Immunological and molecular basics of the primary open angle glaucoma pathomechanism

KATARZYNA SAMELSKA1,2, ANNA ZALESKA-ZMIJEWSKA1,2, BARBARA BALAN3, ANDRZEJ GRAŃCZEWSKI1, JACEK PAWEŁ SZAFLIK1,2, ALEKSANDER JAN KUBIAK2, PIOTR SKOPIŃSKI1,5

1SPKSO Ophthalmic University Hospital, Warsaw, Poland
2Department of Ophthalmology, Medical University of Warsaw, Warsaw, Poland
3Department of Immunology Biochemistry and Nutrition, Medical University of Warsaw, Warsaw, Poland
4Rutgers New Jersey Medical School, Newark, NJ, United States
5Department of Histology and Embryology, Medical University of Warsaw, Warsaw, Poland

Abstract

Glaucoma is a degenerative process of the optic nerve. Increased intraocular pressure is believed to be the main factor leading to the glaucomatous damage. The in vitro and in vivo animal glaucoma research models provide insight into the molecular changes in the retina in response to the injury factor. The damage is a complex process incorporating molecular and immunological changes. Such changes involve NFκB activity and complement activation. The processes affect the human antigen, JNK, MAPK, p53, MT2 and DBA/2J molecular pathways, activate the autophagy processes and compromise neuroprotective mechanisms. Activation and inhibition of immunological responses contribute to cell injury. The immunological mechanisms of glaucomatous degeneration include glial response, the complement, tumor necrosis factor α (TNF-α) pathways and toll-like receptors pathways. Oxidative stress and excitotoxicity are factors contributing to cell death in glaucoma. The authors present an up-to-date review of the mechanisms involved and update on research focusing on a possible innovative glaucoma treatment.

Key words: apoptosis, oxidative stress, glaucoma, complement, autophagy, retinal ganglion cells (RGCs).

(Cent Eur J Immunol 2021; 46 (1): 111-117)

Introduction

Glaucoma is defined as a degenerative disease of the optic nerve manifesting as retinal ganglion cell (RGC) death and progressive visual field loss. Increased intraocular pressure (IOP) is the main factor leading to glaucoma. However, there are patients with normal-tension glaucoma, where optic nerve damage progression does not result from elevated IOP, and patients with ocular hypertension (OHT) where increased IOP does not result in optic nerve damage.

The factors that lead to glaucoma neuropathy independently of IOP include a range of molecular and immunological mechanisms. The rodent models of glaucoma contribute to the research [1, 2].

The ocular hypertension models lead to IOP elevation via diverse mechanisms, e.g. intracameral injections of polystyrene or magnetic microbeads (pre-trabecular models) [9, 10], episcleral vein cauterization [11], laser photocoagulation [12] or hypertonic saline injection [13]. The normal-tension glaucoma models include immunization with ocular antigens – experimental autoimmune glaucoma model [14].

Immunological basics of glaucomatous neurodegeneration

In spite of the lack of lymphatic drainage and the presence of the blood-retina barrier, the immunological and inflammatory reactions in the eye are omnipresent and complex [8].

The RGC death through autoimmune mechanisms is considered a part of glaucomatous damage. It is reported that S100B immunization resulted in higher...
Glial cells’ role in optic nerve metabolism

The glial cells in the axon and the retina belong to various populations [8]. The glial responses in both compartments – the retina and the RGC axon – mediate protection signals as well as degeneration signals. However, studies show that critical processes happen in the optic nerve head (ONH) [15].

Astrocytosis is suggested to be one of the earliest changes seen in inflammatory RGC loss processes [29]. Astrocytes are the cells present abundantly in proximity to RGC axon bundles. Astrocytes play a role in the optic nerve injury response [30]. They repopulate and remodel at the crush site, upregulating ciliary neurotrophic factor (CNTF) production, which contributes to glial scar formation. Stressed RGCs or astroglial cells in ONH release proteins called DAMP that trigger the inflammatory responses. The DAMP family includes, among other members, heat shock proteins (HSPs) and tenascin-C, an activator of TLR-4 [20]. Release of HSPs occurs during cell necrosis, or secretion of HSPs in exosomes. During special types of apoptotic cell death (for example induced by some chemotherapeutics), HSPs can also appear on the extracellular side of the plasma membrane. HSPs and tenascin-C may lead to TLR activation in microglia [17].

