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REVIEW

Glaucoma and optic nerve repair

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Abstract Glaucoma is a leading cause of irreversible blindness worldwide and causes progressive visual impairment attributable to the dysfunction and death of retinal ganglion cells (RGCs). Progression of visual field damage is slow and typically painless. Thus, glaucoma is often diagnosed after a substantial percentage of RGCs has been damaged. To date, clinical interventions are mainly restricted to the reduction of intraocular pressure (IOP), one of the major risk factors for this disease. However, the lowering of IOP is often insufficient to halt or reverse the progress of visual loss, underlining the need for the development of alternative treatment strategies. Several lines of evidence suggest that axonal damage of RGCs occurs primary at the optic nerve head, where axons appear to be most vulnerable. Axonal injury leads to the functional loss of RGCs and subsequently induces the death of the neurons. However, the detailed molecular mechanism(s) underlying IOP-induced optic nerve injury remain poorly understood. Moreover, whether glaucoma pathophysiology is primarily axonal, glial, or vascular remains unclear. Therefore, protective strategies to prevent further axonal and subsequent soma degeneration are of great importance to limit the progression of sight loss. In addition, strategies that stimulate injured RGCs to regenerate and reconnect axons with their central targets are necessary for functional restoration. The present review provides an overview of the context of glaucoma pathogenesis and surveys recent findings regarding potential strategies for axonal regeneration of RGCs and optic nerve repair, focusing on the role of cytokines and their downstream signaling pathways.

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Introduction

Glaucoma is a generic term for a group of heterogeneous ocular neuropathies that eventually lead to gradual axonal degeneration in the optic nerve and progressive loss of retinal ganglion cells (RGCs). Glaucoma is a leading cause of visual impairment and irreversible blindness worldwide, and an estimated 80 million people will be affected in 2020 (Quigley and Broman 2006). Furthermore, another ~100 million people have increased intraocular pressure (IOP), which is a well-known risk factor for glaucoma (Thylefors and Negrel 1994; World Health Organisation 1997). Glaucoma is more common in the elderly, and thus its prevalence is anticipated to increase further with higher life expectancy of humans in the future (Quigley and Vitale 1997). Progression of glaucoma is slow and typically painless, so that patients commonly do not experience any problems until significant visual loss becomes evident (Quigley 2011). As in most neurodegenerative diseases, the cellular pathophysiology of glaucoma is poorly understood, reflecting its complex multifactorial aetiology.

Axonal damage in glaucoma

Clinical observations in humans and various data from animal experiments point to the optic nerve head (ONH) with the laminar region as being the initial site of axonal damage in glaucoma (Fig. 1; Goldberg 2011; Nickells et al. 2012). In glaucomatous rodents, regions of RGC damage are sharply delimited and often match the path of axon bundles, appearing as pie- or fan-shaped wedges radiating from the ONH to the periphery (Jakobs et al. 2005; Schlamp et al. 2006; Howell et al. 2007; Salinas-Navarro et al. 2010;

Soto et al. 2011). Because RGC axons do not remain in highly organized bundles after passage through the lamina, this pattern matches localized damage to axon bundles at the glial lamina (Howell et al. 2007). Moreover, in Bcl-2–associated X protein (BAX)-deficient, chronic glaucomatous DBA/2J mice, which exhibit prolonged RGC survival after axonal injury (Libby et al. 2005; Semaan et al. 2010), axonal segments within and distal to the laminar region rapidly degenerate, whereas proximal segments attached to surviving RGC somas remain intact (Howell et al. 2007), similar to the findings after acute optic nerve crush. These results provide strong experimental evidence for an early axonal insult occurring within or close to the laminar region in glaucoma. Glaucomatous DBA/2J mice carrying the Wld^S allele, which is known to slow or prevent axon degeneration, show less RGC soma degeneration and retention of activity (Howell et al. 2007). Therefore, measures preserving the integrity of axons might also prevent RGC degeneration in glaucoma (Quigley et al. 1981; Nickells et al. 2012).

Increased IOP has been modeled to increase the strain within and across the lamina region, the site at which the sclera is morphologically altered to allow RGC axons to exit the eye (Fig. 1; Burgoyne 2011). Consistently, morphological damage and focal axonal swelling are first detectable in the lamina region in human glaucoma (Quigley et al. 1983), in experimental glaucoma in primates (Anderson and Hendrickson 1974; Quigley and Anderson 1976), and in chronic glaucoma in DBA/2J mice (Howell et al. 2007). However, the molecular or cellular mechanism(s) underlying optic nerve injury remain poorly understood (Weber et al. 2008; Goldberg 2011). On the one hand, pressure-induced distortions of the collagenous plates in the lamina cribrosa of humans have been suggested to damage RGC axons mechanically (Morgan et al. 1998) and/or to compress blood vessels that supply the ONH, causing local ischemia (Findl et al. 1997; Pillunat et al. 1997). Nevertheless, rodents that lack collagenous plates in the lamina can also develop glaucoma (Danias et al. 2003; Mabuchi et al. 2004; Jakobs et al. 2005; Filippopoulos et al. 2006; Schlamp et al. 2006; Howell et al. 2007). Then again, activated ONH glia could release potent neurotoxic factors, such as tumor necrosis factor-α and nitric oxide, causing localized axonal damage in the ONH region (Fig. 1; Neufeld et al. 1997).

