Ferroptosis and glaucoma: implications in retinal ganglion cell damage and optic nerve survival

Ming Yang, Kwok-Fai So, Wai-Ching Lam, Amy Cheuk Yin Lo

Glaucoma and visual pathway degeneration: Glaucoma is the leading cause of irreversible blindness worldwide, which leads to a progressive loss of vision. Glaucoma can be classified into two types: primary open-angle glaucoma and primary closed-angle glaucoma. Primary open-angle glaucoma is caused by the pressure of the trabecular meshwork, and this results in elevation of the intraocular pressure (IOP), leading to retinal ganglion cell (RGC) death. However, many glaucoma patients have normal IOP, this is known as normal-tension glaucoma. Nevertheless, excitoxic damage and oxidative stress can also lead to RGC damage in normal-tension glaucoma (Alamieh et al., 2012). Glaucomatous genes such as TIGR, OPTN, and CYP1B1 have been suggested to contribute to the pathogenesis of glaucoma. However, some glaucomatous patients may remain asymptomatic in the early, moderate, and late stages. Another type of glaucoma is primary closed-angle glaucoma. In this clinical condition, a relative anterior blockage is contributed by the iris obstructing aqueous outflow. The patients may suffer from corneal swelling, headache, nausea, and blurred vision during the acute phase.

Increasing evidence suggests that glaucoma damage is not limited to RGC in the retina, but also extends to the lateral geniculate nucleus, superior colliculus, and the visual cortex, interfering with information transmission in the nervous system. RGC loss may interfere with the ability to regenerate and reorganize the visual pathway once injured. Therefore, the development of therapeutic strategies to prevent RGC degeneration is essential.

At present, clinical treatments of glaucoma mainly include drugs, lasers, and surgery. In general, lowering IOP is recommended as the first-line treatment for open-angle glaucoma. Selective laser trabeculoplasty treatment can also be considered when the angle of closure has not yet resulted in glaucoma. If the outflow channel is obstructed by large-area adhesion and the medical treatment is ineffective, surgery should be considered. Large-area adhesion and the medical treatment glaucoma. If the outflow channel is obstructed by large-area adhesion and the medical treatment is ineffective, surgery should be considered.

Ferroptosis, a distinct form of regulated cell death as a new mechanism of neurodegeneration: Regulated cell death is a genetically programmed cell death associated with the maintenance of homeostasis and disease development. Apoptosis, pyroptosis, and necroptosis are classical forms of regulated cell death that play important roles in various diseases. Ferroptosis was a regulated cell death described by Dixon et al. (2012) who used elegantly designed experiments involving liver cancer cells containing ferroptosis mutations. They found an iron-dependent and lipid peroxidation-triggered cell death pathway, which relies on iron-generated reactive oxygen species, and is independent of caspase, apoptosis, and trisynaptic exhaustion, mitochondria reactive oxygen species generation, the permeability of the mitochondrial membrane, and the concentration of intracellular calcium ions. This distinct form of cell death is significantly different from other forms of cell death morphologically, biochemically, genetically, and metabolically. Three mainstream pathways have been identified in ferroptosis: glutathione peroxidase 4-glutathione (GPX-4-GSH) pathway, ferroptosis suppressor protein 1-ubiquinone-reduced nicotinamide adenine dinucleotide phosphate (FP5-Coq-NADPH) axis, and dihydroorotate dehydrogenase (DHDOD) signaling (Figure 1).

GPX-4 was considered a mainstream ferroptosis suppressor. GPX-4 is one of the members of the GPx enzyme families that reduces hydrogen peroxide through the oxidation of GSH. Therefore, the activity of GPX-4 is directly related to glutathione metabolism, and the reduction of cystine and oxidized glutathione can inhibit GPX-4 activity. GPX-4 has a broader substrate preference and is the only enzyme currently reported to directly reduce complex phospholipid hydroperoxides. Depletion of GPX-4 leads to cell death, therefore it is critical for cell survival. Phospholipid hydroperoxides initiates the Fenton reaction in the presence of free iron, leading to lipid peroxidation and cell death. Recently, FSP1 was identified as an independent anti-ferroptotic system. The FSP1-Coq-NADPH axis is shown to act synergistically with that of GPX-4 and GSH to inhibit lipid peroxidation and cell death in tumors (Bersuker et al., 2019).

