Blocking protein expression delays onset of multiple sclerosis in mice, study says

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(Medical Xpress)—Blocking the expression of just one protein in the brain delays the onset of paralysis in mice with a form of multiple sclerosis, say researchers at the School of Medicine.

Exactly why this happens is still unclear. It may be, in part, that blocking expression of the protein, SIRT1, enhances the production of cells that make the insulating myelin sheath necessary for the transmission of nerve signals. This myelin coating is damaged in autoimmune diseases such as multiple sclerosis and Guillain-Barre syndrome.

Although much more research is needed, the findings suggest that it may one day be possible to induce the brains of patients with myelin-associated diseases or injuries to heal themselves by selectively interfering with the activity of SIRT1.

"We are excited by the potential implications our study has on demyelinating diseases and injuries," said Anne Brunet, PhD, an associate professor of genetics. "It's intriguing because activating SIRT1 is typically considered to be beneficial for metabolism and health, but in this case, inactivating SIRT1 can provide protection against a demyelinating injury."

Brunet, who is also a member of the Stanford Cancer Institute, is the senior author of the research, which was published online May 5 in *Nature Cell Biology*. Postdoctoral scholar Victoria Rafalski, PhD, is the lead author of the study.

Blocking SIRT1 expression appears to work by promoting the development of neural stem cells in the brain into a type of cell called an oligodendrocyte precursor. These cells, in turn, become the mature oligodendrocytes that wrap the long arms of neurons with myelin—a fatty material necessary to facilitate the transmission of the electrical impulses from one nerve cell to another. In humans, most myelination occurs during infancy and adolescence.

Diseases such as multiple sclerosis wreak havoc in the central nervous system by damaging this protective myelin coating and impeding communication between nerve cells.

Because SIRT1 is more highly expressed in the brains of mice with an inducible form of multiple sclerosis, Brunet and her colleagues wondered what role the protein might play in the generation or inhibition of oligodendrocytes. To find out, they created a laboratory mouse in which the gene for SIRT1 is selectively disrupted in neural stem cells when the mouse is injected with a drug called tamoxifen. This technique allows the researchers to effectively turn SIRT1 expression off at will in neural stem cells.

The researchers found that, over time, a subset of the nerve stem cells in which SIRT1 expression had been eliminated began to make proteins indicative of oligodendrocyte precursor cells and eventually began to look like typical oligodendrocytes. Growing the neural stem cells in culture yielded similar results; genetically engineered cells lacking active SIRT1 (or unmodified cells treated with a drug that specifically inhibits the activity of the SIRT1 protein) resulted in a marked increase in the proportion of cells expressing an oligodendrocyte-specific protein marker.

When normal mice and those with inhibited SIRT1 expression were injected with a compound that causes the demyelination of nerve cells,

the SIRT1-inhibited mice recovered more quickly. Furthermore, they were protected for a time from the paralysis that develops after the onset of the multiple-sclerosis-like disorder.

"Our work suggests that SIRT1 may normally limit the proliferation of oligodendrocyte precursors and that it has to be inactivated to transiently increase the number of these myelinating cells," Brunet said.

To understand more about how SIRT1 works in the brain, the researchers identified a panel of genes that are more highly expressed when SIRT1 is absent. These genes included several involved in growth factor signaling, cell metabolism and protein production. One, called PDGFRalpha, activates a pair of signaling pathways within the cell. Blocking those pathways significantly inhibited the increase in oligodendrocyte precursor cells seen when SIRT1 is missing.

"Our study highlights the possibility of pharmacological manipulation of multiple nodes of the pathway to expand the population of oligodendrocyte precursors," said Brunet. "Approaches such as these could have important implications for regenerative medicine."

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