Glial fibrillary acidic protein (GFAP) expression and CNTF production are signs of astrogliosis in the retina [8, 31]. Glial fibrillary acidic protein expression surprisingly is not elevated in the optic nerve upon injury [7]. In glaucoma, astrocytes are the primary producer of TNF-α and TNF-R1 in the ONH. Astrocytes also produce or respond to molecules such as NO, IL-6-type cytokines and endothelins. The ET-1 expression is elevated in ONH in a rat glaucoma model and it is believed to mediate the astrocytic response in the glaucomatous degeneration [31, 32]. It has been reported that induction of reactive astrocytosis promotes oxidative stress in the ONH [33].

Monocytes and activated T-cells are found to accumulate in the optic nerve at the site of damage. It has been reported that monocytes migrate through the endothelium to the ONH prior to RGC degeneration in inherited mouse models of glaucoma. This infiltration may be stopped by the X-ray radiation of the eye [34] or pharmacologically and genetically [2]. Infiltration cessation acts as neuroprotection and prevents glaucoma development. These findings suggest that monocyte infiltration may be a cause of glaucoma. The activated retinal T-cells take part in the autoimmune response to the damage, probably functioning as regulatory T-cells. Plasma CD4+ T cells found in glaucoma patients present greater stimulation, proliferation and proinflammatory cytokine secretion [35].

Muller glia are the most abundant retinal glial cells. Their processes are present in all the retinal layers. They upregulate glutamine synthetase, which produces glutamate, a neurotransmitter toxic to the retina, as well as upregulating NFkB [36]. Moreover, they are known to upregulate GFAP, express TLRs, growth factors and neurotrophic factors, phagocytose debris and express various cytokines and chemokines. Muller cells have neuroprotective properties in excitotoxic damage following RGC injury [37]. It is suggested that the Muller cells may con-
Oxidative stress and excitotoxicity in retinal ganglion cell death

Ischemia and oxidative stress play key roles in glaucoma [31, 38, 39]. Oxidative stress induction by glial (mainly microglial) cells activation has been reported [33, 36]. Oxidative stress also affects ONH astrocytes. The cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway leads to elevation in cAMP, mitochondrial dysfunction, caspase-3 activation and cell death via the AKT/Bim/Bax signaling pathway. Protein kinase A inhibition protects the ONH astrocytes from oxidative stress and increases their survival [40, 41].

Oxidative stress markers have been found not only in the retina but also in the vitreous body of glaucoma patients [42]. Natural antioxidants, such as curcumin, counteract ROS production. Curcumin was found to be neuroprotective in in vitro glaucoma models [43].

The reduced oxygen supply leads to generation of mitochondrial ROS and activation of HIF-1α that targets HSP-27, erythropoietin and vascular endothelial growth factor elevation. The location of an increased level of HIF-1α in glaucomatous eyes is connected with the location of the visual field defect location [38] (Fig. 1). It is suggested that HSP-27, although it plays a protective role in neurodegeneration by binding cytochrome c and preventing apoptosis formation, may have a direct damaging effect on RGCs. The elevation of HSP-27-reactive T cells was reported in glaucoma degeneration [44, 45]. Immunization with HSP-27 reinforces the neurodegenerative effect on S100 RGCs [14].

Glutamate production is the excitotoxicity factor in retinal ischemia (Fig. 2). Glutamate binds to NMDA receptors and allows the Ca²⁺ influx into the RGCs and apoptosis induction [31, 39]. Inducing excitotoxicity and oxidative stress with NMDA intravitreal injections is one of the RGC loss glaucomatous animal models [6]. It has been found that melanopsin-containing RGCs are not susceptible to NMDA-induced RGC loss [46]. Another glutamate receptor, AMPA-R, is also found to increase on RGCs after excitotoxic damage, glucose deprivation and oxygen/glucose deprivation, and AMPA receptor stimulation results in an increase in RGC death [36, 39].

