THERAPEUTIC ADVANCES in
Ophthalmology

Review

Addressing retinal hypoxia: pathophysiology, therapeutic innovations, and future prospects

Ther Adv Ophthalmol

2024, Vol. 16: 1–16

DOI: 10.1177/25158414241280187

Bhargavee Gnanasambandam, Jacob Prince, Siddharth Limaye, Eric Moran, Ben Lee, Justin Huynh, Joseph Irudayaraj and Michael Tsipursky

***Abstract*:** Retinal hypoxia stands as a pivotal yet often underappreciated factor in the etiology and progression of many retinal disorders such as glaucoma, hypertensive retinopathy, diabetic retinopathy, retinal vein occlusions, and retinal artery occlusions. Current treatment methodologies fail to directly address the underlying pathophysiology of hypoxia and aim to improve ischemia through alternative methods. In this review, we discuss the critical role of retinal hypoxia in the pathogenesis of various retinal diseases and highlight the need for innovative therapeutic strategies that address the root cause of these conditions. As our understanding of retinal hypoxia continues to evolve, the emergence of new technologies holds the promise of more effective treatments, offering hope to patients at risk of vision loss.

Plain language summary

A review of old and new therapeutic strategies for addressing oxygen deprivation in retinal diseases

This paper talks about how lack of oxygen in the retina can cause different eye diseases like glaucoma, diabetic retinopathy, and retinal artery occlusions. It explains how our current treatments don't directly fix this lack of oxygen, but rather try to help in other ways. The paper also discusses the science behind why these diseases happen and what happens in the eye when there's not enough oxygen. Ultimately, we finish our discussion with an overview of novel technology that are currently being used in other fields and could be applied in these eye disorders.

Keywords: hypoxia, oxygen nanodelivery, oxygen therapy, retina, retinal hypoxia

Received: 7 January 2024; revised manuscript accepted: 30 July 2024.

Correspondence to:
Bhargavee Gnanasambandam
Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, 506 South Mathews Ave Urbana, Urbana, IL 61801, USA
bg19@illinois.edu

Jacob Prince
Siddharth Limaye
Eric Moran
Ben Lee
Justin Huynh
Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Joseph Irudayaraj
Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA
Revive Biotechnology, Inc., Champaign, IL, USA

Michael Tsipursky
Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA
Revive Biotechnology, Inc., Champaign, IL, USA
Department of Ophthalmology, Carle Foundation Hospital, Urbana, IL, USA

Introduction

Sight is one of the key senses that humans use to assess their surroundings, and the retina is one of the most metabolically active organs in the human body.[1–4] The metabolism of the retina is finely controlled to allow for enough vascular supply to power the neural transmission of light. These factors work closely together, where damage to the vasculature affects the light-transmitting cells. Hypoxia leads to the loss of the retinal ganglion cells (RGCs) via either apoptosis or necrosis, preventing the transmission of light to the visual cortex.[3]

Retinal hypoxia encompasses a rather broad family of conditions.[3,5,6] The common mechanism of these disorders provides a promising target for effective therapeutics. In this review, we discuss the common pathophysiology shared by this family of hypoxic retinal disorders and current therapeutic innovations that primarily address oxygen deficiency to improve treatment outcomes.

Pathophysiology of retinal hypoxia

Anatomically, the retina is supplied by branches of the ophthalmic artery, which comes from the

internal carotid artery. The central retinal artery and short posterior ciliary arteries perfuse the inner retina.[7] The retina is supplied by two vascular systems: the choriocapillaris and the central retinal artery. The choriocapillaris supplies the layers of the outer retina, including the retinal pigment epithelium and photoreceptors, which are oxygenated by the choriocapillaris through diffusion. The central retinal artery supplies oxygen to the inner retina, the retina ganglion cells, and the retinal nerve fiber layers.[7–9] Retinal oxygenation is regulated by circulation of the vascular inner and avascular outer layers. However, the control of oxygen in the retinal arteries and the choroid differs.[10] The retinal arteries are controlled through vasogenic factors released from the endothelium based on intraocular pressure and the metabolic needs of the retina, while choroid perfusion is controlled neurally through sympathetic activation and metabolic factors. The central retinal artery is not as affected by sympathetic innervation.[8,11,12]

