

Glaucoma Pathogenesis and Neurotrophins: Focus on the Molecular and Genetic Basis for Therapeutic Prospects

Nitin Chitranshi^{1,*}, Yogita Dheer¹, Mojdeh Abbasi¹, Yuyi You², Stuart L Graham^{1,2} and Vivek Gupta¹

¹Faculty of Medicine and Health Sciences, Macquarie University, F10A, 2 Technology Place, North Ryde, NSW 2109, Australia; ²Save Sight Institute, Sydney University, Sydney NSW 2000, Australia

Abstract: Background: Retinal ganglion cell (RGC) degeneration is a major feature of glaucoma pathology. Neuroprotective approaches that delay or halt the progression of RGC loss are needed to prevent vision loss which can occur even after conventional medical or surgical treatments to lower intraocular pressure.

Objective: The aim of this review was to examine the progress in genetics and cellular mechanisms associated with endoplasmic reticulum (ER) stress, RGC dysfunction and cell death pathways in glaucoma.

Materials and Methods: Here, we review the involvement of neurotrophins like brain derived neurotrophic factor (BDNF) and its high affinity receptor tropomyosin receptor kinase (TrkB) in glaucoma. The role of ER stress markers in human and animal retinas in health and disease conditions is also discussed. Further, we analysed the literature highlighting genetic linkage in the context of primary open angle glaucoma and suggested mechanistic insights into potential therapeutic options relevant to glaucoma management.

Results: The literature review of the neurobiology underlying neurotrophin pathways, ER stress and gene associations provide critical insights into association of RGCs death in glaucoma. Alteration in signalling pathway is associated with increased risk of misfolded protein aggregation in ER promoting RGC apoptosis. Several genes that are linked with neurotrophin signalling pathways have been reported to be associated with glaucoma pathology.

Conclusion: Understanding genetic heterogeneity and involvement of neurotrophin biology in glaucoma could help to understand the complex pathophysiology of glaucoma. Identification of novel molecular targets will be critical for drug development and provide neuroprotection to the RGCs and optic nerve.

Keywords: Neurotrophins, retinal ganglion cells, gene, glaucoma, apoptosis, endoplasmic reticulum stress.

1. INTRODUCTION

Glaucoma is a neurodegenerative disease of the eye and is the major cause of irreversible vision loss. It has been projected to affect approximately 60 million people by 2020, translating to more than 8.4 million cases of irreversible blindness worldwide [1]. The underlying pathological mechanism associated with disease progression is still under investigation, but evidence from both human and experimental models suggest that elevated intraocular pressure (IOP) obstructs retrograde and anterograde axonal transport of neurotrophins in retinal ganglion cells (RGCs) axons at the level

of the optic nerve head (ONH) [2]. Genome-wide association studies (GWAS) and other genomic analyses have successfully identified over 70 single nucleotide polymorphism (SNPs) associated with primary open angle glaucoma (POAG) [3]. The molecular basis of cell signalling pathways and genetic risk factors can be studied together to understand their contribution to this complex disease and could provide cell signalling and gene regulatory based screening tests. In this review, we summarize the recent advances in the neurotrophin signalling pathways and genomics associations that are identified in glaucoma (Fig. 1). Deprivation of nerve growth factor (NGF) and other neurotrophic factors contributes to disease progression. A better understanding of the gene linked molecular events is necessary to produce novel therapeutic targeted treatment, which may give hope to preserve vision.

*Address correspondence to this author at the Faculty of Medicine and Health Sciences, 75, Talavera Road, Macquarie University, Sydney, NSW 2109, Australia; Tel: +61-298502760; E-mail: nitinchitranshi@gmail.com

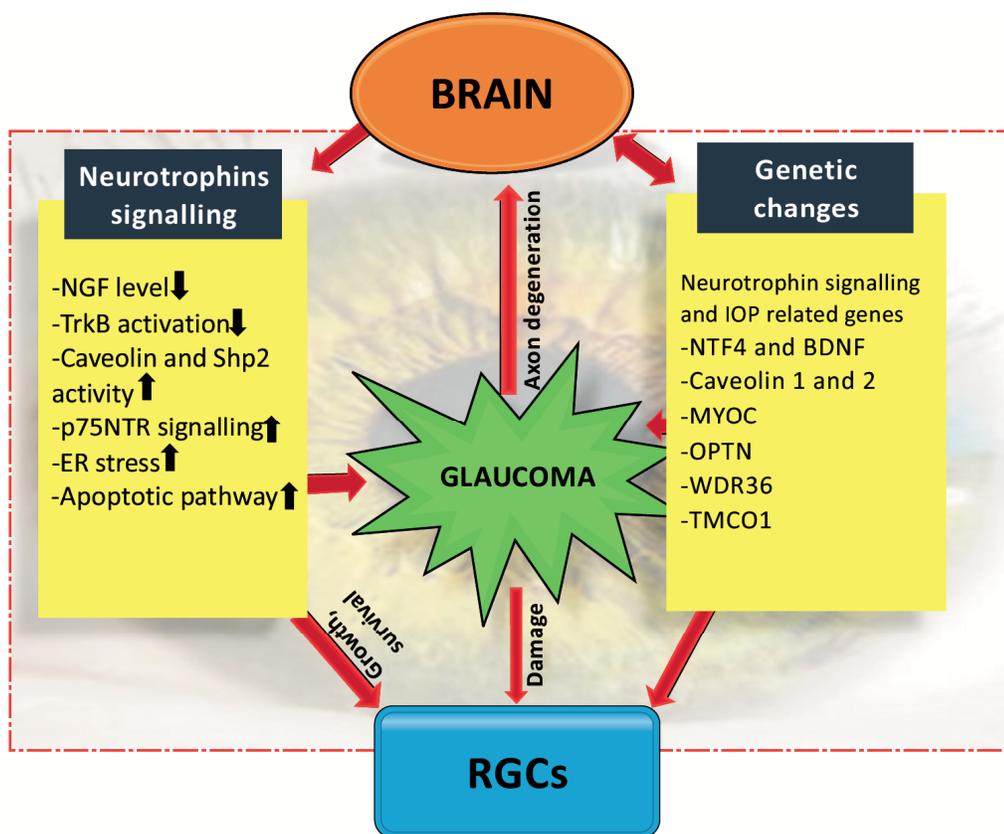


Fig. (1). Schematic representation from brain to eye highlighting association of neurotrophins and genes in glaucoma (NGF, nerve growth factor; TrkB, tropomyosin receptor kinase B; Shp2, SH2 domain containing protein tyrosine phosphatase; p75NTR, p75 neurotrophin receptor; ER, endoplasmic reticulum; IOP, intraocular pressure; NTF4, neurotrophin factor 4; BDNF, brain derived neurotrophic factor; MYOC, myocilin; OPTN, optineurin; WDR36, WD repeat domain 36; TMCO1, transmembrane and coiled-coil domains 1).

2. NEUROTROPHIN ROLE IN RGCs

Neurotrophins play a key role in neuronal cell survival. In healthy or normal conditions, RGCs can receive neurotrophin support from Muller cells [4] or retrograde axonal transport from the brain directly. This has been visualized using live-cell imaging *in vitro* [5]. Human and mouse adult RGCs not only express Trk family receptors but also abundantly express p75NTR receptor during retinal development [6]. The p75NTR receptor is predominantly expressed in Müller glial cells [6, 7]. The immature form of neurotrophin, such as pro-NGF binding to p75NTR leads to its activation and programmed cell death *via* tumor necrosis factor- α (TNF α) production in glial cells [8]. NGF binding to the p75NTR receptor in the absence of TrkA has been suggested to induce apoptosis in developing RGCs [9]. Lack of neurotrophin support has been suggested as a reason for RGCs degeneration and death in glaucoma [10]. A significant question is where do neurotrophins originate, and how do neurotrophins function upon engaging receptors on RGCs? Differential activation of neurotrophin receptors can occur when neurotrophins act at the axonal terminal or at the neuronal cell body [11, 12]. Neurotrophins are also shown to transport retrogradely from the superior colliculus (SC) in the central nervous system (CNS). Retrograde transportation of neurotrophin take place from SC to RGCs cell bodies. Studies in rats demonstrated that acute IOP elevation inhibits the retro-

grade transport of brain-derived neurotrophic factor (BDNF) from SC to the RGCs soma. Deprivation of BDNF to RGCs contributes to the loss of visual signal [11]. NGF also diffuses to presynaptic axon terminals of neurons such as the cholinergic neurons where it binds its receptor TrkA, bringing its dimerization, phosphorylation and the formation of an extended complex of proteins involved in signalling pathways. These complexes are then internalized in part by clathrin-coated membranes and moved to early endosomes that are then retrogradely transported from axons to the cell body through a dynein-microtubule based mechanism. When the signalling endosome reaches the cell body, the signal is communicated to the cytoplasm and the nucleus, triggering gene expression. Lysosomes promote the degradation of this signalling complex [13]. This model proposed for NGF may well apply for other neurotrophins. Many studies have led to the conclusion that BDNF is also locally synthesized in the retina. The RGCs and neighbouring amacrine cells produce BDNF that may act in a paracrine fashion. The RGCs themselves act in autocrine fashion and these neurons have been shown to survive in absence of additional BDNF from the brain and are able to express it in culture [14, 15]. Other neurotrophic factors such as ciliary neurotrophic factor (CNTF) and glial cell-line derived neurotrophic factor (GDNF) have also been reported to be involved in RGCs maintenance and survival [16, 17].

3. NEUROTROPHINS DEPRIVATION THEORY IN GLAUCOMA

Neurotrophins are transported to the retina by retrograde manner. They are responsible for regulation of neuronal growth, function and survival. The long-range retrograde neurotrophin transportation is probably facilitated *via* endosome signalling [18]. Neurotrophins bind to the Trk receptors at axon terminals which is then taken up by cell body retrogradely [19]. In glaucomatous conditions, due to high IOP the retrograde transport is thought to be blocked at the ONH region and RGCs fail to receive BDNF and TrkB support for survival [11, 20]. This deprivation causes an alteration of axoplasmic transport of neurotrophins from target neurons in the SC and lateral geniculate nucleus in the brain [21]. RGCs seem to be especially dependent upon BDNF, NT-4, CNTF, and GDNF [12, 22-24]. Pease and colleagues (2000) demonstrated that experimental glaucoma induces abnormal TrkB axonal distribution, focal accumulation of TrkB and BDNF, increased levels of TrkB in ganglion cell layer (GCL), and increased TrkB in glia [20]. The ability of RGCs to survive in culture with the lack of exogenous BDNF has also been demonstrated [15] suggesting that the deprivation of extrinsic BDNF because of retrograde transport interruption is not the only reason for RGCs death in glaucoma. This is important because BDNF/ TrkB downstream signalling is involved in apoptosis inhibition and has been shown to support survival of retinal explants and cultures. It has also been shown to increase the rate of axonal elongation but only when it is present in the axonal terminals [25-27]. The presence of TrkB and BDNF in the all sub-populations of the RGCs has been demonstrated in the retina [14]. It is believed that neurotrophin deprivation in neurons exerts stress and initiates apoptotic pathways with in the cell through activated JNK which stimulates expression of BH-3-containing proteins that facilitate the actions of a proapoptotic proteins (BAX) causing mitochondrial dysfunction [28, 29]. In summary, neurotrophin deprivation induces cell death and auxiliary therapy could therefore be a potential approach in glaucoma treatment.

4. BDNF-TrkB SIGNALLING

There is evidence for the protective role of BDNF in maintaining the survival of RGCs under conditionally induced apoptosis like optic nerve injury or glaucoma [30]. In regenerating RGCs neurons, BDNF initiates neuritogenesis [31], and can repair damaged optic nerve and RGCs [30, 32]. Our recent studies have established the role of BDNF impairment in structural, functional and molecular neurodegenerative changes in the inner retina that are exacerbated with age and in glaucoma in BDNF^{+/-} mice [33]. TrkB activation leads to an enhanced PI3K/Akt and Erk1/2 signalling in the RGCs and Erk1/2 appears to be responsible for promoting the survival of RGCs [34, 35]. Previous studies have shown that BDNF mediated TrkB signalling modulates glycogen synthase kinase 3 β (GSK3 β) activity in retinoic acid differentiated neuroblastoma, SH-SY5Y cells [36]. BDNF binds to the TrkB receptor to initiate multiple signalling cascades as discussed above, including PI3K activation which in turn leads to the stimulation of Ser/Thr kinase Akt [37]. Akt is a major upstream regulator of GSK3 β and regulates GSK3 β

signalling by its phosphorylation at Ser⁹, thereby inactivating it [38]. The active form of GSK3 β (GSK3 β phosphorylation) inhibits collapsin response mediator protein-2 (CRMP-2) binding to tubulin and promotes microtubule dynamics along with regulating axonal transport and outgrowth in neurons. In order to understand the mechanism of BDNF/ TrkB signalling in RGCs, we have demonstrated that activation of the BDNF-TrkB signalling in PC-12 cell lines regulate GSK3 β activity which is involved in cellular survival, cell fate determination and proliferation [39]. BDNF knockdown in PC-12 cell lines resulted in marked downregulation of GSK3 β phosphorylation [39]. In addition, ONH of BDNF^{+/-} mice illustrated reduced GSK3 β phosphorylation with age [39]. Further studies to stimulate BDNF-TrkB signalling in RGCs neuroprotection may lead to development of effective treatment therapies for glaucoma.

5. GLIAL BDNF-TrkB SIGNALLING

BDNF-TrkB signalling promotes cell survival by the activation of pro-survival pathways [8, 40]. Notably, the expression of TrkB is relatively higher in inner retinal cells like Müller glial cells and RGCs as compared to the photoreceptor cells [8, 41, 42]. This suggests that the neuroprotective roles of BDNF-TrkB signalling in the inner and outer retina is different. Indeed, Kimura *et al.* (2016), reported a direct neuroprotective action of glia on photoreceptor cells. BDNF treated Muller glia cells *in vitro* show upregulated CNTF levels, while upregulation of basic fibroblast growth factor by glia protects the photoreceptor cells undergoing damage [43]. BDNF-TrkB signalling in glial cells produces neuroprotective effects. Two different TrkB knockout mice models were used to confirm the positive role of BDNF-TrkB signalling in RGC survival. These models were TrkB^{flax/flax} mice crossed with *GFAP-Cre* mice to produce TrkB^{GFAP} KO mice in which TrkB is selectively deleted from Muller glial cells, and TrkB^{c-kit} KO mice that have TrkB deleted only from the RGCs. In both of these mice models, a similar degree of neuronal damage from glutamate neurotoxicity was observed. Likewise, apoptosis in the photoreceptor cells induced by methylnitrosourea (MNU), was augmented in TrkB^{GFAP} KO mice. In addition, an optic nerve damage model demonstrated that TrkB^{GFAP} KO mice had a higher percentage of RGC loss in comparison to the wild-type mice [42, 43]. TrkB.T1 is the truncated isoform of TrkB receptor and BDNF binding to this truncated isoform in Muller cells demonstrated protection of photoreceptor cells against light-induced damage [44]. Localization of BDNF and TrkB along with other adaptor protein like Src homology 2 domain containing (Shc) and phospholipase C γ 1 (PLC- γ 1) in the endosomes potentially makes it possible for TrkB to be transported within the cell [45]. This could be a mechanism of BDNF-TrkB translocation in the optic nerve axons. Taken altogether, these studies highlight the neuroprotective role of glial BDNF-TrkB signalling in retinal cells by activating the downstream pro-survival cascades.

6. PHARMACOLOGICAL MODULATION OF TrkB

Even though BDNF is accepted to be neuroprotective in RGCs, its impact on RGC survival has been observed to be transient. While BDNF at first enhances RGC survival, it

loses its protective effect over time [46]. On repeated TrkB activation by higher doses or multiple applications, the pathway becomes desensitized to BDNF. Considering different caveats of BDNF, for example, its short half-life, cross-reactions associated with the prolonged use or expanded doses, and difficulty of delivery, the clinical prospect of utilizing BDNF for neuroprotective therapy has been disappointing [47].

There are not many natural or synthetic compounds that can act as an agonist to the TrkB receptor and mimic the function of BDNF with minimal side effects. For example, TrkB agonist antibody 29D7 enhanced RGCs survival in culture in a dose-dependent manner and enhanced the cAMP elevation, consistent with prior observations on the ability of cAMP to enhance the RGC response to BDNF for the survival and axon growth [48]. Hua *et al.* (2010) also demonstrated the ability of antibody 29D7 to enhance RGCs survival and regeneration *in vivo* after intravitreal injection of 29D7 antibody. The density of surviving RGCs was increased by single antibody 29D7 injection but to a lesser degree than in the BDNF-treated retinas [48].

We and others have shown that naturally occurring flavonoid, 7,8-dihydroxyflavone (7,8-DHF) has potential to activate the TrkB receptor extracellular domain (ECD) triggering conformational changes in the receptor and stimulating phosphorylation of the TrkB receptor intracellular domain (ICD) which is critical for the tyrosine kinase activity of the TrkB receptor and its downstream signalling events [49-51]. The binding of 7,8-DHF and BDNF to TrkB receptor is shown to be on two different sites. 7,8-DHF binds specifically to the ECD of the TrkB receptor and induces TrkB phosphorylation at Tyr⁵¹⁵, Try⁷⁰⁶ and Tyr⁸¹⁶ in ICD in neurons. In neuronal lysates, the BDNF-triggered phosphorylation activity of TrkB and in return TrkB was highly ubiquitinated [52, 53]. In contrast, 7,8-DHF rapidly elicited TrkB phosphorylation in the retinal ganglion cells [54]. Remarkably, no TrkB ubiquitination was detected in 7,8-DHF induced TrkB receptor activation [55]. Another small molecule that mimics the neurotrophic activity of BDNF is deoxygedunin which is a tetranortriterpenoid present in the Indian neem tree (*Azadirachta indica*) [56]. Deoxygedunin also binds to the ECD of TrkB and was shown to elicit strong TrkB activation in hippocampal neurons of rat. Deoxygedunin is also found to stimulate downstream signalling activation of both Erk1/2 and Akt pathways in neuronal culture and prevent neurons from undergoing apoptosis [55, 57].

