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Contents lists available at Lighthouse Scholar

EYE SCIENCE

journal homepage: journal.gzzoc. com

doi: 10.12419/es24071101
View this article at: https://dx.doi.org/10.12419/es24071101

· Review Article ·

Extrinsic regulation of optic nerve regeneration

Qi Zhang(张祺), Jiahui Tang(唐家辉), Zhe Liu(刘哲), Caiqing Wu(吴彩清), Canying Liu(刘灿瑛), Siting Wu(吴思婷), Yehong Zhuo(卓业鸿), Yiqing Li(李轶擎)

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangzhou 510060, China

HIGHLIGHTS

· The review emphasizes the role of extrinsic factors in regulating retinal ganglion cell (RGC) axon regeneration. Traditionally, glial cells and inflammation have been highlighted, but recent discoveries focus on retinal interneurons, specifically amacrine cells (ACs), as crucial regulators.

· Research methods have shifted to include investigation of the synaptic interactions between ACs and RGCs, offering new perspectives beyond traditional focus areas like glial scar inhibition and inflammatory response modulation.

· Modulating the inhibitory glial environment and managing inflammatory responses remain promising areas for intervention to enhance regenerative outcomes, while understanding the exact mechanism behind AC-mediated optic nerve injury will be crucial in designing effective treatments for optic nerve regeneration and restoring vision.

Abstract: Retinal ganglion cells (RGCs) extend through the optic nerve, connecting with neurons in visually related nuclei. Similar to most mature neurons in the central nervous system, once damaged, RGCs are unable to regenerate their axons and swiftly progress to cell death. In addition to cell-intrinsic mechanisms, extrinsic factors within the extracellular environment, notably glial and inflammatory cells, exert a pivotal role in modulating RGC neurodegeneration and regeneration. Moreover, burgeoning evidence suggests that retinal interneurons, specifically amacrine cells, exert a substantial influence on RGC survival and axon regeneration. In this review, we consolidate the present understanding of extrinsic factors implicated in RGC survival and axon regeneration, and deliberate on potential therapeutic strategies aimed at fostering optic nerve regeneration and restoring vision.

Keywords: retinal ganglion cells; optic nerve regeneration; myelin; glial scar; neuroinflammation; amacrine cells

Received date: 2024-05-11; **Accepted date:** 2024-06-04; **Published online:** 2024-06-18

Corresponding author: Yiqing Li, E-mail: liyiqing3@mail.sysu.edu.cn

Full Text

Cite this article as: Zhang Q, Tang JH, Liu Z, Wu CQ, Liu CY, Wu ST, Zhuo YH, Li YQ. Extrinsic regulation of optic nerve regeneration. Eye Science, 2024, 1(2): 1-22. DOI: 10.12419/es24071101.

INTRODUCTION

Retinal ganglion cells (RGCs) play a vital role in visual function, as their axons constitute the optic nerve, traversing from the retina through the optic chiasm to innervate brain nuclei.[1] The optic nerve's extensive journey from the retina to the brain makes it susceptible to numerous injuries.[2] Similar to most mature neurons in the central nervous system (CNS), RGCs cannot regenerate their axons upon damaged, frequently causing lasting visual deficits or blindness. Apart from cell-intrinsic mechanisms within RGCs, their regenerative failure is also modulated by multiple extrinsic factors.[3] Consequently, modifying the extrinsic environment of RGCs has become a key area of focus in optic nerve regeneration research.

Traditionally, glial and inflammatory cells have been regarded as the primary components of the extrinsic environment impacting optic nerve regeneration.[4-5] The glial environment, encompassing myelin and the glial scar, acts as a significant inhibitor of RGC axon regeneration, containing various inhibitory molecules derived from oligodendrocytes and reactive astrocytes.[5] Conversely, intraocular inflammation and its associated chemokines and neurotrophic factors are thought to stimulate RGCs to regenerate their axons after injury.[6] Recently, a novel concept has arisen, suggesting that the capacity of RGCs to regenerate axons is also affected by retinal interneurons within the extrinsic environment, particularly amacrine cells (ACs).[7] Unlike glial and inflammatory cells, ACs engage with RGCs through synaptic interactions.

