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Review

Prospects for mTOR-mediated functional repair after central nervous system trauma

Martin Berry, Zubair Ahmed *, Peter Morgan-Warren, Daniel Fulton, Ann Logan

Neurotrauma Research Group, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

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ABSTRACT

Recent research has suggested that the growth of central nervous system (CNS) axons during development is mediated through the PI3K/Akt/mammalian target of rapamycin (mTOR) intracellular signalling axis and that suppression of activity in this pathway occurs during maturity as levels of the phosphatase and tensin homologue (PTEN) rise and inhibit PI3K activation of mTOR, accounting for the failure of axon regeneration in the injured adult CNS. This hypothesis is supported by findings confirming that suppression of PTEN in experimental adult animals promotes impressive axon regeneration in the injured visual and corticospinal motor systems. This review focuses on these recent developments, discussing the therapeutic potential of a mTOR-based treatment aimed at promoting functional recovery in CNS trauma patients, recognising that to fulfil this ambition, the new therapy should aim to promote not only axon regeneration but also remyelination of regenerated axons, neuronal survival and re-innervation of denervated targets through accurate axonal guidance and synaptogenesis, all with minimal adverse effects. The translational challenges presented by the implementation of this new axogenic therapy are also discussed.

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1. Introduction

Recent research aimed at promoting axon regeneration in the injured central nervous system (CNS) has achieved impressive regrowth of long axonal tracts by activation of the phosphatidylinositol/protein kinase B/mammalian target of rapamycin intracellular signalling pathway (PI3K/Akt/mTOR; mTOR is used throughout as an inclusive term for mTORC1 and mTORC2 — abbreviations of all signalling molecules are given in Fig. 1) (reviewed by Liu et al., 2011; Kanno et al., 2012; Aruni et al., 2012; Maiese et al., 2013; Maiese, 2014; Lu et al., 2014a). These and others studies attribute the poor prognosis for functional restitution to suppression, at around birth, of developmental mTOR-mediated neuroprotection and axogenic protein synthesis (Park et al., 2008, 2010; He, 2010; Pernet and Schwab, 2014). This proposition predicts that treatments which re-establish the sensitivity of the PI3K/Akt pathway to growth factor activation in maturity augur well for the restoration of function in CNS trauma patients.

* Corresponding author.
E-mail address: z.ahmed.1@bham.ac.uk (Z. Ahmed).
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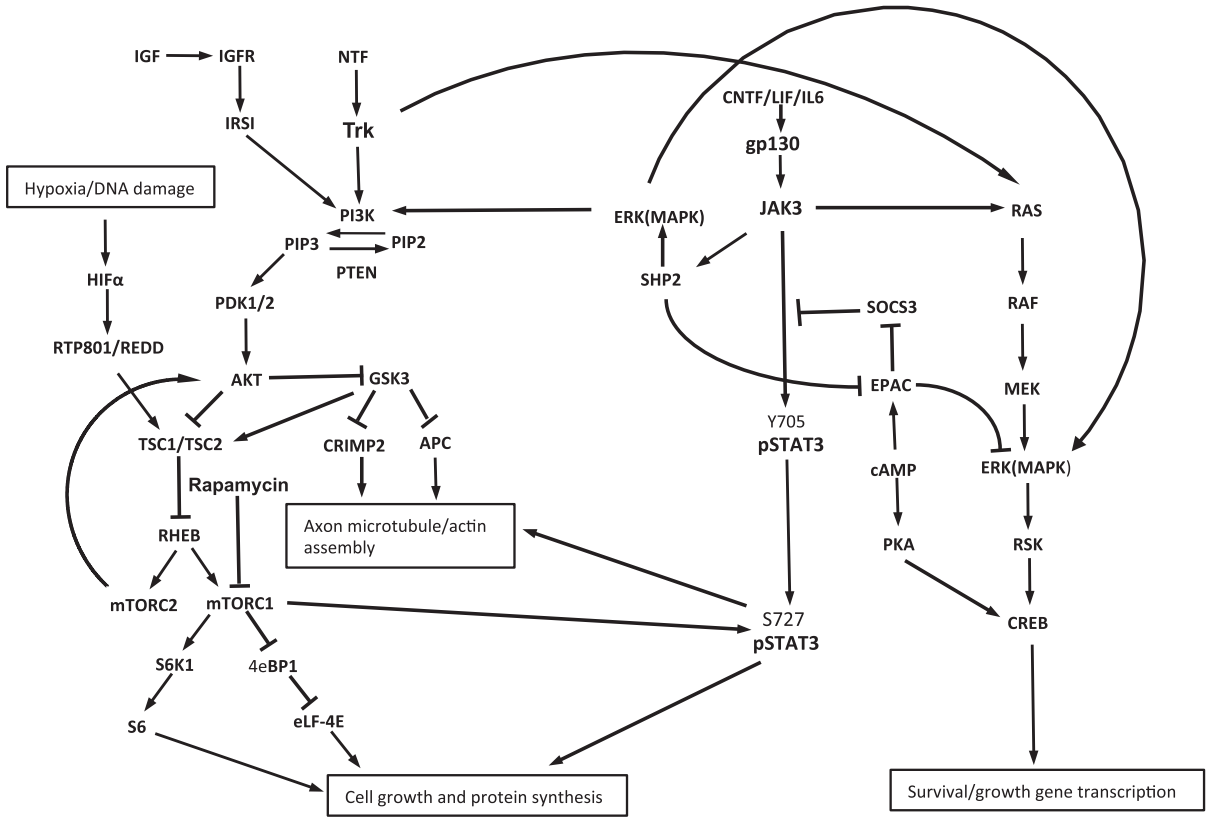