The laminar region has high metabolic demands, which is correlated with increased cyclooxygenase activity and a

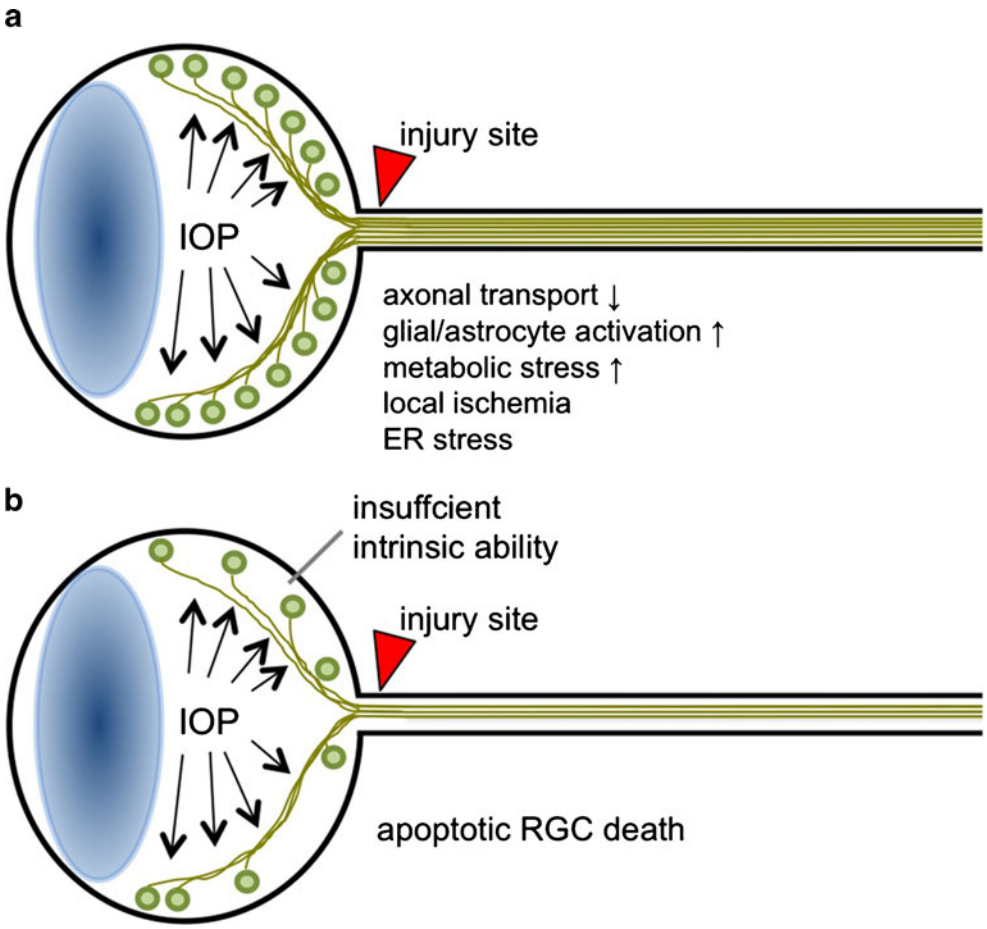

Fig. 1 Pathological features of glaucoma. **a** Representation of a mammalian eye with retinal ganglion cells (*RGC*) projecting axons to the optic nerve. Glaucoma is often characterized by increased intraocular pressure (*IOP*) and localized changes at the optic nerve head, including reduced axonal transport, increased glial activation and metabolic stress, local ischemia and endoplasmic reticulum (*ER*) stress, leading to axonal damage in the laminar region. **b** Axons distal to the injury degenerate, whereas proximal axons survive, but fail to regenerate. Ultimately, RGCs in the retina die by apoptosis, thereby inducing partial visual field loss

