracellular space. Drusen located adjacent to iron-containing RPE-derived material may provide a microenvironment permissive to lipid oxidation; however, whether this process directly promotes ferroptosis in human AMD requires further biochemical and spatial validation[2]. Reactive aldehydes and oxidized phospholipids produced in this microenvironment may diffuse back toward the RPE cell membrane, alter lipid composition and redox status, and increase RPE susceptibility to ferroptosis-related injury.

RPE Ferroptosis and Geographic Atrophy Atrophic AMD has been shown to cause geographic atrophy, which is a type of lesion that is associated with severe visual impairment. It is characterized by sharply delineated atrophic regions of the retina, which are devoid of photoreceptors and RPE cells. The atrophic regions may include areas in which ferroptosis-related RPE injury contributes to secondary photoreceptor degeneration, although other cell-death pathways and inflammatory mechanisms are also likely involved. Prior to the onset of geographic atrophy, patchy RPE cell dysfunction may manifest as pigment mottling, changes in autofluorescence, and diminished dark adaptation. These early manifestations indicate that while ferroptotic stress is present, it is not yet lethal[82].

Ferroptotic RPE cells exhibit a complex array of abnormalities. They have elevated levels of free labile iron, which leads to increased oxidative damage due to the presence of lipid hydroperoxides in both plasma and organelle membranes. Ferroptotic RPE cells also have significantly depleted glutathione stores, which would otherwise be available to help neutralize toxic peroxidized lipids[25]. Additionally, they have impaired ferritin storage and export, which would normally provide protection against iron-induced oxidative damage. Mitochondrial function in ferroptotic RPE cells appears to be severely disrupted, and their respiratory reserves appear to be compromised. Lysosomes in ferroptotic RPE cells contain undegraded phagolysosomal materials and lipofuscin, which contains potent photosensitizers and generators of ROS.

The cumulative effect of this multifaceted cellular stress may compromise RPE membrane integrity and increase the likelihood of ferroptosis-related cell injury. Photoreceptors that rely upon surviving RPE cells for metabolic and chromophore recycling activities subsequently die, not directly because of ferroptosis but rather as a result of the collapse of the essential support system provided by healthy RPE cells.

While the process of ferroptosis in AMD is not simply "on" or "off", it is likely that there exists a continuum of subclinical ferroptotic stress to irreversible ferroptotic death, with a range of intermediate states characterized by partial loss of GPX4 enzymatic activity, localized pockets of lipid peroxidation, and enhanced expression of protective mechanisms. This continuum provides a theoretical framework for identifying time points during the course of disease when modulators of ferroptosis might effectively protect RPE and photoreceptor cells prior to the development of extensive geographic atrophy.

Despite this biological plausibility, the causal role of ferroptosis in human AMD remains incompletely established. Much of the experimental support comes from accelerated *in vitro* or acute injury models, including oxidant exposure, sodium iodate injury, light-induced damage, or immortalized RPE cell systems. These models are useful for testing iron-dependent lipid peroxidation and GPX4/GSH failure, but they only partially model the decades-long, low-grade metabolic dysfunction and sub-RPE deposit ecology of human AMD. Therefore, ferroptosis-related findings in AMD should be interpreted as mechanistically suggestive rather than definitively causal.

Interplay with Neovascular and Exudative AMD In addition to the complexity added by neovascular AMD (*i.e.*, choroidal neovascular membranes penetrating through Bruch's membrane and into or under the retina), with associated exudation, hemorrhage, and fibrovascular scarring, there appears to be a paradox between the ferroptosis-based model of retinal degeneration that emphasizes the role of accumulated iron and lipid peroxidation in degenerating RPE and the extremely vascular and exudative nature of neovascular AMD. Neovascular AMD and ferroptosis are, however, related processes.

The breaks in Bruch's membrane and the abnormal neovessels that result from them create channels for plasma proteins and red blood cells to enter into the sub-RPE or subretinal space where they introduce additional sources of iron in the form of hemoglobin and heme[78]. Iron released from the breakdown of hemoglobin is then able to flow into the labile iron pool. Inflammation caused by exudation and hemorrhage also activate the complement system leading to changes in the expression of both iron handling proteins and antioxidants in RPE, endothelial cells and microglial cells located in proximity to the damaged area. Thus, the environment created by the presence of iron, lipid oxidation products and pro-inflammatory molecules such as those produced by the complement system is highly conducive to ferroptosis[70,83].

Anti-vascular endothelial growth factor (anti-VEGF) therapy has been very successful in inhibiting the formation of new vessels and reducing exudation in neovascular AMD; it does not, however, have a direct effect on iron-driven lipid peroxidation or RPE ferroptosis[84]. It may therefore help explain why some patients continue to experience progressive vision loss despite their exudative disease being controlled, *i.e.*, even when the amount of fluid leaking from the eye is small. From a ferroptosis-informed perspective, neovascular and atrophic AMD may share elements of iron, lipid, and complement dysregulation, although their dominant clinical drivers and treatment responses remain distinct.

To link these concepts to clinically recognisable stages, Table 2[13,85-87] summarizes how ferroptosis-related processes may vary across early, intermediate, and advanced AMD. This table is deliberately conceptual and hypothesis-generating; it is intended to guide future mechanistic and biomarker studies rather than to serve as a validated clinical staging system.

