

OPTIC NERVE NEUROPATHY AND REPAIR IN GLAUCOMA

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Introduction

Glaucoma is one of the leading causes of impaired vision and blindness worldwide. It is a disease involving progressive optic nerve pathology and retinal ganglion cell (RGC) function loss.¹ Optic neuropathy and RGC death are the hallmarks of glaucoma, which are often associated with structural changes in the optic nerve head.^{2,3} Effective therapeutic strategies to treat neuronal damage and restore vision in glaucoma rely heavily on the knowledge and understanding of the cellular and molecular responses in RGCs and the optic nerve.

It is generally believed that damage to RGCs in glaucoma is caused by increased intraocular pressure and a number of other factors including ischemia excitotoxicity⁴ and neurotrophic insufficiency⁵⁻⁸. Other factors have to still be identified. These signals likely act through common final pathways that eventually activate cellular proteases⁹ and trigger cell apoptosis. Since RGCs and the optic nerve do not regenerate, this damage results in permanent loss of vision.

Although glaucoma is no longer viewed simply as elevated intraocular pressure (IOP) that damages the optic nerve, current treatment of glaucoma is directed at lowering IOP to prevent progression of glaucomatous optic neuropathy.¹⁰ Accumulating evidence of pressure-independent causes of glaucomatous optic neuropathy has led to the recognition that lowering IOP alone is insufficient for the long-term preservation of visual function.¹¹ Regardless of the primary trigger of optic nerve and retinal ganglion cell degeneration in glaucoma, the disease often continues to progress even when the risk factor is relieved. Thus, an innovative therapeutic approach is required to prevent progression of glaucomatous optic neuropathy and preserve vision, likely through direct neuroprotection and stimulation of optic nerve and RGC regeneration. Understanding the cellular and molecular mechanisms controlling RGC and optic nerve degeneration and regeneration are both essential for future development of efficacious therapies for glaucoma.

Cellular Events Associated with Glaucomatous Optic Neuropathy

Clinically, glaucoma is characterized by optic neuropathy with cupping of the optic nerve head that is due to the loss of RGC axons and distortion of the supporting tissue in the lamina cribrosa.¹² The initial damage of glaucoma begins at

the level of lamina cribrosa, a sieve-like structure with stacks of connective tissues that are aligned to form cribriform plates with channels through which RGC axons pass.^{5,12} RGC axons, once leave the cell bodies, run centripetally along the innermost layer in the retina and then turn about 90 degrees at the optic nerve head through the lamina cribrosa to form the optic nerve. Damage to these axons at the lamina cribrosa causes a retrograde degeneration of RGCs that leads to an irreversible loss of vision.

IOP evaluation is widely used to test for optic neuropathy in glaucoma.¹³ The relationship between elevated IOP and glaucomatous optic neuropathy has been extensively studied. In general, glaucoma is broadly divided into two types, normal-tension glaucoma and high-tension glaucoma, with optic nerve damage occurring throughout the entire range of IOP levels. Despite the individual variability, the tendency toward optic nerve damage increases with increasing IOP.¹⁴ The current prevailing view is that glaucoma is a disease of the optic nerve in which IOP exceeds the level that can be tolerated by the individual nerve.

Elevated IOP damages RGCs by inducing cell apoptosis.^{2,15,16} When axon damage occurs, it initiates signaling cascades of cell apoptosis in RGC soma, causing cell death.¹⁷ Similar to that occurring in various neurodegenerative diseases in the brain and spinal cord, axons, dendrites and synapses often degenerate well before the cells die.¹⁸ There is increasing evidence that these neuronal changes contribute to the production of clinical symptoms and signs associated with the disease. The retina and RGCs are no exception. Initiation of compartmentalized and autonomous programs that regulate axon and dendritic degeneration, likely, will affect the physiologic behavior of RGCs and are of critical importance in the pathophysiology of glaucoma.¹⁹