7. TrkB REGULATION BY ENDOGENOUS PHOSPHATASE Shp2

Protein tyrosine phosphatase (PTP) is the Src homology 2 (SH2) domain containing phosphatase Shp2 [58]. It is expressed ubiquitously and plays a key role in several cellular signalling pathways affiliated with cell growth, differentiation, mitotic cycle, metabolic control, transcription regulation and cell migration, along with positive or negative regulatory role in TrkB receptor signalling and neural fate in retina [59-62]. Shp2 binds to tyrosine kinase receptors like platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR) *via* its SH2 domains directly or indirectly [63]. In addition, Shp2 has been found

in the receptor complexes in which the Jak/Tyk family of receptor-associated tyrosine kinases phosphorylate tyrosine residues in response to stimulation with CNTF, leukemia inhibitory factor, oncostatin M and interleukin-6 [64]. Shp2 acts either as an adaptor protein [65] or as a modulator of tyrosine phosphorylation [63] in these signalling complexes. It has also been shown that Shp2 acts as a mediator of BDNF-activated signalling [66]. The presence of BDNF in cerebral cortical neurons is suggested to promote the phosphorylation of Shp2 [54, 67, 68]. Although, Shp2 enhances the survival effect of BDNF in these neurons [69], it also acts as a negative regulator of BDNF-activated signalling during neuronal excitotoxicity [66, 70]. Cai *et al.* (2011) demonstrated that Shp2 is essential for the initiation of retinal neurogenesis but is not crucial for tissue differentiation [71]. However, Shp2 deletion in embryonic stages resulted in retinal degenerative changes including optic nerve dystrophy in mice, further explaining its role in retinal development. Also, Shp2 mediated tyrosine dephosphorylation is reported in Semaphorin-4D (Sema4D) induced axonal repulsion in RGCs and hippocampus neurons [72, 73]. Shp2 has been shown to be predominantly expressed in the inner retina including ganglion cell layer (GCL), although it also regulates photoreceptor differentiation and is suggested to protect the outer retina indirectly through Muller glial cell involvement [71, 74]. Studies in our group have demonstrated interaction of TrkB with Shp2 is increased in the RGCs by 2-3 fold in ON axotomy and microbead injected glaucoma animal models. Further, primary culture of rat RGCs showed high TrkB and Shp2 interaction when subjected to glutamate excitotoxic and hydrogen peroxide (H₂O₂) induced oxidative stress conditions [75]. Interestingly, increased dephosphorylation of TrkB was observed in the RGC stress models *in vivo*. Not much is known about how Shp2 regulation of TrkB activity affects the RGC survival in healthy and disease conditions. Therefore, Shp2 may serve as a potential target to explore and understand the mechanisms of RGC death. It also offers an opportunity to explore the potential for Shp2 gene therapy as a therapeutic target in glaucoma conditions. Caveolins (Cav) are integral membrane adaptor proteins that form the principal components of the omega-shaped caveolar structures in the plasma membrane. The various forms of cav are caveolin-1 (cav1), caveolin-2 (cav2), and caveolin-3 (cav3). These variants differ with respect to tissue distribution and their specific function. Origin of ancestry is similar for cav1 and cav2 and is expressed in smooth muscle cells, neuronal cells, endothelial cells, adipocytes and fibroblast in abundance [76, 77]. Cav3 expression is predominantly limited to muscle cells [76], but has also been identified in astroglial cells, vegetative ganglion neurons *etc* [78, 79]. Cav1 alterations have been linked to retinal pathologies including diabetic retinopathy and glaucoma [80, 81] but its role in retinal neuroprotection is still unknown. Recently, Reagan and colleagues (2016) demonstrated the neuroprotective role of cav1 in the retina. Cav1 is involved in recruiting circulating leukocytes during inflammation and these cytokines activate the JAK/STAT pathway, which downregulates apoptotic factors to prevent retinal neuronal death [82, 83].

Cav1 is also shown to interact with toll-like receptors (TLRs) in the retina that recognize and respond to pathogenic stimuli and initiate pro-inflammatory cytokine re-

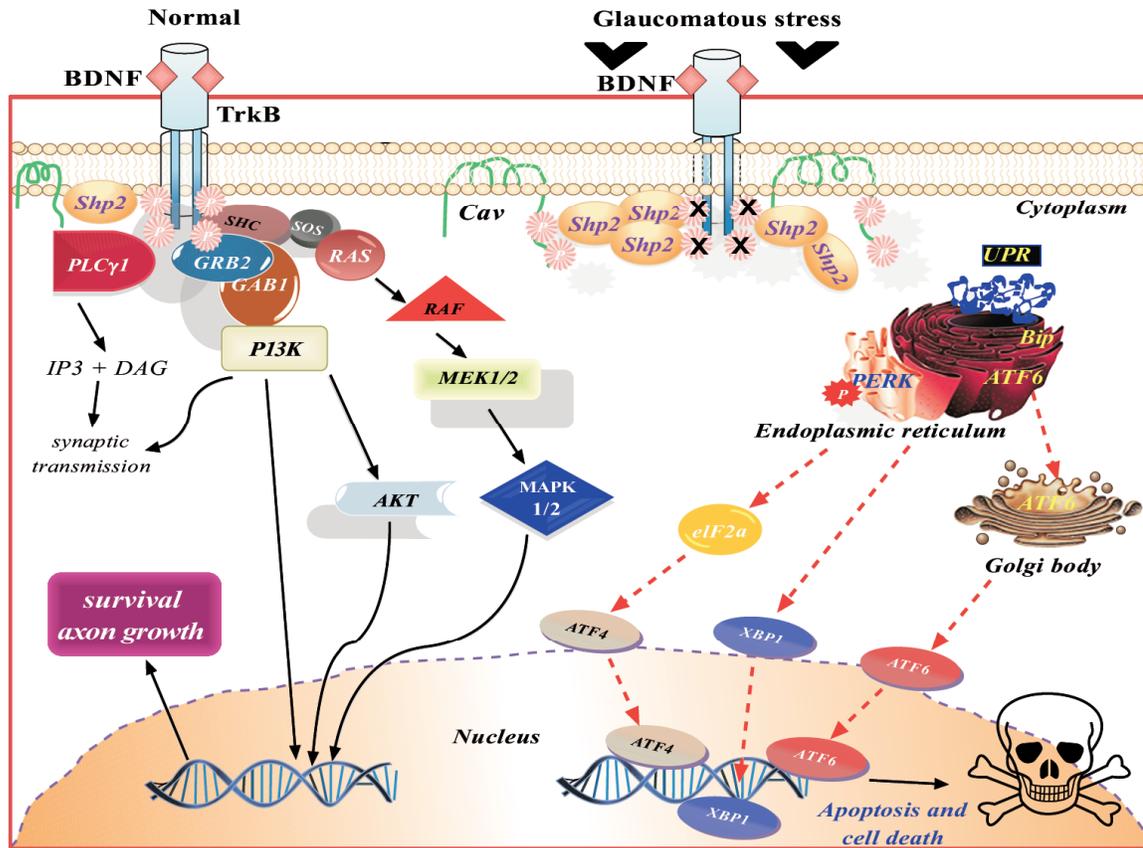


Fig. (2). Schematic representation of the BDNF/ TrkB signalling in normal and glaucomatous conditions. The downstream cellular effects of BDNF-TrkB complex in normal condition promote neuronal survival. Under glaucomatous stress, the downstream survival pathway ceases and induces ER stress and promote cell apoptosis.

sponses. Cav1 associates with TLRs and regulates TLR signalling [84]. Recently, we have shown molecular evidence that Shp2-TrkB interaction in RGCs is mediated through cav. Under ON axotomy and glaucomatous stress cav1 and cav3 undergo hyperphosphorylation and interact with Shp2 in the RGCs [75]. Cav may bind to the SH2 domain of Shp2 and thus diminish the auto-inhibition of Shp2 and enhance its phosphatase activity [85]. There might be the possibility of recruitment of Shp2 by cav acting as a signalling platform and increase its proximity to TrkB receptor, thereby increasing dephosphorylation of TrkB and influencing downstream signalling (Fig. 2). Cav1^{-/-} mice show an enhanced Erk1/2 phosphorylation in the hippocampus [86]. Consistent with Cav-Shp2 interactions in the RGCs, previous studies also that cav1 undergoes hyper-phosphorylation in oxidative and osmotic cellular stress in fibroblast cultures [87, 88]. Trabecular Meshwork (TM) cell lines from POAG patients treated with dexamethasone show a decline in cav1 phosphorylation [89], implicating that cav phosphorylation is affected by glaucoma in the RGCs. Cav is also reported to play a critical in Shp2 activation in astrocytes, retinal homeostasis, preservation of blood retinal barrier permeability and outer retinal functions [90-92].

8. APOPTOSIS IN RGCs

Ganglion cells undergo apoptosis in glaucoma leading to progressive loss of vision - the loss of RGCs is the principal

endpoint in experimental glaucoma [93]. This mechanism of cell death is controlled by gene modulation.

Pro-apoptotic factors can arise in the retina through various mechanisms such as ischemia, inflammation, excitotoxicity, oxidative stress and hyperglycemia [50, 94-98]. Recent evidence suggests that abnormal protein aggregation induced stress may lead to an unfolded protein response in the endoplasmic reticulum (ER) [99]. Furthermore, some of the ER stress signalling proteins control cell fate either by activating pro-apoptotic, Bcl2 or anti-apoptotic Bax molecules in response to cell burden [100].

9. ER STRESS AND UNFOLDED PROTEIN RESPONSE

Intracellular synthesized protein is further processed by the ER. Protein folding, maturation, and trafficking are some of the important functions of this organelle. The folded membranes of ER help the newly synthesized proteins to undergo posttranslational modification and correctly fold in their three-dimensional (3D) conformations. However, only mature (correctly folded) proteins can be taken up by the Golgi bodies for further targeting. ER is the major intracellular organelle that senses environmental changes, cellular stresses, coordinates signalling pathways and controls cell function/ survival [101]. Different pathological and physiological conditions, nutrient scarcity, change in redox status and viral infection can influence the ER ability to facilitate

protein folding, resulting in unfolded or misfolded protein accumulation in the ER lumen and consequently increased ER stress. The unfolded proteins form insoluble protein aggregates that are toxic to the cell. This has been reported in neurodegenerative diseases like glaucoma, Parkinson's disease and Alzheimer's disease [102-105]. Within the cell, an adaptive mechanism is activated that comprises various intracellular signalling pathways to remove toxic proteins, termed the unfolded protein response (UPR). UPR alleviates ER stress by three different strategies; (1) through ER-related molecular chaperons to stimulate re-folding of the folding proteins; (2) inhibit mRNA translation so that no more generation of unfolded proteins take place and (3) stimulate the retrograde transport of the misfolded proteins from the ER lumen into the cytosol for ubiquitination by activation of ER-associated protein degradation (ERAD) [106].

Recent research has shown that the ER stress is associated with neuronal cell death in neurodegenerative diseases like glaucoma [107]. In an animal model of chronic glaucoma and acute ON traumatic injury, an increase in ER stress proteins in the RGCs was observed [108, 109]. Intravitreal injection of N-methyl-D-aspartate (NMDA) given in ischemic insult animal model resulted in increased ER stress protein expression in the inner retinal cells like RGCs, amacrine and microglia. Activation of Bip, ATF4, and CHOP by tunicamycin or NMDA-induced apoptosis in mouse primary RGCs also suggested an imperative role of ER stress in neuronal cell death in the retina [110]. An antipsychotic drug, Valproate demonstrated neuroprotective actions in the ischemic retina from ER stress-induced apoptosis by inhibiting histone deacetylase activity [111]. Neuronal ER stress is emerging as a promising therapeutic target for glaucoma and potentially for other neurodegeneration diseases.

10. SIGNALLING PATHWAYS OF ER STRESS-ASSOCIATED APOPTOSIS

Cell death often occurs if ER stress is chronic and the protein burden on ER is unable to fold the protein accurately and perform necessary cellular function. The three-major proteins involved in UPR are (1) protein kinase RNA (PKR)-like ER kinase (PERK), (2) ATF6 and (3) IRE1 α . Under normal biological conditions, BiP, an ER local chaperon, binds PERK and ATF6 which keeps these ER stress proteins idle. Upon aggregation of ER misfolded proteins, BiP is set free from these complexes and helps in folding of accumulated proteins [112]. The function of PERK is to regulate mRNA translation and to prevent the entry of newly formed unfolded protein to the ER compartment already experiencing stress. PERK phosphorylates the elongation initiation factor 2 α (eIF2 α) and nuclear erythroid 2 p45-related factor 2 (NRF2). Phosphorylated eIF2 α stops polypeptide synthesis and phosphorylated NRF2 induces oxidative stress through cell reinforcement genes such as heme oxygenase 1 (HO-1) [113-115]. Another transcription factor, ATF6 is taken up by the Golgi apparatus upon UPR and cleaved into luminal domain by serine protease site-1, whereas site-2 protease cleaves the N-terminal domain. The separated N-terminal domain of ATF6 then moves into the nucleus and forms a complex with ATF/cAMP response elements (CRE) and ER

stress-response elements (ERSE-1). The ATF6-CRE-ERSE-1 complex initiates transcription of BiP, Grp94 and CHOP [116]. IRE1 α promotes apoptosis by stimulating apoptotic-signalling kinase-1 (ASK1) and downstream activation of JNK and p38 MAPK [117]. Anti-apoptotic marker, Bcl-2 expression is downregulated and Bim upregulated on p38 MAPK activation (Fig. 2).

11. GENES ASSOCIATED WITH GLAUCOMA

A genetic association of POAG has been recognised for decades with a family history commonly identified, although the non-mendelian nature of inheritance indicates a multifactorial etiology that may again vary in different ethnicities [118]. Variants in myocilin (MYOC) [119], optineurin (OPTN) [120], WD repeat domain 36 (WDR36) [121], and neurotrophin 4 (NTF4) [122] have previously been reported as showing an association with POAG. Genome-wide association studies (GWAS) have recognized new loci in POAG such as caveolin 1 or 2 (Cav1/Cav2) [123], transmembrane and coiled-coil domain 1 (TMCO1) [124], ankyrin repeat and SOCS-box containing 10 (ASB10), susceptible loci-TXNRD2, ATXN2, and FOXC1 [125]. New gene associations with glaucoma continue to be discovered in larger cohorts of different ethnicities although there remains a need to identify whether statistical differences observed in these studies are translatable into clinical significance. Molecular mechanisms to identify the potential roles of these genes will be a significant step forward to understand the glaucoma pathophysiology.

11.1. NTF4 and BDNF

Pasutto *et al.* (2009) demonstrated the association of six-heterozygous variants in NT-4 (C7_Y, E48_K, A88_V, R90_H, R206_W and R206_Q) with POAG in European cohort [126]. In contrast to this study, subjects with European ancestry from the south-eastern United States showed no association between coding variants in *NTF4* gene and POAG, moreover, variants R206_W and A88_V were also reported in the control individuals [127]. Interestingly, Rao *et al.* (2010) showed that these variants in *NTF4* were not associated in POAG in an Indian population [128]. A single missense mutation, L113_S in one Chinese patient was found to alter the NT-4 protein structure and disrupt the binding and activity of the TrkB receptor but this could be a rare case of *NTF4* variant in POAG [129]. The composite nature of the disease phenotype and enormous genetic heterogeneity suggests that *NTF4* mutation alone is not sufficient to explain glaucoma pathogenesis. A recent study in 167 Polish patients and 193 healthy individuals showed no significant association between G196_A allele polymorphism of the BDNF gene and POAG [130] although dysregulation of BDNF at the biochemical level has been implicated in the disease pathology.

11.2. Caveolin 1 and 2

Genome-wide association studies (GWAS) resulted in discovery of variations in caveolin gene (*cav1/ cav2*) locus that is associated with POAG [131]. The study on an Icelandic cohort, found that a variant rs4236601_A in *cav1* and *cav2* gene loci on chromosome 7q31 was associated with

POAG. They also performed replication studies in multiple cohorts from Europe and East Asian ancestry. Further studies on this SNP (rs4236601) in Iowa, USA involving 545 POAG patients and 297 control subjects detected no association of the disease with this variation [132]. However, Wiggs *et al.* further confirmed the association of *cav1* and *cav2* SNP with POAG in another cohort of Caucasian US population [123]. Both *cav1* and *cav2* were reported to express in glaucoma TM cell lines [89]. The recent study in *cav1*^{-/-} (*cav1* knockout) mice suggested a possible reduced aqueous humour drainage outflow as demonstrated by slightly higher IOP in these animals [133].

11.3. MYOC

MYOC gene was identified as the first gene associated with POAG and found at locus GLC1A on chromosome 1q23 [134]. The *MYOC* gene was first studied *in vitro* in TM as response of glucocorticoid-induced gene (TIGR) while studying the effects of dexamethasone on TM cell cultures [135]. This gene encodes myocilin protein and intracellular accumulation of its mutant leads to a misfolded form that increases the IOP [136]. Recently, a mutation C1456_T in *MYOC* gene was identified in a Chinese family. Beta-1, 4-galactosyltransferase 3 (*B4GALT3*) gene also showed mutation at G322_A in this POAG family [137]. In a transgenic mouse model of POAG, *MYOC* mutation Y437_H shows a significant increase in IOP with abnormal extracellular matrix accumulation that potentially reduces aqueous outflow [136]. Likewise, *MYOC* mutant Q368_X and Y437_H were shown to activate the IL-1/NF- κ B pathway activity in culture TM-1 cell line [138]. A meta-analysis within Caucasian populations suggested a genetic association between *MYOC* polymorphism and POAG [139].

11.4. OPTN

Optinuerin (*OPTN*) was shown to have protective role in glaucoma progression in response to TM stress [104]. Recent studies on *OPTN* mutation demonstrated that overexpression of E50_K mutation triggers the apoptotic factors and impaired the mitochondrial dynamics (fusion and fission) in retina of aged E50_K^{tg} mice as well as in the primary cultured RGCs [141]. The aged transgenic mice with overexpression of E50_K *OPTN* demonstrated diffused retinal layers with thinner retina. In contrast, low expression of E50_K *OPTN* in aged transgenic mice did not lead to changes in retinal layer thickness [142]. Clinical examination of subjects with glaucoma with E50_K *OPTN* mutation was studied in caucasian families. It was examined subjects with E50_K mutation at a younger age had more advanced optic disc cupping and smaller neuroretinal rim area and were found to have NTG features that appeared to be more severe than that in control subjects with NTG without this mutation [143].

