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INVITED REVIEW

The progress in optic nerve regeneration, where are we?

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Abstract

Optic nerve regeneration is an important area of research. It can be used to treat patients suffering from optic neuropathy and provides insights into the treatment of numerous neurodegenerative diseases. There are many hurdles impeding optic regeneration in mammals. The mammalian central nervous system is non-permissive to regeneration and intrinsically lacks the capacity for axonal regrowth. Any axonal injury also triggers a vicious cycle of apoptosis. Understanding these hurdles provides us with a rough framework to appreciate the essential steps to bring about optic nerve regeneration: enhancing neuronal survival, axon regeneration, remyelination and establishing functional synapses to the original neuronal targets. In this review article, we will go through current potential treatments for optic nerve regeneration, which includes neurotrophic factor provision, inflammatory stimulation, growth inhibition suppression, intracellular signaling modification and modeling of bridging substrates.

Key Words: *optic nerve regeneration; axonal regeneration; neurotrophic factor; inflammatory stimulation; nerve bridging substances*

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Adult Central Nervous System (CNS) Regeneration

The mammalian CNS is inferior to that of invertebrates in the sense that regeneration is extremely limited (Tanaka and Ferretti, 2009). In that sense, it is also inferior to the mammalian peripheral nervous system. The optic nerve has long served as a standard model to study the CNS. The optic nerve has the same organization and three types of glial cells as the CNS white matter. It also provides much easier access. Breakthrough in the field of optic nerve regeneration not only has enabled vision restoration for millions of patients with glaucoma or other secondary optic neuropathies, but also provides insight into the cure of neurodegenerative diseases like Alzheimer's disease and motor neuron diseases.

Hurdles for Optic Nerve Regeneration

There are multiple hurdles for optic nerve regeneration. Firstly, the CNS environment is non-permissive to regeneration. Glial scars form in response to trauma and inhibit axonal extension across the injured site both physically and chemically. Thus, diffusion of growth factors is inhibited due to the presence of a physical barrier and inhibitory molecules. Injured CNS axons are exposed to inhibitory proteins of myelin, such as Nogo and myelin-associated glycoprotein (MAG). Secondly, the CNS intrinsically lacks the capacity to support axonal regrowth. Unlike fish and amphibians, adult mammals lose their neuronal growth and plasticity with age (Tanaka and Ferretti, 2009).

Compared to the peripheral nervous system, there is lower expression of growth factors and regeneration associated genes, such as growth associated protein-43, an important growth associated protein in the nervous system (Linda et al., 1992; Huebner and Strittmatter, 2009). The extracellular matrix also lacks laminin, which is necessary for cell differentiation and migration (Luebke et al., 1995). Finally, axonal injury triggers apoptosis of retinal ganglion cells (RGC). The onset and progression of apoptosis is dependent on the distance of injured site to the eye: the closer the injury site is to the eye, the quicker the onset and progression of apoptosis is. The current hypothesis is that RGC death is protracted due to retrograde transport of neurotrophic factors, which temporarily support RGC survival (Almasieh et al., 2012). The closer the injury site is to the eye, the quicker the reservoir of neurotrophic factors will be depleted. An alternate theory is that there is active uptake of extracellular neurotoxic signals such as calpains, which undergoes retrograde transportation, triggering apoptosis. The triggered apoptosis in turn leads to further RGC death by activation of downstream factors through p53, activating microglia, further neuronal degeneration and cell death (Fischer and Leibinger, 2012). The autonomous endoplasmic reticulum stress pathway in neurons has also been implicated in axotomy-induced RGC death (Hu et al., 2012).

Understanding the obstacles to optic nerve regeneration provides us with a rough framework to understand the essential steps to bring about optic nerve regeneration: enhancing

neuronal survival, axon regeneration, remyelination and the establishment of functional synapses to the original neuronal targets. Current potential treatments for optic nerve regeneration include neurotrophic factor provision, inflammatory stimulation, growth inhibition suppression, intracellular signalling modification and modelling of bridging substrates.

Neurotrophic Factors

Neurotrophic factors are a family of diffusible proteins that mediate neuronal cell growth, differentiation and survival during development. The classical neurotrophic factors can be broadly classified into the neurotrophin family, the neurokines and other growth factors.