Retinal pericytes are one key regulator of vascular flow in both the choroid and retina, acting as protective factors against retinal hypoxia. Pericytes sit around the retinal vessels and regulate neurovascular coupling and blood flow within the choroid and the retina through intra-pericyte tunneling nanotubes.[13–15] The nanotubes are gap junctions that can carry organelles like the mitochondria and support Ca^{2+} release for nerve function. Pericytes express several genes (FOXP1, Ang2, and VEGFR2) that support retinal vessels in times of stress and injury and cover almost 85% of the retinal microvasculature.[13] Even more so, pericytes are essential in the postnatal period to help develop the blood-retinal barrier. Loss of pericytes leads to the breakdown of this barrier, leading to the infiltration of immune cells and the formation of microhemorrhages.[16] Blood-retinal barrier breakdown has been implicated in glaucoma due to damage caused by high pressure and also in diabetic retinopathy due to high-glucose-related reactive oxygen species.[13,15,16]

The retina maintains its energy requirements through aerobic respiration and β-oxidation.[17] However, under metabolic stress and hypoxia, the retina relies more heavily on alternate metabolic pathways such as the pentose phosphate pathway and anaerobic metabolism.[5] Interestingly, hypoxia was also found to lead to an increase in β-oxidation, indicating that this pathway is utilized in both normal and pathological conditions.[5,17] The changes in metabolic pathways can help the cell survive hypoxia.

The primary driver of hypoxia-induced changes in the retina is the activation of hypoxia-inducible factor 1-α (HIF-1α), leading to downstream activation of vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS), as shown in Figure 1.[3,18–20] Additional methods of vascular regulation in the retina are through a local renin-angiotensin system, endothelin-1, and adenosine.[21–23] Pericytes also play an additional role here, as VEGF not only increases pericyte proliferation but also increases angiogenesis.[18] The top seven genes that HIF-1α activates promote the conversion of metabolic processes from oxidative phosphorylation to glycolysis are essential to helping the cell survive hypoxia.[6,24] Of note, with each retinal hypoxia pathology, the system is affected slightly differently. Overproduction of both VEGF and NOS is associated with vasodilation and permeability of retinal vessels, allowing for infiltration of immune cells for the removal of lost tissue.[19] The resulting breakdown of the blood-retinal barrier allows for the pathological accumulation of fluid in extracellular and intracellular spaces, leading to vasogenic or cytotoxic edema, respectively.[25] Additionally, this increased vascular permeability is associated with endothelial dysfunction, microaneurysm and leukocyte vascular plugs that can further damage the tissue, especially in diabetic retinopathy.[26]

In addition to vascular effects of hypoxia on the retina, the RGC also reacts to hypoxia based on NOS and VEGF. There are many causes of RGC death, including excessive release of glutamate and excitatory neurotoxicity. One theory that has been debated so far is the concept of excitatory neurotoxicity. NOS itself produces nitric oxide, which induces vasodilation to encourage better oxygenation in the face of hypoxia.[19,26,27] The increase in glutamate damages the neuron by affecting ion concentration, which disrupts electric and immune homeostasis in the RGCs. Excessive glutamate leads to activation of ionotropic glutamate receptors that cause an increased release of calcium within the cells. The high levels of calcium lead to metabolic failure due to inappropriate activation of enzymes that can affect membrane potential and can prevent signal transmission that may lead to vision loss.[3,28] Lastly, the over-release of glutamate also leads to increased production of tumor necrosis factor-α and interleukin 1β, further exacerbating cell damage.[29]

