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Commentary

The GSK3β pathway in optic nerve regeneration

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Adult neurons in the mammalian central nervous system (CNS) fail to regenerate after injury due to a number of factors including the reduced intrinsic growth capacity together with the hostile environment of the injured CNS microenvironment [1-4]. However recent studies have shown that modifying the intrinsic growth capacity through a number of cell signalling pathways can promote regeneration of adult CNS neurons. For example, intrinsic factors such as cyclic adenosine monophosphate (cAMP), mammalian target of rapamycin (mTOR), and the repressors phosphatase and tensin homolog (PTEN) and suppressor of cytokine signalling 3 (SOCS3) promote CNS axon regeneration [5-7]. The observation that cAMP and mTOR activity are developmentally downregulated and new protein synthesis is suppressed after mTOR inactivation probably explains why some axons do not normally regenerate in the mature CNS.

The retina is an extension of the CNS and optic nerve injury leads to the same problems in terms of neuronal survival and axon regeneration as other parts of the CNS. However, recent studies have demonstrated that inflammatory stimulation, such as oncomodulin [8-10], activation of the JAK/STAT3 pathway [11-13], transcriptional repressors, such as Kruppel-like factors (KLFs) [14,15], Sox11 [16], c-Myc [17], activation of the PTEN/mTOR pathway [18-21], codeletion of PTEN/SOCS3 [5], and activation of BMP4/Smad1 pathway [22], pigment epithelium-derived factor (PEDF) [23-25], and glycogen synthase kinase-3 (GSK3) all promote the survival and regeneration of approximately 10% of retinal ganglion cell (RGC) axons in the murine retina [19]. It seems apparent that no matter what the regenerative strategy in the optic nerve, <10% of RGC survive and regenerate their axons [26,27].

The discovery of the dependence of different subsets of RGC upon specific neurotrophic factor (NTF) combinations implies that phenotypically diverse neurons will require different combinations of NTF for survival and regeneration and eventual re-innervation of appropriate targets. For example, there are over ~30 different types of RGC in the murine retina, which are classified by morphology, gene expression, physiology and regularity of spacing in the retina [19]. The intrinsically photosensitive (ip) RGCs (ipRGCs), contain a range of concentrations of the photosensitive pigment, melanopsin G, giving their variable properties [28,29]. Five types of ipRGC, M1-M5, have been described with varied morphological, molecular and physiological properties and occupy the innermost region of the ganglion cell layer (GCL) juxtaposed to the inner plexiform layer (IPL). These ipRGC have extensive dendritic ramifications that terminate in the ON, OFF and ON/OFF sub-laminae of the IPL [30,31]. M1 ipRGC are strongly melanopsin^{+} and mainly subserve pupillary reflexes and entrainment of the circadian clock [32-34]. M4 ipRGC resemble αRGC in that they have a large somata, expansive dendritic fields ramifying in the ON sub-laminae of the IPL and similar physiological properties [19,33,35,36]. Only M1 and αRGC preferentially survive axotomy but only 2.5% of surviving RGC regenerate their axons, >90% of which are derived from αRGC [19]. Therefore, finding alternative signalling pathways to promote RGC axon regeneration in non-ipRGC/αRGC is a key priority to restore function after optic nerve injury.

With this in mind, we investigated the involvement of the GSK3 pathway after optic nerve injury in RGC survival and axon regeneration (Figure 1). GSK3 is a multifunctional serine/threonine kinase, originally described in mammals with homologs being present in all eukaryotes [37,38]. It inactivates glycogen synthase, an enzyme that regulates the synthesis of glycogen and two homologs are encoded in mammals: GSK3α and GSK3β. GSK3 has diverse functions, including regulation of cell fate, protein synthesis, glycogen metabolism, cell mobility, transformation, proliferation and

