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Review

Research progress of iron metabolism in retinal diseases

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ABSTRACT

Background: Retinal diseases can lead to severe visual impairment and even blindness, but current treatments are limited. For precise targeted therapy, the pathophysiological mechanisms of the diseases still need to be further explored. Iron serves an essential role in many biological activities and helps maintain the function and morphology of the retina. The vision problems caused by retinal diseases are affecting more and more people, the study of iron metabolism in retinal diseases possesses great potential for clinical application.

Main text: Iron maintains a dynamic balance in the retina but in excess is toxic to the retina. Iron overload can lead to various pathological changes in the retina through oxidative stress, inflammation, cell death, angiogenesis and other pathways. It is therefore involved in the progression of retinal diseases such as age-related macular degeneration, glaucoma, diabetic retinopathy, retinitis pigmentosa, and hereditary iron overload. In recent years, iron chelators have been shown to be effective in the treatment of retinal diseases, but the exact mechanism is not yet fully understood. This question prompted further investigation into the specific mechanisms by which iron metabolism is involved in retinal disease.

Conclusions: This review summarizes iron metabolism processes in the retina and mechanistic studies of iron metabolism in the progression of retinal disease. It also highlights the therapeutic potential of iron chelators in retinal diseases.

1. Introduction

Iron is a crucial element in organisms and involved in numerous processes in cellular life activities, such as energy production, the transportation of oxygen, catalysis of metabolic events, and biosynthesis.[1] It is one of the most abundant metals in the retina, and the role of iron metabolism in the retina is self-evident.[2] Iron as an iron sulfur (Fe–S) structural motif involved in various cellular machinery proteins plays a critical role in retinal physiology and pathology.[3] Isomerization of all-trans retinol ester to 11-cis-retinol catalyzed by retinal pigment epithelial (RPE) 65 is a key step in the visual cycle, while iron is a metal ion essential for the activity of RPE65 isomeric hydrolase.[4] The transduction of light depends on phagocytosis of photoreceptor (PR) segments by RPE cells and continuous turnover of membrane discs, a process that requires iron as a cofactor for fatty acid desaturase.[5] Iron is also involved in neurotransmitter secretion as it regulates glutamate secretion by RPE cells via the cytosolic aconitase pathway.[6] Therefore, iron metabolism disorders are closely related to the pathological process of retinal diseases.

Iron can easily change its valence and switch between Fe^{2+} and Fe^{3+} forms, catalyzing the generation of highly reactive hydroxyl radicals via the Fenton and Haber-Weiss reactions.[2] As one of the strongest chemical oxidants, hydroxyl radicals react with almost all types of molecules in cells, including lipids, peptides, proteins, nucleic acids, and sugars. In addition, hydroxyl radicals mediate accumulation of peroxidation by extracting electrons from fatty acids, which ultimately leads to tissue damage.[7] The retina's exposure to bright light, hyperoxia, hypermetabolism, high concentrations of polyunsaturated fatty acids, iron accumulation and reduced efficiency of the intracellular antioxidant defense system render the retina susceptible to oxidative stress-induced cell death. Ferroptosis can induce retinal RPE, PR and retinal ganglion cells (RGCs) death and is involved in the development of retinal diseases such as age-related macular degeneration (AMD), glaucoma and diabetic retinopathy (DR),[8–10] which provides a new way for us to understand the pathogenesis of retinal diseases from the perspective of iron metabolism.

This study seeks to elaborate the process of iron metabolism in the retina, summarize the research progress of iron metabolism in retinal diseases, and discuss the application of iron chelators in retinal diseases.

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2. Main text

2.1. Iron metabolism in the retina

2.1.1. Iron import

There are two forms of iron import in the retina, one is transferrin-bound-iron (TBI) import and the other is non-TBI (NTBI) import.[1] The inner retinal layer is supplied by the retinal vasculature and the outer layer by the choroidal vasculature. The inner and outer blood retinal barriers (BRB) separate the retina from the blood circulation.

The majority of circulating iron exists in hemoglobin, other non-heme iron binds to transferrin (Tf) in the form of ferric iron for transport to various tissues. Since iron laden Tf is unable to cross the BRB, Tf receptor (TfR) are required in order to assist. The Fe^{3+}-Tf-TfR complex complex is then endocytosed across the cell membrane into the cytoplasm to form endsome. This process is regulated by TfR on the cell membrane.[1,11] Immunohistochemistry shows that Tf is expressed in retinal RPE, inner and outer segment of PRs, inner retina and choroid.[3] TfR is expressed in the RPE, ganglion cell layer, inner nuclear layer, outer plexiform layer, inner segment of PRs and choroid.[12] Among them, the distribution of TfR at specific locations in different cells correlates with its function. In the RPE cells, TfR specially locates on the basolateral membrane and transports TBI from the choroid into the RPE, which in turn enters the neuroretina from the basolateral membrane side to the apical membrane by endocytosis to supply iron to cells in the retina. In the vascular endothelial cells, TfR mediates the transcellular input of TBI through the inner BRB.[13]

In addition to the TBI pathway, the NTBI pathway has been found to mediate iron import in recent years. In 2014, Luisa et al. found that class A scavenger receptor, member 5 (Scara5), is present in all cells of the retina, including vascular endothelial cells. They also noted that it binds to serum ferritin (Ft) as it directly mediates Ft import across BRB.[14] In models for retinal iron overload, Dunaief et al. observed increases in Zrt and Irt-like protein Zip8 and Zip14, mediating NTBI input, which explains why intraretinal iron remains increased even when the TBI pathway is inhibited. Zip8 and zip14 are expressed across the sensory retina and RPE layers, particularly in retinal vascular endothelial cells and Müller cells. Given that Müller cells span the entire thickness of the retina, iron in the retina is redistributed and plays an important role in maintaining the homeostasis of retinal iron.[15] In addition, ferroportin (Fpn) is located on the abluminal side of retinal vascular endothelial cells, and iron input from TBI into endothelial cells can be exported to the neuroretina through Fpn here.[16]

2.1.2. Iron storage

In the TBI import pathway, as the pH in the endosome decreases from 7.4 to 5.6, Fe^{3+} will dissociate from the complex.[17] It will then be reduced to Fe^{2+} by six transmembrane epithelial antigen of the prostate 3 (STEAP3) on the endosome membrane[18] and will translocate to the cytoplasm through divalent metal transporter-1 (DMT1) on the endosome membrane.[1] The specific localization of DMT1 in PR, horizontal and bipolar cells suggests that DMT1 may be involved in supplying iron to these cells for phototransduction or neurotransmitter synthesis.[13] Tf-TfR, however, moves to the cell membrane. TfR returns to the cell surface, where Tf is released to the extracellular space for the transport of free iron ions due to intra- and extracellular pH differences.[19] In the cytoplasm, Fe^{2+} is involved in a variety of biochemical reactions, and due to the tight regulation of intracellular iron metabolism, other iron ions form labile iron pool (LIP) in the cytoplasm or are stored in Ft and Mitochondrial Ft (FtMt).[1] Ft is a polypeptide dimer composed of heavy(HFt) and light chains (LFt) and can store up to 4500 Fe^{3+}. HFt in particular has ferroxidase activity, oxidizes Fe^{2+}in LIP to Fe^{3+}, and then stores in the cavity formed by LFt. Ft was expressed in all retinal layers, especially in the inner segments of PR and RPE.[12] FtMt located in the mitochondria structurally resembles HFt and functions as an antioxidant. It was widely expressed in the inner segment of the PR and the inner retina.[20]

