Medical Xpress

Study blocks multiple sclerosis relapses in mice

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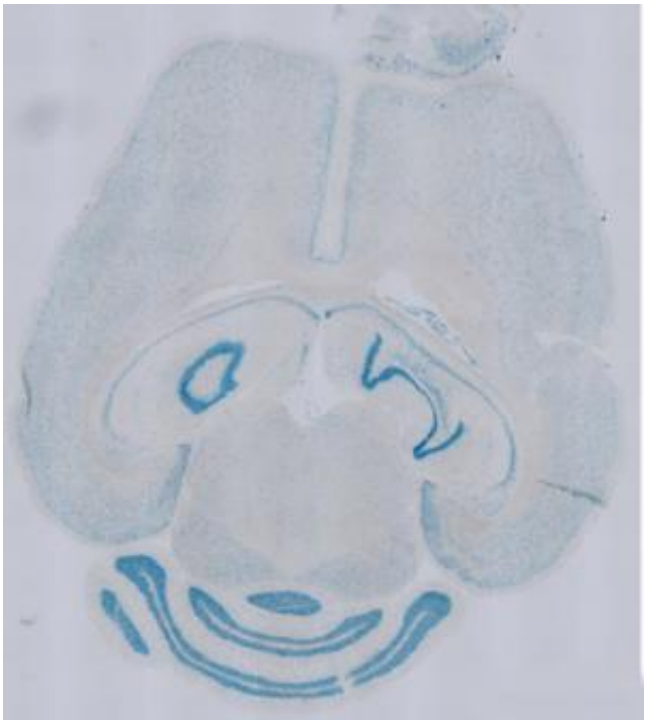

Del-1, a protein previously found to be involved in staving off gum disease, has been found in the brain, where it may play a role in multiple sclerosis and Alzheimer's disease. Credit: University of Pennsylvania

In multiple sclerosis, the immune system goes rogue, improperly attacking the body's own central nervous system. Mobility problems and cognitive impairments may arise as the nerve cells become damaged.

In a new study, researchers from the University of Pennsylvania and co-investigators have identified a key protein that is able to reduce the severity of a disease equivalent to MS in mice. This molecule, Del-1, is the same regulatory protein that has been found to prevent inflammation and bone loss in a mouse model of gum disease.

"We see that two completely different disease entities share a common pathogenic mechanism," said George Hajishengallis, a professor of microbiology in Penn's School of Dental Medicine and an author on the study. "And in this case that means that they can even share therapeutic targets, namely Del-1."

Because Del-1 has been found to be associated with susceptibility to not only multiple sclerosis, but also Alzheimer's, it's possible that a properly functioning version of this protein might help guard again that disease's effects as well.

Penn contributors to the study included Hajishengallis, Penn Dental Medicine postdoctoral researcher Kavita Hosur and Khalil Bdeir, a research associate professor at Penn's Perelman School of Medicine. They collaborated with senior author Triantafyllos Chavakis of Germany's Technical University Dresden and researchers from South Korea's University of Ulsan College of Medicine and other institutions. The work appears online in the journal *Molecular Psychiatry*.

In earlier studies, Hajishengallis, Chavakis and colleagues found that Del-1 acts as a gatekeeper that thwarts the movement and accumulation of immune cells like neutrophils, reducing inflammation. While neutrophils are needed to effectively respond to infection or injury, when too many of them accumulate in a tissue, the resulting inflammation can itself be damaging.

Hajishengallis has found that gum tissue affected by periodontitis, a

severe form of gum disease associated with inflammation and bone loss— had lower levels of Del-1 than healthy tissue. Administering Del-1 directly to the gums protected against these effects.

While researching Del-1 in other tissues, such as gums and lungs, Hajishengallis and Chavakis found that Del-1 was also highly expressed in the brain. In addition, genome-wide screens indicate that the Del-1 gene may contribute to multiple sclerosis risk. For these reasons, the scientists hypothesized that Del-1 might prevent inflammation in the central nervous system just as it does in the gum tissue.

To test their theory, the researchers examined Del-1 expression in brain tissue from people who had died from MS. In MS patients with chronic active MS lesions, Del-1 was reduced compared to both healthy brain tissue and brain tissue from MS patients who were in remission at the time of their death. Similarly, Del-1 expression was reduced in the spinal cords of mice with the rodent equivalent of MS, experimental autoimmune encephalomyelitis (EAE).

Having confirmed this association between reduced Del-1 and MS and EAE, the scientists wanted to see if the reduction itself played a causal role in the disease.

Hajishengallis's and Chavakis's labs had previously utilized mice that lack Del-1 alone or Del-1 together with other molecules of the immune system. The researchers found that mutant mice lacking Del-1 had more severe attacks of the EAE than normal mice, with more damage to myelin, the fatty sheath that coats neurons and helps in the transmission of signals along the cell. Loss of this substance is the hallmark of MS and other neurodegenerative diseases.

Mice without Del-1 that had been induced to get EAE also had significantly higher numbers of inflammatory cells in their spinal cords

at the disease's peak, a fact that further experiments revealed was due to increased levels of the signaling molecule IL-17.

Mice that were induced to get EAE that lacked both Del-1 and the receptor for IL-17 had a much milder form of the disease compared to mice that lacked only Del-1. These doubly depleted mice also had fewer neutrophils and inflammation in their spinal cords.

With a greater understanding of how Del-1 acts in EAE, the researchers were curious whether simply replacing Del-1 might act as a therapy for the disease. They waited until mice had had an EAE attack, akin to a flare-up of MS in human patients, and then administered Del-1. They were pleased to find that these mice did not experience further episodes of the disease.

"This treatment prevented further disease relapse," Chavakis said. "Thus, administration of soluble Del-1 may provide the platform for developing novel therapeutic approaches for neuroinflammatory and demyelinating diseases, especially multiple sclerosis."

The team is pursuing further work on Del-1 to see if they can identify a subunit of the protein that could have the same therapeutic effect.

"It's amazing that our work in periodontitis have found application in a central nervous system disease," Hajishengallis said. "This shows that periodontitis can be a paradigm for other medically important inflammatory diseases."

Provided by University of Pennsylvania

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