Neurotrophic factors in glaucoma

According to the theory of target-derived deprivation of neurotrophic factors, RGC death in glaucoma is caused by a failure of retrograde axonal transport of, among other things, NTFs to the cell soma [47]. Neurotrophic factors are introduced to in vitro and in vivo glaucoma models, among others, by stem cell transplantation [48]. They play a role in pathophysiology of ophthalmic disorders other than glaucoma, such as age-related macular degeneration and Graves’ ophthalmopathy [49].

Neurotrophins, such as brain-derived neurotrophic factor (BDNF), work through cell surface receptors such as Trk and p75 receptors. TrkA binds NGF, TrkB binds BDNF and NT-4/5, TrkC binds NT-3, whereas p75 binds all the neurotrophins with similar affinity. Trk receptors play a role in cell survival, whereas p75 may play a role in cell survival as well as apoptosis [50].
Brain-derived neurotrophic factor binds to Trk receptors and activates Erk1/2 and PI3K pathways. BDNF-TrkB signaling promotes RGCs survival by upregulating neurotrophic factors that stimulate neuroprotection [51]. Erk1/2 plays a role in TrkB-induced survival of axotomized RGCs, which occurs via an MAPK-dependent pathway as a part of the intrinsic pathway of apoptosis. The finding above suggests that activation of the Erk1/2 pathway, but not the PI3K pathway, mediates TrkB-induced RGC survival [52].

TrkB expression is regulated by Shp2, which binds to growth factor receptors. Its effect has been found in RGCs exposed to oxidative stress [53]. The studies investigating the role of Shp2 in BDNF/TrkB signaling show that silencing Shp2 promotes Trk signaling and protects RGCs from susceptibility to ER stress in glaucoma [54]. The perspective of a novel gene therapy providing sustained BDNF/TrkB signaling seems promising for future application in glaucoma treatment [55].

The role of autophagy in neurodegeneration and neuroprotection

Autophagy is executed by autophagy-related genes. The RGCs’ autophagy may be inhibited by autophagy-related gene Atg4 deletion. Atg4-deficient mice showed higher p62 and lower LC3-II retina levels in the optic nerve crush glaucoma model, which suggests that the downregulation of autophagy reduces survival of RGCs [56, 57].

The Rho-associated coiled-coil-containing protein kinase (ROCK) family is the main effector of the Rho family and it comprises of ROCK1 and ROCK2. They are known for their role in RGC death. Inhibition of ROCK kinases results in increased autophagic flux seen in increased LC-II and p62 levels [58]. ROCK suppression was reported to lead to RGC regeneration, which was enhanced by the addition of CNTF [50, 58, 59]. Specific RhoA knock-out was found to promote RGC survival and increase neurite outgrowth following optic nerve crush [59].

Newly introduced anti-glaucoma agents – Rho inhibitors ripasudil (Glanatec, Kowa Company, Ltd, Japan) and netarsudil (Rhopressa, Aerie Pharmaceuticals, USA) – are known inhibitors of ROCK1 and ROCK2 in a trabecular meshwork which results in decreased resistance of aqueous humor outflow and decreased IOP. Their anti-Rho activity has a neuroprotective effect on RGCs by modulating autophagy and inhibiting apoptosis [56, 60, 61]. Targeting autophagy may be a potential neuroprotective strategy in glaucoma.

Apoptosis pathways involved in retinal neurodegeneration

Intrinsic pathway

The intrinsic pathway is triggered by deprivation of the neurotrophic factor or activation of pro-apoptotic Bcl-2 family members (Fig. 3A). The TrkB receptor activates the Erk1/2 and Akt pathways that stimulate BH3-domain proteins to activate mitochondrial dysfunction [31].

