New strategies for neuro protection in glaucoma

Yang Xuejiao¹* and Yan Junwei

¹Department of Ophthalmology, The Affiliated Hospital of Qingdao University, Qingdao, China, ²Department of Vascular Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China

Glaucoma is a progressive, irreversible loss of retinal ganglion cells (RGCs) and axons that results in characteristic optic atrophy and corresponding progressive visual field defect. The exact mechanisms underlying glaucomatous neuron loss are not clear. The main risk factor for glaucoma onset and development is high intraocular pressure (IOP), however traditional IOP-lowering therapies are often not sufficient to prevent degeneration of RGCs and the vision loss may progress, indicating the need for complementary neuroprotective therapy. This review summarizes the progress for neuro protection in glaucoma in recent 5 years, including modulation of neuroinflammation, gene and cell therapy, dietary supplementation, and sustained-release system.

KEYWORDS
retinal ganglion cells, glaucoma, neuroprotection, gliocyte, gene therapy

Introduction

Glaucoma is a progressive, irreversible loss of retinal ganglion cells (RGCs) and axons that results in a characteristic optic atrophy and a corresponding progressive visual field defect. The most common types of glaucoma are primary open-angle glaucoma and primary angle closure glaucoma (PACG) (Dietze et al., 2022). Acute PACG has typical anatomical characteristics, such as shallow anterior chamber, pupillary block, plateau iris, etc., it usually causes acute attack. However, patients with POAG and chronic PACG are often asymptomatic until the optic nerve damage is severe. The exact mechanisms underlying glaucomatous neuron loss are not clear.

Although some scholars believe that it is a neurodegenerative disease (Ramirez et al., 2017), it is not exactly the same as Parkinson’s disease, Alzheimer’s disease, and other neurodegenerative diseases that mainly occur in the middle-aged and the elderly. Glaucoma has a wide age, some young and middle-aged patients with open and chronic closure have very late visual field, obvious C/D cupping and optic nerve atrophy. Because irreversible blindness seriously affects patients’ quality of life and heavy social burden, it is critical to explore the possible pathogenesis of optic nerve injury and effective treatment targets.

The main risk factor for glaucoma onset and development is high intraocular pressure (IOP), and the current treatments available target the lowering of IOP (Dietze et al., 2022). However, degeneration of RGCs and the vision loss may progress despite significant IOP lowering in some patients, indicating that complementary neuroprotective therapy are needed. In recent years, a large number of studies on optic nerve protection have emerged,
this review summarizes the progress for neuro protection in glaucoma in recent 5 years, including modulation of neuroinflammation, gene, and cell therapy, dietary supplementation, and sustained-release system.

**Neuroimmunity**

Immune system dysregulation is increasingly being attributed to the development of a multitude of neurodegenerative diseases (Stothert and Kaur 2021). In recent years, a large amount of studies focus on the glia cells and immune system in the development of glaucomatous optic neuropathy (de Hoz et al., 2018). An excessive microglial response may be a significant degenerative factor for increased cell death (Grotegut et al., 2020), microglia activation and release of pro-inflammatory cytokines are the main contributors for retinal cell death in glaucoma (de Hoz et al., 2018). OPN was found to enhance the proliferation and activation of retinal microglia, and contribute to the eventual RGCs loss and vision function impairment in glaucoma (Yu et al., 2021). Blocking microglial A2A R prevents microglial cell response to elevated pressure and it is sufficient to protect retinal cells from elevated pressure-induced death (Aires et al., 2019). Another study found activation of Adenosine A (3) receptor could hinder the microglia reactivity (Ferreira-Silva et al., 2020), attenuated the impairment in retrograde axonal transport, and afford protection against glaucomatous degeneration. In addition, P2X7 receptor antagonist protects retinal ganglion cells by inhibiting microglial activation in a rat chronic ocular hypertension model (Dong et al., 2018).

