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news

ALS: neighbors matter

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Neuroscience researchers have revealed that surviving amyotrophic lateral sclerosis (ALS) could depend on shutting down the production of a mutant protein – not just in neurons, but in glial support cells. ALS is a fatal neurodegenerative disease that selectively affects the neurons that control muscle movements. An estimated 120,000 new cases are diagnosed internationally each year. While about 90% of these are mysteriously sporadic, ten percent are inherited. Of these familial cases of ALS, ~20% are caused by mutations in the gene for copper-zinc-superoxide dismutase 1 (Cu-Zn SOD1). The recent reports focus on this subtype.

'In America, your neighbors determine your quality of life'

Neighbors versus ancestors

In work presented at the 2004 Society for Neuroscience meeting in San Diego, California, Don Cleveland (http://cmm.ucsd.edu/Lab_Pages/cleveland/ClevelandLabHome.html) headed a team at the University of California at San Diego in creating a genetic model of inherited ALS in mice. They manipulated genes so that in some mice, only neurons expressed the mutant copy of SOD1. In others, neurons produced normal SOD1, but the surrounding glial cells produced the toxic protein. Mice with healthy glial cells survived ALS several months longer than their counterparts with mutant-expressing glia.

Although it is the motor neurons that are affected by ALS – first losing the ability to send intact messages to the muscles and eventually dying off – Cleveland wondered if the genetic makeup of surrounding glial cells was more important to disease progression. He compared the question to human social standings. 'From a European approach, one's ancestors are more important than their neighbors,' he quipped. 'But in America, your neighbors determine your quality of life.'

He found that the 'American' scenario held for neurons in ALS. When neurons expressed mutant SOD1, they were able to survive as long as they were surrounded by healthy glia. But when glial cells expressed mutant SOD1, they attacked healthy neighboring motor neurons. 'The neighborhood matters for the quality of life of motor neurons,' said Cleveland. Microglial activation, a harmful neuroinflammatory response, might be responsible for the assault on neurons.

Cleveland hopes that his findings will lead to a novel strategy for stem cell replacement. 'The likelihood of being able to replace motor neurons is very very slim,' he cautioned, because the cells grow too slowly to reach distant targets. 'But if we could replace non-neuronal cells, that provides a more effective approach.'

Molecular surgical scissors

Another group of researchers, from the Swiss Federal Institute of Technology at Lausanne (EPFL), described a different tack in targeting mutant SOD1. Patrick Aebischer (http://people.epfl.ch/patrick.aebischer) and his colleagues

used RNA interference technology, in which a piece of small interfering RNA (siRNA) targets a specific mRNA for destruction, thus reducing protein expression. Aebischer said they used a lentiviral vector as 'a shuttle that could bring this RNA to all cells' in the area. 'We asked them to produced siRNAs to see if we could diminish the toxic protein.' In cultured neurons and glia, they not only achieved that goal, but also replaced mutant protein with wild-type SOD1, a strategy Aebischer describes as 'molecular surgical scissors.'

By injecting the vector to the spinal cord of an ALS mouse, they were able to delay signs of motor impairment and slow disease progression. Said Aebischer, 'the vector-treated mouse swims like a normal mouse.' In light of Cleveland's report, Aebischer agreed that to be effective, 'we probably have to silence the gene in the vicinity of motor neurons, not just in neurons themselves.' Jeffrey Rothstein (http://www.neuro.jhmi.edu/profiles/rothstein.html) of Johns Hopkins University, who was not involved in either research project, said the interference therapy could potentially stop disease in people who would otherwise die within nine months, adding, 'the advantage of siRNA is stupendous.'

1359-6446/04/$ – see front matter PII: S1359-6446(04)03338-0