Current Ophthalmology Reports (2024) 12:23–29
https://doi.org/10.1007/s40135-024-00323-4

Traumatic Optic Neuropathy: Challenges and Opportunities in Developing Neuroprotective and Neuroregenerative Therapies

Nicole Y. Tsai[1] · Ryan A. Gallo[2] · Daniel Pelaez[3] · David T. Tse[3] · Benyam Kinde[4]

Accepted: 16 April 2024 / Published online: 30 April 2024

Abstract

Purpose of Review Traumatic optic neuropathy (TON) is a devasting disorder that can result in irreversible vision loss. Understanding the current research to promote neuroprotection and neuroregeneration of the optic nerve after injury may shed light on promising therapeutic avenues.

Recent Findings With evolving methods to model traumatic optic neuropathy, recent work manipulating signal transduction and cell damage response pathways reveals new clinical opportunities for patients with traumatic injury to the optic nerve.

Summary Despite years of basic science and clinical research, no treatment for TON exists. The absence of therapies highlights the importance of a comprehensive understanding of molecular pathways involved in retinal ganglion cell survival. Promising therapeutic opportunities may arise from a multi-pronged approach, targeting multiple pathways simultaneously in this complex disease.

Keywords Traumatic optic neuropathy · Retinal ganglion cell death · Neuroprotection

Introduction

Traumatic optic neuropathy (TON) can occur after head or face trauma. TON is relatively rare, with an estimated incidence of 1 in 1 million individuals in a UK study [1]. The majority of injuries occur in men (~ 80%) with a median age of 31 years. Trauma most commonly occurs in the setting of motor vehicle accidents, falls, or assaults. Visual acuity at presentation is a strong predictor of visual outcome, and there is no improvement in final visual acuity in patients who have received corticosteroid therapy or underwent optic canal decompression [2•].

After a traumatic injury to the optic nerve, it has been suggested that a combination of events ultimately leads to retinal ganglion cell (RGC) death. Deficits in axonal transportation, local inflammatory responses, excitotoxicity, oxidative stress, and DNA damage contribute to Wallerian degeneration, RGC dysfunction, and cell death [3–8]. With an inability to regenerate, apoptotic RGCs result in irreversible vision loss.

This review reviews the current state of optic nerve protection and regeneration research related to traumatic optic neuropathy. We assess in vitro, ex vivo, and in vivo models for investigating traumatic optic neuropathy. We summarize investigations into the molecular mechanisms underlying traumatic optic neuropathy and discuss scientific and clinical challenges that make developing clinically meaningful therapies elusive.

Models of Traumatic Optic Neuropathy

In Vitro and Ex Vivo Models

In vitro models offer a faster and simpler way to investigate RGC death mechanisms in a controlled environment. Although primary and human-induced pluripotent stem cell (hiPSC)-derived RGC cultures do not fully replicate the intricacies of optic neuropathies, they help screen potential neuroprotective

✉ Benyam Kinde
bkinde@stanford.edu

[1] Department of Ophthalmology, University of California San Francisco, San Francisco, CA, USA

[2] University of Miami Miller School of Medicine, Miami, FL, USA

[3] Dr. Nasser Ibrahim Al-Rashid Orbital Vision Research Center, Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami, Miami, FL, USA

[4] Spencer Center for Vision Research, 2370 Watson Court, Palo Alto, CA, USA

or regenerative factors and develop cell-based therapies [9–12]. Müller glia (MG) in some species reprogram to a progenitor state after injury to regenerate the retina, which has inspired research into reprogramming mammalian MG into RGCs for optic neuropathies [13–15]. However, a drawback of dissociated cell culture systems is the lack of cell–cell interactions and retinal laminar organization. Primary RGCs are also typically derived from early-born animals. hiPSC-derived retinal organoids form three-dimensional laminar structures with all retinal cell types but lack full maturity, vasculature, and immune cells.

Organotypic retinal explants have been employed to study mature RGCs with conserved histotypic context to overcome the limitations of in vitro models. Rodent and human organotypic retinal cultures have been described and used to study retinal development and disease. Explants of rodent retinas after optic nerve injury have been used to test neuroprotective and regenerative strategies [16–18]. However, the wide variety of culture methods employed can lead to variations in tissue behavior.