Astrocytes perform critical non-cell autonomous roles following CNS injury that involve either neurotoxic or neuroprotective effects. Astrocyte-derived lipoxins A4 and B4 promote neuroprotection from acute and chronic injury neuroprotective signal (Livne-Bar et al., 2017). Statins promotes the survival of RGCs by reduce apoptosis and suppress chronic high IOP induced glial activation (Kim et al., 2021).

**Gene therapy**

Gene therapy, which uses a viral vectors to deliver genetic material into cells, is a promising approach to directly target pathogenetic molecules (Keeler et al., 2017). The retina is a favorable target for gene therapy because of its easy access, established clear functional readouts, partial immune privilege and confined non-systemic localization (Ratican et al., 2018). The success of adeno-associated virus (AAV)-mediated gene replacement therapy for inherited retinal disease (Maguire et al., 2008; Busskamp et al., 2010; Smalley 2017) has made RGC-specific gene expression and AAV editing a promising gene therapy strategy for optic neuropathies. Table 1 lists the gene therapy studies on neuroprotection of glaucoma in recent 5 years, their findings indicate that gene therapy has a broad prospect in protecting both structure and function of RGC. Apart from this, reprogramming cells with defined factors is another promising strategy to produce functional cells for therapeutic purposes (Wang et al., 2021). OSK-induced reprogramming in mouse RGC was found to promote axon regeneration and reverse vision loss (Lu et al., 2020). Math5 and Bm3b transcription factors (TFs) combination can reprogram mature mouse Müller glia into RGC, resulting in proper projection of RGC in the visual pathway, and improved visual function (Xiao et al., 2021). Recently, another study, using a CRISPR-Cas9-based genome-wide screen of 1,893 TFs, found that manipulation of ATF3/CHOP and ATF4/C/EBPβ protected RGC in a glaucoma model (Tian et al., 2022).

**Cell therapy**

Cell therapy provides a new therapeutic strategy for glaucoma. Stem cell therapy mainly involves the transplantation of cells to replace the dead and lost RGC. However, it is associated with a number of major challenges besides ethical issue. Regeneration of RGCs requires full synaptic integration of host inner retinal stem cells and the development of long-distance axons, which project to the brain and accurately form effective synaptic connections with corresponding targets to complete signal transmission. Up to now, the replacement of RGCs has not made a breakthrough (Zhang J. et al., 2021). Several recently studied cell types for transplantation including mouse induced pluripotent stem cell (miPSC) or mouse embryonic stem cell (mESC)-derived RGC (Oswald et al., 2021) and spermatogonial stem cell-derived RGC (Suen et al., 2019). Another study found mesenchymal stem cells (MSC) secreted exosomes can promote survival of RGC and regeneration of their axons (Mead and Tomarev 2017). In addition, further study found that TNF-α stimulated gingival MSC derived exosomes play neuroprotection and anti-inflammation roles by delivering miR-21-5p-enriched exosomes through MEG3/miR-21-5p/PDCD4 axis (Yu et al., 2022).

**Dietotherapy**

In animal models of glaucoma, various diet-related treatments were found as non-IOP-related neuroprotective mechanisms. High VitK1 intake (Deng et al., 2020), Coenzyme Q10 + Vitamin E (Zhang et al., 2017; Ekkier Acar et al., 2020), Nicotinamide riboside of the vitamin B3 family
(Zhang X. et al., 2021), probiotic bacteria (Fafure et al., 2021) and other dietary supplementation (Cammalleri et al., 2020) were proved to attenuate the loss of RGCs by regulating glia-mediated neuroinflammatory or BDNF activity, etc.

New drug loading system

Several preclinical studies demonstrate that neurotrophins (NTs) prevent RGCs loss (Gupta et al., 2022). NTs can be
conjugated to nanoparticles, which act as smart drug carriers. This enables the self-localization of drugs in the retina and the prevention of rapid degradation of drugs (Giannaccini et al., 2018).