The neurotrophin family comprises four peptides, namely brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5). These polypeptides are structurally and functionally related, and mediate their effects through specifically binding to tropomyosin kinase receptors A-C (Henderson, 1996; Fischer and Leibinger, 2012). Ciliary neurotrophic factor (CNTF) and leukaemia inhibitory factor (LIF) make up the neurokine family. Both act through glycoprotein 130 (gp130)-containing signal transduction receptor (Henderson, 1996). Other growth factors include hepatocyte growth factor (HGF), fibroblast growth factor (FGF) and glial cell line derived neurotrophic factor. RGCs express receptors for these growth factors, and intravitreal injection has been shown to enhance RGC survival upon optic nerve injury.

The biological actions of these neurotrophic factors are broad, and include enhancing cell differentiation, cell survival, and synapse stabilization (Mey and Thanos, 1993). BDNF is one of the most effective agents in enhancing survival of axotomized RGCs (Mansour-Robaey et al., 1994). However, trophic factors slow but do not prevent RGC death (Benowitz and Yin, 2010). HGF has been shown to increase neuronal survival and axonal regeneration both *in vitro* and *in vivo* (Tonges et al., 2011). FGF and BDNF have been reported to stimulate axonal sprouting, however the effects are mild. Recent evidence showed that administration of osteopontin significantly potentiates the regenerative response of alpha retinal ganglion cells upon insulin-like growth factor 1 (IGF-1) or BDNF stimulation (Duan et al., 2015). Studies are needed to further investigate whether osteopontin has similar enhancing effects on other neurotrophic factors.

Efforts have been made to activate growth-promoting pathways in injured CNS neurons by exogenously providing trophic factors. These approaches have generated mixed results. Intravitreal application of BDNF promotes survival of axotomized RGCs in optic nerve injury models, while BDNF injection into the superior colliculus also reduces developmental RGC death (Ma et al., 1998; Galindo-Romero et al., 2013). CNTF is more potent in stimulating axonal regeneration in addition to promoting axonal survival than BDNF (Muller et al., 2007, 2009; Lingor et al., 2008). In a rat glaucoma model, intravitreal BDNF injection failed to convey any protective effect while CNTF showed a significant protective effect (Pease et al., 2009). The action of CNTF is closely linked with cAMP level, inflammatory stimulation and activation of the STAT3 pathway (Muller et al., 2007; Kurimoto et al., 2010).

Inflammatory Stimulation

Inflammatory stimulation has been shown to transform RGCs into an active regenerative state (Leibinger et al., 2013a). Following axotomy, intravitreal transplantation of a peripheral nerve segment has been found to enhance the regenerative response of axotomized RGC (Lau et al., 1994). Initially interpreted as the result of trophic factors from the peripheral graft, the stimulated axon regeneration has been primarily attributed to inflammatory stimulation. Infiltrated inflammatory cells such as macrophages and neutrophils both have been found to play an important role and as sources of oncomodulin (Singh and Plemel, 2014). Oncomodulin is a calcium-binding protein from the parvalbumin family that is secreted by activated macrophages and neutrophils present in the vitreous and retina. Lens injury and injection of zymosan and other inflammatory conditions give rise to an influx of inflammatory cells, producing high levels of oncomodulin (Yin et al., 2006, 2009; Heiduschka et al., 2013). Oncomodulin has been proposed to play an important role in axonal regeneration after lens injury (Yin et al., 2009). Elimination of oncomodulin from macrophage-conditioned media eliminates any beneficial effect. Its effect is dependent on the presence of elevated cAMP and mannose (Benowitz and Yin, 2010). Oncomodulin has been found to bind with RGCs only when cAMP is elevated or when the RGC membrane is permeabilized *via* other methods. Thus it is hypothesized that cAMP is responsible for oncomodulin receptor translocation (Meyer-Franke et al., 1998). Thus, while the effect of oncomodulin has been shown to be dependent on the presence of both cAMP and mannose, mannose in turn exerts its effect only in the presence of cAMP. However, genetic evidence also supports the role of injury-induced neurokines. In $CNTF^{-/-}$ mice or $CNTF^{-/-}LIF^{-/-}$ double knockout mice, the growth-promoting effect after lens injury is either reduced or largely blocked, suggesting injury-induced neurokines are necessary in inflammation-induced activation of axonal regeneration (Leibinger et al., 2009). Key mediators of the beneficial effects of inflammatory stimulation have been identified as CNTF, LIF and interleukin-6 (IL-6) (Leibinger et al., 2013b). Signalling pathways involved include JAK/STAT3 and PI3K/ATK/mTOR (Leibinger et al., 2013a).

