• Review Article •

Glaucomatous retinal ganglion cells: death and protection

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Abstract

● Glaucoma is a group of diseases characterized by progressive optic nerve degeneration, with the characteristic pathological change being death of retinal ganglion cells (RGCs), which ultimately causes visual field loss and irreversible blindness. Elevated intraocular pressure (IOP) remains the most important risk factor for glaucoma, but the exact mechanism responsible for the death of RGCs is currently unknown. Neurotrophic factor deficiency, impaired mitochondrial structure and function, disrupted axonal transport, disturbed Ca^{2+} homeostasis, and activation of apoptotic and autophagic pathways play important roles in RGC death in glaucoma. This review was conducted using Web of Science, PubMed, Project, and other databases to summarize the relevant mechanisms of death of RGCs in glaucoma, in addition to outlining protective treatments to improve the degradation of RGCs.

● **KEYWORDS:** glaucoma; retinal ganglion cells; neuroprotection; progressive death; axonal deletion

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INTRODUCTION

Glaucoma is a group of diseases characterized by progressive optic nerve degeneration and is a leading cause of irreversible blindness worldwide. The characteristic pathological change is the death of retinal ganglion cells (RGCs), which ultimately causes visual field loss and irreversible blindness. RGCs are the neurons that transmit visual information from the retina to the brain and are permanently lost once dead. Loss of vision usually begins with the peripheral vision and progresses to the central vision, with devastating consequences for the patient's quality of life.

In 2010, 2.1 million people worldwide were already blind owing to glaucoma; by 2020, glaucoma affected more than 80 million people, with a prevalence of 2.93% in people aged 40-80y according to the European Epidemiological Survey[1]. There are various subtypes of glaucoma, which are classified according to their respective structural changes in the anterior segment of the eye; however, the most common type is primary open-angle glaucoma (POAG). More than 74% of patients have POAG, with more than 5.9 million people permanently blind due to POAG[2].

The influencing factors associated with the development of glaucoma in humans include intraocular pressure (IOP), aging, genetic factors, and vascular disorders[3-5], but the exact detailed aetiology and pathogenesis remains elusive. The known pathogenesis of glaucoma includes 1) damage to the trabecular meshwork, leading to reduced aqueous outflow and elevated IOP; 2) damage to the optic nerve head which in turn damages the unmyelinated optic nerve axons; 3) progressive death of RGCs; 4) progressive loss of neurones in the visual center of the brain.

The progressive death of RGCs occurs as a typical pathological feature of glaucoma. Glaucoma is a complex multifactorial disease, and the molecular pathway causing progressive death of RGCs may result from the convergence of multiple pathways. The influential factors causing progressive death of RGCs include apoptosis[6-7], impaired mitochondrial structure and function[8-10], neurotrophin deprivation[11-12], ischemia, and hypoxia[13-14]. An increase in other risk factors can exacerbate the progressive death of RGCs in glaucoma, which, in turn, leads to the dysfunction and even death of the optic nerve. These research advances have not only increased our understanding of glaucoma pathogenesis but have also helped us to find new neuroprotective therapies. In this review, we aimed to provide an up-to-date description of the cellular and molecular mechanisms that are crucial in RGCs injury

and discuss novel neuroprotective approaches for RGCs in glaucoma (Figure 1).

The mechanisms implicated in RGC damage include neuronutrient deprivation, glutamate excitotoxicity, mitochondrial dysfunction, ischemia and hypoxia, oxidative stress, disruption of Ca^{2+} homeostasis, axonal transport disorders, apoptosis and other death mechanisms which can lead to premature senescence, and inflammation cascade which induce the activation of glial cells with consequent gliosis. The pathways, triggered by each risk factor, often result to be strictly interrelated, contributing to amplifying RGC distress in an irreversible way.

