Swamping bad cells with good in ALS animal models helps sustain breathing

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In a disease like ALS - one that's always fatal and that has a long history of research-resistant biology - finding a proof of principle in animal models is significant.

This week, Johns Hopkins researchers report that transplanting a new line of stem cell-like cells into rat models of the disease clearly shifts key signs of neurodegenerative disease in general and ALS in particular - slowing the animals' neuron loss and extending life.

The new work supports the hypothesis that artificially outnumbering unhealthy cells with healthy ones in targeted parts of the spinal cord preserves limb strength and breathing and can increase survival.

An account of the work appears online this week in *Nature Neuroscience*.

Two parts of the study hold special interest: One is that the target area for the added cells - parts of the cervical spinal cord that control the diaphragm muscles largely responsible for breathing - reap the most benefit. Forty-seven percent more motor neurons survived there than in untreated model animals. Respiratory failure from diaphragm weakness is the usual cause of death in ALS, also called Lou Gehrig's disease.

"While the added cells, in the long run, didn't save all of the nerves to the diaphragm, they did maintain its nerve's ability to function and stave off death significantly longer," says neuroscientist Nicholas Maragakis, M.D., an associate professor of neurology at Johns Hopkins who led the

research team.

"We intentionally targeted the motor neurons in this region," he says, "since we knew that, as in ALS, their death results in respiratory decline."

Also significant is that the transplanted cells, called glial restricted precursors (GRPs), address a well-known flaw in people with ALS and in its animal models. Both humans and models are stunted in their ability to clear away the neurotransmitter glutamate. And excess glutamate - common in ALS - overstimulates the motor neurons that spark muscle movement, causing death. The event, called excitotoxicity, also occurs in other neurological diseases.

So on a more basic level, the study adds clout to the principle - in live animals - that excitotoxicity is a major bad guy in ALS and that finding more effective ways to avoid or lessen it could help protect the nervous system.

In their research, the team transplanted some 900,000 glial restricted precursors overall to specific sites in the cervical spinal cord of each model rat in early stages of disease. The GRPs the scientists used began life as what's called astrocyte progenitor cells from healthy rat spinal cord tissue. Following transplant, they transformed into mature, healthy astrocytes, found living alongside sick motor neurons.

Astrocytes are the most common cells in the central nervous system. Work at Johns Hopkins and elsewhere has shown their crucial role in keeping the CNS in healthy balance. Not only are the cells studded with transporter molecules that mop up glutamate; they also maintain proper ion levels and nutrient support of nerve cells.

The study showed that at least a third of the added GRPs "took root"

after their transplantation. With time, almost 90 percent of the GRPs had differentiated into astrocytes. Unlike the model rats' own astrocytes, the new ones continued to appear healthy.
None of the GRPs damaged the spinal cord or formed tumors - a worry with some stem cell therapies.

Transplanting alternate GRPs - those that the team engineered to lack glutamate transporters - offered none of the protective properties.

"Our findings demonstrate that astrocyte replacement, by transplantation, is both possible and useful," Maragakis explains. "This targeted cell delivery to the cervical spinal cord is a promising strategy to slow that loss of motor neurons in ALS. We hope at some point that these principles will translate to the clinic."

Earlier research by U.S. scientists suggests that, while astrocytes go downhill in ALS, they may not be a primary cause of the disease. The idea is more that they're involved in its progression. Diseased astrocytes, studies show, may make motor neurons more susceptible to death by excitotoxicity.

Source: Johns Hopkins Medical Institutions