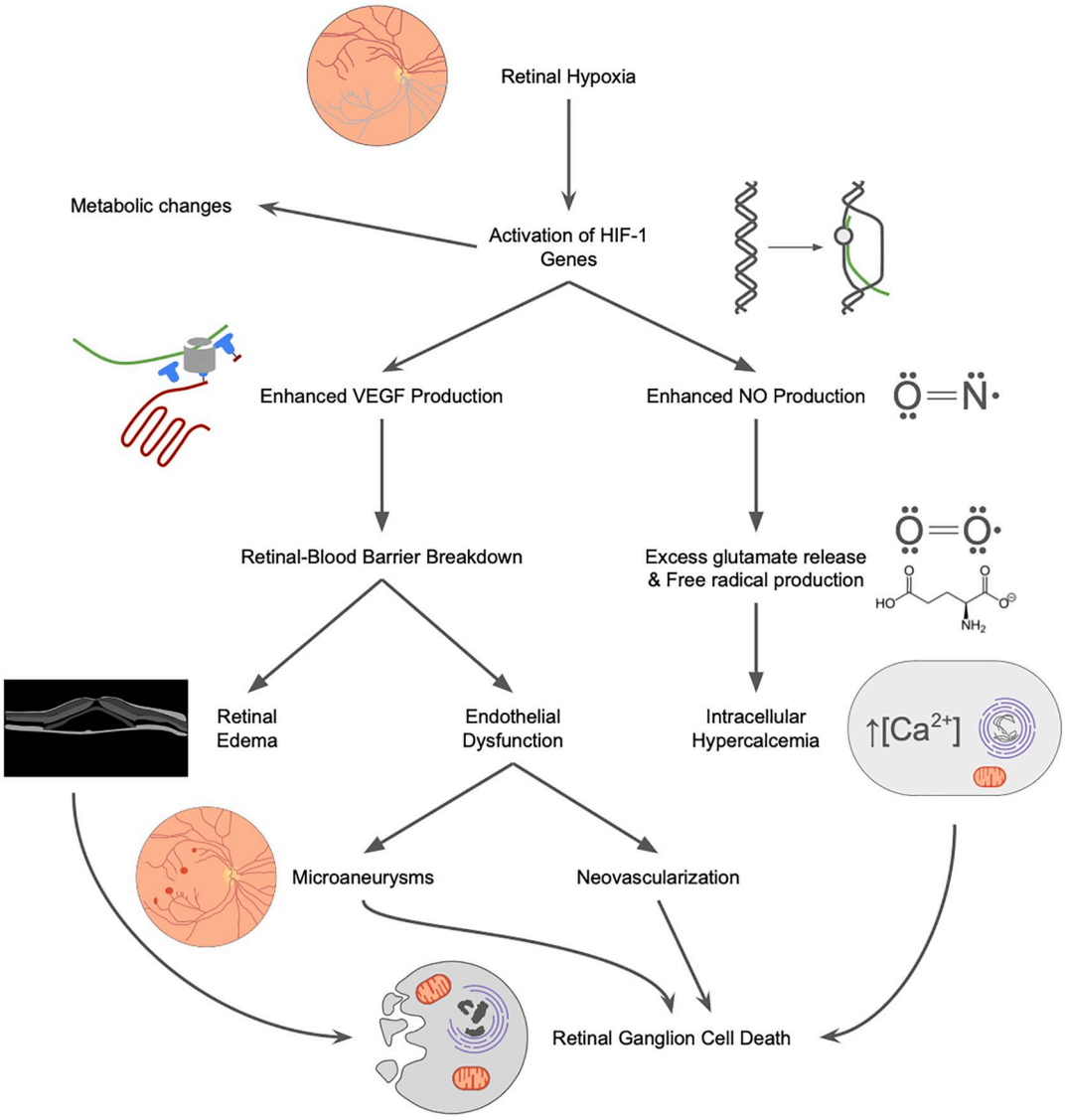

Figure 1. The pathophysiology of retinal hypoxia on retinal ganglion cells.[3,20]

For each of the pathologies discussed below, RGC death pathophysiology will differ. The excitotoxicity theory is just one of the many theories involved in understanding RGC death, and is often related to retinal artery occlusions (RAOs).[3] For instance, this same theory of excitotoxicity was shown to be ineffective in glaucoma with the memantine trials, showing that a treatment used to prevent excitatory neurotoxicity, worked well in the mouse model but did not delay glaucoma disease progression in humans.[30] Other theories for the cause of RGC loss in glaucoma include other theories also include mitochondrial impairment, endoplasmic reticulum stress, axon transport failure, inflammation, and oxidative stress.[20,31] In diabetic retinopathy, there is evidence that cellular damage occurs before the onset of vascular damage due to glutamate excitotoxicity, axon transport failure, and loss of insulin sensitivity.[32–34] The various causes of RGC cell death often interact, leading to complex pathologies where the interplay between different mechanisms might impact treatment outcomes.