Intracellular Pathways Underlying RGC Death

No matter what is the mechanism that initiates glaucomatous retinal damage, evidence implicates that these pathways converge to a common cellular event to trigger RGC death in glaucoma (**Figure 1**). RGC death caused by various insults, including glutamate excitotoxicity, ischemia, and optic nerve injury is similar. Dying cells display pathological features that generally resemble apoptosis. The same neuroprotective agent appears to be effective in preventing cell death in all instances. Now it is generally accepted that in response to cellular damage, cells initiate a suicide program that is executed by proteases called caspases. The cysteine proteases are key initiators and effectors of neuronal apoptosis.

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Typically, there are two pathways leading to the cell apoptosis, the extrinsic (receptor-mediated) apoptotic pathway and the intrinsic (mitochondria-mediated) pathway (**Figure 1**).^{20,21} Extrinsic apoptotic signals mediate through death receptors of tumor necrosis factor (TNF) super-family, such as Fas, which triggers activation of the death initiator caspase-8.^{22,23} Glaucomatous stress has been shown to induce expression of caspase-8 *in vitro*.²⁴ Mitochondrial-dependent apoptosis requires release of cytochrome c that complexes with Apaf-1 and procaspase-9 to initiate proteolytic cascade, leading to activation of effector caspases.²⁵⁻²⁷ Mitochondrial abnormalities have been detected in patients with open-angle glaucoma.²⁸ Several anti-apoptotic agents which oppose mitochondrially dependent pathways have been evaluated for use in glaucoma.²⁹ These studies suggest that both the extrinsic and intrinsic pathways are involved in glaucomatous neuronal damage.

Bcl-2 family genes play critical roles in all pathways of cell apoptosis by regulating the integrity of mitochondrion membranes.³⁰ Bcl-2 family is divided into two groups, anti- and pro-apoptotic members, and they induce opposing effects on the mitochondrion. Pro-apoptotic members, such as Bid and Bax, form channels on the outer mitochondrial membrane and promote the release of pro-death molecules, including cytochrome c, to cause apoptosis. Anti-apoptotic members include Bcl-2, Bcl-x_L and Mcl, which protects cells from both caspase-dependent and-independent apoptosis by stabilizing the mitochondrion integrity. Thus, the balance of pro- and anti-apoptotic Bcl-2 family gene products determines a cell to live or die under the conditions of injury or a disease.³¹ Expression of both pro- and anti-apoptotic members of Bcl-2 family genes has been detected following optic nerve trauma and experimental glaucoma.^{32,33} Moreover, overexpressing Bcl-2 or suppressing the function of pro-apoptotic protein Bax protects most efficiently RGCs from nerve injury-induced cell death in optic nerve axotomy³⁴⁻³⁶ or in an inherited model of glaucoma.³⁷ These data suggest that manipulating the functions of Bcl-2 family genes may be more beneficial in glaucomatous eye than blocking activations of individual caspase.

Controlling Glaucomatous Damage and Neuronal Protection

Although glaucoma is known as a neurodegenerative disease characterized by the slow progressive death of RGCs, the only current available treatment is to lower the IOP, either through medical, open surgical or less invasive laser approaches. Despite the fact that IOP as a major risk factor of glaucoma, lowering the IOP is not always effective at delaying RGC death and vision loss. Therefore, developing methods that can protect RGC death and rescue visual function lost in glaucoma will be an attractive strategy in the future, in addition to lowering IOP.

Vision restoration in glaucoma requires rescue of RGCs and their axons. The concept of neuroprotection for glaucoma is to employ agents that prevent or delay RGC apoptosis and associated loss of vision. Based on the prevailing view of mechanisms underlying RGC degeneration, various

approaches, for example supplying neurotrophic factors, suppressing the induction of iNOS, inhibiting caspases or interfering with apoptotic pathways, have been evaluated for their protection of RGC death in glaucoma (**Figure 2**).