Growth Inhibition

CNS myelin does not support regeneration. Growth inhibitory signals highly expressed in CNS myelin are Nogo-A, MAG, oligodendrocyte-myelin GP (Omgp) and chondroitin sulphate proteoglycans (CSPGs). The first three are myelin proteins and the latter is generated by reactive scar tissues. Contrary to common misconception, both the CNS and the peripheral nervous system (PNS) express these myelin proteins. The difference between their permissiveness for axonal regeneration lies in their difference in response to injury. In

the PNS, macrophages and Schwann cells rapidly clear and downregulate myelin proteins following injury. In the CNS, oligodendrocytes continue to express myelin proteins with no downregulation of expression (Filbin, 2003).

Nogo-A, an isoform of Nogo, is found in the endoplasmic reticulum, oligodendrocyte surface and inner surface of the myelin membrane. Thus when an axon is injured and exposed, it comes into contact with Nogo-A. MAG is located in the periaxonal membrane while Omgp is expressed by oligodendrocytes and neurons. Intriguingly, while Nogo, MAG & Omgp have been shown to induce growth cone collapse and inhibit neuronal outgrowth, the neuronal response to MAG varies from inhibition to promotion, depending on the stage of neuronal development (Filbin, 2003). A combination of neurotrophic factors and neutralized myelin-associated growth inhibitors have been shown to have a complementary effect on axonal regeneration (Weibel et al., 1994). Glial scars inhibit axonal growth by acting as a physical barrier and through generating growth inhibiting factors, such as CSPG. CSPGs inhibit axonal growth through multiple mechanisms. Due to their large size and dense negative charges, they non-specifically hinder the binding of matrix molecules to their cell surface receptors. Evidence shows that CSPG also interacts with Nogo and MAG (Sharma et al., 2012).

Modification of Intracellular Signaling and Gene Therapy

At the molecular level, RGC axonal regeneration can be enhanced through modifying intracellular signalling pathways. Mammalian sterile 20-like kinase 3b (Mst3b) is a purine-sensitive protein kinase that regulates axonal outgrowth in both the embryonal and mature nervous system (Lorber et al., 2009). Suppression of Mst3b blocks axon-promoting effects of oncomodulin and other trophic factors such as BDNF and NGF, whereas expression of active Mst3b still enables axonal regeneration despite the absence of these trophic factors (Lorber et al., 2009; Benowitz and Yin, 2010). Consistent with Mst3b as an ERK downstream-signalling molecule, in a conditional B-RAF gain-of-function mouse model, activation of RAF–MEK signalling promotes axon regeneration after optic crush (O'Donovan et al., 2014).

Signalling cascades associated with neurotrophic factors include CaM kinase, MAP kinase, JAK/STAT and PI 3-kinase/mTOR. Effects of oncomodulin can be blocked by inhibiting CaM kinase while effects of other trophic factors can be blocked by inhibiting MAP kinase, JAK/STAT and PI 3-kinase/mTOR. Alternatively, deleting genes that encode suppressors of these pathways have been shown to result in sustained axonal regeneration. PTEN gene has been identified as a tumor suppressor and is a negative regulator of PI 3-kinase/mTOR. SOCS3 gene suppresses signalling through the JAK/STAT cascade. Deletion of either gene has been shown to promote optic nerve regeneration (Park et al., 2008; Smith et al., 2009). Double knockout of both genes was found to result in a synergistic increase in axonal regeneration, allowing regenerating axons from the injured optic nerve to reach the optic chiasm (Sun et al., 2011). Rho-associated protein kinase (ROCK) is a kinase that mediates various cellular functions such as cell motilitiy, secretion, proliferation and gene expression. There are mainly two isoforms, with ROCK1 mainly expressed in the lung, liver and kidney, and ROCK2 distributed mostly in the brain and heart. ROCK inhibitors are a novel potential class of glaucoma therapeutics, exerting its effect through its effects on the cytoskeleton and many other mechanisms (Wang and Chang, 2014). The ROCK signalling cascade is a known negative regulator of neurite extension, with PTEN being one of its downstream targets. In turn, the ROCK pathway can be activated by several CNS growth inhibitors expressed in myelin, including MAG, Nogo and Omgp (Van de Velde et al., 2015).