FERROPTOSIS IN DIABETIC RETINOPATHY AND ISCHEMIC FUNDUS DISORDERS

Diabetic retinopathy and ischemic fundus disorders lie at the intersection of metabolic stress, vascular dysfunction, blood–retina barrier disruption, and retinal neurodegeneration. Rather than replacing the traditional microvascular model, a ferroptosis-informed perspective highlights how chronic hyperglycemia, fluctuating oxygen availability, inflammatory signaling, and iron-handling disturbance may increase ferroptosis-related vulnerability in endothelial cells, pericytes, glia, and neurons[20].

The Diabetic Neurovascular Unit as a Context for Ferroptosis-Related Vulnerability The diabetic retinal neurovascular unit, comprising endothelial cells, pericytes, Müller cells, microglia, astrocytes, and neurons, is chronically exposed to hyperglycemia, advanced glycation end products, dyslipidemia, fluctuating oxygen availability, and low-grade inflammatory cytokines[26]. These disease-specific stresses may alter iron storage and export, impair antioxidant buffering, and destabilize glial support functions[88]. Müller cells are particularly relevant because they regulate glutamate handling, redox balance, and metal homeostasis within the diabetic retina[89]. Microglia may further contribute to inflammatory signaling and local redox–iron homeostasis. Over time, this microenvironment may create a background in which endothelial cells, pericytes, glia, and neurons become more susceptible to ferroptosis-related injury, especially when additional ischemic or inflammatory insults are present[26-89].

Table 2 Hypothetical conceptual mapping of ferroptosis-related features across AMD stages as a guide for future research

AMD stage/phenotype	Dominant cells and compartment	Key ferroptosis-related processes	Conceptual implications
Early AMD (small drusen, subtle pigment changes)[85]	RPE-Bruch's-choriocapillaris unit	Mild expansion of labile iron; initial accumulation of lipid-rich deposits; upregulated antioxidant responses with partially preserved GPX4 activity	Possible subclinical ferroptosis-related stress; potential window for studying modulation of iron and lipid homeostasis
Intermediate AMD (larger drusen, pigment clumping, functional deficits)[86]	RPE with overlying photoreceptors; Bruch's membrane	More pronounced iron retention and impaired export; increased lipid peroxidation in RPE membranes; mitochondrial and lysosomal dysfunction; partial exhaustion of glutathione-dependent defenses	Potential transition zone where repeated oxidative lipid injury may begin to exceed repair capacity, possibly contributing to future geographic atrophy
Geographic atrophy (advanced non-neovascular AMD)[87]	RPE and photoreceptor layers within atrophic patches	localized collapse of anti-ferroptotic defenses; extensive membrane lipid peroxidation; irreversible loss of RPE and secondary photoreceptor death	Advanced ferroptosis-related vulnerability in atrophic zones; future studies may focus on slowing atrophy expansion and protecting border zones
Neovascular/exudative AMD[13]	RPE, choroidal endothelium, neovascular complexes, subretinal space	Additional iron influx from blood and haem; inflammatory and complement-driven modulation of iron handling; ferroptosis in stressed RPE and vascular cells adjacent to neovascular membranes	Ferroptosis-related stress and angiogenic/inflammatory pathways may interact; combined anti-VEGF and ferroptosis-modulating strategies warrant further investigation after vascular control

AMD: Age-related macular degeneration; RPE: Retinal pigment epithelium; GPX4: Glutathione peroxidase 4; VEGF: Vascular endothelial growth factor.

Microvascular Ferroptosis and Barrier Failure Pericyte dropout and endothelial dysfunction are central features of early diabetic microvascular injury. Diabetic retinopathy is increasingly viewed as a neurovascular disease in which pericyte dysfunction, endothelial injury, neuronal stress, blood–retina barrier failure, ischemia, and inflammatory signaling interact dynamically. More recent experimental studies suggest that ferroptosis-related mechanisms, including iron dysregulation, lipid peroxidation, and glutathione depletion, may also contribute to pericyte or endothelial vulnerability[90-91]. If ferroptosis participates in these processes, it may impair endothelial–pericyte communication, weaken capillary support, disturb endothelial junctions, and thereby contribute to barrier dysfunction, microaneurysm formation, and capillary nonperfusion. However, the extent to which pericyte loss in human diabetic retinopathy is directly mediated by ferroptosis remains uncertain. Pericyte dropout may reflect apoptosis, metabolic dysfunction, inflammatory injury, detachment from the capillary basement membrane, or ferroptosis-related stress, and these mechanisms may coexist or occur sequentially. Therefore, ferroptosis should be interpreted as a potential contributor to diabetic microvascular injury rather than as the established dominant mechanism of pericyte loss.

Ischemia-Reperfusion and Vessel Occlusions as Ferroptotic Accelerants Ischemic fundus disorders, including central or branch retinal vascular occlusions, create abrupt changes in oxygen and nutrient availability followed by variable reperfusion. These insults provide acute settings in which hypoxia, reperfusion-associated oxidative stress, iron mobilization, and inflammatory activation converge. They are useful for testing ferroptosis-related injury under rapid redox shifts, but they should not be assumed to capture the full biology of chronic diabetic or ischemic retinal disease[92].

Neurodegeneration in Diabetic and Ischemic Retinopathy: Beyond "Microangiopathy" Although diabetic retinopathy has traditionally been viewed as a microvascular disease, growing evidence indicates that retinal neurons experience functional and morphological changes at early stages of the disease[93]. Ferroptosis-related pathways may serve as one mechanistic link between vascular pathology and neuronal degeneration in diabetic retinopathy. The inner retinal neurons (bipolar and ganglion) are subjected to the same hyperglycemia, oxidative stress, and iron imbalance as the microvasculature[94]. As blood flow through the retinal vessels decreases (patchy perfusion), the oxygen extraction ratio increases and thus mitochondrial function in neurons will increase, producing greater amounts of ROS.

