Cause of rare but deadly neurological disease identified

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A deadly neurological disease that primarily affects infant boys is caused by increased sensitivity to iron in the brain, according to a new study by researchers at the Stanford University School of Medicine, the University of California-San Francisco and the University of Cambridge.

The researchers also found that a drug that binds to and removes iron enhances the survival of cells involved in the disorder.

The researchers are planning to conduct a clinical trial in Europe in children with the condition, called Pelizaeus-Merzbacher disease, to determine whether the drug can halt or slow its progression.

"The rescue of diseased cells grown in the laboratory was dramatic," said Marius Wernig, MD, professor of pathology at Stanford. "It's unbelievably satisfying to identify a potential treatment for such a devastating disorder."

The study will be published online Oct. 3 in *Cell Stem Cell*. Wernig shares senior authorship of the study with David Rowitch, MD, Ph.D., an adjunct professor of pediatrics and of neurological surgery at the UCSF and Wellcome Trust Senior Investigator at the University of Cambridge. Hiroko Nobuta, Ph.D., a postdoctoral scholar at Stanford and at UCSF, is the lead author.

Often fatal by adolescence

Pelizaeus-Merzbacher disease affects about 1 in every 200,000 to 500,000 people. People with the disease are usually diagnosed in infancy after displaying abnormal head and eye movements, poor muscle tone and developmental delays. The disease is progressive and is often fatal by the early teenage years. Pelizaeus-Merzbacher is caused by mutations in a gene called PLP1 that is involved in the formation of the insulating sheath called myelin that coats the outside of neurons and helps them transmit nerve signals throughout the brain. But until now, it was unclear how mutations in PLP1 caused the disease.

Nobuta used skin cells from a patient with a specific mutation in PLP1 to create what are called induced pluripotent stem cells, which can become nearly any cell in the body when exposed to the proper conditions. She then grew the stem cells under conditions that would stimulate their development into myelin-producing cells called oligodendrocytes.

Nobuta found that stem cells with the disease-associated mutation died before becoming functional oligodendrocytes. In contrast, cells in which the mutation had been corrected developed normally in a laboratory dish and on human brain slices. When transplanted into the brains of mice with a myelination disorder, the corrected cells not only developed normally but also contributed to the myelination of neurons in the animals. In contrast, most of the cells with the uncorrected mutation died after transplant.

"When Hiroko studied the cells more closely, she found that they exhibited many hallmarks of iron toxicity," Rowitch said. "Adding a molecule that can chelate, or bind, iron outside the cell restored the cells' ability to become mature, functional oligodendrocytes."

Reducing levels of cell death

The researchers also injected the drug into week-old mice with a mutation in PLP1 that causes a very severe form of the disease. These mice usually die about 35 days after birth. They found that the drug reduced the levels of cell death and stimulated the formation of new myelin in the brain. They also saw a slight increase in how long the animals survived.

The study and its findings are an extension of earlier work by Wernig. In 2007, he was the first to show that it's possible to directly reprogram mouse skin cells into pluripotent stem cells—the first step toward creating functional neurons in quantities sufficient to study neurological disorders such as schizophrenia and autism.

"As a researcher you hope that something you discover will eventually contribute in some way—perhaps decades later—to patient care, but this happened so much sooner than we anticipated," Wernig said. "It's exciting to think that we could soon be testing this approach in patients."

Provided by Stanford University Medical Center

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