In this review, we consolidate current understanding of extrinsic factors that influence optic nerve regeneration and delve into related therapeutic approaches aimed at enhancing this critical process.

GLIAL ENVIRONMENT

Myelin and Associated Inhibitors

Myelin plays a pivotal role in axonal insulation, facilitating rapid electrical signal conduction, and providing metabolic support within the adult nervous system.[8] In the peripheral nervous system, Schwann cells are responsible for producing myelin and actively promoting axon regeneration after injury. Conversely, in the CNS, oligodendrocytes generate myelin barriers that impede axon regeneration by releasing myelin-associated inhibitors (MAIs), such as Nogo, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp).[9-12] Although structurally distinct, these molecules share the capacity to bind two common receptors: Nogo receptor (NgR) and immunoglobulin-like receptor B (PirB).[13-14] NgR1, expressed by virtually all RGCs, forms a signaling complex with LINGO-1 and either p75NTR or TROY.[15-18] While NgR2 exhibits a stronger binding affinity for MAG compared to NgR1, NgR3 may act as a co-receptor.[19] The interaction of these molecules with receptors on RGC axons disrupts the actin cytoskeleton, causes growth cones collapses, and obstructs axon regeneration (Figure 1).

Genetic interventions aimed at MAIs have revealed that triple knockout mice (Nogo-A, MAG, OMgp) exhibit RGC axon regrowth post-injury, a phenomenon not observed in single or double knockouts, underscoring the prominent role of Nogo-A and the synergistic effects

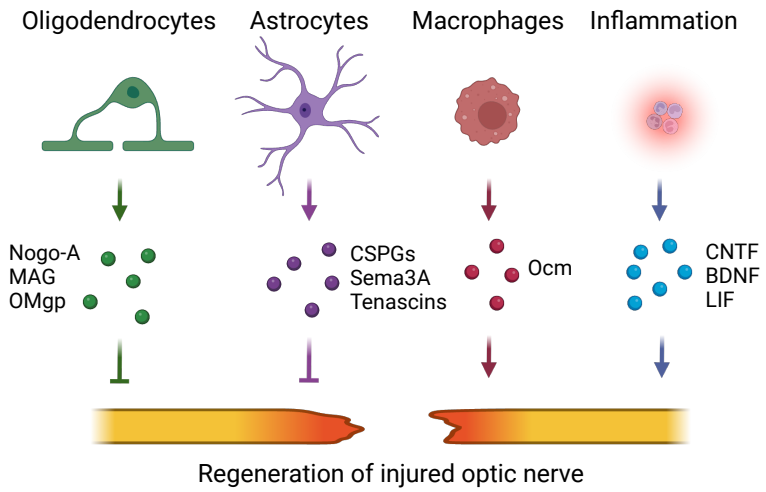

Figure 1 Schematic illustration of traditional extrinsic factors from glial and inflammatory cells that regulate optic nerve regeneration

MAIs, inhibitory molecules from glial scar, Ocm, and neurotrophic factors diversely regulate the post-injury regeneration of the optic nerve. BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; CSPGs, chondroitin sulfate proteoglycans; LIF, leukemia inhibitory factor; MAG, myelin-associated glycoprotein; Ocm, oncomodulin; OMgp, oligodendrocyte-myelin glycoprotein; Sema3A, semaphorin 3A.