2.1.3. Iron export

In mammals, unused or unstored iron is exported via the only known export pathway – Fpn.[21] Because circulating Tf can only bind Fe^{3+}, the exported Fe^{2+} must first be oxidized by ferroxidase to Fe^{3+} before it can enter the next iron cycle. Ceruloplasmin (Cp) is a multicopper oxidase with ferroxidase activity, which increases in various pathological conditions such as glaucoma and diabetic retinopathy.[22,23] Hephaestin (Heph), another multicopper ferroxidase, is a homolog of ceruloplasmin with 50% amino acid identity. Cp and Heph co-localizes with Fpn in RPE and Müller cells, which synergistically promoted iron export from cells. Fpn is present in the RPE, the inner segment of the PR, the outer plexiform layer, the inner plexiform layer, the Müller cell endplate, and vascular endothelial cells.[20] Fpn on RPE is located in the basolateral membrane and mediates iron export to the choroidal circulation; on Müller cell endplates, Fpn can mediate iron export to the vitreous.[20] Hepcidin (HepC) is synthesized by Müller cells, RP, and RPE and is a key hormone in regulating the homeostasis of intracellular iron levels by binding to the extracellular region of Fpn leading to its internalization and degradation and effectively preventing cellular iron export.[24] (Fig. 1).

2.1.4. Excessive iron damage to retina

Although iron is essential for the physiological processes of the retina, excess iron can cause damage to the retina through oxidative stress, inflammation, cell death, angiogenesis, etc. When iron levels exceed intracellular oxidative levels, abnormal generation of reactive oxygen species(ROS) will cause extensive oxidative stress damage to the retina, resulting in increased superoxide radicals, lipid peroxidation in PR cells,[25] disruption of RPE cell phagocytosis and lysosomal function,[26] and induction of ganglion cell death.[27] Iron overload is also involved in retinal inflammatory responses in that it activates the inflammasome pathway and triggers the release of inflammatory factors. Futhermore, iron overload can also induce retinal cell death by apoptosis and ferroptosis. Ferroptosis as a newly identified iron-dependent programmed cell death is characterized by intracellular iron accumulation and lipid peroxidation.[28] Ferroptosis has been found to induce RPE, RGC, PR and capillary endothelial cell death in the retina. It also involved in the progression of diseases such as AMD, glaucoma, diabetic retinopathy and retinitis pigmentosa (RP).[27,29–32] Increased levels of iron in the retina may also promote the expression of G-protein coupled receptor91(GPR91), thereby stimulating the production of the proangiogenic factors, namely vascular endothelial growth factor (VEGF) and angiopoietin.[33]

Iron metabolism involves many key molecules and different diseases have their own pathogenic mechanisms, which will be discussed below.

2.2. Age-related macular degeneration

AMD is the main cause of visual impairment and severe visual loss in the elderly. It is clinically divided into dry AMD (moderate drusen and retinal pigment changes) and wet AMD (neovascular and atrophic).[34] Its exact pathogenesis is not fully understood and may be related to factors such as inflammation, lipid metabolism, complement pathway, oxidative stress, angiogenesis, genetics, and environment.[37–52] (Table 1) In the retina of AMD patients, excess accumulation of iron can be found in the macular area, RPE, Bruch's membrane, drusen and others.[22,23] Tf, Ft, Fpn, which are involved in iron homeostasis, are also increased.[35,36]

Iron overload can produce an inflammatory response through multiple pathways. First, an iron overload can increase the translation of amyloid precursor protein containing iron-responsive elements, and its cleavage product amyloid β (Aβ) is deposited in the RPE. This results in local inflammatory response, as well as an acceleration of the formation of drusen, and ultimately lead to RPE atrophy and PR death.[37] Second, an iron overload significantly reduces the expression of cholesterol efflux transporters ATP binding cassette transporter A1 and ATP binding cassette transporter G1 in RPE, Müller cells and ganglion cells, disrupting

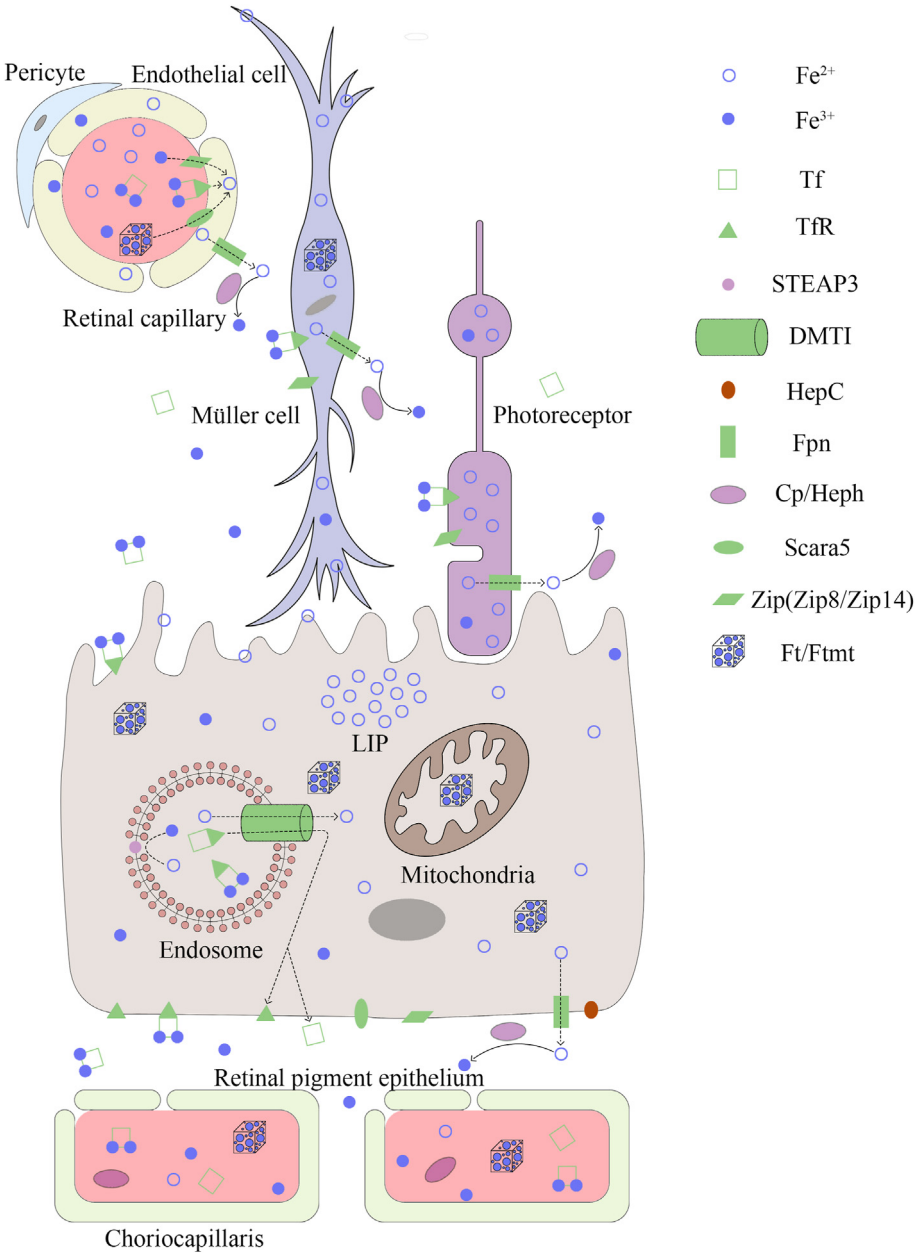

Fig. 1. Iron metabolisim in the retina. Iron in the retina is supplied by two vascular systems, the choroid and the retina, and imports are mediated by two forms, TBI and NTBI. Iron flows between cells and is distributed in various layers of cells to meet the physiological function of each cell, and unutilized iron will be stored in the cell or be exported.