When iron buffering and glutathione-dependent detoxification mechanisms are impaired by chronic hyperglycemia, lipid metabolic disturbance, or inflammation, neurons may become susceptible to ferroptosis-related injury even before overt retinal capillary closure is apparent[95]. This pathologic sequence explains the clinical observation of electrophysiologic and psychophysiologic defects in individuals with diabetes who do not have "vision-threatening" retinopathy, but whose fundus images show no visible capillary closure. Finally, ischemic injury resulting from either microvascular or macrovascular occlusion, when superimposed on baseline redox and iron-handling stress, may contribute to neuronal loss and retinal thinning.

Overall, evidence in diabetic and ischemic fundus disorders supports a plausible role for ferroptosis-related pathways, but direct causal involvement remains variable across

models. Acute ischemia-reperfusion systems are useful for testing iron-dependent lipid peroxidation under controlled conditions, whereas chronic diabetic retinopathy requires longer-term models that better capture fluctuating glycemia, vascular remodeling, inflammation, neuronal adaptation, and coexistence of multiple cell-death pathways.

Combining Ferroptosis Modulation with Existing Standards of Care The most valuable translational insight from ferroptosis modulation is likely that it will never be used alone as a treatment. The potential of ferroptosis modulation is its ability to be used in conjunction with other treatments aimed at reducing the root cause of the problem that caused the disease. Glaucoma has multiple causes of damage to the optic nerve; one cause is elevated IOP that can damage ganglion cell axons through both mechanical and vascular (blood flow) forces[23]. Ferroptosis modulation can help protect remaining ganglion cells that are still viable but at risk due to elevated pressure. Anti-VEGF agents reduce leakage from new blood vessels in AMD, and anti-ferroptotic agents attempt to preserve the function of RPE and photoreceptors in both the neovascular and atrophic pathways of the disease[84]. Diabetic retinopathy is a multi-factorial disease involving both systemic (high glucose levels) and localized (microvascular) factors that contribute to damage to the retina. Glycaemic control and use of anti-VEGF or corticosteroids are effective at controlling the microvascular and vascular aspects of diabetic retinopathy, whereas ferroptosis modulation aims to reduce death of neurons in areas of ischemia. Infectious retinochoroiditis may represent another setting in which ferroptosis modulation could be explored as an adjunctive strategy. In ocular toxoplasmosis models, iron chelation with deferiprone attenuated retinal inflammation, suggesting that modulation of iron-dependent lipid peroxidation may complement, rather than replace, antimicrobial and anti-inflammatory therapies.

Trial designs based upon these considerations indicate that clinical studies evaluating ferroptosis modulators should incorporate measurable endpoints that extend beyond simple anatomical measurements and include structural, functional, biochemical, and imaging-based indicators of ferroptosis-related retinal injury[96]. Clinical trials evaluating ferroptosis modulators must also consider how to safely suppress ferroptosis without eliminating the beneficial effects of removing damaged or maladaptive cells that would otherwise continue to cause harm. Additionally, excessive suppression of ferroptosis could affect normal iron-dependent physiological functions, such as phototransduction and neurotransmission.

Clinical Endpoints for Ferroptosis-Targeted Retinal Therapies For ferroptosis-targeted therapies to become clinically meaningful, future studies should define measurable endpoints that capture both target engagement and visual benefit. Structural endpoints may include optical coherence tomography (OCT)-based neuroretinal thickness, retinal nerve fiber layer and ganglion cell complex thickness in glaucoma, outer nuclear layer thickness and ellipsoid zone integrity in photoreceptor injury, central macular thickness in diabetic macular edema, and atrophy area or lesion growth in AMD and inflammatory chorioretinopathy. Optical coherence tomography angiography (OCTA)-derived vascular density and perfusion indices may also be useful in diabetic retinopathy, ischemic retinopathy, and retinal vasculitis.

Functional endpoints should be selected according to the affected retinal compartment. These may include best-corrected visual acuity, visual field testing, full-field or multifocal electroretinography, microperimetry, contrast sensitivity, dark adaptation, and patient-reported visual function. Electroretinography (ERG)-based measures are particularly relevant when ferroptosis-targeted strategies aim to preserve photoreceptors, bipolar cells, or inner retinal neurons before irreversible structural loss is apparent.

Biochemical endpoints may include aqueous or vitreous markers of lipid peroxidation, iron handling, glutathione–GPX4 activity, and inflammatory activation. Candidate markers include malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), oxidized phospholipids, GSH/GSSG, GPX4- or solute carrier family 7 member 11 (SLC7A11)-related signals, ferritin, transferrin receptor, ferroportin, hepcidin, and selected cytokines or chemokines in inflammatory disease. Imaging-based endpoints may include fundus autofluorescence, OCT/OCTA, adaptive optics where available, iron-sensitive magnetic resonance imaging (MRI) or quantitative susceptibility-based imaging, and future molecular probes for redox-active iron or oxidized phospholipids. These endpoints should be interpreted as complementary rather than interchangeable, because each captures a different layer of ferroptosis-related retinal injury. The candidate clinical and translational endpoints for ferroptosis-targeted retinal therapies are summarized in Table 3.