of MAG and OMgp.[20-21] Selective deletion of Nogo-A in oligodendrocytes, while maintaining its expression in RGCs, has been shown to foster axon regeneration.[22] Furthermore, immunoblocking MAIs with antibodies, particularly Nogo-A antibodies, enhances RGC axon regeneration.[23-24] Manipulating receptors has also yielded promising results. For example, NgR knockout promotes optic nerve regeneration, and AAV-mediated expression of a dominant-negative NgR stimulates axon regrowth.[25-26] The endogenous NgR antagonist, LOTUS, is being investigated as a potential therapeutic target due to its ability to block MAI binding and promotes regeneration.[27-28] Interfering with PirB activity, through genetic manipulation or antibody treatment, has been found to partially mitigate myelin inhibition.[29] A recent study demonstrated that PirB knockdown in RGCs can disrupt inhibitory signals from the glial environment, thereby inducing optic nerve regeneration.[30]

In summary, myelin and its associated inhibitors pose significant barriers to axon regeneration wthin the CNS. By gaining insights into and targeting the molecular interactions between oligodendrocytes and RGCs, as well as modulating the receptors involved, it may be feasible to circumvent these inhibitory effects and foster optic nerve regeneration.

Glial Scar Forming at the Injury Sites

After injury, the adult CNS promptly initiates reactive astrogliosis or glial scarring as a means of protecting and repairing tissue.[31] However, this response also establishes a chemical barrier that hampers axon regeneration. Astrocytes, which are pivotal in supporting synapse development and plasticity, are responsible for forming these glial scars and depositing inhibitory molecules such as tenascins, semaphorins, ephrins, and notably chondroitin sulfate proteoglycans (CSPGs).[32-35] These molecules attach to specific receptors on RGCs, thereby impeding regeneration (Figure 1). The primary receptors that mediate CSPG inhibition encompass the transmembrane protein PTPσ, LAR phosphatase, along

with NgR1 and NgR3.[36] Neuropilin 1 and plexin A1 serve as co-receptors for Sema3A, triggering downstream signaling pathways that further inhibit regeneration.[37] Moreover, Integrin α9β1, a receptor that promotes neurite outgrowth and axon regeneration by binding to TN-C, is diminished or absent in the adult CNS following injury, thus nullifying TN-C's regenerative effects.[38]

Research has demonstrated that the enzyme chondroitinase ABC digests glycosaminoglycan side chains, effectively reducing CSPG inhibition and fostering RGC axon regeneration.[39] Genetic deletion of PTPσ and systemic administration of enoxaparin have also exhibited potential in augmenting axon regrowth.[40] Although intravitreal injection of anti-Sema3A antibodies has been observed to enhance RGC survival, its impact on axon regeneration is still being investigated. Nevertheless, miR-30b and Sema3A small interfering RNA have been proven to suppress Sema3A expression, significantly stimulating axon growth.[41-42] Studies on mice deficient in TN-C or TN-R, subjected to spinal cord injuries, have indicated increased axon penetration through the glial scar.[43] Furthermore, the re-expression of TN-C and the integrin activator kindlin-1 has been shown to promote axon regeneration in both the spinal cord and optic nerve.[44-45]

Overall, by targeting the inhibitory molecules associated with glial scarring and combining these approaches with other therapeutic interventions, there is considerable potential to enhance optic nerve regeneration and restore visual function.

Controversial Role of Microglia

Microglia, which originate from macrophages in the mammalian CNS, plays a crucial role in maintaining physiological homeostasis and responding to pathological conditions. However, their function in CNS repair following injury remains paradoxical.[46] The question of whether cytokines and neurotrophic factors released by microglia promote or hinder optic nerve regeneration remains unresolved. The ambiguity may stem, in part, from difficulties in distinguishing microglia from other immune cells.[47] A recent study introduced a novel CSF1R inhibitor that can eliminate over 99% of microglia without impacting macrophages or other immune cells.[48] Notably, intravitreal administration of this inhibitor did not significantly alter RGC degeneration or axon regeneration after injury. Yet, when microglia and macrophages were co-depleted, a slight but statistically significant inhibition of optic nerve regeneration was observed.[49] This finding suggests that while microglia participate in macrophage recruitment and phagocytosis, they may not be pivotal for RGC degeneration and axon regeneration in the context of acute optic nerve injury.