FACTORS INFLUENCING THE PROGRESSIVE DEATH OF RETINAL GANGLION CELLS

Apoptosis Apoptosis is a type of programmed cell death that plays a vital role in physiological processes and is a feature of the pathophysiology of many diseases (Figure 2). During embryonic development, excess RGCs compete for a small number of neurotrophins simultaneously, and RGCs that are not nourished eventually die through apoptosis. The same phenomenon occurs in adulthood, and apoptosis and the subsequent death of RGCs are the main causes of progressive vision loss in patients with glaucoma. This mechanism of cell death is controlled by gene regulation, and pro-apoptotic factors can be produced in the retina through a variety of mechanisms such as oxidative stress[15], immune dysfunction[16], impaired mitochondrial structure and function[8], and neurotrophin deficiency[17]. Endoplasmic reticulum stress induced by aberrant protein aggregation may lead to reactions involving unfolded proteins[18]. In addition, some endoplasmic reticulum stress signalling proteins control cell fate by activating pro-apoptotic Bcl2 or anti-apoptotic Bax molecules in response to cellular loads[19].

Neurotrophin Deprivation Neurotrophins play key roles in nerve cell survival. Under healthy or normal conditions, RGCs can receive neurotrophic support from Müller cells[20] or directly from retrograde axonal transport in the brain. This process regulates the growth, function, and survival of neuronal cells, with neurotrophic factors binding to the Trk receptor at the end of the axon, which are then retrogradely transported to the cell body[21-22]. In patients with glaucoma, retrograde transport may be blocked in the optic nerve head owing to high IOP; consequently, RGCs are unable to receive trophic support from brain-derived neurotrophic factor (BDNF) and TrkB[23-24]. The fact that RGCs remain viable in the absence of exogenous BDNF has also been confirmed, suggesting that exogenous BDNF deprivation due to the disruption of retrograde transport is not responsible for the growth and functioning of RGCs; hence, BDNF deprivation is not the only cause of death in glaucomatous RGCs.

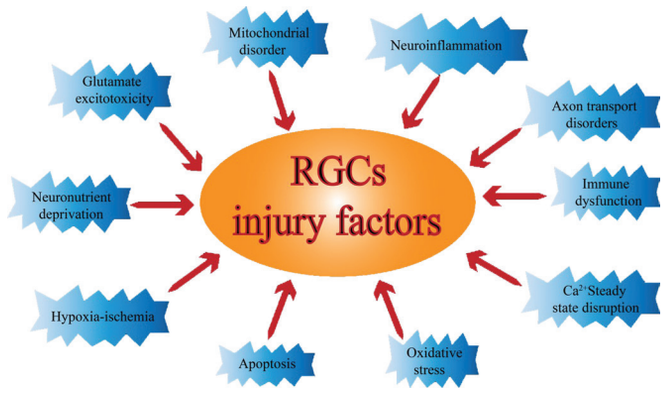

Figure 1 Risk factors contributing to RGC distress in glaucoma RGC: Retinal ganglion cells.

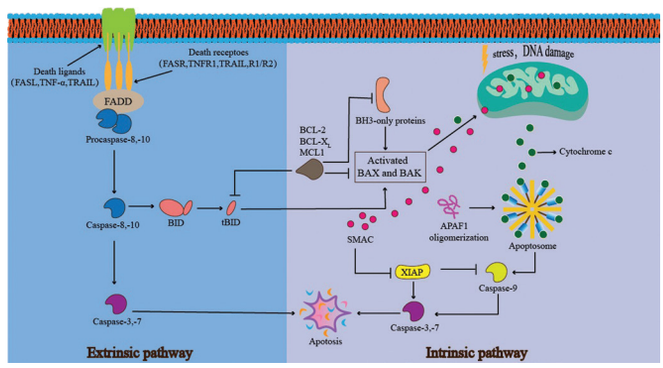

Figure 2 The mechanism of cell apoptosis under glaucoma conditions.

Mitochondrial Dysfunction Mitochondria are important autonomous dynamic organelles in the central nervous system (CNS), and their structural and functional dynamics play crucial roles in cellular and animal physiology. Structurally reflecting the precise balance between ongoing mitochondrial fission and fusion, mitochondrial dynamics regulate the mitochondrial network and intracellular function, and alterations in mitochondrial dynamics help follow disease progression in optic neuropathy[25-26]. As the most common type of glaucoma, patients with POAG exhibit structural and functional mitochondrial abnormalities associated with oxidative stress, reduced mitochondrial respiratory activity, and mitochondrial DNA (mtDNA)[27-28] Maternally inherited mtDNA is highly susceptible to damage owing to a lack of protection from related proteins, its proximity to the mitochondrial respiratory chain, and ROS production, which in turn leads to the development of many diseases[29]. Variants in specific genes may lead to alterations in the stability of complexes I and III, thereby leading to mitochondrial alterations in patients with POAG[30-32].