With these endpoint considerations in mind, therapeutic modulation of ferroptosis in fundus disorders still sits at an early but promising stage. The mechanistic rationale is strong, preclinical signals are encouraging, and the need for true neuroprotective and tissue-preserving strategies is acute. Yet the path to clinical reality will depend on resolving fundamental limitations in our current evidence base and on developing precise tools to measure and control ferroptosis *in vivo*. These considerations also extend to infectious and immune-mediated inflammatory fundus diseases, which have received less attention in the ferroptosis literature but may provide important models for understanding how infection, inflammation, iron metabolism, and retinal cell death intersect.

Table 3 Candidate clinical and translational endpoints for ferroptosis-targeted retinal therapies

Endpoint domain	Candidate measures	Main translational use	Key limitation
Retinal structure	OCT-based neuroretinal thickness, RNFL/GCC thickness, outer nuclear layer thickness, ellipsoid zone integrity, central macular thickness, atrophy area or lesion growth	Measures anatomical preservation and lesion progression	Structural preservation may lag behind molecular injury
Vascular and barrier status	OCTA vessel density/perfusion, capillary nonperfusion, leakage indicators, edema, central retinal thickness	Useful for diabetic retinopathy, ischemic retinopathy, and retinal vasculitis	Vascular changes are not ferroptosis-specific
Visual function	BCVA, visual field testing, full-field ERG, multifocal ERG, microperimetry, contrast sensitivity, dark adaptation, patient-reported visual function	Captures clinically meaningful visual benefit	Functional variability and compensation may obscure early effects
Ocular fluid biomarkers	Aqueous/vitreous MDA, 4-HNE, oxidized phospholipids, GSH/GSSG, GPX4/SLC7A11-related markers, ferritin, transferrin receptor, ferroportin, hepcidin	Supports target engagement and pharmacodynamic assessment	Sampling is invasive and markers may lack pathway specificity
Imaging biomarkers	Fundus autofluorescence, OCT/OCTA, adaptive optics, iron-sensitive MRI, quantitative susceptibility-based imaging, molecular probes for redox-active iron or oxidized lipids	Enables spatial and longitudinal assessment of ferroptosis-related stress	Many tools remain experimental or insufficiently validated
Inflammatory endpoints	Aqueous/vitreous cytokines, chemokines, microglia/macrophage-related signals, vascular leakage, inflammatory lesion activity	Relevant for uveitis, vasculitis, toxoplasmosis, and inflammatory chorioretinopathy	Inflammatory activity may reflect multiple overlapping pathways
Safety endpoints	Retinal toxicity, intraocular inflammation, IOP change, systemic iron-related adverse effects, infection control in infectious disease	Defines therapeutic window and safety profile	Anti-ferroptotic treatment may affect host defense or physiological iron use

OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; BCVA: Best-corrected visual acuity; ERG: Electroretinography; MDA: Malondialdehyde; 4-HNE: 4-hydroxynonenal; GSH: Reduced glutathione; GSSG: Glutathione disulfide; GPX4: Glutathione peroxidase 4; SLC7A11: Solute carrier family 7 member 11; MRI: Magnetic resonance imaging; IOP: Intraocular pressure.

FERROPTOSIS IN INFECTIOUS AND IMMUNE-MEDIATED RETINAL INFLAMMATION

Inflammatory retinal diseases provide a clinically important context for understanding ferroptosis beyond chronic degeneration and vascular stress. Ferroptosis-related lipid peroxidation may generate oxidized lipid mediators and damaged-cell signals that amplify innate immune activation, microglial and macrophage responses, vascular inflammation, and blood-retina barrier disruption. From this perspective, ferroptosis should be considered not only as a terminal form of retinal cell injury, but also as a potential contributor to inflammation-associated tissue damage in selected disease contexts.

Among inflammatory retinal diseases, infectious retinochoroiditis provides a particularly informative context in which ferroptosis-related mechanisms may operate beyond chronic degeneration and vascular stress. Ocular toxoplasmosis, caused by Toxoplasma gondii, is a representative infectious posterior uveitis characterized by retinochoroiditis, retinal inflammation, photoreceptor injury, and variable visual impairment. In contrast to AMD, glaucoma, or diabetic retinopathy, ocular toxoplasmosis introduces a pathogen-driven immune-inflammatory trigger into the ferroptosis framework, thereby broadening the disease spectrum in which iron-dependent lipid peroxidation may contribute to retinal injury.

A landmark study by Yamada *et al*[97] provided experimental evidence supporting a mechanistic link between ferroptosis and ocular toxoplasmosis. In human samples and experimental models, the authors reported altered ocular iron dynamics, increased retinal iron uptake after T. gondii infection, enhanced lipid peroxidation, reduced GPX4 expression, and mitochondrial abnormalities in photoreceptors. Importantly, pharmacological iron chelation with deferiprone reduced retinal iron accumulation and attenuated toxoplasma-induced retinochoroiditis, supporting a functional contribution of ferroptosis to infectious retinal inflammation rather than a merely secondary association[91].

These findings have important conceptual implications. First, they suggest that ferroptosis can be engaged by infection-driven inflammatory cues, not only by aging, metabolic stress, ischemia, or mechanical injury. Second, they position photoreceptors as ferroptosis-sensitive targets in infectious retinochoroiditis, particularly when local iron handling and GPX4-dependent antioxidant defenses are disrupted. Third, they identify ferroptosis as a potential mechanistic link between pathogen-induced oxidative stress, aberrant iron metabolism, immune activation, and retinal cell death. Therefore, ocular toxoplasmosis should be incorporated into the broader discussion of ferroptosis-related mechanisms in fundus diseases as an inflammation-associated model with relatively direct experimental support.

