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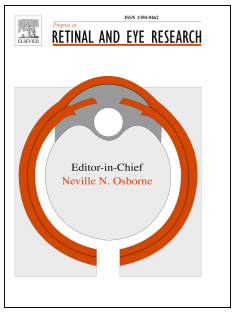

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Martin Berry, Zubair Ahmed, Ann Logan

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RETURN OF FUNCTION AFTER CNS AXON REGENERATION: LESSONS FROM INJURY-RESPONSIVE INTRINSICALLY PHOTOSENSITIVE AND ALPHA RETINAL GANGLION CELLS

Martin Berry[a], Zubair Ahmed[a] and Ann Logan[a]*

[a]Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham B15 2TT, UK

Short title: CNS axon regeneration

Key words: CNS axon regeneration, ipRGC, CNS trauma, recovery of function

*Corresponding author: Prof. A. Logan, Neurotrauma Research Group, Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham B15 2TT, U K. Email: a.logan@bham.ac.uk

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ABSTRACT

This review addresses issues relating to the survival and axon regeneration of both intrinsically photosensitive retinal ganglion cells (ipRGC) and αRGC, and possible ensuing patterns of functional recovery after optic nerve crush, all of which are broadly relevant to recovery from injury in the central nervous system (CNS) as whole. Although much needs to be clarified about the connectivity, function and patterns of myelination of regenerated CNS axons, the results of recent research on activity-induced αRGC axon regeneration associated with functional restitution have highlighted key focal obstacles to recovery including neurotrophic support, axon misguidance, target recognition failure and dysmyelination. Pan RGC survival/axon regeneration requires receptor binding and downstream signalling by a cocktail of growth factors, more generally defined in the CNS by the individual trophic requirements of neuronal subsets within a given disconnected centre. Resolution of the problem of failed axon guidance and target recognition is complicated by a confounding paradox that axon growth inhibitory ligand disinhibition required for axon regeneration may mask axon guidance cues that are essential for accurate re-innervation. The study of the temporal parameters of remyelination of regenerated αRGC axons may become feasible if they establish permanent homologous connections, allowing time for new myelin sheaths to fully form. Unless near complete re-innervation of denervated targets is re-instated in the CNS, debilitating dysfunctional neurological sequelae may ensue from the resulting imbalance in connectivity.

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1. Introduction

Since the definitive demonstrations of retinal ganglion cell (RGC) axon regeneration after optic nerve (ON) crush (ONC) (Berry et al., 1996; Leon et al., 2000), an enigma has emerged that, no matter how many RGC survive, axon regeneration is consistently restricted to <10% RGC (reviewed by (Berry et al., 2008; Berry et al., 2016). This is despite the application of a multiplicity of disparate neuroprotective/axogenic stimuli (reviewed by Harvey et al., 2012), e.g. mammalian target of Rapamycin (mTOR) activation after either deletion of both the phosphatase and tensin homologue (*pten)* and the tuberous sclerosis complex 1 (*tsc1)* genes (Park et al., 2010; Park et al., 2008), and by neurotrophic factors (NTF) derived from Schwann cells (Ahmed et al., 2006; Berry et al., 1999), macrophages (Yin et al., 2009; Yin et al., 2003) and retinal glia (Garcia et al., 2002; Lorber et al., 2009). The

NTF implicated include Oncomodulin (Leon et al., 2000; Yin et al., 2009; Yin et al., 2003) and ciliary neurotrophic factor (CNTF), plus the inflammatory cytokine leukaemia inhibitory factor (LIF) (Diekmann et al., 2013; Leibinger et al., 2009; Muller et al., 2007; Muller et al., 2009). A possible explanation for the above conundrum came when it was discovered that, after *pten* deletion (Park et al., 2008), RGC axon regeneration was the preserve of αRGC, which are phosphorylated $S6^+$ ($pS6^+$) (mTOR stimulated) (Laplante and Sabatini, 2009, 2012), express osteopontin (OP) and insulin-like growth factor receptor 1 (IGFR1) and constitute ~6% all RGC in the mouse (Duan et al., 2015; reviewed by Cui et al., 2015). The discovery of the dependence for the survival and axon regeneration of selected ipRGC and αRGC on specific NTF predicts that different subgroups of RGC and, by inference other multiple groups of phenotypically diverse neurones within the CNS, will require distinct combinations of NTF for survival, axon regeneration and the comprehensive re-innervation of disconnected targets. Opportunities for unravelling the vagaries of functional restitution after CNS injury become available as the physiology and axon regeneration potential of αRGC unfolds. Thus, although the precise connectivity and myelination status of regenerated αRGC axons await clarification, enough is known about their connectivity to gain insights into the precision of guidance of regenerating axons to their original targets, the accuracy of re-innervation and the likely extent of the ensuing functional recovery. Since regenerated axons making functional homotopic connections are expected to establish permanent target links, study also becomes possible of the time course and characteristics of their remyelination, another essential condition for the return of function.

2. ipRGC subtypes

IpRGC and αRGC are included in a list of ~30 different types of RGC in the murine retina, classified by morphology, similarity in gene expression, regularity of spacing in the retina and physiological properties (reviewed by Sanes, 2015). The photosensitive pigment of ipRGC is a melanopsin G protein coupled receptor (GPCR) (Li et al., 2016; Provencio et al., 1998), expressed over a wide range of concentrations by all ipRGC, probably accounting for their variable intrinsic photosensitivity and making phenotypic immunohistochemical anti-melanopsin antibody identification unreliable (Esquiva et al., 2013; Reifler et al., 2015). Nonetheless, 5 subtypes of ipRGC (M1-M5) have been recognised in mice and rats which possess varied molecular, morphological and physiological characteristics (Ecker et al., 2010; Estevez et al., 2012; Reifler et al., 2015; Viney et al., 2007). They all occupy the innermost region of the ganglion cell layer (GCL) juxtaposed of the inner plexiform layer (IPL) and have extensive dendritic ramifications terminating in the ON, OFF and ON/OFF sub-laminae of the IPL (Berson et al., 2002; Warren et al., 2003). M1 are strongly and M2 moderately melanopsin^{+} ipRGC (Berson et al., 2010; Ecker et al., 2010; Schmidt et al., 2014; Schmidt et al., 2011) and mainly subserve pupillary reflexes and entrainment of the circadian clock through connections with the olivary pretectal nucleus (OPN) and suprachiasmatic nucleus (SCN) and intergeniculate leaflet (IGL) (Fig. 1A). The dendrites of the M3 ipRGC subtype are bistratified terminating in both the ON and OFF IPL sublaminae, and physologically resemble M2 cells (Berson et al., 2010; Schmidt et al., 2011). M4 and M5 exhibit weak intrinsic photocurrents (Ecker et al., 2010), have the largest somata and differ in their physiological properties and dendritic stratitfication (Ecker et al., 2010). Although M4 ipRGC express very low levels of melanopsin, they are reliably