Interruption of axonal transport and neurotrophic deprivation are believed to be a cause of RGC death in glaucoma. Neurotrophic factors (NTF) are all-time favorite candidates that promote neuronal survival under optic nerve disease or injury. A range of NTF, including BDNF, acidic and basic FGF, NT-4, CNTF and GDNF, have been shown to rescue the death of RGCs after optic nerve injury (**Figure 2**). Administration of BDNF,⁶ CNTF^{7,38} or GDNF via intravitreal injection or sub-retinal injection of proteins, viral vectors,³⁹⁻⁴⁴ delay RGC death in an inherited model of glaucoma.^{6,7} NTFs rescue neuronal death by inhibiting apoptosis, mediating through Ras/Raf/MAPK, CREB, and PI-3K/Akt pathways⁴⁵⁻⁴⁷ that suppress the expression of pro-apoptotic gene, Bad and induce the expression of anti-apoptotic gene Bcl-2. However, even if a continuous supply of BDNF³⁹ and NT-4⁴⁸ is administered, the rescuing effect of NTF appears to be transient⁴⁹. In part, this may be due to the reducing responsiveness of RGCs. Long-term supply of BDNF decreases the expression of its receptor TrkB in the brain⁵⁰ and axotomized retina.⁵¹ Increasing the level of cAMP enhances the survival effect of BDNF⁵²⁻⁵⁴ by translocating TrkB from cytoplasm to cellular membrane.⁵³ In addition, BDNF increases NO synthesis that is destructive to RGCs,^{55,56} and the neuroprotective effect of BDNF could be enhanced when NOS inhibitor is co-administered.^{55,57} These observations suggest that NTF, although protects RGCs temporarily, may not be a long-term solution for RGC loss in glaucoma.

Recruitment of microglia into the injured area and induction of aberrant immunity are other mechanisms that have been implicated to play a role in neural degeneration in glaucoma. The early thinking of this event is related to the "scavenger" activity toward the debris upon axonal degeneration. However, microglia also have negative properties. Microglia inhibitory factor (MIF) that prevents the microglia invasion protects RGCs from damage.⁵⁸ Recently, Schwartz's group has provided evidence to support a beneficial role of autoimmune T-cells to neurons after CNS injury.⁵⁹ T-cell autoimmunity to myelin basic protein display neuroprotective effect on RGCs after optic nerve injury.⁶⁰ The data suggest that the ability of RGCs and the optic nerve to cope with elevated IOP and glaucomatous neural damage is affected by the immune potency in the diseased retina.⁶¹

Although research data remain circumstantial and speculative, evidence derived from several sources support that excitotoxicity may also play a role in the pathogenesis of glaucoma (**Figure 1**). Excitotoxicity is described as a process of neuronal death caused by excessive or prolonged activation of excitatory neurotransmitter glutamate receptors, which contain three large families: N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainite and metabotropic receptors. Excitotoxic injury involves a self-reinforcing cascade of

events of Na^+ and Ca^{++} influx, which result in ongoing neural depolarization, subsequent further release of glutamate, and activation of Ca^{++} -induced death processes.⁶² Anti-excitotoxic drug Brimonidine delays RGC loss in rodent model of optic nerve trauma and glaucoma,^{63,64} probably providing neuroprotection⁶⁵ by relieving the destructive effect of excess Ca^{++} influx (**Figure 2**).⁶⁶ It improves contrast sensitivity in glaucoma patients.⁶⁷ Moreover, Memantine, an uncompetitive NMDA antagonist, has been shown to provide protection for RGCs and visual function in a glaucoma model of non-human primates.^{68,69} Betaxolol, a selective beta-blocker that inhibits NMDA-stimulated Ca^{++} influx,⁶⁶ preserves visual field in open-angle glaucoma patients, despite its minor effect on reducing IOP,^{70,71} suggesting that its neuroprotective effect may be IOP-independent. Nevertheless, evidence provided by several investigators failed to detect an increase in glutamate levels in the vitreous of both experimental and clinical glaucoma.⁷²⁻⁷⁴ Although plenty of data showed that blocking glutamate receptor activity delays optic nerve trauma- or ischemia-induced cell death,⁷⁵ this may not be applied completely to glaucoma. The intriguing results of glutamate antagonists in glaucoma patients suggest pressure-independent neuroprotective strategies for treating glaucoma; however, these studies have left many unanswered questions, and large scale evidence is still needed.