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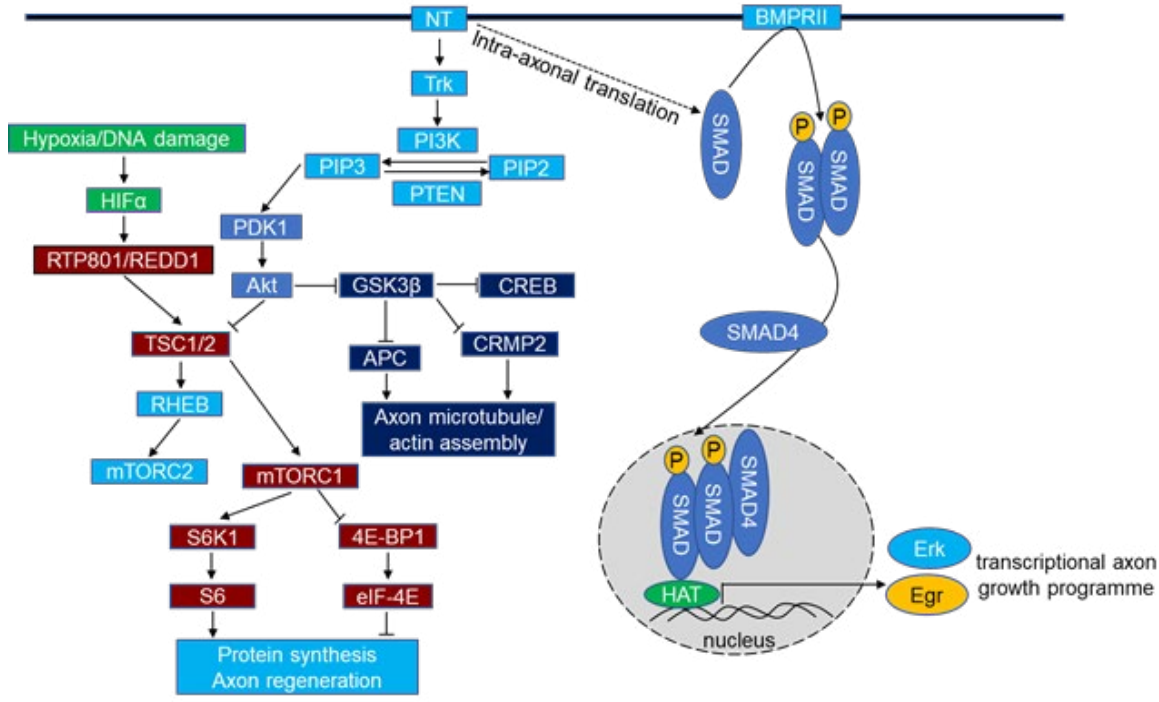

Figure 1: Crosstalk of neurotrophin and BMP signalling in RGCs. Neurotrophins (NTs) act on tyrosine kinase (Trk) receptors and activates phosphatidylinositol kinase (PI3K) activity that converts phosphatidylinositol (4,5) bisphosphate (PIP2) to phosphatidylinositol (3,4,5) triphosphate (PIP3), an effect that is reversed by phosphatase and tensin homolog deleted on chromosome 10 (PTEN). PIP3 then activates phosphatidylinositol-dependent protein kinase 1 (PDK1) and Akt, inhibiting tuberous sclerosis complex (TSC1/2). TSC1/2 can stimulate the Ras homolog enriched in the brain (Rheb) to upregulate mTOR activity. Akt also inhibits GSK3β, which in turn disinhibits CREB-mediated NT transcription, adenomatous polyposis col (APC), and collapsing response mediator protein 2 (CRMP2) to promote growth cone assembly. Bone morphogenetic proteins (BMPs) normally signal through C-terminal phosphorylation of small mothers against decapentaplegic homolog 1 (Smad1), which then makes nuclear entry and regulates transcription of downstream axogenic growth programs (e.g. Extracellular signal-related kinase 1 (Erk1) and Erk2). NT such as brain-derived neurotrophic factor (BDNF) can activate intra-axonal translation of Smads which are then translocated to the soma to be activated by BMP signalosomes, connecting retrograde signalling of BDNF and BMP.