Overall, vision loss is mediated by a breakdown of the fine balance between retinal vasculature and the metabolic needs of the retinal neural cells, which are key for vision transmission. While the

retina does have mechanisms to protect cells from hypoxia, patients with retinal hypoxia will inevitably begin to lose their vision due to irreversible retinal cell damage. In the next part of this review, we discuss various hypoxic pathologies including glaucoma, diabetic retinopathy, hypertensive retinopathy, and RAOs as well as their current treatment methodologies used to address the underlying pathologies.

Glaucoma and retinal hypoxia

Glaucoma, the leading cause of irreversible blindness worldwide, encompasses a family of neurodegenerative diseases, all of which feature a clinically characteristic optic neuropathy.[35,36] While the specific pathogenesis of glaucoma remains poorly understood, the primary cause of vision loss is associated with elevated intraocular pressure. The high pressure leads to damage to the optic nerve and eventual loss of RGCs.[37] The primary treatments for glaucoma, accordingly, aim at reducing intraocular pressure.

The two prevailing theories for glaucoma include the "mechanical" and the "vascular" theories.[38,39] The vascular hypothesis of glaucoma proposes that RGC axons that cross the optic nerve head undergo oxygen and nutrient insufficiency because of compromised blood flow due to elevated intraocular pressure. The unmyelinated axons of the optic nerve head are thought to be highly vulnerable to the decreased oxygen/nutrient supply, due to extremely high energy requirements served by a high local density of mitochondria.[40,41] The mechanical theory proposes that the elevated intraocular pressure causes compression of the nerve bundles, preventing transmission of visual signals through the optic nerve.[42] Over the past few years, there has been increasing support for the vascular hypothesis over the mechanical hypothesis due to the presence of oxidative markers associated with hypoxia in the retina, aqueous humor, and blood serum.[43–45]

While glaucoma is normally considered a pressure-related pathology, another form of glaucoma is normal tension glaucoma (NTG). It is associated with multifactorial optic neuropathy characterized by gradual RGC death and vision loss, even though the intraocular pressure remains within normal limits. In this case, problems in ocular blood flow occur due to vasospasm, small vessel disease, or autoregulation dysfunction. NTG is known to be associated with systemic disorders including Alzheimer's, migraine, and hypotension that are associated with dysautoregulation, which might lead to NTG.[46] In migraine and hypotension, random transient vasospasm leads to dysregulation of blood flow in the eye, leading to microinfarction of the optic nerve.[47–50] Alzheimer's also has a similar pathophysiology, where vascular dysregulation from amyloid deposits changes blood flow.[51,52] These changes in blood flow lead to endothelial dysfunction and activation of the HIF-1α pathway.

The current treatments for all forms of glaucoma include medications that reduce pressure within the eye to promote improved blood flow. The first line agents are β-blockers and prostaglandin analogs, which help reduce intraocular pressure by decreasing the formation of aqueous humor or by increasing the uveoscleral outflow.[53–55] Other medications include carbonic anhydrase inhibitors and α-adrenergic agonists that also similarly treat intraocular pressure by modulating the amount of aqueous humor in the eye.[56]

In addition to these standard treatments, a limited body of research has suggested that hyperbaric oxygen therapy (HBOT) may improve outcomes in glaucoma through two distinct mechanisms. First, HBOT has been shown to reduce intraocular pressure in animal models and healthy test subjects.[57] As such, it has been suggested that this reduction in intraocular pressure may improve glaucoma progression.[58–60] Second, HBOT may also improve glaucoma directly through improved retinal oxygenation, in line with the role of RGC oxygen deprivation in the vascular hypothesis of glaucoma. HBOT is known to induce hyperoxygenation of the retina, despite vasoconstriction induced by the high arterial PO_2.[60–64] Correspondingly, limited clinical studies have shown reduced visual field loss in glaucoma patients, even without meaningful changes in intraocular pressure.[65–67] Considering these results, therapies targeting improved retinal oxygenation to reduce intraocular pressure and/or improve tissue oxygen delivery for the treatment of glaucoma warrant further investigation.

