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Researchers discover new clues about how amyotrophic lateral sclerosis develops

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Johns Hopkins scientists say they have evidence from animal studies that a type of central nervous system cell other than motor neurons plays a fundamental role in the development of amyotrophic lateral sclerosis (ALS), a fatal degenerative disease. The discovery holds promise, they say, for identifying new targets for interrupting the disease's progress.

In a study described online in *Nature Neuroscience*, the researchers found that, in mice bred with a gene mutation that causes human ALS, dramatic changes occurred in oligodendrocytes—cells that create insulation for the nerves of the central nervous system—long before the first physical symptoms of the disease appeared. Oligodendrocytes located near motor neurons—cells that govern movement—died off at very high rates, and new ones regenerated in their place were inferior and unhealthy.

The researchers also found, to their surprise, that suppressing an ALS-causing gene in oligodendrocytes of mice bred with the disease—while still allowing the gene to remain in the motor neurons—profoundly delayed the onset of ALS. It also prolonged survival of these mice by more than three months, a long time in the life span of a mouse. These observations suggest that oligodendrocytes play a very significant role in the early stage of the disease.

"The abnormalities in oligodendrocytes appear to be having a negative impact on the survival of motor neurons," says Dwight E. Bergles, Ph.D., a co-author and a professor of neuroscience at the Johns Hopkins

University School of Medicine. "The motor neurons seem to be dependent on healthy oligodendrocytes for survival, something we didn't appreciate before."

"These findings teach us that cells we never thought had a role in ALS not only are involved but also clearly contribute to the onset of the disease," says co-author Jeffrey D. Rothstein, M.D., Ph.D., a professor of neurology at Johns Hopkins and director of the Johns Hopkins Medicine Brain Science Institute.

Scientists have long believed that oligodendrocytes functioned only as structural elements of the central nervous system. They wrap around nerves, making up the myelin sheath that provides the "insulation" that allows nerve signals to be transmitted rapidly and efficiently. However, Rothstein and others recently discovered that oligodendrocytes also deliver essential nutrients to neurons, and that most neurons need this support to survive.

The Johns Hopkins team of Bergles and Rothstein published a paper in 2010 that described in mice with ALS an unexpected massive proliferation of oligodendrocyte progenitor cells in the spinal cord's motor neurons, and that these progenitors were being mobilized to make new oligodendrocytes. The researchers believed that these cells were multiplying because of an injury to oligodendrocytes, but they weren't sure what was happening. Using a genetic method of tracking the fate of oligodendrocytes, in the new study, the researchers found that cells present in young mice with ALS were dying off at an increasing rate in concert with advancing disease. Moreover, the development of the newly formed oligodendrocytes was stalled and they were not able to provide motor neurons with a needed source of cell nutrients.

To determine whether the changes to the oligodendrocytes were just a side effect of the death of motor neurons, the scientists used a poison to

kill motor neurons in the ALS mice and found no response from the progenitors, suggesting, says Rothstein, that it is the mutant ALS gene that is damaging oligodendrocytes directly.

Meanwhile, in separate experiments, the researchers found similar changes in samples of tissues from the brains of 35 people who died of ALS. Rothstein says it may be possible to see those changes early on in the disease and use MRI technology to follow progression.

"If our research is confirmed, perhaps we can start looking at ALS patients in a different way, looking for damage to oligodendrocytes as a marker for disease progression," Rothstein says. "This could not only lead to new treatment targets but also help us to monitor whether the treatments we offer are actually working."

ALS, also known as Lou Gehrig's disease, named for the Yankee baseball great who died from it, affects nerve cells in the brain and spinal cord that control voluntary muscle movement. The nerve cells waste away or die, and can no longer send messages to muscles, eventually leading to muscle weakening, twitching and an inability to move the arms, legs and body. Onset is typically around age 50 and death often occurs within three to five years of diagnosis. Some 10 percent of cases are hereditary.

There is no cure for ALS and there is only one FDA-approved drug treatment, which has just a small effect in slowing disease progression and increasing survival.

Even though myelin loss has not previously been thought to occur in the gray matter, a region in the brain where neurons process information, the researchers in the new study found in ALS patients a significant loss of myelin in one of every three samples of human tissue taken from the brain's gray matter, suggesting that the oligodendrocytes were abnormal.

It isn't clear if the oligodendrocytes that form this myelin in the gray matter play a different role than in white matter—the region in the brain where signals are relayed.

The findings further suggest that clues to the treatment of other diseases long believed to be focused in the brain's gray matter—such as Alzheimer's disease, Huntington's disease and Parkinson's disease—may be informed by studies of diseases of the white matter, such as multiple sclerosis (MS). Bergles says ALS and MS researchers never really thought their diseases had much in common before.

Oligodendrocytes have been under intense scrutiny in MS, Bergles says. In MS, the disease over time can transform from a remitting-relapsing form—in which myelin is attacked but then is regenerated when existing progenitors create new oligodendrocytes to re-form myelin—to a more chronic stage in which oligodendrocytes are no longer regenerated. MS researchers are working to identify new ways to induce the creation of new oligodendrocytes and improve their survival. "It's possible that we may be able to dovetail with some of the same therapeutics to slow the progression of ALS," Bergles says.

More information: Paper: dx.doi.org/10.1038/nn.3357

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