The Critical Review of Social Sciences Studies

Online ISSN: 3006-7170
Print ISSN: 3006-7162
Volume 3, Number 4, 2025, Pages 411 – 430
Journal Home Page
https://thecrsss.com/index.php/Journal/about

Cellular Pathways and Therapeutic Approaches to Neurodegeneration of Retinal Ganglion Cells in Glaucoma

Zuhaib Nishtar[1], Md Ashraful Islam[2] & Hussain Afzaal[3]

[1]*School of Management and Economics, North China University of Water resources and Electric Power, Zhengzhou City450046, China, Email: Zuhaib.nishtar1991@gmail.com*
[2]*School of Civil Engineering and Architecture, China Three Gorges University, Email: khaledbinwalid999@gmail.com*
[3]*Department of Computer Science, The Islamic University of Bahawalpur, Bhawalpur,63100, Pakistan, Email: hussainmadni03@gmail.com*

ARTICLE INFO

Article History:

Received:	*August*	*25, 2025*
Revised:	*September*	*12, 2025*
Accepted:	*September*	*23, 2025*
Available Online:	*October*	*12, 2025*

Keywords:

Glaucoma; Retinal ganglion cell (RGC) degeneration; intraocular pressure (IOP) reduction; Neuroprotection oxidative stress gene therapy stem cell therapy

Corresponding Author:
Zuhaib Nishtar
Email:
Zuhaib.nishtar1991@gmail.com

ABSTRACT

Glaucoma is one of the main causes of irreversible blindness and characterized by a slow-progressive degeneration of retinal ganglion cells (RGCs) bodies mainly living in GCL, as well as their axons. Although elevated IOP is a primary risk factor, RGC degeneration entails numerous pathological processes such as oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity. It seems clear that by simply lowering IOP with traditional therapies is not enough to prevent the progression of glaucoma because there are people who continue losing their RVF despite having a "normal" IOP. Hence, this review investigates the cellular pathways responsible for RGC loss and examines current or prospective therapeutic strategies to prevent blindness due to neurodegeneration. The aim of Neuroprotection includes targeting excitotoxicity by modulating calcium homeostasis with NMDA receptor antagonists and Calcium channel blockers. Coenzyme Q10 and α-lipoic acid are antioxidant agents that support mitochondrial function and protect against oxidative stress. Anti-inflammatory therapies attack chronic glial activation which further decreases the emission of pro inflammatory cytokines amplifying RGC degeneration. Furthermore, the neurotrophic factors brain-derived growth factor (BDNF) and ciliary ganglionoma associated protein-1 peptide (CDNAp/ CNTF; National Institute of Health R28), which are also necessary for survival or nerve fiber regrowth from mature adult retinal neurons have been characterized. Furthermore, gene therapy and stem cell transplantation as promising approaches can prevent apoptosis of RGCs and restore retinal function. Nonetheless, hurdles still exist with respect to maximizing drug delivery and compliance amongst patients alongside creating individualized therapies. This necessitates future research on the combination of IOP-lowering therapies with neuroprotective strategies or regeneration to target all mechanisms in glaucoma.

Introduction

Glaucoma, a multigene neurodegenerative disease affects millions of individuals suffering from irreversible blindness across the globe. It is a global problem, and combined studies imply that OA will continue to increase in the future with an aging population (G. J. C. Tezel, 2021) due for a rise; just one example being this. The hallmark of the disease is a gradual degeneration and ensuing loss of retinal ganglion cells (RGCs) and their axons, which course from the retina through the optic nerve to brain. Although elevation of intraocular pressure (IOP) is an established risk factor, RGC degeneration in glaucoma has been found to arise through mechanisms independent from mechanical damage (Levkovitch-Verbin, 2015). These mechanisms are oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity and neuroinflammation leading to apoptosis. However, despite IOP-lowering therapies still being the cornerstone of glaucoma treatment, these treatments may not always suffice to prevent vision loss. The increasingly recognized demand for such neuroprotective therapies center on cellular pathways associated with RGC degeneration. This review outlines the mechanisms of RGC degeneration in glaucoma, as well as strategies being developed to protect these essential cells. Elevated IOP is a great contributor of glaucoma, particularly in primary open angle-glaucoma. Elevated IOP causes mechanical strain at the optic nerve head (ONH) leading to a disruption in retrograde transport of essential neurotrophic factors, including brain-derived neurotrophic factor (BDNF), between retina and brain (Shen, Wang, & Yao, 2021). It disrupts normal RGC survival, resulting in cellular stress and inflammation. Chronic IOP elevation damages RGCs in the long term, causing gradual loss of vision. Even if IOP reduction is necessary to delay glaucoma progression, there are additional cellular mechanisms that promote further degeneration and therefore it emerges as a disease beyond pressure-dependent.

A dysfunction of the mitochondria is believed to have a vital role in glaucoma, as RGCs obtain plenty energy involved with mitochondrial function. Damaged mitochondria begin to produce higher levels of Reactive Oxygen Specious (ROS) than they normally should this leads in oxidative stress processes which takes place on cellular components like proteins, lipids and DNA (Munemasa & Kitaoka, 2013). The mechanism of oxidative stress leads to a series molecular events resulting apoptosis, which is one of the major reasons for RGC death. Researchers have already studied the use of antioxidants, like coenzyme Q10 and α-lipoic acid, to improve mitochondrial function in response to ROS accumulation. Although these therapies have shown great promise in preclinical studies, more work needs to be carried out before their clinical utility could be realized. Glutamate: a neurotransmitter necessary for synaptic communication in the retina that becomes toxic when overproduced. In diseases such as glaucoma, high extracellular glutamate can result in excitotoxicity where over activation of NMDA receptors damages RGCs (Yadav, Sharma, & Londhe, 2020). This activation leads to a pathological influx of calcium causing downstream intracellular events signaling cell death. Vincent Gore EXCITOXICITY: A rationale for therapy control of glutamate levels or inhibition NMDA receptors while certain experimental treatments, like meantime, have shown promise in reducing excitotoxicity injury the data on clinical outcomes has been mixed. Through the development of glaucoma, neuroinflammation contributes in another significant manner to RGC degeneration. Glial cells (including microglia and astrocytes) are activated by increased IOP subsequently to RGC injury which leads to the release of pro-inflammatory factors (such as tumor necrosis factor-alpha [TNF-α] or interleukin-1β [IL-1β]) into vitreous humor, contributing further damage through inflammatory mechanisms (Vernazza, Oddone, Tirendi, & Bassi, 2021) RGC death is worsened by systemic inflammation and occurs in conjunction with secondary degeneration among surviving cells as well chronic inflammatory significant. Though inhibition of select molecular pathways by anti-inflammatory therapy (INF) has yielded positive results, achieving immune homeostasis

without inciting additional damage represents a continuing challenge. Loss of RGC in glaucoma mostly occurs via apoptosis or programmed cell death. This most trauma executing process is through caspases activation by cytochrome c release from mitochondria consequent of limbs' disbandment (Pietrucha-Dutczak, Amadio, Govoni, Lewin-Kowalik, & Smedowski, 2018). Subsequent researches further confirm that another important process, autophagy (mechanism of vacuole-lysozomal system to dismantle damaged organs and proteins), plays a great part. Autophagy is blocked in neuron as well, propagating the cell death and counteracting its ability to survive or repair itself with resulting RGC more vulnerable for further degeneration (Osborne, 2008). Now, biotherapies that aim to activate RGC survival by co-targeting apoptosis and autophagy are under active explorations. IOP reduction is still the normative treatment of glaucoma. Aqueous humor production can be decreased with medications (prostaglandin analogs, beta-Blockers and carbonic anhydrase inhibitors) as well aqueous humor outflow augmented thereby reducing IOP (L. Fu et al., 2019). Surgical interventions such as trabeculectomy and minimally invasive glaucoma surgery (MIGS) offer alternatives to non-responders with ocular hypotensive medications. Although these strategies significantly lower IOP, they do not target the primary neurodegenerative pathways associated with glaucoma; hence efforts are underway to develop novel neuroprotective approaches that complement current treatments.

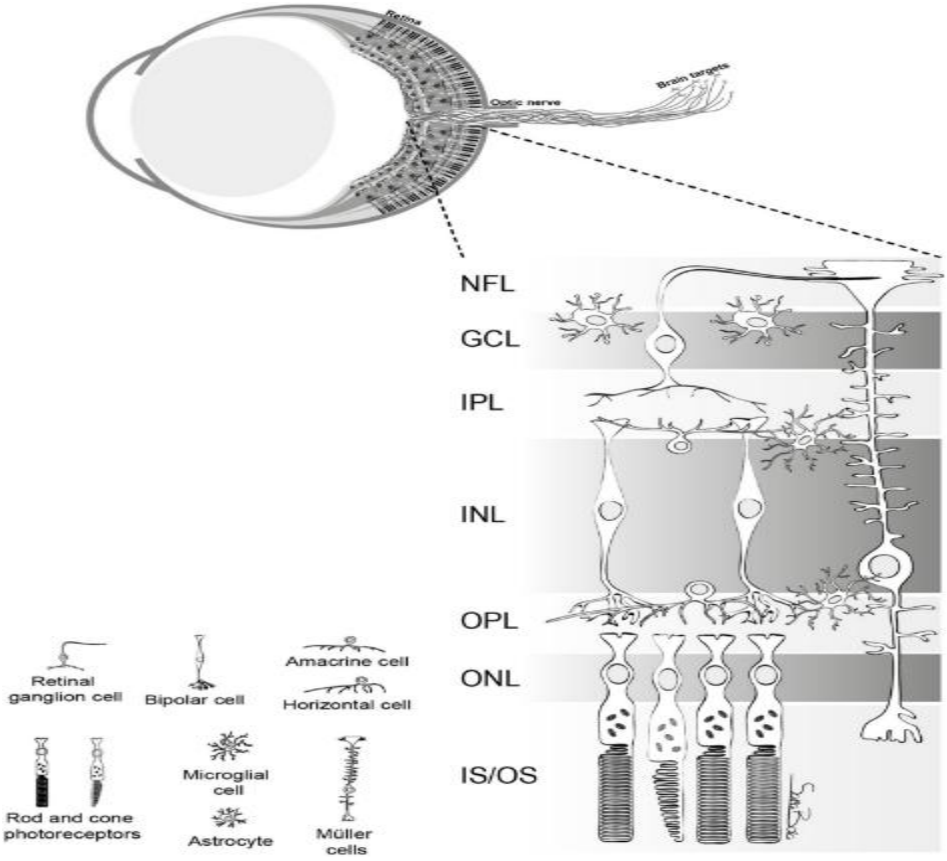

Figure 1: Cellular pathways contributing to retinal ganglion cell (RGC) degeneration