As discussed above, regardless of the mechanisms initiating the neural damage in glaucoma, apoptosis is a common cellular or signaling event leading to RGC death; thus, blocking caspase activation would be a logical step toward neuroprotection in glaucoma. Caspase-3 inhibitor has been shown to prevent RGC death following optic nerve injury,^{76,77} and BIRC-4, a human caspase inhibitor, protect RGCs from glaucomatous damage.⁷⁸ However, similar to that observed with NTF treatment, the effect of caspase inhibitors, which often fail to block TNF- α -mediated RGC death in culture,⁷⁹ is transient,⁸⁰ suggesting the involvement of multiple mechanisms in glaucomatous RGC damage. An anti-apoptotic agent, minocycline, has been demonstrated to have a protective effect on a range of neurodegenerative diseases⁸¹⁻⁸³ not only because it effectively penetrates the blood-brain barrier⁸⁴ and inhibits the activities of caspase-1 and -3,⁸⁵ but also because of its anti-microbial and anti-inflammatory functions. The action of minocycline is associated with a range of stress-induced responses, including decreasing NOS activity,⁸² inhibiting cytochrome c release,⁸⁶ and suppressing free oxygen radical.⁸⁷ Systemic administration of minocycline has been shown to protect cell death in both glaucoma and optic nerve transection models.⁸⁸ By far, manipulating Bcl-2 pathways, which regulate both caspase-dependent and -independent cell death signals, is found to be most effective in promoting RGC survival under injury. Overexpressing Bcl-2 achieved by either a genetic or pharmacological approach efficiently inhibits RGC death upon optic nerve injury.³⁴ Drug that induces Bcl-2 expression, such as the mood-stabilizer lithium, is known to support RGC survival in culture.^{89,90} On the other hand, mice with inherited glaucoma (DBA/2J) and deficient in the pro-apoptotic molecule Bax were completely protected from RGC

loss.³⁷ Thus, supporting the intrinsic anti-apoptotic mechanism via manipulating Bcl-2 pathways may be most effective in counteracting apoptotic signaling events in RGCs in glaucoma.

Stimulation of Optic Nerve Regeneration

Restoring vision requires not only survival of RGCs, but also regeneration or repair of their axons. Although neuroprotection could be achieved to a certain extent after injury, surviving RGCs usually do not regenerate their axons.⁹¹⁻⁹⁴ Despite the intense effort and substantial progress made in the field, regenerating the damaged optic nerve remains a challenge. The critical issue hampering our understanding of the mechanisms controlling optic nerve regeneration often lays in the complexity of the problem and its potential involvement of multiple factors. Previous attempts to manipulate any one of the factors believed to regulate axon regeneration have proven insufficient for supporting regeneration, suggesting that a combined approach may be required.⁹⁵ To this end, we need to know the essential elements required to boost the intrinsic regenerative capacity of RGC axons and to eliminate the growth inhibition presented in the mature optic nerve and brain environment.⁹⁶⁻⁹⁹