RAOs and hypoxia

RAO is a sudden blockage of the central retinal artery or one of its branches leading to sudden, painless monocular vision loss, similar to that of a stroke.[68,69] There are three different types of

RAOs: central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), and transient monocular vision loss.[70–72] CRAO is a condition in which the central retinal artery becomes blocked such that an individual with CRAO will experience painless monocular vision loss in the affected eye.[70,73] BRAO is a similar condition where a branch of the central retinal artery is affected, typically leading to less severe symptoms as compared to CRAO.[73,74]

RAOs have a similar pathophysiology of a stroke through thrombosis or emboli. Embolic RAOs are more common and these emboli can travel from the carotid artery or heart.[69,70,72] Other causes of RAOs include intravascular events, increased orbital pressure, and intraocular pressure.[75] The mechanism of action is associated with glutamate excitotoxicity and excess calcium released due to cell necrosis.[3] Permanent damage to the retina occurs within 2 h of ischemia.[76] Acutely, CRAO and BRAO are signified by a pale retina and the classic macular "cherry red spot" observed on visualization and imaging of the fundus, indicating an ischemic retina.[77] Chronically, signs of an RAO include a pale optic disk, thinning of the retina tissue, attenuated vessels, retinal pigment epithelial mottling, and severely decreased vision.[78]

There is currently no standard treatment for RAOs. Some small studies have explored treatment options such as thrombolytics or other conservative management options, including those that increase the blood oxygen content or reduce intraocular pressure to improve perfusion as well as anti-inflammatory agents.[79,80] Thrombolytics, either intravenous or intra-arterial, have shown the most promise for RAO treatment thus far, but are only effective within a small window of 4.5 h since symptom onset.[69,80] Additionally, intra-arterial thrombolysis is associated with a high rate of stroke.[80] However, for some patients, RAOs can resolve spontaneously within the first 7 days of symptoms onset resulting in spontaneous reperfusion, but the result is ischemic retinal death. Additionally, the average time to presentation for RAOs tends to be over 24 h, making most patients ineligible for therapy.[81–83] All other therapeutic options have also shown limited efficacy.

Alternative options are more conservative to help the clot dislodge on its own. Oxygen-enhancing treatments such as vasodilators and HBOT increase the amount of oxygen getting to the retina. Sublingual isosorbide dinitrate with ocular massage, inhaled carbogen, and pentoxifylline have been studied as vasodilators with pentoxifylline showing the most promise.[79,84–89] Pentoxyphyline showed an almost 5× increase in systolic and diastolic blood flow when compared to a placebo.[87] All other treatments showed only a modest, non-statistically significant improvement in oxygenation.

The other oxygen-enhancing therapy that has been investigated is the use of HBOT to increase the partial pressure of oxygen in arterial blood.[79] With normal physiology, only 50% of oxygen is delivered to the retina, but up to 97% of oxygen can be delivered to the retina in an HBOT.[80] In line with this theoretical benefit, there is a growing body of research showing benefits in retinal occlusion outcomes with HBOT therapy. A variety of small clinical trials, case reports, and case series have shown benefits, primarily in visual acuity outcomes, with HBOT therapy.[90–106] Additionally, a meta-analysis of seven randomized controlled trials using HBOT as a part of combined or standalone therapy in RAO found that treatment with HBOT leads to improved visual outcomes.[106] Although a promising treatment, the overall studies conducted with HBOT in RAO tend to be small, and deployment of HBOT is difficult, leading to limited utilization of HBOT in retinal oxygen therapy.[60,107–109] Despite these limitations, HBOT is a recommended therapeutic option in patients refractory to traditional treatments or ineligible for revascularization or anterior chamber paracentesis.