FSP1 transforms Coq to dihydro ubiquinone (CoQH2) (a reduction reaction), which acts as an antioxidant to prevent cell membrane lipid peroxidation. The overexpression of FSP1 facilitates the production of CoQH2, which acts as an antioxidant to prevent cell membrane lipid peroxidation. In 2021, DHODH was identified to exert an anti-ferroptotic effect. DHODH facilitates the production of CoQH2, which acts as an antioxidant to prevent cell membrane lipid peroxidation. DHODH was considered a mainstream ferroptosis defense system (DHODH) signaling (Figure 1).

An organelle bound by the inner and outer membranes. It is responsible for aerobic respiration, the respiratory chain. Its components of oxygen species is generated during electron transfer in the inner membrane. In 2021, DHODH (Mao et al., 2021), a new GSH-independent anti-ferroptotic protein, was identified. This enzyme is located at the inner mitochondrial membrane, and is responsible for catalyzing the oxidation of dihydroorotic acid to orotic acid (the fourth step of the TCA cycle and pyruvate oxidation pathway). At the same time, Coq in the inner membrane is reduced to CoqH2, which is a free radical trapping antioxidant by receiving electrons. In addition, DHODH facilitates the production of CoqH2, preventing lipid peroxidation and ferroptosis (Mao et al., 2021). The association between DHODH and GPX-4 was further studied. Firstly, the expression level of DHODH was found to positively associate with the resistance of GPX-4 inhibitors in the Cancer Therapeutics Response Portal database. Secondly, inhibition of DHODH not only induced ferroptosis, but also increased the sensitivity of GPX-4, but also triggered high sensitivity to ferroptotic death in high GPX-4-expressing cells and animals. Further in vitro studies also confirmed that simultaneous inhibition of GPX-4 and DHODH, lead to ferroptosis. However, only mitochondrial DHODH was identified to exert an anti-ferroptotic effect.

Overall, these three ferroptosis-defense systems are located in different subcellular locations: GPX-4 in the cytoplasm and mitochondria, FSP1 on the cell membrane, and DHODH in the inner mitochondrial membrane. In the mitochondria, DHODH and mitochondria-localized GPX-4 constitute the main ferroptosis defense system.
Perspective

A schematic diagram showing glaucoma caused axon degeneration and ferroptosis. We hypothesize three potential ferroptosis pathways in RGC.

Figure 1  |  We hypothesize three potential ferroptosis pathways in RGC.

In the cell membrane, GPX4 and FSP1 work together to resist lipid peroxidation. The substrate of GPX4 is GSH, while FSP1 transforms NAD(P)H to NAD(P) and CoQ10, respectively. In the mitochondria, DHODH transforms CoQ10 to CoQ10H2, protecting the mitochondrial membrane from lipid peroxidation with GPX4. Ubiquinone (CoQ10H2): ubiquinoid; DHODH: dihydroorotate dehydrogenase; GPX4: cytoplasmic GPX4; mitochondrial GPX4: GSH glutathione disulfide; GSSG: glutathione disulfide; NADH: reduced nicotinamide adenine dinucleotide; DADPH: reduced nicotinamide adenine dinucleotide phosphate; RGC: retinal ganglion cell.

Figure 2  |  A schematic diagram showing glaucoma caused axon degeneration and ferroptosis.

(Figure 2) Ferroptosis is hypothesized to be involved in glaucoma and the visual pathway. RGC membrane lipid peroxidation and cytoplasm iron overload are two major features of ferroptosis. Gray dots: iron overload in axon. Yellow lipid bilayer: presence of lipid peroxidation. (B) Activation of GPX4, FSP1, and DHODH may rescue axonal degeneration by suppressing ferroptosis. DHODH: dihydroorotate dehydrogenase; FSP1: ferroptosis suppressor protein 1; RGC: retinal ganglion cell. Part of the elements in the figures were adapted from Servier Medical Art (http://smart.servier.com/)

Conclusion and future remarks: In this perspective, we discussed the potential association between ferroptosis and RGC damage as well as optic nerve loss, and its impact on glaucoma. Ferroptosis may not only be involved in RGC and optic nerve degeneration in glaucoma models but also affect axonal survival. We propose that there are sufficient pieces of evidence to support the idea that ferroptosis may play a distinct role in RGC damage and optic nerve degeneration. Part of the elements in the figures were adapted from Servier Medical Art (http://smart.servier.com/).

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C-Editors: Zhao M, Wang Lu; T-Editor: Jia Y