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Illuminating the genetic mechanisms of Lou Gehrig's disease

Recent research improves our understanding of this devastating condition at the genetic level.

A team of scientists has made a significant advance in the understanding of amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease after the American baseball player who was disabled and died from the condition. ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. In particular, it leads to the degeneration and loss of motor neurons, the nerve cells that enable the brain to control muscle movement. As the motor neurons atrophy and die, the patient loses the ability to move his muscles, leading to paralysis and eventual death. Perhaps the best-known sufferer of this disease is the wheelchair-bound British physicist Stephen Hawking.

The study focused on the effects of mutations in a gene known as *SOD1*. It is known that mutations in this gene are a common cause of inherited ALS, although the mechanism by which motor neurons degenerate is not known. The team, which included scientists from RIKEN's Brain Science Institute, the University of California, Washington University, Kyoto University and Kyoritsu University of Pharmacy, used mice engineered to carry a mutant *SOD1* gene.

In particular, the team investigated the effects of a mutant *SOD1* in nervous system cells known as astrocytes, star-shaped cells that surround and support the motor neurons in the spinal column, providing them with nutrients and making sure they stay in place. It was already known that damage due to the mutant *SOD1* in astrocytes accelerates the progress of ALS in its later stages.

The scientists found that reducing the amount of mutant *SOD1* in astrocytes in mice did not significantly delay the onset of the disease or slow its early progression. However, they did find that reducing mutant *SOD1* dramatically slows the later progression of the disease. While the progression from the onset of the disease to the early disease stage was slowed by 14 days on average, the late stage progression was slowed much more,

giving an average extension of survival of 48 days. Overall, survival was extended by about 60 days.

Another cause of damage to motor neurons is the effect of the mutant *SOD1* on microglial cells. These are cells that in effect are the main defense of the immune system of the central nervous system. They move constantly, checking for damaged neuron cells, infectious agents and foreign bodies. The central nervous system is separated from the rest of the body by a barrier that prevents most disease-causing agents from entering. Microglial cells do the work in the CNS that white blood cells do in the rest of the body in defending against infection.

However, when the *SOD1* becomes mutated in microglial cells, they act in a damaging way, producing toxins such as nitric oxide. The scientists discovered that the level of mutant *SOD1* in astrocyte cells affects the timing of this immune response by microglial cells. Damaged astrocytes also worsen the immune response, leading to inflammation and further damage to the motor neurons.

Some approaches to treating ALS aim to slow the disease's progression by supplementing healthy astrocyte cells using, for example, replacement astrocytes derived from stem cells. Others try to control the amount of toxicity in astrocyte cells, with the aim of controlling the damaging immune response of microglial cells. One result of this research is to confirm that these types of therapies are on the right track.

Original work:

Yamanaka, K., Chun, S., Boillee, S., Fujimori-Tonou, N., Yamashita, H., Gutmann, D., Takahashi, R., Misawa, H., Cleveland, D.
Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis.
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