• Review Article •

Ferroptosis and microglial polarization in retinal vein occlusion: pathological mechanisms and therapeutic strategies

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Abstract

● With the acceleration of global aging, the incidence of retinal vein occlusion (RVO) has risen markedly. Its pathogenic mechanisms are closely linked to iron dyshomeostasis and microglial polarization and age-related degenerative changes in retinal microvessels. We systematically summarize the regulatory mechanisms of ferroptosis—an iron-dependent, lipid peroxidation-driven form of cell death, and elucidate the central pathway by which iron overload exacerbates retinal injury through the synergy of hypoxia-reoxygenation (H/R). Specifically, iron metabolic imbalance catalyzes the production of reactive oxygen species (ROS) *via* the Fenton reaction, which drives the polarization of microglia toward the proinflammatory M1 phenotype and activates the acyl-CoA synthetase long-chain family member 4 (ACSL4)-mediated lipid peroxidation cascade. This review proposes novel insights for combinatorial therapeutic strategies targeting key ferroptotic pathways (*e.g.*, the SLC7A11/GPX4 axis) and modulating microglial polarization, while also addressing the translational challenges associated with iron chelators (deferoxamine), lipid peroxidation inhibitors (liproxstatin-1), and targeted delivery systems for RVO.

● **KEYWORDS:** ferroptosis; microglial polarization; retinal vein occlusion; iron metabolism dysregulation; lipid peroxidation

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INTRODUCTION

Retinal vein occlusion (RVO), the second leading cause of vision-threatening retinal vascular disease after diabetic retinopathy[1], affects approximately 5.20 per 1000 individuals globally, with branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) prevalence rates of 4.42 per 1000 and 0.80 per 1000, respectively[2]. The incidence of RVO increases markedly with age and is slightly higher in males than females[3].

Hypertension, a central risk factor for RVO, is present in over 60% of cases, with uncontrolled hypertensive patients exhibiting a 4-7-fold increased risk of developing RVO[3-5]. Diabetes mellitus, a significant comorbidity, affects 42.18% of CRVO and 29.86% of BRVO patients, while hyperlipidemia is observed in 31.25% of CRVO and 13.19% of BRVO cases[6]. Additionally, hyperhomocysteinemia and chronic glaucoma are associated with elevated CRVO susceptibility[3]. Age-related degenerative changes in the retinal microvascular system are an important mechanism for the development of RVO, as evidenced by a decrease in retinal vascular density, enlargement of the avascular zone of the central recess, and weakening of the elasticity of the vascular wall, which lead to hemodynamic abnormalities and increase the risk of venous obstruction[7]. In addition, the thickness of the retinal nerve fiber layer progressively thins with age in the elderly population, which may be related to the weakening of vascular support structures, further exacerbating the potential for venous obstruction. RVO is closely associated with age-related chronic diseases such as hypertension, atherosclerosis, and diabetes mellitus. The world, especially developing countries such as China, is experiencing rapid aging, and RVO can lead to serious complications such as macular edema and neovascular glaucoma, which are more difficult to treat and more expensive to treat in older patients because of the high

number of comorbidities and poorer recovery ability. The application of new technologies such as optical coherence tomography angiography (OCTA) has shown that retinal microvascular abnormalities in the elderly population need to be screened for at an earlier stage; for example, OCTA can quantitatively assess macular vascular density and identify high-risk individuals. China has responded to aging by strengthening health insurance coverage and developing the senior care industry, but specialized prevention and treatment for age-related eye diseases such as RVO still need to be strengthened[7].