Direct Traumatic Optic Neuropathy Mouse Models

Crush and complete or partial transection of the optic nerve are invasive approaches used to investigate RGC axonal degeneration, death, and survival [19–21]. These methods have been used to evaluate factors that can inhibit or delay RGC death or promote regeneration. Optic nerve crush (ONC) and transection closely mimic the clinical scenario of direct TON, which occurs when a foreign body or bone fragment directly damages the optic nerve. The intensity and speed of RGC degeneration vary depending on the force and duration applied by forceps in ONC, the location on the optic nerve, and the mouse strain used, leading to potential bias in experimental results [22, 23]. Calibrated ONC models have been developed to quantify the force applied with greater precision and reduce injury variability [24].

The controlled orbital impact (COI) model is a minimally invasive model of direct TON, where an incision is made at the medial canthus, and the eyeball is retracted from the orbital margin to expose the intraorbital portion of the optic nerve for controlled trauma by an automated blunt impactor [25]. A specialized stereotaxic apparatus is required to control injury velocity, contusion depth, and dwell time. The contralateral optic nerve remains unaffected, and injury-associated mortality and ocular comorbidity are rare.

ONC and transection are also widely used methods to study glaucoma, although these models only partially mimic the pathophysiology of the disease. Glaucoma is a group of chronic, progressive eye diseases characterized by RGC axon degeneration and death, leading to irreversible visual impairment or blindness. Like TON, glaucoma is an axonal damage-mediated process, although the injury likely occurs at the optic nerve head itself [26]. ONC and transection are reliable injury methods for inducing rapid RGC degeneration and death. However, caution should be exercised when extrapolating findings from these acute models to the more insidious process of glaucomatous degeneration. In addition, these models inflict a more severe insult than chronic glaucoma models [22]. Given that elevated intraocular pressure is a significant glaucoma risk factor, other animal models have been developed to induce ocular hypertension, such as microbead injection, silicone oil-induced, and genetic (DBA/2 J) models [27, 28]. Although TON and glaucoma lead to RGC axon degeneration and death, the underlying pathophysiology likely differs significantly.

Indirect Traumatic Optic Neuropathy Mouse Models

Indirect TON often follows non-penetrating (blunt) traumatic brain injury or primary ocular trauma, likely due to the transmission of compressive forces to the orbital apex and optical canal that results in ischemia, edema, or RGC axon shearing [29, 30]. Mouse models using blunt skull trauma, ocular blast injury, and focal sonication-induced injury have been developed to investigate indirect TON.

The closed-head, single-impact weight-drop model of traumatic brain injury (TBI) creates reproducible optic nerve trauma with associated microglial activation, astrogliosis, and axonal degeneration [31]. Approximately a 10% mortality rate occurred immediately after injury. The repetitive mild traumatic brain injury (r-mTBI) model uses an electromagnetic coil-based device to deliver a controlled injury to the central mouse skull, causing RGC degeneration across the entire retina and functional decline in both eyes equally and simultaneously within three weeks [32, 33]. This model requires a specialized stereotaxic setup to control strike velocity, depth, and dwell time, allowing for a broad and reproducible range of injuries. Motor and cognitive impairments are observed in both TBI models [34, 35].

The ocular blast model delivers controlled injury directly to an exposed eye via a paintball gun while the rest of the mouse is protected in a rigid tube[36]. This model provides simple and easily modifiable injury without direct contact. However, this model carries risks of severe anterior and posterior segment ocular injuries and a high mortality rate of 24–46%, which is likely due to blast wave-induced brain damage. Proper animal positioning in the protective tube mitigates ocular comorbidities that confound optic nerve findings.

The sonication-induced TON (SI-TON) model utilizes a sonifer to deliver a tunable and focal ultrasonic pulse through the supraorbital ridge to the optic nerve without invasive surgery [37]. Trials at 60 and 80 Joules revealed no orbital fractures, globe injuries, or mortalities. SI-TON leads to significantly reduced RGC numbers in the central and middle retina and a significantly reduced RGC function in the affected eye after one week. However, the scatter of ultrasound energy from the primary injury site results in delayed neuropathic progression in the contralateral optic

nerve, making it an unsuitable control. Proper positioning of the sonifer is vital to avoid inconsistent injuries or ocular comorbidities.

Large Animal Models

Nonrodent mammalian species are essential for facilitating clinical translation. Rhesus macaques are genetically similar to humans and have a similar visual system as well [38, 39]. Studies involving complete or partial optic nerve transection in rabbits and monkeys and ONC in squirrels, goats, and monkeys mirror the histopathological and functional changes seen after direct TON [40–43]. Large animal models also enable trials of potential therapeutic interventions otherwise unfeasible in rodent models, such as trans-nasal endoscopy approaches [44].