labelled with yellow fluorescent protein (YFP) in Kcng4 transgenic mice (crossed with the reporter line Thy-fl-STOP-fl-YFP). M4 ipRGC principally innervate the dorsal lateral geniculate nucleus (dLGN) and superior colliculus (SC) (Fig. 1B) (Ecker et al., 2010; Estevez et al., 2012; Schmidt et al., 2014). Similarly, small numbers of most ipRGC subtypes also project axons to the ventral lateral geniculate nucleus (vLGN), lateral habenular nucleus (LHN), hypothalamic preoptic areas (PA), subparaventricular zone (SPZ) and supra optic nucleus (SON), probably regulating sleep and the release of pituitary hormones (LVPA); negative masking and autonomic neural functions (SPZ); and neurosecretion regulated through the hypothalamic-hypophyseal axis (SON) (Cui et al., 2015; Dacey et al., 2005; Ecker et al., 2010; Hattar et al., 2006; Morin et al., 2003). Morphological, immuno-cytological, electrophysiological and retrograde axon tracer studies confirm that ipRGC have overlapping projections to many other principal RGC axon destinations, most of which are contralateral, although those to the SCN are bilateral and often branched. This dispersed connectivity suggests that disparate ipRGC collaterals may moderate the function of a range of primary ipRGC targets.

3. Relationship between ipRGC and αRGC

In the mouse, M4 ipRGC resemble ON-αRGC in sharing both morphological (large somata that co-label with a melanopsin reporter, SMI-32 heavy chain neurofilament protein antibody, expansive dendritic fields ramifying in the ON sub-lamina of the IPL and axon projection to the DLGN and SC) and physiological properties (responding to rod/cone signalling, photosensitive to sustained ambient light intensity and enhancing contrast sensitivity through melanopsin

phototransduction, possibly setting contrast detection thresholds) (Ecker et al., 2010; Estevez *et al*., 2012; Schmidt et al., 2014; Zhao et al., 2014; Duan et al., 2015; Bray et al., 2017; Sonoda et al., 2018). The above findings have fostered the assertion that ON-αRGC 'completely overlap' and are 'synonymous' with M4 ipRGC (Sonoda et al., 2016, 2018;Schmidt et al., 2014). In rats, rabbits and guinea pigs, M4 ipRGC also bare morphological resemblance to ON αRGC (Manookin et al., 2008; Zhang et al., 2005). In mice, ON α-RGC have also been called Type or Class 1 RGC (Sexton and Van Gelder, 2015), ON, inner α and RGA RGC, among other designations (Badea and Nathans, 2004; Coombs et al., 2006; Sun et al., 2002). At least 4 types of murine αRGC exist (ON-transien (t), OFF-t, ON-sustained (s) and OFF-s) (Krieger et al., 2017), the sustained bipolar cell synaptic inputs of M4 ipRGC (Estevez et al., 2012) identifies them as ONs αRGC.

In the Kcng4-cre line studied by Duan et al., (2015), all αRGC subtypes were YFP^+ and all non-αRGC were unlabelled, and the 'near complete overlap' in CTB- and YFP-labelled regenerating axons after *pten* deletion showed that regrowing axons largely stemmed from αRGC. Although it remains undiscovered which αRGC subtypes regrow their axons, a corollary to the above is that the RGC axon regeneration reported in *pten* deletion studies are all likely to derive from αRGC. Since relative frequencies have not been defined, at least 25% of αRGC could comprise the ON-s αRGC subtype (M4 ipRGC). Melanopsin over-expression promotes RGC axon regeneration through the mTOR pathway, similar to that seen after *pten* deletion (Li et al., 2016), suggesting that the axons of M4 ipRGC (ON-s αRGC) are included in the population of αRGC regenerating their axons. Alpha RGC axon projections terminate in the DLGN and SC and thus connections to other

centres made by regenerating αRGC axons result from path finding and target recognition errors.

4. Survival of axotomoised ipRGC

Some 80% RGC die by 14d after ONC (Berkelaar et al., 1994), probably through caspase-2 (Casp2) mediated apoptosis (Ahmed et al., 2011; Vigneswara and Ahmed, 2016; Vigneswara et al., 2014). Numbers continue to fall after 14d but a residual population, comprising M1 and αRGC preferentially but not exclusively survive (Duan et al., 2015; Perez de Sevilla Muller et al., 2014). Their viability may be attributed to: (i), the preservation of endogenous mTOR signalling (Li et al., 2008), possibly through persistent expression of the sphingosine 1-phosphate receptor (S1PR) (Joly and Pernet, 2016); (ii) mTOR-activating NTF, delivered through either retinal collaterals (Joo et al., 2013; Schmidt et al., 2013; Semo et al., 2014) or secreted by retinal glia (Chidlow et al., 2008; Fischer et al., 2008; Leibinger et al., 2012); (iii), the neurotrophic effects of melanopsin photo-transduction (Cui et al., 2015); (iv), resistance to the toxic effects of increased titres of extracellular glutamate (DeParis et al., 2012; Hartwick et al., 2008; Li et al., 1999) caused by impaired reactive retinal astrocyte uptake (Uhlmann et al., 2002; Wong et al., 2003); and (v), OP-/IGF1-/BDNF-induced mTORC1 regulation of both autophagia and caspase expression (Chen et al., 2013; Dunlop and Tee, 2014; Heras-Sandoval et al., 2014). Bray *et al*. (2017) found that 80% αRGC ultimately die by 6w after ONC and treatment with CNTF, possibly because they are disconnected from target-derived NTF or that, in the absence of myelination, are deprived of oligodendrocyte trophic support (see later). The observation that OP+IGF1 and OP+BDNF treatment