Neuroprotective agents are in development to save RGCs, with the hopes of preventing or treating vision loss independent from IOP reduction. Blockade of NMDA receptors by a-1-amino-3,5-dicarboxylic acid results in an amelioration of excitatory amino-acid-induced neurotoxicity. Stabilizing intracellular calcium levels with a drug acting on them, such as nimodipine (a class of drugs named Calcium channel blockers that stabilize the amount of circulating calcium within

cells), may also protect against RGC loss in glaucoma (Ghanem, Wareham, Calkins, & Research, 2024). Although these agents have shown promise in preclinical studies, additional clinical trials are needed to evaluate the safety and effectiveness of such compounds for glaucoma patients. The interest in antioxidant therapies is based on the role of oxidative stress in glaucoma. For example, oxidative damage and mitochondria impairment have been attenuated by compounds such as coenzyme Q10, α-lipoic acid or N-acetylcysteine (Cuenca et al., 2014). Clinical trials are underway to determine if these antioxidants can arrest the progression of glaucoma in humans. Yet there are still questions about how to dose and administer it efficiently enough in people for its intended therapeutic benefit. The goal of anti-inflammatory therapies is to alleviate the deleterious effects caused by chronic neuroinflammation. While non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have been used more generally in the past, emerging treatments are aimed at defining a target for neuroprotection with potential agents such as TNF-α inhibitors having greater specificity to prevent secondary brain injury given their molecular targets compared to other approaches (Howell et al., 2011). Confining lethal inflammation but keeping the beneficial immune response against glaucoma would be a hard constraint in design of anti-inflammatory drugs for this disease. Gene therapy for glaucoma: In experimental studies, gene therapy has been shown to protect RGC survival through the regulation of neurotrophic factors (Maneu, Lax, & Cuenca, 2022). Concomitant with this, stem cell therapy strives to replace lost RGCs and rejuvenate damaged optic nerve fibers. While these are still in experimental stages, they seem promising for the future of glaucoma treatment. BDNF and ciliary neurotrophic factor (CNTF) otherneurothropic factors, are two classical nerve growth factors capable of protecting the survival and promoting regeneration in RGCs. Delivery strategies using viral vectors and slow-release implants are already being exploited by researchers to improve the therapeutic potential of these factors (Cheung, Guo, Cordeiro, & Science, 2008). Neurotrophic factors have extended encouraging experimental results for treatment of glaucoma but ongoing work is required to investigate the optimal way in which they should be delivered and also their duration of therapeutic effect.

Glaucoma is a multifactorial disorder with multiple cellular pathways contributing to retinal ganglion cell (RGC) degeneration. Suppression of IOP is still the major treatment approach although it does not arrest entirely progression of neurodegeneration. New treatment modalities to target oxidative stress, excitotoxicity, neuroinflammation and apoptosis may bring the new frontier in reducing long term vision loss of glaucoma patients. Future research will seek further understanding of how patient profiles can be addressed with personalized therapeutic strategies. Similarly, it is anticipated that the improvement of drug delivery systems to allow better pharmacokinetic profiles (e.g., sustained-release formulations) will also improve treatment outcomes. If the cellular pathways responsible for RGC degeneration could be intercepted, glaucoma progression might therefore delayed or even blocked altogether reducing pain felt by these millions of peoples who affected with this disease.

Time- and mild nutrition-dependent that localized at early stage cellular pathways linked to RGC neurodegeneration

The retinal ganglion cells (RGCs) are the neurons that transmit visual information from eye to brain. These cells progressively degenerate in glaucoma ultimately leading to permanent loss of vision. Although increased intraocular pressure (IOP) has been defined as a definitive risk factor, there are several cell types and mechanisms by which RGC degeneration is modulated in addition to the identified process of mechanical insult. These include oxidative stress, mitochondrial dysfunction, excitotoxicity of glutamate that cells are exposed to follow by neuroinflammation and

the balance between apoptosis and autophagy. Knowledge regarding these mechanisms is crucial for developing therapeutic interventions that could help in the preservation of RGCs and prevention from visual loss. Increased IOP imposes a mechanical stress on the optic nerve head (ONH) at which axons from RGCs leave the eye. Mechanical Stress On Optic Nerve The mechanical strain from IOP compresses axons and blocks Axonal transport, inhibiting the flow of essential growth factors such as brain-derived neurotrophic factor (BDNF) between retina & brain (Russo, Nucci, Corasaniti, Bagetta, & Morrone, 2015). However, this deprivation leaves RGCs vulnerable to apoptosis-inducing cellular stress responses due leading cell-death pathways. Mechanical insult: induces glial activation (astrocytes and microglia), leading to inflammation and subsequent RGC death. While lowering IOP can retard the progression of glaucoma, it fails to completely arrest RGC degeneration which suggests other cellular mechanisms are also involved.

The mitochondrion is the prominent source of mitochondrial dysfunction in RGC degeneration during glaucoma. RGCs are metabolically demanding, with their energy needs predominantly met by mitochondria. Dysfunction of mitochondria resulting in depletion of energy and overproduction the reactive oxygen species (ROS) occurs when mitochondrial function is disturbed (Kang et al., 2021). ROS are reactive oxygen free radicals which when goes out of equilibrium in an organism creates oxidative stress and causes cellular damages to lipid, protein and DNA leadings cell death. Because of the induction of oxidative stress, a self-perpetuating cycle is initiated whereby mitochondrial dysfunction leads to further accumulation of long-lived defective protein and oxidation products which in turn worsen RGC loss. Thus, antioxidant therapies to maintain mitochondrial health are potential approaches in reducing oxidative stress and protecting RGCs. Glutamate excitoxicity is another important mechanism in RGC death. Although glutamate is the major excitatory neurotransmitter in the retina, excessive extracellular levels become toxic. This causes those RGCs to be over activated, with a too large influx of calcium into the NMDA (N-methyl-D-aspartate) receptors and ultimately induces apoptosis in them (García-Bermúdez et al., 2021). Because of this calcium overload the pro-apoptotic factors are released, leading to RGC death. Although clinical efficacy remains to be established, NMDA receptor antagonists targeting another neurotransmitter signaling system—glutamate—have shown promise in preclinical models.

The glaucomatous RGC death exhibited an important inflammatory component resulting from neuroinflammation. Activation of glial cells facilitates inflammation and cell death in IOP elevation and RGC injury. These cells release pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), and interleukin−1β (IL−1β) to accelerate RGC apoptosis (Almasieh et al., 2012). This chronic neuroinflammation results in a toxic milieu facilitating the degeneration of injured and uninjured RGCs. Current research is evaluating the effectiveness of anti-inflammatory therapies designed to suppress glial activation and infiltrating macrophages, or block individual inflammatory cascades with the goal of preventing RGC loss and subsequent visual impairment. Apoptosis, or programmed cell death is the final common pathway by which many of RGCs are lost in glaucoma. These mitochondrial pathways regulate apoptosis, with the release of cytochrome c initiating caspase activation and ultimately disassembly of cellular components (Y. Yang & Sun, 2023). Apoptosis is not the only process by which cells maintain themselves; autophagy (self-eating) does this also. In glaucoma, cell-autonomous apoptosis and autophagy are deranged leading to cellular vulnerability and degenerescence. Reestablishing this balance with drugs that increase autophagy or suppress apoptosis, therefore, is exciting area of research. Together, these interconnected cellular pathways mediate the continued pattern of RGC death in glaucoma. Those two pathways offer their own challenges and therapeutic opportunities. Even though IOP-lowering therapies are necessary, they only impact one arm of the glaucoma disease pathology. Comprehensive treatments that effectively preserve RGCs and prevent vision loss require targeting

downstream molecular mechanisms associated with oxidative stress, excitotoxicity, neuroinflammation and apoptosis.