cholesterol homeostasis and promoting the occurrence of inflammation.[38] Third, this overload induces Complement C3 expression in the non-classical transforming growth factor-β signaling pathway through extracellular signal-regulated kinase 1/2, small mothers against decapentaplegic 3 and CCAAT/enhancer-binding protein-δ, leading to inflammatory response.[39] Finally, an excess of iron induces NOD-like receptor family, pyrin domain containing 3 inflammasome activation depends upon accumulation of AluRNA, which accrete due to impaired double-stranded RNA-specific endoribonuclease1, eventually causing RPE death.[40]

Iron overload is also involved in AMD progression through many oxidative stress pathways. (1) It up-regulates retinal wingless-related integration site/β-catenin signaling and its downstream target genes, such as VEGF, promotes AMD progression through oxidative stress.[41] (2) The overload impairs the phagocytosis and lysosomal function of PR outer segments by RPE through oxidative stress,[26] which accelerates the deposition of lipophorin in drusen, RPE and Bruch's membrane, and promotes the death of PR and RPE cells in AMD patients.[42] (3) Bone morphogenetic protein (Bmp6) is secreted by the RPE and affects iron homeostasis by increasing the degradation of Fpn through up-regulation of HepC.[43] In the early stages of AMD, oxidative stress leads to iron accumulation in the retina by inhibiting the BMP/small mothers against decapentaplegic 3 signaling pathway, which in turn inhibits the expression of HepC.[44] In the late stages, Bmp6 increases due to iron overload. The interaction of iron overload and oxidative stress forms a vicious cycle that ultimately promotes the progression of aging, apoptosis, angiogenesis, and other processes.[43] (4) FtMt plays an antioxidant role in AMD[45] and triggers mitophagy to remove damaged mitochondria under normoxic conditions. However with aging, its content increases, which stabilizes hypoxia-inducible factor-1α (HIF-1α) and promotes the secretion of VEGF, and the main cause of choroidal neovascularization in wet AMD. In dry AMD, the accumulation of subretinal yellowish white

Table 1
Study of iron metabolism in pathogenesis of AMD.

Pathogenesis	Pathway	References
Inflammation	• Increases the translation of APP; its cleavage product Aβ deposits in the RPE	37
	• Induces NLRP3 inflammasome activation depends upon accumulation of AluRNA, which accrete due to impaired DICER1	40
Lipid metabolism	• Reduces the expression of cholesterol efflux transporters ABCA1 and ABCG1	38
Complement pathway	• Induces Complement C3 expression in the non-classical TGF-β signaling pathway through ERK1/2, SMAD3 and C/EBP-δ	39
Oxidative stress	• Up-regulates retinal Wnt/β-catenin signaling	41
	• Impairs the phagocytosis and lysosomal function of photoreceptor outer segments by RPE	47,48
	• Bmp6 affects iron homeostasis by increasing the degradation of Fpn through up-regulation of HepC	43
	• Drusen impedes oxygen supply, leading to FtMt maturation and mitophagy reduction	46
Angiogenesis	• Up-regulates retinal Wnt/β-catenin signaling and its downstream target genes, such as VEGF	41
	• Increased FtMt stabilizes HIF-1α and promotes the secretion of VEGF	46
Genetics	• Genetic variants in TfR2, HO-1, HO-2, IRP-1, and IRP-2	48–50
Environment	• Promotes the oxidation and degradation of retinoids under light	42,52

AMD - Age-related macular degeneration; APP - amyloid precursor protein; Aβ - amyloid β; RPE - retinal pigment epithelium; NLRP3 - NOD-like receptor family, pyrin domain containing 3; DICER1 - double-stranded RNA-specific endoribonuclease1; ABCA1 - ATP binding cassette transporter A1; ABCG1 - ATP binding cassette transporter G1; TGF-β - transforming growth factor-β; ERK1/2 - extracellular signal-regulated kinase 1/2; SMAD3 - small mothers against decapentaplegic 3; C/EBP-δ - CCAAT/enhancer-binding protein-δ; Wnt - wingless-related integration site; Bmp6 - bone morphogenetic protein 6; Fpn - ferroportin. HepC - Hepcidin; FtMt - mitochondria ferritin; VEGF - vascular endothelial growth factor; HIF-1α - hypoxia-inducible factor-1α; TfR2 - transferrin receptor2; HO-1 - heme oxygenase 1; HO-2 - heme oxygenase 2; IRP-1 - Iron-regulatory proteins-1; IRP-2 - Iron-regulatory proteins-2; DMT1 - divalent metal transporter-1.

deposits and drusen hinders the oxygen supply of the choroid to the retina, and under this hypoxic condition, the maturation of FtMt is reduced. Additionally, the protective effect against oxidative stress is weakened, and mitophagy is also reduced, which results in RPE degeneration and geographic atrophy and promots the progression of dry AMD.[46] Isolated Müller glial cells from transgenic mice expressing human Tf were protected against iron-mediated stress and could resist iron overload-mediated neuroretinal oxidative stress toxicity, and this mechanism is related to Tf binding iron and reducing oxidative stress.[47]

Polymorphisms in some iron homeostasis genes have been identified as risk factors for AMD, and variants in genes for TfR2,[48] heme oxygenase 1 and heme oxygenase 2,[49] Iron-regulatory proteins-1 and Iron-regulatory proteins-2[50] play a regulatory role in the development and progression of AMD. In addition, the expression of miRNAs that control the translation of TfR1 and DMT1 proteins is modified in the serum of AMD patients.[51]

Iron overload promotes the oxidation and degradation of retinoids under light, causing the death of PR and the accumulation of lipid. This also initiates light-mediated injurious mechanism, which confirms the relationship between the risk of AMD and sunlight exposure proposed in epidemiological studies.[42,52]

2.3. Glaucoma

Glaucoma is the most common cause of irreversible blindness in the world, which is characterized by progressive death of RGCs causing optic atrophy,but the mechanism of RGC death has not been fully elucidated.[53] Alterations in iron homeostasis have been found in glaucoma patients. Compared with healthy individuals, glaucoma patients have a different distribution of iron in the retina, with iron overload around Müller cells, RGCs, and optic nerve axons and reduced iron in cones.[54] In the retina of glaucoma patients and monkeys, the mRNA and protein expression levels of iron regulatory proteins Tf, Cp and Ft were increased.[55] Iron metabolism plays an important role in the pathogenesis of glaucomatous neuropathy through cell death, oxidative stress, inflammation, mitochondrial dysfunction, and gene mutations.