supports αRGC survival (Duan et al., 2015) predicts that other novel NTF treatments are required to promote pan-RGC axon regeneration. However, although the preservation of axotomised RGC viability is a prerequisite for axon regeneration, the two conditions are not causally linked, as illustrated by the observations that: (i), the viability of most RGC is protected by siCasp2 treatment, but <10% of surviving RGC regenerate their axons (Ahmed et al., 2011; Vigneswara et al., 2012); and (ii), M1 and αRGC survive axotomy but only the latter regenerate their axons (Duan et al., 2015). In general, the viability of all axotomised CNS axons is critically dependent on the preservation of collaterals proximal to the site of transection which sustain the retrograde transport of target-derived neuroprotective NTF (reviewed by (Nielson et al., 2011). Most RGC axons lack collaterals in the ON, but other axotomised CNS neurons (e.g. CST neurons –(Nielson et al., 2010) with conserved proximal collaterals may not require intervention of an anti-apoptotic treatment.

5. Regeneration of ipRGC and αRGC

Although M1 and αRGC preferentially survive axotomy in mice, unequivocal axon regeneration is largely restricted to 2.5% of surviving RGC with >90% of these derived from αRGC (Duan et al., 2015). Alpha-RGC are OP-rich (Duan et al., 2015) and, while IGF1 and its receptor are expressed in most RGC and Müller cells (Bu et al., 2013; Tagami et al., 2009), there is selective maintenance of expression in αRGC after ONC. In the normal mouse ON, αRGC axons run a linear parallel course, some possess short branches with bulbous endings (Fig. 2) but, in the absence of treatment after ONC, some grow spontaneously within the proximal ON

segment where they spiral, loop and branch, but few traverse the crush site and penetrate the distal ON segment, and none reach the chiasm (Bray et al., 2017).

When αRGC axons regenerate after unilateral and bilateral ONC in response to mTOR activation, they do grow through the lesion site from the proximal into the distal ON segment where they also exhibit aberrant behaviour by branching and making multiple U-turns; some grow proximally returning through the lesion towards the ipsilateral eye (Luo et al., 2013; Yungher et al., 2015 - reviewed by Pernet and Schwab, 2014). Those growing centrally, reach the chiasm where they take all exit options, entering the contralateral uninjured ON, ipsilateral and contralateral optic tracts and hypothalamus, but re-innervation of the dLGN and SC was not reported by Luo *et al.* (2013) and Yungher *et al*. (2015) and the density of projections is consistently and uncharacteristically greater in the ipsilateral than contralateral optic tract (Fig. 3A). More optimistic results have been reported using a synergistic treatment of *pten* deletion combined with Zymosan and cyclic adenosine monophosphate (cAMP) (de Lima et al., 2012a; de Lima et al., 2012b; Kurimoto et al., 2010) - reviewed by (Benowitz et al., 2017), when regenerating RGC axons re-innervate the contralateral dLGN and SC, but many ectopic connections are also made with the SCN, OPN, vLGN, medial terminal nucleus (mTN) and ipsilateral dLGN (Fig. 3B). CNTF potentiates the effects of *pten* suppression when αRGC axons grow aberrantly in the ON segments proximal and distal to an ONC (Bray et al., 2017; Yungher et al., 2015), although up to ~23% may originate from a non-αRGC origin (Fig. 4). The observation that the misguidance of RGC axon regeneration induced by CNTF (see later) is as extensive as that of αRGC after mTOR stimulation (Luo et al., 2013; Pernet et al., 2012), implies that regenerating CNS axons lack guidance (Diekmann et al., 2013; Luo et al., 2013) and thus, in the

absence of therapies which prevent/correct either deviant axon growth or failures in target recognition, path finding failure is a major obstacle to achieving functional restitution after CNS injury. The development of treatments to correct pathfinding errors will need to address the paradox that axon misdirection is, in part, a consequence of scar-/myelin-derived axon growth inhibitory ligand (AGIL) neutralisation (Ahmed et al., 2006; Berry et al., 2016; Sandvig et al., 2004), required to achieve disinhibited CNS axon regeneration (Berry et al., 2008).

After NTF treatment, CNS axons regenerate without supplementation with an AGIL neutralising therapy, probably because NTF have an inherent disinhibition/axogenic double action. Axon growth is promoted along with induction of either regulated intramembranous proteolysis (RIP) of the $p75^{NTR}$ signalling moiety of the trimeric Nogo receptor complex (Ahmed et al., 2009; Ahmed et al., 2006) or the moderation of RhoA and/or GSK3β activity (Dent and Gertler, 2003; Nakayama et al., 2015; Zhou and Snider, 2005) – reviewed by (Berry et al., 2016). Although the ensuing blockade of both AGIL receptor binding and intracellular signalling are prerequisites for axon regeneration, many AGIL are also repulsive path finding cues (Bolsover et al., 2008; Giger et al., 2010) and thus their neutralisation inevitably leads to guidance errors.

The failure of regenerating axons to home into their original targets may also be attributable to: (i), a partial or complete obliteration in the mature CNS of former guidance cues that define connectivity trajectories during development (reviewed by (Koeberle and Bahr, 2004); (ii), an inability to read ontogenetic axon growth cone repulsive/attraction path finding signals that persist in the adult; and (iii), non-recognition of original post-synaptic contact sites within targets. Notwithstanding all

of the above, the capacity of the CNS to remodel aberrant connectivity by synapse elimination and dendritic plasticity may constitute a natural mechanism for correcting erroneous projections (Hong and Chen, 2011).