Emerging evidence highlights the critical roles of ferroptosis and microglial polarization in RVO pathogenesis. While significant progress has been made in understanding ferroptosis-mediated regulation of microglial polarization in the central nervous system (CNS)[8-12], it is critical to emphasize that the retina—an extension of the visual CNS[13-14]—exhibits spatiotemporally distinct ferroptosis regulatory mechanisms due to its specialized neurovascular microenvironment. The tripartite cascade triggered by RVO—venous hypertension, hypoxic stress, and neuroinflammatory conditions—likely induces ferroptosis activation patterns distinct from those in brain parenchyma. Studies reveal cell type-specific localization of iron metabolism proteins in the retina: under physiological conditions, ferritin (iron storage protein) predominantly localizes to rod bipolar cells and photoreceptors, while ferroportin (iron exporter) is expressed in retinal pigment epithelial cells and Müller glia, reflecting spatially precise iron homeostasis regulation[15]. This tissue-specific regulatory network suggests that direct extrapolation of CNS findings may overlook retina-specific iron metabolic crosstalk. Consequently, this review systematically addresses knowledge gaps and translational potential through four dimensions: 1) pathological microenvironment-specific interactions in RVO; 2) ferroptosis-mediated regulation of microglial polarization; 3) feedback regulation of ferroptosis by polarized microglia; 4) targeted therapeutic strategies.

Pathophysiological Mechanism of RVO RVO induces retinal capillary damage, triggering a cascade of pathological events that culminate in retinal dysfunction[2]. Compromised capillaries release elevated levels of inflammatory cytokines, including interleukin (IL)-18, S100A12, and Annexin A1 (ANXA1)[16], which exacerbate retinal injury[2]. These cytokines stimulate vascular endothelial growth factor (VEGF) production, leading to blood-retinal barrier disruption, increased vascular permeability, and macular edema—a primary cause of vision loss in RVO[17]. VEGF-mediated barrier breakdown further amplifies vascular leakage and retinal damage[2]. RVO-induced retinal ischemia promotes neovascularization, which predisposes patients to complications such as vitreous hemorrhage, retinal detachment, and neovascular glaucoma. These sequelae often result in irreversible vision loss[17-18].

Amino acid metabolic pathways play a central role in the ferroptosis regulatory network. Specifically, the cystine/glutamate antiporter system is formed by the covalent linkage of solute carrier family members SLC7A11 (light chain subunit) and SLC3A2 (heavy chain subunit) *via* a disulfide bond, creating a heterodimer that mediates transmembrane transport of cystine influx and glutamate efflux at a 1:1 stoichiometric ratio[19]. Intracellularly imported cystine is reduced to cysteine, which serves as a critical precursor for glutathione (GSH) biosynthesis. GSH exists in two redox states: reduced (GSH) and oxidized (GSSG). Under physiological conditions, the reduced form predominates, exerting antioxidant defense functions by scavenging reactive oxygen species (ROS) and thereby suppressing ferroptosis[20]. Experimental evidence demonstrates that downregulation of SLC7A11 directly impairs cystine uptake, leading to intracellular GSH depletion and ferroptosis activation[21]. Notably, nuclear factor erythroid 2-related factor 2 (Nrf2), a master transcriptional regulator of antioxidant responses, binds directly to the promoter region of the *SLC7A11* gene to enhance its transcription. This mechanism expands intracellular cysteine reserves, boosts GSH synthesis capacity, and ultimately achieves effective inhibition of ferroptosis[22].

Microglia, the primary immune cells of the CNS, influence neuroinflammation and neurodegenerative disease progression through their polarization states. Recent studies reveal that ferroptosis regulates microglial polarization through three hierarchical mechanisms, thereby modulating neuroinflammation and CNS disease trajectories: 1) Iron dyshomeostasis drives polarization phenotype switching. Iron overload is a central inducer of M1 polarization. In Parkinson's disease (PD)-associated neuroinflammation, iron excess drives microglial polarization toward the pro-inflammatory M1 phenotype through ROS-dependent pathways. M1-polarized microglia amplify neuroinflammation by releasing pro-inflammatory cytokines [*e.g.*, tumor necrosis factor (TNF)-α, IL-1β], exacerbating dopaminergic neuron damage[23]. Conversely, iron chelators [*e.g.*, deferiprone (DFP)] reduce intracellular iron levels, inhibit ROS generation, and block M1 polarization while promoting anti-inflammatory M2 polarization. M2 microglia secrete neurotrophic factors [*e.g.*, brain derived neurotrophic factor (BDNF)] and anti-inflammatory mediators [*e.g.*, IL-10, TGF-β] to exert neuroprotective effects. Similarly, in Alzheimer's disease models, ghrelin alleviates neuroinflammation and cognitive deficits by inducing M2 polarization and suppressing ferroptosis[24]; 2) Lipid peroxidation-inflammation positive

