One gene predicts rapid ALS progression 80 percent of the time

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(Medical Xpress)—The debilitating symptoms of amyotrophic lateral sclerosis, or ALS, appear to be increased by a lack of inflammation-reducing T cells, report scientists from the Methodist Neurological Institute in an upcoming print issue of *The EMBO Molecular Medicine Journal*.The researchers found that expression of the gene FoxP3—which helps control the production of anti-inflammatory T cells—was an indicator of disease progression in 80 percent of the patients they studied. Low FoxP3 levels were likely in patients whose ALS would develop rapidly, and vice versa.

"This is the first demonstration that regulatory T cells may be slowing disease progression, since low FoxP3 indicates a rapidly progressing disease," said Assistant Professor of Neurology Jenny Henkel, Ph.D., the study's lead author. "Levels of FoxP3 may now be used as a prognostic indicator of future disease progression and survival."

ALS is a neurodegenerative disease that slowly and inexorably causes paralysis, then death. Loss of motor control may begin in the arms or legs, or with impaired speech, and ultimately compromise breathing. ALS is sometimes called Lou Gehrig's disease. About 5 in 100,000 people are affected, and there is no known cure.

The relationship between inflammation and ALS progression is well established in humans and animal models, and many genes influencing disease development have been identified.

"While inflammation exacerbates disease in ALS patients, this inflammation is suppressed in some patients," Henkel said. "The data in our article suggest that regulatory T cells can suppress this inflammation."

In their EMBO paper, Henkel, Professor of Neurology and Chair Stanley Appel, M.D., and their team provided supportive evidence that the genes FoxP3, TGFβ, IL4, and Gata3 are involved in ALS development. But Henkel and Appel's work also suggests FoxP3 is the best indicator of disease progression when ALS symptoms first appear.

"While expression of FoxP3, TGFβ, IL4, and Gata3 may serve as indicators for latter stages of the disease, our work suggests only FoxP3 was a prognostic indicator early in the disease," Henkel said. "After following a group of ALS patients for three and a half years, low FoxP3 levels predicted a rapidly progressing disease 80 percent of the time."

Foxp3 and Gata3 are transcription factors that influence production of regulatory T cells, and Th2 "helper" T cells. TGFβ and IL-4 (interleukin 4) are anti-inflammatory cytokines.

Henkel, Appel, and their team studied three patient groups. In the first group, the researchers took blood samples from 54 ALS patients at different stages of the disease and from 33 healthy control volunteers. Flow cytometry and PCR were used to determine the character of white blood cells, specifically regulatory T cells, and to measure the expression levels of genes of interest. A second patient group (102 ALS, 28 healthy) was studied specifically to assess the predictive power of FoxP3 expression in ALS disease development. A third group consisting of deceased persons (affected and healthy) was studied for the purpose of establishing endpoints for T cell production and gene expression. Development of ALS was assessed using the Appel ALS score, a widely used standard that Appel developed.

The relationship between inflammation and ALS progression is complex. Inflammation is an important initial response to injury or microbial attack, Appel says, but prolonged inflammation can actually make the damage worse.

"While this inflammation is tolerable for the short term, when the inflammation persists, the pro-inflammatory cytokines and certain chemicals produced by glial cells called microglia will injure and eventually kill the surrounding neurons," Appel said. "Our research verifies that inflammation is accelerating disease progression, that regulatory T cells and Th2 cells may slow disease progression, and that modifying regulatory T cells appears to be a viable treatment option."

Henkel and Appel said researchers are closing in on specific targets for modifying the inflammation that drives progression of the disease, and that they are closer than ever to developing new treatments for this severely debilitating condition.

Provided by The Methodist Hospital System

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