The role of glutamate excitotoxicity in the pathogenesis of glaucoma has been demonstrated in past studies, with excess glutamate binding to cell surface N-methyl-D-aspartate receptors (NMDARs) triggering massive calcium influx and activation of the RGC proapoptotic signaling cascade. In addition, glutamate-induced activation of NMDARs was found to increase iron uptake via the iron import channel DMT1.[56,57] Following intravitreal injection of NMDA, RGCs undergo iron accumulation and trigger RGC apoptosis.[58] Iron chelators protect RGCs from NMDA excitotoxicity-induced apoptosis by decreasing intracellular iron content and oxidative stress in rats.[58,59] In addition, nuclear receptor coactivator 4-mediated degradation of HFt is also responsible for the imbalance of iron homeostasis after pathological ocular hypertension, after which iron accumulation and the occurrence of ferroptosis are involved in the progressive loss of RGCs.[60] Tf can interfere with different cell death mechanisms such as apoptosis and iron death in the pathogenesis of glaucoma and has a protective effect on RGCs exposed to ocular hypertension.[54]

In addition, iron metabolism is also involved in the oxidative stress mechanism of glaucoma. In glaucoma, the inflammation triggered by Aβ and p-tau deposition during the amyloid precursor protein amyloidosis of RGC triggers the release of cytokines, up-regulates retinal HepC expression, and causes iron overload. Iron catalyzes ROS to activate inflammatory factors through the Fenton reaction, further promoting Aβ production and aggregation.[61] The redox state of RGC cells therefore forms a positive feedback pathway with Fe^{2+}, aggravating RGC death in glaucoma.

Mitochondrial dysfunction plays a key role in RGC loss in glaucoma,[62] ROS and lipid peroxides triggered by iron overload damage mitochondria. Ferroptosis inhibitors can promote RGC survival and protect retinal structure by maintaining mitochondrial function.[27]

Mutations in optineurin have been implicated in the pathogenesis of glaucoma,[63] in which variants at the m98K site induce RGC death by increases the degradation of TfR through the autophagy-lysosome pathway, coexpression of transferrin receptor or supplementation of media with an iron donor reduced M98K-induced cell death.[64]

2.4. Diabetic retinopathy

Diabetic retinopathy is a sight-threatening diabetic complication that seriously affects the quality of life of the middle-aged and elderly population.[65] Iron, Cp, and Tf are increased in the retina of DR patients,[23,66] and increased iron levels in the vitreous are associated with the occurrence of proliferative DR.[67] There may be several reasons for iron overload: (1) hyperglycemia destroys the heme in hemoglobin and myoglobin, and iron ions dissociate from the heme[68]; (2) intraretinal hemorrhage or vitreous hemorrhage aggravates iron overload in patients with proliferative DR; (3) the high expression of angiotensin II in DR may promote the production of Tf, thereby increasing iron intake[66]; (4) iron transport from the vascular endothelium to the retina increases when Müller cells are lost or dysfunctional.[69]

Iron overload affects the integrity of the BRB and accelerates the loss of retinal cells by enhancing oxidative stress and NOD-like receptor family, pyrin domain containing 3 inflammasome signaling pathways.[70] In addition, an excess of iron induces retinal renin expression through the succinate receptor GPR91 signaling pathway.[33] GPR91 regulates pro-angiogenic factors such as VEGF and angiopoietins, which are involved in the formation of new blood vessels in DR.[70] Overexpression

of the renin-angiotensin system is involved in neurodegeneration and vascular changes in DR.[71] Therefore, iron overload accelerates the progression of DR. In DR, capillary occlusion causes severe hypoxia and activates HIF, which is closely related to angiogenesis.[72] Iron plays a role in HIF transcriptional regulation of pro-angiogenic genes.[73] Futhermore, HIF plays a key role in regulating iron metabolism by regulating the expression of iron-related proteins, such as DMT1, Fpn, and TfR.[74]

2.5. Retinitis pigmentosa

Retinitis pigmentosa is the most commonly inherited retinal degenerative disease characterized by irreversible death of PR, and there is no effective treatment.[75] Iron overload was found to exist in the retina of two RP animal models, retinal degeneration10 mice (rd10 mice) and Royal Collegeof Surgeons Rats,[76,77] and iron metabolism-related proteins, Tf, TfR, Ft and Cp were also increased in rd10 mice.[76] Iron leads to PR death by inducing oxidative stress, and cones are more susceptible to iron-mediated oxidative stress injury than rods.[78] Phagocytosis of Fe^{2+}-oxidized photoreceptor outer segments further damages the RPE, reducing RPE phagocytosis and lysosomal function and leading to RPE autofluorescence.[25,26] In response to iron overload, the rd10 mice' retina alleviates oxidative stress by chelating excess iron by increasing the expression of Tf. Overexpressed or intraperitoneally injected human transferrin effectively inhibited PR death.[79] In addition, iron chelators were also effective in rescuing retinal degeneration in RP.[80,81]

2.6. Hereditary iron overload

Accumulation of iron can be found in the retina of patients with inherited iron overload disorders, which involve mutations in genes encoding proteins for iron homeostasis, thus leading to an imbalance in retinal iron metabolism.

2.6.1. Aceruloplasminemia

Aceruloplasminemia (aCP) is an autosomal recessive disorder that occurs more often in adulthood and is caused by mutations in the gene encoding ceruloplasmin, which can lead to tissue iron overload due to impaired iron output.[82] In autopsies of patients with aCP, iron accumulation in the retina can be observed.[83] Case reports for many patients with aCP have described retinal changes associated with iron overload, such as macular degeneration (similar to drusen), melanotic changes (increase or decrease), RPE changes (hypertrophy, atrophy) and other pathological findings similar to AMD.[84,85]

2.6.2. Hereditary hemochromatosis

Hereditary hemochromatosis (HH) is a common genetic disorder and can be seen as mutations in iron metabolism-related genes such as hemochromatosis gene (HFE), Fpn, hemojuvelin(Hjv), TfR2, with HFE having the most mutations.[86] HFE is located in the RPE layer of the retina and regulates intracellular iron uptake. It dose so by reducing the affinity of TfR for Tf and binding to TfR into a stable complex. HFE also regulates the level of HepC.[87] In HFE knockout mouse models, Ft accumulation has been found to be present in the retina, with reduced numbers of ganglion cells, disruption of the inner and outer nuclear layers, RPE cell hypertrophy and proliferation, and differential regulation of cell cycle-related genes.[88] Hjv knockout mice are a rare juvenile model of HH in which Hjv regulates iron levels by regulating HepC expression. Retinal iron overload, neovascularization, reactive gliosis, and BRB destruction also occur in this model.[89]