The family of BCL-2 proteins contains pro-apoptotic (e.g. BAX) as well as anti-apoptotic (e.g. Bcl-2) proteins. BAX activation, its relocation to MOM and forming dimer units lead to pore formation and release of cytochrome c into the cytosol (Fig. 3B) [62]. Cytochrome c then binds to Apaf-1, which leads to apoptosome formation (Fig. 3C) and activation of various caspases (caspase-2, caspase-3, caspase-8, caspase-9). The inhibition of caspases through Afk1 inhibition, as well as inhibition of c-Jun, attenuates RGC death [63]. It was found that targeting caspase-2 ex-

![Fig. 3. Intrinsic apoptotic pathway. Description in the text](image-url)
pression may also play a neuroprotective role in RGC survival [64]. Cytochrome C also activates further pathways via transmitters such as SMAC/DIABLO, AIF, EndoG, HTRA2 [32] (Fig. 3D).

The intrinsic apoptotic pathway is mediated by certain kinases: MAPks. M KK4 and M KK7 are the MAPks that regulate JNK. It has been found that murine RGCs deficient in Mkk4 or Mkk7 genes showed higher survival rates in glaucoma models. However, the deficiency of both Mkk4 and Mkk7 at the same time resulted in inappropriate RGC development [65].

Extrinsic pathway

The extrinsic apoptotic pathway is induced by a specific ligand (e.g. TNF-α, FasL, TRAIL) (Fig. 4A). FasL in its soluble form, as well as TNF-α, is synthetized from a membrane-bound protein. It then binds to Fas/CD95 trans-membrane receptor which belongs to the death receptor family [31]. All these ligands activate FADD (Fig. 4B), leading to activation of caspase cascade [32]. TNF-α gene expression is up-regulated by NFκB. TNF-α production involves cleaving its precursor with the use of TACE (Fig. 4C). Then TNF-α binds to TNFR1 and TNFR2 – the death receptors.

The protective role of human antigen in glaucomatous damage

Human antigen R (HuR) protein is part of the embryonic lethal abnormal vision (ELAV) family, also called ELAV1, and is a protein that in humans is encoded by the ELAVL1 gene. This encoded protein contains 3 RNA-binding domains and binds cis-acting uracil and adenine elements. One of its best-known functions is to stabilize mRNAs in order to regulate gene expression. It prevents neurodegeneration by controlling the oxidative metabolism in neurons [66]. It is known to promote the expression of stress response genes (Hsp70 and p53), cytokines and pro-inflammatory factors, such as TNF-α [67]. It is found in both the retina and the optic nerve. Human antigen expression is increased in the glaucomatous retina in both mice and humans. Increased HuR expression corresponds to reactive gliosis in the optic nerve [67].

Conclusions

The current glaucoma treatment works primarily by lowering the intraocular pressure. However, contemporary research underlines the importance of molecular and intracellular changes in the pathogenesis of RGC death. The knowledge of the inflammatory process taking place in glaucoma progression is vital for finding new strategies of protection against glaucoma. Gene therapy involving changes in expression of certain molecules gives hopes for developing new effective glaucoma treatment. The molecular pathways involved in neuroprotection highlighted in our review provide potential targets for innovative treatments in glaucoma.

The authors declare no conflict of interest.

