Method to Express Regenerative Proteins in Spinal Cord Injured Axons

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Technology description

Spinal cord injury and other traumatic axonal injuries have very few avenues of treatment. A major goal of therapy is to promote axonal growth and regeneration, with the ultimate goal of improving motor and sensory function in patients. Few therapeutic options are available outside the high doses of methylprednisolone administered after injury. Stem cell transplants and neurodegenerative substances have been proposed, but validated results are lacking.

Gene therapy strategies that increase the expression of axonal regeneration-promoting proteins is one potential strategy for axonal injuries, but the unique morphology of the affected neurons make this approach difficult. The spinal cord consists of axons of neurons whose cell body is in the brain. Attempts to use typical gene therapy viruses that infect the cell body and are then translocated to the cell nucleus would be problematic. Obtaining access to neurons in the brain would require brain surgery. Targeting of the virus selectively to injured neurons would not be straightforward. The heterologous protein may exhibit toxic effects when expressed throughout the neuron. Lastly, the heterologous protein might not be efficiently trafficked to the injury site, which may be several feet away from the cell body, where it could mediate its regenerative effects.

WCMC researchers in the lab of Dr. Samie Jaffrey have discovered that protein translation can occur not only in cell bodies, but also in the axons of neuronal cells when axonal ribosomes are presented with an RNA that includes an internal ribosome entry site (IRES). Since RNA possessing an IRES can recruit ribosomes, the translation of any protein whose coding sequence lies downstream of the IRES is possible. They demonstrated that certain RNA alphaviruses, expressing suitable coat proteins, when applied to axons, can enter the axons and induce the expression of proteins whose gene sequence is operably linked to an IRES sequence.

This method of delivering the modified RNA virus to the site of injury to cause the axonal synthesis of regenerative proteins, dominant negative variants of RhoA or RhoA-activated kinase, adenylyl cyclase, src kinase, cyclic AMP-response element-binding protein (CREB), has promise for regenerating axons to improve spinal cord injury prognosis.

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