2.7. Treatment

Substantial literature indicates that iron chelators have broad prospects in the application of retinal diseases and have shown positive effects in the treatment of AMD, glaucoma, RP, etc.[58,59,79–81,90] Iron chelators inhibit the Fenton reaction by chelating excess iron ions. They also play a role in reducing retinal pathological damage, anti-oxidation, and anti-apoptosis. At present, there are three types of chelators. The first is chemical chelators, which include deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). DFO was the first iron chelator approved by the Food and Drug Administration (FDA) in 1968 for the treatment of chronic iron overload in patients with acute iron intoxication and transfusion-dependent anemia. As a hydrophilic iron chelator, DFO must be administered by slow subcutaneous infusion, intramuscularly or intravenously.[91] Its use in ophthalmology is limited by the means of administration and side effects. Zinc DFO, a zinc complex of DFO with better cell permeability, has already demonstrated the protection of PR in rd10 mice.[80] DFX received FDA approval in 2005 for the treatment of transfusional iron overload, but to date there is no evidence that it reduces brain or retinal iron levels. DFP was approved by the FDA in 2011. It later received approval for use in Europe and Asia due to its low molecular weight and easy penetration across the blood-brain barrier. However, reversible agranulocytosis occurs in approximately 1%–2% of thalassemic patients treated with oral DFP,[92] necessitating continuous monitoring of blood counts during use. DFP can reduce retinal iron levels and oxidative stress, thereby reducing retinal degeneration.[93] The second is natural chelators, usually from plants, such as curcumin, polyphenols, and flavonoids. These can chelate iron and have been shown to be effective in mouse models of retinal degeneration.[94,95] Tf is an endogenous iron chelator, and each Tf can chelate two iron ions. Tf has shown therapeutic potential in diseases such as AMD and RP.[47,54,79] It should be noted that the long-term therapeutic effect of iron chelators remains to be seen. In the future, iron chelator drugs should be able to cross the BRB, target iron-overloaded tissues and have a sufficiently long half-life and rapid elimination pathways.

3. Conclusions

Iron is an extremely common element on Earth, and it has a clear impact on the retina. Iron metabolism involves many processes in retinal physiology and pathology, and a large number of studies have confirmed its key role in retinal diseases, but there are still many outstanding problems that need to be solved urgently. The process of iron metabolism still requires further exploration, especially with regard to the regulatory processes of key molecules, such as DMT1 and Zip. Iron overload is involved in the progression of retinal diseases through a variety of mechanisms, and further clarifying the specific regulatory mechanisms will provide us with new ideas for targeted precision therapy. Iron chelator therapy has shown positive effects in animal models of retinal diseases and offers solid application prospects; however, more clinical trials are needed to verify its clinical application value in the future.

Study approval

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Author contributions

XT conceived the idea for the article, CL drafted the manuscript. XT, CL, CX and HT critically revised the work for intellectual content. All authors read and approved the final manuscript.

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Declaration of competing interest

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Abbreviations

RPE	retinal pigment epithelium
PR	photoreceptors
RGCs	retinal ganglion cells
AMD	age-related macular degeneration
DR	diabetic retinopathy
TBI	tranferrin-bound-iron
NTBI	non-transferrin-bound-iron
BRB	blood retinal barriers
Tf	transferrin
TfR	transferrin receptor
Scara5	scavenger receptor class A, member 5
Ft	ferritin
Zip	zrt- and irt-like protein
Fpn	ferroportin
STEAP3	six transmembrane epithelial antigen of the prostate 3
DMT1	divalent metal transporter-1
LIP	labile iron pool
FtMt	mitochondria ferritin
CP	ceruloplasmin
Heph	hephaestin
HepC	hepcidin
ROS	reactive oxygen species
RP	retinitis pigmentosa
GPR91	G-protein coupled receptor91
VEGF	vascular endothelial growth factor
Aβ	amyloid β
Bmp6	bone morphogenetic protein 6
HIF-1α	hypoxia-inducible factor-1α
NMDARs	N-methyl-D-aspartate receptors
rd10	mice retinal degeneration10 rats
aCP	aceruloplasminemia
HH	hereditary hemochromatosis
HFE	hemochromatosis gene
Hjv	hemojuvelin
DFO	deferoxamine
DFP	deferiprone
DFX	deferasirox
FDA	Food and Drug Administration