feedback loop. Long-chain acyl-CoA synthetase 4 (ACSL4)-mediated lipid metabolic dysregulation [*e.g.*, polyunsaturated fatty acid (PUFA) esterification] in ferroptosis directly triggers lipid peroxidation. Its byproduct, 4-hydroxynonenal, reinforces M1 polarization *via* the toll like recepter 4 (TLR4)/NF-κB pathway[25]. Concurrently, M1-derived pro-inflammatory cytokines (*e.g.*, TNF-α) suppress GSH synthesis, exacerbating ferroptosis and creating a vicious cycle; 3) Bidirectional regulation between polarization phenotypes and ferroptosis susceptibility. Differential ferroptosis responses of M1/M2 phenotypes serve as dynamic regulatory nodes. M1 microglia exhibit robust ferroptosis resistance due to inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO), which scavenges lipid peroxides and counteracts glutathione peroxidase 4 (GPX4) inactivation. This self-protective mechanism enables prolonged survival of M1 microglia in pro-inflammatory environments. In contrast, M2 microglia, lacking iNOS/NO-mediated antioxidant protection, display heightened susceptibility to iron accumulation-induced lipid peroxidation. Their ferroptosis may accelerate anti-inflammatory function loss in PD[23]. The ferroptosis-microglial polarization interplay forms a three-tiered "metabolic drive-inflammation amplification-phenotypic feedback" network. Mechanistic insights into this crosstalk provide novel therapeutic targets (*e.g.*, DFP, ACSL4 inhibitors, Nrf2 agonists) for neurodegenerative diseases and brain tumors.

Ferroptosis-Microglia Interaction Mechanisms

Pathological microenvironment-specific crosstalk in retinal vein occlusion The core pathology of RVO involves localized ischemia caused by venous thrombosis, followed by hypoxia-reoxygenation (H/R)-induced reperfusion injury. During this process, the synergistic effects of H/R and iron overload exacerbate cellular damage through multiple mechanisms. Under hypoxia, mitochondrial dysfunction disrupts electron transport chain activity, generating superoxide anions (O_2^-)[26]. Subsequent reoxygenation reactivates oxygen supply, further promoting ROS bursts. These ROS amplify lipid peroxidation *via* the Fenton reaction (Fe^{2+}-catalyzed conversion of H_2O_2 to hydroxyl radicals), directly damaging cellular and mitochondrial membranes[26-27]. Elevated erythrocyte oxidative stress in RVO patients correlates with blood hyperviscosity, suggesting that iron dysregulation may worsen microcirculatory dysfunction by impairing erythrocyte deformability[27].

In the RVO pathological microenvironment, blood-retinal barrier (BRB) disruption manifests as ischemic microenvironmental alterations and upregulated expression of VEGF and hypoxia-inducible factor-1α (HIF-1α). Müller glial cells contribute to this process by maintaining the inner BRB integrity and serving as critical sites for VEGF-A production[28]. Following BRB breakdown, resident retinal microglia become activated, and circulating macrophages infiltrate hypoxic regions. This macrophage recruitment peaks at postoperative day 7 and persists for at least 28d. Infiltrating macrophages migrate through BRB breaches into the retina, concomitant with upregulated expression of inflammatory markers such as CD68 and major histocompatibility complex (MHC)-II[28].

Regulation of Microglial Polarization by Ferroptosis Iron dysmetabolism and ferroptosis cascades constitute critical pathophysiological events during RVO progression. Vascular leakage-induced erythrocyte extravasation drives hemoglobin degradation *via* heme oxygenase-1 (HO-1) catalysis, generating excessive free Fe^{2+}[29-30], This process is bidirectionally regulated by oxidative stress and inflammatory cytokines (*e.g.*, IL-6), with amplification through Nrf2 signaling to enhance iron release[31]. Iron overload mechanisms involve aberrant non-transferrin-bound iron (NTBI) uptake pathways, ferritinophagy-mediated ferritin degradation, and functional suppression of the iron exporter ferroportin. In retinal iron-overload models, despite reduced transferrin receptor 1 (TFR1) expression, zinc-regulated iron transporters ZIP8/ZIP14 and divalent metal transporter 1 (DMT1) persistently mediate iron influx[32]. Ferritin degradation *via* ferritinophagy accelerates stored iron release, while ceruloplasmin-deficient models confirm its pivotal role in retinal iron accumulation[33]. Inflammatory cytokines and hepcidin inhibit ferroportin expression through TLR4 signaling, blocking iron efflux[34]. Free Fe^{2+} catalyzes hydrogen peroxide conversion to hydroxyl radicals *via* the Fenton reaction, initiating PUFA lipid peroxidation[35-37].