Increased Intraocular Pressure (IOP) and mechanical pressure

IOP is the primary risk factor in glaucoma with high potential to induce retinal ganglion cells (RGCs) death. The balance between the production of aqueous humor and its drainage, in turn determines normal IOP level in healthy eyes. But in glaucoma, an imbalance between the production and drainage of aqueous humor leads to abnormally high IOP. This increased pressure exerts mechanical strain on the optic nerve head (ONH), a location where retinal ganglion cell axons converge and exit the eye to create of the optic nerves. It was assumed previously that mechanical deformation and compression of the ONH are essential for glaucoma progression and RGC degeneration. The ONH is especially sensitive to mechanical loading because of the changes it undergoes in response to raised IOP. With elevated pressure, the lamina cribs Rosa (the mesh through which RGC axons pass) is deformed, squeezing and obstructing the axons – effectively pinching off intracellular transport. It is necessary for the transport of neurotrophic factors having brain-derived neurotropic factor (BDNF) between retina and brain to occur, Burgoyne 2011. The deprivation of the necessary trophic support leads to cellular stress and will eventually result in apoptosis—the fundamental method by which RGCs die. Repetitive ONH mechanical compression triggers a cascade of secondary events that can promote RGC degeneration. Mechanical stress plays a crucial role in the pathogenesis of glial cell activation (astrocytes, microglia) caused by optic nerve deformation. These inflammation-induced glial cells secrete proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), thereby leading to inflammatory responses in the ONH (Boccuni & Fairless, 2022). Chronic inflammation promotes a hostile milieu for cell survival and leads to the enhanced loss of RGCs, resulting in additional neurodegeneration.

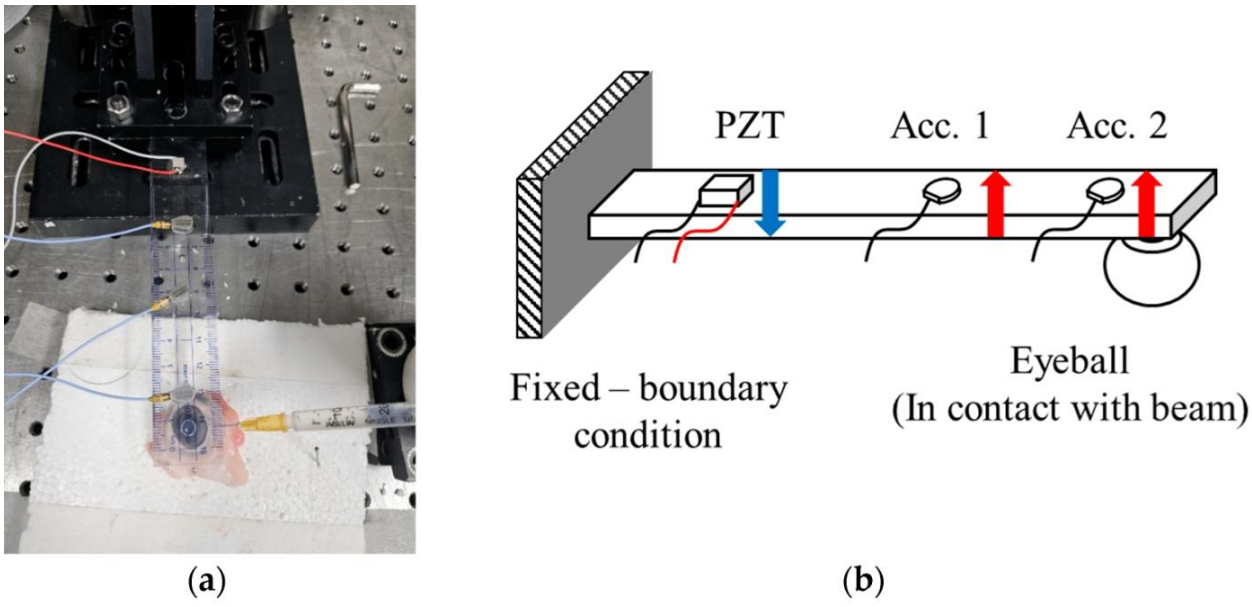

Figure 2: IOP in glaucoma with high potential to induce retinal ganglion cells (RGCs)

Mechanical stress also stiffens the extracellular matrix in and subsequently passing through, making it less supportive of axonal health. Such stiffening would enhance the mechanical

impairment of axonal function and thus underlie the progressive nature of RGC loss in glaucoma. Moreover, it has also been postulated that since mechanical stress damages mitochondria in RGCs this may be further accentuated by various ROS initiating mitochondrial damage through oxidative mechanisms thereby producing a vicious cycle of events (Zhao et al., 2023). These pathways underscore the multifactorial basis of glaucoma and illustrate how mechanical stress collaborates with biochemical alterations eventually leading to RGC loss. It still provides a tremendous advantage by reducing IOP, which is the single most important factor in modifying mechanical stress on the ONH and disease progression of glaucoma. Drugs like prostaglandin analogs, β-blockers, and carbonic anhydrase inhibitors lower IOP by increasing the outflow of aqueous humor or decreasing its production (Agarwal & Agarwal, 2021). Nevertheless, there may be ongoing RGC degeneration despite effective IOP reduction, indicating that elevated IOP is only one contributor to glaucoma. Despite medical management, IOP may remain too high leading to the consideration of surgical form of interventions. Surgeries such as trabeculectomy and minimally invasive glaucoma surgery (MIGS) seek to increase the outflow of aqueous humor, relieving pressure on the optic nerve. Although these interventions can attenuate disease progression they are incapable of fully recovering lost RGC in this respect selective complementary therapeutic strategies directed at the cellular mechanisms involving neurodegeneration must also be developed. In summary, elevated IOP is critically important to the pathogenesis of glaucoma as a mechanical stress on the ONH that disrupts axonal transport and activates glial cells leading ultimately to oxidative damage. Although IOP reduction is necessary for the treatment of glaucoma, it addresses only a mechanical component in RGC degeneration. Treatments that lower IOP are not sufficient to prevent or slow all forms of glaucomatous optic neuropathy, as shown by the decline in visual function despite effective reduction in elevated pressure (Kelada, Hill, Yap, Manzar, & Cordeiro, 2021) and presumably reflect a complex interplay between mechanical and biochemical pathogenic factors. Regardless of where they stem from, RGC degeneration is at an advanced stage when patients seek medical attention for their glaucoma; hence methods designed to protect these vulnerable cells must be combined with conventional treatments aimed only at lowering intraocular pressure (Tatton, 1999).

Auto immunities Mitochondrial Dysfunction and Oxidative Stress

Impaired mitochondrial function and/or raised oxidative stress have been regarded as the pivotal effectors in retinal ganglion cell (RGC) death during glaucoma. Secondly, since RGCs are involved in conveying visual information from the retina to brain, it has a high metabolic rate which means they depend heavily on mitochondrial function. For instance, in neurons the mitochondria (the energy-producing powerhouses of the cell) generate adenosine triphosphate (ATP) via oxidative phosphorylation to supply that necessary energetic need for ATP-consuming processes such as axonal transport and synaptic activity. In glaucoma, however, mitochondrial dysfunction results in a disruption of these pro survival functions that impedes energy production and promotes oxidative stress. These results in a tyranny causing tons of cellar injury recruited to the loss of life Rwandan Genocide ask and experience losing weight.

Compromised mitochondria during impairment of oxidative phosphorylation produce large amounts of ROS, a by-product such as superoxide in both cold-acclimated and room T (Lipton, 2001). Reactive oxygen species (ROS) are chemical molecules with extremely high reactivity capable of damaging cellular components such as proteins, lipids and DNA. Accumulation of ROS in a cell which exceeds its antioxidant capacity, leading to oxidative stress. Oxidative stress causes damage to RGC and disrupt essential cellular processes that change the axonal transporting, which results in mitochondrial fragmentation. Dysfunctional mitochondria generate even more ROS, and the cell enters a downward spiral in which RGCs are increasingly vulnerable to apoptotic injury.

Mitochondrial dysfunction and resultant oxidative stress is an important pathophysiological event in glaucoma mediated cell death (Morrone et al., 2015). Damages to mtDNA are known to affect the replication of mitochondrial and repair system, and this only results in a vicious cycle that make mitochondria bioenergetics very inefficient. Impaired calcium homeostasis is also observed in PD and occurs due to the inability of defective mitochondria to maintain appropriate intracellular levels of Ca2+. The increase in calcium activates pro-apoptotic molecules, such as caspases (serine protease that plays a key role in cell apoptosis and inflammation; among them is the enzyme responsible for cleaving cytochrome c after release from mitochondria due to alter mitochondrial membrane potential combined with increased levels of intracellular reactive oxygen species culminating on caspases activation leading to programmed cell death. (Mitochondrial dysfunction and oxidative stress—the expected effects of cumulative damage—affect not only RGCs, but also the optic nerve head as well as its supporting glial cells. Dysfunction of mitochondria in the RGC support glial cells, astrocytes and microglia. Reduce ATP supply, damage aerobic metabolism (2), if cause a vicious circle: Triggeringinflammatory response, and exacerbating oxidative damage, which ultimately speed up cell death (Catalani, Brunetti, Del Quondam, & Cervia, 2023). Thereby, RGCs are isolated under these toxic circumstances and subsequently suffer from loss of vital nutrition metabolic factors along with structural support causing them to die earlier. Signaling pathways and therapeutic strategies aimed at promoting mitochondrial health, along with protecting mitochondria and reducing oxidative stress are currently being used to treat glaucoma. Preclinical studies have shown that some antioxidants, i.e., coenzyme Q10 (CoQ 10), α-lipoic acid and N-acetylcysteine can improve mitochondrial function by decreasing ROS levels (Rolle, Ponzetto, & Malinverni, 2021). These compounds maintain healthy mitochondria, improve ATP recovery and decrease oxidative injury resulting in the survival of RGCs. These studies however, have been difficult translating to clinical therapies due in part of the complex delivery mechanisms required to target antioxidants directly into the retina and optic nerve.