References

1. Pantopoulos K, Porwal SK, Tartakoff A, et al. Mechanisms of mammalian iron homeostasis. *Biochemistry*. Jul 2012;51(29):5705–5724. https://doi.org/10.1021/bi300752r.
2. Picard E, Daruich A, Youale J, et al. From rust to quantum biology: the role of iron in retina physiopathology. *Cells*. Mar 2020;9(3):705. https://doi.org/10.3390/cells9030705.
3. Maio N, Rouault TA. Iron-sulfur cluster biogenesis in mammalian cells: new insights into the molecular mechanisms of cluster delivery. *Biochim Biophys Acta*. Jun 2015;1853(6):1493–1512. https://doi.org/10.1016/j.bbamcr.2014.09.009.
4. Moiseyev G, Takahashi Y, Chen Y, et al. RPE65 is an iron(II)-dependent isomerohydrolase in the retinoid visual cycle. *J Biol Chem*. Feb 2006;281(5):2835–2840. https://doi.org/10.1074/jbc.M508903200.
5. Shichi H. Microsomal electron transfer system of bovine retinal pigment epithelium. *Exp Eye Res*. Jan 1969;8(1):60–68. https://doi.org/10.1016/s0014-4835(69)80081-3.
6. McGahan MC, Harned J, Mukunnemkeril M, et al. Iron alters glutamate secretion by regulating cytosolic aconitase activity. *Am J Physiol Cell Physiol*. May 2005;288(5):C1117–C1124. https://doi.org/10.1152/ajpcell.00444.2004.
7. Stoyanovsky DA, Tyurina YY, Shrivastava I, et al. Iron catalysis of lipid peroxidation in ferroptosis: regulated enzymatic or random free radical reaction? *Free Radic Biol Med*. Mar 2019;133:153–161. https://doi.org/10.1016/j.freeradbiomed.2018.09.008.
8. Totsuka K, Ueta T, Uchida T, et al. Oxidative stress induces ferroptotic cell death in retinal pigment epithelial cells. *Exp Eye Res*. Apr 2019;181:316–324. https://doi.org/10.1016/j.exer.2018.08.019.
9. Yang M, So KF, Lam WC, et al. Cell ferroptosis: new mechanism and new hope for retinitis pigmentosa. *Cells*. Aug 2021;10(8):2153. https://doi.org/10.3390/cells10082153.
10. Huang S, Liu K, Su Y, et al. Research progress of ferroptosis in glaucoma and optic nerve damage. *Mol Cell Biochem*. Sep 2022. https://doi.org/10.1007/s11010-022-04545-7, 10.1007/s11010-022-04545-7.
11. Hunt RC, Dewey A, Davis AA. Transferrin receptors on the surfaces of retinal pigment epithelial cells are associated with the cytoskeleton. *J Cell Sci*. Apr 1989;92(Pt 4):655–666. https://doi.org/10.1242/jcs.92.4.655.
12. Yefimova MG, Jeanny JC, Guillonneau X, et al. Iron, ferritin, transferrin, and transferrin receptor in the adult rat retina. *Invest Ophthalmol Vis Sci*. Jul 2000;41(8):2343–2351.
13. He X, Hahn P, Iacovelli J, et al. Iron homeostasis and toxicity in retinal degeneration. *Prog Retin Eye Res*. Nov 2007;26(6):649–673. https://doi.org/10.1016/j.preteyeres.2007.07.004.
14. Mendes-Jorge L, Ramos D, Valença A, et al. Correction: L-ferritin binding to Scara5: a new iron traffic pathway potentially implicated in retinopathy. *PLoS One*. Jun 2017;12(6), e0180288. https://doi.org/10.1371/journal.pone.0180288.
15. Sterling J, Guttha S, Song Y, et al. Iron importers Zip8 and Zip14 are expressed in retina and regulated by retinal iron levels. *Exp Eye Res*. Feb 2017;155:15–23. https://doi.org/10.1016/j.exer.2016.12.008.
16. Baumann BH, Shu W, Song Y, et al. Ferroportin-mediated iron export from vascular endothelial cells in retina and brain. *Exp Eye Res*. Oct 2019;187, 107728. https://doi.org/10.1016/j.exer.2019.107728.
17. Steere AN, Byrne SL, Chasteen ND, et al. Kinetics of iron release from transferrin bound to the transferrin receptor at endosomal pH. *Biochim Biophys Acta*. Mar 2012;1820(3):326–333. https://doi.org/10.1016/j.bbagen.2011.06.003.
18. Ohgami RS, Campagna DR, Greer EL, et al. Identification of a ferrireductase required for efficient transferrin-dependent iron uptake in erythroid cells. *Nat Genet*. Nov 2005;37(11):1264–1269. https://doi.org/10.1038/ng1658.
19. Dautry-Varsat A, Ciechanover A, Lodish HF. pH and the recycling of transferrin during receptor-mediated endocytosis. *Proc Natl Acad Sci U S A*. Apr 1983;80(8):2258–2262. https://doi.org/10.1073/pnas.80.8.2258.
20. Hahn P, Dentchev T, Qian Y, et al. Immunolocalization and regulation of iron handling proteins ferritin and ferroportin in the retina. *Mol Vis*. Aug 2004;10:598–607.
21. Donovan A, Lima CA, Pinkus JL, et al. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. *Cell Metabol*. Mar 2005;1(3):191–200. https://doi.org/10.1016/j.cmet.2005.01.003.
22. Farkas RH, Chowers I, Hackam AS, et al. Increased expression of iron-regulating genes in monkey and human glaucoma. *Invest Ophthalmol Vis Sci*. May 2004;45(5):1410–1417. https://doi.org/10.1167/iovs.03-0872.
23. Gerhardinger C, Costa MB, Coulombe MC, et al. Expression of acute-phase response proteins in retinal Müller cells in diabetes. *Invest Ophthalmol Vis Sci*. Jan 2005;46(1):349–357. https://doi.org/10.1167/iovs.04-0860.
24. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. Dec 2004;306(5704):2090–2093. https://doi.org/10.1126/science.1104742.
25. Shu W, Baumann BH, Song Y, et al. Ferrous but not ferric iron sulfate kills photoreceptors and induces photoreceptor-dependent RPE autofluorescence. *Redox Biol*. Feb 2020;34, 101469. https://doi.org/10.1016/j.redox.2020.101469.
26. Chen H, Lukas TJ, Du N, et al. Dysfunction of the retinal pigment epithelium with age: increased iron decreases phagocytosis and lysosomal activity. *Invest Ophthalmol Vis Sci*. 2009;50(4):1895–1902. https://doi.org/10.1167/iovs.08-2850.
27. Guo M, Zhu Y, Shi Y, et al. Inhibition of ferroptosis promotes retina ganglion cell survival in experimental optic neuropathies. *Redox Biol*. Dec 2022;58, 102541. https://doi.org/10.1016/j.redox.2022.102541.
28. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. May 2012;149(5):1060–1072. https://doi.org/10.1016/j.cell.2012.03.042.
29. Totsuka K, Ueta T, Uchida T, et al. Oxidative stress induces ferroptotic cell death in retinal pigment epithelial cells. *Exp Eye Res*. Apr 2019;181:316–324. https://doi.org/10.1016/j.exer.2018.08.019.
30. Yang M, So KF, Lam WC, et al. Cell ferroptosis: new mechanism and new hope for retinitis pigmentosa. *Cells*. Aug 2021;10(8):2153. https://doi.org/10.3390/cells10082153.
31. Chen C, Chen J, Wang Y, et al. Ferroptosis drives photoreceptor degeneration in mice with defects in all-trans-retinal clearance. *Jan-Jun J Biol Chem*. 2021;296, 100187. https://doi.org/10.1074/jbc.RA120.015779.
32. Zhang J, Qiu Q, Wang H, et al. TRIM46 contributes to high glucose-induced ferroptosis and cell growth inhibition in human retinal capillary endothelial cells by facilitating GPX4 ubiquitination. *Exp Cell Res*. Oct 2021;407(2), 112800. https://doi.org/10.1016/j.yexcr.2021.112800.
33. Gnana-Prakasam JP, Ananth S, Prasad PD, et al. Expression and iron-dependent regulation of succinate receptor GPR91 in retinal pigment epithelium. *Invest Ophthalmol Vis Sci*. Jun 2011;52(6):3751–3758. https://doi.org/10.1167/iovs.10-6722.
34. Mitchell P, Liew G, Gopinath B, et al. Age-related macular degeneration. *Lancet*. Sep 2018;392(10153):1147–1159. https://doi.org/10.1016/S0140-6736(18)31550-2.
35. Biesemeier A, Yoeruek E, Eibl O, et al. Iron accumulation in Bruch's membrane and melanosomes of donor eyes with age-related macular degeneration. *Exp Eye Res*. Aug 2015;137:39–49. https://doi.org/10.1016/j.exer.2015.05.019.

