

MODULATION OF THE DLK/JNK PATHWAY AS A METHOD FOR INHIBITING AXONAL DEGENERATION

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Background: Axonal degeneration is a feature commonly associated with many neuropathological conditions including response to injury, exposure to neurotoxins, hereditary neuropathies, glaucoma, and neurodegenerative diseases. The degenerative process is active when neuronal insults trigger a self-destruction mechanism within the axon; however the molecular pathway in the neuron that promotes axonal degeneration is unknown. The identification of a molecular pathway and pharmacological agents that protect axons from degeneration may be of therapeutic benefit in a wide range of neurological disorders.

Technology Description: The MAP kinase DLK and its downstream MAP kinase JNK have been identified as key components of the pathway promoting axonal degeneration. Genetic deletion of DLK in mice, pharmacological inhibition of mixed lineage kinases such as DLK, and pharmacological inhibition of JNK all delay axonal degeneration of dorsal root ganglion (DRG) neurons in response to axotomy. The DLK mutant also inhibits the in vitro degeneration of DRG axons in response to the chemotherapeutic agent vincristine, whose dose-limiting side effect is axonal degeneration. Finally, the mouse DLK mutant also shows delayed degeneration in vivo following transection of the sciatic nerve. The most novel aspects of this study are the identification of the first components in the endogenous neuronal pathway that triggers axonal degeneration, identification of both genetic and pharmacological interventions that inhibit axonal degeneration, and demonstration that this pathway is relevant both in vitro and in vivo. Inhibition of this pathway has therapeutic potential as a treatment for the many neurological disorders in which axonal degeneration is a prominent feature.

Key Advantages:

- Can allow for higher doses of chemotherapeutic agents, such as vincristine, to be administered to cancer patients, without inducing peripheral neuropathy.
- Can protect axons and neuronal function following injury; slow the progression of early onset axonal loss in cases of peripheral neuropathies and neurodegenerative diseases, and can preserve retinal ganglion cell axons and vision in glaucoma patients.
- Pharmacological treatment has shown efficacy in vitro and in vivo, providing support for further clinical trials.