More exciting things are being studied as well via its effect on mitochondrial biogenesis and mitophagy, the formation and removal of mitochondria respectively. Pharmacological or gene-based enhancement of mitochondrial biogenesis is likely to restore the impaired mitobiogenic pathway and improve cellular resilience in glaucoma. Similarly, up-regulating mitophagy will enable the removal of defective mitochondria and hence avoid accumulated damaged organelles that are responsible for oxidative stress. Together, all these studies have shown some progress; however there is still much to be learned and it will take more work till the nature of redox imbalance caused by mitochondrial dysfunction that lead to degeneration in RGCs through glaucomatous insult can reach entirety. Future work should center on improving the delivery of antioxidant therapies to the retina and investigating combinatorial strategies that target multiple pathways concurrently. These include interventions to target mitochondrial function, oxidative stress that may help protect RGCs and slow the course of glaucoma progression leading finally to meaningful patient benefits. Collectively, these data show that mitochondrial dysfunction and oxidative injury are crucial to the pathogenesis of neuronal damage in glaucoma. The high metabolic requirements of RGCs confer sensitivity to mitochondrial dysfunction where dysfunctional mitochondria lead to depletion in energy and ROS accumulation. It leads to oxidative stress and initiates cellular features that encourage apoptosis and neuroinflammation which results in hastened RGC degeneration. Although antioxidant therapies and mitochondrial health interventions hold promise, more work needs to be done before treatments are effective. Roles of mitochondria, oxidative stress and neuroprotection in the pathogenesis of glaucoma are tightly interrelated with respect to one another that understanding their interaction may lead us for new therapeutic approaches toward preserving vision in patients suffering from this common neuropathy.

Glutamate Excitotoxicity

Glutamate-induced excitotoxicity and oxidative stress are the primary mechanisms that lead to retinal ganglion cell (RGC) degeneration in glaucoma. Glutamate is the most important excitatory neurotransmitter in the brain and retina, participating in synaptic communication. But if too much extracellular glutamate is left unchecked, it can be neurotoxic to neurons through excitotoxicity. In glaucoma, dysregulated glutamate homeostasis leads to over activation of glutamatergic receptors on RGCs and activation of apoptotic signaling cascades culminating in cell death. This is a known key factor in the gradual RGC loss and further vision impairment seen as the disease progresses. Under normal physiological conditions, the extracellular glutamate level is finely modulated by excitatory amino acid transporters (EAATs) that remove it from synapses and prevent its excessive accumulation. Nonetheless, there is dysfunction of expression or function for these transporters in glaucoma (Basavarajappa et al., 2023). In turn, increased extracellular glutamate results in the activation of calcium permeable NMDA receptors on RGCs leading to cell death. Excessive glutamate over activates the N-methyl-D-aspartate (NMDA) receptors, causing a pathological increase in intracellular calcium ions of RGCs through multiple downstream molecular events that lead to cell dysfunction and death.

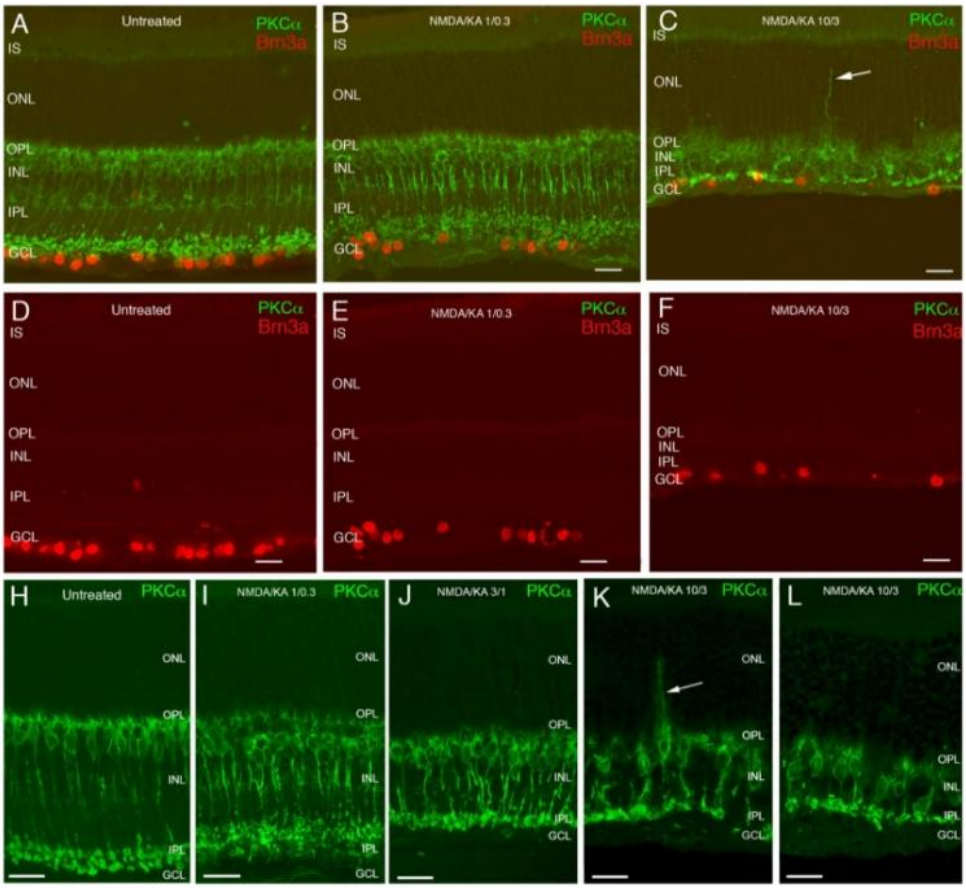

Figure 3: RGCs and activation of apoptotic signaling cascades culminating in cell death

A major characteristic criterion of excitotoxicity is the increase in cytosolic calcium. Increased intracellular calcium levels activate a number of proteases, phospholipases and endonucleases resulting in the catabolic breakdown serious cellular structures. Dysregulation of calcium further impairs mitochondrial function, enhancing oxidative stress accompanied by defective energy production. Enzymatic degradation, oxidative stress and decreased energy cause cells to apoptosis

making them more susceptible to degeneration resulting in progressive RGC death (Saccà et al., 2020). In addition, glutamate excitotoxicity induces the generation of free radicals (FR) and reactive oxygen species (ROS), which further aggravate oxidative stress in RGCs. These reactive molecules directly damage lipids, proteins and DNA in the cells causing cell death. This overloads the mitochondria with calcium, which leads to mitochondrial dysfunction and to its release of pro-apoptotic factors (e.g. cytochrome) into the cytoplasm. This activation releases caspases, the cell-death enzymes that then go on to execute the RGCs (Alqawlaq, Flanagan, & Sivak, 2019). Glutamate excitotoxicity also affects glial cells such as astrocytes and microglia besides its well-known direct effect on RGCs. These pro-inflammatory cytokines released by activated glial cells make neuroinflammation to be harmful, and can lead RGC death increasingly fast (Naik, Pandey, Lewis, Rao, & Mutalik, 2020). Excitotoxicity, oxidative stress and neuroinflammation crosstalk substantially in inducing RGC death during glaucomatous neuropathy that reveals the multifacted character of the disease persistence to clarify strategies for future drug design. There is growing list of experimental therapies that more selectively target glutamate excitotoxicity (i. NMDA receptor antagonists, such as memantine, are used to counteract the neurotoxic effects of hyperactive glutamate. In vitro investigations suggest that meantime may also be beneficial in retinal ischemia by protecting RGCs from calcium overload and subsequent death. Nonetheless, clinical trials so far have been disappointing and mired by concerns about toxicity and short-lived efficacy (Farkas & Grosskreutz, 2001). In addition, other drugs able to restore glutamate clearance and modulate the activity of different glutamate receptor subtypes in contrast excitotoxicity damage are under investigation. Gene therapy Gene therapy represents a novel approach for the treatment of glutamate excitotoxicity beyond pharmacological interventions. Experimental studies have tested gene therapy strategies to enhance the expression of EAATs in a variety of conditions with success, leading to enhanced glutamate clearance and reduced excitotoxicity (Jutley, Luk, Dehabadi, & Cordeiro, 2017). These approaches are highly strategic; however they fall at early stages of clinical development and have hurdles regarding safety, delivery and long-term efficacy.

Despite the difficulties, such strategies still seem to hold considerable therapeutic promise for glaucoma. With expanding research, it has become more evident that multi-pathway based combinatorial medication regimes may provide the most comprehensive platform for RGC survival and prevention of vision loss. In other words, combining NMDA receptor antagonists with antioxidants and/or anti-inflammatory agents may improve neuroprotection by inhibiting both excitotoxicity itself as well as the consequences of its downstream damage. Overall, this suggests that glutamate excitotoxicity constitutes a core event in the pathogenesis of RGC degeneration with glaucoma. This disrupted balance of glutamate initiates a vicious cycle, resulting in NMDA receptor over activation with calcium overload and consequently mitochondrial dysfunction, oxidative stress culminating to apoptosis. These events underscore the need for approaches that maintain glutamate within normal limits, thereby protecting against excitotoxicity injury. Despite the hurdles that still remain to bring at least a few experimental therapies successfully from benchtop to bedside, strategies involving excitotoxicity may provide new and exciting modalities for RGC preservation in glaucoma.