survival [37,38]. The two isoforms of GSK3 are not functionally identical and redundant, despite sharing a high degree of similarity and functional overlap. For example, GSK3β plays a prominent role in the CNS and regulates neuronal development, neurogenesis, neuronal migration, differentiation and survival. GSK3beta is constitutively active in resting cells and undergoes rapid phosphorylation, which regulates its function. Phosphorylation at tyrosine 216 (Tyr216) confers full activity of GSK3β, whilst phosphorylation of serine 9 (Ser9) inhibits GSK3β activity. Ser9 phosphorylation is the most common regulatory mechanism for GSK3β, with many kinases including p70 S6 kinase, extracellular signal-regulated kinases (ERKs), p90RSK (also called MAP-MAP kinase-1), protein kinase B (also called Akt), certain isoforms of protein kinase C (PKC) and cyclic AMP-dependent protein kinase (protein kinase A, PKA), phosphorylating Ser9.

The role of GSK3 in CNS axon regeneration, including optic nerve regeneration, is controversial. Some report that GSK3 activity is required for axonal growth or myelin disinhibition, others report that the opposite is true [39-43]. These reported differences may be due to factors including cell types studies, neuronal age, the axon environment and the fact that GSK3 has diverse functions in nerve regeneration. Collapsin response mediator protein 2 (CRMP2), which is normally inhibited by GSK3-mediated phosphorylation, promotes microtubule polymerisation and myelin disinhibition, whilst microtubule associated protein 1B (MAP1B), is directly phosphorylated by GSK3 and promotes axon growth. In addition, expression of non-physiological levels of either isoforms of GSK3, mainly GSK3β, may be detrimental since compensation by GSK3α and vice-versa can occur. Indeed, peripheral nerve regeneration was accelerated by elevated GSK3 activity using the phosphorylation resistant GSK3α^{S21A}/βS9A [GSK3(α/β)S/A] double knock-in mouse strains, an effect which was based on phosphorylated MAP1B-associated inhibition of microtubule detyrosination and subsequent increase in microtubule dynamics in axonal growth cones. Using this transgenic mouse plus RGC specific GSK3α and GSK3β knockout mice, elevation of GSK3 activity in GSK3$^{S/A}$ mice was compromised whilst GSK3β knockout mice potentiated inflammatory-stimulation-mediated RGC axon regeneration [43]. Rapamycin-mediated inhibition of mTOR has no effect on GSK3β activation, but inhibition of GSK3β activates mTOR in cultured dorsal root ganglion neurons, probably by releasing the tuberous

sclerosis complex 1 (TSC1) from direct GSK3β-dependent activation [44].

Therefore, we hypothesised that suppression of GSK3β activity in RGC may enhance RGC survival and axon regeneration. We showed that knockdown of GSK3β using translationally relevant short interfering RNA (siRNA; siGSK3β) in adult mixed retinal cultures promoted significant RGC survival and the number of RGC with neurites (i.e. growth initiation) but did not affect neurite length (i.e. neurite elongation), effects that were sensitive to Rapamycin (i.e. mTOR-mediated) [45]. In agreement with this, knockdown of GSK3β *in vivo* promoted significant RGC survival and modest RGC axon regeneration. Our study therefore suggested that GSK3β not only promoted RGC survival but also axon regeneration.