The Kruppel-like family (KLF) of transcription factors regulates the development and regeneration of the nervous system, showing different levels of expression pre- and post-natally (Moore et al., 2009). KLF-4 has been identified to suppress RGC axonal growth. The regeneration induced by KLF-4 deletion can be greatly enhanced by exogenous CNTF, or removal of SOCS3, suggesting a crosstalk mechanism between KLF4 and STAT3 (Qin et al., 2013).

cAMP is a second messenger that augments axon regeneration through multiple mechanisms, but it has little effect on its own (Kurimoto et al., 2010). cAMP renders growth cones unresponsive to growth inhibitory signals, increases the expression of growth-promoting proteins and alters gene expression. Elevation of the intracellular cAMP level also enhances the response of the injured RGCs to trophic factors. cAMP also appears to enable oncomodulin binding to RGC surface receptors, possibly by stimulating receptor translocation. It has also been shown to prolong binding of oncomodulin to its receptor.

Bridging Substrates

Bridging techniques have been adopted in repairing nerve gaps caused by trauma. It is well established that optic axons regenerate along a peripheral nerve graft, which provides a bridge to guide axons across barriers, a growth permissive environment and also a bed of neurotrophic factors (So and Aguayo, 1985). The peripheral nerve graft thus enhances neuronal survival and studies show that regenerating RGCs are able to establish connections into the superior colliculus and also form functional synaptic connections (Bray et al., 1987; Sauve et al., 1995). Artificial substrates have also been developed to serve this purpose. A peptide nanofiber scaffold has been shown to stimulate axonal regeneration with return of functional vision in hamsters (Ellis-Behnke et al., 2006; Qin et al., 2013). The scaffold prevents scar formation, provides a permissive environment for axonal regrowth and breaks down into peptides that can be potentially used by the surrounding tissue.

Future Frontiers

There have been breakthroughs at multiple levels in the search of a solution to optic nerve regeneration since the pioneer work by So and Aguayo (1985). Although these advancements are encouraging, there is a long way to secure

functional restoration of the visual pathway. A source of future inspiration may lie in fish and salamanders. Anamniotes (lower vertebrates) such as fish and salamanders retain the capacity not only for axonal regrowth, but also for neurogenesis following CNS injury. Birds and mammals, however, lose this capacity during embryonic development (Tanaka and Ferretti, 2009). One major reason for this is attributed to glial cells, astrocytes and their derivatives like myelin and the astrocytic scar (Johnson, 1993; Garcia and Koke, 2009). The differences and similarities of CNS regeneration between lower vertebrates and higher vertebrates are being intensely studied. Since many molecular pathways in the CNS are shared, the adult zebrafish is a powerful model to study CNS regeneration (Becker and Becker, 2008).

Retinal projections are topographically arranged and orderly reconnection of axons with their central target is required. Whether mature axons can regenerate into the brain at their full length, navigate to appropriate target areas and restore visual function should be further investigated.

de Lima et al. (2012) showed that in a mouse model subjected to a combination of zymosan injection, cAMP injection and deletion of *PTEN* gene, the powerful synergistic effect allowed RGC to regenerate into the lateral geniculate nucleus, superior colliculus and other visual centers. More importantly, this resulted in partial restoration of visual functions like the optomotor response and depth perception (So and Aguayo, 1985). Visual training is needed to establish fully functional visual connections. In lizards, optic nerve regeneration to the optic tectum was possible but was shown to be dysfunctional (Beazley et al., 1997). A randomized trial comparing monocular visual stimulation with prey to the injured eye and the non-injured eye showed that consistent visual stimulation to the injured eye resulted in return of pupil responses and ability to capture prey at 1 year (Beazley et al., 2003). Other methods to facilitate neural function reorganization include pulsed magnetic field stimulation (Rodger et al., 2012; Makowiecki et al., 2014). Analysis of visual recovery in zebrafish showed two phases of recovery (Kato et al., 2004). In the first phase, retinal projections are limited to the outer layer of the optic tectum, and the fish show a gross optomotor response (Bilotta, 2000). The slow phase allows for recovery of high resolution vision, and involves complete restoration of visual circuits and refinement of synaptic terminals (McDowell et al., 2004). This full recovery of detailed vision remains our ultimate challenge.