high density of voltage-gated sodium channels and mitochondria in this unmyelinated portion of the ONH compared with the myelinated optic nerve (Minckler et al. 1977; Barron et al. 2004; Morgan 2004). Therefore, axon segments in the lamina are probably vulnerable to metabolic stress (Yu-Wai-Man et al. 2011). High IOP has been shown to decrease ATP levels in DBA/2J optic nerves (Baltan et al. 2010) and to alter mitochondrial functions (Ju et al. 2008), a finding also described in glaucoma patients (Abu-Amero and Bosley 2006). The hydrolysis of ATP is, among others, required for axonal transport, and the disruption of axonal transport has been described to occur early in glaucoma (Anderson and Davis 1996; Anderson 1999; Goldberg 2011). Both anterograde and retrograde transport are compromised in the ONH of monkeys with experimental glaucoma (Anderson and Hendrickson 1974; Radius and Anderson 1981; Dandona et al. 1991), and organelles accumulate in both the prelaminar and postlaminar regions of the ONH (Gaasterland et al. 1978). Experimentally elevated IOP also reportedly alters axonal transport in rats (Pease et al. 2000; Quigley et al. 2000; Salinas-Navarro et al. 2010; Chidlow et al. 2011), and the first signs of axonal damage in glaucomatous DBA/2J mice comprise the localized accumulation of organelles in some, but not all, RGC axons in the glial lamina (Jakobs et al. 2005; Howell et al. 2007).

Even transient and modest IOP elevations for 24 h can induce axonal transport defects at the lamina in experimental animals (Levy 1974; Quigley and Anderson 1976; Minckler et al. 1977). Transport normalizes after IOP reduction, indicating that disturbed axonal transport precedes glaucoma induced RGC damage, and that early axonal dysfunction might be reversible (Buckingham et al. 2008). Indeed, electrophysiologic measurements of RGC function demonstrate recovery after acute pressure lowering in glaucomatous patients. However, the mechanism by which increased IOP results in the disruption of axonal transport is so far not understood. Axonal transport deficits could alter cellular homeostasis and evoke further dysregulation of cellular processes in RGC somas (Fig. 1; Abe and Cavalli 2008). Accordingly, increased free radicals and reactive oxygen species have been found in glaucomatous eyes. In addition, hyper-phosphorylated tau and other abnormally folded proteins have been reported to accumulate in retinas of glaucoma patients (Gupta et al. 2008). This could cause endoplasmic reticulum stress, which is indeed detected in RGCs after IOP elevation (Shimazawa et al. 2007). Nevertheless, the blockage of retrograde transport has been argued to occur too slowly to signal damage to RGC somas, as alterations in protein phosphorylation and gene expression occur within 30 min after acute optic nerve damage (Lukas et al. 2009). Irrespective of the underlying pathophysiology of glaucoma, optic nerve axons are damaged, and RGC somas ultimately die by apoptosis, leading to irreversible visual loss (Corredor and Goldberg 2009).

Neuroprotection in glaucoma

A long-standing goal of glaucoma treatment is to decelerate and/or prevent the progression of RGC death, so that visual function is maintained for as long as possible (Chang and Goldberg 2012). As RGC survival depends on neurotrophic support, the identification of neuroprotective factors has received much attention. The classic neurotrophin family comprises four diffusible trophic proteins, namely nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 4/5 (NT4/5), and neurotrophin 3 (NT3), which bind to specific tyrosine kinase receptors (TrK-A, -B, and -C; Ebadi et al. 1997). Among these, BDNF and NT4/5 have been reported to confer significant neuroprotection to injured RGCs (Mey and Thanos 1993; Cohen et al. 1994; Mansour-Robaey et al. 1994; Pernet and Di Polo 2006). BDNF is released by RGC target neurons in the brain, binds to TrK-B on axonal termini and is transported back to the RGC somas. This retrograde transport of neurotrophic factors might be reduced upon axonal damage in glaucoma. Indeed, Trk-B receptors with bound BDNF accumulate in the lamina region of rats with experimental glaucoma (Pease et al. 2000), and the application of exogenous BDNF protects RGCs in animal glaucoma models (Di Polo et al. 1998; Cheng et al. 2002). RGCs also express several receptors of other trophic factors such as fibroblast growth factor receptor (FGFR1), glial-cell-derived neurotrophic factor (GDNF) family receptor α 1 (Ret/GFRα1), hepatocyte growth factor receptor (HGFR), and granulocyte-macrophage colony-stimulating-factor receptor (GM-CSF-α-R). Accordingly, intravitreal application of FGF2, GDNF, HGF, and GM-CSF reportedly increase the survival of mature RGCs upon optic nerve injury (Bahr et al. 1989; Koeberle and Ball 1998; Schallenberg et al. 2009; Tonges et al. 2011). However, these neuroprotective effects are transient and only delay the progress of neuronal degeneration rather than preventing it (Di Polo et al. 1998; Leaver et al. 2006), possibly because RGCs become less responsive to trophic factors after injury (Goldberg and Barres 2000). Electrical stimulation of RGCs or pharmacological increase of intracellular cAMP levels greatly potentiates the pro-survival effects of neurotrophic factors and might enhance their efficacy (Corredor and Goldberg 2009).