INFLAMMATION

Intraocular inflammation, whether induced by lens injury or zymosan injection, has been shown to delay RGC degeneration and enhance axon regeneration beyond optic nerve lesions, exerting a significant impact on neurological outcomes.[50-51] Macrophages and neutrophils, which are key immune cells that accumulate at the site of injury, engage interactions with RGCs *via* cytokines and neurotrophic factors, thereby modulating the process of axon regeneration (Figure 1).

Macrophages

Macrophages play a crucial role in converting the inhibitory environment at lesion sites into one that is conductive to regeneration.[52] Following lens injury or zymosan injection, increased macrophage levels are accompanied by the accumulation of oncomodulin

(Ocm), a calcium-binding protein that is released by activated macrophages and neutrophils.[53] Ocm interacts with RGCs in a cAMP-dependent manner, functioning as a potent growth factor that promotes axon regeneration.[54-55] Combination treatments utilizing Ocm alongside cAMP analogs have been found to mimic the regenerative effects of inflammation, whereas antibodies targeting Ocm neutralize these beneficial effects.[55] Recently, armadillo-repeat protein C10 (ArmC10) has been identified as the high-affinity receptor for Ocm. Genetic deletion of ArmC10 has been shown to inhibit inflammation-induced axon regeneration in the injured optic nerves of mice.[56]

Neutrophils

Neutrophils swiftly accumulate following injury, preceding the influx of macrophages in zymosan-induced intraocular inflammation, and are pivotal in promoting optic nerve regeneration. These cells exhibit elevated levels of Ocm, and their absense or neutralization with anti-Ocm intervention markedly diminishes regenerative effects, highlighting their essential collaboration with macrophages.[6] Inhibition studies implicate pattern recognition receptors as potential mediators of these effects.[57] Furthermore, the use of specific antibodies targeting distinct neutrophil subsets provide additional evidence for their contribution to axon regeneration.[58] A recently discovered subset of immature neutrophils has exhibited neuroprotective qualities, driving optic nerve regeneration *in vivo*, partially through the release of a blend of growth factors.[59] Moreover, a recent study demonstrated that transfer of IL-4/G-CSF-polarized bone marrow neutrophils into experimental models of optic nerve injury stimulates substantial axon regeneration.[60] Conversely, selective targeting of neutrophils with anti-Ly6G has also been found to safeguard the inflamed vasculature and augment RGC axon regeneration.[61]

Chemokines

Chemokine CXCL12, also known as stromal cell–derived factor 1 (SDF1), functions as a chemoattractant for axonal growth cones within an inhibitory milieu, thereby hindering the distal regeneration of growth-stimulated axons in the optic nerve. Specific deletion of the receptor CXCR4 in RGCs mitigates abnormal axonal growth and enhances long-distance regeneration.[62] Conversely, another study revealed that SDF1 synergizes potently with Ocm treatment, fostering the regeneration of a greater number of RGC axons.[63] Additionally, other chemokines, including CXCL2 and CX3CL1, have demonstrated their ability to support RGC survival and axon regeneration by modulating glial activation and inflammation.[64-65]

Neurotrophic Factors

Ciliary neurotrophic factor (CNTF) is a well-established and potent neurotrophic agent for treating optic nerve injury.[66] However, the administration of recombinant CNTF alone exhibits limited regenerative efficacy. It is noteworthy that the knockout of SOCS3 restores CNTF's regenerative potential.[67] Furthermore, AAV-mediated expression of CNTF promotes optic nerve regeneration independently through neuroinflammatory pathways that involving CCL5.[58] Recent advancements in CNTF delivery systems, such as the use of chitosan or thermosensitive hydrogels, have facilitated a steady and consistent release of CNTF, resulting in full-length optic nerve regeneration and, notably, visual function recovery.[62, 68] Additionally, leukemia inhibitory factor (LIF) synergizes with CNTF to enhance RGC survival and promote axon regeneration.[66] Conversely, brain-derived neurotrophic factor (BDNF) protects RGCs but

attenuates inflammation-induced axon regeneration.[69]