The current view concerning the mechanisms governing the optic nerve regenerative failure reflects both the intrinsic inability of mature RGCs to reinitiate axonal growth program and presence of a CNS environment that is non-permissive for such growth (**Figure 3**).^{97,98,100} The intrinsic axonal growth capacity occurs as a developmental program of RGCs.¹⁰¹ Embryonic RGCs readily regenerate their axons once injured; however, at a certain point in development, RGCs undergo a profound and irreversible loss of axon growth capacity and lose the ability to regenerate axons even if within a permissive environment.^{101,102} This developmental switch of the intrinsic growth capacity by RGC axons was later identified to be regulated by anti-apoptotic gene Bcl-2.¹⁰³ A loss of Bcl-2 expression in RGCs correlates with the onset of optic nerve regenerative failure,¹⁰¹ and overexpression of Bcl-2 not only protects RGCs from injury-induced cell death, but also promotes robust optic nerve regeneration *in vitro* and *in vivo* in an early neonatal stage (**Figure 4**).^{92,103} Almost 70% of severed RGC axons in Bcl-2 transgenic mice regenerate axons into the brain targets.^{92,103} In contrast, another anti-apoptotic member of the Bcl-2 family member, Bcl-X_L, albeit promotes RGC survival, fails to stimulate optic nerve regeneration after injury,¹⁰⁴ suggesting a novel activity of Bcl-2 in RGC axonal regrowth. Evidence indicates that Bcl-2, which resides in the endoplasmic reticulum (ER), regulates intracellular Ca^{2+} response after neural injury, and in turn activates MAPK and CREB to support the intrinsic growth potential of RGC axons (**Figure 3**).⁹³ These studies demonstrate that Bcl-2 is central to the regulation of intrinsic developmental program for axonal regrowth by RGCs and is sufficient to support optic nerve regeneration *in vivo* up to a certain point in development.

In addition to Bcl-2, several other molecules have been reported to support the intrinsic growth potential of RGC axons (**Figure 3**). For example, lens injury stimulates the production of a macrophage-derived factor oncomodulin that can enhance the intrinsic growth ability of RGC axons.^{105,110} Heiduschka et al reported that lens injury improves optic nerve regeneration and that regenerating axons could reach the brain and restore visual evoked potential in rats.¹⁰⁹ Another factor, CNTF, has been shown to promote axonal regeneration^{91,111,112} even at a low dosage without enhancing the survival of axotomized RGCs,⁹¹ supporting the notion that CNTF may increase the intrinsic growth ability of RGC axons. The cyclic nucleotide cAMP, a well-known second messenger that regulates diverse neuronal functions, can also act within RGCs to enhance their axons' intrinsic growth potential.^{113,116} Elevation of cAMP in RGCs promotes the translocation of MAPK and recruiting TrkB to cell membranes.⁵³ The endogenous levels of cAMP in dorsal root ganglion (DRG) neurons mark their developmental loss to grow axons onto an inhibitory substrate, such as myelin.¹¹⁷ Myelin-associated glycoprotein decreases neurite outgrowth from mature DRG neurons that exhibit low levels of cAMP as compared with neonatal DRG neurons.¹¹⁸ In addition, application of cAMP analogue significantly improves optic nerve regeneration *in vivo*¹¹⁹ and enhances the regenerative effect of CNTF to the severed optic nerve.^{120,122} Likely, cAMP activates PKA, hence inhibits Rho signaling,¹²³ which is the common downstream signal regulating axonal growth inhibition triggered by various growth inhibitory proteins to promote axonal regeneration.^{123,124}

Failure of the optic nerve to regenerate is also attributed to the presence of growth inhibitors in the mature brain environment. As mentioned earlier, mice overexpressing Bcl-2 support robust optic nerve regeneration only up to a certain age (first postnatal week), but not in the adult—when the CNS environment is known to be inhibitory to axonal growth.⁹² These data, consistent with those reported by others, implicate two parallel mechanisms at work controlling the optic nerve regeneration: (1) the intrinsic growth potential of RGC axons, and (2) growth inhibition developed in the CNS glial environment that prevents optic nerve regeneration.