11.5. WDR36

The alterations in *WDR36* alone are not sufficient to cause POAG, notwithstanding, the relationship of *WDR36* sequence variants with more severe disease in affected individuals [144]. *WDR36* encodes protein thought to be involved with T-cell activation and proliferation and in ribo-

somal RNA processing [145]. The loss of *WDR36* in zebrafish line with viral insert *wdr36*^{chi3630a^{Tg}} showed reduction in *WDR36* protein and was found to activate p53 stress response pathway without alteration in pro-apoptotic gene, *bax* [121]. In contrast, variant of *WDR36* D658_G mutation in Australian families was reported to be a neutral variant for glaucoma [146]. These studies were also supported by *WDR36* mutation variant (N355_S, A449T, R529_Q and D658_G) may be only rare disease-causing gene in glaucoma in German population [147]. In Japanese populations, *WDR36* was not reported as a major contributing factor to POAG [148]. At the molecular level, expression studies in yeast indicated that *WDR36* sequence variants can produce changes in cellular phenotype [149].

11.6. TMC01

TMC01 is highly expressed in the human TM, ciliary body and retina [150]. The location of this gene is upstream to the *MYOC* gene at chromosome 1q24.1. The function of *TMC01* is to encode transmembrane coiled domain protein that localize in the Golgi apparatus, ER or mitochondria in different cell types and this protein has been suggested to be possibly involved in RGCs apoptosis [151]. Recent studies in the Han Chinese population identified the SNP rs4656461 and rs7555523 in *TMC01* to be associated with POAG [152]. In addition, a study in a Pakistani cohort (total 268 POAG patients) confirmed that the SNP rs4656461 in *TMC01* was highly associated with POAG [153]. Furthermore, black South African and Saudi cohorts showed no association of the *TMC01* gene variants with POAG [124, 154]. GWAS studies and meta-analysis of >6,000 subjects of European ancestry identified a significant association of *TMC01* variants with IOP changes (SNP rs7518099) [155]. Additional studies are needed to identify the effect of these polymorphisms and mutations in populations with different ethnicities and to match for age and gender differences.

12. THERAPEUTIC PROSPECTS IN GLAUCOMA

This section outlines various therapeutic prospects to protect the retina in glaucoma by targeting neurotrophin signalling, apoptotic pathways and by modulating ER stress response.

13. CAN NEUROTROPHIN THERAPY SCALE DOWN RGC DAMAGE IN GLAUCOMA?

Neurotropic factor supplementation has been shown to protect the RGCs in ocular hypertension (OHT) animal models *via* intravitreal injection of human recombinant BDNF [156]. The disadvantage of using BDNF is that it requires repeated intravitreal injections to achieve a recognizable neuroprotective effect [157]. Ko and colleagues have shown an increase in RGC protection after four intravitreal injections of BDNF therapy. BDNF enhances and prolongs RGCs survival both *in vivo* [30, 158, 159] and *in vitro* [5, 25] after optic nerve injury and axotomy. However, TrkB expression in RGCs is down-regulated after axotomy, making the cells less sensitive to the neuroprotective actions of BDNF. TrkB gene transfer to RGCs coupled with intravitreal BDNF administration significantly increased RGC survival after axotomy [160]. The neuroprotective effects of BDNF can be

enhanced by associative administration of other growth factors, for example, FGF2 and NT-3 [161, 162]. FGF2 administered after ON injury increased BDNF and TrkB expression in RGCs [161].

Several other growth factors also have protective effects on the RGCs. Recombinant CNTF intravitreal injections exhibit neuroprotective effects in OHT animal model. A single intravitreal injection of low dose CNTF (2 µg CNTF) exerted a neuroprotective effect with 15% less RGC loss in 6 weeks [16]. This effect correlated with upregulation of STAT3 in cells within the RGC layer and the inner nuclear layer [163]. However, partial neuroprotective effect on the RGCs upon exogenous administration of CNTF was reported in ocular hypertension model [164]. While short-term advantageous effects have been shown at times for single intraocular administrations of NGF, long-term neuroprotection in glaucoma patients likely requires a sustained NGF supply.

Gene therapy techniques could be applied to neurotrophin factor supplementation to meet the requirements for sustained delivery in glaucoma. By using viral vectors to increase endogenous retinal production of select NGF(s), it might be possible to reduce RGC damage over a long period. For example, adenovirus (AdV) vector mediated over-expression of BDNF in Müller glial cells prolonged the survival of RGCs in a rat model of optic nerve transection [165]. In another approach, repeated intravitreal injection of AdV vector for GDNF delivery prior to optic nerve axotomy lead to 125%-fold increase in RGC survival at 14 days post axotomy [166]. However, the efficacy of AdV-mediated gene transfer is limited by its relatively short duration of expression and by the fact that AdV triggers significant inflammatory reactions. AdV has also been shown to be highly immunogenic in clinical trials [167]. Alternatively, adeno-associated virus (AAV), could be used and it has been shown that these vectors do not integrate into the host genome. AAV-FGF2 transduction of the retina protected RGCs in models of optic nerve crush and excitotoxicity [168]. Martin and colleagues (2003) used AAV to transduce retinal cells in the laser-induced OHT model of glaucoma [169]. They used a hybrid promoter of cytomegalovirus (CMV), chicken β-actin (CAG) enhancer and the woodchuck hepatitis post-transcriptional regulatory element (WPRE) to deliver BDNF gene incorporated in an AAV viral vector. The promoter could efficiently transduce more than 70,000 cells within the RGC layer per eye. A single intravitreal injection of AAV-BDNF gene therapy reduced the axonal loss in the ON from 52.3% to 32.3% four weeks after the laser induced experimental model of glaucoma in rodents. Likewise, CNTF gene therapy also promoted long term survival and regeneration of rat RGCs after 7 weeks of ON crush [170]. Using a similar vector, Leaver and colleagues (2006) showed increase in RGC protection in retinas injected with CNTF compared to viral vector containing no CNTF. However, a combination of CNTF-BDNF had no significant improvement in RGC axon survival in laser induced rat glaucoma model and the reason for lack of improved effect was not clear [16]. Recent advances in recombinant AAV engineering have led to the development of vectors that are less susceptible to ubiquitin-mediated degradation and can be used for expression modulation over a long period of time [171].

14. TARGETING NEUROTROPHIN RECEPTORS IN GLAUCOMA

NGF signalling pathways are often subject to complex regulation and accordingly increase of neurotrophic factor levels does not always benefit neuronal survival. In addition to promoting cell survival *via* Trk family receptor, NGF can bind to p75NTR receptor and trigger pro-apoptotic signals. Indeed, it has been suggested that a cause of failure of NGF in glaucoma may be related to over-activation of p75NTR due to administration of a selective Trk family agonist [172]. In that capacity, design of modified receptor-defined ligands as compared to naturally occurring neurotrophic factors, is being investigated as an approach to achieve greater neuroprotection. Lebrun-Julien *et al.* (2009) demonstrated that combined TrkA activation and p75NTR inhibition in p75NTR null mice was protective for survival of RGCs following optic nerve injury [173]. This study indicated that the deleterious effects of p75NTR in Muller cells may regulate neuronal death by emancipating neurotoxins or indirectly by diminishing their sympathetic functions. Also, p75NTR activation could attenuate the beneficial effects of BDNF delivery and inhibition of p75NTR was shown to unmask a potent neuroprotective effect of NGF [173]. BDNF combined with CNS-specific leucine -rich repeat protein LINGO-1 (LINGO-1 negatively regulates p75NTR signalling) antagonists have been found to promote long-term RGC survival in a laser-induced OHT rat model [174]. Fu *et al.* demonstrated that LINGO-1-TrkB receptor complex adversely controls TrkB activation in the retina after OHT injury. Antibody-1A7 or soluble LINGO-1 (LINGO-1-Fc) commonly used as LINGO-1 antagonist, protected RGCs from death by activating the BDNF-TrkB signalling pathway in animal models of OHT [175]. Alternatively, novel ligands which specifically activate TrkB and not p75NTR might be of interest. A monoclonal antibody and a natural flavonoid, 7,8-DHF which specifically activates TrkB have shown RGC neuroprotection in the optic nerve transection and OHT animal models [48, 50]. In the light of these outcomes, it is likely that selectively activating multiple Trk receptors while blocking p75NTR using natural/synthetic receptor ligands may exert more robust neuroprotective effect than just delivering the neurotrophic factors alone.

Our group has demonstrated that Shp2 interacts with the TrkB receptor in RGCs and negatively affects its action in ON transection and chronically elevated IOP rodent models. The Shp2-TrkB binding is suggested to be mediated through the adapter protein, caveolin. Under stress conditions, caveolin isoforms 1 and 3 undergo hyperphosphorylation in RGCs and further bind to Shp2 phosphatase. The increase in phosphatase activity of Shp2 in glaucomatous stress reduces TrkB activity [75]. These proteins may be good candidates for targeted gene therapy studies in glaucoma. Pernet *et al.*, (2005) used AAV to transduce RGCs with genes encoding MEK1, the upstream activator of Erk1/2. MEK1 activation induced *in vivo* phosphorylation of Erk1/2 in RGC bodies and axons. A single injection of AAV encoding MEK1 gene increased RGC survival at 2 weeks after axotomy [176]. In addition, we have also shown the neuroprotective effect of sphingosine-1-phosphate analogue fingolimod (FTY720) in a chronic OHT animal model. Administration of FTY720

reduced the loss of electrophysiological responses and protected against GCL and ON loss. It was observed that the fingolimod effects were associated with increased activation of Akt and Erk1/2. SIPR receptor expression was found to be increased in the RGCs in experimental glaucomatous condition [177].

15. CROSS-TALK OF BDNF WITH VEGF

Vascular endothelial growth factor (VEGF) plays an important role both in physiological and pathological angiogenesis. BDNF signalling is identified as potential proangiogenic factor and stimulates VEGF expression through PI3K pathway for promotion of endothelial cell survival in neuroblastoma cells [178, 179]. Similarly, VEGF, an angiogenic factor, was also shown to stimulate axonal outgrowth from dorsal root ganglia by acting as a neurotrophic factor [180]. Apart from its angiogenesis function, VEGF can also stimulate non-vascular cells such as Tenon's fibroblasts, a target for antifibrotic treatment in glaucoma filtration surgery [181]. VEGF is usually released after retinal ischemia and can further spread through the aqueous humor to the anterior segment of the eye. The latter results in neovascularization of the iris and angle, causing secondary closed angle glaucoma [182]. Inhibition of VEGF signalling remains an important focus for the treatment of retinal and choroid neovascularization and in retina edema. VEGF binds to both of its receptor forms VEGFR1 and VEGFR2. VEGFR1 may be important in development by sequestering VEGF, preventing its interaction with VEGFR2, which is responsible for endothelial cell mitogenesis, survival and permeability [183]. Therapeutically targeting VEGF has been successful with intravitreal injections of VEGF neutralising antibodies preventing vision loss and salvaging visual activity in age-related macular degeneration (AMD) patients [184]. Ranizumab therapy has been shown to protect against retinal thickness loss and it improved visual acuity in patients with diabetic macular edema [185]. VEGF also has neurogenic and neuroprotective effects [186]. RGCs overexpressing VEGF in transgenic mice were protected from axotomy-induced degeneration [187]. It will be interesting to determine how neurotrophin factor signalling overlaps with angiogenic factors and how manipulating one pathway would affect the other [49].

16. INHIBITING APOPTOTIC PATHWAY IN THE RGCs IN GLAUCOMA

Apoptosis is a programmed cell death that has essential roles in physiological processes but also is a feature in the pathophysiology of many diseases. Dkhissi *et al.* (1999) observed DNA fragmentation using the terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) method in the GCL and INL in an avian glaucoma-like disorder model [188]. The apoptosis in RGCs was also studied in experimental glaucoma animal models by activation of the tumor suppressor protein, p53, which functions to activate the proapoptotic pathways [189]. Considering these observations, it was suggested that anti-apoptotic molecules may preserve the phenotype damage of ON in glaucoma. Etanercept, TNF- α inhibitor, when given intraperitoneally, blocked the TNF- α activity in experimental OHT produced due to

activation of microglia and reduced axonal degeneration and loss of RGCs [190]. Clinically, a new therapy was investigated in glaucoma using TNF- α antagonist as suppressors of inflammation [190]. Furthermore, intravitreal injection of second-generation tetracycline drug, minocycline, has been shown to exhibit neuroprotection in experimental glaucoma and optic nerve transection animal models. Minocycline increased the expression of antiapoptotic gene Bcl-2 and at the same time decreased the expression of apoptotic gene Bax [191]. Also, TNF- α , inhibitor of apoptosis protein (IAP1) and Gadd45 α was upregulated in retinas with optic nerve transection [191]. Calcineurin inhibitor, FK506 when administered orally, showed RGC and ON protection from apoptosis by decreasing Bad dephosphorylation and inhibiting mitochondrial cytochrome c release under experimentally induced high IOP [192]. In addition, agents that alter the expression of endogenous anti-apoptotic proteins can also be employed for neuroprotection function in injured ON. For instance the use of brimonidine, an α 2 adrenergic receptor agonist decreases the level of Bcl-2 and also reduces mitochondrial-dependent apoptosis in RGCs of post-mortem eyes from glaucoma individuals [193]. Similarly, suppressing downstream signalling of pro-apoptotic pathways may induce RGC neuroprotection. Indeed C-terminal binding protein 2 (CtBP2) was recently shown to be neuroprotective in CNS injury in DBA/2J mice. Lentivirus mediated overexpression of CtBP2 in cultured RGCs subjected to L-glutamate-induced apoptosis showed a decrease in expression of Bax and caspase-3 [194]. Cobalt chloride induced hypoxia in primary rat RGCs treated with GABA receptor agonist baclofen, prevented the RGC apoptosis through Akt activation [195].

17. TARGETING ER STRESS MARKER PROTEINS IN THE RGCs IN GLAUCOMA

Several studies have focussed on utilizing the therapeutic application of synthetic chaperons to subdue ER retention of the misfolded proteins, minimizing their generation and to amend the ER folding capacity. UPR is triggered in ON axotomy resulting in RGCs death. RGCs shown to have upregulated CHOP in ON injury and promote neuronal apoptosis. CHOP knockout (KO) mice demonstrated increased RGCs survival by 24% after two weeks of ON axotomy [196]. Alternatively, the overexpression of XBP-1 in RGCs was carried out using intravitreal AAV injection in WT and CHOP KO mice [196]. AAV viral vector expressing *XBP-1*, showed considerably increased RGCs survival in both WT and transgenic mice. RGC survival was increased by 64% in animals overexpressing *XBP-1* whereas AAV-GFP control mice demonstrated only 20% RGC survival. RGCs survival was increased to 82% in transgenic mice (CHOP KO mice) overexpressing XBP-1 following ON crush injury compared to the wild type animals. Altogether, this experiment suggested an opposite action of XBP-1 and CHOP in controlling RGCs survival and apoptosis after ON injury [106, 109]. Recently, Nakano *et al.* (2006) designed two novel compounds KUS121 and KUS187 and treated PC12 cells with these two substances. Both compounds induced mitochondrial respiratory chain complex III and V inhibition by reducing cellular ATP levels. CHOP expression was reduced

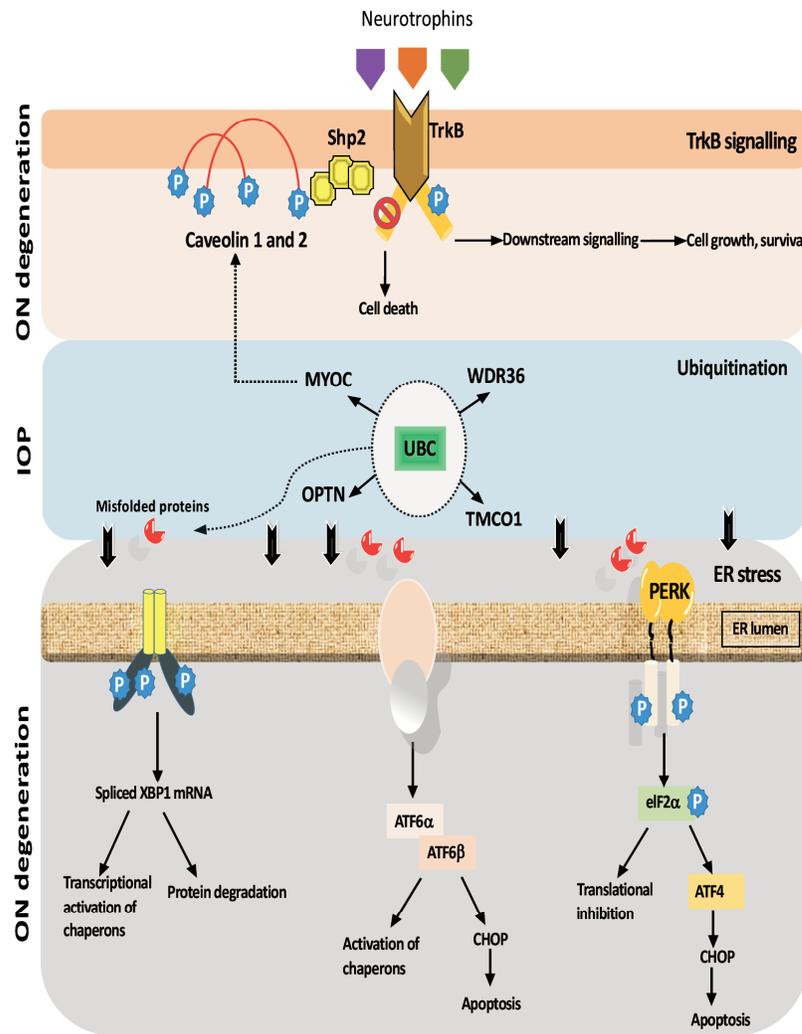


Fig. (3). Downstream consequences of neurotrophin signalling pathway affecting gene function and ER stress marker is possibly implicated in progression of RGCs axon damage in glaucoma.

in cultured PC12 cells upon treatment with these KUS inhibitors. *In vivo* neuroprotective effects on RGCs were also demonstrated by KUS inhibitor treatment in mice in the ON axotomy model as well as experimentally increased IOP model. The rescue of RGCs in ON axotomy and high IOP was associated with low expression levels of Grp78 or Bip [197]. RGC death was also induced by the activation of chemokines (CXCL10) and chemokines receptors such as CXCR3. Experimentally induced ischemia and retinal stress modulate the expression of CXCL10 and CXCR3. Upregulation of chemokines and its receptor increases the expression of Grp78, CHOP and ATF4 in RGCs [198]. However, when the mice were treated with ER stress blockers 4-phenylbutyric acid and tauroursodeoxycholic [199], the chemokines expression was attenuated by 61% and 43% respectively. Moreover, in CXCR3 KO mice, the ER stress inhibitor did not transform the expression of ER stress markers, suggesting that the downstream event of CXCR3 activation is not associated with ER stress [198]. It may therefore be essential to comprehend the dual biological functions of UPR signalling both in survival and apoptosis before exploring therapeutic application focusing ER stress.