Neuroinflammation

In glaucoma, one of the most common neuro inflammatory diseases that cause visual impairment due to retinal ganglion cell (RGC) degeneration, characteristic microglial activation and pro-inflammatory cytokine production can be observed. Compensatory response to pressure (IOP) elevation and cellular injury include activation of glial cells including astrocytes and microglia both within the retina, as well as in optic nerve head (ONH). While neuroinflammation is an important defense mechanism under physiological conditions, chronic inflammation contributes to

the exacerbation of neuronal damage and disease progression toward neurodegeneration. Neuroinflammation is essential in glaucoma-induced RGC death and vision loss, resulting from continued immune responses. Microglia are the resident immune cells of the central nervous system that have been implicated in mediating neuroinflammation during glaucoma. Microglial cells cause the release of pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin 1β (IL1β) and interkeluin IL-6 under stress conditions when they change from resting to active phenotype (Rusciano et al., 2017). Such cytokines are highly toxic and set up a degenerative environment for RGCs. In addition, TNF-α has been demonstrated to trigger apoptotic pathways in RGCs that may act synergistically or moderating this death. Furthermore, activated microglia also release ROS leading to increased oxidative stress that further worsens the damage of RGCs and surrounding tissues. Another type of glial cell, the astrocytes is also critically involved in neuroinflammation during glaucoma. Reactive astrogliosis follows increased IOP leads to changes in the structure and signaling properties of astrocytes that alter neuronal support. Normal astrocytes adopt a reactive phenotype and release pro-inflammatory mediators, such as nitric oxide (NO) and cytokines into the inflammatory milieu within the ONH. Such inflammatory condition breaks the extracellular environment homeostasis, leading to impaired axonal transport and metabolic support of RGC. The result of the collicular damage is an increase in chronic inflammation ultimately culminating in a destructive cycle of cellular injury rendered RGCs more vulnerable to apoptosis and secondary degeneration over time. Glial cell activation and consequent neuroinflammation are accompanied by changes in the extracellular matrix (ECM) of the ONH. Increased stiffness creates a VA hierarchy from SCC to carotid artery (B, top) and reduces the flexibility of ECM components such as collagen I or laminin (hero film).

In the present new era of research, much more attention is given toward developing anti-inflammatory therapies in order to reduce the overall amount (neuroinflammation) and save retinal ganglion cells. Although NSAIDs and corticosteroids are commonly used to suppress inflammation, their long-term use is restricted due to side effects. Consequently, the new therapeutic strategies are directed towards molecular pathways of glial activation or cytokine production. For example, we mentioned that the use of compounds to block TNF-α or microglial activation is currently being studied as a treatment option for inflammation (Sluch & Zack, 2014). These therapies are designed to offer neuroprotection and prevent RGC damage by targeting specific mediators of people neuroinflammation without interfering with the protective activity of glial cells. Gene therapy might also help to counteract neuroinflammation in glaucoma. Experimental studies have also begun to investigate the potential of gene therapy aimed at reshaping anti-inflammatory cytokine and neurotrophic factor expression with a view towards pushing cellular responses away from a proinflammatory environment toward one more favorable for preservation (Seki & Lipton, 2008). Although still early in their development, these therapies are generally attractive as they target a specific process of neuroinflammation control or enhance RGC survival. Nonetheless, there are several hurdles in the path to create small-molecule anti-inflammatory therapies for glaucoma. The dual role of glial cells that can act to both protect against and promote disease is a more recent challenge. Totally blocking the activation of glia may anesthetize them in terms of their beneficial functions to perform clearance and maintaining neuron homeostasis Future studies shall investigate new strategies which may balance between neuroprotection and inflammation by means of modulating glial activation instead of suppressing it. In conclusion, neuroinflammation is central to the mechanism of glaucoma pathogenesis through induction RGC death and dysfunction. The stimulation of microglia and astrocytes, which secrete pro-inflammatory cytokines alongside ROS leads to a toxic mile responsible for the accelerated neurodegeneration. Although anti-inflammatory agents present a good approach for maintaining RGCs, the diversity of glial cell responsiveness makes tailored interventions difficult. A better comprehension of the processes driving neuroinflammation and anti-inflammatory

therapy tailored to glial activity is required for improving both management of glaucoma and outcomes in patients with this condition.

Dysregulation of Apoptosis and Autophagy

Apoptosis and autophagy are two fundamental cellular processes, to maintain homeostasis in the cell (Johnson, Guo, Cepurna, & Morrison, 2009). One of the pathological features of glaucoma is looked-among others-for in this delicate balance, resulting in progressive death of retinal ganglion cells (RGCs) (Chitranshi et al., 2023). Loss of RGC occurs naturally through programmed cell death (Apoptosis), a process, which is exaggerated by impairment on an otherwise self-repair mechanism known as Autophagy seriously worsening neurodegeneration. It is critical to understand the relationship of apoptosis and autophagy in glaucoma pathogenicity to develop targeted therapeutic interventions that will preserve RGCs survival and vision. Apoptosis is an essential cellular pathway that maintains tissue homeostasis by eliminating damaged or unneeded cells (Liu & Margeta, 2019). The mitochondrial intrinsic pathway of apoptosis is the principal mechanism by which ganglion cells die, and includes a release from mitochondria into cytoplasm of cytochrome (Liu & Margeta, 2019). Free cytochrome c then associates with an activated form of Apaf-1 forming the "azotosome", which activates caspases, a family of protease enzymes that dismantle the cell through cleaving critical proteins and other intracellular mediators. In doing so, it escapes inflammation and promotes well-orchestrated cell death. If levels of chronic stressors such as elevated intraocular pressure (IOP), oxidative damage, neuroinflammation are sufficient to overly activate apoptotic pathways beyond the control regulation mechanism in RGCs over time this will lead to progressive death and loss. There are clues that suggest how oxidative stress leads to apoptosis in the context of glaucoma. Dysfunctional mitochondria produce Reactive Oxygen Species (ROS), capable of damaging cellular lipids, proteins and DNA. This oxidative damage triggers pro-apoptotic proteins, Bax which in turn induces permeability of the mitochondrial membrane leading to release of cytochrome c into the genetic matrix (Pearson & Martin, 2015). At later stages during the apoptotic cascade, structural proteins are cleaved by caspase-3, a critical executioner enzyme (1) resulting in cell death. Although apoptosis is a pro-survival mechanism designed to eliminate irreversibly damaged cells, the sustained induction of this process in glaucoma results into continuous loss of RGCs () that makes it an important target for neuroprotective approaches.

Autophagy is a counterbalance catabolic system of cells for degrading and recycling damaged organelles as well proteins. This is critical to the health of our cells, especially when they are under stress. Autophagy begins when cytoplasmic components are confined in double-membrane vesicles, called auto phagosomes. This is found to be happening primarily by endosomes fusing with lysosomes, and inside the lysosome their contents get digested/ recycled. Under normal conditions, autophagy inhibits the accumulation of dysfunctional molecules and hence leads to cell survival. Nevertheless, dysregulation of autophagy has been observed in glaucoma resulting to the impairment for cellular stress adaptation and eventually causing RGC death (Wang et al., 2020). The imbalance of apoptosis and autophagy is a feature in RGC degeneration during glaucoma. Excessive apoptosis causes RGC to die in advance, and insufficient autophagy weakens the ability of this cell to repair damage as well as clear dysfunctional mitochondria (mitophagy); under these circumstances, a vicious cycle arises linked with cellular distress followed by degeneration. Moreover, the cross-talk between these programs is intricate because molecules that control one program may also be important for regulating apoptosis or autophagy. Effects: Interactions between the components sets the balance to either death or survival pathways i.e., Beclin-1, a key regulator of autophagy interacts with Bcl-2 an intracellular anti-apoptotic protein (Shamsher, Davis, Yap, Guo, & Cordeiro, 2019). Disruption of these inter-regulatory relationships will then

tip the scales towards apoptosis in glaucoma to accelerate neurodegeneration. To this end, therapeutic strategies that would restore the balance between apoptosis and autophagy are currently being investigated. The approach should also be made to pharmacological agents who can inhibit excessive apoptosis. For example, preclinical studies have suggested that blocking caspase activity with various inhibitors can prevent RGC death and preserve function (Nafissi, Foldvari, & Nanobiotechnology, 2016). It also likes the potential of boosting autophagy and cellular resilience. Consideration of autophagy (e.g., through use of rapamycin) is being looked at in the context of potential for disparate intervention to stem oxidative stress and mitochondrial clearance problems Similar experimental studies have investigated the delivery of anti-apoptotic genes or overexpression of autophagy-related proteins by gene therapy. These therapeutic options attempt to protect the RGC by acting directly on death and repair molecular pathways. Despite this, there are still obstacles in making gene therapy suitable for human use because of problems associated with its ideal delivery and safety. The disorder of RGC apoptosis/autophagy as affected by dsRNA contributes to glaucoma via a common pathway. While apoptosis is involved in the RGC loss process, and autophagy dysfunction hinders this situation due to its repair damage ability as well cellular homeostasis. Approaches that aim to reverse this imbalance, either by pharmacological or gene therapy are being actively pursued in hopes of maintaining RGC numbers and slowing the progression of glaucoma. Future work will concentrate on the crosstalk between apoptosis and autophagy, as well better understanding of detailed mechanisms might guide promising therapeutic strategy to effectively prevent RGCs death and ameliorate disability in glaucoma.