The role of GSK3β in promoting neuroprotection is controversial, with a dual regulation identified suggesting that GSK3β not only promotes the intrinsic apoptotic pathway but also inhibits the extrinsic apoptotic pathway (Figure 2) [46-53]. In the intrinsic apoptotic pathway, GSK3 is pro-apoptotic and acts on Bax, Bim and Bid causing mitochondrial depolarisation and release of cytochrome c which then activates apoptosis. Conversely, GSK3 prevents death inducing signalling complex (DISC) formation and prevents apoptosis by the extrinsic pathway. In addition, inhibition of GSK3β not only protects against glutamate-induced NMDA-receptor-mediated toxicity but also suppresses the up-regulation of pro-apoptotic dynamin-related protein (Drp1) in the retina [54-56]. Lithium-induced inhibition of GSK3β also protects against axotomy-induced RGC death, despite enhancing mTOR activity, an effect that was sensitive to Rapamycin and mediated through phosphorylated S6 (pS6) [5,57]. Interestingly, most pS6^{+} RGC are melanopsin^{+} ipRGC and hence are resistant to apoptosis, suggesting that inhibition of GSK3β likely mediates neuroprotection of non-ipRGCs.

Despite the role of GSK3β in axon regeneration being controversial, our results demonstrated that inhibition of GSK3β is important for both RGC growth initiation and axon elongation. Others have shown that inhibition of GSK3β after nerve growth factor activation of the PI3K-Akt pathway was required for axon growth, but our study agrees with the observation that Akt-induced phosphorylation of GSK3β may not be the sole determinant of GSK3β activity [58]. GSK3β is a key axogenic factor and regulates *ntf* gene expression and phosphorylation of axon growth substrates such as the nuclear factor of activated T cells (NFAT), CREB