Diabetic retinopathy and hypoxia

Diabetic retinopathy is a leading cause of reduced visual acuity and blindness in patients with type 1 and type 2 diabetes mellitus. Diabetic retinopathy has a global prevalence of 22.27% in those with diabetes.[110] Diabetic retinopathy remains one of the leading causes of vision loss overall and is expected to have increasing prevalence over the next few decades.[110] The pathophysiology of diabetic retinopathy is complex and is thought to involve a combination of oxidative stress, inflammation, neovascularization, neurodegeneration, and neurovascular unit dysfunction.[111]

Hypoxia and retinal oxygen deprivation play a critical positive feedback role in microvascular dysfunction and neovascularization. Hypoxia plays a role in initiating microvascular damage,

and, as the disease progresses, worsening hypoxia contributes to microaneurysm formation, capillary necrosis, and neovascularization. More specifically, early endothelial cell death leads to increased capillary permeability, loss of vascular perfusion, and microaneurysm formation. This vaso-degeneration eventually leads to areas of retinal hypoperfusion and hypoxia, increasing the production of VEGF and neovascularization.[111,112] Neovascularization is a key component of proliferative diabetic retinopathy, while microaneurysm formation and increased vascular permeability are key components of diabetic macular edema.[111] As such, hypoxia contributes significantly to these two sight-threatening endpoints of diabetic retinopathy.[112]

Currently, anti-VEGF is the leading treatment used to prevent neovascularization and stabilize disease. Emerging research demonstrates improvement of retinal perfusion following treatment with anti-VEGF. In particular, improvements in perfusion have been noted on ultrawide-field fluorescein angiography and a slowing of the progression of non-perfusion has been documented in patients undergoing anti-VEGF treatment.[113,114] More recent treatments have included antibodies that target VEGF-A and Angpt-2 for longer-term neovascularization prevention.[115] Treatment with panretinal laser photocoagulation (PRP) is also common in the management of diabetic retinopathy. This older treatment modality is thought to increase choroidal oxygenation and decrease metabolic oxygen load by destroying outer regions of the retina, thereby relieving hypoxia in regions spared by PRP.[116] However, the scarring caused by PRP causes reduction of visual field in treated patients.

Given the critical nature of tissue hypoxia in both the early and late stages of diabetic retinopathy, HBOT is a promising therapeutic approach. Specifically, HBOT leads to hyperoxygenation of the retina resulting in reduced production of VEGF, helping prevent neovascularization and macular edema.[61–63,117] Importantly, hyperoxygenated choroidal vasculature appears to provide excess oxygen to the retina despite vasoconstriction induced by the high arterial PO_2.[62,63,96,114] Furthermore, elevated VEGF levels are found in types of both proliferative and nonproliferative diabetic retinopathy, lending HBOT as a potential treatment for both disease states.[96,117]

In line with this theoretical benefit, a small set of studies have shown that HBOT therapy can lead to improved features of diabetic retinopathy in humans, including clinical trials and a case report showing improved visual acuity as well as a prospective cohort study showing stabilization/regression of diabetic retinopathy lesions.[60,118–122] Additional research has been done in diabetic rat models, showing reduced vascular permeability and improved retinal response to light.[123–125] Ultimately, this research shows that improving retinal oxygenation is a promising therapeutic target for the treatment of diabetic retinopathy.

Current use of oxygen therapy and new technology applications

Currently, HBOT is the primary method of oxygen delivery for the treatment of ocular disorders, including RAO, diabetic retinopathy, and glaucoma. While HBOT has been shown to improve visual acuity and other metrics associated with disease progression, HBOT is an expensive and often inaccessible form of treatment. Additionally, HBOT is associated with a variety of ocular and systemic side effects. In particular, hyperoxic myopia is a common side effect of HBOT leading to progressive visual change over the course of treatment but is typically reversible.[61,62,126–133] HBOT is also associated with permanent cataract formation with visual loss, although these changes occur gradually and typically become severe only during longitudinal treatment regiments of greater than 150 sessions, a longer treatment course than required for most conditions.[133,134] In premature infants, HBOT can result in retinopathy of prematurity.[135–138] Systemically, the most common side effect of HBOT is middle ear barotrauma, which is typically mild but can in rare cases result in conductive or sensorineural hearing loss as well as vertigo.[135] Other common side effects include temporary sinus and dental pain from mild barotrauma that resolves with the cessation of treatment.[136] Less frequently, HBOT can lead to severe pulmonary barotrauma and central nervous system oxygen toxicity, with rare reported cases of pneumothorax and seizures.[136]