CNS glial cells—mainly, oligodendrocytes or myelin forming cells and astrocytes, which respond to injury and form glial scars—have been proposed also to contribute to axon growth obstacles in the adult CNS environment.^{96,98} It has been shown that the failure of optic nerve regeneration is inhibited by the formation of astrocytic scars. Mutant mice overexpressing Bcl-2 and simultaneously displaying a weakened scar-forming ability showed a prolonged period of optic nerve regeneration in comparison with mice expressing Bcl-2 alone, until the point when myelin develops in the mature CNS. Furthermore, RGC axons in adult mice overexpressing Bcl-2 could regenerate into a zone of optic nerve where the reactive astrocytes were removed by a pharmacological approach, implicating an essential role of astrocytic scar in axon growth inhibitor during optic nerve regeneration.⁹² Extracellular matrix molecules associated

with glial scars, particularly chondroitin sulfate glycoprotein (CSPG), have been suggested to represent a critical barrier to axon regeneration.^{125,127} Removal of CSPG around lesion site enhances axonal regeneration (**Figure 3**), albeit to a limited extent.^{128,129} On the other hand, within the last decade, studies of the mechanisms of CNS growth inhibition led to a major advance—the molecular cloning of myelin-associated growth inhibitor Nogo^{130,131} and the receptor NgR (**Figure 3**).¹³²⁻¹³⁷ Expression of Nogo by CNS myelin is thought to be a major factor in CNS regenerative failure. In addition to Nogo, at least two other proteins—myelin-associated glycoprotein (MAG) and oligodendrocyte/myelin-associated glycoprotein (OMgp) - have been identified that can also cause growth cone collapse and inhibit neurite outgrowth in culture.^{138,140} Nogo, MAG and OMgp all bind a common receptor, NgR (a GPI-linked cell surface molecule), and its co-receptors p75 and Troy, to inhibit neurite extension.^{132,141,143} Neutralizing antibodies against CNS myelin preparation or Nogo, mainly IN-1 or its derivatives, have been shown to induce considerable slow neurite sprouting from the axons of corticospinal neurons and promote functional recovery after spinal cord trauma.^{144,145} More recent data suggest that myelin and CSPG may mediate a common signaling pathway through epidermal growth factor receptor to retard axonal growth. This is the first report showing a single receptor that transduces the inhibitory signal from both classical axon growth inhibitors presented by reactive astrocytes and myelin. While the most logical step is to examine the CNS regeneration following removal of these components, the results obtained from Nogo or NgR-deficient mice are inconclusive.^{147,151} The data suggest that in order for regeneration to occur, a combined approach manipulating both the intrinsic growth potential of RGC axons as well as improving the nature of the CNS environment is required.

Conclusion

Glaucoma is a chronic neurodegenerative disease of the eye. Currently, the mechanism and pathogenesis of the disease remains unclear. The glaucomatous-induced death of RGCs and axon degeneration could be attributed by many factors. Considering a combined strategy that targets multiple factors to prevent RGC loss and neurodegeneration may be beneficial in glaucoma. Ultimately, finding ways to regenerate the optic nerve and reconnect the target innervations will be the goal to restore vision for glaucoma patients, especially for those with severe visual impairment.

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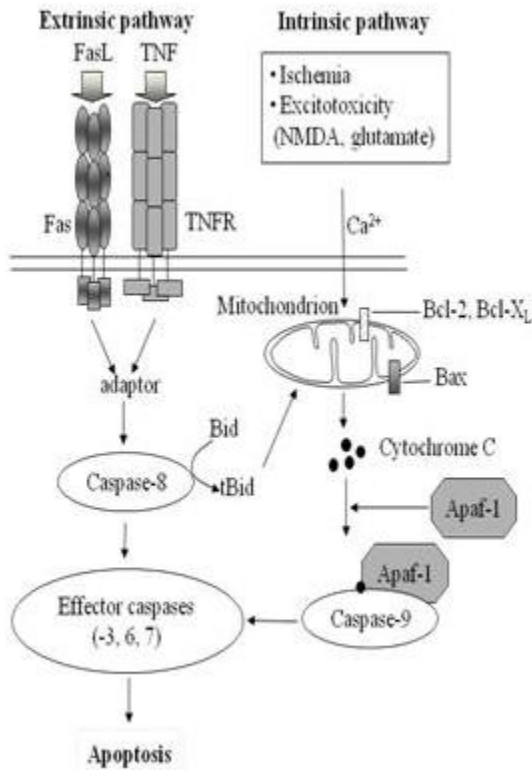


