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Healthy Neighbors Rescue Degenerating Motor Neurons

The life or death of motor neurons in patients afflicted with amyotrophic lateral sclerosis (ALS) may rest with a somewhat overlooked group of support cells that helps guide, nourish and remove toxins from neurons.

Howard Hughes Medical Institute researchers and their colleagues have discovered that non-neuronal cells, called astrocytes and glia, can protect neurons containing ALS-causing mutations from degeneration. Their studies also show that if non-neuronal cells harbor ALS mutations, then damage can occur in neighboring motor neurons that are otherwise healthy.

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— Lawrence S. B. Goldstein

According to the researchers, their findings suggest that it may be possible to insert healthy astrocytes into ALS patients to reduce or prevent motor-neuron degeneration. Motor neurons control muscle action, and they are progressively weakened in ALS, leading to paralysis and death.

The collaborating teams of researchers, which included Howard Hughes Medical Institute investigator Lawrence Goldstein, published their findings in the October 3, 2003, issue of the journal *Science*. Goldstein, Don Cleveland and their colleagues at the University of California at San Diego, collaborated with researchers at McGill University Health Care Centre in Montreal, Harvard University, Massachusetts General Hospital and Boston University School of Medicine.

The researchers studied an inherited form of ALS, in which the mutant gene *SOD1* produces an aberrant form of the enzyme superoxide dismutase 1. The abnormal *SOD1* enzyme plays a central role in the progression of the disease. Inherited forms of ALS constitute about ten percent of ALS cases, and mutations in *SOD1* are responsible for about 20 percent of the inherited cases of ALS.

Although hereditary forms of ALS account for only a small fraction of the overall incidence of the disease, said Goldstein, they can nevertheless provide clues to the origins of ALS in general. “A useful analogy is cancer, in which there are hereditary cancers and sporadic cancers,” he said. “And the mechanisms that are revealed by studying the hereditary forms are very useful to understanding the sporadic forms.” The major question, he said, is how mutant *SOD1* contributes to ALS.

“My colleague Don Cleveland has contributed to a body of evidence that shows that it's not a disruption of the normal function of mutant *SOD1* that causes disease. Rather, it appears to be some abnormal property of the protein conferred by these mutations.” One major scientific question, said Goldstein, was whether the abnormal *SOD1* in the motor neurons themselves or in adjacent non-neural supporting cells caused disease. A related question was whether mutant cells—neuronal or non-neuronal—could pathologically affect adjacent cells.

To answer these questions, the collaborating teams produced “chimeric” mice—each using a different method—that harbored either normal neuronal and mutant *SOD1* non-neuronal cells, or vice versa. The researchers then examined whether the mutant cells could affect the normal, or wild-type, cells in the mice.

“With this multi-site consortium, three different sets of chimeras were made by three different methods, and we all arrived at more or less the same answer,” said Goldstein. “We found that motor neurons may not be at fault, even though they are the ones that are dying. Although we have not definitively proven it, our findings strongly suggest that *SOD1* mutations in non-neuronal cells can transmit symptoms of the disease to normal motor neurons. And conversely, when motor neurons have the mutation, healthy non-neuronal cells appear to be able to rescue them.

“We found that the presence of normal non-neuronal cells could extend the life of mutant neuronal cells, the lifetime of the animals, and sometimes even maintain them in a disease-free state,” said Goldstein. “This was quite a surprise. Even though you can draw diagrams on a blackboard theorizing how this protective effect might happen, it's surprising how strong the data are.”

The researchers are now trying to identify which type of non-neural cell—astrocytes or glial cells—is responsible for the protective effect. They are also developing more well-defined chimeras, in which all of the motor neurons contain mutant *SOD1*. By systematically varying the percentage of normal cells among different non-neuronal cells, the researchers hope to pinpoint the source of the protective contribution of these cells. Also, they plan the converse experiment, in which the motor neurons are normal, and non-neural cells are mutant.

The results of these studies could suggest a route to therapy for the disease, said Goldstein. “It is certainly not going to be easy, but it is theoretically possible to introduce healthy astrocytes into a patient to protect his motor neurons, rather than to attempt to introduce motor neurons, which are

extremely large and extended.

“In any case, it's virtually certain that in order to figure out how to treat this disease, you must understand the mechanism,” said Goldstein. “You must understand which cells you need to replace. And I believe that this study represents an important step toward that goal.”