UI studies find molecular basis for brain defects in certain muscular dystrophies

IOWA CITY, Iowa -- Piecing together a biochemical and genetic puzzle, University of Iowa researchers and their colleagues have revealed a new molecular mechanism that appears to be the root cause of a subset of muscular dystrophies.

Most muscular dystrophies, as the name suggests, weaken and destroy muscles. However, dystrophies such as Fukuyama Congenital Muscular Dystrophy, Walker-Warburg Syndrome (WWS) and Muscle-Eye-Brain (MEB) disease also involve brain abnormalities that cause severe mental retardation in patients.

"They are an interesting group of dystrophies because they affect more than just muscle," said Kevin Campbell, Ph.D., the Roy J. Carver Chair of Physiology and Biophysics and interim head of the department, UI professor of neurology, and a Howard Hughes Medical Institute (HHMI) Investigator.

The results of two new studies by Campbell and his colleagues, which appear in the July 25 issue of the journal Nature, provide new diagnostic tools that will help physicians make precise diagnoses and accurate prognoses for patients with these congenital muscular dystrophies. The lead authors of the two papers are Dan Michele, Ph.D., a UI postdoctoral fellow in physiology and biophysics and neurology, and Steven Moore, M.D., Ph.D., UI professor of pathology and a staff physician with the Veterans Affairs Medical Center in Iowa City.

"These results improve our understanding of muscular dystrophy, and the more we understand, the better equipped we'll be to develop therapies," Campbell said. "The findings also are important for appropriate genetic counseling."

As genetic causes of muscular dystrophies have been discovered, a pattern has emerged. Many muscular dystrophy-causing genetic mutations affect protein components of the dystrophin-glycoprotein complex. This large complex of proteins provides an essential bridge between structures inside and outside of cells and appears to be critical for the physical integrity of muscle. It seemed likely that a defective component of the complex also would cause the dystrophies involving brain abnormalities.

In the Nature articles, Campbell and his colleagues show that dystroglycan, a protein in the complex, is the key player in these dystrophies, but not because of any defect in the protein itself. Rather, the genetic defect lies in enzymes normally responsible for adding sugar residues to this core
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protein -- a process known as glycosylation. As a result, certain sugars are not added to dystroglycan.

Although Campbell discovered dystroglycan more than 10 years ago, this is the first time it has been directly implicated in muscular dystrophy. Over the years, the Campbell lab has developed antibody probes to analyze dystroglycan. Using these antibodies, Michele and his colleagues showed that dystroglycan protein is present in muscle cells of patients with Fukuyama and MEB disease. However, the protein does not have its full complement of sugar attachments. The team further found that the abnormal glycosylation pattern prevents dystroglycan from interacting with its normal biological partners, such as laminin molecules, at the surface of cells in muscle and brain.

"When Kevin's laboratory started studying the biochemistry of dystroglycan, we had no idea that it might be clinically relevant and yet now those studies allow us to describe these clinical diseases," Michele said.

While Michele and his colleagues were pursuing the biochemical clues about how dystroglycan functions in cells, Moore set out to determine the role of dystroglycan in brain function.

Using sophisticated genetic techniques, the UI scientists created mice that lacked dystroglycan specifically in their brains. The team then examined the mice and found severe brain development defects, which closely resembled the brain defects in humans with Fukuyama, WWS and MEB. This convinced the research group that dystroglycan dysfunction was indeed responsible for brain abnormalities in patients with congenital muscular dystrophies.

"When the brain develops normally, neurons are generated near the center of the brain and then migrate out towards the surface to form a normal cerebral cortex," Moore explained. "In both the congenital muscular dystrophies and the mouse deletion-model that we made, that migration is abnormal. Simply by deleting the protein (dystroglycan) from brain, we can mimic the brain developmental abnormalities present in patients with the congenital muscular dystrophies."

Campbell added that the findings also might implicate disruption of dystroglycan function in other genetic and acquired neurological disorders where errors in neuronal migration are involved. The new information that dystroglycan and its glycosylation are involved in neuronal migration also is important for understanding normal brain development.

Moore, working with former UI professor Toshinori Hoshi, Ph.D., further showed that the absence of brain dystroglycan disrupted a brain process known as long-term potentiation in the mice. This process is associated with the strengthening of connections between brain cells, which in turn influences learning and memory. So, it appears that mice lacking this protein have brain deficits, which likely impair learning and memory. This suggests that dystroglycan has a role in brain function beyond that of neuronal migration.

In addition to their biochemical studies of dystroglycan, Michele and his colleagues also examined the brains of another mouse model of muscular dystrophy known as the myd mouse. As in the (more)
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human diseases, the genetic defect of the myd mouse disrupts the biochemical process that adds sugar units to dystroglycan. And like the human diseases, the defect disrupts interactions between dystroglycan and its biological partners.

Although the myd mouse is an established model of muscular dystrophy, no one had looked at how the defect affected the brain. When Michele and his colleagues investigated, they found brain abnormalities that look like the developmental defects seen in humans who have congenital muscular dystrophies such as Fukuyama Congenital Muscular Dystrophy.

Thus, two lines of research converged to implicate errors in dystroglycan glycosylation as the cause of brain developmental abnormalities seen in the human congenital muscular dystrophies. The research indicates that there are disrupted connections between the important dystrophin-glycoprotein complex and other biological components in both muscle and brain of patients with Fukuyama and MEB disease and the myd mouse. These findings support Campbell's hypothesis that the complex is critical, and disruptions results in muscular dystrophy disorders.

The studies were funded in part by the Howard Hughes Medical Institute, the National Institutes of Health, and the Muscular Dystrophy Association.

In addition to involving UI researchers, the two studies included scientists at Albany Medical College, Johns Hopkins University, the University of Wisconsin, the National Institute of Neuroscience, Tokyo, and Helsinki University Hospital.

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