18. BUILDING BRIDGES BETWEEN NEUROTROPHIN PATHWAY AND GENETICS RESEARCH IN GLAUCOMA

The BDNF-TrkB signalling pathway has been implicated as a mediator for survival, development and synaptic plasticity of neurodegenerative neurons in POAG [200]. BDNF and NGF serum levels are reduced in the early and moderate glaucoma stages [201]. Mutation in *OPTN* has been observed in POAG and amyotrophic lateral sclerosis (ALS) and its deficiency leads to a reduced secretion of neurotrophic factors [202]. *OPTN* in association with Tank binding kinase 1 (*TBK1*) gene are involved in neuroinflammation and autophagy [203]. These two genes, *OPTN* and *TBK1*, are important components of the pathway required for removal of pathological ribonucleoprotein inclusions [203]. Depletion or dysregulation of *OPTN* and *TBK1* may lead to protein aggregates which is one of the main characteristics associated with loss of neurons in neurodegenerative disorders like ALS, Parkinson's, Huntington's and Alzheimer's diseases [204] (Fig. 3).

Degradation of aggregated and misfolded proteins is the critical pathway by which protein cellular homeostasis is regulated in POAG. Ubiquitin-proteasome system (UPS) is responsible for the elimination of misfolded or damaged proteins (Fig. 3). RGCs and retinal pigment epithelium are rich in ubiquitin [205]. The mutated form of *OPTN* (E50_K) that causes glaucoma leads to malfunction of UPS [206] and overexpression of wild type *OPTN* results in increased apoptosis in PC12 and RGC5 cells [207]. On the other hand, when PC12 cells transfected with wild-type and mutated *MYOC* (P37_L) plasmid they showed inhibition in neurite outgrowth and number [207]. When myocilin is overexpressed or mutated, the UPS function is compromised, and autophagy is induced [208]. In human trabecular meshwork line TM-1 mutant *MYOC* activate the IL-1/NF- κ B inflammatory stress response and the glaucoma marker SELE, whereas the wild-type *MYOC* has anti-inflammatory activity [138]. Mutations in *OPTN* are associated with NTG while mutations in *MYOC* induce blockage of aqueous humor outflow [119], suggesting that alteration of the UPS system is implicated in both NTG and POAG.

It will be important to integrate the role of system biology and functional genomics to discover the exact role of these cellular pathways. Glaucoma is clearly a complex disease with at least 70 loci identified so far which highlights variance in POAG phenotype. There is a lack of functional validation and detailed analysis of the *in vivo* function of these genes. More experimental data based on the animal models may help clarify this in the near future.

CONCLUSION

The detrimental effects of glaucoma can be prevented to a certain extent if effective treatment can be provided at the appropriate time. This disease involves optic nerve atrophy and loss of RGCs and can occur even under normal IOP conditions. The fate of RGCs is programmed by complex interplay of several molecular signalling pathways that are functioning simultaneously. RGC death can be triggered by many acute and chronic insults such as neurotrophic factor deprivation, synaptic dysfunction, protein-protein interaction, gene dysregulation, neuronal stress due to ischemia/hypoxia and excitotoxicity, activation of apoptotic pathways and UPR under ER stress. Simulating neuroprotective endogenous mechanisms has the potential to significantly transform the equilibrium between the pro/apoptotic and the pro/survival pathways, leading to a delay in RGCs death with beneficial effects in glaucoma.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work was supported by funds from Ophthalmic Research Institute of Australia (ORIA, 9201400700), National

Health and Medical Research Council (NHMRC, 1084767), Hillcrest foundation and Macquarie University.

REFERENCES

- Davis, B.M.; Crawley, L.; Pahlitzsch, M.; Javaid, F.; Cordeiro, M.F. Glaucoma: the retina and beyond. *Acta Neuropathol.*, **2016**, *132*(6), 807-826. [http://dx.doi.org/10.1007/s00401-016-1609-2] [PMID: 27544758]
- Stowell, C.; Burgoyne, C.F.; Tamm, E.R.; Ethier, C.R.; Lasker, I.I.A.; Glaucomatous Neurodegeneration, P. Biomechanical aspects of axonal damage in glaucoma: A brief review. *Exp. Eye Res.*, **2017**, *157*, 13-19. [http://dx.doi.org/10.1016/j.exer.2017.02.005] [PMID: 28223180]
- Abu-Amero, K.; Kondkar, A.A.; Chalam, K.V. An updated review on the genetics of primary open angle glaucoma. *Int. J. Mol. Sci.*, **2015**, *16*(12), 28886-28911. [http://dx.doi.org/10.3390/ijms161226135] [PMID: 26690118]
- Seki, M.; Tanaka, T.; Sakai, Y.; Fukuchi, T.; Abe, H.; Nawa, H.; Takei, N. Müller cells as a source of brain-derived neurotrophic factor in the retina: noradrenaline upregulates brain-derived neurotrophic factor levels in cultured rat Müller cells. *Neurochem. Res.*, **2005**, *30*(9), 1163-1170. [http://dx.doi.org/10.1007/s11064-005-7936-7] [PMID: 16292510]
- Takahara, Y.; Inatani, M.; Hayashi, H.; Adachi, N.; Iwao, K.; Inoue, T.; Iwao, M.; Tanihara, H. Dynamic imaging of axonal transport in living retinal ganglion cells *in vitro*. *Invest. Ophthalmol. Vis. Sci.*, **2011**, *52*(6), 3039-3045. [http://dx.doi.org/10.1167/iovs.10-6435] [PMID: 21310905]
- Lebrun-Julien, F.; Bertrand, M.J.; De Backer, O.; Stellwagen, D.; Morales, C.R.; Di Polo, A.; Barker, P.A. ProNGF induces TNF α -dependent death of retinal ganglion cells through a p75NTR non-cell-autonomous signaling pathway. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*(8), 3817-3822. [http://dx.doi.org/10.1073/pnas.0909276107] [PMID: 20133718]
- Ibáñez, C.F.; Simi, A. p75 neurotrophin receptor signaling in nervous system injury and degeneration: paradox and opportunity. *Trends Neurosci.*, **2012**, *35*(7), 431-440. [http://dx.doi.org/10.1016/j.tins.2012.03.007] [PMID: 22503537]
- Kimura, A.; Namekata, K.; Guo, X.; Harada, C.; Harada, T. Neuroprotection, growth factors and BDNF-TrkB signalling in retinal degeneration. *Int. J. Mol. Sci.*, **2016**, *17*(9), E1584. [http://dx.doi.org/10.3390/ijms17091584] [PMID: 27657046]
- Harada, C.; Harada, T.; Nakamura, K.; Sakai, Y.; Tanaka, K.; Parada, L.F. Effect of p75NTR on the regulation of naturally occurring cell death and retinal ganglion cell number in the mouse eye. *Dev. Biol.*, **2006**, *290*(1), 57-65. [http://dx.doi.org/10.1016/j.ydbio.2005.08.051] [PMID: 16343477]
- Dekeyser, E.; Geeraerts, E.; Buyens, T.; Van den Haute, C.; Baekelandt, V.; De Groef, L.; Salinas-Navarro, M.; Moons, L. Tackling glaucoma from within the brain: An unfortunate interplay of BDNF and TrkB. *PLoS One*, **2015**, *10*(11), e0142067. [http://dx.doi.org/10.1371/journal.pone.0142067] [PMID: 26560713]
- Quigley, H.A.; McKinnon, S.J.; Zack, D.J.; Pease, M.E.; Kerrigan-Baumrind, L.A.; Kerrigan, D.F.; Mitchell, R.S. Retrograde axonal transport of BDNF in retinal ganglion cells is blocked by acute IOP elevation in rats. *Invest. Ophthalmol. Vis. Sci.*, **2000**, *41*(11), 3460-3466. [PMID: 11006239]
- Feng, L.; Chen, H.; Yi, J.; Troy, J.B.; Zhang, H.F.; Liu, X. Long-term protection of retinal ganglion cells and visual function by brain-derived neurotrophic factor in mice with ocular hypertension. *Invest. Ophthalmol. Vis. Sci.*, **2016**, *57*(8), 3793-3802. [http://dx.doi.org/10.1167/iovs.16-19825] [PMID: 27421068]
- Huber, L.A.; Teis, D. Lysosomal signaling in control of degradation pathways. *Curr. Opin. Cell Biol.*, **2016**, *39*, 8-14. [http://dx.doi.org/10.1016/j.ceb.2016.01.006] [PMID: 26827287]
- Vecino, E.; García-Crespo, D.; García, M.; Martínez-Millán, L.; Sharma, S.C.; Carrascal, E. Rat retinal ganglion cells co-express brain derived neurotrophic factor (BDNF) and its receptor TrkB. *Vision Res.*, **2002**, *42*(2), 151-157. [http://dx.doi.org/10.1016/S0042-6989(01)00251-6] [PMID: 11809469]
- García, M.; Forster, V.; Hicks, D.; Vecino, E. *In vivo* expression of neurotrophins and neurotrophin receptors is conserved in adult porcine retina *in vitro*. *Invest. Ophthalmol. Vis. Sci.*, **2003**,

- 44(10), 4532-4541. [http://dx.doi.org/10.1167/iovs.03-0419] [PMID: 14507902]
- [16] Pease, M.E.; Zack, D.J.; Berlinicke, C.; Bloom, K.; Cone, F.; Wang, Y.; Klein, R.L.; Hauswirth, W.W.; Quigley, H.A. Effect of CNTF on retinal ganglion cell survival in experimental glaucoma. *Invest. Ophthalmol. Vis. Sci.*, **2009**, *50*(5), 2194-2200. [http://dx.doi.org/10.1167/iovs.08-3013] [PMID: 19060281]
- [17] Hauck, S.M.; Kinkl, N.; Deeg, C.A.; Swiatek-de Lange, M.; Schöffmann, S.; Ueffing, M. GDNF family ligands trigger indirect neuroprotective signaling in retinal glial cells. *Mol. Cell. Biol.*, **2006**, *26*(7), 2746-2757. [http://dx.doi.org/10.1128/MCB.26.7.2746-2757.2006] [PMID: 16537917]
- [18] Cosker, K.E.; Courchesne, S.L.; Segal, R.A. Action in the axon: generation and transport of signaling endosomes. *Curr. Opin. Neurobiol.*, **2008**, *18*(3), 270-275. [http://dx.doi.org/10.1016/j.conb.2008.08.005] [PMID: 18778772]
- [19] Ascaño, M.; Richmond, A.; Borden, P.; Kuruvilla, R. Axonal targeting of Trk receptors via transcytosis regulates sensitivity to neurotrophin responses. *J. Neurosci.*, **2009**, *29*(37), 11674-11685. [http://dx.doi.org/10.1523/JNEUROSCI.1542-09.2009] [PMID: 19759314]
- [20] Pease, M.E.; McKinnon, S.J.; Quigley, H.A.; Kerrigan-Baumrind, L.A.; Zack, D.J. Obstructed axonal transport of BDNF and its receptor TrkB in experimental glaucoma. *Invest. Ophthalmol. Vis. Sci.*, **2000**, *41*(3), 764-774. [PMID: 10711692]
- [21] Tanaka, H.; Ito, Y.; Nakamura, S.; Shimazawa, M.; Hara, H. Involvement of brain-derived neurotrophic factor in time-dependent neurodegeneration in the murine superior colliculus after intravitreal injection of N-methyl-D-aspartate. *Mol. Vis.*, **2009**, *15*, 662-669. [PMID: 19347051]
- [22] Ma, Y.T.; Hsieh, T.; Forbes, M.E.; Johnson, J.E.; Frost, D.O. BDNF injected into the superior colliculus reduces developmental retinal ganglion cell death. *J. Neurosci.*, **1998**, *18*(6), 2097-2107. [http://dx.doi.org/10.1523/JNEUROSCI.18-06-02097.1998] [PMID: 9482796]
- [23] Wen, R.; Tao, W.; Li, Y.; Sieving, P.A. CNTF and retina. *Prog. Retin. Eye Res.*, **2012**, *31*(2), 136-151. [http://dx.doi.org/10.1016/j.preteyeres.2011.11.005] [PMID: 22182585]
- [24] Yan, Q.; Wang, J.; Matheson, C.R.; Ulrich, J.L. Glial cell line-derived neurotrophic factor (GDNF) promotes the survival of axotomized retinal ganglion cells in adult rats: comparison to and combination with brain-derived neurotrophic factor (BDNF). *J. Neurobiol.*, **1999**, *38*(3), 382-390. [http://dx.doi.org/10.1002/(SICI)1097-4695(19990215)38:3<382::AID-NEU7>3.0.CO;2-5] [PMID: 10022580]
- [25] Thanos, S.; Bähr, M.; Barde, Y.A.; Vanselow, J. Survival and axonal elongation of adult rat retinal ganglion cells. *Eur. J. Neurosci.*, **1989**, *1*(1), 19-26. [http://dx.doi.org/10.1111/j.1460-9568.1989.tb00770.x] [PMID: 12106170]
- [26] Frade, J.M.; Bovolenta, P.; Martínez-Morales, J.R.; Arribas, A.; Barbas, J.A.; Rodríguez-Tébar, A. Control of early cell death by BDNF in the chick retina. *Development*, **1997**, *124*(17), 3313-3320. [PMID: 9310326]
- [27] de Rezende Corrêa, G.; Soares, V.H.; de Araújo-Martins, L.; Dos Santos, A.A.; Giestal-de-Araújo, E. Ouabain and BDNF crosstalk on ganglion cell survival in mixed retinal cell cultures. *Cell. Mol. Neurobiol.*, **2015**, *35*(5), 651-660. [http://dx.doi.org/10.1007/s10571-015-0160-3] [PMID: 25651946]
- [28] Virdee, K.; Bannister, A.J.; Hunt, S.P.; Tolkovsky, A.M. Comparison between the timing of JNK activation, c-Jun phosphorylation, and onset of death commitment in sympathetic neurons. *J. Neurochem.*, **1997**, *69*(2), 550-561. [http://dx.doi.org/10.1046/j.1471-4159.1997.69020550.x] [PMID: 9231712]
- [29] Tsuruta, F.; Sunayama, J.; Mori, Y.; Hattori, S.; Shimizu, S.; Tsujimoto, Y.; Yoshioka, K.; Masuyama, N.; Gotoh, Y. JNK promotes Bax translocation to mitochondria through phosphorylation of 14-3-3 proteins. *EMBO J.*, **2004**, *23*(8), 1889-1899. [http://dx.doi.org/10.1038/sj.emboj.7600194] [PMID: 15071501]
- [30] Mansour-Robaey, S.; Clarke, D.B.; Wang, Y.C.; Bray, G.M.; Aguayo, A.J. Effects of ocular injury and administration of brain-derived neurotrophic factor on survival and regrowth of axotomized retinal ganglion cells. *Proc. Natl. Acad. Sci. USA*, **1994**, *91*(5), 1632-1636. [http://dx.doi.org/10.1073/pnas.91.5.1632] [PMID: 8127857]
- [31] Cohen-Cory, S.; Fraser, S.E. Effects of brain-derived neurotrophic factor on optic axon branching and remodelling *in vivo*. *Nature*, **1995**, *378*(6553), 192-196. [http://dx.doi.org/10.1038/378192a0] [PMID: 7477323]
- [32] Chen, H.; Weber, A.J. BDNF enhances retinal ganglion cell survival in cats with optic nerve damage. *Invest. Ophthalmol. Vis. Sci.*, **2001**, *42*(5), 966-974. [PMID: 11274073]
- [33] Gupta, V.; You, Y.; Li, J.; Gupta, V.; Golzan, M.; Klistorner, A.; van den Buuse, M.; Graham, S. BDNF impairment is associated with age-related changes in the inner retina and exacerbates experimental glaucoma. *Biochim. Biophys. Acta*, **2014**, *1842*(9), 1567-1578. [http://dx.doi.org/10.1016/j.bbadis.2014.05.026] [PMID: 24942931]
- [34] Cheng, L.; Sapieha, P.; Kitterlova, P.; Hauswirth, W.W.; Di Polo, A. TrkB gene transfer protects retinal ganglion cells from axotomy-induced death *in vivo*. *J. Neurosci.*, **2002**, *22*(10), 3977-3986. [http://dx.doi.org/10.1523/JNEUROSCI.22-10-03977.2002] [PMID: 12019317]
- [35] Rajala, A.; Gupta, V.K.; Anderson, R.E.; Rajala, R.V. Light activation of the insulin receptor regulates mitochondrial hexokinase. A possible mechanism of retinal neuroprotection. *Mitochondrion*, **2013**, *13*(6), 566-576. [http://dx.doi.org/10.1016/j.mito.2013.08.005] [PMID: 23993956]
- [36] Mai, L.; Jope, R.S.; Li, X. BDNF-mediated signal transduction is modulated by GSK3beta and mood stabilizing agents. *J. Neurochem.*, **2002**, *82*(1), 75-83. [http://dx.doi.org/10.1046/j.1471-4159.2002.00939.x] [PMID: 12091467]
- [37] Patapoutian, A.; Reichardt, L.F. Trk receptors: mediators of neurotrophin action. *Curr. Opin. Neurobiol.*, **2001**, *11*(3), 272-280. [http://dx.doi.org/10.1016/S0959-4388(00)00208-7] [PMID: 11399424]
- [38] Hu, Y.S.; Long, N.; Pigino, G.; Brady, S.T.; Lazarov, O. Molecular mechanisms of environmental enrichment: impairments in Akt/GSK3β, neurotrophin-3 and CREB signaling. *PLoS One*, **2013**, *8*(5), e64460. [http://dx.doi.org/10.1371/journal.pone.0064460] [PMID: 23700479]
- [39] Gupta, V.; Chitranshi, N.; You, Y.; Gupta, V.; Klistorner, A.; Graham, S. Brain derived neurotrophic factor is involved in the regulation of glycogen synthase kinase 3β (GSK3β) signalling. *Biochem. Biophys. Res. Commun.*, **2014**, *454*(3), 381-386. [http://dx.doi.org/10.1016/j.bbrc.2014.10.087] [PMID: 25451258]
- [40] Liu, X.; Grishanin, R.N.; Tolwani, R.J.; Renteria, R.C.; Xu, B.; Reichardt, L.F.; Copenhagen, D.R. Brain-derived neurotrophic factor and TrkB modulate visual experience-dependent refinement of neuronal pathways in retina. *J. Neurosci.*, **2007**, *27*(27), 7256-7267. [http://dx.doi.org/10.1523/JNEUROSCI.0779-07.2007] [PMID: 17611278]
- [41] Cui, Q.; Tang, L.S.; Hu, B.; So, K.F.; Yip, H.K. Expression of trkA, trkB, and trkC in injured and regenerating retinal ganglion cells of adult rats. *Invest. Ophthalmol. Vis. Sci.*, **2002**, *43*(6), 1954-1964. [PMID: 12037005]
- [42] Harada, C.; Guo, X.; Namekata, K.; Kimura, A.; Nakamura, K.; Tanaka, K.; Parada, L.F.; Harada, T. Glia- and neuron-specific functions of TrkB signalling during retinal degeneration and regeneration. *Nat. Commun.*, **2011**, *2*, 189. [http://dx.doi.org/10.1038/ncomms1190] [PMID: 21304518]
- [43] Harada, T.; Harada, C.; Kohsaka, S.; Wada, E.; Yoshida, K.; Ohno, S.; Mamada, H.; Tanaka, K.; Parada, L.F.; Wada, K. Microglia-Müller glia cell interactions control neurotrophic factor production during light-induced retinal degeneration. *J. Neurosci.*, **2002**, *22*(21), 9228-9236. [http://dx.doi.org/10.1523/JNEUROSCI.22-21-09228.2002] [PMID: 12417648]
- [44] Liu, Z.Z.; Zhu, L.Q.; Eide, F.F. Critical role of TrkB and brain-derived neurotrophic factor in the differentiation and survival of retinal pigment epithelium. *J. Neurosci.*, **1997**, *17*(22), 8749-8755. [http://dx.doi.org/10.1523/JNEUROSCI.17-22-08749.1997] [PMID: 9348344]
- [45] Huang, E.J.; Reichardt, L.F. Trk receptors: roles in neuronal signal transduction. *Annu. Rev. Biochem.*, **2003**, *72*, 609-642. [http://dx.doi.org/10.1146/annurev.biochem.72.121801.161629] [PMID: 12676795]
- [46] Klöcker, N.; Cellerino, A.; Bähr, M. Free radical scavenging and inhibition of nitric oxide synthase potentiates the neurotrophic effects of brain-derived neurotrophic factor on axotomized retinal ganglion cells *In vivo*. *J. Neurosci.*, **1998**, *18*(3), 1038-1046.