Molecular Investigation into the Pathophysiology of Traumatic Optic Neuropathy

As part of the central nervous system, mature RGCs possess reduced capacity to regenerate their axons after traumatic injury, resulting in irreversible vision loss. The mainstay of research has been to find interventions to boost neuron intrinsic regulators of survival and regeneration as well as extrinsic factors to provide a permissive environment for regrowth.

Here, we will overview experimental research targeting RGC intrinsic mediators of neuroprotection and regeneration. Neuroprotection encompasses administering therapies to halt the progression of vision loss, and regeneration entails regrowing axons and forming new eye-brain connections to support vision restoration.

Manipulation of Signal Transduction Pathways

PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway has been the subject of intense study within the axon regeneration field for the past two decades. The highly conserved pathway activates the kinase mTOR to regulate cell cycling and growth. Genetic deletion of PTEN, a master regulator inhibiting the mTOR pathway, continues to be one of the most potent single interventions for stimulating RGC axon regrowth, with axons regenerating up to the optic chiasm after ONC [45•]. Modulation of downstream players within the mTOR pathway, including CNTF/LIF [46], IGF-1, and SPP1 activation [47] as well as deletion of the negative inhibitor TSC1 [45•], has also been found to increase RGC survival and axon regrowth, albeit not to the same extent as PTEN deletion.

JAK/STAT Pathway

The JAK/STAT pathway, another highly conserved signaling cascade pathway, concludes with activation of the STAT transcription factor family, which binds to DNA sequences and modulates gene expression. Among the seven STAT proteins in mammals, STAT3 activation is most important for axonal regeneration. Conditional deletion of SOCS3, a JAK/STAT inhibitor, improves RGC survival and axon regeneration and has been coupled with PTEN deletion and CNTF overexpression to induce more dramatic axon outgrowth past the optic chiasm following ONC [48]. Moreover, in a model of distal optic nerve injury, PTEN/SOCS3 co-deletion, as well as SPP1/IGF1/CNTF co-overexpression, were sufficient to induce RGC axon regrowth and functional synapse formation within the superior colliculus [49]. Subsequent studies leveraging high-throughput single-cell RNA sequencing have shed light on the transcriptional changes following each of these perturbations in isolation and in combination [50•, 51].

DLK/LZK Pathway

In RGCs, the kinase DLK and LZK are upregulated at the site of axonal injury and retrogradely transported to the soma, where they trigger cell death through activating transcription factors, including JUN, KLF6, ATF3, and SOX11 [11, 52]. While the DLK signaling cascade initiates cell death in RGCs, the pathway has been considered a "double-edged sword" since it also mediates regenerative responses [52]. Co-deletion of DLK and LZK as well as DLK inhibition by the small molecule sunitinib has been found to increase RGC survival [53, 54]; however, axon regrowth is substantially reduced and remains suppressed even with PTEN deletion. Therefore, the DLK/LZK pathway is more commonly thought to signal axonal injury rather than be responsible for neuronal survival or regeneration.

Interestingly, in an impact acceleration model of traumatic brain injury, which is more analogous to a TON of the eye, many RGCs were able to terminate activation of DLK/LZK signaling and survive following injury [54]. This stands in contrast to axotomy, in which RGCs cannot recover and require combined DLK and LZK inhibition to prevent cell death [54]. This finding underscores the importance of closely modeling the injury types seen in TON.

Cell Damage Response Pathways

Mitochondrial/Oxidative Phosphorylation Manipulation

Mitochondria synthesize energy in living cells through oxidative phosphorylation and produce reactive oxygen species (ROS) as a byproduct. Under cell stress conditions,

excess ROS levels accumulate to activate BAX-dependent pathways. Activation of BAX culminates in increased mitochondrial membrane permeability and release of mitochondrial components (such as cytochrome c) into the cytoplasm to initiate apoptosis. Models of traumatic optic injury have shown that ROS levels in RGCs significantly increase as much as over 50% in 2–4 weeks following blast injury [55]. As such, antioxidants and small molecules to improve mitochondrial health, reduce ROS formation, and prevent apoptosis signaling have seen significant interest as potential therapies. Erythropoietin [56], which possesses antioxidant properties, Vitamin E [55], and small molecules to reduce ROS formation, including elamipretide [5] and resveratrol [57], have demonstrated increased RGC survival. Ketogenic and antioxidant-rich diets have also been shown to promote modest neuroprotection following ONC [55, 58]. Furthermore, steroids, which have been historically used to stabilize vision following TON, have been thought to exert neuroprotective effects through their antioxidant properties [59]. Another more recent approach under investigation has been to introduce exogenous healthy mitochondria into stressed RGCs, with the thought that these mitochondria will reduce oxidative dysfunction: transplantation of mitochondria isolated from the liver into RGCs was shown to modestly increase RGC survival and axon regeneration following ONC [60].

