MOTOR NEURON DISEASE

Activated protein C slows ALS-like disease in an animal model

Administration of activated protein C (APC) in a mouse model of amyotrophic lateral sclerosis (ALS) after the animals show signs of disease onset not only slows progression of their symptoms, but also extends their overall survival.

"I think these findings may change the way forward with developing new treatments for ALS in the future. Once we identify the most effective form of APC, we expect to get to clinical trials within 4–5 years," reports senior author Berislav Zlokovic (University of Rochester Medical Center, New York, USA).

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ALS, also known as Lou Gehrig disease, is a progressive and fatal neurodegenerative disease that leads to extensive paralysis, and is one of the most common neurodegenerative diseases worldwide. A number of treatments are being developed for this condition, but additional new therapies are desperately needed.

Many familial cases of ALS are attributable to mutations in the superoxide dismutase 1 (*SOD1*) gene. In the present study, transgenic mice expressing a mutant form of *SOD1* were used as a model platform to test the potential therapeutic effect of APC and its analogs. When given after the onset of disease in the mice, proteolytically active APC was able to cross the blood–spinal cord barrier via the endothelial protein C receptor to delay microglial activation and to prevent further leakage of hemoglobin-derived products back across the blood–spinal cord barrier (Figure 1). The protein also caused transcriptional downregulation of *SOD1* in microvessels, motor neurons and microglial cells. Downregulation of *SOD1* in microglial cells was thought to mediate slowing of disease progression, since excising the *SOD1* gene from endothelial cells has been shown to have no effect on disease outcome. "The enzymatic activity of APC but not its anticoagulant activity was critical for its beneficial effects, which is why we think that the most promising form of APC for therapy will be one with greatly reduced anticoagulant activity but preserved cytoprotective ability," explains Zlokovic.

Several analogs of APC are currently being tested. Wild-type recombinant APC is currently approved by the FDA for the treatment of sepsis, and is also being tested in a clinical trial for acute ischemic stroke. "It is clear from our research and other studies that transient exposure to APC, without continuous infusion, can produce long-lasting neuroprotective effects. Now that accumulation of SOD1 aberrant species has been linked by some recent studies to sporadic ALS, strategies based on activation of the APC pathway are promising directions for treating patients with familial, and possibly sporadic, ALS", concludes Zlokovic.

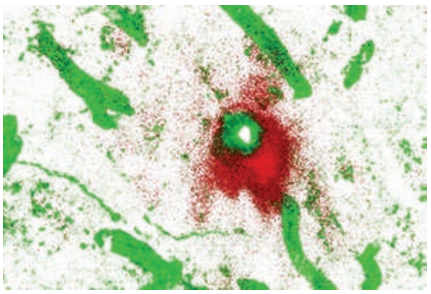

Figure 1 | Capillary leakage of serum proteins in a mouse model of amyotrophic lateral sclerosis. Serum proteins are colored red and spinal cord microvessels are colored green. Image provided by Professor Berislav Zlokovic.

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