- [http://dx.doi.org/10.1523/JNEUROSCI.18-03-01038.1998] [PMID: 9437024]
- [47] Jang, S.W.; Liu, X.; Yepes, M.; Shepherd, K.R.; Miller, G.W.; Liu, Y.; Wilson, W.D.; Xiao, G.; Bianchi, B.; Sun, Y.E.; Ye, K. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*(6), 2687-2692. [http://dx.doi.org/10.1073/pnas.0913572107] [PMID: 20133810]
- [48] Hu, Y.; Cho, S.; Goldberg, J.L. Neurotrophic effect of a novel TrkB agonist on retinal ganglion cells. *Invest. Ophthalmol. Vis. Sci.*, **2010**, *51*(3), 1747-1754. [http://dx.doi.org/10.1167/iovs.09-4450] [PMID: 19875669]
- [49] Chitranshi, N.; Gupta, V.; Kumar, S.; Graham, S.L. Exploring the Molecular Interactions of 7,8-Dihydroxyflavone and Its Derivatives with TrkB and VEGFR2 Proteins. *Int. J. Mol. Sci.*, **2015**, *16*(9), 21087-21108. [http://dx.doi.org/10.3390/ijms160921087] [PMID: 26404256]
- [50] Gupta, V.K.; You, Y.; Li, J.C.; Klistorner, A.; Graham, S.L. Protective effects of 7,8-dihydroxyflavone on retinal ganglion and RGC-5 cells against excitotoxic and oxidative stress. *J. Mol. Neurosci.*, **2013**, *49*(1), 96-104. [http://dx.doi.org/10.1007/s12031-012-9899-x] [PMID: 23054592]
- [51] Dheer, Y.; Chitranshi, N.; Gupta, V.; Abbasi, M.; Mirzaei, M.; You, Y.; Chung, R.; Graham, S.L.; Gupta, V. Bexarotene modulates retinoid-X-receptor expression and is protective against neurotoxic endoplasmic reticulum stress response and apoptotic pathway activation. *Mol. Neurobiol.*, **2018**. [http://dx.doi.org/10.1007/s12035-018-1041-9] [PMID: 29637440]
- [52] Makkerh, J.P.; Ceni, C.; Auld, D.S.; Vaillancourt, F.; Dorval, G.; Barker, P.A. p75 neurotrophin receptor reduces ligand-induced Trk receptor ubiquitination and delays Trk receptor internalization and degradation. *EMBO Rep.*, **2005**, *6*(10), 936-941. [http://dx.doi.org/10.1038/sj.embor.7400503] [PMID: 16113645]
- [53] Arévalo, J.C.; Waite, J.; Rajagopal, R.; Beyna, M.; Chen, Z.Y.; Lee, F.S.; Chao, M.V. Cell survival through Trk neurotrophin receptors is differentially regulated by ubiquitination. *Neuron*, **2006**, *50*(4), 549-559. [http://dx.doi.org/10.1016/j.neuron.2006.03.044] [PMID: 16701206]
- [54] Gupta, V.K.; You, Y.; Gupta, V.B.; Klistorner, A.; Graham, S.L.; Trk, B. TrkB receptor signalling: implications in neurodegenerative, psychiatric and proliferative disorders. *Int. J. Mol. Sci.*, **2013**, *14*(5), 10122-10142. [http://dx.doi.org/10.3390/ijms140510122] [PMID: 23670594]
- [55] Liu, X.; Obianyo, O.; Chan, C.B.; Huang, J.; Xue, S.; Yang, J.J.; Zeng, F.; Goodman, M.; Ye, K. Biochemical and biophysical investigation of the brain-derived neurotrophic factor mimetic 7,8-dihydroxyflavone in the binding and activation of the TrkB receptor. *J. Biol. Chem.*, **2014**, *289*(40), 27571-27584. [http://dx.doi.org/10.1074/jbc.M114.562561] [PMID: 25143381]
- [56] Liu, C.; Chan, C.B.; Ye, K. 7,8-dihydroxyflavone, a small molecular TrkB agonist, is useful for treating various BDNF-implicated human disorders. *Transl. Neurodegener.*, **2016**, *5*, 2. [http://dx.doi.org/10.1186/s40035-015-0048-7] [PMID: 26740873]
- [57] Jang, S.W.; Liu, X.; Chan, C.B.; France, S.A.; Sayeed, I.; Tang, W.; Lin, X.; Xiao, G.; Andero, R.; Chang, Q.; Ressler, K.J.; Ye, K. Deoxygedunin, a natural product with potent neurotrophic activity in mice. *PLoS One*, **2010**, *5*(7), e11528. [http://dx.doi.org/10.1371/journal.pone.0011528] [PMID: 20644624]
- [58] Lorenz, U. SHP-1 and SHP-2 in T cells: two phosphatases functioning at many levels. *Immunol. Rev.*, **2009**, *228*(1), 342-359. [http://dx.doi.org/10.1111/j.1600-065X.2008.00760.x] [PMID: 19290938]
- [59] Tsang, Y.H.; Han, X.; Man, W.Y.; Lee, N.; Poon, R.Y. Novel functions of the phosphatase SHP2 in the DNA replication and damage checkpoints. *PLoS One*, **2012**, *7*(11), e49943. [http://dx.doi.org/10.1371/journal.pone.0049943] [PMID: 23189174]
- [60] Neel, B.G.; Gu, H.; Pao, L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem. Sci.*, **2003**, *28*(6), 284-293. [http://dx.doi.org/10.1016/S0968-0004(03)00091-4] [PMID: 12826400]
- [61] Kontaridis, M.I.; Yang, W.; Bence, K.K.; Cullen, D.; Wang, B.; Bodyak, N.; Ke, Q.; Hinek, A.; Kang, P.M.; Liao, R.; Neel, B.G. Deletion of Ptpn11 (Shp2) in cardiomyocytes causes dilated cardiomyopathy via effects on the extracellular signal-regulated kinase/mitogen-activated protein kinase and RhoA signaling pathways. *Circulation*, **2008**, *117*(11), 1423-1435. [http://dx.doi.org/10.1161/CIRCULATIONAHA.107.728865] [PMID: 18316486]
- [62] Abbasi, M.; Gupta, V.; Chitranshi, N.; You, Y.; Dheer, Y.; Mirzaei, M.; Graham, S.L. Regulation of brain-derived neurotrophic factor and growth factor signaling pathways by tyrosine phosphatase Shp2 in the retina: A brief review. *Front. Cell. Neurosci.*, **2018**, *12*, 85. [http://dx.doi.org/10.3389/fncel.2018.00085] [PMID: 29636665]
- [63] Agazie, Y.M.; Hayman, M.J. Molecular mechanism for a role of SHP2 in epidermal growth factor receptor signaling. *Mol. Cell. Biol.*, **2003**, *23*(21), 7875-7886. [http://dx.doi.org/10.1128/MCB.23.21.7875-7886.2003] [PMID: 14560030]
- [64] Schaper, F.; Gendo, C.; Eck, M.; Schmitz, J.; Grimm, C.; Anhuf, D.; Kerr, I.M.; Heinrich, P.C. Activation of the protein tyrosine phosphatase SHP2 via the interleukin-6 signal transducing receptor protein gp130 requires tyrosine kinase Jak1 and limits acute-phase protein expression. *Biochem. J.*, **1998**, *335*(Pt 3), 557-565. [http://dx.doi.org/10.1042/bj3350557] [PMID: 9794795]
- [65] Hanafusa, H.; Torii, S.; Yasunaga, T.; Matsumoto, K.; Nishida, E. Shp2, an SH2-containing protein-tyrosine phosphatase, positively regulates receptor tyrosine kinase signaling by dephosphorylating and inactivating the inhibitor Sprouty. *J. Biol. Chem.*, **2004**, *279*(22), 22992-22995. [http://dx.doi.org/10.1074/jbc.M312498200] [PMID: 15031289]
- [66] Rusanescu, G.; Yang, W.; Bai, A.; Neel, B.G.; Feig, L.A. Tyrosine phosphatase SHP-2 is a mediator of activity-dependent neuronal excitotoxicity. *EMBO J.*, **2005**, *24*(2), 305-314. [http://dx.doi.org/10.1038/sj.emboj.7600522] [PMID: 15650750]
- [67] Easton, J.B.; Moody, N.M.; Zhu, X.; Middlemas, D.S. Brain-derived neurotrophic factor induces phosphorylation of fibroblast growth factor receptor substrate 2. *J. Biol. Chem.*, **1999**, *274*(16), 11321-11327. [http://dx.doi.org/10.1074/jbc.274.16.11321] [PMID: 11096222]
- [68] Zhou, L.; Talebian, A.; Meakin, S.O. The signaling adapter, FRS2, facilitates neuronal branching in primary cortical neurons via both Grb2- and Shp2-dependent mechanisms. *J. Mol. Neurosci.*, **2015**, *55*(3), 663-677. [http://dx.doi.org/10.1007/s12031-014-0406-4] [PMID: 25159185]
- [69] Araki, T.; Yamada, M.; Ohnishi, H.; Sano, S.; Uetsuki, T.; Hatanaka, H. Shp-2 specifically regulates several tyrosine-phosphorylated proteins in brain-derived neurotrophic factor signaling in cultured cerebral cortical neurons. *J. Neurochem.*, **2000**, *74*(2), 659-668. [http://dx.doi.org/10.1046/j.1471-4159.2000.740659.x] [PMID: 10646517]
- [70] Kim, H.J.; Han, A.M.; Shim, J.H.; Yoon, H.H.; Kwon, H.; Kwon, Y.K. Shp2 is involved in neuronal differentiation of hippocampal precursor cells. *Arch. Pharm. Res.*, **2007**, *30*(6), 750-754. [http://dx.doi.org/10.1007/BF02977638] [PMID: 17679554]
- [71] Cai, Z.; Simons, D.L.; Fu, X.Y.; Feng, G.S.; Wu, S.M.; Zhang, X. Loss of Shp2-mediated mitogen-activated protein kinase signaling in Muller glial cells results in retinal degeneration. *Mol. Cell. Biol.*, **2011**, *31*(14), 2973-2983. [http://dx.doi.org/10.1128/MCB.05054-11] [PMID: 21576358]
- [72] Kruger, R.P.; Abrandt, J.; Guan, K.L. Semaphorins command cells to move. *Nat. Rev. Mol. Cell Biol.*, **2005**, *6*(10), 789-800. [http://dx.doi.org/10.1038/nrm1740] [PMID: 16314868]
- [73] Fuchikawa, T.; Nakamura, F.; Fukuda, N.; Takei, K.; Goshima, Y. Protein tyrosine phosphatase SHP2 is involved in Semaphorin 4D-induced axon repulsion. *Biochem. Biophys. Res. Commun.*, **2009**, *385*(1), 6-10. [http://dx.doi.org/10.1016/j.bbrc.2009.05.024] [PMID: 19433062]
- [74] Pinzon-Guzman, C.; Xing, T.; Zhang, S.S.; Barnstable, C.J. Regulation of rod photoreceptor differentiation by STAT3 is controlled by a tyrosine phosphatase. *J. Mol. Neurosci.*, **2015**, *55*(1), 152-159. [http://dx.doi.org/10.1007/s12031-014-0397-1] [PMID: 25108518]
- [75] Gupta, V.K.; You, Y.; Klistorner, A.; Graham, S.L. Shp-2 regulates the TrkB receptor activity in the retinal ganglion cells under glaucomatous stress. *Biochim. Biophys. Acta*, **2012**, *1822*(11), 1643-1649. [http://dx.doi.org/10.1016/j.bbdis.2012.07.016] [PMID: 22878065]
- [76] Okamoto, T.; Schlegel, A.; Scherer, P.E.; Lisanti, M.P. Caveolins, a family of scaffolding proteins for organizing "preassembled signaling complexes" at the plasma membrane. *J. Biol. Chem.*, **1998**, *273*(10), 5419-5422. [http://dx.doi.org/10.1074/jbc.273.10.5419] [PMID: 9488658]