Fig. 1. Activators of the mTOR axogenic pathway. Tyrosine receptor kinase (Trk) receptors bind neurotrophic factors (NTF) including nerve growth factor (NGF)/brain-derived neurotrophic factor (BDNF)/neurotrophin 3/4 (NT3/4) which in turn activate the Trk/PI3K/Akt pathway; hypoxia, DNA damage and stress activate the HIF/RTP801/TSC pathway downstream of Akt; and the gp130 receptor complex binds the cytokines leukaemia inhibitory factor (LIF), interleukin 6 (IL6) and ciliary neurotrophic factor (CNTF), and activates the janus kinase (JAK)/signal transducers and activators of transcription (STAT), cAMP and RAS/CREB pathways (Akt — serine/threonine kinase; APC — adenomatous polyposis coli microtubule plus-end-binding protein; CREB — cAMP response element binding protein; CRMP — collapsin response mediator protein; eIF4E — eukaryotic initiation factor 4E; 4E-BP1 — eIF4E binding to protein 1; Epac — exchange protein directly activated by cyclic adosine mono-phosphate (cAMP); ERK — extracellular signal-regulated kinase; GSK3β — glycogen synthase kinase 3β; HIFα — hypoxia inducible factor alpha; IGF — insulin-like growth factor; IGFR — IGF receptor; IRS1 — insulin receptor substrate 1; MAPK — mitogen-activated protein kinase; MEK — MAPK/ERK kinase; mTORC1 — mTOR (mammalian target of rapamycin) + Raptor (regulatory association protein to mTOR) + GβL-G (protein β-subunit-like protein); mTORC2 — mTOR + Rictor (rapamycin independent companion of mTOR) + GβL + Sin1; PDK1/2 — phosphatidylinositol-dependent kinase 1/2; PI3K — phosphatidylinositol 3-kinase; PIP2 — phosphatidylinositol (3,4) bisphosphate; PIP3 — phosphatidylinositol (3,4,5) trisphosphate; PKA — protein kinase A; SHP-2 — a Src homology 2 (SH2) domain containing non-transmembrane PTP; PTEN — phosphatase and tensin homologue; RAF — proto-oncogene serine/threonine–protein kinases; REDD/RTP801 — regulated in development and DNA damage response protein; RAS — rat sarcoma protein; RHEB — Ras homologue enriched in brain protein; RSK — 40S ribosomal protein S6 kinase; S6K1 — p70 ribosomal protein S6 kinase 1; S6 — ribosomal protein S6; S727 — phosphostat3 serine 727; SOCS3 — suppressor of cytokine signalling 3; TSCI/2 — tuberous sclerosis complex 1/2; Y705 — phosphostat3 tyrosine727).

During mammalian CNS development, the viability of neurons and growth of axons is supported by neurotrophic factors (NTF) such as: (i), neurotrophins (NT) including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophic factor 3 (NT3), and NT4/5, which activate the PI3K/Akt intracellular signalling pathway after engaging tyrosine kinase receptors (Trk); and (ii), cytokines such as ciliary neurotrophic factor (CNTF), interleukin-6 (IL-6) and leukaemia inhibitory factor (LIF) all of which bind to the trimeric gp130 receptor complex and activate PI3K through JAK/SHP2 signalling (Heinrich et al., 2003; Park et al., 2004; Müller et al., 2007, 2009) — negatively regulated by suppressor of cytokine signalling 3 (SOCS3) (Nicholson et al., 2000) (Fig. 1). The PI3K/Akt pathway controls cell survival and axogenic protein synthesis (reviewed by Fonseca et al., 2014) through mTORC1 and also cytoskeletal growth cone dynamics by modulation of GSK3β activity (Zhou and Snider, 2005; Liu et al., 2012), potentiated through the mTORC2/Akt loop. CNS axon growth declines during maturation, possibly through suppression of NTF responsiveness engendered by a progressive up-regulation of the PI3K antagonist, phosphatase and tensin homologue (PTEN), a decline in IL-6 secretion by astrocytes and neurons (Codeluppi et al., 2014), a rise in the ratio of repressors:enhancers of transcriptional axon growth Kruppel-like factors (KLF) (Arlotta et al., 2005; Moore et al., 2009), and soaring titres of scar- and myelin-derived axon growth inhibitory factors (AGIF), the potency of which is enhanced by a postnatal decline in intracellular cAMP (Shewan et al., 2002; Peace and Shewan, 2011; Cai et al., 2001). Further suppression of mTOR is induced in mature CNS neurons after axotomy (Liu et al., 2010; Park et al., 2010) but *pten* gene deletion re-activates the PI3K/Akt pathway promoting new axon growth and additional NTF/cytokine priming may be required to initiate axon sprouting (Leibinger et al., 2012; Fischer and Leibinger, 2012; Lee et al., 2014).

Because of the cellular omnipresence of the mTOR pathway, many phenotypes in the CNS are affected indiscriminately by mTOR-related treatments unless cell targeting techniques are employed. The cellular functions of mTOR include the regulation of metabolism, growth, proliferation and viability (Laplante and Sabatini, 2009; Dibble and Cantley, 2015) and the uncontrolled dysregulation of any of these responses could provoke potentially deleterious side effects in the CNS. In experimental animals, Cre/loxP recombination and delivery of DNA and si/shRNA PI3K/Akt/mTOR therapies to neurons is achieved using phenotypic promoters and neurotropic adeno-associated virus (AAV) serotypes with minimal effects on non-neuronal cells. However, although genes may be successfully targeted to particular neurons using phenotypic promoters (e.g. Thy1 for RGC), AAV vector neurotropism is age-dependent and not absolute (Harvey et al., 2002; Aschauer et al., 2013; Gholizadeh et al., 2013) and may lead to potentially deleterious

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