Ischaemia, Hypoxia and Oxidative Stress The structural and functional integrity of the retina depends on a normal supply of oxygen. As one of the most metabolically active tissues, the retina consumes oxygen at a much faster rate than the other tissues. Retinal ischaemia occurs when acute vascular occlusion results in insufficient retinal circulation to meet the metabolic

demands of the retina, which may be caused by systemic circulatory failure[33], such as severe left ventricular failure and hypovolemic shock or by local circulatory failure. In contrast, the presence of double circulation in the retina makes it more sensitive to ischaemia and hypoxia[34-35]. A study on retinal structure and function in mice[36] revealed that a high-fat diet leads to retinal ischaemia and hypoxia and that apolipoprotein E (ApoE) deficiency increases the susceptibility to ischaemia in mice. These changes trigger neuroinflammation, exacerbating apoptosis in RGCs. Reperfusion following ischaemia renders the retina more susceptible to oxidative damage. RGCs are particularly sensitive to acute, transient, and mild systemic postischemic hypoxic stress[37]. The loss of RGCs and their axonal fibres following retinal hypoxia has been demonstrated in experimental studies.

Disruption of Ca^{2+} Homeostasis Similar to neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, disruption of intracellular Ca^{2+} homeostasis in RGCs in glaucoma also plays a key role in the pathogenesis of glaucoma[38]. Disruption of Ca^{2+} homeostasis leads to various intracellular events, which in turn promote apoptosis and RGC death[39]. Excessive intracellular Ca^{2+} levels can trigger cytoskeletal degradation by enhancing the activity of specific enzymes such as phospholipases, proteases, and protein kinases. Moreover, Ca^{2+} channels play a key role in maintaining the physiological functions of RGCs. For example, voltage-gated Ca^{2+} channel (VGCC) blockers attenuate the damage of RGCs in the retinal ischemia/hypoxia model, demonstrating that VGCC is involved in the process of RGC damage[40]; additionally, VGCC blockers exhibit neuroprotective effects. In a rat model of experimental glaucoma with chronic ocular hypertension, T-type Ca^{2+} channels were shown to be involved in Ca^{2+} homeostasis and apoptosis of glaucomatous RGCs[41].

Impaired Axonal Transport Axonal transport is the active bidirectional transport of various substances via motor proteins along microtubules. This process is fundamental for neuronal function and survival[42]. In both primate glaucoma animal models and human glaucoma studies, it was found that disruption of axonal transport preceded RGC death and was predominantly manifested as retrograde transport[42-43]. The presence of axonal transport disorders has been confirmed in rodent models. One such model is the DBA/2J, a POAG mouse model that mimics elevated IOP in the human eye, in which intracranial labelling with fluorescently labelled cholera toxin B revealed the presence of impaired axonal transport in the blood-brain barrier of DBA/2J mice[44-45]. Similarly, in another glucocorticoid-induced POAG mouse model injected with cholera toxin B, transmission electron microscopy analysis showed complete disruption of axonal transport at week 8[46] Interestingly, impaired axonal transport was also confirmed in a rat glaucoma model, and it was found that the accumulation of tau protein disrupted axonal transport[47-48].

Immune Dysfunction The eyes are an immunologically privileged part of the body[40]. The vasculature of the eye is located outside the central light pathway, as its presence impairs vision. Therefore, many regions of the eye have evolved responses that deliver immune cells to sites of dysplasia or damage. Although the purpose of these immune responses is repair or protection, the cytokines released by immune cells impair vision by inducing inflammation and fibrosis[40]. Resistance to RGC death correlates with immune potency[49], suggesting that immune dysfunction contributes to the onset and progression of glaucoma. Similarly, the transfer of found to impair the RGCs of the healthy mice[50]. Studies related to the rat glaucoma model confirmed that elevated levels of heat shock proteins cause progressive death of RGCs[51-52]. The introduction of heat shock proteins into rats by immunisation induces glaucoma[53-55].