GPX4, a key ferroptosis suppressor, requires GSH as a cofactor to detoxify lipid peroxides. Studies demonstrate that siRNA-mediated GPX4 knockdown suffices to induce ferroptosis, while GPX4-overexpressing HT-1080 cells exhibit ferroptosis resistance, and GPX4-deficient cells display heightened susceptibility[38]. In oxygen-induced retinopathy (OIR) mouse models, HO-1 knockout upregulates GPX4 and reduces lipid peroxidation[39]. High glucose or inflammatory cytokines impair SLC7A11 function, limiting cystine uptake and subsequent GSH synthesis, thereby diminishing GPX4 activity. GPX4 inactivation leads to lipid peroxide accumulation, causing mitochondrial membrane oxidative damage and triggering pro-ferroptotic signals (*e.g.*, ACSL4 activation)[40]. These molecular events culminate in plasma membrane rupture, forming the pathological basis of ferroptosis execution.

In RVO, ferroptosis drives microglial polarization through iron metabolism imbalance and lipid peroxidation signaling pathways. In ischemia-reperfusion (IR) models, iron overload generates ROS *via* the Fenton reaction, leading to the accumulation of lipid peroxides such as malondialdehyde

(MDA), coupled with reduced activity of antioxidant enzymes GPX4 and ferroptosis suppressor protein 1 (FSP1). These events collectively drive microglial polarization toward the pro-inflammatory M1 phenotype[41]. Iron dysmetabolism is characterized by the upregulation of transferrin (TF) and DMT1, which enhance iron influx[41-42]. For example, in IR models, early upregulation of the cystine/glutamate antiporter SLC7A11 promotes GSH synthesis. However, subsequent downregulation of SLC7A11 expression results in the collapse of antioxidant defenses, exacerbating ferroptosis[41]. Additionally, sustained upregulation of acyl-CoA synthetase ACSL4 facilitates the esterification of PUFAs, generating oxidation-prone lipid substrates that further amplify microglial inflammatory responses[41]. The iron chelator deferoxamine (DFO) reverses this process by reducing Fe^{2+} and MDA levels[43].

Feedback Regulation of Ferroptosis by Polarized Microglia Microglial polarization in RVO is primarily characterized by activation. During experimental RVO, resident microglia are activated, and circulating macrophages are recruited into the retina. The polarization state of microglia forms a bidirectional regulatory loop with ferroptosis. Studies demonstrate that in ischemic retinal regions induced by RVO, microglia exhibit pronounced M1 polarization marked by significant upregulation of CD68, CD80, and MHC-II expression[28,44]. This pro-inflammatory phenotype exacerbates ferroptosis through multiple mechanisms: activated M1 microglia generate excessive ROS and pro-inflammatory cytokines (*e.g.*, TNF-α, IL-1β, IL-6), leading to neuronal iron overload in the retina[45]. A similar positive feedback loop is observed in diabetic retinopathy models, where M1-polarized microglia recruit peripheral macrophages *via* C-C motif chemokine ligand 2 (CCL2) chemokine secretion, sustaining a pro-inflammatory microenvironment[44].

