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Neuroprotection in Glaucoma

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1. Introduction

Glaucoma is a distinctive group of optic neuropathies characterized by progressive degeneration of neuronal tissue due to death of retinal ganglion cells, with accompanying gradual visual field loss. [1, 2] It is the leading cause of irreversible blindness worldwide [3] and complex genetic and environmental risk factors have been implicated in its progression. [4-7] Neuroprotection for glaucoma refers to any intervention that aims either to prevent optic nerve damage and retinal ganglion cell death or to preserve already diseased neuronal tissue and its function, with the ultimate goal of maintaining vision. Thus, neuroprotective agents can be thought of as pharmacological antagonists of intracellular injury and death pathways.

Agents that lower the intra-ocular pressure (IOP) have been shown to slow glaucoma progression in several controlled clinical trials and even arrest the progression in some cases [8-10], yet their effectiveness is limited in preventing retinal ganglion cell loss. Retinal ganglion cell damage in glaucoma is not confined to the neurons that are insulted primarily, but neighboring neurons are injured secondarily as well. [11] Therefore, efforts that focus on discovering alternative therapeutic approaches independent of IOP reduction have placed neuroprotective treatment modalities at the frontiers of glaucoma research.

2. Apoptosis and necrosis in glaucoma

Apoptosis and necrosis constitute the two major pathways to cell death. [12] In 1972, Kerr, Wyllie and Currie used the Greek term 'apoptosis' (from the Greek: dropping off of petals from plants) to describe a specific morphological aspect of cell death. [13] Apoptosis is accompanied by rounding-up of the cell, reduction of cellular volume, chromatin condensa-

tion, and engulfment by resident phagocytes. Apoptosis is the best-characterized type of programmed cell death, and these morphological changes are largely mediated by the activation of the caspase family of cysteine proteases. [14] In contrast, 'necrosis' (from the Greek: death) is associated with a gain in cell volume, swelling of organelles, plasma membrane rupture and subsequent release of intracellular contents with ensuing inflammation. Until recently necrosis had been considered a passive, unregulated form of cell death. New evidence indicates that some forms of necrosis can be induced by regulated signal transduction pathways such as those mediated by receptor interacting protein kinases (RIP Kinases). RIP kinases cross talk with caspases and lie downstream of cell death signals such as the Fas Ligand or the Tumor Necrosis Factor- α (TNF- α). [15] This programmed form of necrosis is termed programmed necrosis or necroptosis. [12, 16, 17]