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References

Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A (2012) The molecular basis of retinal ganglion cell death in glaucoma. Prog Retin Eye Res 31:152-181.

Beazley LD, Sheard PW, Tennant M, Starac D, Dunlop SA (1997) Optic nerve regenerates but does not restore topographic projections in the lizard Ctenophorus ornatus. J Comp Neurol 377:105-120.

Beazley LD, Rodger J, Chen P, Tee LB, Stirling RV, Taylor AL, Dunlop SA (2003) Training on a visual task improves the outcome of optic nerve regeneration. J Neurotrauma 20:1263-1270.

Becker CG, Becker T (2008) Adult zebrafish as a model for successful central nervous system regeneration. Restor Neurol Neurosci 26:71-80.

Benowitz LI, Yin Y (2010) Optic nerve regeneration. Arch Ophthalmol 128:1059-1064.

Bilotta J (2000) Effects of abnormal lighting on the development of zebrafish visual behavior. Behav Brain Res 116:81-87.

Bray GM, Villegas-Perez MP, Vidal-Sanz M, Aguayo AJ (1987) The use of peripheral nerve grafts to enhance neuronal survival, promote growth and permit terminal reconnections in the central nervous system of adult rats. J Exp Biol 132:5-19.

de Lima S, Koriyama Y, Kurimoto T, Oliveira JT, Yin Y, Li Y, Gilbert HY, Fagiolini M, Martinez AM, Benowitz L (2012) Full-length axon regeneration in the adult mouse optic nerve and partial recovery of simple visual behaviors. Proc Natl Acad Sci U S A 109:9149-9154.

Duan X, Qiao M, Bei F, Kim IJ, He Z, Sanes JR (2015) Subtype-specific regeneration of retinal ganglion cells following axotomy: effects of osteopontin and mTOR signaling. Neuron 85:1244-1256.

Ellis-Behnke RG, Liang YX, You SW, Tay DK, Zhang S, So KF, Schneider GE (2006) Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. Proc Natl Acad Sci U S A 103:5054-5059.

Filbin MT (2003) Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. Nat Rev Neurosci 4:703-713.

Fischer D, Leibinger M (2012) Promoting optic nerve regeneration. Prog Retin Eye Res 31:688-701.

Galindo-Romero C, Valiente-Soriano FJ, Jimenez-Lopez M, Garcia-Ayuso D, Villegas-Perez MP, Vidal-Sanz M, Agudo-Barriuso M (2013) Effect of brain-derived neurotrophic factor on mouse axotomized retinal ganglion cells and phagocytic microglia. Invest Ophthalmol Vis Sci 54:974-985.

Garcia DM, Koke JR (2009) Astrocytes as gate-keepers in optic nerve regeneration--a mini-review. Comp Biochem Physiol A Mol Integr Physiol 152:135-138.

Heiduschka P, Renninger D, Fischer D, Muller A, Hofmeister S, Schraermeyer U (2013) Lens injury has a protective effect on photoreceptors in the RCS rat. ISRN Ophthalmol 2013:814814.

Henderson CE (1996) Role of neurotrophic factors in neuronal development. Curr Opin Neurobiol 6:64-70.

Hu Y, Park KK, Yang L, Wei X, Yang Q, Cho KS, Thielen P, Lee AH, Cartoni R, Glimcher LH, Chen DF, He Z (2012) Differential effects of unfolded protein response pathways on axon injury-induced death of retinal ganglion cells. Neuron 73:445-452.

Huebner EA, Strittmatter SM (2009) Axon regeneration in the peripheral and central nervous systems. Results Probl Cell Differ 48:339-351.

Johnson AR (1993) Contact inhibition in the failure of mammalian CNS axonal regeneration. Bioessays 15:807-813.

Kato S, Nakagawa T, Ohkawa M, Muramoto K, Oyama O, Watanabe A, Nakashima H, Nemoto T, Sugitani K (2004) A computer image processing system for quantification of zebrafish behavior. J Neurosci Methods 134:1-7.