Nevertheless, the current evidence should be interpreted with appropriate caution. The strongest mechanistic data are

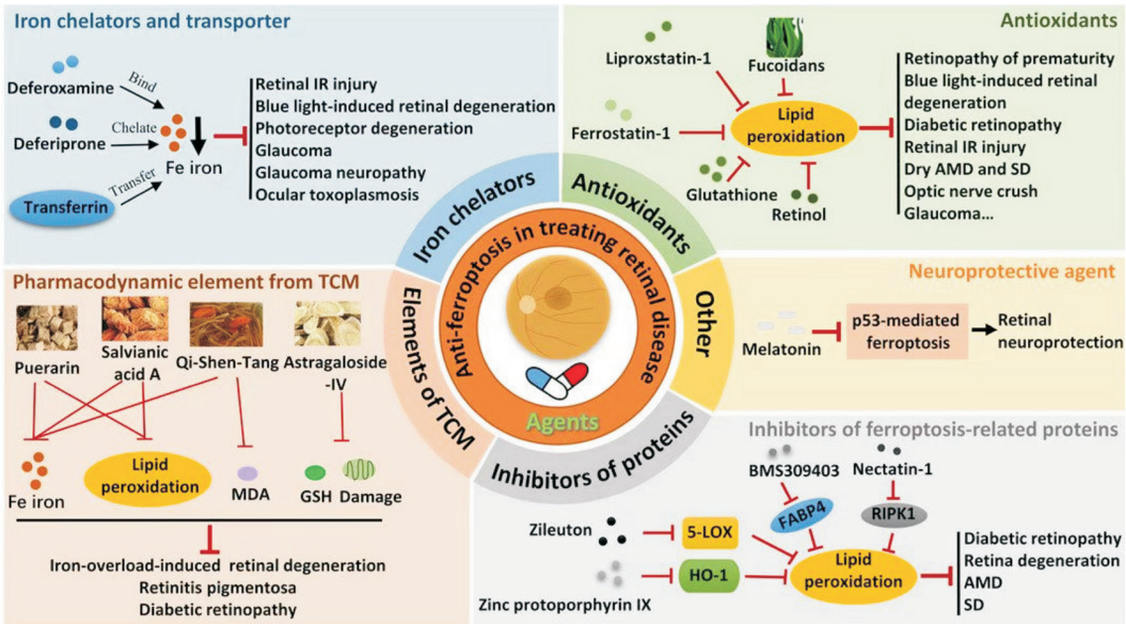

Figure 2 Therapeutic strategies targeting ferroptosis in retinal diseases Ocular toxoplasmosis is included as an emerging infectious retinochoroiditis model in which iron chelation and modulation of iron-dependent lipid peroxidation have shown experimental relevance[95]. IR: Ischemia–reperfusion; MDA: Malondialdehyde; AMD: Age-related macular degeneration; SD: Stargardt disease; GSH: Reduced glutathione; TCM: Traditional Chinese medicine; HO-1: Heme oxygenase-1; 5-LOX: 5-lipoxygenase; FABP4: Fatty acid-binding protein 4; RIPK1: Receptor-interacting serine/threonine-protein kinase 1.

presently centered on ocular toxoplasmosis, whereas evidence in autoimmune uveitis, retinal vasculitis, inflammatory chorioretinopathy, other infectious posterior uveitides, viral retinitis, and bacterial endophthalmitis-associated retinal injury remains more limited or indirect. Future studies should define the cell-type specificity, temporal sequence, and therapeutic window of ferroptosis-related mechanisms in infectious and immune-mediated retinal inflammation, while also distinguishing ferroptosis from necrosis, apoptosis, pyroptosis, autophagy-related cell death, and other inflammatory injury pathways.

Figure 2 provides a conceptual overview of how ferroptosis-modulating strategies can be positioned along the ferroptotic cascade and aligned with major fundus disease categories, including ocular toxoplasmosis as an emerging infectious retinochoroiditis model[95].

LIMITATIONS, CHALLENGES, AND FUTURE DIRECTIONS

Although ferroptosis provides an attractive framework for interpreting selected features of fundus disease, it should not be regarded as a uniform cause across disease entities, and the available evidence is limited by factors that affect interpretation and translation. It is very difficult to accurately distinguish between ferroptosis and other forms of programmed cell death in complex retinal tissues. Experimental methods define ferroptosis based on iron dependency, accumulation of phospholipid hydroperoxides, loss of glutathione, and inhibition of ferroptosis, however, *in vivo* retinal lesions typically consist of multiple waves of apoptosis, necroptosis, pyroptosis, and autophagy-induced death. Because bulk measurements of lipid peroxidation or iron deposition in whole retina or macular biopsies measure averages across various cell types and pathways, there is a risk of attributing iron- and oxidant-rich phenotypes to ferroptosis even when apoptosis, necroptosis, pyroptosis, autophagy-related cell death, or nonspecific oxidative injury may also be involved. Therefore, to claim ferroptosis as a primary mechanism in specific retinal lesions, researchers should move beyond single-marker or bulk-tissue definitions and develop integrated, cell-type-resolved operational criteria that combine biochemical, spatial, genetic, and functional evidence.