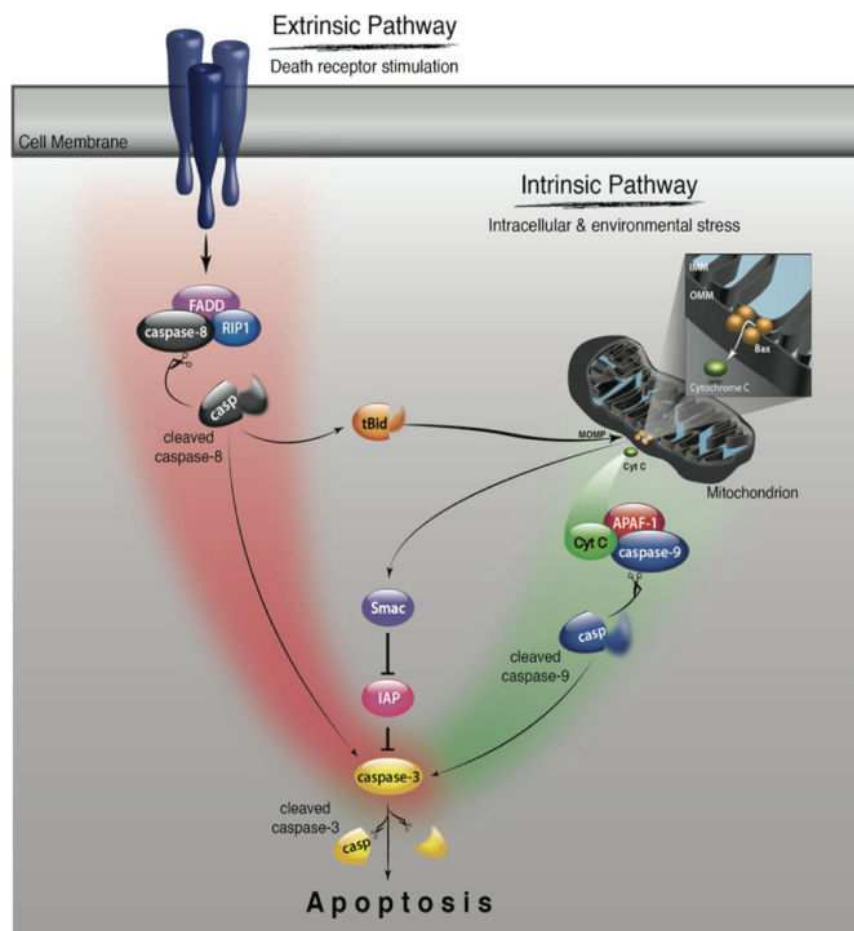


Figure 1. The extrinsic pathway is initiated by binding of death ligands such as TNF- α and Fas ligand to their cell-surface death receptors such as TNF receptor and Fas. The death domains of these receptors recruit adaptor molecules like FADD and caspase-8, which leads to the activation of caspase-8. Activated caspase-8 cleaves the effector caspases such as caspase-3, thereby activating them and inducing apoptosis. The extrinsic pathway interacts with the intrinsic pathway via caspase-8-mediated cleavage of Bid. The intrinsic pathway is initiated by release of mitochondrial intermembrane proteins such as cytochrome c and Smac/Diablo into the cytosol. Released cytochrome c forms an apoptosome with Apaf-1 and caspase-9, which leads to caspase-9 activation. Smac/Diablo enhances caspase activation through the neutralization of IAP proteins.

Cysteine aspartate-specific proteases or caspases are central to the execution of apoptosis. Their activation occurs mainly through two distinct pathways: extrinsic and intrinsic (Fig. 1). [18] The extrinsic pathway is initiated by binding of extracellular death ligands such as TNF- α and Fas ligand to their cell-surface death receptors, TNF receptor and Fas. [19] The death domains of these receptors recruit adaptor molecules like Fas-associated death domain (FADD) and caspase-8, forming the death inducing signaling complex (DISC). [20] The formation of DISC leads to activation of caspase-8, which in turn mediates cleavage of effector caspases. The extrinsic pathway can cross-talk with the intrinsic pathway through caspase-8-mediated cleavage of Bid, a BH3-only member of the Bcl-2 family of proteins. [21, 22] Bid cleavage releases a truncated fragment that triggers the release of mitochondrial proteins, thereby initiating the intrinsic caspase cascade as described below.

The intrinsic pathway is mediated by mitochondria. [23] In response to intracellular and environmental stress, mitochondria release inter-membrane proteins such as cytochrome c and second mitochondria-derived activator of caspases (Smac)/direct inhibitor of apoptosis-binding protein with low pI (Diablo) into the cytosol. Released cytochrome c triggers the formation of an apoptosome along with apoptotic protease activating factor-1 (Apaf-1) and caspase-9 in the presence of ATP, which leads to caspase-9 activation. [24] Smac/Diablo enhances caspase activation through the neutralization of inhibitor of apoptosis (IAP) (Fig. 1). [25, 26]

Necrosis is mainly regulated by a set of protein Kinases called RIP Kinases. RIP1 switches its function to a regulator of cell death when it is deubiquitinated by A20 or cylindromatosis (CYLD). [27, 28] Deubiquitination of RIP1 abolishes its ability to activate NF- κ B after TNF- α stimulation, and leads to the formation of cytosolic DISC with FADD and caspase-8, the so-called complex II. [29] As described above in caspase signaling, DISC formation leads to caspase-8 activation and subsequent apoptosis. In contrast to TNF signaling, Fas directly recruits RIP1, FADD and caspase-8 to the plasma membrane and forms DISC (Fig. 2). [30] During apoptosis, RIP1 is cleaved and inactivated by caspases. [31] Although many cell lines are protected against death receptor-induced apoptosis by use of pan-caspase inhibitors, Vercammen and others found that, in mouse L929 fibrosarcoma cells, caspase inhibition does not prevent TNF- or Fas-induced cell death and the cells acquire a necrotic morphology. [32, 33] In 2000, Holler and others discovered that RIP1 kinase is a key molecule that induces necrotic cell death mediated by death receptors. [34]

In 2005, Degterev, Yuan, and others using chemical library screening, identified small compounds named necrostatins that specifically inhibit death receptor-mediated necrosis. [16] Necrostatins have been shown to specifically inhibit RIP1 kinase phosphorylation during necrosis without affecting death receptor-induced NF- κ B activation. [35] RIP1 kinase activity appears to be important for necrosome formation, as necrostatin-1 abolishes the formation of the RIP1-RIP3 complex and RIP3 kinase phosphorylation during necrosis. [36, 37] Cho and others propose that another unknown kinase activated by RIP1 may mediate RIP3 phosphorylation, based on the findings that ectopically expressed RIP1 does not phosphorylate RIP3. [36] The activities of RIP1 and RIP3 may be mutually regulated in a necrosome signaling complex. RIPK activation leads likely to increased reactive oxygen species (ROS) production. Activated RIP3 interacts with metabolic enzymes such as glycogen phosphory-

lase (PYGL), glutamate-ammonia ligase (GLUL) and glutamate dehydrogenase 1 (GLUD1). [38] Activation of these enzymes eventually stimulates the Krebs cycle and oxidative phosphorylation, thereby increasing mitochondrial ROS production. Secondly, after TNF- α stimulation, RIP1 forms a complex with TNFR, Riboflavin kinase, and NADPH oxidase 1. [39, 40] NADPH oxidase is the best characterized non-mitochondrial source of ROS and forms a membrane bound enzyme complex with p22phox and Rac. [41] Thirdly, RIP1 kinase activates autophagic degradation of catalase, which converts hydrogen peroxide to water and oxygen, thereby increasing ROS accumulation. [42] More recently, activation of the necrosome has shown to interact with the mixed lineage kinase domain-like (MLKL) and phosphoglycerate mutase 5 (PGAM5) resulting in the fusion of mitochondria and necrotic cell death. [43, 44]