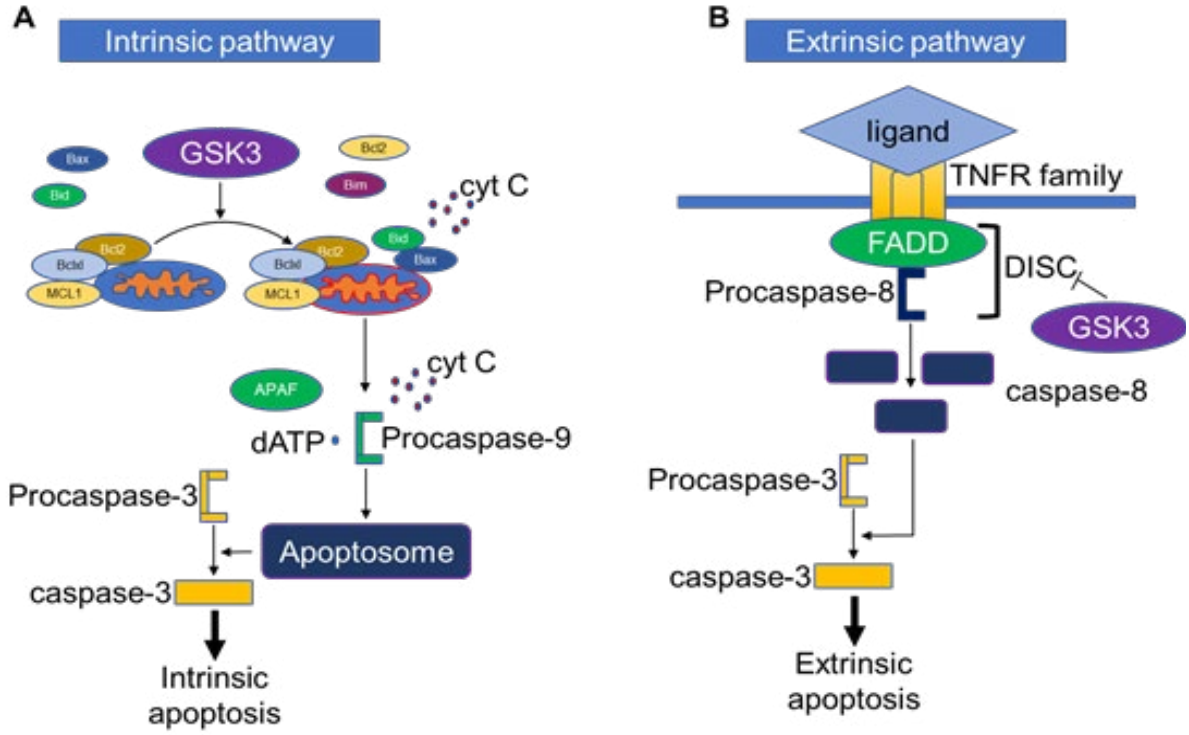

Figure 2: GSK3 has opposite effects in the intrinsic and extrinsic apoptotic pathways. A. Mitochondria lose their integrity and release cytochrome C (cyt C) which then bind to apoptotic protease activating factor (APAF), adenosine triphosphate (ATP) and procaspase-9, forming the apoptosome and activation of the intrinsic death pathway. GSK plays a pro-apoptotic role by activating the formation of the apoptosome and eventual apoptosis. B. Ligand binding to tumor necrosis factor receptor (TNFR) family such as TNFR, Fas, death receptor (DR)4 and DR5 all activate trimerization of the receptor to which Fas-associated death domain (FADD) and procaspase-8 can bind. This promotes the formation of the death inducing signalling complex (DISC), leading to activation of effector caspases and completion of extrinsic apoptosis. GSK3 inhibits the formation of the DISC by associating with death receptor and so prevents activation of the extrinsic apoptotic pathway.

and β-catenin [59-61]. Our results demonstrated that inhibition of GSK3β altered pCRMP2 levels downstream of RhoA/ROCK whilst others have shown that inactivation of CRMP2 inhibits microtubule polymerisation resulting in axon growth cone collapse [62-64]. Although MAP1B is normally activated after GSK3β-dependent phosphorylation, leading to axon growth cone advance [61,65], our results showed that MAP1B did not play a major role in siGSK3β dependent RGC axon regeneration.

GSK3β also regulates axon growth cone microtubule dynamics and is implicated in growth cone collapse induced by CNS myelin- and scar-derived inhibitory molecules [66,67]. Although RGC growth is normally inhibited by myelin associated axon growth inhibitory molecules such as myelin associated glycoprotein (MAG), Nogo and chondroitin sulphate proteoglycans (CSPG), inhibition of GSK3β reversed RGC neurite outgrowth in the presence of inhibitory concentrations of Nogo-peptide substrates, thus agreeing with previous observations [68,69]. Conversely, overexpression of GSK3β attenuates myelin-dependent axon growth inhibition whilst GSK3β inhibitors neither promotes nor represses neurite outgrowth in the presence of CNS axon growth inhibitors [41]. These seemingly discrepant studies can be reconciled by a model where inhibition of GSK3β can both enhance and prevent axon growth depending on the substrates involved [70].

Many substrates of GSK3 normally require phosphorylation by a distinct kinase, an event called priming, before they can be phosphorylated by GSK3. Some of the substrates of GSK3 regulate microtubule assembly at the growth cone. These include APC and CRMP2, which are primed substrates, and GSK3 phosphorylation abrogates their microtubule binding affinity [50,71]. Dephosphorylated CRMP2 and APC are enriched in the growth cone and promote axon formation and NT-induced axon growth [71,72], whilst inhibition of GSK3 activity, specifically towards primed substrates [73,74] results in reduced CRMP2 phosphorylation and increased axon outgrowth [70]. In contrast, MAP1b is an unprimed substrate, which can be phosphorylated by GSK3 [75], promoting microtubule dynamics and allow efficient probing of the intracellular space and their ability to respond to extracellular signals, all of which are essential for axon growth [65,76]. Thus, a working model proposes that preferential suppression of GSK3 activity towards primed substrates promotes axon growth, whereas inhibition towards unprimed substrates blocks axon growth (Figure 3) [70]. In this way, GSK3 can coordinate essential properties of axonal microtubules to ensure optimal microtubule assembly in axons during axon regeneration.

