proteinspotlight
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Issue 69, April 2006

www.proteinspotlight.org

Nipped by a no-go

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Injury to the adult central nervous system (CNS) and neurodegenerative diseases often engender lifelong consequences to the organism. Could the key to the mysteries of nerve regeneration lie concealed in the amino terminus of a notorious protein? Independent research groups working on either side of the Atlantic have answered in the affirmative. Indeed, the legendary inability of neurons to regenerate and repair lesions in the adult CNS can be attributed to a battery of inhibitory and repellent proteins, one of which - dubbed Nogo - is released by nerve fibres following injury.

What do stroke, post-traumatic epilepsy and spinal cord paralysis have in common? All three are neurological conditions that can be imputed to the inability of neurons to repair damage in the adult brain and spinal cord. Adult CNS neurons stop growing once neuronal networks are established. Upon lesion, they fail to find a way out of this deadlock, which results in functional deficit. *"Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated"* wrote the Spanish neuroscientist Santiago Ramón y Cajal (1852-1934), more than a century ago in his treatise on nerve regeneration. Ever since its inception, the dogma regarding the lack of regeneration in the adult CNS had left scientists bewildered – until the day it was evinced what it was that balked these nerve cells. Surprisingly, it is the neurons' own protection – the myelin sheath wrapped around their axon – which releases factors that themselves inhibit repair upon injury. A molecular catch-22!

One of these factors, Nogo – a myelin-associated protein – jealously guards the sentinels of regeneration by curbing growing neuritis – the tiny neuronal extensions that burgeon and make electrical contacts. First described by the group of Martin Schwab at the University of Zurich in 1990, Nogo has since been cloned and characterised. Competing neck-to-neck with his American counterparts in a fervent race to clone the inhibitory molecule, the Swiss neuroscientist completed it at the same time as his contenders and named it Nogo, after the customary "go" and "no go" commands used in behavioural tests involving primates. An amino-terminal cytosolic fragment of Nogo and a 66-amino acid extracellular loop are both capable of independently blocking the outgrowth of neurites and the spreading of neurons.

'Senegalese cripple in wheelchair'
Nicholas D. Wolfson

Courtesy of the artist

How exactly does Nogo manage to keep axon-sprouting at bay? A quick look at the molecular mechanism reveals that – like most inhibitory ligands – Nogo accomplishes such a feat by way of its cognate receptor: Nogo-66 receptor. Nogo-66 receptor is a lipid-anchored protein found in the membrane of the axon, which transduces the no-go signal to the axon and

stymies its efforts to sprout. The identification of the receptor came as a groundbreaking revelation in the field of CNS injury. Indeed, Nogo-66 receptor is promiscuous and able to respond simultaneously to other inhibitory signals besides Nogo, thus amplifying the inhibition.

Further inhibitory signals are provided by other myelin inhibitors which perform a complex arabesque, along with Nogo, in engaging its receptor. And as in most, if not all, biological systems, a host of proteins orchestrate to produce, relay and enhance the message to the neuron. In order to facilitate this co-operation, receptor and co-receptor stay in proximity – thick as thieves – and segregate to lipid-rich regions in the axonal membrane, termed rafts. The web tightens around the axon as the signal is accentuated and axon repellent molecules in the CNS – whose normal function is to guide axons to their right destinations – start firing cues which stimulate the no-go signal… The consequence of these molecular events is a collapse of the growth cone – a structure that serves as a platform for axon regeneration. The fate of the axon is now sealed.

Why has Nature preserved a self-defeating strategy? Why is the regeneration of nerves following injury prevented? The answer lies in the complex regulatory mechanism the adult CNS deploys in order to pre-empt any uncontrolled or haphazard rewiring. Once development is complete, it is important that the axons of nerve cells remain terminally branched; any unwarranted sprouting might lead to neuronal connections going haywire. Terminal branching has to be checked, and scientists believe that molecules such as Nogo act as watchdogs.

Needless to mention, Nogo is in the limelight for therapeutic approaches to CNS injury and has been, for several years, the focus of fierce scientific parley. Several lines of evidence have demonstrated that the suppression of Nogo can open the floodgates to regenerating axons; a number of attempts have proven effective in rats and monkeys. Indeed, when function-blocking antibodies to Nogo were infused into rats whose spinal cords had been artificially cut, regeneration was restored. What is more, the rats could swim, and cross not only a narrow beam but also the rungs of a ladder without slipping. Similar results have been observed in monkeys whose spinal cords had been partially damaged experimentally. Currently, antibodies to Nogo are being tested in human clinical trials. Some scientists claim that blocking the receptor would be more effective.

Although there is hope for anti-Nogo antibodies as “walk again” drugs, an effective therapy is likely to be multi-pronged – the game of adult CNS regeneration has many players. It is likely that a successful approach would not only suppress the inhibitory function of several factors to axon regeneration but would actually increase their innate regenerative capacity. Concluding a passage in his two-volume opus on the lack of central nervous regeneration, Cajal wrote, *“It is for the science of the future to change, if possible, this harsh decree.”* Decades later, it appears his dream is coming true.

Cross-references to Swiss-Prot

Nogo protein, *Homo sapiens* (human): Q9NQC3
Nogo-66 receptor, *Homo sapiens* (human): Q9BZR6

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Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).