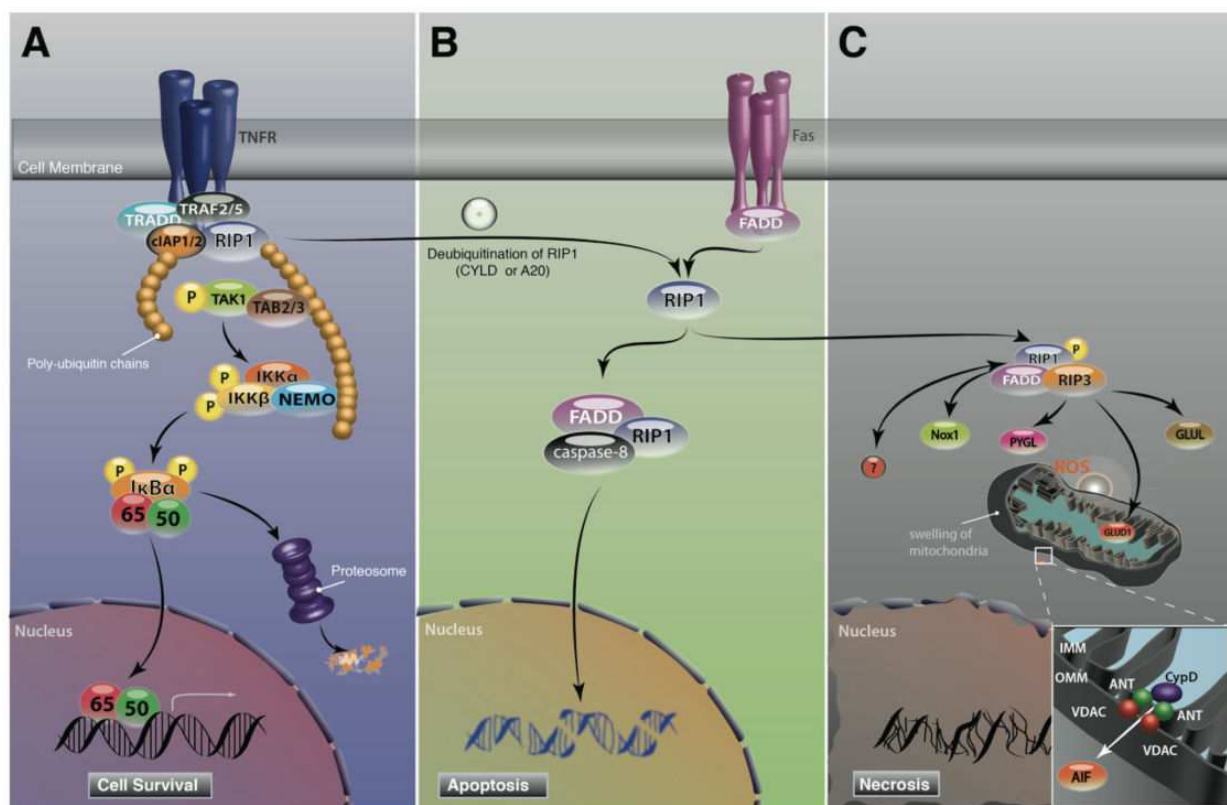


Figure 2. Schematic of the RIPK signaling pathway.

A, In response to TNF- α stimulation, RIP1 is recruited to TNFR and forms a membrane associated complex I with TRADD, TRAF2/5 and cIAP1/2, which in turn leads to polyubiquitination of RIP1 and pro-survival NF- κ B activation.

B, RIP1 switches function to a regulator of cell death when RIP1 is unubiquitinated by A20 or CYLD. Deubiquitination of RIP1 leads to the formation of cytosolic DISC with FADD and caspase-8, the so-called complex II. In contrast to TNF signaling, Fas stimulation directly forms DISC. Activation of caspase-8 in DISC leads to apoptosis induction. During apoptosis, RIP1 is cleaved and inactivated by caspase-8. C, In conditions where caspases are blocked or cannot be activated efficiently, RIP1 binds to RIP3, and both RIP1 and RIP3 kinases are phosphorylated at the RIP1-RIP3 complex. RIP1 kinase phosphorylation is critical for necrosis induction. In response to TNF- α , RIP1 binds to NADPH oxidase 1 and produces superoxide. Activated RIP3 binds to PYGL, GLUL and GLUD1 and increases the production of mitochondrial ROS. ROS overproduction leads to mitochondrial dysfunction, resulting in the release of mitochondrial pro-death proteins. Activation of the necrosome has been shown to interact with mixed lineage kinase domain-like (MLKL) and phosphoglycerate mutase 5 (PGAM5) resulting in the fusion of mitochondria and necrotic cell death