- [77] Galbiati, F.; Volonte, D.; Gil, O.; Zanazzi, G.; Salzer, J.L.; Sargiacomo, M.; Scherer, P.E.; Engelman, J.A.; Schlegel, A.; Parenti, M.; Okamoto, T.; Lisanti, M.P. Expression of caveolin-1 and -2 in differentiating PC12 cells and dorsal root ganglion neurons: caveolin-2 is up-regulated in response to cell injury. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*(17), 10257-10262. [http://dx.doi.org/10.1073/pnas.95.17.10257] [PMID: 9707634]
- [78] Nishiyama, K.; Trapp, B.D.; Ikezu, T.; Ransohoff, R.M.; Tomita, T.; Iwatsubo, T.; Kanazawa, I.; Hsiao, K.K.; Lisanti, M.P.; Okamoto, T. Caveolin-3 upregulation activates beta-secretase-mediated cleavage of the amyloid precursor protein in Alzheimer's disease. *J. Neurosci.*, **1999**, *19*(15), 6538-6548. [http://dx.doi.org/10.1523/JNEUROSCI.19-15-06538.1999] [PMID: 10414982]
- [79] Kiss, A.L.; Turi, A.; Müller, N.; Kántor, O.; Botos, E. Caveolae and caveolin isoforms in rat peritoneal macrophages. *Micron*, **2002**, *33*(1), 75-93. [http://dx.doi.org/10.1016/S0968-4328(00)00100-1] [PMID: 11473817]
- [80] Klaassen, I.; Van Noorden, C.J.; Schlingemann, R.O. Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. *Prog. Retin. Eye Res.*, **2013**, *34*, 19-48. [http://dx.doi.org/10.1016/j.preteyeres.2013.02.001] [PMID: 23416119]
- [81] Thorleifsson, G.; Walters, G.B.; Hewitt, A.W.; Masson, G.; Helgason, A.; DeWan, A.; Sigurdsson, A.; Jonasdottir, A.; Gudjonsson, S.A.; Magnusson, K.P.; Stefansson, H.; Lam, D.S.; Tam, P.O.; Gudmundsdottir, G.J.; Southgate, L.; Burdon, K.P.; Gottfredsdottir, M.S.; Aldred, M.A.; Mitchell, P.; St Clair, D.; Collier, D.A.; Tang, N.; Sveinsson, O.; Macgregor, S.; Martin, N.G.; Cree, A.J.; Gibson, J.; Macleod, A.; Jacob, A.; Ennis, S.; Young, T.L.; Chan, J.C.; Karwatowski, W.S.; Hammond, C.J.; Thordarson, K.; Zhang, M.; Wadelius, C.; Lotery, A.J.; Trembath, R.C.; Pang, C.P.; Hoh, J.; Craig, J.E.; Kong, A.; Mackey, D.A.; Jonasson, F.; Thorsteinsdottir, U.; Stefansson, K. Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. *Nat. Genet.*, **2010**, *42*(10), 906-909. [http://dx.doi.org/10.1038/ng.661] [PMID: 20835238]
- [82] Reagan, A.; Gu, X.; Hauck, S.M.; Ash, J.D.; Cao, G.; Thompson, T.C.; Elliott, M.H. Retinal caveolin-1 modulates neuroprotective signaling. *Adv. Exp. Med. Biol.*, **2016**, *854*, 411-418. [http://dx.doi.org/10.1007/978-3-319-17121-0_54] [PMID: 26427439]
- [83] Chucair-Elliott, A.J.; Elliott, M.H.; Wang, J.; Moiseyev, G.P.; Ma, J.X.; Politi, L.E.; Rotstein, N.P.; Akira, S.; Uematsu, S.; Ash, J.D. Leukemia inhibitory factor coordinates the down-regulation of the visual cycle in the retina and retinal-pigmented epithelium. *J. Biol. Chem.*, **2012**, *287*(29), 24092-24102. [http://dx.doi.org/10.1074/jbc.M112.378240] [PMID: 22645143]
- [84] Jiao, H.; Zhang, Y.; Yan, Z.; Wang, Z.G.; Liu, G.; Minshall, R.D.; Malik, A.B.; Hu, G. Caveolin-1 Tyr14 phosphorylation induces interaction with TLR4 in endothelial cells and mediates MyD88-dependent signaling and sepsis-induced lung inflammation. *J. Immunol.*, **2013**, *191*(12), 6191-6199. [http://dx.doi.org/10.4049/jimmunol.1300873] [PMID: 24244013]
- [85] Pawson, T.; Gish, G.D.; Nash, P. SH2 domains, interaction modules and cellular wiring. *Trends Cell Biol.*, **2001**, *11*(12), 504-511. [http://dx.doi.org/10.1016/S0962-8924(01)02154-7] [PMID: 11719057]
- [86] Takayasu, Y.; Takeuchi, K.; Kumari, R.; Bennett, M.V.; Zukin, R.S.; Francesconi, A. Caveolin-1 knockout mice exhibit impaired induction of mGluR-dependent long-term depression at CA3-CA1 synapses. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*(50), 21778-21783. [http://dx.doi.org/10.1073/pnas.1015553107] [PMID: 21098662]
- [87] Volonté, D.; Galbiati, F.; Pestell, R.G.; Lisanti, M.P. Cellular stress induces the tyrosine phosphorylation of caveolin-1 (Tyr(14)) via activation of p38 mitogen-activated protein kinase and c-Src kinase. Evidence for caveolae, the actin cytoskeleton, and focal adhesions as mechanical sensors of osmotic stress. *J. Biol. Chem.*, **2001**, *276*(11), 8094-8103. [http://dx.doi.org/10.1074/jbc.M009245200] [PMID: 11094059]
- [88] Sanguinetti, A.R.; Cao, H.; Corley Mastick, C. Fyn is required for oxidative- and hyperosmotic-stress-induced tyrosine phosphorylation of caveolin-1. *Biochem. J.*, **2003**, *376*(Pt 1), 159-168. [http://dx.doi.org/10.1042/bj20030336] [PMID: 12921535]
- [89] Surgucheva, I.; Surguchov, A. Expression of caveolin in trabecular meshwork cells and its possible implication in pathogenesis of primary open angle glaucoma. *Mol. Vis.*, **2011**, *17*, 2878-2888. [PMID: 22128235]
- [90] Jo, A.; Park, H.; Lee, S.H.; Ahn, S.H.; Kim, H.J.; Park, E.M.; Choi, Y.H. SHP-2 binds to caveolin-1 and regulates Src activity via competitive inhibition of CSK in response to H2O2 in astrocytes. *PLoS One*, **2014**, *9*(3), e91582. [http://dx.doi.org/10.1371/journal.pone.0091582] [PMID: 24632723]
- [91] Li, X.; McClellan, M.E.; Tanito, M.; Garteiser, P.; Towner, R.; Bissig, D.; Berkowitz, B.A.; Fliesler, S.J.; Woodruff, M.L.; Fain, G.L.; Birch, D.G.; Khan, M.S.; Ash, J.D.; Elliott, M.H. Loss of caveolin-1 impairs retinal function due to disturbance of subretinal microenvironment. *J. Biol. Chem.*, **2012**, *287*(20), 16424-16434. [http://dx.doi.org/10.1074/jbc.M112.353763] [PMID: 22451674]
- [92] Tian, X.F.; Xia, X.B.; Xu, H.Z.; Xiong, S.Q.; Jiang, J. Caveolin-1 expression regulates blood-retinal barrier permeability and retinal neovascularization in oxygen-induced retinopathy. *Clin. Experiment. Ophthalmol.*, **2012**, *40*(1), e58-e66. [http://dx.doi.org/10.1111/j.1442-9071.2011.02656.x] [PMID: 21794046]
- [93] Vrabcic, J.P.; Levin, L.A. The neurobiology of cell death in glaucoma. *Eye (Lond.)*, **2007**, *21*(Suppl. 1), S11-S14. [http://dx.doi.org/10.1038/sj.eye.6702880] [PMID: 18157171]
- [94] Osborne, N.N.; Casson, R.J.; Wood, J.P.; Chidlow, G.; Graham, M.; Melena, J. Retinal ischemia: mechanisms of damage and potential therapeutic strategies. *Prog. Retin. Eye Res.*, **2004**, *23*(1), 91-147. [http://dx.doi.org/10.1016/j.preteyeres.2003.12.001] [PMID: 14766318]
- [95] Barot, M.; Gokulgandhi, M.R.; Mitra, A.K. Mitochondrial dysfunction in retinal diseases. *Curr. Eye Res.*, **2011**, *36*(12), 1069-1077. [http://dx.doi.org/10.3109/02713683.2011.607536] [PMID: 21978133]
- [96] Wang, Y.; Shen, D.; Wang, V.M.; Yu, C.R.; Wang, R.X.; Tuo, J.; Chan, C.C. Enhanced apoptosis in retinal pigment epithelium under inflammatory stimuli and oxidative stress. *Apoptosis*, **2012**, *17*(11), 1144-1155. [http://dx.doi.org/10.1007/s10495-012-0750-1] [PMID: 22911474]
- [97] Ientile, R.; Macaione, V.; Teletta, M.; Pedale, S.; Torre, V.; Macaione, S. Apoptosis and necrosis occurring in excitotoxic cell death in isolated chick embryo retina. *J. Neurochem.*, **2001**, *79*(1), 71-78. [http://dx.doi.org/10.1046/j.1471-4159.2001.00532.x] [PMID: 11595759]
- [98] Feenstra, D.J.; Yego, E.C.; Mohr, S. Modes of retinal cell death in diabetic retinopathy. *J. Clin. Exp. Ophthalmol.*, **2013**, *4*(5), 298. [PMID: 24672740]
- [99] Jing, G.; Wang, J.J.; Zhang, S.X. ER stress and apoptosis: a new mechanism for retinal cell death. *Exp. Diabetes Res.*, **2012**, *2012*, 589589. [http://dx.doi.org/10.1155/2012/589589] [PMID: 22216020]
- [100] Wang, X.; Olberding, K.E.; White, C.; Li, C. Bcl-2 proteins regulate ER membrane permeability to luminal proteins during ER stress-induced apoptosis. *Cell Death Differ.*, **2011**, *18*(1), 38-47. [http://dx.doi.org/10.1038/cdd.2010.68] [PMID: 20539308]
- [101] Schwarz, D.S.; Blower, M.D. The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell. Mol. Life Sci.*, **2016**, *73*(1), 79-94. [http://dx.doi.org/10.1007/s00018-015-2052-6] [PMID: 26433683]
- [102] Cornejo, V.H.; Hetz, C. The unfolded protein response in Alzheimer's disease. *Semin. Immunopathol.*, **2013**, *35*(3), 277-292. [http://dx.doi.org/10.1007/s00281-013-0373-9] [PMID: 23609500]
- [103] Varma, D.; Sen, D. Role of the unfolded protein response in the pathogenesis of Parkinson's disease. *Acta Neurobiol. Exp. (Warsz.)*, **2015**, *75*(1), 1-26. [PMID: 25856519]
- [104] Anholt, R.R.; Carbone, M.A. A molecular mechanism for glaucoma: endoplasmic reticulum stress and the unfolded protein response. *Trends Mol. Med.*, **2013**, *19*(10), 586-593. [http://dx.doi.org/10.1016/j.molmed.2013.06.005] [PMID: 23876925]
- [105] Mirzaei, M.; Gupta, V.B.; Chick, J.M.; Greco, T.M.; Wu, Y.; Chitranshi, N.; Wall, R.V.; Hone, E.; Deng, L.; Dheer, Y.; Abbasi, M.; Rezaeian, M.; Braidy, N.; You, Y.; Salekdeh, G.H.; Haynes, P.A.; Molloy, M.P.; Martins, R.; Cristea, I.M.; Gygi, S.P.; Graham, S.L.; Gupta, V.K. Age-related neurodegenerative disease associated pathways identified in retinal and vitreous proteome from human glaucoma eyes. *Sci. Rep.*, **2017**, *7*(1), 12685. [http://dx.doi.org/10.1038/s41598-017-12858-7] [PMID: 28978942]
- [106] Bravo, R.; Parra, V.; Gatica, D.; Rodriguez, A.E.; Torrealba, N.; Paredes, F.; Wang, Z.V.; Zorzano, A.; Hill, J.A.; Jaimovich, E.; Quest, A.F.; Lavandero, S. Endoplasmic reticulum and the unfolded protein response: dynamics and metabolic integration. *Int. Rev.*

- Cell Mol. Biol.*, **2013**, *301*, 215-290. [http://dx.doi.org/10.1016/B978-0-12-407704-1.00005-1] [PMID: 23317820]
- [107] Peters, J.C.; Bhattacharya, S.; Clark, A.F.; Zode, G.S. Increased endoplasmic reticulum stress in human glaucomatous trabecular meshwork cells and tissues. *Invest. Ophthalmol. Vis. Sci.*, **2015**, *56*(6), 3860-3868. [http://dx.doi.org/10.1167/iovs.14-16220] [PMID: 26066753]
- [108] Doh, S.H.; Kim, J.H.; Lee, K.M.; Park, H.Y.; Park, C.K. Retinal ganglion cell death induced by endoplasmic reticulum stress in a chronic glaucoma model. *Brain Res.*, **2010**, *1308*, 158-166. [http://dx.doi.org/10.1016/j.brainres.2009.10.025] [PMID: 19853589]
- [109] Hu, Y. Axon injury induced endoplasmic reticulum stress and neurodegeneration. *Neural Regen. Res.*, **2016**, *11*(10), 1557-1559. [http://dx.doi.org/10.4103/1673-5374.193225] [PMID: 27904477]
- [110] Kang, M.J.; Ryoo, H.D. Suppression of retinal degeneration in *Drosophila* by stimulation of ER-associated degradation. *Proc. Natl. Acad. Sci. USA*, **2009**, *106*(40), 17043-17048. [http://dx.doi.org/10.1073/pnas.0905566106] [PMID: 19805114]
- [111] Zhang, Z.; Tong, N.; Gong, Y.; Qiu, Q.; Yin, L.; Lv, X.; Wu, X. Valproate protects the retina from endoplasmic reticulum stress-induced apoptosis after ischemia-reperfusion injury. *Neurosci. Lett.*, **2011**, *504*(2), 88-92. [http://dx.doi.org/10.1016/j.neulet.2011.09.003] [PMID: 21939735]
- [112] Gardner, B.M.; Walter, P. Unfolded proteins are Ire1-activating ligands that directly induce the unfolded protein response. *Science*, **2011**, *333*(6051), 1891-1894. [http://dx.doi.org/10.1126/science.1209126] [PMID: 21852455]
- [113] Marciniak, S.J.; Garcia-Bonilla, L.; Hu, J.; Harding, H.P.; Ron, D. Activation-dependent substrate recruitment by the eukaryotic translation initiation factor 2 kinase PERK. *J. Cell Biol.*, **2006**, *172*(2), 201-209. [http://dx.doi.org/10.1083/jcb.200508099] [PMID: 16418533]
- [114] Cullinan, S.B.; Zhang, D.; Hannink, M.; Arvisais, E.; Kaufman, R.J.; Diehl, J.A. Nrf2 is a direct PERK substrate and effector of PERK-dependent cell survival. *Mol. Cell Biol.*, **2003**, *23*(20), 7198-7209. [http://dx.doi.org/10.1128/MCB.23.20.7198-7209.2003] [PMID: 14517290]
- [115] Chitranshi, N.; Dheer, Y.; Gupta, V.; Abbasi, M.; Mirzaei, M.; You, Y.; Chung, R.; Graham, S.L.; Gupta, V. PTPN11 induces endoplasmic stress and apoptosis in SH-SY5Y cells. *Neuroscience*, **2017**, *364*, 175-189. [http://dx.doi.org/10.1016/j.neuroscience.2017.09.028] [PMID: 28947394]
- [116] Sano, R.; Reed, J.C. ER stress-induced cell death mechanisms. *Biochim. Biophys. Acta*, **2013**, *1833*(12), 3460-3470. [http://dx.doi.org/10.1016/j.bbamcr.2013.06.028] [PMID: 23850759]
- [117] Wang, Y.; Yamada, E.; Zong, H.; Pessin, J.E. Fyn activation of mTORC1 stimulates the IRE1 α -JNK pathway, leading to cell death. *J. Biol. Chem.*, **2015**, *290*(41), 24772-24783. [http://dx.doi.org/10.1074/jbc.M115.687020] [PMID: 26306048]
- [118] Mabuchi, F.; Sakurada, Y.; Kashiwagi, K.; Yamagata, Z.; Iijima, H.; Tsukahara, S. Involvement of genetic variants associated with primary open-angle glaucoma in pathogenic mechanisms and family history of glaucoma. *Am. J. Ophthalmol.*, **2015**, *159*(3), 437-44. [http://dx.doi.org/10.1016/j.ajo.2014.11.023]
- [119] Kim, B.S.; Savinova, O.V.; Reedy, M.V.; Martin, J.; Lun, Y.; Gan, L.; Smith, R.S.; Tomarev, S.I.; John, S.W.; Johnson, R.L. Targeted disruption of the myocilin gene (*Myoc*) suggests that human glaucoma-causing mutations are gain of function. *Mol. Cell Biol.*, **2001**, *21*(22), 7707-7713. [http://dx.doi.org/10.1128/MCB.21.22.7707-7713.2001] [PMID: 11604506]
- [120] Sarfarazi, M.; Rezaie, T. Optineurin in primary open angle glaucoma. *Ophthalmol. Clin. North Am.*, **2003**, *16*(4), 529-541. [http://dx.doi.org/10.1016/S0896-1549(03)00061-0] [PMID: 14740994]
- [121] Skarie, J.M.; Link, B.A. The primary open-angle glaucoma gene *WDR36* functions in ribosomal RNA processing and interacts with the p53 stress-response pathway. *Hum. Mol. Genet.*, **2008**, *17*(16), 2474-2485. [http://dx.doi.org/10.1093/hmg/ddn147] [PMID: 18469340]
- [122] Chen, L.J.; Ng, T.K.; Fan, A.H.; Leung, D.Y.; Zhang, M.; Wang, N.; Zheng, Y.; Liang, X.Y.; Chiang, S.W.; Tam, P.O.; Pang, C.P. Evaluation of *NTF4* as a causative gene for primary open-angle glaucoma. *Mol. Vis.*, **2012**, *18*, 1763-1772. [PMID: 22815630]
- [123] Wiggs, J.L.; Kang, J.H.; Yaspan, B.L.; Mirel, D.B.; Laurie, C.; Crenshaw, A.; Brodeur, W.; Gogarten, S.; Olson, L.M.; Abdrabou, W.; DelBono, E.; Loomis, S.; Haines, J.L.; Pasquale, L.R.; Consortium, G. Common variants near *CAV1* and *CAV2* are associated with primary open-angle glaucoma in Caucasians from the USA. *Hum. Mol. Genet.*, **2011**, *20*(23), 4707-4713. [http://dx.doi.org/10.1093/hmg/ddr382] [PMID: 21873608]
- [124] Kondkar, A.A.; Mousa, A.; Azad, T.A.; Sultan, T.; Alawad, A.; Altuwajri, S.; Al-Obeidan, S.A.; Abu-Amro, K.K. Polymorphism rs7555523 in transmembrane and coiled-coil domain 1 (*TMCO1*) is not a risk factor for primary open angle glaucoma in a Saudi cohort. *J. Negat. Results Biomed.*, **2016**, *15*(1), 17. [http://dx.doi.org/10.1186/s12952-016-0060-1] [PMID: 27687253]
- [125] Bailey, J.N.; Loomis, S.J.; Kang, J.H.; Allingham, R.R.; Gharahkhani, P.; Khor, C.C.; Burdon, K.P.; Aschard, H.; Chasman, D.I.; Igo, R.P., Jr; Hysi, P.G.; Glastonbury, C.A.; Ashley-Koch, A.; Brilliant, M.; Brown, A.A.; Budenz, D.L.; Buil, A.; Cheng, C.Y.; Choi, H.; Christen, W.G.; Curhan, G.; Qi, Q.; De Vivo, I.; Fingert, J.H.; Foster, P.J.; Fuchs, C.; Gaasterland, D.; Gaasterland, T.; Hewitt, A.W.; Hu, F.; Hunter, D.J.; Khawaja, A.P.; Lee, R.K.; Li, Z.; Lichter, P.R.; Mackey, D.A.; McGuffin, P.; Mitchell, P.; Moroi, S.E.; Perera, S.A.; Pepper, K.W.; Qi, Q.; Realini, T.; Richards, J.E.; Ridker, P.M.; Rimm, E.; Ritch, R.; Ritchie, M.; Schuman, J.S.; Scott, W.K.; Singh, K.; Sit, A.J.; Song, Y.E.; Tamimi, R.M.; Topouzis, F.; Viswanathan, A.C.; Verma, S.S.; Vollrath, D.; Wang, J.J.; Weisschuh, N.; Wissinger, B.; Wollstein, G.; Wong, T.Y.; Yaspan, B.L.; Zack, D.J.; Zhang, K.; Study, E.N.; Weinreb, R.N.; Pericak-Vance, M.A.; Small, K.; Hammond, C.J.; Aung, T.; Liu, Y.; Vithana, E.N.; MacGregor, S.; Craig, J.E.; Kraft, P.; Howell, G.; Hauser, M.A.; Pasquale, L.R.; Haines, J.L.; Wiggs, J.L.; Wiggs, J.L. Genome-wide association analysis identifies *TXNRD2*, *ATXN2* and *FOXC1* as susceptibility loci for primary open-angle glaucoma. *Nat. Genet.*, **2016**, *48*(2), 189-194. [http://dx.doi.org/10.1038/ng.3482] [PMID: 26752265]
- [126] Pasutto, F.; Matsumoto, T.; Mardin, C.Y.; Sticht, H.; Brandstätter, J.H.; Michels-Rautenstrauss, K.; Weisschuh, N.; Gramer, E.; Ramdas, W.D.; van Koolwijk, L.M.; Klaver, C.C.; Vingerling, J.R.; Weber, B.H.; Kruse, F.E.; Rautenstrauss, B.; Barde, Y.A.; Reis, A. Heterozygous *NTF4* mutations impairing neurotrophin-4 signaling in patients with primary open-angle glaucoma. *Am. J. Hum. Genet.*, **2009**, *85*(4), 447-456. [http://dx.doi.org/10.1016/j.ajhg.2009.08.016] [PMID: 19765683]
- [127] Liu, Y.; Liu, W.; Crooks, K.; Schmidt, S.; Allingham, R.R.; Hauser, M.A. No evidence of association of heterozygous *NTF4* mutations in patients with primary open-angle glaucoma. *Am. J. Hum. Genet.*, **2010**, *86*(3), 498-499. [http://dx.doi.org/10.1016/j.ajhg.2009.11.018] [PMID: 20215012]
- [128] Rao, K.N.; Kaur, I.; Parikh, R.S.; Mandal, A.K.; Chandrasekhar, G.; Thomas, R.; Chakrabarti, S. Variations in *NTF4*, *VAV2*, and *VAV3* genes are not involved with primary open-angle and primary angle-closure glaucomas in an Indian population. *Invest. Ophthalmol. Vis. Sci.*, **2010**, *51*(10), 4937-4941. [http://dx.doi.org/10.1167/iovs.10-5553] [PMID: 20463313]
- [129] Vithana, E.N.; Nongpiur, M.E.; Venkataraman, D.; Chan, S.H.; Mavinahalli, J.; Aung, T. Identification of a novel mutation in the *NTF4* gene that causes primary open-angle glaucoma in a Chinese population. *Mol. Vis.*, **2010**, *16*, 1640-1645. [PMID: 20806036]
- [130] Nowak, A.; Szaflik, J.P.; Gacek, M.; Przybyłowska-Sygut, K.; Kamińska, A.; Szaflik, J.; Majsterek, I. BDNF and HSP gene polymorphisms and their influence on the progression of primary open-angle glaucoma in a Polish population. *Arch. Med. Sci.*, **2014**, *10*(6), 1206-1213. [http://dx.doi.org/10.5114/aoms.2014.45089] [PMID: 25624860]
- [131] Thorleifsson, G.; Walters, G.B.; Hewitt, A.W.; Masson, G.; Helgason, A.; DeWan, A.; Sigurdsson, A.; Jonasdottir, A.; Gudjonsson, S.A.; Magnusson, K.P.; Stefansson, H.; Lam, D.S.C.; Tam, P.O.S.; Gudmundsdottir, G.J.; Southgate, L.; Burdon, K.P.; Gottfredsdottir, M.S.; Aldred, M.A.; Mitchell, P.; St Clair, D.; Collier, D.A.; Tang, N.; Sveinsson, O.; Macgregor, S.; Martin, N.G.; Cree, A.J.; Gibson, J.; Macleod, A.; Jacob, A.; Ennis, S.; Young, T.L.; Chan, J.C.N.; Karwatowski, W.S.S.; Hammond, C.J.; Thordarson, K.; Zhang, M.; Wadelius, C.; Lotery, A.J.; Trembath, R.C.; Pang, C.P.; Hoh, J.; Craig, J.E.; Kong, A.; Mackey, D.A.; Jonasson, F.; Thorsteinsdottir, U.; Stefansson, K. Common variants near *CAV1* and *CAV2* are associated with primary open-angle glaucoma. *Nat. Genet.*, **2010**, *42*(10), 906-909. [http://dx.doi.org/10.1038/ng.661] [PMID: 20835238]
- [132] Kuehn, M.H.; Wang, K.; Roos, B.; Stone, E.M.; Kwon, Y.H.; Alward, W.L.; Mullins, R.F.; Fingert, J.H. Chromosome 7q31 POAG