In this context, the use of stem cells might be promising. Stem cells cannot yet be transformed into RGCs and stimulated to grow axonal connections from the eye to the brain. Nevertheless, they may, in the short term, at least provide dysfunctional RGCs, which are still alive in glaucoma, with survival and growth factors. Accordingly, intravitreally

injected stem cells have been shown to enhance RGC axon and cell body survival in a preclinical model of glaucoma (Johnson et al. 2010).

Animal models of glaucoma have demonstrated that RGC death occurs only relatively late in the disease (Goldberg 2011). Acute elevation of IOP first slows axonal transport before axons degenerate. However, RGC somas can persist for prolonged periods in a stressed state prior to apoptotic degeneration (Jakobs et al. 2005; Libby et al. 2005; Howell et al. 2007; Soto et al. 2008). Increased survival per se is, however, not sufficient to enable RGCs to regrow injured axons. For example, mice overexpressing the anti-apoptotic protein Bcl-2 show almost no RGC death after axotomy, but do not regenerate axons into the optic nerve (Chierzi et al. 1999; Inoue et al. 2002). Therefore, merely preventing RGC apoptosis after axonal damage will not enhance the regrowth of injured axons. Ideal glaucoma therapies should therefore also encourage axon regeneration to re-establish connections from the eye to the brain.

Regeneration in glaucoma

Despite the need for strategies to promote RGC axon regeneration in glaucoma, clinically established treatments to repair damaged axonal connections in the visual system are currently not available. Regenerative failure has been mainly attributed to the growth-inhibitory environment of the optic nerve and the insufficient intrinsic ability of mature RGCs to regrow axons.

The mature optic nerve per se has been described as a poor substrate for axonal growth. Receptors on growing axons have been shown to interact with inhibitory molecules in their environment, leading to the destabilization of the actin cytoskeleton in filopodia and lamellipodia and the subsequent collapse of the growth cone (Yiu and He 2006; Berry et al. 2008). A number of these inhibitory proteins have been identified, such as Nogo, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp; McKerracher et al. 1994; Chen et al. 2000; Wang et al. 2002b). Even though these three myelin-associated proteins are structurally heterogeneous, they all bind to the Nogo receptor (NgR; Domeniconi et al. 2002; Wang et al. 2002a). The glycosyl-phosphatidyl inositol (GPI)-linked NgR interacts with $p75^{NTR}$ or with TNF receptor superfamily, member 19 (TROY) and leucine-rich repeat and Ig domain containing 1 (LINGO-1) to form functional receptor complexes (Wang et al. 2002a; Wong et al. 2002; Yamashita et al. 2002; Mi et al. 2004). Knockdown or expression of a dominant negative NgR in RGCs increases optic nerve regeneration in vivo only with concomitant stimulation of the intrinsic RGC growth state (Fischer et al. 2004a; Su et al. 2009), indicating that neutralization of myelin inhibition alone might be insufficient to promote regeneration in the optic nerve. However, other growth inhibitors or axonal receptors might additionally contribute to axon growth inhibition in the injured optic nerve. Accordingly, PirB has recently been described as a distinct receptor for Nogo, MAG, and OMgp (Atwal et al. 2008; Cai et al. 2012). In addition, inflammation-induced glial scar formation at a lesion site represents another barrier for axonal regeneration after traumatic nerve injury (Silver and Miller 2004). Resident microglia and astrocytes are activated and secrete growth-inhibitory molecules such as semaphorins, Tenascin-R and chondroitin sulfate proteoglycans (CSPGs; McKeon et al. 1991; Niederost et al. 1999; Tang 2003). Whether inhibitory processes and the release of toxic proteins also contribute to RGC dysfunction and inhibition of axonal regeneration in glaucoma remains unknown. However, ONH glia release tissue growth factor-β, which has been shown to induce CSPG secretion and fibrotic scarring (Lagord et al. 2002; Logan and Berry 2002), upon increased IOP (Neufeld and Liu 2003).