Kurimoto T, Yin Y, Omura K, Gilbert HY, Kim D, Cen LP, Moko L, Kugler S, Benowitz LI (2010) Long-distance axon regeneration in the mature optic nerve: contributions of oncomodulin, cAMP, and pten gene deletion. J Neurosci 30:15654-15663.

Lau KC, So KF, Tay D (1994) Intravitreal transplantation of a segment of peripheral nerve enhances axonal regeneration of retinal ganglion cells following distal axotomy. Exp Neurol 128:211-215.

Leibinger M, Andreadaki A, Diekmann H, Fischer D (2013a) Neuronal STAT3 activation is essential for CNTF- and inflammatory stimulation-induced CNS axon regeneration. Cell Death Dis 4:e805.

Leibinger M, Muller A, Andreadaki A, Hauk TG, Kirsch M, Fischer D (2009) Neuroprotective and axon growth-promoting effects following inflammatory stimulation on mature retinal ganglion cells in mice depend on ciliary neurotrophic factor and leukemia inhibitory factor. J Neurosci 29:14334-14341.

Leibinger M, Muller A, Gobrecht P, Diekmann H, Andreadaki A, Fischer D (2013b) Interleukin-6 contributes to CNS axon regeneration upon inflammatory stimulation. Cell Death Dis 4:e609.
Linda H, Piehl F, Dagerlind A, Verge VM, Arvidsson U, Cullheim S, Risling M, Ulfhake B, Hokfelt T (1992) Expression of GAP-43 mRNA in the adult mammalian spinal cord under normal conditions and after different types of lesions, with special reference to motoneurons. Exp Brain Res 91:284-295.
Lingor P, Tonges L, Pieper N, Bermel C, Barski E, Planchamp V, Bahr M (2008) ROCK inhibition and CNTF interact on intrinsic signalling pathways and differentially regulate survival and regeneration in retinal ganglion cells. Brain 131:250-263.
Lorber B, Howe ML, Benowitz LI, Irwin N (2009) Mst3b, an Ste20-like kinase, regulates axon regeneration in mature CNS and PNS pathways. Nat Neurosci 12:1407-1414.
Luebke AE, Dickerson IM, Muller KJ (1995) In situ hybridization reveals transient laminin B-chain expression by individual glial and muscle cells in embryonic leech central nervous system. J Neurobiol 27:1-14.
Ma YT, Hsieh T, Forbes ME, Johnson JE, Frost DO (1998) BDNF injected into the superior colliculus reduces developmental retinal ganglion cell death. J Neurosci 18:2097-2107.
Makowiecki K, Harvey AR, Sherrard RM, Rodger J (2014) Low-intensity repetitive transcranial magnetic stimulation improves abnormal visual cortical circuit topography and upregulates BDNF in mice. J Neurosci 34:10780-10792.
Mansour-Robaey S, Clarke DB, Wang YC, Bray GM, Aguayo AJ (1994) Effects of ocular injury and administration of brain-derived neurotrophic factor on survival and regrowth of axotomized retinal ganglion cells. Proc Natl Acad Sci U S A 91:1632-1636.
McDowell AL, Dixon LJ, Houchins JD, Bilotta J (2004) Visual processing of the zebrafish optic tectum before and after optic nerve damage. Vis Neurosci 21:97-106.
Mey J, Thanos S (1993) Intravitreal injections of neurotrophic factors support the survival of axotomized retinal ganglion cells in adult rats in vivo. Brain Res 602:304-317.
Meyer-Franke A, Wilkinson GA, Kruttgen A, Hu M, Munro E, Hanson MG, Jr., Reichardt LF, Barres BA (1998) Depolarization and cAMP elevation rapidly recruit TrkB to the plasma membrane of CNS neurons. Neuron 21:681-693.
Moore DL, Blackmore MG, Hu Y, Kaestner KH, Bixby JL, Lemmon VP, Goldberg JL (2009) KLF family members regulate intrinsic axon regeneration ability. Science 326:298-301.
Muller A, Hauk TG, Fischer D (2007) Astrocyte-derived CNTF switches mature RGCs to a regenerative state following inflammatory stimulation. Brain 130:3308-3320.