RETINAL INTERNEURONS

As previously discussed, the roles of glial and inflammatory cells in the context of optic nerve injury have been thoroughly investigated. However, another vital group of cells, the interneurons, which maintain close connections with RGCs, have been relatively overlooked. These interneurons interact primarily with RGCs *via* synapses, forming the intricate retinal circuits. In the mammalian retinal circuitry, photoreceptors convert light into neural signals, which they then transmit to interneurons. Within the outer plexiform layer, horizontal cells engage with photoreceptors, exerting feedback inhibition on photoreceptors and feedforward inhibition on bipolar cells (BCs).[70] In the inner plexiform layer, BCs establish excitatory synapses with over 40 distinct types of ganglion cells.[71] Various types of ACs modulate these synapses through both pre-synaptic and post-synaptic inhibition.

ACs, as the primary inhibitory interneurons within the retinal circuit, diminish RGC activity by releasing inhibitory neurotransmitters such as glycine, gamma-aminobutyric acid (GABA), and dopamine.[72] Nearly all ACs form inhibitory synapses with RGCs and can be categorized into two types: glycinergic narrow-field and GABAergic wide-field. Unlike typical neurons, ACs utilize the same dendrites for both receiving and transmitting signals to BCs, RGCs, and other ACs.[70]

Amacrine Cells-Mediated Optic Nerve Regeneration

To investigate the factors within the retina that influence the rapid decline of growth potential in neonatal RGCs, Goldberg and colleagues aged embryonic RGCs in culture, aligning their growth patterns with those of neonatal RGCs. Their findings revealed that embryonic RGCs do not inherently lose their growth capacity under these conditions. However, when these RGCs were aged within retinal explants or cultured with isolated ACs, their axon growth potential diminished significantly.[73] Furthermore, ACs were identified as crucial players in the proper patterning of RGC axon during development.[74] These studies revealed a contact-dependent mechanism through which ACs inhibit the growth of developing RGC axon in culture (Figure 2). While this conclusion merely skimmed the surface of the phenomenon, it hinted that this inhibition might encompass retinal interneurons apart beyond glial cells.

A decade later, direct evidence emerged regarding AC-regulated optic nerve regeneration. Reports indicated that ionic zinc (Zn^{2+}) accumulates in ACs processes promptly after optic nerve crush and continues to rise for the first 24 hours. Zn^{2+} is subsequently transferred to

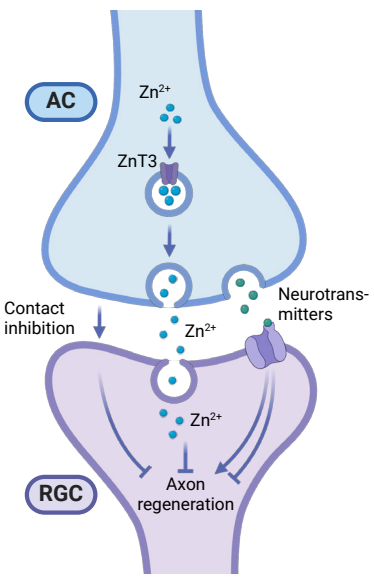

Figure 2 Schematic illustration of AC-mediated optic nerve regeneration

ACs regulate optic nerve regeneration through contact inhibition, presynaptic Zn^{2+} release, and various neurotransmitters. ACs, amacrine cells; RGCs, retinal ganglion cells.

RGCs *via* synaptic vesicular release, thereby suppressing RGC survival and axon regeneration (Figure 2).[75] By genetically deleting the Zn^{2+} transporter 3 (ZnT-3) or chelation with TPEN, Zn^{2+} release from ACs is reduced, promoting optic nerve regeneration and maintaining RGCs survival for 3 months. Additionally, Zn^{2+} chelation exhibits a potent synergistic effect when combined with canonical pro-regenerative manipulations, such as *Pten* knockout and *Klf9* knockout.[75-76]