- locus: ocular expression of caveolins and lack of association with POAG in a US cohort. *Mol. Vis.*, **2011**, *17*, 430-435. [PMID: 21321670]
- [133] Elliott, M.H.; Ashpole, N.E.; Gu, X.; Herrnberger, L.; McClellan, M.E.; Griffith, G.L.; Reagan, A.M.; Boyce, T.M.; Tanito, M.; Tamm, E.R.; Stamer, W.D. Caveolin-1 modulates intraocular pressure: implications for caveolae mechanoprotection in glaucoma. *Sci. Rep.*, **2016**, *6*, 37127. [http://dx.doi.org/10.1038/srep37127] [PMID: 27841369]
- [134] Green, C.M.; Kearns, L.S.; Wu, J.; Barbour, J.M.; Wilkinson, R.M.; Ring, M.A.; Craig, J.E.; Wong, T.L.; Hewitt, A.W.; Mackey, D.A. How significant is a family history of glaucoma? Experience from the glaucoma inheritance study in tasmania. *Clin. Experiment. Ophthalmol.*, **2007**, *35*(9), 793-799. [http://dx.doi.org/10.1111/j.1442-9071.2007.01612.x] [PMID: 18173405]
- [135] Polansky, J.R.; Fauss, D.J.; Chen, P.; Chen, H.; Lütjen-Drecoll, E.; Johnson, D.; Kurtz, R.M.; Ma, Z.D.; Bloom, E.; Nguyen, T.D. Cellular pharmacology and molecular biology of the trabecular meshwork inducible glucocorticoid response gene product. *Ophthalmologica*, **1997**, *211*(3), 126-139. [http://dx.doi.org/10.1159/000310780] [PMID: 9176893]
- [136] Kasetti, R.B.; Phan, T.N.; Millar, J.C.; Zode, G.S. Expression of mutant myocilin induces abnormal intracellular accumulation of selected extracellular matrix proteins in the trabecular meshwork. *Invest. Ophthalmol. Vis. Sci.*, **2016**, *57*(14), 6058-6069. [http://dx.doi.org/10.1167/iovs.16-19610] [PMID: 27820874]
- [137] Liao, R.F.; Zhong, Z.L.; Ye, M.J.; Han, L.Y.; Ye, D.Q.; Chen, J.J. Identification of mutations in myocilin and beta-1,4-galactosyltransferase 3 genes in a chinese family with primary open-angle glaucoma. *Chin. Med. J. (Engl.)*, **2016**, *129*(23), 2810-2815. [http://dx.doi.org/10.4103/0366-6999.194641] [PMID: 27900994]
- [138] Itakura, T.; Peters, D.M.; Fini, M.E. Glaucomatous MYOC mutations activate the IL-1/NF- κ B inflammatory stress response and the glaucoma marker SELE in trabecular meshwork cells. *Mol. Vis.*, **2015**, *21*, 1071-1084. [PMID: 26396484]
- [139] Guo, H.; Li, M.; Wang, Z.; Liu, Q.; Wu, X. Association of MYOC and APOE promoter polymorphisms and primary open-angle glaucoma: a meta-analysis. *Int. J. Clin. Exp. Med.*, **2015**, *8*(2), 2052-2064. [PMID: 25932136]
- [140] Kroeber, M.; Ohlmann, A.; Russell, P.; Tamm, E.R. Transgenic studies on the role of optineurin in the mouse eye. *Exp. Eye Res.*, **2006**, *82*(6), 1075-1085. [http://dx.doi.org/10.1016/j.exer.2005.11.004] [PMID: 16442524]
- [141] Shim, M.S.; Takihara, Y.; Kim, K.Y.; Iwata, T.; Yue, B.Y.; Inatani, M.; Weinreb, R.N.; Perkins, G.A.; Ju, W.K. Mitochondrial pathogenic mechanism and degradation in optineurin E50K mutation-mediated retinal ganglion cell degeneration. *Sci. Rep.*, **2016**, *6*, 33830. [http://dx.doi.org/10.1038/srep33830] [PMID: 27654856]
- [142] Tseng, H.C.; Riday, T.T.; McKee, C.; Braine, C.E.; Bomze, H.; Barak, I.; Marean-Reardon, C.; John, S.W.; Philpot, B.D.; Ehlers, M.D. Visual impairment in an optineurin mouse model of primary open-angle glaucoma. *Neurobiol. Aging*, **2015**, *36*(6), 2201-2212. [http://dx.doi.org/10.1016/j.neurobiolaging.2015.02.012] [PMID: 25818176]
- [143] Aung, T.; Rezaie, T.; Okada, K.; Viswanathan, A.C.; Child, A.H.; Brice, G.; Bhattacharya, S.S.; Lehmann, O.J.; Sarfarazi, M.; Hitchings, R.A. Clinical features and course of patients with glaucoma with the E50K mutation in the optineurin gene. *Invest. Ophthalmol. Vis. Sci.*, **2005**, *46*(8), 2816-2822. [http://dx.doi.org/10.1167/iovs.04-1133] [PMID: 16043855]
- [144] Hauser, M.A.; Allingham, R.R.; Linkroum, K.; Wang, J.; LaRocque-Abramson, K.; Figueiredo, D.; Santiago-Turla, C.; del Bono, E.A.; Haines, J.L.; Pericak-Vance, M.A.; Wiggs, J.L. Distribution of WDR36 DNA sequence variants in patients with primary open-angle glaucoma. *Invest. Ophthalmol. Vis. Sci.*, **2006**, *47*(6), 2542-2546. [http://dx.doi.org/10.1167/iovs.05-1476] [PMID: 16723468]
- [145] Mao, M.; Biery, M.C.; Kobayashi, S.V.; Ward, T.; Schimmack, G.; Burchard, J.; Schelteme, J.M.; Dai, H.; He, Y.D.; Linsley, P.S. T lymphocyte activation gene identification by coregulated expression on DNA microarrays. *Genomics*, **2004**, *83*(6), 989-999. [http://dx.doi.org/10.1016/j.ygeno.2003.12.019] [PMID: 15177553]
- [146] Hewitt, A.W.; Dimasi, D.P.; Mackey, D.A.; Craig, J.E. A Glaucoma Case-control Study of the WDR36 Gene D658G sequence variant. *Am. J. Ophthalmol.*, **2006**, *142*(2), 324-325. [http://dx.doi.org/10.1016/j.ajo.2006.02.041] [PMID: 16876519]
- [147] Weisschuh, N.; Wolf, C.; Wissinger, B.; Gramer, E. Variations in the WDR36 gene in German patients with normal tension glaucoma. *Mol. Vis.*, **2007**, *13*, 724-729. [PMID: 17563723]
- [148] Miyazawa, A.; Fuse, N.; Mengkegale, M.; Ryu, M.; Seimiya, M.; Wada, Y.; Nishida, K. Association between primary open-angle glaucoma and WDR36 DNA sequence variants in Japanese. *Mol. Vis.*, **2007**, *13*, 1912-1919. [PMID: 17960130]
- [149] Footz, T.K.; Johnson, J.L.; Dubois, S.; Boivin, N.; Raymond, V.; Walter, M.A. Glaucoma-associated WDR36 variants encode functional defects in a yeast model system. *Hum. Mol. Genet.*, **2009**, *18*(7), 1276-1287. [http://dx.doi.org/10.1093/hmg/ddp027] [PMID: 19150991]
- [150] van Koolwijk, L.M.; Ramdas, W.D.; Ikram, M.K.; Jansonius, N.M.; Pasutto, F.; Hysi, P.G.; Macgregor, S.; Janssen, S.F.; Hewitt, A.W.; Viswanathan, A.C.; ten Brink, J.B.; Hosseini, S.M.; Amin, N.; Despriet, D.D.; Willemse-Assink, J.J.; Kramer, R.; Rivadeneira, F.; Struchalin, M.; Aulchenko, Y.S.; Weisschuh, N.; Zenkel, M.; Mardin, C.Y.; Gramer, E.; Welge-Lüssen, U.; Montgomery, G.W.; Carbonaro, F.; Young, T.L.; Bellenguez, C.; McGuffin, P.; Foster, P.J.; Topouzis, F.; Mitchell, P.; Wang, J.J.; Wong, T.Y.; Czumowska, M.A.; Hofman, A.; Uitterlinden, A.G.; Wolfs, R.C.; de Jong, P.T.; Oostra, B.A.; Paterson, A.D.; Mackey, D.A.; Bergen, A.A.; Reis, A.; Hammond, C.J.; Vingerling, J.R.; Lemij, H.G.; Klaver, C.C.; van Duijn, C.M.; Klaver, C.C.; van Duijn, C.M. Common genetic determinants of intraocular pressure and primary open-angle glaucoma. *PLoS Genet.*, **2012**, *8*(5), e1002611. [http://dx.doi.org/10.1371/journal.pgen.1002611] [PMID: 22570627]
- [151] Burdon, K.P.; Macgregor, S.; Hewitt, A.W.; Sharma, S.; Chidlow, G.; Mills, R.A.; Danoy, P.; Casson, R.; Viswanathan, A.C.; Liu, J.Z.; Landers, J.; Henders, A.K.; Wood, J.; Souzeau, E.; Crawford, A.; Leo, P.; Wang, J.J.; Rochtchina, E.; Nyholt, D.R.; Martin, N.G.; Montgomery, G.W.; Mitchell, P.; Brown, M.A.; Mackey, D.A.; Craig, J.E. Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. *Nat. Genet.*, **2011**, *43*(6), 574-578. [http://dx.doi.org/10.1038/ng.824] [PMID: 21532571]
- [152] Chen, Y.; Hughes, G.; Chen, X.; Qian, S.; Cao, W.; Wang, L.; Wang, M.; Sun, X. Genetic variants associated with different risks for high tension glaucoma and normal tension glaucoma in a chinese population. *Invest. Ophthalmol. Vis. Sci.*, **2015**, *56*(4), 2595-2600. [http://dx.doi.org/10.1167/iovs.14-16269] [PMID: 25711633]
- [153] Micheal, S.; Ayub, H.; Khan, M.I.; Bakker, B.; Schoenmaker-Koller, F.E.; Ali, M.; Akhtar, F.; Khan, W.A.; Qamar, R.; den Hollander, A.I. Association of known common genetic variants with primary open angle, primary angle closure, and pseudoexfoliation glaucoma in Pakistani cohorts. *Mol. Vis.*, **2014**, *20*, 1471-1479. [PMID: 25489222]
- [154] Williams, S.E.; Carmichael, T.R.; Allingham, R.R.; Hauser, M.; Ramsay, M. The genetics of POAG in black South Africans: a candidate gene association study. *Sci. Rep.*, **2015**, *5*, 8378. [http://dx.doi.org/10.1038/srep08378] [PMID: 25669751]
- [155] Ozel, A.B.; Moroi, S.E.; Reed, D.M.; Nika, M.; Schmidt, C.M.; Akbari, S.; Scott, K.; Rozsa, F.; Pawar, H.; Musch, D.C.; Lichter, P.R.; Gaasterland, D.; Branham, K.; Gilbert, J.; Garnai, S.J.; Chen, W.; Othman, M.; Heckenlively, J.; Swaroop, A.; Abecasis, G.; Friedman, D.S.; Zack, D.; Ashley-Koch, A.; Ulmer, M.; Kang, J.H.; Liu, Y.; Yaspan, B.L.; Haines, J.; Allingham, R.R.; Hauser, M.A.; Pasquale, L.; Wiggs, J.; Richards, J.E.; Li, J.Z.; Li, J.Z. Genome-wide association study and meta-analysis of intraocular pressure. *Hum. Genet.*, **2014**, *133*(1), 41-57. [http://dx.doi.org/10.1007/s00439-013-1349-5] [PMID: 24002674]
- [156] Domenici, L.; Origlia, N.; Falsini, B.; Cerri, E.; Barloscio, D.; Fabiani, C.; Sansò, M.; Giovannini, L. Rescue of retinal function by BDNF in a mouse model of glaucoma. *PLoS One*, **2014**, *9*(12), e115579. [http://dx.doi.org/10.1371/journal.pone.0115579] [PMID: 25536045]
- [157] Ko, M.L.; Hu, D.N.; Ritch, R.; Sharma, S.C. The combined effect of brain-derived neurotrophic factor and a free radical scavenger in experimental glaucoma. *Invest. Ophthalmol. Vis. Sci.*, **2000**, *41*(10), 2967-2971. [PMID: 10967052]
- [158] Mey, J.; Thanos, S. Intravitreal injections of neurotrophic factors support the survival of axotomized retinal ganglion cells in adult