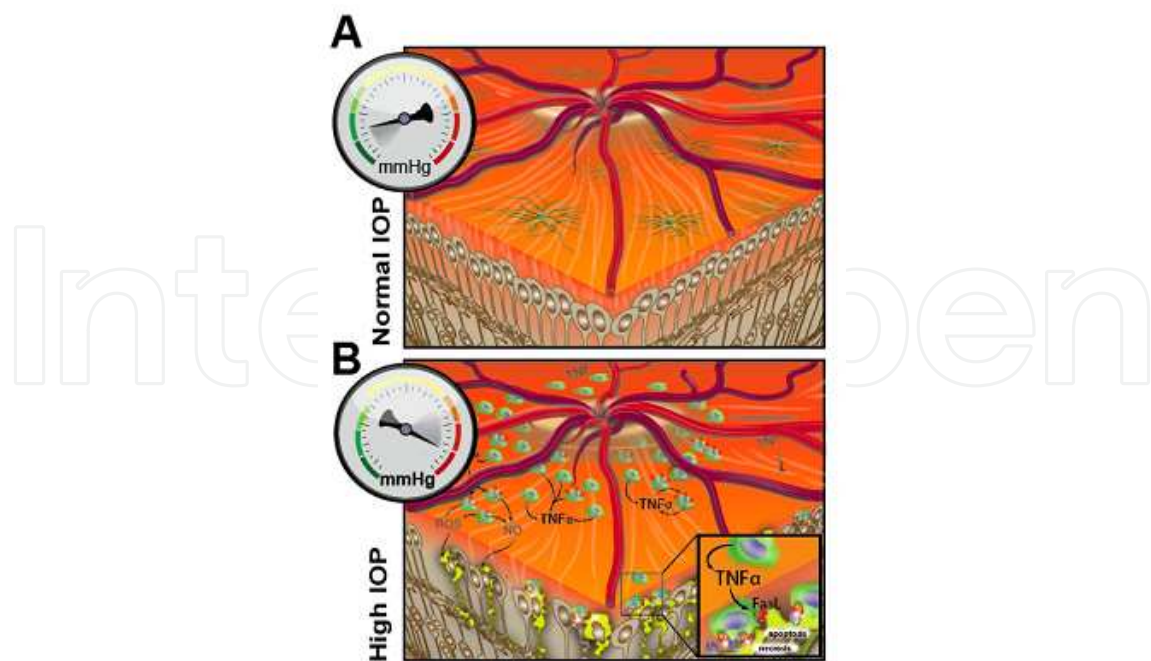


Figure 3. Schematic of changes in animal models of high IOP mediated optic nerve damage. A, In normal IOP microglia are quiescent and cells are in normal state. B, Elevated IOP leads to increased numbers of activated microglia with amoeboid morphology around the optic nerve head. These microglia appear to secrete TNF- α leading to RGC death. Other molecules, including FasL on microglia, nitric oxide (NO), and reactive oxygen species (ROS) may also play a role in RGC death. Changes in blood supply and ischemia also contribute to the death of RGCs.

In chronic glaucoma, apoptosis of retinal ganglion cells has been shown as the main pathway to cell death. [2, 45, 46] The exact mechanism though is not clear. Since a significant proportion of patients who suffer from glaucoma have high IOP, it has been hypothesized that high IOP induces stress to retinal ganglion cells either directly [47, 48] or indirectly to their axons at the lamina cribrosa [49] thus leading to apoptosis. However, although high IOP has been thought to be the main causative factor, the fact that glaucoma can occur in the presence of IOP within the normal range, while can be absent in a subset of subjects with high IOP indicates that the underlying etiology of this disease remains unknown and in essence fail to fully fulfill Koch's postulates [50, 51].

Mechanisms believed to cause stress to retinal ganglion cells and to initiate the apoptotic cascade include: biomechanical stress [52, 53], excitotoxicity [54-57], tissue hypoxia [58, 59], altered nutritional blood supply [60, 61], mitochondrial dysfunction [62-65], Müller glial cell activation [66], protein misfolding [67-69], oxidative stress [70, 71], dysfunctional autoimmunity [72], neurotrophin deprivation [73, 74], and inflammation. [75, 76]