Sunitinib is a protein kinase inhibitor with activity against the neuroprotective targets dual leucine zipper kinase (Dlk) and leucine zipper kinase (Lzk). It was found to enhance survival of RGCs for neuroprotection. Recently, a hypotonic, thermosensitive gel-forming eye drop (Kim et al., 2022) and a sunitinib-pamoate complex (SPC) microcrystals for subconjunctival injection (Hsueh et al., 2021) were devised to continuously release for 1 and 20 weeks.

Others

Cannabinoids (Cbs) was found to target several factors that related with the progression of glaucoma, it promotes neuroprotection, abrogates changes in ECM protein, and normalizes the IOP levels in the eye (Maguire et al., 2022; Somvanshi et al., 2022).

In summary, various neuroprotective therapy (Figure 1) can help us to better understand the pathological basis of visual function impairment and progression in glaucoma. At present, many scholars have committed to clinical translation to save RGCs and visual function of glaucoma patients from the molecular and cellular levels. These new strategies will bring hope for the prevention and treatment of glaucoma.

References

Aires, I. D., Boia, R., Rodrigues-Nevés, A. C., Madeira, M. H., Marques, C., Ambrosio, A. F., et al. (2019). Blockade of microglial adenosine A2A receptor suppresses elevated pressure-induced inflammation, oxidative stress, and cell death in retinal cells. Glia 67, 896–914. doi:10.1002/glia.23579

Bosco, A., Anderson, S. R., Bren, K. T., Romero, C. O., Steele, M. R., Chiiodo, V. A., et al. (2018). Complement C3-targeted gene therapy restricts onset and progression of neurodegeneration in chronic mouse glaucoma. Mol. Ther. 26, 2379–2396. doi:10.1016/j.ymthe.2018.08.017

Busskamp, V., Duebel, J., Balya, D., Fradot, M., Viney, T. J., Siegert, S., et al. (2010). Genetic reactivation of cone photoreceptors restores visual responses in retinitis pigmentosa. Science 329, 413–417. doi:10.1126/science.1190897

Campallieri, M., Dal Monte, M., Amato, R., Bagnoli, P., and Rusciano, D. (2020). A dietary combination of forskolin with homotaurine, spearmint and B vitamins protects injured retinal ganglion cells in a rodent model of hypertensive glaucoma. Nutrients 12, E189. doi:10.3390/nu1204189

de Hor, R., Ramirez, A. I., Gonzalez-Martín, R., Ajoy, D., Rojas, B., Salazar-Garcia, E., et al. (2018). Bilateral early activation of retinal microglial cells in a mouse model of unilateral laser-induced experimental ocular hypertension. Exp. Eye Res. 171, 12–28. doi:10.1016/j.exer.2018.03.006

Deng, C., Yao, K., Peng, F., Zhan, B., Chen, Z., Chen, W., et al. (2020). The effect of dietary vitamin K1 supplementation on subretinal meshwork and retina in a chronic ocular hypertensive rat model. Invest. Ophthalmol. Vis. Sci. 61, 40. doi:10.1167/iovs.61.8.40

Dietze, J., Blair, K., and Havens, S. J. (2022). Glaucoma. Treasure Island (FL): StatPearls. Treasure Island (FL).

Donahue, R. J., Feherman, R. L., Gustafson, J. R., and Nickells, R. W. (2021). BCL2L1 gene therapy moderates neuropathology in the Dba/2j mouse model of inherited glaucoma. Cell. Death Dis. 12, 781. doi:10.1038/s41419-021-04968-z

Dong, L., Hu, Y., Zhou, L., and Cheng, X. (2018). P2X7 receptor antagonist protects retinal ganglion cells by inhibiting microglial activation in a rat chronic ocular hypertension model. Mol. Med. Rep. 17, 2289–2296. doi:10.3892/mmr.2017.8137

Ekinci Acar, S., Sazancioglu, M. S., Colak, A., Aksan, Z., and Sepici Dincel, A. (2020). Neuroprotective effects of topical coenzyme Q10 + vitamin E in mechanic optic nerve injury model. Eur. J. Ophthalmol. 30, 714–722. doi:10.1177/1120672119833271