RGC signaling pathways that mediate growth inhibition could be efficient clinical targets for promoting axonal regeneration. Several myelin- and glial-associated inhibitory signals converge on the proteins ras homolog gene A and rho-associated protein kinase (RhoA, ROCK) to induce growth cone collapse (Mueller 1999; Lingor et al. 2007). Treatment of acutely injured RGCs with ADP ribosyltransferase C3, an irreversible RhoA inhibitor, allows severed axons to cross the lesion site and to grow into the distal nerve segment (Lehmann et al. 1999; Bertrand et al. 2005). Similarly, treatment of RGCs with specific ROCK inhibitors reduces myelin and CSPG inhibition in vitro and allows axons to regenerate beyond the lesion site of the optic nerve in vivo (Lingor et al. 2007, 2008; Ahmed et al.2009). Experimental data from glaucoma studies have shown that Rho and ROCK inhibitors can enhance ocular blood flow and increase aqueous humor drainage through the trabecular meshwork, thereby decreasing IOP (Rao and Epstein 2007). Several ROCK inhibitors are currently being tested in clinical trials for their IOP-lowering effects, but could also prove useful for enhancing optic nerve regeneration.

The extension of microtubules during axonal growth depends on the net-polymerization of tubulin dimers. Microtubule dynamics in growth cones are affected by actin polymerization and are therefore also indirectly modulated by RhoA/ROCK signaling (Mimura et al. 2006; Conde and Caceres 2009). The anti-cancer drug Paclitaxel (Taxol) promotes microtubule polymerization at low concentrations and uncouples their interaction with actin filaments, thereby improving growth cone motility and decreasing sensitivity towards growth-inhibitory molecules (Derry et al. 1995, 1997; Sengottuvel et al. 2011). Consistently, Taxol promotes

the axonal growth of primary RGCs per se and also on inhibitory myelin and CSPG substrates in vitro (Sengottuvel et al. 2011; Fischer and Leibinger 2012). Taxol treatment in vivo markedly increases regeneration after acute optic nerve injury, allowing RGC axons to grow across the injury site (Sengottuvel et al. 2011). In addition, glial scar formation is delayed, and CSPG secretion is reduced at the injury site upon Taxol treatment (Hellal et al. 2011; Sengottuvel et al. 2011). Whether the application of low Taxol concentrations might be a promising approach for glaucoma treatment probably needs to be first investigated by using glaucoma animal models. Because of the relatively short-term effects of Taxol in comparison with the long-term progression of most types of chronic glaucoma, appropriately localized and continuous delivery methods need to be developed to potentially enhance axon regeneration in glaucomatous optic nerves.

Stimulation of RGC growth state

Adult RGCs normally fail to regenerate after acute axonal injury, and only a few injured neurons re-extend axons in vitro or in vivo (Vidal-Sanz et al. 1987, 1988; Muller et al. 2007). However, puncture of the lens capsule induces a low-grade inflammatory response in the eye and transforms axotomized RGCs into a robust regenerative state, which is characterized by altered gene expression (Fischer et al. 2000, 2004b; Leon et al. 2000). As a result, RGC death is markedly delayed, and lengthy axons are regenerated into the inhibitory environment of a crushed optic nerve (Fischer et al. 2000, 2001; Leon et al. 2000). Thus, lens injury exerts neuroprotective, axon-growth-promoting, and disinhibitory effects. Nevertheless, lens injury as a treatment approach for glaucoma in humans is rather inappropriate, as it rapidly promotes cataract formation. Therefore, the identification of the molecular basis of this positive inflammatory response might identify more realistic targets for the translation to human glaucoma treatment.

Intravitreal injection of β- or γ-crystallins or of toll-like receptor 2 agonists, such as zymosan or Pam_3Cys, have been shown to mimic fully the beneficial effects of lens injury on axonal regeneration (Leon et al. 2000; Fischer et al. 2008; Hauk et al. 2010). The induced inflammatory response is characterized by macrophages infiltrating the eye and by the activation of retinal astrocytes and Müller cells to secrete the cytokines ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF; Muller et al. 2007; Fischer 2008; Leibinger et al. 2009). The key role of CNTF and LIF in promoting the beneficial effects of inflammatory stimulation (IS) upon lens injury has been demonstrated in experimental studies of knockout mice. Neuroprotective and axon growth-promoting effects of IS are absent in mice deficient for CNTF and LIF (Leibinger et al. 2009). In vitro, CNTF and LIF each potently enhance RGC neurite outgrowth, even in the absence of increased cyclic adenosine monophosphate (cAMP) levels (Jo et al. 1999; Muller et al. 2007, 2009; Leibinger et al. 2009; Ahmed et al. 2010; Sengottuvel et al. 2011). Nevertheless, cAMP elevation potentiates the beneficial effects of CNTF and IS (Cui et al. 2003; Park et al. 2004; Muller et al. 2007, 2009). However, the beneficial effects of intravitreally applied recombinant CNTF are less pronounced than those of IS (Muller et al. 2007, 2009; Lingor et al. 2008), possibly because of the short half-life of exogenous CNTF in the vitreous. Consistently, a constant CNTF supply via viral expression results in significantly greater regeneration, with axons reaching the optic chiasm 5 weeks after an intraorbital optic nerve crush (Leaver et al. 2006; Hellstrom et al. 2011). Because of these promising experimental results, CNTF is going to be tested in clinical trials for human glaucoma, for example, by using encapsulated CNTF-expressing cells for drug delivery (clinicaltrials.gov NCT01408472).