Microbial Action Microbes (Figure 3) play a vital role in the homeostasis and health of the host, and are involved in nerve signaling, immune system maturation, and more[56]. A healthy eye microbiome has been shown to act as a barrier against pathogen entry into the body[57]. The study of the interaction between human ocular surface microbiome and lacrimal proteome provides a new direction for the targeted treatment of glaucoma[58]. Along with the concept of the gut-eye axis, the researchers proposed that patients with irritable bowel disease are at a higher risk of developing glaucoma[59-61].

PROTECTION AND TREATMENT OF RETINAL GANGLION CELLS

To date, no medical or surgical treatments can inhibit or reverse optic nerve damage in patients with glaucoma. The traditional treatment for glaucoma involves lowering the IOP of these patients using drugs, lasers, and surgical procedures. Only a few drugs have been found to be neuroprotective in pharmacological studies, and regarding laser treatment, adverse events such as a transient increase in IOP and low-grade iritis can occur. Although surgical treatment is the most effective traditional treatment, surgical intervention can aggravate the decline of cell number and morphological damage, and postoperative follow-up has found that more than 50% of patients have postoperative recurrence. The appearance of Descemet membrane endothelial keratoplasty can reduce the loss of endothelial cells, but it has little effect[62]. Therefore, new protection and treatment methods have emerged to solve the disadvantages of these traditional methods (Figure 4).

Gene Therapy Many neurodegenerative diseases have genetic characteristics, and most genetic diseases[63] are caused by genetic alterations. This is similar to mutations, insertions, deletions, or even mutations in the mtDNA of a gene[64], which

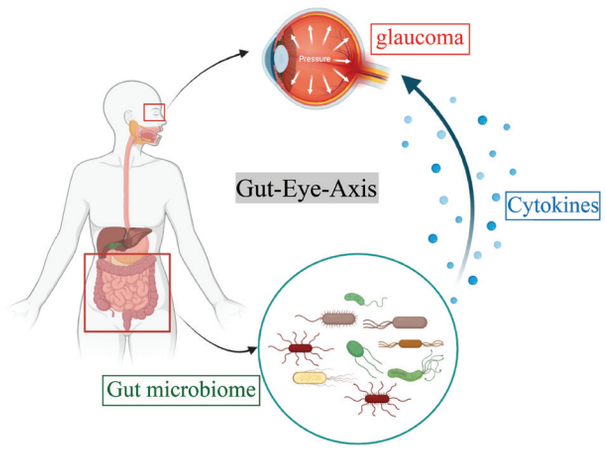

Figure 3 The conception atlas of the gut-eye-axis.

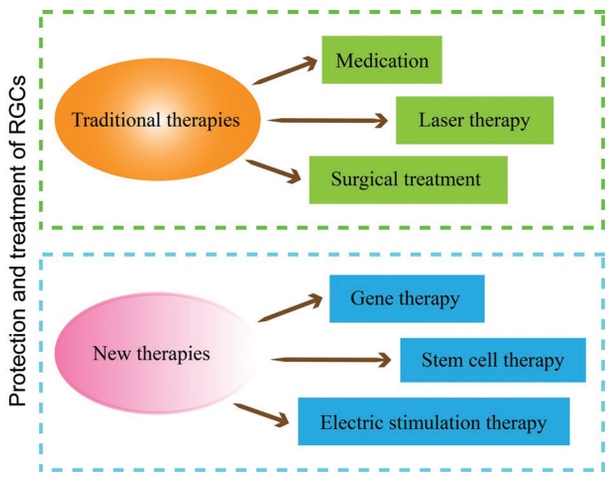

Figure 4 Protection and treatment of RGCs Traditional treatment with drugs, laser and surgery, as well as new treatment with gene therapy, stem cell therapy and electrical stimulation therapy.