Muller A, Hauk TG, Leibinger M, Marienfeld R, Fischer D (2009) Exogenous CNTF stimulates axon regeneration of retinal ganglion cells partially via endogenous CNTF. Mol Cell Neurosci 41:233-246.
O'Donovan KJ, Ma K, Guo H, Wang C, Sun F, Han SB, Kim H, Wong JK, Charron J, Zou H, Son YJ, He Z, Zhong J (2014) B-RAF kinase drives developmental axon growth and promotes axon regeneration in the injured mature CNS. J Exp Med 211:801-814.
Park KK, Liu K, Hu Y, Smith PD, Wang C, Cai B, Xu B, Connolly L, Kramvis I, Sahin M, He Z (2008) Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. Science 322:963-966.
Pease ME, Zack DJ, Berlinicke C, Bloom K, Cone F, Wang Y, Klein RL, Hauswirth WW, Quigley HA (2009) Effect of CNTF on retinal ganglion cell survival in experimental glaucoma. Invest Ophthalmol Vis Sci 50:2194-2200.
Qin S, Zou Y, Zhang CL (2013) Cross-talk between KLF4 and STAT3 regulates axon regeneration. Nat Commun 4:2633.
Rodger J, Mo C, Wilks T, Dunlop SA, Sherrard RM (2012) Transcranial pulsed magnetic field stimulation facilitates reorganization of abnormal neural circuits and corrects behavioral deficits without disrupting normal connectivity. FASEB J 26:1593-1606.
Sauve Y, Sawai H, Rasminsky M (1995) Functional synaptic connections made by regenerated retinal ganglion cell axons in the superior colliculus of adult hamsters. J Neurosci 15:665-675.
Sharma K, Selzer ME, Li S (2012) Scar-mediated inhibition and CSPG receptors in the CNS. Exp Neurol 237:370-378.
Singh B, Plemel JR (2014) Neutrophil contribution in facilitating optic nerve regeneration. J Neurosci 34:1081-1082.
Smith PD, Sun F, Park KK, Cai B, Wang C, Kuwako K, Martinez-Carrasco I, Connolly L, He Z (2009) SOCS3 deletion promotes optic nerve regeneration in vivo. Neuron 64:617-623.
So KF, Aguayo AJ (1985) Lengthy regrowth of cut axons from ganglion cells after peripheral nerve transplantation into the retina of adult rats. Brain Res 328:349-354.
Sun F, Park KK, Belin S, Wang D, Lu T, Chen G, Zhang K, Yeung C, Feng G, Yankner BA, He Z (2011) Sustained axon regeneration induced by co-deletion of PTEN and SOCS3. Nature 480:372-375.
Tanaka EM, Ferretti P (2009) Considering the evolution of regeneration in the central nervous system. Nat Rev Neurosci 10:713-723.
Tonges L, Ostendorf T, Lamballe F, Genestine M, Dono R, Koch JC, Bahr M, Maina F, Lingor P (2011) Hepatocyte growth factor protects retinal ganglion cells by increasing neuronal survival and axonal regeneration in vitro and in vivo. J Neurochem 117:892-903.
Van de Velde S, De Groef L, Stalmans I, Moons L, Van Hove I (2015) Towards axonal regeneration and neuroprotection in glaucoma: Rho kinase inhibitors as promising therapeutics. Prog Neurobiol 131:105-119.
Wang SK, Chang RT (2014) An emerging treatment option for glaucoma: Rho kinase inhibitors. Clin Ophthalmol 8:883-890.
Weibel D, Cadelli D, Schwab ME (1994) Regeneration of lesioned rat optic nerve fibers is improved after neutralization of myelin-associated neurite growth inhibitors. Brain Res 642:259-266.
Yin Y, Henzl MT, Lorber B, Nakazawa T, Thomas TT, Jiang F, Langer R, Benowitz LI (2006) Oncomodulin is a macrophage-derived signal for axon regeneration in retinal ganglion cells. Nat Neurosci 9:843-852.
Yin Y, Cui Q, Gilbert HY, Yang Y, Yang Z, Berlinicke C, Li Z, Zaverucha-do-Valle C, He H, Petkova V, Zack DJ, Benowitz LI (2009) Oncomodulin links inflammation to optic nerve regeneration. Proc Natl Acad Sci U S A 106:19587-19592.