Axon growth stimulatory signaling cascades

In addition to the direct application of IS mediators such as CNTF, the manipulation of downstream signaling cascades of these cytokines might be a promising approach to increase axonal regeneration in glaucoma. CNTF and LIF belong to the family of interleukin-6 (IL-6)-type cytokines. These cytokines mediate their effects through the signal transducing receptor glycoprotein 130 (gp130) and, in case of CNTF and LIF, the LIF-receptor (LIFR; Fig. 2; Heinrich et al. 2003). LIF directly interacts with LIFR, which subsequently forms a heterodimeric complex with gp130. CNTF first binds to the CNTF-receptor α (CNTFRα), which then recruits the signaling subunits LIFR and gp130 to form a ternary receptor complex (Fig. 2). All these receptor components are expressed by mature and axotomized RGCs (Muller et al. 2007; Leibinger et al. 2009, 2012), suggesting a direct effect of these cytokines on RGCs (Sarup et al. 2004). Upon cytokine stimulation, LIFR and gp130 associate with Janus-kinases (JAK1, JAK2, and TYK2) and become tyrosine-phosphorylated (Fig. 2; Heinrich et al. 2003). The phosphorylated receptors serve as docking sites for signal transducer and activator of transcription (STAT; mainly STAT3) and protein tyrosine phosphatase SHP2 (Rane and Reddy 2000; Muller et al. 2007). In turn, STAT3 monomers become phosphorylated, dimerize, and translocate into the nucleus to activate the expression of genes with STAT3 response elements (Fig. 2; Stahl et al. 1994; Hemmann et al. 1996). Phosphorylated SHP2, on the other hand, activates the mitogen-activated protein

