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New compounds protect nervous system from the structural damage of MS

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A newly characterized group of pharmacological compounds block both the inflammation and nerve cell damage seen in mouse models of multiple sclerosis, according to a study conducted at the Icahn School of Medicine at Mount Sinai and published online this week in the journal *Nature Neuroscience*.

Multiple sclerosis is a disease of the brain and spinal cord, where for unknown reasons, the body's immune system begins an inflammatory attack against myelin, the protective nerve coating that surrounds nerve fibers. Once myelin is stripped from these fibers, the nerve cells become highly susceptible to damage, which is believed to underlie their destruction, leading to the steady clinical decline seen in progressive forms of multiple sclerosis.

"The compounds identified in this study, when administered orally, both reduced the inflammation that is a hallmark of multiple sclerosis and protected against the nerve cell damage seen in mouse models of the disease," said Jeffery Haines, PhD, a post-doctoral fellow at Mount Sinai and the study's lead author. "The multiple sclerosis drugs currently on the market and being tested elsewhere seek to reduce the immune attack on cells, but none target neurodegeneration nor do they work to restore nerve cell function. The findings of this new study represent an exciting step in the process of advancing new oral treatment options."

Previous research conducted at Mount Sinai found that the trafficking of protein molecules between the nucleus (the cellular compartment

containing the genetic information of the cell) and the cytoplasm is altered in neurodegenerative disease. The molecule that shuttles proteins between the nucleus and cytoplasm, XPO1 (also called CRM1,) has been implicated in multiple sclerosis and a number of other diseases.

Specifically, the Mount Sinai study was designed to test whether pharmacological compounds designed to block the function of XPO1/CRM1 could stop disease progression in mouse models that exhibit some of the characteristics of MS. Researchers found that two chemical agents (called KPT-276 and KPT-350) prevented XPO1/CRM1 from shuttling cargo out of the nucleus of nerve cells, which protected them from free radicals and structural damage. The compounds also stopped inflammatory cells from multiplying, thereby reducing inflammation.

Mice showing hindlimb paralysis were able to regain motor function within two weeks after KPT-276 or KPT-350 were orally administered.

"The study results elucidate the molecular mechanisms underlying disease progression in multiple sclerosis models, providing a basis for future clinical trials to determine safety and efficacy of these chemical agents in humans with demyelinating disorders," says Patrizia Casaccia, MD, PhD, Professor of Neuroscience, Genetics and Genomic Sciences at Mount Sinai and senior author of the study.

Because traffic of molecules between the nucleus and the cytoplasm of nerve cells is altered in several other neurodegenerative disorders, targeting nuclear transport may have broader therapeutic implications in diseases like amyotrophic lateral sclerosis (ALS) and Alzheimer's disease.

Provided by The Mount Sinai Hospital