References

1. Struebing FL, Geisert EE (2015): What animal models can tell us about glaucoma. Prog Mol Biol Transl Sci 134: 365-380.
2. Fernandes KA, Harder JM, Williams PA, et al. (2015): Using genetic mouse models to gain insight into glaucoma: past results and future possibilities. Exp Eye Res 141: 42-56.
21. Reinehr S, Reinhard J, Gandej M, et al. (2016): Simultaneous
20. Soto I, Howell GR (2014): The complex role of neuroin-
18. Kuehn MH, Kim CY, Ostojic J, et al. (2006): Retinal syn-
17. Wei X, Cho KS, Thee EF, et al. (2019): Neuroinflammation
16. Williams PA, Tribble JR, Pepper KW, et al. (2016): Inhibition
15. Williams PA, Marsh-Armstrong N, Howell GR, et al. (2017): Neuroinflammation in glaucoma: a new opportunity. Exp Eye Res 157: 20-27.
14. Bosco A, Romero CO, Breen KT, et al. (2015): Neurodegeneration severity can be predicted from early microglia alterations monitored in vivo in a mouse model of chronic glaucoma. Dis Model Mech 8: 443-455.
13. Morrison JC, Moore CG, Deppmeier LM, et al. (1997): A rat model of glaucoma incorporating rapid-onset elevation of intraocular pressure. Sci Rep 4: 5910.
12. Jha P, Banda H, Tytarenko R, et al. (2011): Complement mediated apoptosis leads to the loss of retinal ganglion cells in animal model of glaucoma. Mol Immunol 48: 2151-2158.
11. Lauzi J, Anders F, Liu H, et al. (2019): Neuroprotective and neuroregenerative effects of CRMP-5 on retinal ganglion cells in an experimental in vivo and in vitro model of glaucoma. PLoS One 14: e0207190.
10. Krishnan A, Kocab AJ, Zack JS, et al. (2019): A small peptide antagonist of the Fas receptor inhibits neuroinflammation and prevents axon degeneration and retinal ganglion cell death in an inducible mouse model of glaucoma. J Neuroinflammation 16: 184.
9. Smedowski A, Pietrucha-Dutczak M, Kaarmiranta K, et al. (2014): A rat experimental model of glaucoma incorporating rapid-onset elevation of intraocular pressure. Sci Rep 4: 5910.
8. Mac Nair CE, Fernandes KA, Schlamp CL, et al. (2014): A rat model of glaucoma incorporating rapid-onset elevation of intraocular pressure. Sci Rep 4: 5910.
7. Qu J, Jakobs TC (2013): The time course of gene expression during reactive gliosis in the optic nerve. PLoS One 8: e67094.
6. Lambuk I, Jafri AJA, Iezhitsa I, et al. (2019): Dose-dependent effects of NMDA on retinal and optic nerve morphology in rats. Int J Ophthalmol 12: 746-753.
5. Harder JM, Williams PA, Soto I, et al. (2018): Jnk2 deficiency increases the rate of glaucomatous neurodegeneration in ocular hypertensive DBA/2J mice. Cell Death Dis 9: 705.
4. Williams PA, Braine CE, Kizhatil K, et al. (2019): Radiation treatment inhibits monocyte-like cell extravasation protects from neurodegeneration in DBA/2J glaucoma. Mol Neurodegener 14: 6.
3. Bosco A, Romero CO, Breen KT, et al. (2015): Neurodegenerative phenomena in a mouse model of chronic glaucoma. Dis Model Mech 8: 443-455.
2. Harder JM, Braine CE, Williams PA, et al. (2017): Early immune responses are independent of RGC dysfunction in glaucoma with complement component C3 being protective. Proc Natl Acad Sci U S A 114: E3839-E3848.
1. Katarzyna Samelska et al.