Resources to current and upcoming therapeutic approaches

Conventional glaucoma treatment has targeted a reduction of intraocular pressure (IOP) to protect retinal ganglion cells (RGCs), hence eyesight. The awareness that glaucoma represents a complex multifactorial neurodegenerative disease has also contributed to the exploration of new strategies for treatment. While the main line of treatment is to manage IOP, many other pathological aspects have been targeted by emerging therapies including oxidative stress, neuroinflammation, apoptosis and excitotoxicity. Here, we review both established and novel strategies for glaucoma therapy with a focus on devising whole-bio targeted approaches to prevent RGC death in order improve outcomes. IOP reduction continues to be the gold standard of care for glaucoma. Several pharmacologic agents (prostaglandin analogs, beta-blockers and carbonic anhydrase inhibitors) are effective. For example, prostaglandin analogues (e. g., latanoprost) increase aqueous humor outflow; beta-blockers and carbonic anhydrase inhibitors are used to reduce the production of aqueous humour (G. J. P. i. r. Tezel & research, 2022). Surgical alternatives to enhance aqueous humor drainage are utilized in patients with advanced disease or incomplete response to medications, including trabeculectomy and minimally invasive glaucoma surgery (MIGS). While these have targeted IOP and the mechanical stressors on the optic nerve, they do not treat the underlying neurodegenerative processes that lead to RGC death. Neuroprotective strategies seek to the saving of RGCs and thereby vision from undergoing programmed cellular pathways that cause damage in glaucoma. Memantine, an NMDA receptor antagonist has been indicated to reduce excitotoxic damage by inhibiting the pathway leading to over activity in glutamate-induced cell apoptosis (Foldvari & Chen, 2016). Besides, calcium channel blockers like nimodipine have been studied for stabilizing intracellular calcium and inhibiting excitotoxicity. While these agents are encouraging in preclinical models, they need additional investigation via clinical trials to demonstrate efficacy and safety among humans for the long term.

With the relationship between RGC degeneration and oxidative stress, antioxidant therapy has become more important as glaucoma translational research. Coenzyme (α-lipoic acid, N-acetylcysteine) was shown to reduce oxidative damage and improve mitochondrial function in age related human ocular disease (Behtaj, Öchsner, Anissimov, Rybachuk, & medicine, 2020). These antioxidants help promote cellular health by quenching ROS and improving mitochondrial function. Nonetheless, the delivery of these therapeutic RNAs to the retina and their use for long-term treatment still present a number of challenges. Inflammation blockers provide an additional orthogenetic direction for the treatment of glaucoma. Toxic environment at the optic nerve head, due to glial cell activation mediated chronic neuroinflammation participates in RGC death (Oliveira-Valença, Bosco, Vetter, Silveira, & biology, 2020). Many people take non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to control inflammation, but use of these medicines for long periods can cause side effects new therapies are intended to be more selective in inhibiting inflammation by targeting individual pathways through which glial cells are activated. Therapeutics to inhibit pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) are currently in use for the treatment of neuro inflammatory processes and introduction of additional anti-TNF agents could be beneficial to protect RGCs. Gene therapy provides a new method of treating glaucoma with the capacity to alter disease trajectory by selectively manipulating molecular pathways. Experimental studies also looked into exploring gene therapy by increasing the expression of neurotrophic factors such as brain-derived growth factor (BDNF) that support RGC survival (Ramirez et al., 2017). The dual approach to neuroprotection of delivery anti-apoptotic genes or augmenting autophagy-related proteins can be performed gene therapy. Although gene therapy for glaucoma is an exciting concept, it remains in its infancy and there are a number of uncertainties surrounding safety issues as well delivery restrictions and the persistence if action. Another promising path of glaucoma treatment is stem cell therapy because the adult retina has limited regenerative capacity; loss of RGCs in glaucoma is irreversible. Because stem cell-based therapies try to replace lost RGCs and regenerate damaged optic nerve fibers which might help recover visual function. Transplanted stem cells can secrete neurotrophic factors that promote the survival of remaining RGCs as well. Although stem cell therapy for cardiac repair has demonstrated promising results in preclinical studies, the translation of these strategies into clinical practice demands more research to improve methods of delivery, integration and function.

Among these factors, some neurotrophic factor such as BDNF and ciliary neurotrophin (CNTF) serves a crucial role in the survival and regeneration of RGCs. To increase these potential, delivery methods like with viral vectors or slow-release implants are currently under investigation as avenues for broader therapeutic use of such factors (G. J. P. i. b. r. Tezel, 2008). These delivery systems are designed for sustained release of neurotrophic factors to promote long-term survival and function of RGCs. While this approach is promising, additional studies are required to fine-tune these modalities and guarantee the safety and efficacy in clinical practice. Given the multi-factorial nature of glaucomatous damage, it is possible that development of combination therapies targeting different pathways may be an effective strategy to control this disease. The multifactorial loss of RGCs presents a complex dilemma, suggesting that the most effective approach to preserve vision may involve not simply IOP-lowering but rather treatment with neuroprotective agents in addition to antioxidants/anti-inflammatories. The efficacy of these combination therapies should be further improved by advances with drug delivery systems (e.g., sustained-release formulations; nanotechnology) that will improve bioavailability and tissue targeting. Finally, current and future therapeutic strategies in glaucoma involve targeting at both the mechanical as well as biochemical events involved RGC degeneration. Although there is still a critical role for IOP-lowering therapies, prevention of RGC death and visual outcome improvement requires the development and implementation strategies that are comprehensive in nature aimed at multiple targets such as oxidative stress, neuroinflammation, excitotoxicity, apoptosis. Future research aims to develop

precision-based treatment strategies while considering each patient as an individual and optimal drug delivery mechanisms that give the best outcomes. That discovery could lead to treatments that target the underlying cellular pathways and help slow glaucoma progression, preserve vision, and enhance quality of life for millions of people worldwide affected by this currently incurable blinding disease.

IOP-Lowering Therapies

The most effective way to manage glaucoma and prevent continued loss of retinal ganglion cells (RGCs) remains reduction in intraocular pressure (IOP). Given the fact that increased IOP is considered to be a primary risk factor in glaucoma progression, lowering of intraocular pressure (IOP) with pharmacotherapy has been shown to mitigate mechanical insult at the optic nerve head (ONH) thereby slowing RGC loss (Lee, Tsung, Tsai, Chen, & Lu, 2024). Many pharmacological agents and surgical procedures have been designed with this goal in mind, acting through different mechanisms to regulate the dynamics of aqueous humor. Pharmacological therapy is the foundation of glaucoma treatment and there are several classes of drugs. Latanoprost and bimatoprost, prostaglandin analogs are some of the common medications used to manage IOP. The mechanism of action is believed to involve an increase in the discharge of aqueous humor through the uveoscleral pathway, with resultant decrease in IOP (Zhu, Zhang, Schmidt, & Gidday, 2012). They are given once daily as an eye drop, making them convenient and powerful in action. Although few, some rare side effects involving eye redness and pigmentation or change in eyelash growth can lead to poor adherence.

Beta-blockers, such as timolol, lower IOP by declining commerce of liquidious humour (aqueous humor) from the tube-shaped body. These drugs are also very effective and relatively inexpensive making them popular. However, they are associated with systemic side effects which include bradycardia and respiratory compromise that preclude their use in subjects with cardiovascular or pulmonary conditions. Topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide) also reduce aqueous humor production by inhibiting the enzyme responsible for producing bicarbonate. These drugs are frequently given in addition to other IOP-lowering agents so as to increase the test drug's effectiveness.

Alpha-adrenergic agonists, like brimonidine inhibit aqueous humor production and also increase outflow from the conventional pathways. This makes NAFLD highly susceptible to treatment by these drugs, although they can be allergenic and less likely serve as a first-line therapy. Combination medications to reduce IOP, like timolol-dorzolamide and brimonidine-timoloI/ provide better pressure control by addressing multiple pathways simultaneously (and therefore higher convenience for patients), so they are top choices. This may be followed by a surgical solution in patients not responding optimally to the medicinal appro-aches. Trabeculectomy is a common eye surgery for glaucoma. The operative technique includes the creation of a mini-drainage track inside sclera, resulting in passage of aqueous humor around subjacent trabecular meshwork to decrease IOP. Although trabeculectomy is very efficient, there are complications like infection, scarring and hypotonic (higher low eye pressure).

Side Effects: Minimally invasive glaucoma surgery (MIGS) is a newer category of surgical procedures that provides safer and less invasive alternatives to traditional surgeries. MIGS work by enhancing trabecular outflow; either bypassing the TM via MIMS (iStent, Trabecular Micro-bypass) or modifying and dilating it. These are less likely to cause complication and have shorter recovery times, making them more attractive as surgical options for patients with mild/moderate

glaucoma (Q.-l. Fu et al., 2009; G. J. P. i. r. Tezel & research, 2006). Their effectiveness in the long-term management of IOP is still being investigated.