6. Axon regeneration of RGC of unknown phenotype

In untreated animals after ONC, very small numbers of RGC axons of unknown phenotype spontaneously regenerate their axons within the proximal ON segment, a few traverse the ON lesion, but their growth is transitory and limited in distance within the distal ON segment (Berry et al., 1996; Bray et al., 2017; Campbell et al., 1999; Park et al., 2010; Park et al., 2008). As mentioned above, after *pten* deletion and OP+IGF1/OP+BDNF treatment, ~6% of RGC axons regenerate in the ON, primarily derived from αRGC. Thus, the NTF requirements of the remaining ~94% RGC may be deduced by screening for axogenic factors (other than OP+IGF1/OP+BDNF combinations). Another approach has been to deliver transcription factors (TF), implicated in axon growth *de novo* during development, to axotomised adult RGC. Sox11 is one such TF which has a screening advantage of inducing αRGC death. Over expression of Sox11 in non-αRGC promotes axon regeneration 4mm into the distal ON segment, although the Sox11 sensitive non-αRGC phenotype has not been identified (Norsworthy et al., 2017). Surprisingly and perhaps paradoxically, *pten* deletion potentiates Sox11-induced RGC axon growth (Fig. 5). However, potential drawbacks of Sox11 therapy are that, although axogenic programmes are re-activated, synaptogenesis is suppressed and lethal neurotoxicity may extend beyond αRGC to other neurons (Norsworthy et al., 2017), suggesting that a more universal application within the CNS may precipitate wide spread

neuronal loss, synaptic dysfunction and disturbed target recognition. There has been an esculating research effort aimed at promoting CNS axon regeneration using axogenic TF therapies and future progress in this endeavour is likely to achieve significant progress (Palmisano and Di Giovanni, 2018; Tedeschi, 2011; Venkatesh and Blackmore, 2017). However, such treatments have so far achieved only modest axon regeneration possibly because, unlike NTF, NF may may not induse RIP of the $p75^{NTR}$ co-receptor resulting in suboptimal disinhibition of axon growth in the presence of myelin-derived AGIL.

Many NTF regimens have the potential to promote axonal regeneration of RGC of unknown phenotype (Harvey et al., 2012), but few researchers have excluded the downstream mediation of mTOR in their experiments. CNTF and *c-myc* potentiate αRGC axon regeneration (Belin et al., 2015; Bray et al., 2017; Yungher et al., 2015), while the former and possibly the latter may also stimulate non-αRGC axogenesis. *In vitro*, CNTF-stimulated RGC neurite extension is little affected by Rapamycin treatment (Leibinger et al., 2012), although growth is blocked using a PI3K inhibitor, indicating that CNTF-stimulation of some RGC neurite/axon growth is mTOR independent, mediated through a JAK/STAT/Akt route, possibly by the inactivation of GSK3β (Leibinger et al., 2017). The RGC axogenic properties of CNTF (Fischer et al., 2008; Fischer and Leibinger, 2012; Hellstrom and Harvey, 2011; Hellstrom et al., 2011; Leaver et al., 2006; Pernet et al., 2013) may be regulated by S1PR1, since co-suppression of this bioactive sphingolipid receptor during CNTF treatment promotes greater regeneration over longer distances than CNTF alone (Joly et al., 2017; Joly and Pernet, 2016).

Multiple Schwann cell-derived NTF (discussed by (Berry et al., 1996; Villegas-Perez et al., 1988) stimulate peripheral nerve regeneration and the growth of axons of up to 9.5% RGC into sciatic nerve grafts (SNG) sutured to the ON (Harvey et al., 2012; Robinson and Madison, 2000; Thanos et al., 1993; Vidal-Sanz et al., 1987; Villegas-Perez et al., 1988). Possibly in response to Schwann cell-derived BDNF (Yi et al., 2016), there is enhanced survival of axotomised M1 melanopsin^{+} ipRGC after ON/SNG, compared to ONC alone, but αRGC axons do not grow into SNG (Robinson and Madison, 2004). Peripheral sensory axons can regenerate after Rapamycin treatment, possibly through either the PI3K/Akt/GSK3β pathway (Christie et al., 2010; Gobrecht et al., 2014; Huang et al., 2017; Saijilafu et al., 2013) and/or an alternative PI3K/GSK3β route independent of Akt phosphorylation (Zhang et al., 2014). Following intravitreal (*ivit*) implantation of SNG, Schwann cell NTF supplemented by macrophage-derived NTF (Lorber et al., 2008), also promote RGC axon growth into the distal ON segment and through the chiasm after ONC (Berry et al., 1996; Berry et al., 1999). This *ivit* SNG-induced RGC axon regenertion also exhibits gross errors of misguidance, but it is not known if the regenerating axons derive from αRGC exclusively or include mTOR-independent non-αRGC axons. Only a small number of RGC axons enter SNG anastomosed to the cut end of the ON (Dezawa and Adachi-Usami, 2000; Harvey et al., 2009; Watanabe and Fukuda, 2002) implying that novel NTF, predicted to preserve the viability and stimulate axon regeneration of non-αRGC, are unlikely to be Schwann cell-derived.

Krüppel-like factors (KLF) regulate axon growth during development. KLF9 is a neurite growth suppressor, the increased expression of which in neonatal RGC is correlated with a progressive loss of axon growth potential (Moore et al., 2009). ShRNA knockdown of KLF9 mRNA in axotomised adult RGC promotes RGC

survival and axon regeneration through the distal ON segment and chiasm into the optic tracts (Apara et al., 2017). Although it is not known which RGC phenotypes are responsive to KLF9 mRNA knockdown, the effect may be mTOR insensitive and thus provide a novel means of stimulating the regeneration of non-αRGC.

7. ON scarring and axon regeneration

Immediately after CNS injury, damaged tissue is removed by inflammatory cells which also secrete scar-inducing cytokines (Berry et al., 1999). CNS scars obstruct and the AGIL they secrete inhibit the regeneration of axons and the re-innervation of targets (Berry et al., 1999; Logan and Berry, 2002; Stichel and Muller, 1994, 1995). Paradoxically however, blocking scar formation promotes little axon regeneration (Fischer et al., 2004; GrandPre et al., 2002; Simonen et al., 2003; Zheng et al., 2003), unless supplemented with NTF treatment (reviewed by (Berry et al., 2008). Nevertheless, in all CNS axon-regenerating paradigms, no scar tissue is deposited and regenerating axons cross sites of injury unimpeded. Moreover, dissolution of chronic scar tissue is also induced by late regenerating axons implying that old scars are not an impediment to reconnection with denervated targets even in long standing cases of CNS injury. For example, in *bax* knockout mice, AAV-CNTF treatment at 56d after ONC (when a mature scar is well established) promotes RGC axons regeneration of *bax*-neuroprotected RGC and the dissolution of the mature scar. Thereafter, RGC axons continue growing into the distal ON segment for at least 3,000µm; some enter the chiasm where they penetrate the hypothalamus and both optic tracts, but others become misdirected into the contralateral ON (Yungher et al., 2017). Similarly, no scar tissue is seen to have developed in the figures