Studies have also investigated blocking downstream apoptotic pathways: cell death can be dramatically blocked following optic nerve injury by either BAX deletion or Bcl-2 overexpression, with nearly all RGCs surviving following ONC [61–63]. However, surviving RGCs enter a senescent state: RGC-specific gene markers are downregulated in these mice, and surviving cells cannot regenerate their axons and no longer functionally behave as RGCs [61, 62].

ER Stress

Following disease or injury, unfolded proteins accumulate in the ER, triggering the unfolded protein response and activating three main ER stress pathways initiated by the ER stress sensors: IRE1, PERK, and ATF6. Studies have shown that the PERK-eIF2α-ATF4-CHOP pathway is involved in RGC death and axon degeneration, while the IRE1α-XBP1 pathway is neuroprotective [64]. Many small molecules targeting the ER stress response pathway with encouraging pre-clinical data have been reported and are reviewed in greater detail elsewhere [65]. Perhaps most strikingly, the peIF2α inhibitor ISRIB has been shown to reverse aspects of memory deficits in a mouse model of traumatic brain injury [66] and possess blood–brain barrier penetrance [65]. Moreover, retrobulbar injection of ISRIB was demonstrated to promote RGC and axon survival in a mouse glaucoma model [51].

DNA Damage Response

The ATM-Chk2 and ATR-Chk1 protein kinase cascades are central to the DNA damage response. These pathways trigger apoptosis or senescence in mature post-mitotic neurons in neurodegenerative disease [67]. Apart from chronic conditions, the DNA damage response has also more recently been implicated in responses to acute injury: Optic nerve crush has been shown to activate the DNA damage response, as reported by increases in the double-strand break marker γH2Ax both 1- and 24-days post-injury [7]. Furthermore, inhibition of the ATM-Chk2 pathway with the small molecules KU-60019 and mirin delivered through twice weekly injections immediately following ONC in rats resulted in > 90% RGC survival and significant RGC axon regeneration [7]. These improved outcomes were similarly seen following weekly treatment with the Chk1, and to a lesser extent Chk2, inhibitor prexasertib, which also led to improved RGC function as measured by electroretinography (ERG) [8]. What specific players in the ATM-Chk2/ATR-Chk1 pathways are activated following optic nerve injury to mediate RGC death remain incompletely understood and are the subject of increased research.

Reprogramming Factors

Recent studies employing gene therapy to revert RGCs to a youthful epigenetic state that is more permissive for regrowth have also shown encouraging preclinical results. Following optic nerve crush, ectopic expression of three of the four Yamanaka factors, OCT4, SOX2, and KLF4 (OSK), was shown to promote RGC survival and axon regrowth into the optic chiasm [68]. Moreover, partial recovery of visual acuity was seen in models of optic nerve crush, glaucoma, and aging [68]. A subsequent study applying the OSK factors to a nonhuman primate model of non-arteritic anterior ischemic optic neuropathy (NAION) has suggested that OSK treatment is translatable to primates as well: increased pattern ERG responses were seen following OSK treatment compared to controls [69]. While reprogramming factors and anti-aging research as a whole have seen great biopharmaceutical interest, more work is needed to characterize their safety profile and conceptually integrate these findings into what is previously known regarding signal transduction pathways in optic nerve regeneration. For example, STAT3 upregulation was seen following OSK treatment [68]; however, the degree to which other well-studied RGC-regeneration signaling pathways are affected remains unknown.

