Gene find sheds light on motor neuron diseases like ALS

October 22 2008

Scientists have identified a gene in mice that plays a central role in the proper development of one of the nerve cells that goes bad in amyotrophic lateral sclerosis, or Lou Gehrig's disease, and some other diseases that affect our motor neurons.

The study is the result of a collaboration by scientists at the University of Rochester Medical Center who normally focus on the eye, working together with a developmental neuroscientist at Harvard who focuses on the cerebral cortex. The work appears in the Oct. 23 issue of the journal *Neuron*.

The work centers on corticospinal neurons, crucial nerve cells that connect the brain to the spinal cord. These neurons degenerate in patients with ALS, and their injury can play a central role in spinal cord injury as well. These are the longest nerves in the central nervous system – nerves sometimes several feet long that run from the brain to the spinal cord. As the ends of the nerves degenerate, patients lose the ability to control their muscles.

The team led by Lin Gan, Ph.D., of Rochester and Jeffrey D. Macklis, M.D., D.HST, of Harvard showed that a protein known as Bhlhb5 is central to how the brain's progenitor cells ultimately become corticospinal motor neurons, one type of neuron that deteriorates in ALS. The same group of neurons also degenerates in patients with a rare neurological disease known as hereditary spastic paraplegia.

The work by the Harvard and Rochester scientists marks an important step in scientists' understanding of how stem cells in the brain eventually grow into the extraordinary network of circuits that make up the human nervous system. Understanding how the body determines the destiny of stem and progenitor cells is crucial if physicians are to ultimately use the cells to create new treatments for motor neuron diseases like ALS and HSP, as well as other conditions such as Parkinson's and Huntington's diseases and spinal cord injury.

Macklis' team is a world leader in discovering how the brain determines the destiny of its cells. The process is a bit like what happens on a construction site, where a foreman taps the expertise of a variety of workers – carpenters, plumbers, bricklayers, and so on – as needed to build a given structure. In the brain, teams of molecular signaling molecules are brought together to create nerve cells out of raw material where and when needed. Hundreds of such signaling molecules are brought together instantly and continually to allow the brain to create the nerve cells it needs for growth and development.

"How does the brain take a broad class of neurons and decide which ones to send to the spinal cord, or which will connect to our visual centers?" said Macklis, who is director of the Center for Nervous System Repair at Massachusetts General Hospital and at Harvard.

"We're looking at how the most sophisticated portion of the brain, the neocortex, creates the right kind of neurons where and when they're needed. Understanding how our brain circuits are initially built is the first step to repairing or reversing many diseases of the nervous system," added Macklis.

The team showed that the molecular interactions that help control the destiny of the brain's progenitor cells can take place a bit later than some scientists have considered. The team found that Bhlhb5 plays an

important role in determining the fate of progenitor cells that that have already exited the cell cycle and are well on their way to being refined into more precise types of cells.

The team showed that when Bhlhb5 is knocked out in mice, cells that normally develop into neurons which connect the brain to the spinal cord don't do so. Those mice share many traits with people with hereditary spastic paraplegia, also known as familial spastic paralysis. Doctors estimate that approximately 10,000 to 20,000 Americans have some form of HSP. Symptoms vary widely, but generally patients have weakness or stiffness in their legs that often results in use of a walker or wheelchair. Most patients live full lives, but many experience a range of other difficulties, including blindness, skin problems, nerve damage in the fingers and toes, and deafness. Some patients are completely disabled, while others have little difficulty. No cure or treatment currently exists.

A next step, Gan said, would be to analyze the function of the counterpart to the Bhlhb5 gene in patients. Scientists reported recently that the gene itself is not mutated in patients with HSP, but it's possible that the effect of the gene is somehow changed, perhaps by a different genetic mutation, in some patients with HSP. Already, more than 20 gene mutations are known to cause various forms of HSP, offering an array of targets to try to treat or cure the disease.

"This is a perfect example illustrating why we study genetics in the mouse," said Gan, who is associate professor in the Department of Ophthalmology at the University of Rochester Eye Institute. "We've been able to pinpoint a gene that may play a role in a disease affecting thousands of people, and the work would have been impossible to do directly in people. We did the research in mice, and now we can go back to take a closer look in patients."

Last year, the Rochester team showed that Bhlhb5 plays a role in determining what types of neurons are created in the eye. The eye is the usual focal point for Gan, who is director of the De Stephano Laboratory for Retinal Genomics at the University of Rochester Medical Center. His team studies the genes that play a role in creating the eye, keeping it healthy, and which might play a role in blinding eye diseases such as retinitis pigmentosa, macular degeneration, and glaucoma.

Source: University of Rochester