3. Animal models

Animal experimental models in glaucoma research are produced by inducing either an elevation in intraocular pressure or damage to the axons of retinal ganglion cells. [77] Several

methods have been employed to raise intraocular pressure in animal models. They range from obliteration of episcleral vessels [78] to iatrogenic sclerosis of the trabecular meshwork (laser-induced [79] or through retroinjection of hypertonic saline into the limbal plexus [80]) or to mechanical obstruction of the trabecular meshwork with polystyrene beads. [81] Direct damage to retinal ganglion cell axons can be achieved via axotomy or crushing of axons. Retinal ganglion cell death occurs in 1-2 weeks from the time of optic nerve transection or crushing of axons in a fairly predictable fashion. [82] Interestingly, there is a specific mouse strain (DBA/J2) which inherently produces a much slower degeneration of retinal ganglion cells; a process thought to more closely mimic human disease than other induced mouse models of glaucoma. [83] Mutations in the transmembrane glycoprotein Gpnmb (premature stop codon at position 150 -GpnmbR150X) and the presence of the Tyrp1b gene allele (the b mutation is in a heme-associated domain and renders the protein susceptible to rapid proteolytic degradation) in the DBA/2J mouse model are thought to cause pigment dispersion and iris atrophy respectively. Both proteins are highly expressed in melanocytes and are involved in melanin and cell growth regulation. The decreased levels of Gpnmb and Tyrp1 lead to cell death and abnormal melanin content release that deposits onto the trabecular meshwork resulting in elevated IOP. [84] Of note, these mutations have not been shown to cause glaucoma in patients.

The ideal animal model should manifest slow focal injury to retinal ganglion cell axons at the optic nerve head that leads to sectoral death of retinal ganglion cells without loss of other retinal neurons. [77] The currently used animal models for glaucoma research are far from ideal and their limitations are partly responsible for the failure to translate results from the bench to the bedside. For the elevated IOP models, it is clear that there are different susceptibilities of retinal ganglion cell damage among different species (mice, rats, monkeys) and among different strains or age of the same species. [51, 85, 86] For the axotomy models, acute damage to retinal ganglion cell axons is different from the slow progression seen clinically in glaucoma, and thus it remains unclear whether studies with these models can safely reproduce glaucomatous damage as it occurs in humans. [82] For the DBA/2J mouse, there is significant variability in glaucoma progression among animals and between eyes of the same animal, which renders any comparison study particularly difficult. [77]

An inherent limitation of using animal models for the study of any human disease process is that animal models often lack the heterogeneity, compounded comorbidities, and polypharmacy that are present in human pathologic conditions. Moreover, it is difficult to extrapolate from animal studies what the appropriate dose of a putative neuroprotective agent would be in human subjects since pre-clinical studies rarely assess for a dose-response curve, therapeutic index, and central nervous system penetration. [87, 88]

4. Success in the lab

Efforts in pre-clinical studies have targeted the various mechanisms that produce axonal degeneration and retinal ganglion cell death and have led to the discovery of an array of neu-

roprotective agents. [89] First, apoptosis of retinal ganglion cells has been inhibited in the lab through the use of anti-excitotoxic agents that primarily inhibit or interfere with the glutamate excitotoxic cascade. [90] Glutamate is a natural neurotransmitter that is required by the organism for proper cell signaling including retinal ganglion cells. Glutamate acts through many types of glutamate receptors/ion channels. One of these receptors/ion channels is the *N*-methyl-D-aspartate (NMDA) type, which leads to calcium flux upon activation. Persistent activation of this channel by glutamate or NDMA leads to excitotoxicity. Glutamate induced excitotoxicity has been shown in some but not all animal models and elevated glutamate levels have been detected in some but not all studies (reviewed in [91]). Memantine is an uncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) type of glutamate receptor/channel. It can only bind to this ion channel in its "open" state, that is after glutamate has already bound to its receptor and has caused the channel to open. [92] Studies on several animal models of glaucoma have supported the neuroprotective role of memantine on retinal ganglion cells. [93]. Activated glutamate receptor leads to increased calcium flux. Calcium levels are important in many neuronal signaling events and aberrant calcium levels are thought to be important mediators of neuronal cell death. Increased levels of intracellular calcium can be very detrimental to the health of the cell. Most recently, inhibitors of the L-type voltage-gated calcium channel, clonidine [94] and lomerizine [95] as well as the alpha-2 adrenergic agonist brimonidine [96] have also been shown to limit glutamate-induced excitotoxicity. Although the exact mechanism of action of brimonidine remains unknown, intraperitoneal pre-treatment with brimonidine has been shown by several groups to increase survival of retinal ganglion cells after optic nerve or retinal injury in animal models of NDMA excitotoxicity, optic nerve crush and ischemia. [97-100]