36. Pamphlett R, Cherepanoff S, Too LK, et al. The distribution of toxic metals in the human retina and optic nerve head: implications for age-related macular degeneration. *PLoS One*. Oct 2020;15(10), e0241054. https://doi.org/10.1016/j.exer.2015.05.019.
37. Guo LY, Alekseev O, Li Y, et al. Iron increases APP translation and amyloid-beta production in the retina. *Exp Eye Res*. Oct 2014;129:31–37. https://doi.org/10.1016/j.exer.2014.10.012.
38. Ananth S, Gnana-Prakasam JP, Bhutia YD, et al. Regulation of the cholesterol efflux transporters ABCA1 and ABCG1 in retina in hemochromatosis and by the endogenous siderophore 2,5-dihydroxybenzoic acid. *Biochim Biophys Acta*. Apr 2014;1842(4):603–612. https://doi.org/10.1016/j.bbadis.2014.01.010.
39. Li Y, Song D, Song Y, et al. Iron-induced local complement component 3 (C3) up-regulation via non-canonical transforming growth factor (TGF)-β signaling in the retinal pigment epithelium. *J Biol Chem*. May 2015;290(19):11918–11934. https://doi.org/10.1074/jbc.M115.645903.
40. Gelfand BD, Wright CB, Kim Y, et al. Iron toxicity in the retina requires alu RNA and the NLRP3 inflammasome. *Cell Rep*. Jun 2015;11(11):1686–1693. https://doi.org/10.1016/j.celrep.2015.05.023.
41. Mandala A, Armstrong A, Girresch B, et al. Fenofibrate prevents iron induced activation of canonical Wnt/β-catenin and oxidative stress signaling in the retina. *NPJ Aging Mech Dis*. Oct 2020;6:12. https://doi.org/10.1038/s41514-020-00050-7.
42. Ueda K, Kim HJ, Zhao J, et al. Iron promotes oxidative cell death caused by bisretinoids of retina. *Proc Natl Acad Sci U S A*. May 2018;115(19):4963–4968. https://doi.org/10.1073/pnas.1722601115.
43. Hadziahmetovic M, Song Y, Wolkow N, et al. Bmp6 regulates retinal iron homeostasis and has altered expression in age-related macular degeneration. *Am J Pathol*. Jul 2011;179(1):335–348. https://doi.org/10.1016/j.ajpath.2011.03.033.
44. Chen L, Ma B, Liu X, et al. H_2O_2 induces oxidative stress damage through the BMP-6/SMAD/hepcidin axis. *Dev Growth Differ*. Feb 2020;62(2):139–146. https://doi.org/10.1111/dgd.12650.
45. Arosio P, Levi S. Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. *Biochim Biophys Acta*. Aug 2010;1800(8):783–792. https://doi.org/10.1016/j.bbagen.2010.02.005.
46. Wang X, Yang H, Yanagisawa D, et al. Mitochondrial ferritin affects mitochondria by stabilizing HIF-1α in retinal pigment epithelium: implications for the pathophysiology of age-related macular degeneration. *Neurobiol Aging*. Nov 2016;47:168–179. j.neurobiolaging.2016.07.025.
47. Picard E, Fontaine I, Jonet L, et al. The protective role of transferrin in Müller glial cells after iron-induced toxicity. *Mol Vis*. May 2008;14:928–941.
48. Wysokinski D, Danisz K, Pawlowska E, et al. Transferrin receptor levels and polymorphism of its gene in age-related macular degeneration. *Acta Biochim Pol*. Apr 2015;62(2):177–184. https://doi.org/10.18388/abp.2014_843.
49. Synowiec E, Szaflik J, Chmielewska M, et al. An association between polymorphism of the heme oxygenase-1 and -2 genes and age-related macular degeneration. *Mol Biol Rep*. Mar 2012;39(3):2081–2087. https://doi.org/10.1007/s11033-011-0955-3.
50. Synowiec E, Pogorzelska M, Blasiak J, et al. Genetic polymorphism of the iron-regulatory protein-1 and -2 genes in age-related macular degeneration. *Mol Biol Rep*. Jun 2012;39(6):7077–7087. https://doi.org/10.1007/s11033-012-1539-6.
51. Szemraj M, Oszajca K, Szemraj J, et al. MicroRNA expression analysis in serum of patients with congenital hemochromatosis and age-related macular degeneration (AMD). *Med Sci Mon Int Med J Exp Clin Res*. Aug 2017;23:4050–4060. https://doi.org/10.12659/msm.902366.
52. Imamura T, Hirayama T, Tsuruma K, et al. Hydroxyl radicals cause fluctuation in intracellular ferrous ion levels upon light exposure during photoreceptor cell death. *Exp Eye Res*. Dec 2014;129:24–30. https://doi.org/10.1016/j.exer.2014.10.019.
53. Kang JM, Tanna AP. Glaucoma. *Med Clin*. May 2021;105(3):493–510. https://doi.org/10.1016/j.mcna.2021.01.004.
54. Youale J, Bigot K, Kodati B, et al. Neuroprotective effects of transferrin in experimental glaucoma models. *Int J Mol Sci*. Oct 2022;23(21), 12753. https://doi.org/10.3390/ijms232112753.
55. Farkas RH, Chowers I, Hackam AS, et al. Increased expression of iron-regulating genes in monkey and human glaucoma. *Invest Ophthalmol Vis Sci*. May 2004;45(5):1410–1417. https://doi.org/10.1167/iovs.03-0872.
56. Chen Y, Khan RS, Cwanger A, et al. Dexras1, a small GTPase, is required for glutamate-NMDA neurotoxicity. *J Neurosci*. Feb 2013;33(8):3582–3587. https://doi.org/10.1523/JNEUROSCI.1497-12.2013.
57. Cheah JH, Kim SF, Hester LD, et al. NMDA receptor-nitric oxide transmission mediates neuronal iron homeostasis via the GTPase Dexras1. *Neuron*. Aug 2006;51(4):431–440. https://doi.org/10.1016/j.neuron.2006.07.011.
58. Sakamoto K, Suzuki T, Takahashi K, et al. Iron-chelating agents attenuate NMDA-Induced neuronal injury via reduction of oxidative stress in the rat retina. *Exp Eye Res*. Jun 2018;171:30–36. https://doi.org/10.1016/j.exer.2018.03.008.
59. Cui QN, Bargoud AR, Ross AG, et al. Oral administration of the iron chelator deferiprone protects against loss of retinal ganglion cells in a mouse model of glaucoma. *Exp Eye Res*. Apr 2020;193, 107961. https://doi.org/10.1016/j.exer.2020.107961.
60. Yao F, Peng J, Zhang E, et al. Pathologically high intraocular pressure disturbs normal iron homeostasis and leads to retinal ganglion cell ferroptosis in glaucoma. *Cell Death Differ*. Aug 2022. https://doi.org/10.1038/s41418-022-01046-4, 10.1038/s41418-022-01046-4.
61. Ashok A, Singh N, Chaudhary S, et al. Retinal degeneration and alzheimer's disease: an evolving link. *Int J Mol Sci*. Oct 2020;21(19):7290. https://doi.org/10.3390/ijms21197290.
62. Tang J, Zhuo Y, Li Y. Effects of iron and zinc on mitochondria: potential mechanisms of glaucomatous injury. *Front Cell Dev Biol*. Aug 2021;9, 720288. https://doi.org/10.3389/fcell.2021.720288.
63. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science*. Feb 2002;295(5557):1077–1079. https://doi.org/10.1126/science.1066901.
64. Sirohi K, Chalasani ML, Sudhakar C, et al. M98K-OPTN induces transferrin receptor degradation and RAB12-mediated autophagic death in retinal ganglion cells. *Autophagy*. Jan 2013;9(4):510–527. https://doi.org/10.4161/auto.23458.