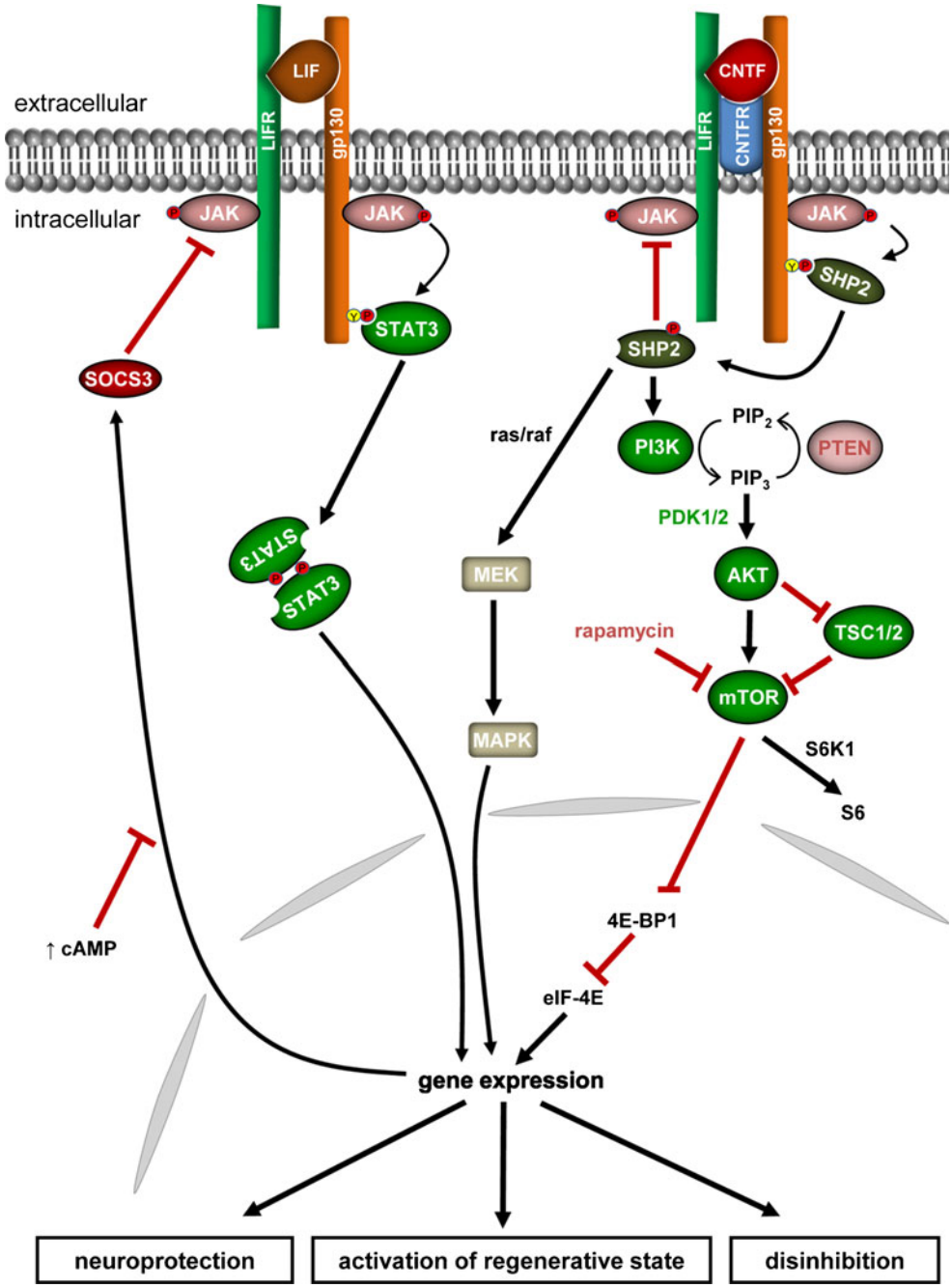

Fig. 2 Representation of signaling pathways upon inflammatory stimulation (IS). Binding of interleukin-6 (IL-6)-type cytokines ciliary neurotrophic factor (*CNTF*) and leukemia inhibitory factor (*LIF*) to their receptors (*CNTFR*, *LIFR*, and glycoprotein 130 [*gp130*]) activates Janus-kinases (*JAK*), which then either phosphorylate the transcription factor signal transducer and activator of transcription-3 (*STAT3*; JAK2) or activate the protein tyrosine phosphatase *SHP2* (JAK1). Phosphorylated STAT3 forms dimers, which translocate into the nucleus to initiate STAT3-response-element-dependent gene expression. Phosphorylated SHP2 activates the mitogen-activated protein kinase (*MAPK*)/extracellular signal regulated kinase and phosphoinositid-3-kinase (*PI3K/Akt*) signaling pathways. PI3K converts phosphatidylinositol-(4,5)-bisphosphate (*PIP2*) into phosphatidylinositol-(3,4,5)-trisphosphate (*PIP3*), which stimulates phosphatidylinositol-dependent kinase 1/2 (*PDK1/2*) to activate Akt. Phosphatase and tensin homolog (*PTEN*) counteracts PI3K by catalyzing the conversion of PIP3 to PIP2. One of the activated downstream signaling targets of Akt is the mammalian target of rapamycin (*mTOR*), whose activation can be specifically blocked by rapamycin. Activated mTOR inhibits the E4-binding protein1 (*E4-BP1*), a repressor of the eukaryotic translation initiation factor 4E (*EIF-4E*). Additionally, S6 Kinase 1 (*S6K1*) and its target, the ribosomal protein *S6* are also controlled by mTOR. Activated SHP2 can also inhibit JAK-mediated activation of STAT3, thereby negatively regulating IL-6-type cytokine signaling. STAT3-induced gene expression of suppressor of cytokine signaling 3 (*SOCS3*) also serves as a negative feedback loop, as it inhibits JAK2 activation. Further, so far unknown signaling pathways might also be involved in mediating the neuroprotective and axon growth-promoting effects of IS

kinase/extracellular signal regulated kinase (MAPK/ERK) and phosphoinositid-3-kinase (PI3K/Akt) signaling pathways (Fukada et al. 1996; Kim and Baumann 1999; Ernst and Jenkins 2004; Park et al. 2004; Leibinger et al. 2012). However, neurite outgrowth experiments in cell culture with pharmacological inhibitors suggest that MAPK/ERK activation is not directly involved in axon growth stimulation in RGCs, but rather activates the secretion of CNTF by retinal Müller cells and astrocytes (Muller et al. 2009). In addition, activated SHP2 can inhibit the JAK-mediated activation of STAT3, thereby negatively regulating IL-6-type cytokine signaling (Fig. 2; Lehmann et al. 2003).