Antiapoptotic strategies utilize neurotrophins [101] or aim at the activation of Bcl-2 antiapoptotic pathways. [102] Neurotrophins are factors that signal the survival and growth of neurons. The first neurotrophin to be discovered was Nerve Growth Factor (NGF) in the 1960s. In 1986 Levi-Montalcini and Cohen shared the Nobel prize "for their discovery of growth factors for neurons." Neurotrophins are peptides that bind to cell surface receptors and activate survival signals, thus suppressing the apoptotic process (Fig. 4). [80, 103, 104] Exogenous administration of brain-derived neurotrophic factor (BDNF) or nerve growth factor (NGF) has delayed but not prevented retinal ganglion cell death. [105-108] Injection of BDNF, ciliary neurotrophic factor (CNTF), neurotrophin-4 (NT-4), fibroblast growth factor-2 (FGF-2), and neurturin (a ligand for a glial cell line-derived neurotrophic factor family related receptor A2 - GFRA2) into the vitreous has also increased survival of retinal ganglion cells. [105, 109, 110] Neurotrophin delivery and overexpression via viral vector delivery seems to promote survival of retinal ganglion cells even further. [106] Finally, agents that interact with the two major neurotrophin cell surface receptor systems, tropomyosin-related kinase (Trk) receptor and p75 neurotrophin receptor (p75NTR), can also prolong survival of retinal neuronal tissue (Fig. 4). [111-113] Neurotrophins are difficult to be used in clinics because of their polypeptidic nature: they are destroyed in the acidic milieu of the stomach, while their size hinders their ability of crossing the blood-brain barrier. Thus, special techniques have to be invented, such as intravitreal implants of cells producing these molecules locally, such as the CNTF producing cells by Neurotech (Cumberland, RI, USA).

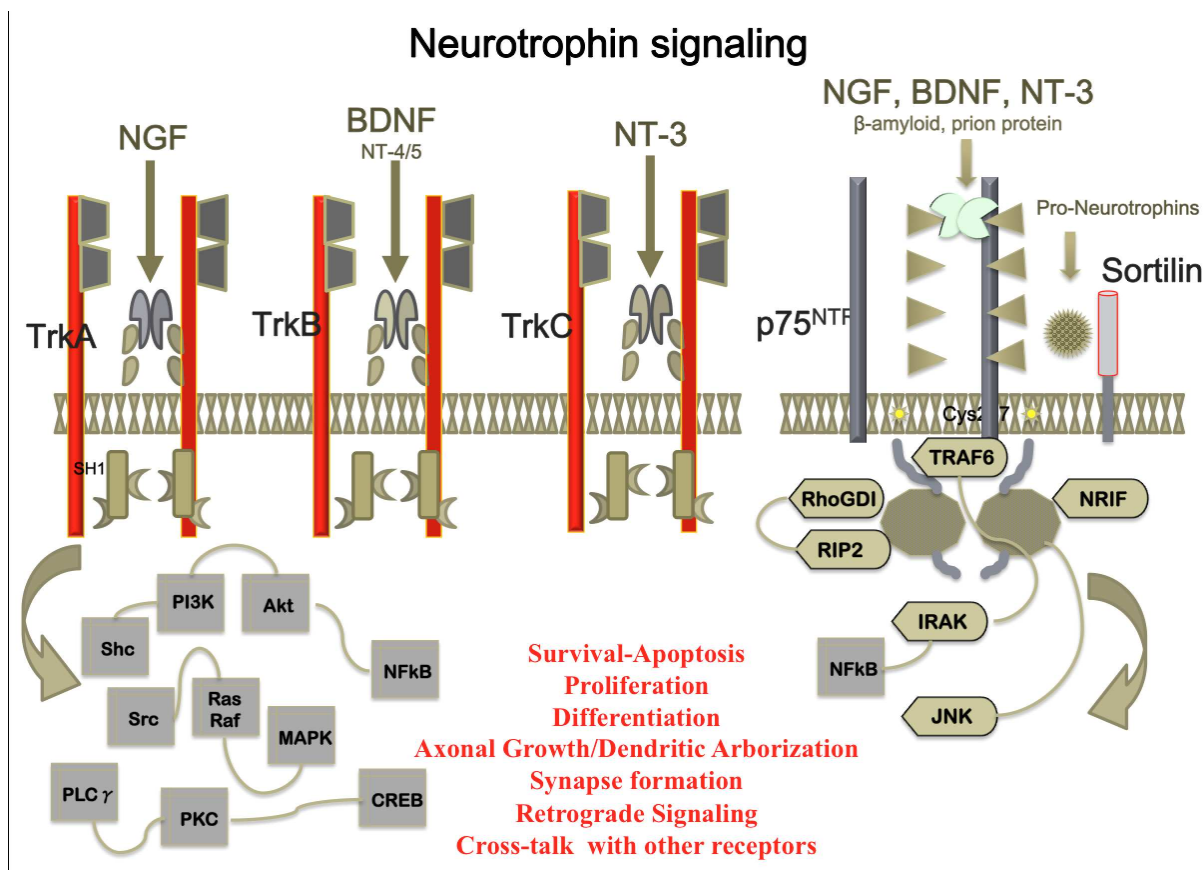


Figure 4. Neurotrophin Signaling Summary. (courtesy of Dr A. Gravanis). Neurotrophins include the first to be discovered: Nerve Growth Factor (NGF) as well as Brain Derived Neurotrophic Factor (BDNF) and Neurotrophin 3 and 4 (NT-3 and NT-4). There are two classes of receptors for neurotrophins: p75 and the "Trk" family of Tyrosine kinase receptors. P75 can bind all factors, whereas Trk receptors are specific for their ligands. Binding of neurotrophins to their receptors leads to activation of many pro-survival signals including PI3K, Akt, and MAPK among others.

