Nature Reviews Drug Discovery | Published online 31 Dec 2015; doi:10.1038/nrd.2015.27

STROKE

GDF10 spurs on axonal sprouting after stroke

Following a stroke, the human brain has a limited capacity for repair. Whereas most research in this field has focused on the signalling molecules that prevent greater recovery, the factors responsible for the small amount of neural regrowth that does occur after stroke have been largely unstudied. Now, a paper in *Nature Neuroscience* highlights growth and differentiation factor 10 (GDF10) as an important signal for axonal sprouting in cortex adjacent to the infarct and for functional recovery after stroke.

GDF10 is a secreted growth factor that signals through transforming growth factor-β (TGFβ) receptor. The authors of the current study had previously used transcriptional profiling to show that GDF10 is highly upregulated in sprouting neurons after stroke in rat models.

Natallia Khlapushyna/Alamy Stock Photo

Using microarray analysis and immunohistochemistry, the investigators found increased expression of GDF10 in the peri-infarct cortex in mice, macaques and human post-mortem tissue. *In vitro*, addition of GDF10 enhanced axonal outgrowth of mouse primary cortical neurons. Conversely, application of *Gdf10*-specific short interfering RNA inhibited the growth of axons.

To test for these effects in human cells, the team used neurons derived from human induced pluripotent stem cells. GDF10 promoted marked outgrowth of axons of these cells, and the effects were prevented by blocking TGFβ receptor signalling. Moreover, knockdown of *Smad1* and *Smad2*, which signal downstream from TGFβ receptor, also blocked the growth-promoting effects of GDF10.

Next, the authors examined the effect of GDF10 delivery in forelimb motor cortex in mice following a stroke in this brain region. GDF10 was administered via a biopolymer hydrogel injected into the stroke cavity 7 days after stroke, to produce sustained release over 2–3 weeks at the stroke site. Cortical injection of a neuronal tracer 3 weeks later enabled visualization of newly made neuronal connections. Compared with mice that received control protein after stroke, mice that received GDF10 showed a marked increase in neuronal projections.

In addition to the effects on neuron growth, GDF10 administration increased astrogliosis and blood vessel area in the peri-infarct area, whereas *Gdf10*-knockdown decreased microglial staining. These findings indicate that GDF10 signalling has a broad range of effects after stroke.

Importantly, the beneficial effects of GDF10 at the cellular level translated into functional improvements. Mice that underwent stroke in the forelimb motor cortex showed impairments in three tests of forelimb motor control for 11–15 weeks. However, administration of GDF10-loaded hydrogel at 1 week after stroke restored motor performance to that of non-stroke mice within 4 weeks.

Given that the only approved pharmacotherapy for stroke, tissue plasminogen activator, must be administered within 4.5 hours of infarction, the ability of GDF10 to promote recovery in mice when given a week after stroke is a particularly appealing property. The authors note that short-lived or local delivery would be needed to avoid possible harmful effects of systemic GDF10 exposure, such as fibrosis.

Katie Kingwell

ORIGINAL ARTICLE Li, S. *et al.* GDF10 is a signal for axonal sprouting and functional recovery after stroke. *Nat. Neurosci.* **18**, 1737–1745 (2015)