Suppressor of cytokine signaling 3 (SOCS3) is one of the genes that is induced upon JAK/STAT3 activation. SOCS3 acts as a feedback inhibitor for JAK activation, avoiding excessive STAT3 phosphorylation (Nicholson et al. 2000) and limiting the physiological consequences of STAT3-mediated signaling (Shouda et al. 2001; Jo et al. 2005). Up-regulation of SOCS3 expression is indeed detected in axotomized RGCs after IS, reaching maximal levels ~2.5 days post injury (Fischer et al. 2004b). Consistently, SOCS3-deficient RGCs regenerate axons beyond the lesion site of a crushed optic nerve, and the effects of intravitreal CNTF injections are enhanced in conditional SOCS3 knockout mice, confirming SOCS3 as an intrinsic brake for CNTF-induced axonal regeneration (Smith et al. 2009; Sun et al. 2011). In addition, SOCS3 expression is suppressed by increased cAMP levels (Fig. 2; Park et al. 2009), which might explain why IL-6-type cytokines and IS-induced axonal regeneration are enhanced by cAMP-elevating substances (Cui et al. 2003; Muller et al. 2007; Leibinger et al. 2012). As CNTF expression is up-regulated upon IOP increase in retinas of glaucomatous rats (Wu et al. 2007), the inhibition of SOCS3 might be sufficient to promote axonal regeneration in the context of glaucoma.

The PI3K/Akt pathway is negatively regulated by phosphatase and tensin homolog (PTEN), which catalyzes the conversion of PIP3 to PIP2 and thereby counteracts the activity of PI3K (Fig. 2). Genetic deletion of PTEN is reportedly neuroprotective and potently promotes RGC axon regeneration to an extent similar to IS (Park et al. 2008; Sun et al. 2011). Further downstream, mammalian target of rapamycin (mTOR) controls protein expression via S6 Kinase 1 (S6K1) and E4-binding protein1 (E4-BP1; Fig. 2). Consistently, enhanced axonal regrowth promoted by PTEN deletion is blocked by mTOR inhibition. Moreover, the deletion of tuberous sclerosis complex 1 (TSC1), a negative regulator of mTOR signaling, constitutively activates mTOR and mimicks the effects of PTEN deletion (Park et al. 2008). Whether PTEN inhibition or, for that matter, PI3K/Akt/mTor activation is beneficial in the context of glaucoma still needs to be investigated. Interestingly, the clinically established anti-glaucoma drug Latanoprost has been shown to promote RGC neurite outgrowth in culture via activation of the PI3K/Akt pathway (Zheng et al. 2011).

In agreement with the view that mTor activation potently enhances neuroprotection and axon regeneration, treatment with IL-6-type cytokines and IS prevents the down-regulation of mTOR activity in axotomized RGCs (Leibinger et al. 2012). However, mTOR inhibition by rapamycin inhibits neither the cytokine-mediated axon outgrowth stimulation in culture nor the neuroprotective effects of IS in vivo. Instead, rapamycin treatment compromises long distance, but not short distance, axon regeneration in the optic nerve following IS, indicating that mTOR activity is important for sustaining RGCs in an active regenerative state (Leibinger et al. 2012). In addition, mTOR activity seems to reduce myelin inhibitory effects. Although rapamycin does not reduce the axonal growth of cultured RGCs on a growth-permissive substrate, mTOR inhibition markedly reduces CNTF-induced axonal growth on myelin and CSPGs containing inhibitory substrates (Leibinger et al. 2012). These experimental data suggest that the manipulation of intrinsic growth control pathways will provide new therapeutic approaches to promote substantial axon regeneration in the injured visual system.

Concluding remarks

The lowering of IOP will remain an important aspect of glaucoma therapy, as it often decelerates the progression of glaucomatous degeneration. Since the onset and early progression of glaucoma is asymptomatic, glaucoma is often diagnosed only after substantial damage to retinal axons has occurred. However, damage of optic nerve axons currently leads inevitably to irreversible functional loss, since RGCs are unable to regenerate axonal connections and subsequently die. Thus, before ultimate cell death, RGCs might be merely dysfunctional, possibly opening a treatment window for the regeneration of injured axons. Research over the last two decades indicates that mature RGCs can principally be transformed into an active regenerative state that enables these neurons to survive injury and to re-grow axons over long distances into the optic nerve. Molecules and relevant signaling cascades that either limit or facilitate axonal regeneration have been identified and potentially provide novel therapeutic targets. Combinatorial treatments that simultaneously delay RGC death and overcome the growth-inhibitory environment of the glial scar and optic nerve myelin, together with approaches promoting axonal growth, have so far yielded the strongest regeneration in experimental settings. These results are encouraging, but several milestones still have to be reached before clinical treatments aiming to improve visual function can be envisioned for glaucomatous patients. Importantly, the methods to enhance the number and length

of regenerating axons need to be further optimized. In addition, strategies have to be developed to guide and topographically reconnect axons to their targets in the brain. Moreover, regenerated axons need to be appropriately re-myelinated in order to ensure proper function. Finally, these approaches have to be assessed for their therapeutic suitability in human patients. Nevertheless, novel therapies might eventually provide IOP-independent treatments for glaucoma.

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