Therapeutic Hypothermia

The application of therapeutic hypothermia for neuroprotection stems from its use to improve neurological outcomes

following cardiac arrest; it is thought that slowing down metabolic processes through cooling reduces oxygen demands, thereby reducing hypoxic injury. While the use of therapeutic hypothermia for TBI remains less clear, preclinical studies applying therapeutic hypothermia for traumatic optic neuropathy have shown encouraging results: following ONC injury, hypothermic treatment given immediately afterward for 3 h increased visual acuity, RGC survival, and expression of pro-survival genes [70]. Recently, a hypothermia mimetic molecule (zr17-2) was also shown to improve RGC survival and electroretinography measures following ONC [71].

Clinical Considerations and Challenges

Though great strides have been made toward understanding and developing therapies for traumatic optic neuropathy, much work remains to be done. Regrowth of sufficient axons through the entire optic pathway to sustain meaningful visual recovery remains a major challenge. To date, long-distance regeneration of RGC axons has only been achieved through combinatorial strategies targeting multiple genes or pathways; studies perturbing multiple independent pathways prior to optic nerve injury have shown that pro-survival/pro-regenerative effects synergize and are more substantial than current single intervention manipulations. As such, while identifying new factors within novel signaling pathways remains important, exploring optimal combinations of interventions based on their regulatory mechanisms should be considered and will be essential to explore.

Advances in sequencing technologies have aided in this endeavor: studies leveraging single-cell sequencing to re-explore the effects of previous interventions have led to the discovery of new mediators of neuronal survival and axon regeneration, as well as clarify the molecular effects of individual versus combinatorial interventions [50•, 51]. Integrating high-throughput CRISPR screens with multi-omics data has also uncovered what transcription factor networks regulate the RGC injury response [72]. With these large datasets, critical intricacies in how different RGC-types respond to injury and treatment has become more apparent. For instance, work profiling transcriptomic responses following ONC has demonstrated that RGC types differ in their innate resilience and regeneration potential. Furthermore, their responses to genetic manipulations greatly vary [50•].

Another challenge for translating interventions from the lab to the clinic has been that the most potent interventions have involved reactivating protooncogenes and perturbing master cell growth regulators. For example, a predominant strategy for boosting axon regeneration has been to combine PTEN deletion with additional growth-inducing interventions. Safety concerns regarding the risk of cancer also exist with the use of Yamanaka factors for epigenetic reprogramming. As for cell survival, BAX deletion resulted in nonfunctional RGC-like cells that survived but could not regenerate their axons and transmit visual information. Broadly reactivating these master regulator genes without regard to temporal control may be deleterious for retinal function and long-term health. Therefore, careful study of affected signaling pathways, functionality of RGCs after perturbation, and long-term health of the retina is warranted.

Timing

Next, the timing of each intervention requires further investigation: studies to date, namely genetic perturbations, primed RGCs for regrowth before the injury is given, which does not realistically capitulate what is seen in real-world situations. Finding an intervention that may be administered after injury and remains effective for preserving sight and restoring vision would be needed for clinical applicability.

Delivery

Another practical consideration once therapies reach greater maturity is the mode of delivery, whether through intraocular, infraorbital, or systemic means. Challenges shared across developing therapies for retinal disease include the fact that the blood-retina barrier precludes the delivery of many systemically delivered drugs. Furthermore, the inner limiting membrane is a barrier limiting the delivery of intravitreally injected drugs. The discovery of small molecules that may pass through these barriers or new modes of delivery would help circumvent this issue.

Presentation

Lastly, one consideration specific to studying traumatic optic neuropathy is its heterogeneous presentation. Unlike controlled models of injury, the degree to which the optic nerve and supporting structures are damaged, and the location of the injury, varies. Injuries closer to the eye as opposed to the brain are harder to treat, as RGC axons will need to regrow greater distances to reconnect to their targets. Furthermore, damage to blood vessels supplying the retina can result in ischemic damage and a decreased permissive environment for regrowth. Carefully stratifying patients and understanding to what degree the optic nerve has been damaged will be very important as therapies mature for use in the clinic. Furthermore, tailoring each experimental model of TON to clinical scenarios to determine therapy applicability will be essential.

Conclusion

The past decade has seen significant advances in understanding optic nerve injury. By better modeling the nuances of traumatic optic neuropathy and increasing understanding of the disease process, the field continues to advance and work toward therapies to address this unmet clinical need.