22. Harder JM, Braine CE, Williams PA, et al. (2017): Early immune responses are independent of RGC dysfunction in glaucoma with complement component C3 being protective. Proc Natl Acad Sci U S A 114: E3839-E3848.
23. Wiggs JL (2015): Glaucoma genes and mechanisms. Prog Mol Biol Transl Sci 134: 315-342.
24. Nakazawa T, Nakazawa C, Matsubara A, et al. (2006): Tumor necrosis factor-alpha mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma. J Neurosci 26: 12633-12641.
25. Tezel G (2008): TNF-alpha signaling in glaucomatous neurodegeneration. Prog Brain Res 173: 409-421.
26. Tezel G, Wax MB (2004): The immune system and glaucoma. Curr Opin Ophthalmol 15: 80-84.
27. Kondkar AA, Sultan T, Almobarak FA, et al. (2018): Association of increased levels of plasma tumor necrosis factor alpha with primary open-angle glaucoma. Clin Ophthalmol 12: 701-706.
28. Binkowska A, Michalak G, Kopuzc M, et al. (2019): Soluble tumour necrosis factor receptor I is a promising early indicator of complicated clinical outcome in patients following severe trauma. Cent Eur J Immunol 44: 423-432.
29. Schneider M, Fuchshofer R (2016): The role of astrocytes in optic nerve head fibrosis in glaucoma. Exp Eye Res 142: 49-55.
30. Tehranri S, Davis L, Cepurna WO (2019): Optic nerve head astrocytes display axon-dependent and -independent reactivity in response to acutely elevated intraocular pressure. Invest Ophthalmol Vis Sci 2: 312-321.
31. Almasieh M, Wilson AM, Morquette B, et al. (2012): The molecular basis of retinal ganglion cell death in glaucoma. Prog Retin Eye Res 31: 152-181.
32. Howell GR, Macalinao DG, Sousa GL, et al. (2011): Molecular clustering identifies complement and endothelin induction as early events in a mouse model of glaucoma. J Clin Invest 121: 1429-1444.
33. Ghosh AK, Rao VR, Wisniewski VJ, et al. (2020): Differential activation of glialprotective intracellular signaling pathways in primary optic nerve head astrocytes after treatment with different classes of antioxidants. Antioxidants 9: 324.
34. Howell GR, Soto I, Zhu X, et al. (2012): Radiation treatment inhibits monocyte entry into the optic nerve head and prevents neuronal damage in a mouse model of glaucoma. J Clin Invest 122: 1246-1261.
35. Yang X, Zeng Q, Göktaş E, et al. (2019): T-Lymphocyte subset distribution and activity in patients with glaucoma. Invest Ophthalmol Vis Sci 60: 877-888.
36. Lebrun-Julien F, Duplan L, Pernet V, et al. (2009): Excitotoxic death of retinal neurons in vivo occurs via a non-cell-autonomous mechanism. J Neurosci 29: 5536-5545.
37. Brice S, Drexler K, Müller B, et al. (2020): Endogenous Wnt/β-catenin signaling in Müller cells protects retinal ganglion cells from excitotoxic damage. Mol Vis 26: 135-149.
38. Tezel G (2006): Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res 25: 490-513.
39. Park YH, Broyles HV, He S, et al. (2016): Involvement of AMPA receptor and its flip and flop isoforms in retinal ganglion cell death following oxygen/glucose deprivation. Invest Ophthalmol Vis Sci 57: 508-526.
40. Ju WK, Shim MS, Kim KY, et al. (2019): Inhibition of cAMP/PKA pathway protects optic nerve head astrocytes against oxidative stress by Akt/Bax phosphorylation-mediated Mfn1/2 oligomerization. Oxid Med Cell Longev; 8060962.
41. Shim MS, Kim KY, Bu JH, et al. (2019): Elevated intracellular cAMP exacerbates vulnerability to oxidative stress in optic nerve head astrocytes. Oxid Med Cell Longev 2019; 8060962.
42. Schwab C, Paar M, Fengler VH, et al. (2020): Vitreous albumin redox state in open-angle glaucoma patients and controls: a pilot study. Int Ophthalmol 40: 999-1006.
43. Radomska-Łeśniewska D, Osiecka-Iwan A, Hyc A, et al. (2019): Therapeutic potential of curcumin in eye diseases. Cent Eur J Immunol 44: 181-189.
44. Chen H, Cho KS, Vu THK, et al. (2018): Commensal microbiota-flora-induced T cell responses mediate progressive neurodegeneration in glaucoma. Nat Commun 10: 3209.