Proposed Operational Criteria for Defining Ferroptosis in Retinal Disease A recurring translational bottleneck is the absence of standardized *in vivo* criteria for defining ferroptosis in retinal disease. No single marker, including iron accumulation, lipid peroxidation, glutathione depletion, or GPX4 reduction, is sufficient on its own to establish ferroptosis in complex retinal tissues. These changes may also occur in apoptosis, necroptosis, pyroptosis, autophagy-related cell death, inflammation-associated tissue injury, or nonspecific oxidative stress. Therefore, future translational studies should adopt an orthogonal, multi-domain evidence framework rather than relying on isolated bulk biochemical measurements. Accordingly, disease-specific claims should be reported as

possible, probable, or functionally supported ferroptosis involvement according to the strength of evidence, rather than described using undefined metaphorical terms.

A reasonable minimum evidence set should include four complementary domains. First, studies should demonstrate iron dysregulation or iron dependency, such as expansion of redox-active iron pools, altered ferritin/transferrin receptor/ferroportin/hepcidin signaling, or attenuation of injury by iron chelation. Second, studies should document lipid peroxidation with as much biochemical specificity as possible. Although MDA, 4-HNE, and total ROS may be useful screening markers, they should ideally be complemented by more specific readouts such as oxidized PUFA-containing phospholipids, C11-BODIPY-based lipid ROS detection, or targeted lipidomic profiling. Third, impairment of anti-ferroptotic defense systems should be assessed, including GSH depletion, reduced GPX4 expression or activity, altered SLC7A11-mediated cystine import, or disruption of complementary protective axes such as ferroptosis suppressor protein 1 (FSP1)–coenzyme Q10 (CoQ10). Fourth, these molecular changes should be localized to relevant retinal cell types or lesion compartments, such as RPE cells, photoreceptors, retinal ganglion cells, endothelial cells, pericytes, Müller cells, or microglia, rather than inferred solely from whole-retina homogenates.

For stronger causal inference, biomarker evidence should be paired with functional rescue. Pharmacological interventions such as iron chelators, lipid radical-trapping antioxidants, or ferroptosis inhibitors, and genetic manipulation of core ferroptosis-related nodes such as GPX4, SLC7A11, Acyl-CoA synthetase long-chain family member 4 (ACSL4), FSP1, or nuclear receptor coactivator 4 (NCOA4), can help determine whether ferroptosis-related pathways are functionally involved in retinal injury. Ideally, such interventions should reduce lipid peroxidation, preserve retinal structure, and improve or stabilize visual function. However, because many interventions have pleiotropic effects, rescue experiments should be interpreted together with parallel assessment of apoptosis, necroptosis, pyroptosis, and autophagy-related pathways.

Based on these considerations, ferroptosis in retinal disease may be reported in graded terms. “Possible ferroptosis involvement” may be appropriate when iron dysregulation, lipid peroxidation, and antioxidant defense failure are observed without cell-type localization or rescue evidence. “Probable ferroptosis involvement” may be used when these markers co-localize within relevant retinal cells or lesions and align with structural or functional injury. “Functionally supported ferroptosis” should be reserved for settings in which ferroptosis-targeted pharmacological or genetic modulation attenuates both molecular injury markers and retinal structural or functional damage. Such graded terminology may help prevent over-attribution of nonspecific oxidative injury to ferroptosis and improve comparability across preclinical, translational, and clinical studies.

Applying these operational criteria to the current ocular literature highlights an important limitation: few studies meet all domains simultaneously. Many reports document iron accumulation, MDA or 4-HNE elevation, total ROS increase, or GPX4/GSH alteration, but fewer combine these markers with cell-type localization, lipid-specific readouts, exclusion of overlapping cell-death pathways, and functional rescue by ferroptosis-targeted pharmacological or genetic interventions. Consequently, a substantial proportion of current evidence should be regarded as supporting possible or probable ferroptosis involvement rather than definitive causality. This distinction is particularly important when interpreting studies based on whole-retina homogenates, immortalized cell lines, or acute injury models. The proposed operational criteria for defining ferroptosis in retinal disease are summarized in Table 4.

Animal models are also a source of additional variability. Most of what is currently known regarding ocular ferroptosis was derived from experiments performed in rat eyes, immortalized RPE lines, and acute injury models involving either extreme light exposure, or toxic chemicals. Although the models are excellent at defining mechanisms involved in ferroptosis, they are quite different from the aging human fundus, with its macula, long disease course, and presence of systemic comorbidities. Thus, the models may overstate the role of ferroptosis compared to other processes, and the next generation of models will need to rely more heavily on human retinal organoids, induced pluripotent stem cell (iPSC)-derived RPE, choroidal endothelial cells and microglia, and large animal eyes with macula-like characteristics. Importantly, these models should be utilized to determine if ferroptosis can be induced in addition to examining how it interacts with realistic IOPs, metabolic dysregulations, complement activations, and chronic inflammation.

Another limitation is temporal resolution. Most experimental studies are conducted at a single time point after an induced insult, while glaucoma, AMD, and diabetic retinopathy each take years to develop. In infectious retinochoroiditis, the temporal relationship among pathogen replication, immune activation, iron accumulation, lipid peroxidation, and retinal cell death is also likely to be highly dynamic. This makes it unclear if ferroptosis is a primary initiator of damage, a mid-disease course amplifier, or a late executor layered atop other forms of degeneration or inflammation. Longitudinal designs in both models and patients that assess ferroptosis related markers alongside structural imaging and functional testing will be necessary to address this issue.