Author Contributions All authors wrote and reviewed the manuscript.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests The authors declare that they have no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Lee V, et al. Surveillance of traumatic optic neuropathy in the UK. Eye (Lond). 2010;24(2):240–50.
2.• Levin, L.A., et al. The treatment of traumatic optic neuropathy: The international optic nerve trauma study. Ophthalmology, 1999;106(7): 1268–77.**Findings from this study suggest no difference between observation, cortiocosteroid treatment, and optic canal decompression in the management of traumatic optic neuropathy**.
3. Risner ML, et al. Neuroprotection by Wld. Mol Neurodegener. 2021;16(1):36.
4. Berkelaar M, et al. Axotomy results in delayed death and apoptosis of retinal ganglion cells in adult rats. J Neurosci. 1994;14(7):4368–74.
5. Tse BC, et al. Mitochondrial targeted therapy with elamipretide (MTP-131) as an adjunct to tumor necrosis factor inhibition for traumatic optic neuropathy in the acute setting. Exp Eye Res. 2020;199:108178.
6. Tse BC, et al. Tumor necrosis factor inhibition in the acute management of traumatic optic neuropathy. Invest Ophthalmol Vis Sci. 2018;59(7):2905–12.
7. Tuxworth RI, et al. Attenuating the DNA damage response to double-strand breaks restores function in models of CNS neurodegeneration. Brain Commun. 2019;1(1):fcz005.
8. Taylor MJ, et al. Inhibition of Chk2 promotes neuroprotection, axon regeneration, and functional recovery after CNS injury. Sci Adv. 2022;8(37):eabq2611.
9. Kerrison JB, Zack DJ. Neurite outgrowth in retinal ganglion cell culture. Methods Mol Biol. 2007;356:427–34.
10. Welsbie DS, et al. Functional genomic screening identifies dual leucine zipper kinase as a key mediator of retinal ganglion cell death. Proc Natl Acad Sci U S A. 2013;110(10):4045–50.
11. Welsbie DS, et al. Enhanced functional genomic screening identifies novel mediators of dual leucine zipper kinase-dependent injury signaling in neurons. Neuron. 2017;94(6):1142–54 e6.
12. Agarwal D, et al. Human retinal ganglion cell neurons generated by synchronous BMP inhibition and transcription factor mediated reprogramming. NPJ Regen Med. 2023;8(1):55.
13. Raymond PA, et al. Molecular characterization of retinal stem cells and their niches in adult zebrafish. BMC Dev Biol. 2006;6:36.
14. Langhe R, et al. Muller glial cell reactivation in Xenopus models of retinal degeneration. Glia. 2017;65(8):1333–49.
15. Singhal S, et al. Human Muller glia with stem cell characteristics differentiate into retinal ganglion cell (RGC) precursors in vitro and partially restore RGC function in vivo following transplantation. Stem Cells Transl Med. 2012;1(3):188–99.
16. Bull ND, et al. Use of an adult rat retinal explant model for screening of potential retinal ganglion cell neuroprotective therapies. Invest Ophthalmol Vis Sci. 2011;52(6):3309–20.
17. Stutzki H, et al. Inflammatory stimulation preserves physiological properties of retinal ganglion cells after optic nerve injury. Front Cell Neurosci. 2014;8:38.
18. Cen LP, et al. Human periodontal ligament-derived stem cells promote retinal ganglion cell survival and axon regeneration after optic nerve injury. Stem Cells. 2018;36(6):844–55.
19. Barron KD, et al. Qualitative and quantitative ultrastructural observations on retinal ganglion cell layer of rat after intraorbital optic nerve crush. J Neurocytol. 1986;15(3):345–62.
20. Aguayo AJ, et al. Degenerative and regenerative responses of injured neurons in the central nervous system of adult mammals. Philos Trans R Soc Lond B Biol Sci. 1991;331(1261):337–43.
21. Galindo-Romero C, et al. Axotomy-induced retinal ganglion cell death in adult mice: quantitative and topographic time course analyses. Exp Eye Res. 2011;92(5):377–87.
22. Kalesnykas G, et al. Retinal ganglion cell morphology after optic nerve crush and experimental glaucoma. Invest Ophthalmol Vis Sci. 2012;53(7):3847–57.
23. Tran NM, et al. Single-cell profiles of retinal ganglion cells differing in resilience to injury reveal neuroprotective genes. Neuron. 2019;104(6):1039–55 e12.
24. Liu X, et al. Correlation between retinal ganglion cell loss and nerve crush force-impulse established with instrumented tweezers in mice. Neurol Res. 2020;42(5):379–86.
25. Ibrahim AS, et al. A controlled impact of optic nerve as a new model of traumatic optic neuropathy in mouse. Invest Ophthalmol Vis Sci. 2018;59(13):5548–57.
26. Howell GR, et al. Axons of retinal ganglion cells are insulted in the optic nerve early in DBA/2J glaucoma. J Cell Biol. 2007;179(7):1523–37.
27. Sappington RM, et al. The microbead occlusion model: a paradigm for induced ocular hypertension in rats and mice. Invest Ophthalmol Vis Sci. 2010;51(1):207–16.
28. Zhang J, et al. Silicone oil-induced ocular hypertension and glaucomatous neurodegeneration in mouse. Elife 2019;8:e45881.
29. Anderson RL, Panje WR, Gross CE. Optic nerve blindness following blunt forehead trauma. Ophthalmology. 1982;89(5):445–55.