GSK3 can also regulate axon regeneration by transcriptional control via the β-catenin and NFAT transcription factors. For

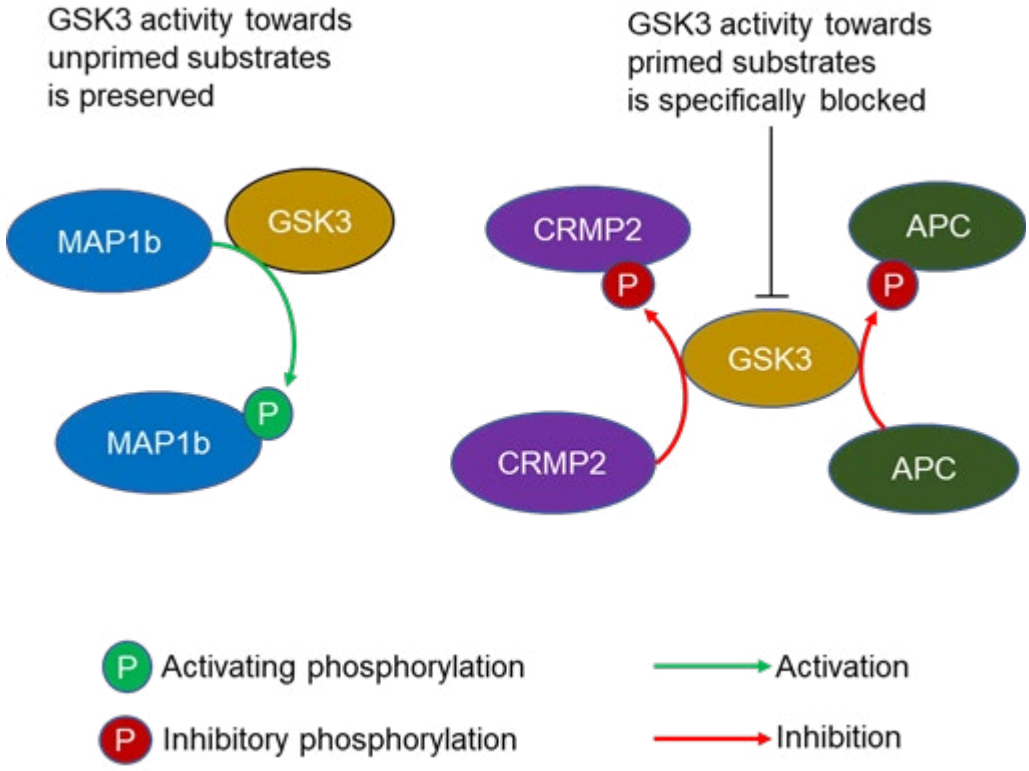

Figure 3: Differential regulation of GSK3 substrates during axon regeneration. During axon regeneration, GSK3 activity towards primed substrates is blocked while its activity towards unprimed substrates is preserved. Inhibition of GSK3 activity towards collapsin response mediator protein (CRMP) 2 and adenomatosis polyposis coli (APC) allows CRMP2 and APC to bind microtubules, thereby increasing microtubule polymerization and stability. In contrast, GSK3's activity towards microtubule-associated protein (MAP) 1b is preserved in the growth cone and maintains microtubules in a dynamic state, promoting axon growth.

example, Wnt3a induces axon growth from developing sensory neurons via accumulation of β-catenin and subsequent activation of TCF4 [77]. Since CREB is a well-established transcription factor downstream of neurotrophins, deletion of CREB in *Creb* null mice display impaired axon growth [78]. Neurotrophins and netrins also induce the transcription of axon growth promoting genes triggering nuclear translocation of NFAT, which is required for axon growth [79].

In conclusion, it is clear that the activity of GSK3 is controlled *via* protein-protein interactions and considering the number of substrates that interact with GSK3, the regulation appears complex and dynamic. Some substrates of GSK3 require priming before they can be phosphorylated by GSK3 while others do not require priming, adding to its complexity but also its specificity. Further work will be required to determine the contribution of GSK3 in CNS neuroprotection and axon regeneration.

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