Tumor necrosis factor- α (TNF- α) can lead to death of retinal ganglion cells by inducing mitochondrial damage and activation of caspases. [114] Inhibition of TNF- α via the use of etanercept [115] or an anti-TNF- α neutralizing antibody [116] can protect retinal ganglion cells in mouse models of glaucoma.

Providing free radical scavengers, such as coenzyme Q10 [117, 118] or thioredoxin [119], or inhibiting the formation of free radicals by blocking the action of nitric oxide synthase [120] has shown promise as an alternative neuroprotective strategy. Inflammatory and immune mechanisms also play a role in glaucomatous damage of retinal ganglion cells. [121] Immunomodulation [122], inhibition of calcineurin by tacrolimus [123], and subcutaneous injection of granulocyte-colony stimulating factor [124] also have neuroprotective potential in glaucoma.

Other mechanisms that have been investigated in the lab with encouraging results include the use of mesenchymal stem cells, which are thought to exert their effect through production of neurotrophins or stimulation of inflammation [125, 126]. A recent study has shown that amyloid β ($A\beta$) is found to be elevated in an animal model of ocular hypertension induced glaucoma and that inhibition of the generation of amyloid β led to preservation of

RGCs. [67] Other studies have shown that treatment with minocycline reduces RGC death in experimental glaucoma. [127] The antiapoptotic effects of minocycline are not very clear and seem to be pleiotropic. They are exerted, at least in part, by modulating inflammation and metalloproteinases and by reducing mitochondrial calcium overloading. Minocycline stabilizes the mitochondrial membrane and inhibits release of cytochrome c and other apoptotic factors into the cytoplasm, thus resulting in decreased caspase activation and nuclear damage. Minocycline also exerts caspase-independent neuroprotective effects including upregulation of anti-apoptotic factor Bcl-2. Another promising agent is Rasagiline, a monoamine oxidase inhibitor that has been found have neuroprotective and anti-apoptotic effects partially through increase in the mitochondrial family of Bcl-2 proteins, prevention in the fall in mitochondrial membrane potential, prevention of the activation of caspase 3, and of translocation of glyceraldehyde-3-phosphate dehydrogenase from the cytoplasm to the nucleus. It can also affect the secretion of amyloid precursor protein (APP) and it has been shown to delay RGC cell death in experimental glaucoma [128]. However, it has to be noted that it has not taken approval by the United States Food and Drug Administration in a Parkinson's disease trial. Erythropoietin (EPO) activates the NF- κ B pathway and results in pro-survival and anti-oxidant enzyme upregulation and has been shown to be protective of RGC in the DBA/2J mouse of pigmentary glaucoma [129]. Citicholine (cytidine 5'-diphosphocholine) which exhibits neuroprotective effects by preserving cardiolipin and sphingomyelin among other actions, has been tested in patients with anterior ischemic optic neuropathy and showed preliminary benefits. [130]

5. Difficulties in designing a clinical trial

Over the last 30 years, numerous pharmacologic agents and gene therapeutic approaches have been shown to be neuroprotective in animal models of retinal and optic nerve injury. To date, none of the trials on neuroprotection of the visual system have shown efficacy and none of the agents developed in the laboratory have translated into a definitive clinical treatment. [131] There are several reasons for the universal failure of clinical trials to confirm pre-clinical results; they stem from the nature of glaucoma itself and from the poor design of previous neuroprotective trials. [51, 131] First, the long, slow course of glaucomatous optic neuropathy hinders our efforts to measure whether an improvement in progressive worsening has been achieved and asks for a design of therapeutic trials that last several years. Second, the rate of worsening varies among patients and thus a larger sample size is required to account for this inherent variability in disease progression. Third, the current standard of outcome measurement remains visual field testing and this carries a significant test-retest variance even among patients who are adept in taking the test. Fourth, any neuroprotection clinical trial would have to include patients that are already on topical medications that lower IOP. IOP-lowering agents have proven effective in slowing glaucoma progression in several controlled clinical trials [8-10] and it would be unethical to preclude neuroprotection study patients from using IOP-lowering medications.