Table 4 Proposed operational criteria for defining ferroptosis in retinal disease

Evidence domain	Recommended readouts	Interpretive value	Main limitation
Iron dysregulation/ iron dependency	Labile iron pool, Fe^{2+} probes, ferritin, transferrin receptor, ferroportin, hepcidin, NCOA4, response to iron chelation	Supports involvement of iron-dependent injury	Iron accumulation is not specific to ferroptosis
Lipid peroxidation	C11-BODIPY lipid ROS, MDA, 4-HNE, oxidized PUFA-containing phospholipids, targeted lipidomics	Captures lipid oxidative damage central to ferroptosis-related injury	MDA, 4-HNE, and total ROS are not specific
Anti-ferroptotic defense failure	GSH/GSSG ratio, GPX4 expression/activity, SLC7A11, FSP1–CoQ10 axis, GCH1–BH4 axis	Indicates reduced capacity to detoxify lipid peroxides	May also reflect generalized oxidative stress
Cell-type/lesion localization	Immunofluorescence, *in situ* probes, spatial transcriptomics, single-cell RNA-seq, laser-capture microdissection	Links ferroptosis-related markers to RPE, photoreceptors, RGCs, endothelial cells, pericytes, or glia	Bulk tissue assays may obscure cellular heterogeneity
Functional rescue	Iron chelators, ferrostatin-1/liproxstatin-1, lipid radical trapping, GPX4/SLC7A11/FSP1/ACSL4/NCOA4 modulation	Strengthens causal inference and target engagement	Pharmacological agents may have pleiotropic effects
Exclusion and pathway crosstalk	Parallel assessment of apoptosis, necroptosis, pyroptosis, autophagy-related cell death, and inflammatory injury	Reduces over-attribution to ferroptosis	Multiple cell-death pathways may coexist

MDA: Malondialdehyde; 4-HNE: 4-hydroxynonenal; PUFA: Polyunsaturated fatty acid; ROS: Reactive oxygen species; GSH: Reduced glutathione; GSSG: Glutathione disulfide; GPX4: Glutathione peroxidase 4; SLC7A11: Solute carrier family 7 member 11; FSP1: Ferroptosis suppressor protein 1; CoQ10: Coenzyme Q10; GCH1: GTP cyclohydrolase 1; BH4: Tetrahydrobiopterin; RPE: Retinal pigment epithelium; RGC: Retinal ganglion cell; ACSL4: Acyl-CoA synthetase long-chain family member 4; NCOA4: Nuclear receptor coactivator 4.

Despite the proposed operational framework above, robust *in vivo* biomarkers for assessing ferroptosis-related activity in the human eye remain lacking. Current evidence still relies heavily on post-mortem tissue analysis, indirect systemic biomarker assessment, and non-specific imaging surrogates. Sensitive and repeatable markers of ferroptosis-related stress within the eye are needed, including vitreous or aqueous analytes reflecting lipid peroxidation and iron-handling states, imaging probes reporting redox-active iron or oxidized phospholipids, and blood biomarkers that correlate with intraocular ferroptosis-related activity. To develop and validate these biomarkers, it will be necessary to have collaborative relationships among chemists, imaging experts and clinicians. Such biomarkers will be important for mechanism-based clinical trials, target-engagement assessment, and determining whether candidate therapeutics modulate ferroptosis-related pathways *in vivo*.

Similarly, therapeutic specificity and safety are challenges for modulating ferroptosis. Iron, lipid peroxidation and glutathione dependent defenses are integral to the normal physiological state and systemic health of the retina. Aggressive chelation may disrupt essential enzymatic functions; overly broad radical trapping may blunt adaptive redox signaling and host defense; and excessively reinforcing anti-ferroptotic pathways may trap permanently damaged/dysfunctional cells and alter immune surveillance. Therefore, future ferroptosis modulatory therapies will have to be extremely finely-tuned temporally, spatially and quantitatively. This suggests that local delivery, targeted constructs, and combinatorial regimens that modestly increase ferroptotic thresholds will be preferable to completely ablating the pathway.

Disease and patient heterogeneity will also complicate translation. Clinically identical labels such as “neovascular AMD” and “moderate glaucoma”, conceal significant variability in genetic background, systemic environment and local tissue states. Similarly, evidence for ferroptosis in infectious retinochoroiditis is currently strongest for ocular toxoplasmosis, and whether similar mechanisms contribute to other infectious or immune-mediated posterior segment diseases remains uncertain. In some eyes, ferroptosis-related mechanisms may make a substantial contribution to tissue injury; in others, they may be secondary to apoptosis, necroptosis, pyroptosis, autophagy-related cell death, mechanical failure, or nonspecific oxidative stress. The next phase of research should explicitly accept this heterogeneity instead of averaging it out. Genotype-based stratification, systemic biomarkers of iron and redox status, and emerging intraocular biomarkers of ferroptosis will be critical for designing trials capable of identifying true benefit in the subpopulations most likely to respond to therapy.