30. Crompton MR. Visual lesions in closed head injury. Brain. 1970;93(4):785–92.
31. Evanson NK, et al. Optic tract injury after closed head traumatic brain injury in mice: A model of indirect traumatic optic neuropathy. PLoS One. 2018;13(5):e0197346.
32. Tzekov R, et al. Repetitive mild traumatic brain injury causes optic nerve and retinal damage in a mouse model. J Neuropathol Exp Neurol. 2014;73(4):345–61.
33. Khan RS, et al. RGC and vision loss from traumatic optic neuropathy induced by repetitive closed head trauma is dependent on timing and force of impact. Transl Vis Sci Technol. 2021;10(1):8.
34. Yang SH, et al. A murine model of mild traumatic brain injury exhibiting cognitive and motor deficits. J Surg Res. 2013;184(2):981–8.
35. Mouzon B, et al. Repetitive mild traumatic brain injury in a mouse model produces learning and memory deficits accompanied by histological changes. J Neurotrauma. 2012;29(18):2761–73.
36. Hines-Beard J, et al. A mouse model of ocular blast injury that induces closed globe anterior and posterior pole damage. Exp Eye Res. 2012;99:63–70.
37. Tao W, et al. A novel mouse model of traumatic optic neuropathy using external ultrasound energy to achieve focal, indirect optic nerve injury. Sci Rep. 2017;7(1):11779.
38. Yan G, et al. Genome sequencing and comparison of two nonhuman primate animal models, the cynomolgus and Chinese rhesus macaques. Nat Biotechnol. 2011;29(11):1019–23.
39. Lin KH, et al. Advanced retinal imaging and ocular parameters of the rhesus macaque eye. Transl Vis Sci Technol. 2021;10(6):7.
40. Scherer J, Schnitzer J. Intraorbital transection of the rabbit optic nerve: consequences for ganglion cells and neuroglia in the retina. J Comp Neurol. 1991;312(2):175–92.
41. Levkovitch-Verbin H, et al. Optic nerve transection in monkeys may result in secondary degeneration of retinal ganglion cells. Invest Ophthalmol Vis Sci. 2001;42(5):975–82.
42. Xiao X, et al. Establishing the ground squirrel as a superb model for retinal ganglion cell disorders and optic neuropathies. Lab Invest. 2021;101(9):1289–303.
43. Zhang Y, et al. In vivo evaluation of retinal ganglion cells and optic nerve's integrity in large animals by multi-modality analysis. Exp Eye Res. 2020;197:108117.
44. Zhang Y, et al. Cold protection allows local cryotherapy in a clinical-relevant model of traumatic optic neuropathy. Elife 2022;11:e75070.
45.• Park, K.K., et al. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. Science 2008;322(5903):963–6.**A seminal paper which was first to demonstrate that genetic deletion of PTEN, a master regulator of the mTOR pathway, is a potent method for stimulating RGC regrowth**.
46. L. Xie, Y. Yin, L. Benowitz Chemokine CCL5 promotes robust optic nerve regeneration and mediates many of the effects of CNTF gene therapy. Proc Natl Acad Sci U S A, 2021;118(9):e2017282118.
47. Duan X, et al. Subtype-specific regeneration of retinal ganglion cells following axotomy: effects of osteopontin and mTOR signaling. Neuron. 2015;85(6):1244–56.
48. Sun F, et al. Sustained axon regeneration induced by co-deletion of PTEN and SOCS3. Nature. 2011;480(7377):372–5.
49. Bei F, et al. Restoration of visual function by enhancing conduction in regenerated axons. Cell. 2016;164(1–2):219–32.
50.• Jacobi, A., et al. Overlapping transcriptional programs promote survival and axonal regeneration of injured retinal ganglion cells. Neuron 2022;110(16):2625–2645 e7.**Single-cell RNA sequencing after manipulating the expression of PTEN, SOCS3 and CNTF levels resulted in increased RGC survival and regeneration and overlapping transcriptional programs after optic nerve injury**.