illustrated by Belin et al. (2015), when ON regeneration is induced in adult mouse RGC by the axogenic transcriptional factor *c-myc* up to 6d after ONC, when an incipient scar should be present (Belin et al., 2015). Acute scar formation may be arrested and chronic scar tissue dispersed by regenerating axons regulating both the release of fibrolytic factors from reactive glia including metalloproteinases (MMP) and plasminogens, and the blockade of tissue inhibitors of MMP (TIMPs) (Ahmed et al., 2005). The ensuing inhibition of meningeal fibroblast migration into the wound also has the potential to reduce acute scarring initiated by interactions between EphB2 bearing fibroblast and ephrin-B2^{+} reactive astrocytes (Bundesen et al., 2003). MMP/plasmin may also neutralize the scar-derived AGIL semaphorins/ephrins thereby supplementing the disinhibited axon regeneration attributable to NTF-induced RIP of p75^{NTR} after NOGO binding of myelin-derived AGIL. Thus, it seems likely that prospective poly-therapies designed to promote functional CNS axon regeneration may not require the inclusion of anti-inflammatory and scar-blocking/dissolution treatments in both acute and chronic lesions, unless scarring is exceptionally dense as in lesions of the spinal cord where anti-inflammatory Maresin 1 (Francos-Quijorna et al., 2017) and anti-scarring Decorin regimens (Ahmed et al., 2014; Esmaeili et al., 2014) may be useful.

8. Return of function after α-RGC axon regeneration

The connections of α-RGC (Dacey et al., 2005; Ecker et al., 2010) and M4 ipRGC (ON-s αRGC) (Estevez et al., 2012) with the dLGN and SC (Zhao et al., 2014) indicate roles in high contrast sensitivity (Schmidt et al., 2014), visual perception and visually guided behaviour (Ecker et al., 2010; Zhao et al., 2014).

Restitution of these functions is contingent on re-establishment of the original synaptology in the dLGN and SC through accurate path finding and target recognition of long distance RGC regenerating axons and probably explains the partial return of depth perception and the optomotor (optokinetic) reflexes after *pten* deletion combined with Zymosan+cAMP treatment (de Lima et al., 2012a). But may be difficult to reconcile with the observations that circadian entrainment and pupillary reflexes, all subserved by M1 ipRGC, which do not regenerate their axons in response to mTOR stimulation and exclusively innervate the SCN/IGL and the OPN, respectively (Ecker et al., 2010; Hattar et al., 2006; Hattar et al., 2002). Nonetheless, deletion of *pten* combined with Zymosan+cAMP treatment after ONC (de Lima et al., 2012a) could promote RGC axon regeneration in non-αRGC (see above) either through the release of Oncomodulin from activated macrophages (Leon et al., 2000; Yin et al., 2009; Yin et al., 2003) and/or CNTF/LIF from retinal glia (Fischer and Leibinger, 2012). Similarly, after either AAV shPTEN+*cntf*+cAMP treatment (Yungher et al., 2015) or *pten*+*socs3* co-deletion (Sun et al., 2011, Li et al., 2015), most RGC axons enter the SCN and form active synapses, presumed to be formed by regenerated misdirected α-RGC and not homotopic M1 ipRGC axons which do not regenerate (Duan et al., 2015), unless the JAK/STAT pathway stimulates axogenesis of M1 ipRGC.

More recent research shows that visual stimulation (Goldberg, 2012) and Melanopsin over-expression (Li et al., 2016) can promote target specific axon regeneration of αRGC and probably some non-αRGC, associated with functional restoration of visual behaviours (Goldberg, 2012; Li et al., 2016; Lim et al., 2016). Light stimulation mediates accurate guided αRGC axon regeneration through Ca^{++}-induced mTORC1 expression regulated by light-induced melanopsin coupling with G

protein/11 (Gp/11) (Li et al., 2016). Neural stimulation (Plazas et al., 2013) and the ensuing differential levels GPCR activity control turning behaviour of growth cones in the developing neuropil by inducing the expression of both repulsion and attraction to chemokines (Palczewski and Orban, 2013; Xiang et al., 2002) and similar activity may explain the accurate axon guidance observed by regenerating adult adult αRGC recorded by Lim et al., (2015). The effects of visual stimulation on αRGC axon regeneration is critically dependent on the integrity of retinal circuitary after ONC which can be protected by Insulin administration before RGC begin to die (Agostinone et al., 2018). Such treatment restores dendritic arbour morphology and synaptic connectivity and rescues retinal responses to light stimulation by activating mTOR in RGC. Thus, light stimulation combined with Insulin treatment may provide an optimal therapy for ipRGC and possibly non-ipRGC axon regeneration and target re-innervation.

Nonetheless, if the incidence of aberrant connections/synaptology by regenerating αRGC axons is representative of regenerating CNS axons over all, abnormal function may ensue unless pruning of mismatched contacts or the death of parent misconnected neurons occurs. Alternatively, the normal pattern of profuse ipRGC collateral innervation may favour both the observed unrestrained connectivity with multiple targets by regenerating αRGC and the subsequent observed wide ranging scope of the ensuing functional recovery.