6. Failed and ongoing trials

Success in the lab has not paralleled success in neuroprotection clinical trials. A Cochrane review in 2010 failed to identify any neuroprotection studies with significant results. [132] The largest neuroprotection study to date consisted of two industry-supported, parallel, randomized, phase III clinical trials on oral memantine in patients with chronic progressive open angle glaucoma. A total of 2,200 patients were enrolled into the trials at 89 sites and they were followed for at least 4 years. Despite the success of memantine in animal models of glaucoma, both clinical trials failed to show efficacy with respect to their primary outcome measures. The results of these two trials are as of yet unpublished and only two press releases hinted on their results. [133] The first release stated, "Two measures of visual function were selected in the statistical analysis plan to assess the efficacy of memantine in glaucoma. The functional measure chosen as the endpoint (glaucomatous field progression) did not show a benefit of memantine in preserving visual function. In a number of analyses using the secondary functional measure, memantine demonstrated a statistically significant benefit of the high-dose compared to placebo." The second release stated, "Allergan unmasked the second Phase III clinical trial examining the safety and efficacy of oral memantine as a treatment for glaucoma. Although the study showed that the progression of disease was significantly lower in patients receiving the higher dose of memantine compared to patients receiving the low dose of memantine, there was no significant benefit compared to patients receiving placebo. Therefore, the study failed to meet its primary endpoint and to sufficiently replicate the results of the first Phase III trial." In going forward, knowing the specifics of these trials and the reasons for failure would facilitate a more well-thought design of future trials; yet, the results remain unpublished.

The second most studied agent in neuroprotection trials is the highly selective alpha-2 adrenergic agonist, brimonidine, which had also shown great promise in animal studies. The first trial included 9 patients with Leber's hereditary optic neuropathy in whom use of brimonidine after loss of vision in one eye failed to prevent loss of vision in the second eye, which naturally occurs within weeks to months after first eye involvement. [134] The second trial also failed to show efficacy of brimonidine in aiding recovery of vision loss in patients with anterior ischemic optic neuropathy, though the trial itself may have been underpowered. [135]

The last trial assessing the neuroprotective effects of brimonidine was the Low-Pressure Glaucoma Treatment Study, which recruited patients with normal-tension glaucoma and randomized them to either treatment with brimonidine or with timolol. [136] Timolol has no neuroprotective properties and it thus served as a control for the pressure-lowering effects of brimonidine. However, the IOP was only minimally lowered in both groups, which raises concerns about patient adherence to the treatment regimen. [51] Results of the trial were published in 2011 and showed that low-pressure glaucoma patients treated with brimonidine were less likely to have visual field progression than patients treated with timolol. [137]

A review of ongoing trials at clinicaltrials.gov revealed one phase I trial that is still recruiting patients and aims to investigate the safety and efficacy of the NT-501 clinical neurotro-

phic factor (CNTF) implant in patients with chronic progressive open angle glaucoma (trial identifier: NCT01408472).

7. Hope for success

Designing neuroprotection trials in glaucoma is challenging. Modifications in study design, patient selection, and outcome measures can aid in the clinical testing of neuroprotective agents with positive pre-clinical results. [51] Instead of the standard randomized controlled clinical trial prototype, neuroprotection trials in glaucoma may be served better by using a so-called futility design strategy. Detection of beneficial agents with robust treatment effects in a short period of time in a single treatment group (i.e. there is no need for a control group) are advantages of futility design. Clearly, a major disadvantage of this approach is the inability to adequately assess for side effects and time-dependent treatment effects in a trial that has fewer patients and a shorter testing time frame. [138, 139] In addition, selection of patients whose disease is rapidly can maximize the opportunity to detect differences after the use of neuroprotective agents. Older age, higher baseline intraocular pressure, bilateral disease, low perfusion pressure, presence of exfoliation, disc hemorrhages, and thinner central corneal thickness are all risk factors for rapid progression and should be used in the selection of the study population in neuroprotection trials. [51, 140] The agent in question also should reach its target tissue(s), the retina and optic nerve head. Steps should be taken to ensure patient adherence with medication administration or the results of any neuroprotective trial that is performed on a background of co-administered IOP-lowering therapy are deemed to be confounded. [141]. If the IOP is reduced to an identical degree, while one agent (like brimonidine or other neuroprotectant) shows fewer injuries to the visual fields, this would indirectly support the additional neuroprotective effect of the agent on top of its IOP lowering effects.

In terms of endpoints for such trials, visual field testing is likely more suitable than structural measures since it has been employed extensively to measure progression of disease. Its disadvantages of high variability in some test point areas, the patient effort it requires, and the insensitivity to show the earliest stages of damage are well known. Nevertheless, it has been well established as a method to assess glaucoma progression. Given the lack of reliable software to measure progression using structural tests, such as the Heidelberg Retinal Tomograph or Optical Coherence Tomography, visual field testing remains the most reliable endpoint to use. If structural measures are to be used in the future, one should keep in mind that the more optic nerve damage present at the outset, the less sensitive structural change will be. [51]

8. Conclusion

Novel neuroprotective agents and mechanisms show promise in pre-clinical studies and animal models. However, translating these findings into effective treatments still remains a

challenge. This challenge can be met by a careful study design, appropriate selection of the study population, and use of better outcome measures and clinical end points. In addition, the various laboratory investigations suggest that there are multiple pathways that play a role in the loss of retinal ganglion cells. It is thus necessary to espouse combinatorial treatment approaches, if we want to successfully provide neuroprotection in the clinical setting.

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