Several practical future directions follow from these limitations. Mechanistically, integrated atlases of ferroptosis are needed, spanning cell types, disease stages, and time, using single-cell and spatial transcriptomics, lipidomics, and iron mapping in human tissue, organoids, and advanced animal models. Methodologically, the development of ferroptosis-reporting probes, minimally invasive sampling techniques, targeted lipidomic approaches, and cell-type-resolved analytical platforms should be prioritized to enable longitudinal studies that relate biochemical readouts, lesion localization, and visual function. Therapeutically, initial efforts

are expected to focus on short-duration, locally-delivered interventions in clearly defined insult windows such as retinal detachment repair, acute vein or artery occlusions, and high-risk intraocular surgical procedures. These “test bed” models can provide proof of principle for safety, target engagement, and neuroprotection prior to application to chronic diseases requiring prolonged treatment courses.

Ferroptosis modulation will likely also be examined as a complementary strategy to existing standard treatments. Reasonable combinations could include pressure reduction plus ganglion cell-directed ferroptosis modulation in glaucoma, anti-VEGF therapy plus RPE-targeted anti-ferroptotic supplementation in AMD, and glycemic and vascular risk modification plus neurovascular ferroptosis modulation in diabetic retinopathy and ischemic disorders. Correspondingly, clinical trial design will need to evolve to accommodate these changes, incorporating composite outcome measures that capture OCT/OCTA-defined structural preservation, visual function, ocular fluid biomarkers, imaging-based indicators of iron or lipid peroxidation, inflammatory activity, and safety.

Finally, there is a conceptual challenge: to integrate ferroptosis into retinal biology without making it an all-encompassing explanation. Success will depend on careful use of terminology, strict adherence to experimental rigor, and willingness to modify or discard ferroptosis-centric hypotheses when supported by evidence from multiple levels. If discipline is maintained, ferroptosis will move from being a popular idea to a precise and clinically relevant aspect of fundus disease, providing a foundation for a new generation of neuroprotective and tissue-preserving therapies based on iron and lipid biology.

CONCLUSION

Ferroptosis has moved from a theoretical concept to an increasingly investigated form of regulated cell death that may contribute to selected fundus diseases under conditions of iron dysregulation, lipid peroxidation, and impaired antioxidant defense. Across glaucoma, AMD, diabetic and ischemic retinopathies, acute retinal detachment and trauma, hereditary retinal degeneration, and infectious or immune-mediated retinochoroiditis, recurring ferroptosis-related features have been reported to varying degrees: expansion of redox-active iron pools, enrichment of membranes with peroxidation-prone lipids, and weakening of glutathione–GPX4 and related antioxidant defenses. What varies is not the underlying logic, but where in the retina this triad is focused, how quickly it develops, and which upstream stresses drive it. This review argues that ferroptosis-related mechanisms may provide a useful, but not exclusive, framework for comparing clinically distinct retinal phenotypes across different spatial and temporal contexts.

Mechanistically, the retina has biological features that make ferroptosis-related vulnerability plausible. The neurosensory retina and RPE are iron-dependent, lipid-rich, and chronically exposed to light and fluctuating oxygen, operating near the edge of redox stability. Disturbances in iron handling, mitochondrial function, lipoprotein trafficking, or antioxidant capacity may therefore increase ferroptosis susceptibility in specific cell populations, including retinal ganglion cells at the optic nerve head, macular RPE, diabetic microvascular cells, or genetically stressed photoreceptors. This shared framework does not replace existing models based on pressure, angiogenesis, glycaemia, infection, or immunity, but provides a biochemical bridge that links these upstream stresses to retinal neuronal, photoreceptor, vascular, and RPE injury.

Translationally, this perspective suggests that durable preservation of vision will likely require combination approaches: standard-of-care therapies targeting upstream drivers, paired with precise modulation of ferroptotic tone in vulnerable retinal compartments. Iron handling, lipid composition, and antioxidant resilience may therefore represent important therapeutic axes, particularly in disease contexts where ferroptosis-related mechanisms are supported by experimental or biomarker evidence. At the same time, the field is still early. Evidence is dominated by preclinical models; *in vivo* biomarkers of ferroptosis in human eyes are lacking; and the specificity, timing, and safety of ferroptosis-targeted interventions remain open questions.

Future progress will depend on disciplined integration rather than uncritical enthusiasm: better temporal and cell type–resolved mapping of ferroptosis, development of reliable biomarkers, adoption of multi-domain operational criteria, incorporation of inflammation-aware disease models, and careful trial designs that pair ferroptosis-related target engagement with measurable structural, functional, biochemical, imaging-based, and safety endpoints. If these challenges can be met, ferroptosis-related biology may become a clinically actionable dimension of retinal research, adding mechanistic depth to selected disease contexts and informing strategies that may slow or prevent vision loss in appropriately defined patient subgroups.

ACKNOWLEDGEMENTS

Authors’ Contributions: Zhang NY, Kong HQ, and Liao YQ designed the project, analyzed most of the data, and wrote the manuscript; Pan YJ, Sun W and Xi L assisted in project design and manuscript revision; Yu HH and Shi YH designed the project, supervised the study, and revised the manuscript. All the authors read and approved the final manuscript.

AI-Generated Content Disclosure: No artificial intelligence tools were used for this work.

Foundations: Supported by National Natural Science Foundation of China (No.U24A20707; No.82171075); Guangdong Basic and Applied Basic Research Foundation (No.2023B1515120028); Brolucizumab Efficacy and Safety Single-Arm Descriptive Trial in Patients with Persistent Diabetic Macular Edema (No.2024-29).

Conflicts of Interest: Zhang NY, None; **Kong HQ,** None; **Liao YQ,** None; **Pan YJ,** None; **Sun W,** None; **Xi L,** None; **Yu HH,** None; **Shi YH,** None.

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