In contrast to the ferroptosis-promoting effects of M1-polarized microglia, M2 polarization in RVO represents a potential therapeutic strategy. Retinal ischemia and inflammation caused by RVO can be mitigated by promoting microglial transition to the M2 phenotype. Experimental evidence shows that M2 microglia aggregate in neovascularized regions and secrete anti-inflammatory factors such as IL-10 and TGF-β[44]. ROCK inhibitors reduce ischemic retinal damage by suppressing the monocyte chemoattractant protein-1 (MCP-1)/CCR2 axis[44]. Ferrostatin-1 (Fer-1) significantly attenuates M1 polarization by scavenging lipid peroxides and promotes M2 phenotypic switching[41,46]. PLX5622 alleviates ischemic injury, increasing retinal ganglion cell (RGC) survival by 50%[47]. Lithium chloride (LiCl) downregulates Lipopolysaccharide (LPS)-induced M1 markers (*e.g.*, iNOS, TNF-α, IL-6) and inhibits morphological activation of microglia (*e.g.*, ameboid transformation from ramified states). This occurs *via* blockade of NF-κB nuclear translocation and reduced phosphorylation of signaling proteins (*e.g.*, p-PI3K, p-Akt). Although LiCl does not directly enhance M2 markers (*e.g.*, Arg-1, IL-4), it protects retinal structure and function by suppressing M1-driven neuroinflammation and neuronal damage. *In vivo* studies confirm that LiCl reduces inflammatory cell infiltration, alleviates retinal edema, and improves electroretinographic responses[48]. This dual regulatory mechanism highlights the pivotal role of microglial polarization in ferroptosis, suggesting that targeted modulation of microglial phenotype switching may offer novel therapeutic avenues for RVO pathology.

Targeted Therapeutic Strategies In the pathological microenvironment of RVO, hypoxia-reoxygenation-induced iron overload not only directly damages neurons but also activates microglia to release IL-18 and other factors, further upregulating VEGF and ROS, forming a "ischemia-oxidative stress-inflammation" triad of vicious cycles. These multi-layered interactions provide a theoretical foundation for developing novel combination therapies targeting iron metabolism, oxidative stress, and neuro-immune axes. Current strategies focus on key ferroptosis regulatory nodes. HO-1 knockdown upregulates GPX4 and reduces lipid peroxidation to suppress ferroptosis[39]. In retinal ischemia-reperfusion (I/R) injury, DFO, an iron chelator, ameliorates visual dysfunction by binding excess Fe^{3+}, thereby inhibiting Fenton reaction-mediated ROS and MDA generation while restoring GSH levels. DFO also modulates iron metabolism proteins: it downregulates transferrin receptor (TfR) expression while upregulating ferritin (FTH) and antioxidant pathway components (system Xc^--GSH-GPX4 axis), including SLC7A11 and GPX4, to enhance cellular antioxidant capacity[43]. Liproxstatin-1 (Lip-1), a potent ferroptosis inhibitor, suppresses lipid peroxidation and inflammation, significantly reducing RGC apoptosis and ferroptosis, improving visual function, and lowering retinal oxidative stress[49]. The free radical scavenger edaravone mitigates both oxidative damage and inflammation in murine retinal ischemia models. Microglial polarization regulation has emerged as a critical strategy: in experimental branch retinal vein occlusion (eBRVO) models, PLX5622 attenuates retinal inflammation by depleting microglia, reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and VEGF[47]. Additionally, adenosine A2A receptor (A2AR) antagonism may protect retinal function by controlling neuroinflammation[50]. However, clinical translation faces major challenges, including low BRB penetration efficiency, inadequate long-term drug stability, and difficulties in achieving cell-specific targeting[51].

DISCUSSION

This review systematically synthesizes the interplay between ferroptosis and microglial polarization in RVO, explores

the molecular mechanisms by which ferroptosis regulates microglial polarization and its role in retinal injury (Figure 1), and discusses therapeutic strategies and research advancements in detail. The translational application of ferroptosis modulators in RVO faces three major challenges: species-specific differences in GPX4 expression, BRB penetration limitations, and the urgent need for localized delivery systems. GPX4, a key ferroptosis regulator, exhibits significant functional and expression variability across species. GPX4 exists in three isoforms (cytoplasmic cGPX4, mitochondrial mGPX4, and nuclear nGPX4), with distinct spatiotemporal expression patterns in mice versus humans[52]. For instance, GPX4 knockout in mice causes sperm abnormalities and infertility[53], whereas human GPX4 mutations are linked to neonatal spinal developmental defects[52]. Such species differences hinder direct translation of preclinical findings (from murine or zebrafish models) to humans, particularly given potential variations in retinal GPX4 regulation[52,54]. To address this, strategies targeting post-translational modifications (*e.g.*, ubiquitination, phosphorylation) of GPX4 may bypass species-specific drug sensitivity issues[55-56]. Integrating single-cell sequencing and proteomics to map conserved GPX4 regulatory networks across species could also identify cross-species therapeutic targets[57].