Overall, the development of novel, targeted oxygen delivery methodologies for ocular disorders may help eliminate the systemic side effects associated with HBOT and improve access to treatment. Hyperoxic myopia likely occurs due to oxidative changes in the crystalline lens of the

eye, leading to a corresponding change in the refractive index of the lens.[128,139] Correspondingly, there is some evidence that suggests that increasing systemic oxygenation while reducing the partial pressure of oxygen in contact with the external eye, such as through an oronasal mask, helps prevent the occurrence of and improves recovery from hyperoxic myopia.[140,141] Cataract formation in HBOT therapy is also thought to occur due to oxidative stress on the crystalline lens.[134,135,142] However, there is no similar data directly demonstrating reduced cataract risk with reduced delivery of oxygen partial pressure to the eye surface. As such, therapies that improve oxygenation of the eye vasculature without increasing oxygen delivered to the external eye surface, may be less likely to induce hyperoxic myopia, but may carry similar risk of cataract formation with extensive use.

Other novel, targeted oxygen delivery modalities for the treatment of retinal disease have been proposed in the literature. One study aimed to develop an oxygen delivery system that consists of stable, nontoxic oxygen nanobubbles (ONBs) encapsulated in medical-grade water. The ONBs were characterized to be stable in storage, noncytotoxic in vitro, have good oxygen retention, and successfully release oxygen to mitigate ischemic conditions in the retina.[143] Specifically, the CRAO model of ischemia/perfusion showed that ONBs were able to mitigate oxygen deprivation and thus preserve anatomical and functional outcomes in rat eyes.[144–146] While HBOT does increase oxygen delivery to the retina, it only lasts while the patient is in the HBOT chamber.[61,62] ONBs allow the opportunity to titrate the delivery of oxygen directly into the vitreous cavity and retina lasts at least 12 h and allows for continuous oxygenation.[144]

Additionally, other methods of oxygen delivery originally designed to treat other pathologies may apply to retinal hypoxia.[147] In recent years, there have been several studies showing the efficacy of oxygen nanodelivery for a variety of treatments, as seen in Table 1.[148] Oxygen nanodelivery methods can be subdivided into three major categories: Hypoxia-relieving, oxygen-carrying, and oxygen-producing nanomaterials.[149,150] Hypoxia-relieving nanomaterials are those that directly address hypoxia by improving blood flow or targeting HIF-1α directly. Of the options for oxygen nanodelivery, nanoparticles represent a more conservative approach, much like the current method for treating retinal hypoxia.[149,151] This could be a promising approach for treatment of long-term retinal hypoxia associated with changes in vasculature and local structures. Oxygen-carrying and oxygen-producing nanomaterials directly deliver oxygen to the tissue. Oxygen-carrying nanoparticles use perfluorocarbons, hemoglobin, or other oxygen-binding materials to release oxygen in tissues. Some challenges with oxygen-carrying nanoparticles include stability of the particle, poor circulation time, and premature release of oxygen.[152–154] Oxygen-producing nanomaterials use catalase that converts locally produced peroxide (H_2O_2) into oxygen, allowing delivery of oxygen to ischemic tissues only.[150,155,156] There is already a diverse body of research into oxygen-producing nanoparticles that could allow for improved retinal oxygenation and decreased retinal loss in both chronic and acute retinal hypoxia.

The repression of HIF-1α genes has been heavily studied in the context of cancer.[158] While the hypoxia response through HIF-1α activation in the retina is adaptive and not a process that needs to be halted, downstream suppression of HIF could be an effective target for retinal hypoxia for future treatments.[111,159] In Table 2, different uses of nanodelivery methods for HIF-1α targeting are reviewed. Many of the innovations discussed below-utilized nanoparticles that are selectively absorbed and activated in hypoxic tissues or contain a HIF-1α neutralizing element. Some of these nanoparticles are formulated to release in hypoxic areas with variable cargo, while others had HIF-1α neutralizing cargo.[160] A similar application of HIF-1α neutralization could be applied to downstream targets in the retina.

Conclusion

It is evident that hypoxia plays a critical role in the pathophysiology of many retinal diseases. As the retina poorly adapts to hypoxic environments, there is a need to develop better technologies for combating hypoxia. There are a limited number of retinal disease treatments that directly address hypoxia. HBOT is the most commonly used oxygen treatment for these disorders, but cost and accessibility prevent widespread use. While there is a large body of current research on oxygen nanodelivery in other areas of medicine, few have applied such treatment options to treat retinal hypoxia. Technologies for targeted delivery could be the wave of the future in ultimately saving

Table 1. Summary of various oxygen nanodelivery methods and their applications.

