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Neural gene therapy

# Sensational finding

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In this issue of *Gene Therapy*,[1] David Fink and co-workers at the University of Michigan provide new evidence that gene therapy with vascular endothelial growth factor (*VEGF*), which encodes a hypoxia-inducible angiogenic protein with neurotrophic, neuroprotective and neuroproliferative properties, might be used to treat neurological disorders. Specifically, Fink *et al* have used gene therapy to deliver VEGF in a way that helps target it to peripheral neurons and reduces the likelihood of systemic side effects.

Disorders of the peripheral nerves are important sources of morbidity and mortality in their own right, but also serve as a proving ground for treatments that may eventually be applicable to the central nervous system as well. This is, at least in part, due to the greater accessibility of peripheral than central nerves to therapeutic reagents, such as VEGF.

VEGF was identified originally as an angiogenic and vascular permeability factor, but was later found to have direct effects on neurons,[2] including neuroprotective effects.[3] One of the most intriguing recent developments regarding a potential role for VEGF in the pathogenesis and treatment of neurological disease relates to motor neuron disease. Carmeliet and co-workers at the University of Leuven found that genetic modifications in the noncoding region of *VEGF*, which interfere with its induction by hypoxia, yield a phenotype in mice that is characterized by degeneration of motor neurons.[4] Moreover, similar variations in humans result in decreased blood levels of VEGF and an increased risk for amyotrophic lateral sclerosis (ALS),[5] one form of motor neuron disease. In transgenic mice that express a mutant human gene for ALS ($SOD1^{G93A}$), the phenotype can be rescued by retrograde transport from muscle to motor neurons of a VEGF-expressing lentiviral vector (Figure 1).[6]

Polyneuropathy, which can involve sensory, autonomic and motor nerves, is a common and potentially fatal complication of both type 1 and type 2 diabetes. Sensory involvement can produce neuropathic pain, as well as reduced sensitivity to cutaneous stimulation (hypesthesia), which can, in turn, lead to skin ulcers and the need for limb amputation. Autonomic manifestations include cardiac arrhythmia, orthostatic hypotension, gastroparesis, urinary incontinence and erectile dysfunction. Reduced incidence and slower progression of diabetic neuropathy can result from better control of hyperglycemia. However, current measures directed at improving neuropathic symptoms are only modestly effective, which helps explain why gene therapy approaches to treating diabetic neuropathy have received considerable interest.

In prior studies on peripheral nerves of rats with streptozotocin-induced diabetes, both neural function and neural blood flow improved following intramuscular delivery of plasmid DNA encoding VEGF.[7] Similar findings have been reported after intramuscular administration of naked VEGF DNA to rabbits with primary ischemic neuropathy. However, the ability to target affected neurons more selectively has the attraction that unwanted side effects of VEGF on, for example, proliferating blood vessels associated with diabetic retinopathy might be avoided.

Fink and co-workers previously used subcutaneously administered, replication-defective herpes simplex virus (HSV) vectors expressing neurotrophic factors to treat neuropathies induced by streptozotocin, pyridoxine or cisplatin in mice.[8–10] In the current study, they used VEGF, and gave it 2 weeks after streptozotocin, in order to assess its potential for correction rather than prevention. Subcutaneous HSV-VEGF reached the dorsal root (sensory) ganglia (Figure 1), where it produced VEGF. VEGF overexpression here was associated with preservation of nerve fibers, evidenced by an increased density of cutaneous innervation, and elevated expression of calcitonin gene-related peptide and substance P in the dorsal horn of the spinal cord. HSV-VEGF also increased sensory nerve amplitudes and thermal pain perception, indicative of improved sensory nerve function. Autonomic (sweating) function improved as well, most likely because HSV-VEGF gained access to autonomic ganglia (Figure 1). Finally, the vascularity of affected nerves was increased.

These are exciting results, not least because there is now substantially more clinical experience with VEGF

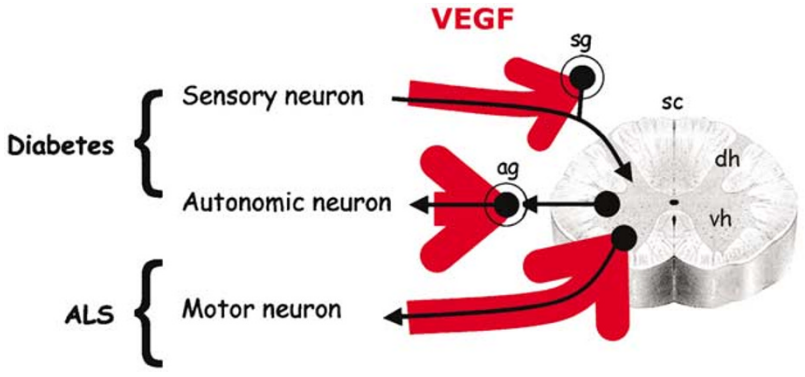


***Figure 1*** *Retrograde transport of a VEGF-expressing viral vector (red arrows) from subcutaneous tissue to sensory or autonomic ganglia, and from muscle to motor neurons, has now been shown to improve function in animal models of diabetic polyneuropathy[1] and motor neuron disease.[6] Abbreviations: sg, sensory ganglion; ag, autonomic ganglion; sc, spinal cord; dh, dorsal horn; vh, ventral horn.*

(as an angiogenesis factor) than with many other growth factors that might be tried for peripheral nerve disease. Naturally, questions remain. The observation that HSV-VEGF preserved the neurovascular supply highlights an obvious uncertainty that has not yet been resolved in the case of motor neuron disease either: is the primary effect of VEGF neuronal or vascular? VEGF can protect neurons directly, because it does so even in *in vitro* settings where no vessels are present. However, does it protect motor, sensory or autonomic neurons directly *in vivo*?

A second outstanding question relates to the mechanism of protection. Most identified effects of VEGF, including most of its effects on the nervous system, are mediated through the VEGFR2 (FLK1) receptor, and downstream *via* a variety of protein kinase transduction systems. This is likely to be the pathway through which VEGF provides protection from streptozotocin neuropathy as well, but it remains to be demonstrated.

A final question relates to how far we can extrapolate these findings to humans. Rodent models of diabetic neuropathy, like rodent models of motor neuron disease, differ from the human disease in respects that might be therapeutically important. In contrast to streptozotocin neuropathy, neuropathy in diabetic patients is a chronic disease with uncertain pathogenesis, and often coexists with other disorders that might alter the response to therapy. Nonetheless, the fact that concerns like these are the major outstanding problems is a sure sign of progress. ■

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