Fakur, A. A., Edem, E. E., Obisesan, A. O., Enye, L. A., Adekeye, A. O., Adefunmi, A. E., et al. (2021). Fermented maize slurry (Og) and its supernatant (Omidun) mitigate elevated intraocular pressure by modulating BDNF expression and glial plasticity in the retina-gut axis of glaucomatous rats. J. Compartment. Integr. Med. 0. doi:10.1515/jcmi-2021-0114

Feng, F., Zhuang, P., Feng, X., Liu, P., Liu, D., Huang, H., et al. (2022). NMNAT2 is downregulated in glaucomatous RGCs, and RGC-specific gene therapy rescues neurodegeneration and visual function. Mol. Ther. 30, 1421–1431. doi:10.1016/j.ymthe.2022.01.035

Ferreira-Silva, J., Aires, I. D., Boia, R., Ambrósio, A. F., and Santiago, A. R. (2020). Neurotrophin-conjugated nanoparticles prevent retina damage induced by oxidative stress. Cell. Mol. Life Sci. 77, 1255–1267. doi:10.1007/s00018-017-2691-x

Funding

This work was supported by the National Natural Science Foundation of China (81600726), Natural Science Foundation of Shandong Province (ZR2016HB53), 2021 Qingdao Medical and Health Scientific Research Project and Youth Science Foundation of the affiliated hospital of Qingdao University.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author contributions

YX contributed to writing of the manuscript. YJ contributed to manuscript revision.

Giannaccini, M., Usai, A., Chiellini, F., Guadagni, V., Andreazzoli, M., Ori, M., et al. (2018). Neurotrophin-conjugated nanoparticles prevent retina damage induced by oxidative stress. Cell. Mol. Life Sci. 75, 1255–1267. doi:10.1007/s00018-017-2691-x

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author contributions

YX contributed to writing of the manuscript. YJ contributed to manuscript revision.
Grotegut, P., Perunal, N., Kuehn, S., Smit, A., Dick, H. R., Grus, F. H., et al. (2020). Minocycline reduces inflammatory response and cell death in a S100B retina degeneration model. J. Neuroinflammation 17, 375. doi:10.1186/s12974-020-02023-y

Guo, X., Zhou, J., Starr, C., Mohns, E. J., Li, Y., Chen, E. P., et al. (2021). Preservation of vision after CaMKII-mediated protection of retinal ganglion cells. Cell. 184, 4299–4314.e12. doi:10.1016/j.cell.2021.06.031

Gupta, V., Chitranshi, N., Gupta, V., You, Y., Rajput, R., Paulo, J. A., et al. (2022). TrkB receptor agonist α-7, 8 dihydroxy cannabinol modulates neuroprotection and intraocular pressure: A potential multi-target therapeutic intervention for glaucoma. Biochim. Biophys. Acta. Mol. Basis Dise. 1868, 166325. doi:10.1016/j.bbadis.2021.166325

Shen, J., Xiao, R., Bair, J., Wang, F., Vandenberghe, L. H., Dartt, D., et al. (2018). Novel engineered, membrane-localized variants of vascular endothelial growth factor (VEGF) protect retinal ganglion cells. A proof-of-concept study. Cell Death Dis. 9, 1018. doi:10.1038/s41419-018-1049-0

Smalley, E. (2017). First AAV gene therapy poised for landmark approval. Nat. Biotechnol. 35, 988–999. doi:10.1038/nbt.4117

Somvanshi, R. K., Zou, S., Kadhim, S., Padania, S., Hsu, E., and Kumar, U. (2022). Cannabinoid modulates neuroprotection and intraocular pressure: A potential multi-target therapeutic intervention for glaucoma. Biochim. Biophys. Acta. Mol. Basis Dise. 1868, 166325. doi:10.1016/j.bbadis.2021.166325

Stothert, A. R., and Kaur, T. (2021). Innate immunity to spiral ganglion neuron loss: A neuroprotective role of fraktalkine signaling in injured cochlea. Front. Cell. Neurosci. 15, 694292. doi:10.3389/fncell.2021.694292