9. Remyelination of regenerated αRGC axons

Another mandatory provision for recovery of function is that regenerated axons become myelinated to ensure that normal axonal conduction

velocities are re-established in the new trajectories. However, study of remyelination of regenerated axons has been hampered by the rapidity of axon degeneration after failed target re-innervation. Bei *et al*. (2016) found that, after either *pten*/socs3 co-deletion or *op/igf1/cntf* co-over-expression, the SC is re-innervated and functional synapses formed, but head turning in response to a rotating grating is not executed. Poor recovery of visual tracking was attributed to dysmyelination of regenerated axons and the resultant disturbed action potential propagation which, when corrected by treatment with voltage-gated potassium channel blockers, partially restored function. Loss of nodes of Ranvier and initial axon ion clustering occurs within 1 week of ONC in surviviving proximal RGC axon segments but, after *pten* deletion and cAMP+Zymosan administration, functioning initial segment and nodal excitable domains are re-established which in regenerating axons first appear proximally with later remyelination and nodal reassembly progressing distally through the ON crush site but such recovery does not extend to the chiasm, even by 3 months after ONC (Marin et al., 2016). De Lima *et al*. (2012a, b) also described the myelination of presumptive αRGC regenerated axons in the distal ON segment but, in support of the conclusions of Bei *et al*. (2016), sheaths were very variable in thickness and lamellae number not positively correlated with axon diameter, indicating that conduction velocities are impaired. The myelination status of mature ipRGC axons is poorly defined, although there is electrophysiological and anatomical evidence that some M1 axons innervating the SCN are both hypo- and un-myelinated (Do and Yau, 2010). Remyelination of regenerated CNS axons is contingent on: (i), the extent of oligodendrocyte death after axotomy; (ii), the availability of essential growth factors (secreted by activated astrocytes, microglia and macrophages) which both regulate the proliferation of oligodendrocyte precursor cells (OPC) and their

differentiation into myelinating oligodendrocytes (Alizadeh *et al*., 2015; Lloyd and Miron, 2016); (iii), Schwann cell invasion, their interaction with OPC and ultimate axon myelination (Berry *et al*., 2016; Blakemore, 1975; Jasmin and Ohara, 2002); and (iv), activity-driven modulation of re-myelination (reviewed by (Almeida and Lyons, 2017). Despite concerted research efforts (reviewed by (Alizadeh et al., 2015), no effective therapy has been formulated for promoting re-myelination of either demyelinated or regenerated CNS axons. However, homologous αRGC axon connections made within the dLGN and SC may become stable for long enough to allow remyelination to run to completion and provide the first descriptions of the natural history of remyelination of regenerated CNS axons.

10. Future directions and conclusions

αRGC axons regenerate and some, notably after light stimulation, make homologous functional connections in the dLGN and SC. Disinhibited axon regeneration is largely an exclusive reponse of αRGC to axotomy driven by OP+IGF1/OP+BDNF stimulation of mTOR implying that the trophic requirements of the remaining RGC may be derived by screening novel NTF/TF either in the presence of Rapamycin or by eliminating αRGC. M1 and 3243αRGC spontaneously survive axotomy but all other RGC will require neuroprotection to remain viable after ONC. Action potential propogation also drives remyelination which becomes a feasible subject of study in those regenerated αRGC axons that make permanent stable homotopic connections. It is likely that centres elsewhere in the CNS will also benefit from neuroprotection and neurostimulation together with cocktails of NTF/TF, possibly supplemented with factors like Insulin, GCPR and/or KLF to kick-start axon

regeneration. The axons of light-stimulated αRGC also connect with multiple nuclei innervated by other ipRGC. The extent to which the latter are homotopic M4 ipRGC collateral trajectories or aberrant ectopic connections remains uncertain. If vagaries in recovery, similar to those occurring after αRGC axon regeneration, also apply to brain and spinal cord injuries, misguidance and dysmyelination will need correction to achieve functional restitution. Also highlighted is the assertion that to achieve return of function in the traumatised CNS additional strategies including axon growth disinhibition and anti-scarring therapies may be unnecessary.

Figure Legends

Figure 1. Diagrammatic representation of the normal principal ipsilateral and contralateral connections of M1 and M2ipRGC (**A**) and contralateral projections of αRGC (**B**) (the connections of other ipRGC axons are less well documented – see text); ipRGC have minor projections to multiple other ipRGC targets not illustrated and further study will clarify the extent to which innervation of these targets is by direct or collateral projections. M1 and M2 axons fail to regenerate, whereas αRGC regenerate their axons (Duan *et al*., 2015) after ONC and accurate target reconnection would be expected to re-establish the connections illustrated (see text and Fig. 3) (ON, optic nerve; OC, optic chiasm; OT, optic tract; SQB, superior quadrigeminal brachium; SCN, suprachiasmatic nucleus; DLGB, dorsal lateral geniculate body; IGL, intergeniculate leaflet; VLGN, ventral lateral geniculate nucleus; OPN, olivary pretactal nucleus; SC, superior colliculus; dashed line=midline).

Figure 2. Immunolabelling-enabled 3D imaging of whole solvent cleared adult mouse ON after labelling RGC with Thy1-H-YFP. **A**, YFP^+ αRGC axons (white) in a maximum intensity projection image (MIPI) of a full thickness ON (optic chiasm to the right). **B**, Traces superimposed on MIPI (scale bar in A and B=500µm). **C**, Example traces of single YFP^+ αRGC axons (each colour (assigned arbitrarily). **D**, **E**, High magnification view of boxed area in **A**. **F**, **G**, Example of a short branch with terminal expansion of an uninjured axon (scale bar=10µm). Note the orderly and parallel course of all axons (illustrated). (Modified Fig. 3 from Bray *et al*., 2017, re-used under the Creative Commons Attribution 4.0 Interntaional (CC BY 4.0) licence).

Figure 3. Some of the aberrant connectivity exhibited by regenerating presumptive αRGC axons demonstrated using cholera toxin B axon tracing and GAP43 immunostaining after combinatorial treatments which include *pten* deletion as reported by Luo *et al.,* 2013 and Yungher *et al.,* 2015 (**A**) and by Kurimoto *et al.,* 2010 and de Lima *et al*., 2012a (**B**). Since other axogenic factors (e.g. CNTF, Oncomodulin, cAMP, etc.) were included in the combinatorial treatments, it is possible that some non-αRGC axons may be included in the projections illustrated. In (**A**), thickness of lines indicates that projections are predominantly ipsilateral (arrows with '?', signify projections innervating undefined target neurons; HT=hypothalamic targets, including medial preoptic area and lateral hypothalamus – a small number of axons also invade the fornix and amygdala – not shown). In (**B**), abnormal connections with the SCN, VLGN, OPN and SC are illustrated (see Fig. 1B for normal ipRGC axon connections, abbreviations and definition of format).