Author (year)	Nanoparticle formulation	Application	Method
Zhuang et al. (2018)[152]	Hybrid natural-synthetic polymer-based nanoemulsion	Hemorrhagic shock	Oxygen carrier
Khan et al. (2019)[155]	Ultrasound activated doxorubicin conjugated lipid-based nanobubbles	Improve chemotherapy penetration into hypoxic solid tumors	Oxygen producer
Kim et al. (2021)[153]	Pegylated lipid nanoparticles	Treatment of molar incisor hypomineralization to improve dentin and enamel production	Oxygen carrier
Han et al. (2022)[156]	Maillard reaction-based catalase and dextran sulfate-based oxygen delivery	Pancreatic cancer	Oxygen producer
Kim et al. (2023)[154]	Oxygen-carrying hemoglobin-based gel that produces reactive oxygen species with infrared laser	Solid tumor therapy	Oxygen carrier
Guan et al. (2022)[157]	Polymer-based nanoparticles functionalized with catalase for oxygen delivery	Acute myocardial infarction	Oxygen producer
Li et al. (2016)[151]	Gold-nanoparticle and recombinant endostatin	Stabilize tumor vasculature	Hypoxia-reliever

Table 2. Summary of various HIF-1α targeted nanodelivery methods and their applications.

Author (year)	Nanoparticle formulation	Application	Method
Imai et al. (2015)[161]	Hemagglutinating virus of Japan-liposome method	Oral squamous cell carcinoma	HIF-1α inhibiting oligodeoxynucleotides
Thambi et al. (2014)[162]	Hypoxia-responsive nanoparticles → self-assembly nanoparticles with hydrophobically modified 2-nitroimidazole derivative conjugated to the backbone of the carboxymethyl dextran	Squamous carcinoma (immortalized cell line testing only)	Doxorubicin
Poon et al. (2011)[163]	Multilayer polyelectrolyte assemblies (pH-sensitive outer sheath layer)	HeLa, MDA-MB-435, KB, and A549 cells	Targets cancer cells during hypoxia
Liu et al. (2012)[164]	Micellar nanoparticles	Prostate cancer	siRNA against HIF-1α
Thomas et al. (2020)[165]	Antibiotic encapsulated syndecan-1 actively targeted nanoparticle	Pancreatic cancer	Echinomycin
Li et al. (2019)[166]	Mesoporous silica nanoparticle with thermally sensitive nucleus targeting agent and anti-CD133 surface modification	Cancer stem cells	Chemotherapy loaded
Zhao et al. (2015)[167]	Lipid-polymer hybrid nanoparticle	Pancreatic cancer	Gemcitabine and HIF-1α
Yang et al. (2016)[168]	Silver nanoparticles	Immortalized cancer cell line	Silver in nanoparticle is used as treatment

HIF-1α, hypoxia-inducible factor 1-α.

someone's vision. While this review is limited given the primary focus on oxygen therapy in ophthalmology, future work could focus on a co-delivery system with a drug and assessment of clinical efficacy, cost, accessibility, and adaptation of these treatments among diverse patient populations.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Bhargavee Gnanasambandam: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Jacob Prince: Data curation; Resources; Writing – original draft; Writing – review & editing.

Siddharth Limaye: Data curation; Visualization; Writing – original draft; Writing – review & editing.

Eric Moran: Data curation; Writing – original draft.

Ben Lee: Data curation; Writing – original draft.

Justin Huynh: Writing – review & editing.

Joseph Irudayaraj: Conceptualization; Supervision.

Michael Tsipursky: Conceptualization; Project administration; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.T. and J.I. is a co-founder of Revive Biosciences Inc. All other authors have no financial disclosures.

Availability of data and materials
Not applicable.

ORCID iDs
Bhargavee Gnanasambandam https://orcid.org/0000-0001-5716-1620

Justin Huynh https://orcid.org/0000-0002-4640-6124

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