Figure 1. The extrinsic and the intrinsic pathways regulating cell apoptosis. Intrinsic pathway of apoptosis is a mitochondrion-mediated event that is induced by damaging signals such as ischemia, excitotoxicity and neural trauma. Such signals lead to cytochrome c released from mitochondrion via a series of intracellular events. Apaf-1 (Apoptosis protease activating factor-1) protein is in latent state until it binds to cytochrome c. The cytochrome c/Apaf-1 complex binds and activates pro-caspase-9 and, consequently, leads to the cleavage and activation of effectors caspases-3, 6 and 7, and apoptosis. Extrinsic pathway of apoptosis is a receptor-mediated event. Activation of Fas receptor or tumor necrosis factor receptor (TNFR) by Fas ligand or TNF, correspondingly, activates adaptor protein that triggers caspase-8 cleavage and activation. Caspase-8 serves 2 roles: (1) It directly activates downstream effector caspases to induce apoptosis. (2) It can also convert Bid to its truncated form (tBid) which transfers the death signal to the mitochondrion. Once tBid is translocated into the outer membrane of mitochondrion and it would affect the membrane permeability and lead to cytochrome c release into cytoplasm. Subsequently, cytochrome c will activate the downstream pathway of the intrinsic pathway of apoptosis.

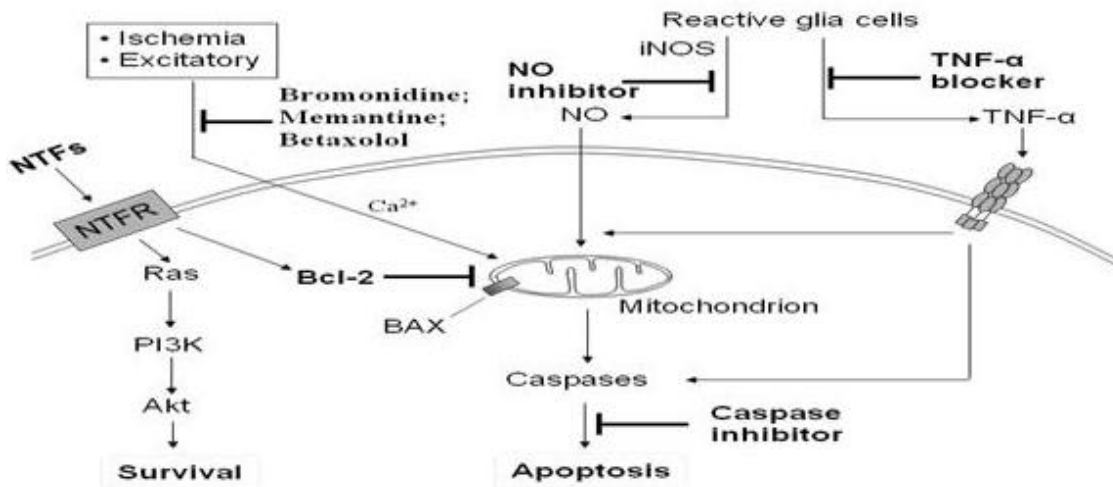


Figure 2. General scheme of neuroprotective approaches for blocking RGC death in glaucoma.