Furthermore, a subsequent study revealed that ACs become hyperactive in response to RGC axon injury in adult mice. As the primary presynaptic source of inhibition for RGCs, this hyperactivity diminishes RGC electrical activity following injury. By preventing this AC-induced hyperinhibition — either through the overexpressing of inwardly rectifying K^+ channels or *via* intravitreal injections of a mixture containing GABA and glycine receptor blockers — RGC survival after ONC is enhanced, and modest axon regeneration is promoted (Figure 2).[77]

A recent study has pinpointed a distinct AC subtype, dopaminergic ACs (DACs), which play a role in the pathogenesis of optic nerve injury and regulate optic nerve regeneration. Following optic nerve injury, DACs respond promptly by decreasing their neuronal activity and reducing retinal dopamine release. Stimulating DACs with levodopa administration elevates dopamine release, ultimately fostering optic nerve regeneration (Figure 2).[78] However, despite several theories summarizing the mechanisms underlying AC-RGC interactions in optic nerve regeneration, these mechanisms remain largely unknown.

Antagonistic Axon-Dendrite Interplay

The first theory revolves around the antagonist interplay between axons and dendrites, proposing that dendritic synapses connecting adult RGCs to ACs hinder axon regeneration. In adult zebrafish, renowned for their ability to regenerate CNS axons, RGCs exhibit rapid synapse degeneration and dendrite retraction after optic nerve crush. Axon regeneration only commences following substantial dendrite shrinkage, with dendritic regrowth taking place once axons reconnect with target neurons in the optic tectum. This finding implies a competitive dynamic between axonal and dendritic processes.[79] Additional studies also suggest that impeding dendrite shrinkage obstructs axon regeneration. For instance, inhibiting mTOR with rapamycin shortly after ONC preserves synapses and dendrites but impedes axon regeneration. However, postponing rapamycin treatment until after synapse and dendrite deterioration has occurred does not impact regeneration, indicating that dendrite shrinkage may actually facilitate axon regrowth.[80]

In mammals, although dendrite shrinkage may pave the way for axon regrowth, they typically fail to regenerate axons due to inhibitory surroundings. Signals emanating from ACs can redirect neonatal RGCs from an axon growth mode to a dendrite growth mode. Treatments with CNTF, cAMP analogs, or the Rho-GTPase inhibitor BA-210 enhance RGC survival and axon regeneration but result in abnormal dendritic structures.[81-83] In a DLK knockout background, severing dendrites promotes axon regeneration, and in C. elegans, axon regeneration is augmented when dendritomy accompanies axotomy.[84-85]

Overall, the retraction of RGC dendrite from synaptic connections with interneurons appears to facilitate axon regeneration and nerve repair. Nevertheless, further research is required to substantiate this antagonistic interplay and the precise role of synaptic inhibition in the context of optic nerve regeneration.

Inhibitory Neurotransmitter

The second theory emphasizes the significance of various neurotransmitters released by ACs, which may play a pivotal role in the pathophysiological mechanisms underlying optic nerve injury. Neurotransmitter diversity is crucial for the intricacy and functionality of neuronal communication. Within retinal circuits, RGC dendrites possess receptors for glycine, GABA-A, and dopamine, which convey inhibitory signals from ACs, whereas BC axon terminals harbor glycine and GABA-C receptors for AC-mediated inhibition.[86] These inhibitory neurotransmitters and their receptors represent potential therapeutic avenues in the aftermath of optic nerve injury.

In the context of spinal cord injury, there is an elevation of aminoacidergic neurotransmitters (glycine, GABA, glutamate), with excessive glutamate and glycine contributing to excitotoxicity, while GABA fosters neuron survival and regeneration.[87-89] Although this phenomenon has been less explored in mammals and optic nerve injury, some evidence indicates that inhibitory neurotransmitters also influence regeneration. Following ONC, the adminstration of antagonists for inhibitory neurotransmitter receptors into the vitreous body enhances RGC responsiveness to growth factors and promotes axon regeneration, notably with IGF-1, owing to the preservation of IGF-1 receptors in RGC primary cilia.[77]