- rats *in vivo*. *Brain Res.*, **1993**, 602(2), 304-317. [http://dx.doi.org/10.1016/0006-8993(93)90695-J] [PMID: 8448673]
- [159] Pernet, V.; Di Polo, A. Synergistic action of brain-derived neurotrophic factor and lens injury promotes retinal ganglion cell survival, but leads to optic nerve dystrophy *in vivo*. *Brain*, **2006**, 129(Pt 4), 1014-1026. [http://dx.doi.org/10.1093/brain/awl015] [PMID: 16418178]
- [160] Pollock, G.S.; Robichon, R.; Boyd, K.A.; Kerkel, K.A.; Kramer, M.; Lyles, J.; Ambalavanar, R.; Khan, A.; Kaplan, D.R.; Williams, R.W.; Frost, D.O. TrkB receptor signaling regulates developmental death dynamics, but not final number, of retinal ganglion cells. *J. Neurosci.*, **2003**, 23(31), 10137-10145. [http://dx.doi.org/10.1523/JNEUROSCI.23-31-10137.2003] [PMID: 14602830]
- [161] Blanco, R.E.; Soto, I.; Duprey-Diaz, M.; Blagburn, J.M. Up-regulation of brain-derived neurotrophic factor by application of fibroblast growth factor-2 to the cut optic nerve is important for long-term survival of retinal ganglion cells. *J. Neurosci. Res.*, **2008**, 86(15), 3382-3392. [http://dx.doi.org/10.1002/jnr.21793] [PMID: 18655198]
- [162] Park, H.; Poo, M.M. Neurotrophin regulation of neural circuit development and function. *Nat. Rev. Neurosci.*, **2013**, 14(1), 7-23. [http://dx.doi.org/10.1038/nrn3379] [PMID: 23254191]
- [163] Bok, D.; Yasumura, D.; Matthes, M.T.; Ruiz, A.; Duncan, J.L.; Chappelow, A.V.; Zolotukhin, S.; Hauswirth, W.; LaVail, M.M. Effects of adeno-associated virus-vectored ciliary neurotrophic factor on retinal structure and function in mice with a P216L rds/peripherin mutation. *Exp. Eye Res.*, **2002**, 74(6), 719-735. [http://dx.doi.org/10.1006/exer.2002.1176] [PMID: 12126945]
- [164] Ji, J.Z.; Elyaman, W.; Yip, H.K.; Lee, V.W.; Yick, L.W.; Hugon, J.; So, K.F. CNTF promotes survival of retinal ganglion cells after induction of ocular hypertension in rats: the possible involvement of STAT3 pathway. *Eur. J. Neurosci.*, **2004**, 19(2), 265-272. [http://dx.doi.org/10.1111/j.0953-816X.2003.03107.x] [PMID: 14725620]
- [165] Di Polo, A.; Aigner, L.J.; Dunn, R.J.; Bray, G.M.; Aguayo, A.J. Prolonged delivery of brain-derived neurotrophic factor by adenovirus-infected Müller cells temporarily rescues injured retinal ganglion cells. *Proc. Natl. Acad. Sci. USA*, **1998**, 95(7), 3978-3983. [http://dx.doi.org/10.1073/pnas.95.7.3978] [PMID: 9520478]
- [166] Schmeer, C.; Straten, G.; Kügler, S.; Gravel, C.; Bähr, M.; Isenmann, S. Dose-dependent rescue of axotomized rat retinal ganglion cells by adenovirus-mediated expression of glial cell-line derived neurotrophic factor *in vivo*. *Eur. J. Neurosci.*, **2002**, 15(4), 637-643. [http://dx.doi.org/10.1046/j.1460-9568.2002.01893.x] [PMID: 11886444]
- [167] Raper, S.E.; Chirmule, N.; Lee, F.S.; Wivel, N.A.; Bagg, A.; Gao, G.P.; Wilson, J.M.; Batshaw, M.L. Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. *Mol. Genet. Metab.*, **2003**, 80(1-2), 148-158. [http://dx.doi.org/10.1016/j.ymgme.2003.08.016] [PMID: 14567964]
- [168] Sapieha, P.S.; Peltier, M.; Rendahl, K.G.; Manning, W.C.; Di Polo, A. Fibroblast growth factor-2 gene delivery stimulates axon growth by adult retinal ganglion cells after acute optic nerve injury. *Mol. Cell. Neurosci.*, **2003**, 24(3), 656-672. [http://dx.doi.org/10.1016/S1044-7431(03)00228-8] [PMID: 14664816]
- [169] Martin, K.R.; Quigley, H.A.; Zack, D.J.; Levkovitch-Verbin, H.; Kielczewski, J.; Valenta, D.; Baumrind, L.; Pease, M.E.; Klein, R.L.; Hauswirth, W.W. Gene therapy with brain-derived neurotrophic factor as a protection: retinal ganglion cells in a rat glaucoma model. *Invest. Ophthalmol. Vis. Sci.*, **2003**, 44(10), 4357-4365. [http://dx.doi.org/10.1167/iovs.02-1332] [PMID: 14507880]
- [170] Leaver, S.G.; Cui, Q.; Plant, G.W.; Arulpragasam, A.; Hisheh, S.; Verhaagen, J.; Harvey, A.R. AAV-mediated expression of CNTF promotes long-term survival and regeneration of adult rat retinal ganglion cells. *Gene Ther.*, **2006**, 13(18), 1328-1341. [http://dx.doi.org/10.1038/sj.gt.3302791] [PMID: 16708079]
- [171] Yan, Z.; Sun, X.; Evans, I.A.; Tyler, S.R.; Song, Y.; Liu, X.; Sui, H.; Engelhardt, J.F. Postentry processing of recombinant adeno-associated virus type 1 and transduction of the ferret lung are altered by a factor in airway secretions. *Hum. Gene Ther.*, **2013**, 24(9), 786-796. [http://dx.doi.org/10.1089/hum.2013.137] [PMID: 23948055]
- [172] Lad, S.P.; Peterson, D.A.; Bradshaw, R.A.; Neet, K.E. Individual and combined effects of TrkA and p75NTR nerve growth factor receptors. A role for the high affinity receptor site. *J. Biol. Chem.*, **2003**, 278(27), 24808-24817. [http://dx.doi.org/10.1074/jbc.M212270200] [PMID: 12702729]
- [173] Lebrun-Julien, F.; Morquette, B.; Douillette, A.; Saragovi, H.U.; Di Polo, A. Inhibition of p75(NTR) in glia potentiates TrkA-mediated survival of injured retinal ganglion cells. *Mol. Cell. Neurosci.*, **2009**, 40(4), 410-420. [http://dx.doi.org/10.1016/j.mcn.2008.12.005] [PMID: 19146958]
- [174] Fu, Q.L.; Li, X.; Yip, H.K.; Shao, Z.; Wu, W.; Mi, S.; So, K.F. Combined effect of brain-derived neurotrophic factor and LINGO-1 fusion protein on long-term survival of retinal ganglion cells in chronic glaucoma. *Neuroscience*, **2009**, 162(2), 375-382. [http://dx.doi.org/10.1016/j.neuroscience.2009.04.075] [PMID: 19422885]
- [175] Fu, Q.L.; Hu, B.; Li, X.; Shao, Z.; Shi, J.B.; Wu, W.; So, K.F.; Mi, S. LINGO-1 negatively regulates TrkB phosphorylation after ocular hypertension. *Eur. J. Neurosci.*, **2010**, 31(6), 1091-1097. [http://dx.doi.org/10.1111/j.1460-9568.2010.07127.x] [PMID: 20377621]
- [176] Pernet, V.; Hauswirth, W.W.; Di Polo, A. Extracellular signal-regulated kinase 1/2 mediates survival, but not axon regeneration, of adult injured central nervous system neurons *in vivo*. *J. Neurochem.*, **2005**, 93(1), 72-83. [http://dx.doi.org/10.1111/j.1471-4159.2005.03002.x] [PMID: 15773907]
- [177] You, Y.; Gupta, V.K.; Li, J.C.; Al-Adawy, N.; Klistorner, A.; Graham, S.L. FTY720 protects retinal ganglion cells in experimental glaucoma. *Invest. Ophthalmol. Vis. Sci.*, **2014**, 55(5), 3060-3066. [http://dx.doi.org/10.1167/iovs.13-13262] [PMID: 24744204]
- [178] Nakamura, K.; Martin, K.C.; Jackson, J.K.; Beppu, K.; Woo, C.W.; Thiele, C.J. Brain-derived neurotrophic factor activation of TrkB induces vascular endothelial growth factor expression via hypoxia-inducible factor-1alpha in neuroblastoma cells. *Cancer Res.*, **2006**, 66(8), 4249-4255. [http://dx.doi.org/10.1158/0008-5472.CAN-05-2789] [PMID: 16618748]
- [179] Zhang, L.; Hu, Y.; Sun, C.Y.; Li, J.; Guo, T.; Huang, J.; Chu, Z.B. Lentiviral shRNA silencing of BDNF inhibits *in vivo* multiple myeloma growth and angiogenesis via down-regulated stroma-derived VEGF expression in the bone marrow milieu. *Cancer Sci.*, **2010**, 101(5), 1117-1124. [http://dx.doi.org/10.1111/j.1349-7006.2010.101515.x] [PMID: 20331634]
- [180] Sondell, M.; Sundler, F.; Kanje, M. Vascular endothelial growth factor is a neurotrophic factor which stimulates axonal outgrowth through the flk-1 receptor. *Eur. J. Neurosci.*, **2000**, 12(12), 4243-4254. [http://dx.doi.org/10.1046/j.0953-816X.2000.01326.x] [PMID: 11122336]
- [181] Fischer, C.V.; Mans, V.; Horn, M.; Naxer, S.; Klettner, A.; van Oterendorp, C. The antiproliferative effect of bevacizumab on human tenon fibroblasts is not mediated by vascular endothelial growth factor inhibition. *Invest. Ophthalmol. Vis. Sci.*, **2016**, 57(11), 4970-4977. [http://dx.doi.org/10.1167/iovs.16-19938] [PMID: 27654424]
- [182] Simha, A.; Braganza, A.; Abraham, L.; Samuel, P.; Lindsley, K. Anti-vascular endothelial growth factor for neovascular glaucoma. *Cochrane Database Syst. Rev.*, **2013**, (10), CD007920. [PMID: 24089293]
- [183] Holmes, K.; Roberts, O.L.; Thomas, A.M.; Cross, M.J. Vascular endothelial growth factor receptor-2: structure, function, intracellular signalling and therapeutic inhibition. *Cell. Signal.*, **2007**, 19(10), 2003-2012. [http://dx.doi.org/10.1016/j.cellsig.2007.05.013] [PMID: 17658244]
- [184] Martin, D.F.; Maguire, M.G.; Fine, S.L.; Ying, G.S.; Jaffe, G.J.; Grunwald, J.E.; Toth, C.; Redford, M.; Ferris, F.L., III. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*, **2012**, 119(7), 1388-1398. [http://dx.doi.org/10.1016/j.ophtha.2012.03.053] [PMID: 22555112]
- [185] Bressler, S.B.; Qin, H.; Beck, R.W.; Chalam, K.V.; Kim, J.E.; Melia, M.; Wells, J.A., III. Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch. Ophthalmol.*, **2012**, 130(9), 1153-1161. [http://dx.doi.org/10.1001/archophthalmol.2012.1107] [PMID: 22965591]
- [186] Storkebaum, E.; Carmeliet, P. VEGF: a critical player in neurodegeneration. *J. Clin. Invest.*, **2004**, 113(1), 14-18. [http://dx.doi.org/10.1172/JCI20682] [PMID: 14702101]
- [187] Kilic, U.; Jarve, A.; Guo, Z.; Spudich, A.; Bieber, K.; Barzena, U.; Bassetti, C.L.; Marti, H.H.; Hermann, D.M. Human

- vascular endothelial growth factor protects axotomized retinal ganglion cells *in vivo* by activating ERK-1/2 and Akt pathways. *J. Neurosci.*, **2006**, *26*(48), 12439-12446. [http://dx.doi.org/10.1523/JNEUROSCI.0434-06.2006] [PMID: 17135405]
- [188] Dkhissi, O.; Chanut, E.; Wasowicz, M.; Savoldelli, M.; Nguyen-Legros, J.; Minvielle, F.; Versaux-Botteri, C. Retinal TUNEL-positive cells and high glutamate levels in vitreous humor of mutant quail with a glaucoma-like disorder. *Invest. Ophthalmol. Vis. Sci.*, **1999**, *40*(5), 990-995. [PMID: 10102297]
- [189] Nickells, R.W. Apoptosis of retinal ganglion cells in glaucoma: an update of the molecular pathways involved in cell death. *Surv. Ophthalmol.*, **1999**, *43*(Suppl. 1), S151-S161. [http://dx.doi.org/10.1016/S0039-6257(99)00029-6] [PMID: 10416758]
- [190] Roh, M.; Zhang, Y.; Murakami, Y.; Thanos, A.; Lee, S.C.; Vavvas, D.G.; Benowitz, L.I.; Miller, J.W. Etanercept, a widely used inhibitor of tumor necrosis factor- α (TNF- α), prevents retinal ganglion cell loss in a rat model of glaucoma. *PLoS One*, **2012**, *7*(7), e40065. [http://dx.doi.org/10.1371/journal.pone.0040065] [PMID: 22802951]
- [191] Levkovitch-Verbin, H.; Waserzoog, Y.; Vander, S.; Makarovsky, D.; Ilija, P. Minocycline mechanism of neuroprotection involves the Bcl-2 gene family in optic nerve transection. *Int. J. Neurosci.*, **2014**, *124*(10), 755-761. [http://dx.doi.org/10.3109/00207454.2013.878340] [PMID: 24410139]
- [192] Huang, W.; Fileta, J.B.; Dobberfuhr, A.; Filippopolous, T.; Guo, Y.; Kwon, G.; Grosskreutz, C.L. Calcineurin cleavage is triggered by elevated intraocular pressure, and calcineurin inhibition blocks retinal ganglion cell death in experimental glaucoma. *Proc. Natl. Acad. Sci. USA*, **2005**, *102*(34), 12242-12247. [http://dx.doi.org/10.1073/pnas.0505138102] [PMID: 16103353]
- [193] Tatton, W.G.; Chalmers-Redman, R.M.; Tatton, N.A. Apoptosis and anti-apoptosis signalling in glaucomatous retinopathy. *Eur. J. Ophthalmol.*, **2001**, *11*(Suppl. 2), S12-S22. [PMID: 11592526]
- [194] Wang, W.; Zhang, G.; Gu, H.; Liu, Y.; Lao, J.; Li, K.; Guan, H. Role of CtBP2 in the Apoptosis of Retinal Ganglion Cells. *Cell. Mol. Neurobiol.*, **2015**, *35*(5), 633-640. [http://dx.doi.org/10.1007/s10571-015-0158-x] [PMID: 25627828]
- [195] Fu, P.; Wu, Q.; Hu, J.; Li, T.; Gao, F. Baclofen protects primary rat retinal ganglion cells from chemical hypoxia-induced apoptosis through the Akt and PERK pathways. *Front. Cell. Neurosci.*, **2016**, *10*, 255. [http://dx.doi.org/10.3389/fncel.2016.00255] [PMID: 27867349]
- [196] Hu, Y.; Park, K.K.; Yang, L.; Wei, X.; Yang, Q.; Cho, K.S.; Thielen, P.; Lee, A.H.; Cartoni, R.; Glimcher, L.H.; Chen, D.F.; He, Z. Differential effects of unfolded protein response pathways on axon injury-induced death of retinal ganglion cells. *Neuron*, **2012**, *73*(3), 445-452. [http://dx.doi.org/10.1016/j.neuron.2011.11.026] [PMID: 22325198]
- [197] Nakano, N.; Ikeda, H.O.; Hasegawa, T.; Muraoka, Y.; Iwai, S.; Tsuruyama, T.; Nakano, M.; Fuchigami, T.; Shudo, T.; Kakizuka, A.; Yoshimura, N. Neuroprotective effects of VCP modulators in mouse models of glaucoma. *Heliyon*, **2016**, *2*(4), e00096. [http://dx.doi.org/10.1016/j.heliyon.2016.e00096] [PMID: 27441270]
- [198] Ha, Y.; Liu, H.; Xu, Z.; Yokota, H.; Narayanan, S.P.; Lemtalsi, T.; Smith, S.B.; Caldwell, R.W.; Caldwell, R.B.; Zhang, W. Endoplasmic reticulum stress-regulated CXCR3 pathway mediates inflammation and neuronal injury in acute glaucoma. *Cell Death Dis.*, **2015**, *6*, e1900. [http://dx.doi.org/10.1038/cddis.2015.281] [PMID: 26448323]
- [199] Ozcan, U.; Yilmaz, E.; Ozcan, L.; Furuhashi, M.; Vaillancourt, E.; Smith, R.O.; Görgün, C.Z.; Hotamisligil, G.S. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science*, **2006**, *313*(5790), 1137-1140. [http://dx.doi.org/10.1126/science.1128294] [PMID: 16931765]
- [200] Tejada, G.S.; Díaz-Guerra, M. Integral Characterization of Defective BDNF/TrkB Signalling in Neurological and Psychiatric Disorders Leads the Way to New Therapies. *Int. J. Mol. Sci.*, **2017**, *18*(2), E268. [http://dx.doi.org/10.3390/ijms18020268] [PMID: 28134845]
- [201] Oddone, F.; Roberti, G.; Micera, A.; Busanello, A.; Bonini, S.; Quaranta, L.; Agnifili, L.; Manni, G. Exploring serum levels of brain derived neurotrophic factor and nerve growth factor across glaucoma stages. *PLoS One*, **2017**, *12*(1), e0168565. [http://dx.doi.org/10.1371/journal.pone.0168565] [PMID: 28068360]
- [202] Sippl, C.; Bosserhoff, A.K.; Fischer, D.; Tamm, E.R. Depletion of optineurin in RGC-5 cells derived from retinal neurons causes apoptosis and reduces the secretion of neurotrophins. *Exp. Eye Res.*, **2011**, *93*(5), 669-680. [http://dx.doi.org/10.1016/j.exer.2011.08.011] [PMID: 21896272]
- [203] Cirulli, E.T.; Lasseigne, B.N.; Petrovski, S.; Sapp, P.C.; Dion, P.A.; Leblond, C.S.; Couthouis, J.; Lu, Y.F.; Wang, Q.; Krueger, B.J.; Ren, Z.; Keebler, J.; Han, Y.; Levy, S.E.; Boone, B.E.; Wimbish, J.R.; Waite, L.L.; Jones, A.L.; Carulli, J.P.; Day-Williams, A.G.; Staropoli, J.F.; Xin, W.W.; Chesi, A.; Raphael, A.R.; McKenna-Yasek, D.; Cady, J.; Vianney de Jong, J.M.; Kenna, K.P.; Smith, B.N.; Topp, S.; Miller, J.; Gkazi, A.; Al-Chalabi, A.; van den Berg, L.H.; Veldink, J.; Silani, V.; Ticozzi, N.; Shaw, C.E.; Baloh, R.H.; Appel, S.; Simpson, E.; Lagier-Tourenne, C.; Pulst, S.M.; Gibson, S.; Trojanowski, J.Q.; Elman, L.; McCluskey, L.; Grossman, M.; Shneider, N.A.; Chung, W.K.; Ravits, J.M.; Glass, J.D.; Sims, K.B.; Van Deerlin, V.M.; Maniatis, T.; Hayes, S.D.; Oudureau, A.; Swarup, S.; Landers, J.; Baas, F.; Allen, A.S.; Bedlack, R.S.; Harper, J.W.; Gitler, A.D.; Rouleau, G.A.; Brown, R.; Harms, M.B.; Cooper, G.M.; Harris, T.; Myers, R.M.; Goldstein, D.B. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. *Science*, **2015**, *347*(6229), 1436-1441. [http://dx.doi.org/10.1126/science.aaa3650] [PMID: 25700176]
- [204] Korac, J.; Schaeffer, V.; Kovacevic, I.; Clement, A.M.; Jungblut, B.; Behl, C.; Terzic, J.; Dikic, I. Ubiquitin-independent function of optineurin in autophagic clearance of protein aggregates. *J. Cell Sci.*, **2013**, *126*(Pt 2), 580-592. [http://dx.doi.org/10.1242/jcs.114926] [PMID: 23178947]
- [205] Ha, T.; Moon, K.H.; Dai, L.; Hatakeyama, J.; Yoon, K.; Park, H.S.; Kong, Y.Y.; Shimamura, K.; Kim, J.W. The retinal pigment epithelium is a notch signaling niche in the mouse retina. *Cell Reports*, **2017**, *19*(2), 351-363. [http://dx.doi.org/10.1016/j.celrep.2017.03.040] [PMID: 28402857]
- [206] Shen, X.; Ying, H.; Qiu, Y.; Park, J.S.; Shyam, R.; Chi, Z.L.; Iwata, T.; Yue, B.Y. Processing of optineurin in neuronal cells. *J. Biol. Chem.*, **2011**, *286*(5), 3618-3629. [http://dx.doi.org/10.1074/jbc.M110.175810] [PMID: 21059646]
- [207] Koga, T.; Shen, X.; Park, J.S.; Qiu, Y.; Park, B.C.; Shyam, R.; Yue, B.Y. Differential effects of myocilin and optineurin, two glaucoma genes, on neurite outgrowth. *Am. J. Pathol.*, **2010**, *176*(1), 343-352. [http://dx.doi.org/10.2353/ajpath.2010.090194] [PMID: 19959812]
- [208] Qiu, Y.; Shen, X.; Shyam, R.; Yue, B.Y.; Ying, H. Cellular processing of myocilin. *PLoS One*, **2014**, *9*(4), e92845. [http://dx.doi.org/10.1371/journal.pone.0092845] [PMID: 24732711]