alters the structure and function of its corresponding proteins and ultimately lead to the development of related diseases[65-67]. Therefore, the emergence of gene therapy has disrupted existing, more limited, traditional treatment methods. Gene therapy, which is based on the development of sequencing technology, is an approach that addresses incurable genetic diseases by adding, suppressing, replacing[68], or editing[69] disease-causing genes. Gene therapy using adeno-associated viruses (AAV)[70] is now generally preferred because of its high safety[71] and persistence[72], especially in ophthalmic diseases, where it achieves long-term stable transgene expression. In recent years, 12 AAV serotypes have been identified[73] and intravitreal injection of AAV2, followed by AAV9, can transduce RGCs[74-76]. In particular, the common serotype AAV2 has been successfully used in clinical trials for ocular diseases[77-79], and other serotypes-mediated gene therapies are also being tested in clinical trials, which will open new milestones for the cure of genetic diseases such as glaucoma.

Stem Cell Therapy Differences in RGC damage in glaucoma make treatment particularly challenging[80-81]. Although surgical interventions can be effective in controlling the IOP, a subset of patients still experience persistent RGC death and optic nerve damage. Because adult mammalian RGCs lack the ability to regenerate themselves, the unlimited proliferative capacity and multidirectional differentiation potential of stem cells could allow them to differentiate into RGCs. This potential transformation could alter the difficulty of treating glaucoma. The feasibility of stem cell therapy has been demonstrated in several animal models. For example, mouse embryonic stem cell-derived RGCs injected into the retinal surface of RGC-injured mice have been found to establish cellular connections between donor RGCs and the host retina[82]. When mesenchymal stem cells were injected into an animal model of glaucoma, the survival rate of RGCs significantly increased[83] Transplantation of pluripotent stem cell-derived optic nerves into an animal model of retinal defects resulted in a greater improvement in visual behaviour[84-85].

Electrical Stimulation Therapy Electrical stimulation therapy involves using low electrical currents to elicit nerve impulses externally. This stimulation prompts nerve cells to release neurotransmitters, which then act on the target organ. The protective effects of electrical stimulation therapy on the optic nerve[86], particularly corneal electrical stimulation (TES), have been extensively studied. After using corneal electrical stimulation in a rat model of optic nerve transection, a decrease in the mortality rate of RGCs was observed. Additionally, there was a reduction in the production of TNF-α by glial cells[87]. In the same rat model, TES delayed optic nerve degeneration without the use of exogenous trophic factors[88]. DBA/2J, a typical mouse model of glaucoma, was subjected to TES and found to preserve axons, reduce inflammation, and increase neurotrophic factors[89]. By contrast, early use of TES in a rat model of traumatic optic neuropathy restored optic nerve dysfunction[90].

CONCLUSIONS AND OUTLOOK

Glaucoma, a neurodegenerative disease, has garnered significant interest over the years. The progressive death of RGCs stands out as a major pathological feature, although the exact mechanism remains unclear. Substantial progress has been achieved in identifying and characterizing the molecular pathways implicated in the progressive death of RGCs in animal models of acute and chronic optic nerve injury. Because of the diversity of molecular signaling, it is possible for different molecular pathways to be impaired at different stages of glaucoma onset and progression, as well as in different forms of glaucoma. For example, at the molecular level, some patients exhibit impaired axonal transport and neurotrophic factor deficiencies, while others show increased oxidative or excitotoxic stress. The specific mechanisms of action of autoantibodies and heat shock proteins in glaucoma, whether they are damaging or protective, remain unresolved. An in-

depth understanding of the molecular changes occurring during various stages of glaucoma progression is therefore crucial for developing targeted treatments with minimal adverse effects. Although novel therapeutic approaches have been shown to be safe and efficient for use in animal models of glaucoma, animal models do not fully reflect human disease. Therefore, preclinical data must be validated in *in vivo* experimental paradigms and ideally should be confirmed by different research groups prior to clinical studies. Once the feasibility of the treatment is confirmed, it should be implemented in clinical practice following assessment of its effective dose range and duration of intervention. Comprehensive evaluation and documentation of key points during clinical will be essential. Despite the challenges, advancements in new treatments to prevent vision loss in glaucoma are progressing, bolstered by improvements in animal models and the development of imaging and molecular diagnostic tools.

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Conflicts of Interest: Cui N, None; **Jia J,** None; **He Y,** None.

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