Suem, H. C., Qian, Y., Liao, J., Luk, C. S., Lee, W. T., Ng, J. K. W., et al. (2019). Transplantation of retinal ganglion cells derived from male germline stem cell as a potential treatment to glaucoma. Stem Cells Dev. 28, 1365–1375. doi:10.1089/scd.2019.0060

Tian, F., Cheng, Y., Zhou, S., Wang, Q., Monavarpashani, A., Gao, K., et al. (2022). Core transcription programs controlling injury-induced neurodegeneration of retinal ganglion cells. Neuron 110, 2607–2624.e9. doi:10.1016/j.neuron.2022.06.003

Visvanathan, S., Baker, A. N., Lagali, P. S., Coupland, S. G., Miller, H., Haurwitz, W. W., et al. (2022). XIAP gene therapy effects on retinal ganglion cell structure and function in a mouse model of glaucoma. Gene Ther. 29, 147–156. doi:10.1038/s41434-021-00281-7

Wang, H., Yang, Y., Liu, J., and Qian, L. (2021). Direct cell reprogramming Approaches, mechanisms and progress. Nat. Rev. Med. Cell. Biol. 22, 410–424. doi:10.1038/s41555-020-00335-x

Wang, Q., Zhang, P., Huang, H., Li, L., Liu, L., Webber, H. C., et al. (2020). Mouse γ-synuclein promoter-mediated gene expression and editing in mammalian retinal ganglion cells. J. Neurosci. 40, 3896–3914. doi:10.1523/NEUROSCI.01202-20.2020

Wojcik-Gryciana, A., Gajewska-Wozniak, O., Kordacka, K., Boguszewski, P. M., Wałęszczyk, W., and Skup, M. (2020). Neuroprotection of retinal ganglion cells with AAV2-BDNF pretreatment restoring normal TrkB receptor protein levels in glaucoma. Int. J. Mol. Sci. 21, E2626. doi:10.3390/ijms21172626

Xiao, D., Jin, K., Qiu, S., Lei, Q., Huang, W., Chen, H., et al. (2021). In vivo regeneration of ganglion cells for vision restoration in mammalian retinas. Front. Cell. Dev. Biol. 9, 75544. doi:10.3389/fcell.2021.75544

Yu, H., Zhong, H., Li, N., Chen, K., Chen, J., Sun, J., et al. (2021). Osteopontin activates retinal microglia causing retinal ganglion cells loss via p38 MAPK signaling pathway in glaucoma. FASEB J. 35, e24105. doi:10.1096/fj.202002281R

Yu, Z., Wen, Y., Jiang, N., Li, Z., Guan, J., Zhang, Y., et al. (2022). TNF-a stimulation enhances the neuroprotective effects of gangival MSCs derived exosomes in retinal ischemia-reperfusion injury via the MEK/ERK–Smad–Smad3 signaling pathway in glaucoma. Biomaterials 284, 121484. doi:10.1016/j.biomaterials.2022.121484

Zhang, J., Wu, S., Jin, Z. B., and Wang, N. (2021). Stem cell-based regeneration and restoration for retinal ganglion cell: Recent advancements and current challenges. Frontiers in Cell and Developmental Biology 11, 987. doi:10.3389/fcell.2021.1070987

Zhang, X., Tohari, A. M., Marchegiani, F., Zhou, X., Reilly, J., Tiao, L., et al. (2017). Therapeutic potential of Co-enzyme Q10 in retinal diseases. Curr. Curr. 43, 4329–4339. doi:10.2174/0929673243666170831100516

Zhang, X., Zhang, N., Chennek, M. A., Girardot, P. E., Wang, J., Sellers, J. T., et al. (2021). Systemic treatment with Nicotinamide riboside is protective in two mouse models of retinal ganglion cell damage. Pharmacetics 13, 893. doi:10.3390/ pharmaceutics13060893