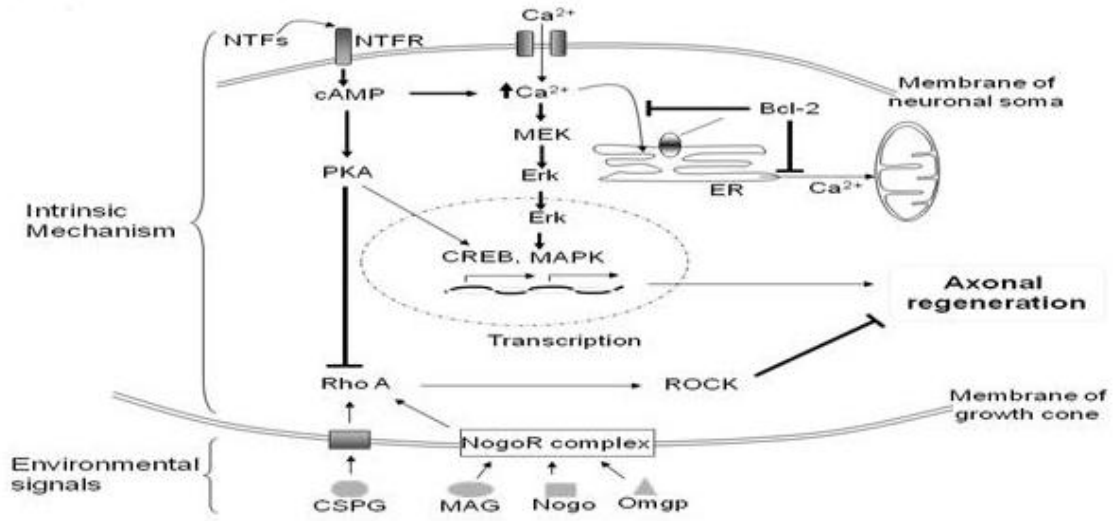


Figure 3. Schematic illustration of signaling pathways controlling RGC axonal regeneration.

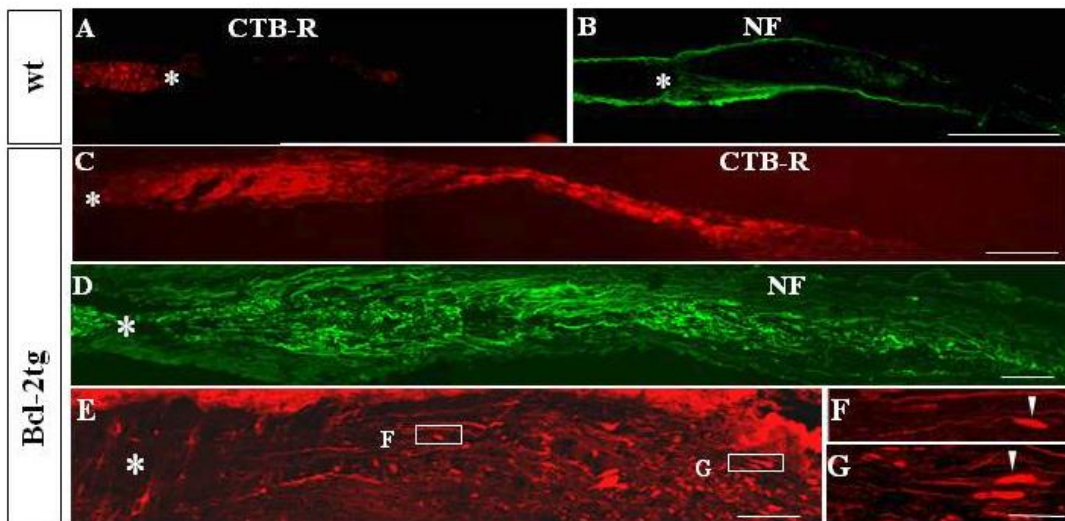


Figure 4. Robust and rapid optic nerve regeneration in P3 *Bcl-2tg* mice.