The BRB, composed of tight junction proteins (*e.g.*, Claudin-5, ZO-1) and transporters, restricts permeation of macromolecular drugs and nanoparticles[58]. Most ferroptosis modulators (*e.g.*, iron chelators) are hydrophilic and poorly penetrate the BRB *via* passive diffusion[59]. Furthermore, BRB integrity in RVO patients is often compromised by inflammation and oxidative stress, reducing drug accumulation in lesions[60]. Innovations in delivery systems include: ROS-responsive hydrogels loaded with exosomes and liproxstatin-1, enabling sustained release for over 1mo and significant visual recovery[49]. IL-27-loaded exosomes (i27-exosomes), which penetrate intact BRB and achieve efficient retinal drug delivery, validated in uveitis models[61]. Focused ultrasound with microbubbles to transiently open the BRB, enhancing drug distribution (*e.g.*, anti-VEGF agents) in preclinical studies[62]. Targeted nanoparticles functionalized with BRB-specific receptors (*e.g.*, transferrin receptor) to improve specificity[61].

Systemic administration (*e.g.*, intravenous injection) risks off-target organ accumulation (*e.g.*, hepatotoxicity, iron overload)[54], while current local delivery methods (*e.g.*, intravitreal injections) face issues like frequent dosing and poor patient compliance[62-63]. Promising solutions include: sustained-release systems using polylactic-co-glycolic acid (PLGA) microspheres or hydrogels to extend drug release to several months[63]. Adeno-associated viral vector (AAV)-mediated gene therapy to overexpress GPX4 or

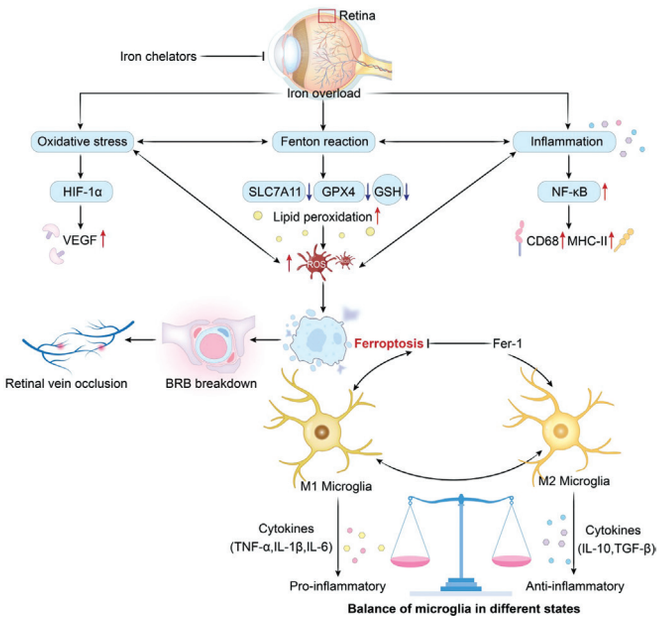

Figure 1 Crosstalk between ferroptosis and microglial polarization in retinal vein occlusion RVO The schematic depicts the pathological interplay of ferroptosis and microglial polarization dynamics in RVO progression. RVO: Retinal vein occlusion; HIF: Hypoxia-inducible factor; SLC7A11: Solute carrier family 7 member 11; GPX4: Glutathione peroxidase 4; GSH: Glutathione; NF-κB: Nuclear factor-kappa B; CD68: Cluster of differentiation 68; MHC: Major histocompatibility complex; TNF: Tumor necrosis factor; IL: Interleukin; TGF: Transforming growth factor. Created by Adobe illustrator.

ferroptosis inhibitors, enabling long-term efficacy with a single treatment[52,57]. Stimuli-responsive prodrugs activated by light or enzymes in retinal hypoxic regions for enhanced targeting[64]. With advancements in exosome delivery, gene editing, and ultrasound-microbubble technologies, ferroptosis modulators hold promise as transformative therapies for RVO within the next 5-10y.

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