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SIGNAL TRANSDUCTION

Deleting PTEN for better or worse

Manipulating neurogenesis could have a role in the treatment of both neurodevelopmental disorders and neurodegenerative diseases. Two new studies show that PTEN (phosphatase and tensin homolog) and its downstream signalling pathway might be promising targets for developing such treatments.

PTEN regulates neurogenesis by inhibiting the phosphoinositide 3-kinase (PI3K)–AKT signalling pathway; AKT phosphorylates tuberous sclerosis complex (TSC) 1/2, preventing it from suppressing mammalian target of rapamycin complex 1 (mTORC1). Previous studies showed that mice lacking *Pten* in neurons have enlarged brains and behavioural abnormalities that resemble those seen in people with autism. Parada and colleagues investigated whether manipulation of the PI3K–AKT pathway could reverse the effects of PTEN loss.

Daily administration of the mTOR1 inhibitor rapamycin for 4–6 weeks to young (5–6 week-old), presymptomatic *Pten*-mutant mice prevented hippocampal and cortical hypertrophy and dendritic overgrowth as well as the loss of neuronal polarity (which can result in ectopic axonal projections) in hippocampal granule cells. In adult (10–12 week-old), symptomatic mutant mice rapamycin significantly reversed the neuronal hypertrophy in and enlargement of the dentate gyrus, but not the loss of polarity. The treatment also prevented the development of increased anxiety and abnormal social behaviour and the occurrence of spontaneous seizures. Finally, the authors showed that *Tsc1*-knockout mice had an increased brain/body weight ratio and cortical and hippocampal hypertrophy similar to that of *Pten*-knockout mice, providing more evidence that the PI3K–AKT–mTOR pathway mediates the effects of *Pten* ablation.

Although *Pten* deletion during development clearly has deleterious effects, Wu and colleagues investigated whether *Pten* ablation in adult mice could be used to stimulate adult neurogenesis and repair. The authors created mice in which *Pten* was deleted in adult neural stem cells in the subependymal zone (SEZ). Compared with control mice, these mice had an enlarged SEZ containing more neuroblasts that expressed Ki-67 and doublecortin (markers of proliferation and migrating neuroblasts, respectively), indicating that *Pten*-deleted neural stem cells could proliferate and differentiate. Using bromodeoxyuridine labelling to track the progenitor cells, the authors found that, like control cells, the mutant cells migrated along the rostral migratory stream. Moreover, the granule cell layer of the olfactory bulb was enlarged in the mutant mice, indicating that the progenitors had migrated into the appropriate layer of the bulb. The mutant granule cells were functional: conditional *Pten*-deleted mice showed normal olfactory discrimination and habituated faster than controls to novel odours.

The authors next investigated whether these effects could be harnessed to repair neuronal damage. Chemical ablation of the olfactory sensory epithelium resulted in impaired odour detection in both control and conditional *Pten*-deleted mice. However, the mutant mice showed faster recovery from this impairment after 6 weeks. In an ischaemic-stroke model, more doublecortin-positive cells were found around the infarct site in mutant mice than in control mice. However, bromodeoxyuridine staining revealed that 90 days after the stroke, the number of newborn neurons in the site no longer differed between control and mutant mice, indicating that *Pten* deletion promotes post-stroke adult neurogenesis and migration to the injury site, but not long-term survival of neurons.

These studies show that PTEN and its downstream signalling pathway might be promising targets for treatments aimed at boosting neural stem cell proliferation in neurodegenerative diseases and at reversing symptoms of neurodevelopmental disorders that are associated with dysregulated neurogenesis.

Leonie Welberg

ORIGINAL RESEARCH PAPERS Zhou, J. *et al.* Pharmacological inhibition of mTORC1 suppresses anatomical, cellular, and behavioral abnormalities in neural-specific *Pten* knock-out mice. *J. Neurosci.* **29**, 1773–1783 (2009) | Gregorian, C. *et al.* *Pten* deletion in adult neural stem/progenitor cells enhances constitutive neurogenesis. *J. Neurosci.* **29**, 1874–1886 (2009)