Figure 4. Immunolabelling-enabled 3D maximum intensity projections of YFP^+ (white) αRGC axons in 4 adult ON 6w after ONC and NTF treatment (optic chiasm to the right; each colour represents a single axon; scale bar=100µm). Note the tortuous growth of most regenerating axons in the ON segments both proximal and distal to the lesion (red *) compared to the trajectories of axons in the uninjured ON (Fig. 2) - no regenerating axons reached the brain in this study– see text. (Modified Fig. 6 from Bray *et al.,* 2017, reused under the Creative Commons Attribution 4.0 Interntaional (CC BY 4.0) licence).

Figure 5. Combinecd effect of Sox11 and *pten* deletion (ΔPten) at 6-7w on mouse non-αRGC axons (labelled with cholera toxin B). Compared to ΔPten controls,

axons invaded the optic tracts after traversing the optic chiasm (OC) in ΔPten/Sox11-treated mice (scale bar = 100µm; ON lesion=*). (Modified Fig. 4 from Norseworthy *et al.,* 2017, with permission).

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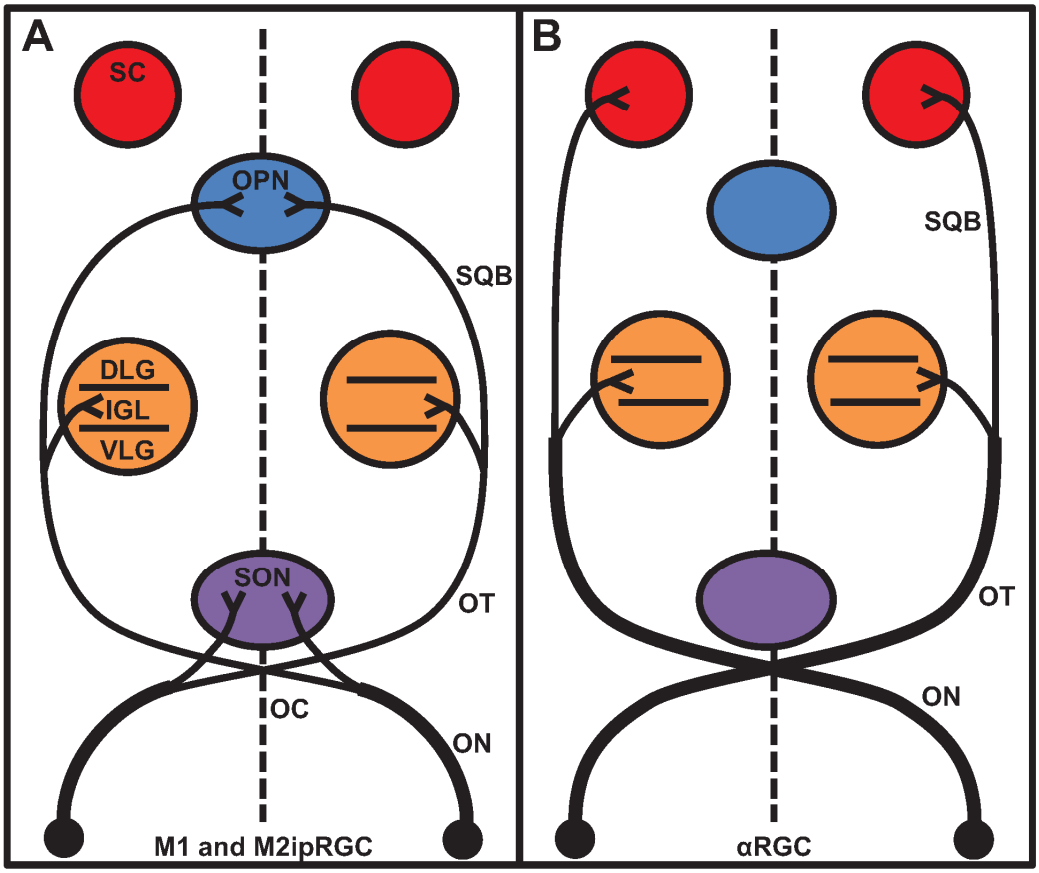
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Figure 1