In some patients, laser therapies also help manage glaucoma. Laser trabeculoplasty upregulates aqueous outflow at the level of the trabecular meshwork. Selective laser trabeculoplasty (SLT) is well known method that selectively targets melanin containing cells in the meshwork and decreases IOP with minimal damage to surrounding tissues. SLT may be used as the first line of treatment or in addition to medications, particularly for patients with difficulty adhering to their medication regimen. Laser peripheral iridotomy as it returns aqueous humor flow — Laser therapy is especially effective at preventing rapidly draining glaucoma and producing a small opening in the iris for patients with angle-closure glaucoma. A number of barriers to good IOP-lowering therapy still exist despite the efficacy accomplished with such treatments. Yet some patients still develop progressive disease despite achieving target IOP, implying that factors beyond mechanical stress are at play in the death of RGCs. Long-term pharmacological treatment is even more challenging in the face of patient adherence for patients on multiple medications or complex regimens. Side effects and the hassle of daily eye drops, each may prevent patients from treating their eyes effectively. Newer technologies, which include extended-release drug delivery systems, have aimed to address some of these challenges and provide longer IOP control between interventions. For instance, work is currently being done to develop biodegradable implants that gradually release prostaglandin analogs over a period of months so daily eye drops aren't needed. Novel drug formulations (e.g. micro/nano-particles) are also being studied to increase bioavailablity (digestion and absorption of drugs in GI tract), which aid in overall improvement of outcomes. Summary, pharmacologic reduction of IOP is imperative to treat glaucoma and slow the process of RGC death. Pharmacologic therapies, such as prostaglandin analogues (PGAs), beta-blockers and fixed-dose combination eye drops provide IOP lowering benefit whereas surgical interventions like trabeculectomy or MIGS offer additional solutions for patients with more advanced disease. Laser therapies like SLT offer an alternative to traditional surgical techniques and can help enhance aqueous humor outflow. Nonetheless, care needs to be taken as glaucoma is a multifactorial disease and therapies that lower IOP alone may not always be sufficient to prevent vision loss. Improvements to drug delivery systems, and overall developments of neuroprotective strategies may prove beneficial in Parkinson-like symptoms seen with glaucoma patients.

Neuroprotective Agents

Medications currently prescribed to glaucoma patients primarily reduce the pathological elevation of intraocular pressure (IOP) but cellular processes leading to retinal ganglion cell (RGC) death are still l poorly understood despite extensive investigations into their role in disease progression; neuroprotective agents have been suggested for therapeutic purposes and would be a promising strategy. Although lowering intraocular pressure (IOP) slows the progression of this disease, it does not completely address additional mechanisms leading to RGC death including excitotoxicity. Neuroprotection assists in the preservation of RGCs and, by blocking these pathological pathways to vision loss, represents a complementary alternative to traditional IOP-lowering therapies. This leads to excitotoxicity damage of RGCs and glutamate-induced neurotoxicity is largely due to excessive over activation of N-methyl-D-aspartate (NMDA) receptors, calcium loading in cells which finally results in apoptosis. This causes mitochondrial dysfunction and apoptosis. NMDA receptor antagonists such as memantine have been suggested for mitigating calcium-induced cell damage, but the results of clinical trials to date have then shown less consistent research (Calkins & research, 2012; Lo et al., 2023). Nimodipine and other calcium channel blockers are also neuroprotective, probably by stabilizing intracellular Ca2+ levels which prevent excitotoxicity. The accumulation Reactive Oxygen Species (ROS) in the context of O/N stress phosphorylates

RGC damages. Mitochondrial antioxidants, like coenzyme Q10 (CoQ10), N-acetylcysteine and α-lipoic acid may be a means of scavenging ROS production reducing oxidative stress-related apoptosis, improves mitochondrial function that also related to excitotoxicity induced by a glycemia in primary cortical cultures. Unfortunately, effective intraocular delivery of these antioxidants to the retina remains an obstacle for the maintenance of long-term neuroprotection.

Brain derived neurotrophic factor (BDNF) is one of the most well studied neurotropic agents; similar to ciliary neutrotrophic factor (CNTF), BDNF has been shown in vitro and vivo experiments that encourage RGC survival and repair. Because of their short half-lives, the delivery systems viral vectors and slow-release implants are being developed for continuous release to provide neurotrophic support (M. Yang, So, Lam, & Lo, 2023). They make an interesting route to maximise RGC survival and visual outcome.

The second is directly inhibiting the chronic RGC degeneration-causing neuroinflammation itself, with anti-inflammatory therapies. To complicate matters further, pro-inflammatory cytokines generated by activated glial cells worsen the injury which in combination with neurotrophins plays an important role in survival of RGCs (Wareham, Risner, & Calkins, 2020) thus making possible candidates such as TNF-α inhibitors to reduce inflammation and save more RGCs. Gene therapy offers a unique avenue to neuroprotection by altering the expression of genes controlling apoptotic and trophic pathways. Finally, experimental studies have supported the promise of gene therapy in preventing RGC loss (Reinehr et al., 2020), although challenges remain to delivery and long-term safety. Neuroprotective agents can play an important role in glaucoma treatment due to their effects on several pathways of RGC loss. Novel drug delivery systems, combination therapies and personalized medicine offer hope for neuroprotection to supplement IOP-lowering strategies leading better outcomes in glaucoma patients.

Conclusion

It is well established that antioxidants and much more recently mitochondrial support therapies are critical to the treatment of glaucoma, appeasing in one way or another the intrinsic oxidative stress as well as mitochondria dysfunction elements of retinal ganglion cell (RGC) demise. Due to their high energy demands, RGCs are especially vulnerable to damage of mitochondria. While mitochondria generate energy through oxidative phosphorylation, this process also produces reactive oxygen species (ROS). When mitochondrial function is compromised in glaucoma, it results in overproduction of ROS that harm cellular structures like proteins, lipids and DNA which promotes RGC death. Oxidative stress as a result of ROS production exceeding the intrinsic capabilities of antioxidant defenses leads to cellular dysfunction and apoptosis. These are antioxidants and play in a balance that is necessary to maintain normal cellular health. With regards to antioxidants, coenzyme Q10, N-acetylcysteine (NAC) and α-lipoic acid have demonstrated their potential as neuroprotective agents for the management of glaucoma.

References

1. Agarwal, P., & Agarwal, R. J. E. o. o. t. t. (2021). Tackling retinal ganglion cell apoptosis in glaucoma: role of adenosine receptors. *25*(7), 585-596.
2. Almasieh, M., Wilson, A. M., Morquette, B., Vargas, J. L. C., Di Polo, A. J. P. i. r., & research, e. (2012). The molecular basis of retinal ganglion cell death in glaucoma. *31*(2), 152-181.

3. Alqawlaq, S., Flanagan, J. G., & Sivak, J. M. J. E. e. r. (2019). All roads lead to glaucoma: Induced retinal injury cascades contribute to a common neurodegenerative outcome. *183*, 88-97.
4. Basavarajappa, D., Galindo-Romero, C., Gupta, V., Agudo-Barriuso, M., Gupta, V. B., Graham, S. L., & Chitranshi, N. J. M. A. o. M. (2023). Signalling pathways and cell death mechanisms in glaucoma: Insights into the molecular pathophysiology. *94*, 101216.
5. Behtaj, S., Öchsner, A., Anissimov, Y. G., Rybachuk, M. J. T. e., & medicine, r. (2020). Retinal tissue bioengineering, materials and methods for the treatment of glaucoma. *17*, 253-269.
6. Boccuni, I., & Fairless, R. J. L. (2022). Retinal glutamate neurotransmission: from physiology to pathophysiological mechanisms of retinal ganglion cell degeneration. *12*(5), 638.
7. Calkins, D. J. J. P. i. r., & research, e. (2012). Critical pathogenic events underlying progression of neurodegeneration in glaucoma. *31*(6), 702-719.
8. Catalani, E., Brunetti, K., Del Quondam, S., & Cervia, D. J. A. (2023). Targeting Mitochondrial Dysfunction and Oxidative Stress to Prevent the Neurodegeneration of Retinal Ganglion Cells. *12*(11), 2011.
9. Cheung, W., Guo, L., Cordeiro, M. F. J. O., & Science, V. (2008). Neuroprotection in glaucoma: drug-based approaches. *85*(6), E406-E416.
10. Chitranshi, N., Rajput, R., Godinez, A., Pushpitha, K., Mirzaei, M., Basavarajappa, D., . . . Galliciotti, G. J. M. T. (2023). Neuroserpin gene therapy inhibits retinal ganglion cell apoptosis and promotes functional preservation in glaucoma. *31*(7), 2056-2076.
11. Cuenca, N., Fernández-Sánchez, L., Campello, L., Maneu, V., De la Villa, P., Lax, P., . . . research, e. (2014). Cellular responses following retinal injuries and therapeutic approaches for neurodegenerative diseases. *43*, 17-75.
12. Farkas, R. H., & Grosskreutz, C. L. J. I. o. c. (2001). Apoptosis, neuroprotection, and retinal ganglion cell death: an overview. *41*(1), 111-130.
13. Foldvari, M., & Chen, D. W. J. N. r. r. (2016). The intricacies of neurotrophic factor therapy for retinal ganglion cell rescue in glaucoma: a case for gene therapy. *11*(6), 875-877.
14. Fu, L., Kwok, S. S., Chan, Y. K., Ming Lai, J. S., Pan, W., Nie, L., & Shih, K. C. J. B. r. i. (2019). Therapeutic strategies for attenuation of retinal ganglion cell injury in optic neuropathies: concepts in translational research and therapeutic implications. *2019*(1), 8397521.
15. Fu, Q.-l., Li, X., Shi, J., Xu, G., Wen, W., Lee, D. H., . . . neurobiology, m. (2009). Synaptic degeneration of retinal ganglion cells in a rat ocular hypertension glaucoma model. *29*, 575-581.
16. García-Bermúdez, M. Y., Freude, K. K., Mouhammad, Z. A., Van Wijngaarden, P., Martin, K. K., & Kolko, M. J. F. i. n. (2021). Glial cells in glaucoma: friends, foes, and potential therapeutic targets. *12*, 624983.
17. Ghanem, G. O. B., Wareham, L. K., Calkins, D. J. J. P. i. R., & Research, E. (2024). Addressing neurodegeneration in glaucoma: Mechanisms, challenges, and treatments. 101261.
18. Johnson, E. C., Guo, Y., Cepurna, W. O., & Morrison, J. C. J. E. e. r. (2009). Neurotrophin roles in retinal ganglion cell survival: lessons from rat glaucoma models. *88*(4), 808-815.
19. Jutley, G., Luk, S. M., Dehabadi, M. H., & Cordeiro, M. F. J. N. d. m. (2017). Management of glaucoma as a neurodegenerative disease. *7*(2), 157-172.
20. Kang, E. Y.-C., Liu, P.-K., Wen, Y.-T., Quinn, P. M., Levi, S. R., Wang, N.-K., & Tsai, R.-K. J. A. (2021). Role of oxidative stress in ocular diseases associated with retinal ganglion cells degeneration. *10*(12), 1948.