45. Tsai T, Grotegut P, Reinher S, et al. (2019): Role of heat shock proteins in glaucoma. Int J Mol Sci 20: 5160.
46. Vidal-Villegas B, Pierdomenico JD, Imperial-Ollero JAM, et al. (2019): Melanopsin+RGCs are fully resistant to NMDA-Induced excitotoxicity. Int J Mol Sci 20: 3012.
47. Herzog KH, Bartheld CS (1998): Contributions of the optic tectum and the retina as sources of brain-derived neurotrophic factor for retinal ganglion cells in the chick embryo. J Neurosci 18: 2891-2906.
48. Dąbrowska A, Skopiński P (2017): Stem cells in regenerative medicine – from laboratory to clinical application – the eye. Cent Eur J Immunol 42: 173-180.
49. Krajewska-Węglewicz L, Radomska-Łeśniewska D, Dorobek M, et al. (2018): Update on pathogenesis and immunology of Graves’ ophthalmopathy. Cent Eur J Immunol 43: 458-465.
50. Miller FD, Kaplan DR (2001): Neurotrophin signalling pathways regulating neuronal apoptosis. Cell Mol Life Sci 58: 1045-1053.
51. Kimura A, Namekata K, Guo X, et al. (2016): Neuroprotection, growth factors and BDNF-TrkB signalling in retinal degeneration. Int J Mol Sci 17: 1584.
52. Cheng L, Sapieha P, Kittlerová P, et al. (2002): TrkB gene transfer protects retinal ganglion cells from axotomy-induced death in vivo. J Neurosci 22: 3977-3986.
53. Chitranshi N, Dheer Y, Abbasi M, et al. (2018): Glaucoma pathogenesis and neurotrophins: focus on the molecular and genetic basis for therapeutic prospects. Curr Neuropharmacol 16: 1018-1035.
54. Chitranshi N, Dheer Y, Mirzaei M, et al. (2018): Loss of Shp2 rescues BDNF/TrkB signalling and contributes to improved retinal ganglion cell neuroprotection. Front Cell Neurosci 27: 424-441.
55. Osborne A, Wang AXZ, Tassoni A, et al. (2018): Design of a novel gene therapy construct to achieve sustained brain-derived neurotrophic factor signaling in neurons. Hum Gene Ther 29: 828-841.
56. Lingor P, Tönges L, Pieper N, et al. (2008): ROCK inhibition and CNTF interact on intrinsic signaling pathways and differentially regulate survival and regeneration in retinal ganglion cells. Brain 131: 250-263.
57. Rodríguez-Muela N, Germain F, Mariño G, et al. (2012): Autophagy promotes survival of retinal ganglion cells after optic nerve axotomy in mice. Cell Death Differ 19: 162-169.
58. Koch JC, Tönges L, Barski E, et al. (2014): ROCK2 is a major regulator of axonal degeneration, neuronal death and axonal regeneration in the CNS. Cell Death Dis 5: e1225.
59. Koch JC, Tönges L, Michel U, et al. (2014): Viral vector-mediated downregulation of RhoA increases survival and axonal regeneration of retinal ganglion cells. Front Cell Neurosci 8: 273.
60. Tanna AP, Johnson M (2018): Rho kinase inhibitors as a novel treatment for glaucoma and ocular hypertension. Ophthalmol 125: 1741-1756.
61. Yu J, Lan S, Wang R, et al. (2015): Fusudil alleviates traumatic optic neuropathy by inhibiting Rho signaling pathway. Int J Clin Exp Med 8: 13377-13382.
62. Maes ME, Schlamp CL, Nickells RW (2017): BAX to basics: How the BCL2 gene family controls the death of retinal ganglion cells. Prog Retin Eye Res 57: 1-25.
63. Lingor P, Koerberle P, Kügler S, et al. (2005): Down-regulation of apoptosis mediators by RNAi inhibits axotomy-induced retinal ganglion cell death in vivo. Brain 128: 550-558.
64. Ahmed Z, Kalinski H, Berry M, et al. (2011): Ocular neuroprotection by siRNA targeting caspase-2. Cell Death Dis 2: e173.
65. Syc-Mazurek SB, Rausch RL, Fernandes KA, et al. (2018): Mkk4 and Mkk7 are important for retinal development and axonal injury-induced retinal ganglion cell death. Cell Death Dis 9: 1095.
66. Skliris A, Papadaki O, Kafalas P, et al. (2015): Neuroprotection requires the functions of the RNA-binding protein HuR. Cell Death Different 22: 703-718.
67. Smedowski A, Liu X, Podracka L, et al. (2018): Increased intracocular pressure alters the cellular distribution of HuR protein in retinal ganglion cells – a possible sign of endogenous neuroprotection failure. Biochim Biophys Acta Mol Basis Dis 1864: 296-306.