51. Fang F, et al. RGC-specific ATF4 and/or CHOP deletion rescues glaucomatous neurodegeneration and visual function. Mol Ther Nucleic Acids. 2023;33:286–95.
52. Tedeschi A, Bradke F. The DLK signalling pathway–a double-edged sword in neural development and regeneration. EMBO Rep. 2013;14(7):605–14.
53. Watkins TA, et al. DLK initiates a transcriptional program that couples apoptotic and regenerative responses to axonal injury. Proc Natl Acad Sci U S A. 2013;110(10):4039–44.
54. Welsbie DS, et al. Targeted disruption of dual leucine zipper kinase and leucine zipper kinase promotes neuronal survival in a model of diffuse traumatic brain injury. Mol Neurodegener. 2019;14(1):44.
55. Bernardo-Colon A, et al. Antioxidants prevent inflammation and preserve the optic projection and visual function in experimental neurotrauma. Cell Death Dis. 2018;9(11):1097.
56. Kashkouli MB, et al. Erythropoietin: a novel treatment for traumatic optic neuropathy-a pilot study. Graefes Arch Clin Exp Ophthalmol. 2011;249(5):731–6.
57. Kim SH, et al. The neuroprotective effect of resveratrol on retinal ganglion cells after optic nerve transection. Mol Vis. 2013;19:1667–76.
58. Venanzi AW, et al. Context-dependent effects of the ketogenic diet on retinal ganglion cell survival and axonal regeneration after optic nerve injury. J Ocul Pharmacol Ther. 2023;39(8):509–18.
59. Yu-Wai-Man P, Griffiths PG. Steroids for traumatic optic neuropathy. Cochrane Database Syst Rev. 2013;2013(6):CD006032.
60. Nascimento-Dos-Santos G, et al. Neuroprotection from optic nerve injury and modulation of oxidative metabolism by transplantation of active mitochondria to the retina. Biochim Biophys Acta Mol Basis Dis. 2020;1866(5):165686.
61. Donahue RJ, et al. BAX-depleted retinal ganglion cells survive and become quiescent following optic nerve damage. Mol Neurobiol. 2020;57(2):1070–84.
62. Chierzi S, et al. Optic nerve crush: axonal responses in wild-type and bcl-2 transgenic mice. J Neurosci. 1999;19(19):8367–76.
63. Maes ME, Schlamp CL, Nickells RW. BAX to basics: How the BCL2 gene family controls the death of retinal ganglion cells. Prog Retin Eye Res. 2017;57:1–25.
64. Hu Y, et al. Differential effects of unfolded protein response pathways on axon injury-induced death of retinal ganglion cells. Neuron. 2012;73(3):445–52.
65. Chu HS, et al. Targeting the integrated stress response in ophthalmology. Curr Eye Res. 2021;46(8):1075–88.
66. Chou A, et al. Inhibition of the integrated stress response reverses cognitive deficits after traumatic brain injury. Proc Natl Acad Sci U S A. 2017;114(31):E6420–6.
67. Konopka A, Atkin JD. The role of DNA damage in neural plasticity in physiology and neurodegeneration. Front Cell Neurosci. 2022;16:836885.
68. Lu Y, et al. Reprogramming to recover youthful epigenetic information and restore vision. Nature. 2020;588(7836):124–9.
69. Ksander B, et al. Epigenetic reprogramming- A novel gene therapy that restores vision loss in a nonhuman primate model of NAION. Invest Ophthalmol Vis Sci. 2023;64(8):474–474.
70. Rey-Funes M, et al. Hypothermia prevents retinal damage generated by optic nerve trauma in the rat. Sci Rep. 2017;7(1):6966.
71. Contartese DS, et al. A hypothermia mimetic molecule (zr17-2) reduces ganglion cell death and electroretinogram distortion in a rat model of intraorbital optic nerve crush (IONC). Front Pharmacol. 2023;14:1112318.
72. Tian F, et al. Core transcription programs controlling injury-induced neurodegeneration of retinal ganglion cells. Neuron. 2022;110(16):2607–24 e8.