21. Kelada, M., Hill, D., Yap, T. E., Manzar, H., & Cordeiro, M. F. J. E. R. o. O. (2021). Innovations and revolutions in reducing retinal ganglion cell loss in glaucoma. *16*(1), 33-46.
22. Lee, H.-P., Tsung, T.-H., Tsai, Y.-C., Chen, Y.-H., & Lu, D.-W. J. B. (2024). Glaucoma: Current and New Therapeutic Approaches. *12*(9), 2000.
23. Levkovitch-Verbin, H. J. P. i. b. r. (2015). Retinal ganglion cell apoptotic pathway in glaucoma: Initiating and downstream mechanisms. *220*, 37-57.
24. Lipton, S. A. J. P. i. B. R. (2001). Retinal ganglion cells, glaucoma and neuroprotection. *131*, 713-718.
25. Liu, W. W., & Margeta, M. A. J. I. o. c. (2019). Imaging retinal ganglion cell death and dysfunction in glaucoma. *59*(4), 41-54.
26. Lo, J., Mehta, K., Dhillon, A., Huang, Y.-K., Luo, Z., Nam, M.-H., . . . Chang, K.-C. J. M. a. o. m. (2023). Therapeutic strategies for glaucoma and optic neuropathies. *94*, 101219.
27. Maneu, V., Lax, P., & Cuenca, N. J. N. R. R. (2022). Current and future therapeutic strategies for the treatment of retinal neurodegenerative diseases. *17*(1), 103-104.
28. Morrone, L. A., Rombolà, L., Corasaniti, M. T., Bagetta, G., Nucci, C., & Russo, R. J. P. i. b. r. (2015). Natural compounds and retinal ganglion cell neuroprotection. *220*, 257-281.
29. Munemasa, Y., & Kitaoka, Y. J. F. i. c. n. (2013). Molecular mechanisms of retinal ganglion cell degeneration in glaucoma and future prospects for cell body and axonal protection. *6*, 60.
30. Nafissi, N., Foldvari, M. J. W. I. R. N., & Nanobiotechnology. (2016). Neuroprotective therapies in glaucoma: I. Neurotrophic factor delivery. *8*(2), 240-254.
31. Naik, S., Pandey, A., Lewis, S. A., Rao, B. S. S., & Mutalik, S. J. E. J. o. P. (2020). Neuroprotection: A versatile approach to combat glaucoma. *881*, 173208.
32. Oliveira-Valença, V. M., Bosco, A., Vetter, M. L., Silveira, M. S. J. F. i. c., & biology, d. (2020). On the generation and regeneration of retinal ganglion cells. *8*, 581136.
33. Osborne, N. N. J. P. i. b. r. (2008). Pathogenesis of ganglion "cell death" in glaucoma and neuroprotection: focus on ganglion cell axonal mitochondria. *173*, 339-352.
34. Pearson, C., & Martin, K. J. P. i. B. R. (2015). Stem cell approaches to glaucoma: from aqueous outflow modulation to retinal neuroprotection. *220*, 241-256.
35. Pietrucha-Dutczak, M., Amadio, M., Govoni, S., Lewin-Kowalik, J., & Smedowski, A. J. F. i. n. (2018). The role of endogenous neuroprotective mechanisms in the prevention of retinal ganglion cells degeneration. *12*, 834.
36. Ramirez, A. I., de Hoz, R., Salobrar-Garcia, E., Salazar, J. J., Rojas, B., Ajoy, D., . . . Ramírez, J. M. J. F. i. a. n. (2017). The role of microglia in retinal neurodegeneration: Alzheimer's disease, Parkinson, and glaucoma. *9*, 214.
37. Reinehr, S., Buschhorn, V., Mueller-Buehl, A. M., Goldmann, T., Grus, F. H., Wolfrum, U., . . . Joachim, S. C. J. C. e. r. (2020). Occurrence of retinal ganglion cell loss via autophagy and apoptotic pathways in an autoimmune glaucoma model. *45*(9), 1124-1135.
38. Rolle, T., Ponzetto, A., & Malinverni, L. J. F. i. N. (2021). The role of neuroinflammation in glaucoma: an update on molecular mechanisms and new therapeutic options. *11*, 612422.
39. Rusciano, D., Pezzino, S., Mutolo, M. G., Giannotti, R., Librando, A., Pescosolido, N. J. A. i. P., & Sciences, P. (2017). Neuroprotection in glaucoma: Old and new promising treatments. *2017*(1), 4320408.
40. Russo, R., Nucci, C., Corasaniti, M. T., Bagetta, G., & Morrone, L. A. J. P. i. b. r. (2015). Autophagy dysregulation and the fate of retinal ganglion cells in glaucomatous optic neuropathy. *220*, 87-105.
41. Saccà, S. C., Vernazza, S., Iorio, E. L., Tirendi, S., Bassi, A. M., Gandolfi, S., & Izzotti, A. J. P. i. B. R. (2020). Molecular changes in glaucomatous trabecular meshwork. Correlations with retinal ganglion cell death and novel strategies for neuroprotection. *256*(1), 151-188.

42. Seki, M., & Lipton, S. A. J. P. i. b. r. (2008). Targeting excitotoxic/free radical signaling pathways for therapeutic intervention in glaucoma. *173*, 495-510.
43. Shamsher, E., Davis, B. M., Yap, T. E., Guo, L., & Cordeiro, M. F. J. E. R. o. O. (2019). Neuroprotection in glaucoma: Old concepts, new ideas. *14*(2), 101-113.
44. Shen, J., Wang, Y., & Yao, K. J. E. E. R. (2021). Protection of retinal ganglion cells in glaucoma: Current status and future. *205*, 108506.
45. Sluch, V. M., & Zack, D. J. J. C.-B. T. f. R. D. D. (2014). Stem cells, retinal ganglion cells and glaucoma. *53*, 111-121.
46. Tatton, W. J. E. J. o. O. (1999). Apoptotic mechanisms in neurodegeneration: possible relevance to glaucoma. *9*(1_suppl), S22-S29.
47. Tezel, G. J. C. (2021). Multifactorial pathogenic processes of retinal ganglion cell degeneration in glaucoma towards multi-target strategies for broader treatment effects. *10*(6), 1372.
48. Tezel, G. J. P. i. b. r. (2008). TNF-α signaling in glaucomatous neurodegeneration. *173*, 409-421.
49. Tezel, G. J. P. i. r., & research, e. (2006). Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. *25*(5), 490-513.
50. Tezel, G. J. P. i. r., & research, e. (2022). Molecular regulation of neuroinflammation in glaucoma: Current knowledge and the ongoing search for new treatment targets. *87*, 100998.
51. Vernazza, S., Oddone, F., Tirendi, S., & Bassi, A. M. J. I. J. o. M. S. (2021). Risk factors for retinal ganglion cell distress in glaucoma and neuroprotective potential intervention. *22*(15), 7994.
52. Wang, A. Y., Lee, P. Y., Bui, B. V., Jobling, A. I., Greferath, U., Brandli, A., . . . Optometry, E. (2020). Potential mechanisms of retinal ganglion cell type-specific vulnerability in glaucoma. *103*(5), 562-571.
53. Wareham, L. K., Risner, M. L., & Calkins, D. J. J. C. o. r. (2020). Protect, repair, and regenerate: towards restoring vision in glaucoma. *8*, 301-310.
54. Yadav, K. S., Sharma, S., & Londhe, V. Y. J. L. s. (2020). Bio-tactics for neuroprotection of retinal ganglion cells in the treatment of glaucoma. *243*, 117303.
55. Yang, M., So, K.-F., Lam, W.-C., & Lo, A. C. Y. J. N. R. R. (2023). Ferroptosis and glaucoma: implications in retinal ganglion cell damage and optic nerve survival. *18*(3), 545-546.
56. Yang, Y., & Sun, X. J. C. E. R. (2023). Retinal ganglion cell death in glaucoma: advances and caveats. *48*(1), 1-10.
57. Zhao, W.-j., Fan, C.-l., Hu, X.-m., Ban, X.-x., Wan, H., He, Y., . . . Neurobiology, M. (2023). Regulated cell death of retinal ganglion cells in glaucoma: molecular insights and therapeutic potentials. *43*(7), 3161-3178.
58. Zhu, Y., Zhang, L., Schmidt, J. F., & Gidday, J. M. J. M. M. (2012). Glaucoma-induced degeneration of retinal ganglion cells prevented by hypoxic preconditioning: a model of glaucoma tolerance. *18*, 697-706.