65. Song P, Yu J, Chan KY, et al. Prevalence, risk factors and burden of diabetic retinopathy in China: a systematic review and meta-analysis. *J Glob Health*. Jun 2018;8(1), 010803. https://doi.org/10.7189/jogh.08.010803.
66. Ciudin A, Hernández C, Simó R. Iron overload in diabetic retinopathy: a cause or a consequence of impaired mechanisms? *Exp Diabetes Res*. Aug 2010;2010, 714108. https://doi.org/10.1155/2010/714108.
67. Konerirajapuram NS, Coral K, Punitham R, et al. Trace elements iron, copper and zinc in vitreous of patients with various vitreoretinal diseases. *Indian J Ophthalmol*. Jun 2004;52(2):145–418.
68. Cussimanio BL, Booth AA, Todd P, et al. Unusual susceptibility of heme proteins to damage by glucose during non-enzymatic glycation. *Biophys Chem*. Sep 2003;105(2–3):743–755. https://doi.org/10.1016/s0301-4622(03)00100-5.
69. Baumann B, Sterling J, Song Y, et al. Conditional müller cell ablation leads to retinal iron accumulation. *Invest Ophthalmol Vis Sci*. Aug 2017;58(10):4223–4234. https://doi.org/10.1167/iovs.17-21743.
70. Chaudhary K, Promsote W, Ananth S, et al. Iron overload accelerates the progression of diabetic retinopathy in association with increased retinal renin expression. *Sci Rep*. Feb 2018;8(1):3025. https://doi.org/10.1038/s41598-018-21276-2.
71. Kurihara T, Ozawa Y, Nagai N, et al. Angiotensin II type 1 receptor signaling contributes to synaptophysin degradation and neuronal dysfunction in the diabetic retina. *Diabetes*. Aug 2008;57(8):2191–2198. https://doi.org/10.2337/db07-1281.
72. Zhang D, Lv FL, Wang GH. Effects of HIF-1α on diabetic retinopathy angiogenesis and VEGF expression. *Eur Rev Med Pharmacol Sci*. Aug 2018;22(16):5071–5076. https://doi.org/10.26355/eurrev_201808_15699.
73. Anderson CP, Shen M, Eisenstein RS, et al. Mammalian iron metabolism and its control by iron regulatory proteins. *Biochim Biophys Acta*. Sep 2012;1823(9):1468–1483. https://doi.org/10.1016/j.bbamcr.2012.05.010.
74. Xu MM, Wang J, Xie JX. Regulation of iron metabolism by hypoxia-inducible factors. *Sheng Li Xue Bao*. Oct 2017;69(5):598–610.
75. Fahim A. Retinitis pigmentosa: recent advances and future directions in diagnosis and management. *Curr Opin Pediatr*. Dec 2018;30(6):725–733. https://doi.org/10.1097/MOP.0000000000000690.
76. Deleon E, Lederman M, Berenstein E, et al. Alteration in iron metabolism during retinal degeneration in rd10 mouse. *Invest Ophthalmol Vis Sci*. Mar 2009;50(3):1360–1365. https://doi.org/10.1167/iovs.08-1856.
77. Yefimova MG, Jeanny JC, Keller N, et al. Impaired retinal iron homeostasis associated with defective phagocytosis in Royal College of Surgeons rats. *Invest Ophthalmol Vis Sci*. Feb 2002;43(2):537–545.
78. Rogers BS, Symons RC, Komeima K, et al. Differential sensitivity of cones to iron-mediated oxidative damage. *Invest Ophthalmol Vis Sci*. Jan 2007;48(1):438–445. https://doi.org/10.1167/iovs.06-0528.
79. Picard E, Jonet L, Sergeant C, et al. Overexpressed or intraperitoneally injected human transferrin prevents photoreceptor degeneration in rd10 mice. *Mol Vis*. Dec 2010;16:2612–2625.
80. Obolensky A, Berenshtein E, Lederman M, et al. Zinc-desferrioxamine attenuates retinal degeneration in the rd10 mouse model of retinitis pigmentosa. *Free Radic Biol Med*. Oct 2011;51(8):1482–1491. https://doi.org/10.1016/j.freeradbiomed.2011.07.014.
81. Wang K, Peng B, Xiao J, et al. Iron-chelating drugs enhance cone photoreceptor survival in a mouse model of retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. Oct 2017;58(12):5287–5297. https://doi.org/10.1167/iovs.17-22096.
82. Harris ZL, Takahashi Y, Miyajima H, et al. Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. *Proc Natl Acad Sci U S A*. Mar 1995;92(7):2539–2543. https://doi.org/10.1073/pnas.92.7.2539.
83. Wolkow N, Song Y, Wu TD, et al. Aceruloplasminemia: retinal histopathologic manifestations and iron-mediated melanosome degradation. *Arch Ophthalmol*. Nov 2011;129(11):1466–1474. https://doi.org/10.1001/archophthalmol.2011.309.
84. Furashova O, Mielke S, Lindner U. Asymptomatic ocular manifestations of aceruloplasminemia in two adult Caucasian siblings: a multi-modal imaging approach. *Retin Cases Brief Rep*. May 2021. https://doi.org/10.1097/ICB.0000000000001166, 10.1097/ICB.0000000000001166.
85. Dunaief JL, Richa C, Franks EP, et al. Macular degeneration in a patient with aceruloplasminemia, a disease associated with retinal iron overload. *Ophthalmology*. Jun 2005;112(6):1062–1065. https://doi.org/10.1016/j.ophtha.2004.12.029.
86. Murphree CR, Nguyen NN, Raghunathan V, et al. Diagnosis and management of hereditary haemochromatosis. *Vox Sang*. May 2020;115(4):255–262. https://doi.org/10.1111/vox.12896.
87. Martin PM, Gnana-Prakasam JP, Roon P, et al. Expression and polarized localization of the hemochromatosis gene product HFE in retinal pigment epithelium. *Invest Ophthalmol Vis Sci*. Oct 2006;47(10):4238–4244. https://doi.org/10.1167/iovs.06-0026.
88. Gnana-Prakasam JP, Thangaraju M, Liu K, et al. Absence of iron-regulatory protein Hfe results in hyperproliferation of retinal pigment epithelium: role of cystine/glutamate exchanger. *Biochem J*. Nov 2009;424(2):243–252. https://doi.org/10.1042/BJ20090424.
89. Tawfik A, Gnana-Prakasam JP, Smith SB, et al. Deletion of hemojuvelin, an iron-regulatory protein, in mice results in abnormal angiogenesis and vasculogenesis in retina along with reactive gliosis. *Invest Ophthalmol Vis Sci*. May 2014;55(6):3616–3625. https://doi.org/10.1167/iovs.13-13677.

90. Ghaffarieh A, Ciolino JB. Potential of application of iron chelating agents in ophthalmic diseases. *Semin Ophthalmol*. May 2021;36(4):157–161. https://doi.org/10.1080/08820538.2021.1887900.
91. Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med*. Apr 2011;364(2):146–156. https://doi.org/10.1056/NEJMct1004810.
92. Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. *Acta Haematol*. Nov 2009;122:155–164. https://doi.org/10.1159/000243800.
93. Hadziahmetovic M, Song Y, Wolkow N, et al. The oral iron chelator deferiprone protects against iron overload-induced retinal degeneration. *Invest Ophthalmol Vis Sci*. 2011;52(2):959–968. https://doi.org/10.1167/iovs.10-6207.
94. Farajipour H, Rahimian S, Taghizadeh M. Curcumin: a new candidate for retinal disease therapy? *J Cell Biochem*. Dec 2018. https://doi.org/10.1002/jcb.28068, 10.1002/jcb.28068.
95. Majumdar S, Srirangam R. Potential of the bioflavonoids in the prevention/treatment of ocular disorders. *J Pharm Pharmacol*. Aug 2010;62(8):951–965. https://doi.org/10.1211/jpp.62.08.0001.