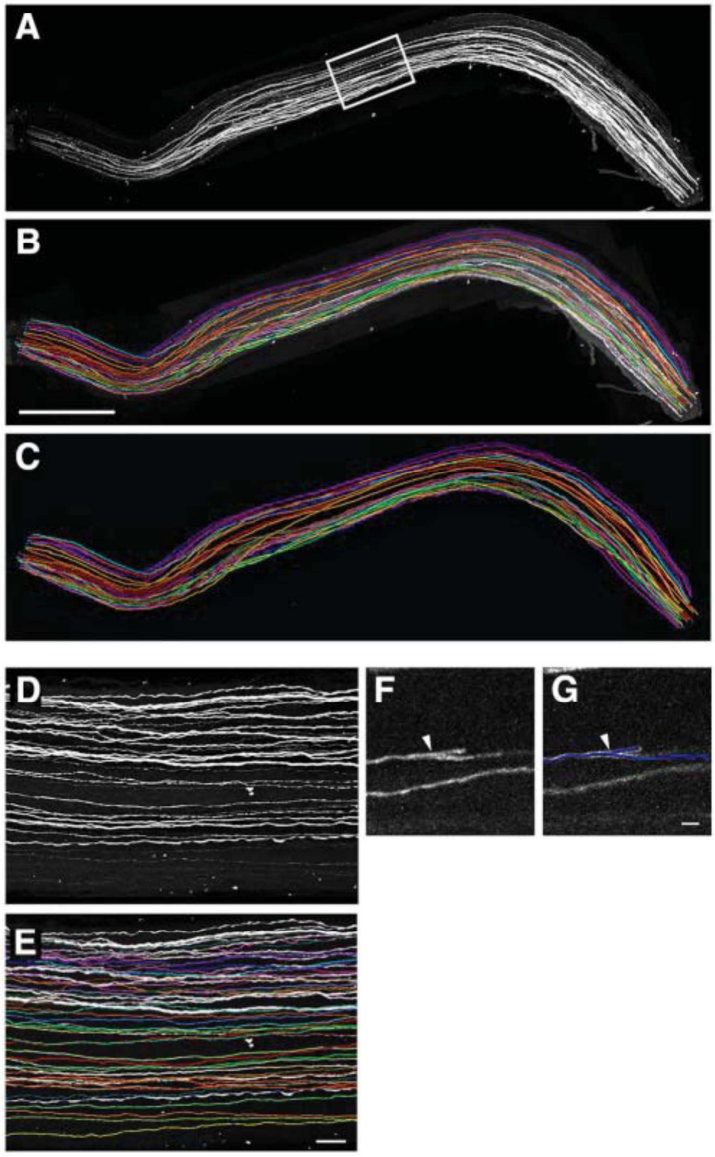

Figure 2

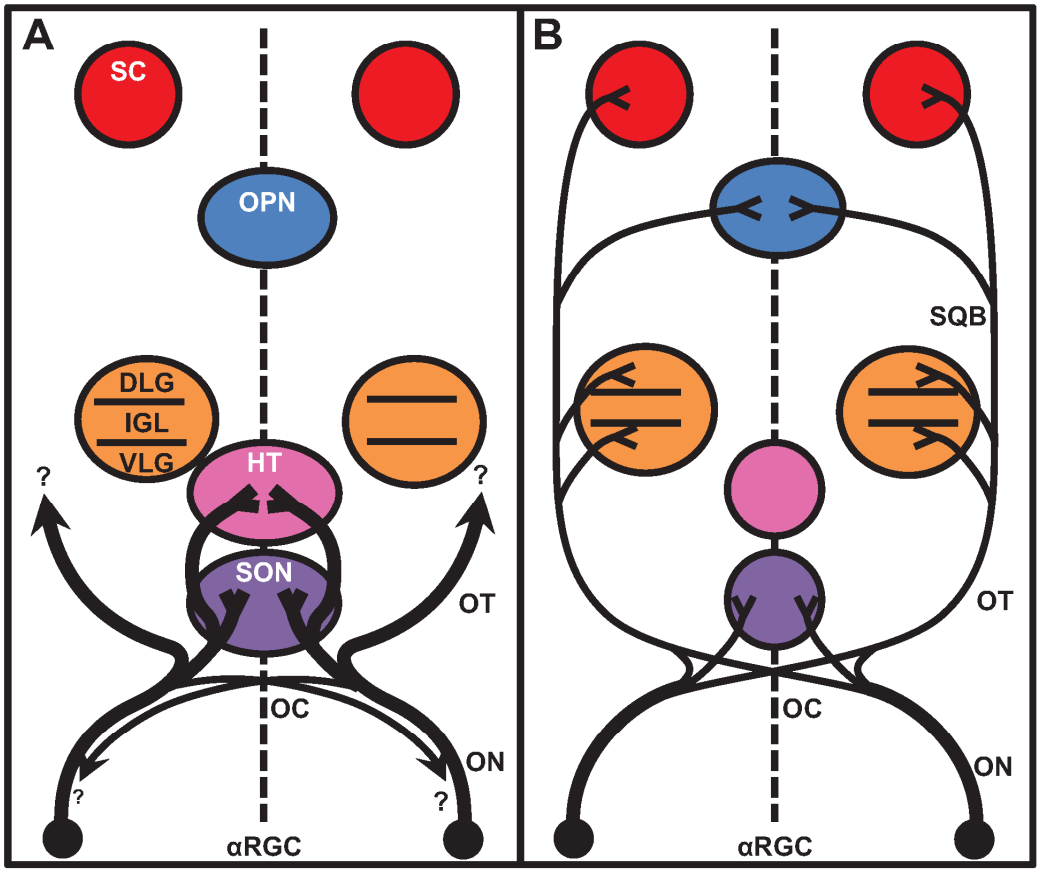

Figure 3

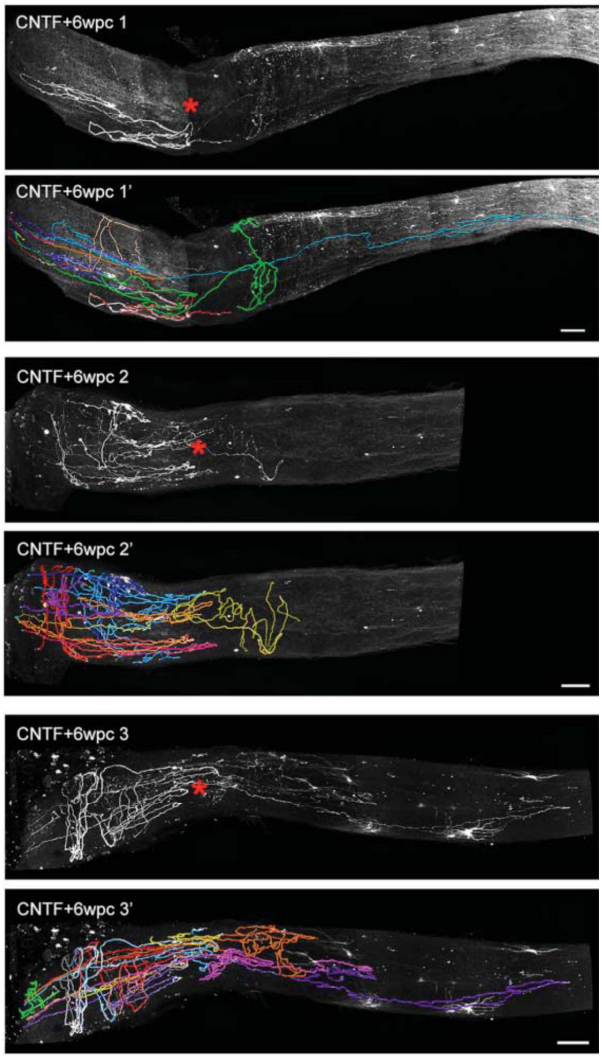
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Figure 4

Figure 5

Highlights

- Less than 10% of retinal ganglion cell (RGC) axons regenerate despite the multiplicity of axogenic stimuli.
- Five subtypes of intrinsically photosensitive RGC (ipRGC; M1-M5) are present in the murine retina
- Only M1 spontaneously survive optic nerve axotomy
- Only αRGC regenerate their axons and are mammalian target of Rapamycin (mTOR)-dependent