RGC activity, modulated by neurotransmitters released from ACs, impacts their growth state. Studies have demonstrated that increased electrical activity enhances BDNF-induced axon outgrowth in immature RGCs.[90] Additionally, light stimulation or transcorneal electrical stimulation has been found to stimulate RGC axon regeneration.[91] When visual stimulation or chemogenetics are combined with mTOR activation, they can enhance complete optic nerve regeneration and partially restore visual functions and behaviors.[92-93] RGC activation and depolarization result in the inlux of Ca^{2+}, initiating activity-dependent transcription and elevating cAMP levels. This process promotes the expression of growth-related genes and establishes a link between neuronal activity and regeneration.[94-95]

In conclusion, further research is required to clarify the specific roles of neurotransmitters in optic nerve injury, including their protective or neurotoxic effects, the receptors they bind to, and their downstream signaling pathways.

Other Synaptic Vesicular Contents

The third theory delves into other synaptic vesicular components, with a particular emphasis on Zn^{2+}. Following ONC, Zn^{2+} levels surge in ACs and are subsequently transferred to RGCs through synaptic vesicular release. Eliminating ZnT-3, which diminishes Zn^{2+} accumulation within AC vesicles, has been shown to enhance axon regeneration.[75] Furthermore, the production of nitric oxide (NO) specific to ACs may aid in the accumulation of mobile Zn^{2+} in ACs after injury. Upon RGC axon injury, ACs exhibit hyperactive, resulting in Ca^{2+} influx and the subsequent production of NO production *via* NO synthetase activation.[96] This sequence generates reactive nitrogen species, leading to oxidative stress and the release of Zn^{2+} from metallothioneins, thereby elevating mobile Zn^{2+} levels in ACs.[97-98]

SUMMARY

This review centers on the extrinsic regulation of optic nerve regeneration, with a focus on the intricate interactions between RGCs and their surrounding

environment. While glial and inflammatory cells are well-recognized extrinsic factors that impact optic nerve regeneration, recent findings underscore the crucial role of ACs in regulating RGC survival and axon regeneration. Following optic nerve injury, ACs become hyperactivated, secreting inhibitory neurotransmitters and vesicular components such as zinc, which impede RGC regeneration. Several theories have been postulated to explain the mechanisms underlying AC-mediated optic nerve regeneration. Yet, the exact mechanism triggering AC hyperactivation immediately after RGC axon injury remains elusive. One hypothesis posits that post-injury dysregulation of Cl^- gradients in interneurons initiates positive feedback loops between BCs and ACs, resulting in early AC hyperactivation.

In conclusion, strategies targeting the interactions of AC-RGC, modulation of the inhibitory glial environment, and management of inflammatory responses present promising avenues for promoting optic nerve regeneration. This review synthesizes current understanding of these extrinsic factors and delves into potential interventions aimed at enhancing regenerative outcomes and restoring visual function.

Correction notice

None

Acknowledgement

Figures were created with BioRender.com.

Author Contributions

(I) Conception and design: Qi Zhang and Yiqing Li

(II) Administrative support: Yehong Zhuo and Yiqing Li

(III) Provision of study materials or patients: Jiahui Tang, Zhe Liu, and Caiqing Wu

(IV) Collection and assembly of data: Siting Wu

(V) Data analysis and interpretation: Canying Liu

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

Fundings

This work was supported by the National Natural Science Foundation of China (82471067), Guangdong Basic and Applied Basic Research Foundation (2022A1515012168), Science and Technology Program of Guangzhou (202201020492), and Open Research Funds of the State Key Laboratory of Ophthalmology (2023KF01).

Conflict of Interests

None of the authors has any conflicts of interest to disclose. All authors have declared in the completed the ICMJE uniform disclosure form.

Patient consent for publication

None

Ethical Statement

None

Provenance and Peer Review

This article was a standard submission to our journal. The article has undergone peer review with our anonymous review system.

Data Sharing Statement

None

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