A survival factor for axons: roles in disease and downstream mechanism

https://neurodegenerationresearch.eu/survey/title-of-pia-survival-factor-for-axons-roles-in-disease-and-downstream-mechanism/

Title of project or programme

Title of PI A survival factor for axons: roles in disease and downstream mechanism

Principal Investigators of project/programme grant

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- United Kingdom

Source of funding information

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876504.92

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36

The project/programme is most relevant to

- Neurodegenerative disease in general

Keywords

Research abstract in English

In neurodegenerative disorders axons typically degenerate before neuronal cell death. This sequence of events, and particularly the early loss of distal axons, is known as ‘dying back’ degeneration. The causes of axon degeneration include protein aggregation, inflammation, neurotoxicity and ischaemia, and many of these diverse stresses converge on a common degenerative pathway involving axonal transport impairment. Axonal transport is the bidirectional trafficking of molecules and organelles along axons for huge cellular distances. It is essential for axon survival but deficient in multiple sclerosis, glaucoma, motor neuron disease and many other disorders.

Despite the prevalence of axonal transport impairment, the specific molecular changes leading to axon degeneration are poorly understood. Cutting axons, which causes Wallerian degeneration, is a useful experimental model that can help identify the key molecular events. A mutant protein named Wallerian degeneration slow (WldS) delays Wallerian degeneration by tenfold and alleviates some ‘dying back’ disorders, showing that the mechanisms are related. Thus, axons do not die by passive wasting when isolated from cell bodies but by a specific and regulatable process.

WldS is an aberrant protein that occurs naturally in only one strain of mouse, so until now it has been largely unclear how we might use it to protect axons in human disease. Recently, we identified the NAD+ synthesising enzyme Nmnat2 as an endogenous regulator of the same pathway in primary neuronal cultures. Nmnat2 is an unstable protein, so if axonal transport fails to replenish it, continual protein turnover in axons takes Nmnat2 below a threshold level that triggers Wallerian degeneration.

Nmnat2 is now the key to understanding the degenerative mechanism and thereby identifying suitable steps to target pharmacologically, but for the full picture it must also be studied in vivo. We hypothesise that depleting Nmnat2 is sufficient to initiate Wallerian-like degeneration in vivo and that failure to deliver it to distal axons in some axonopathies is the direct cause of ‘dying back’ axon loss. We also hypothesise that Nmnat2 and WldS control a common downstream pathway, which we can activate very specifically by removing Nmnat2. Thus, we can now factor out the many non-specific consequences of cutting axons or of blocking axonal transport, and focus specifically on events leading to axon degeneration. This is a unique opportunity to move towards translation for axonal transport disorders and for significant progress in understanding how axon survival and degeneration are controlled at the molecular level.

Lay summary
In which category does this research fall?

- Basic research