Study opens new avenue for developing treatments for genetic muscle-wasting disease

March 15 2010

Scientists from the Ottawa Hospital Research Institute (OHRI) and the University of Ottawa have identified a promising new approach for developing drugs to treat Spinal muscular atrophy (SMA), the leading inherited cause of death in infants and toddlers. Dr. Rashmi Kothary and his doctoral student Melissa Bowerman have found that an enzyme called RhoA is overly active in a mouse model of the disease and blocking this enzyme can greatly increase survival. The study is published in *Human Molecular Genetics*.

The research began as an attempt to understand the molecular pathways that are involved in SMA. Scientists have known for many years that this disease is caused by inherited mutations in a gene called survival motor neuron 1 (SMN1). These mutations cause nerve cells to lose their ability to control muscles, but researchers have never fully understood why. Several years ago, Dr. Kothary's team developed a model of SMA using nerve-like cells in the laboratory. They showed that the internal scaffold that gives these cells their shape was defective, and enzymes involved in maintaining the scaffold, such as RhoA, were not being regulated properly.

In the current study, Dr. Kothary's team investigated a compound called Y-27632, which is known to block the RhoA pathway. The compound was developed by other researchers more than 20 years ago and it has been used extensively in laboratory studies, although it has never been tested in humans. Mice with a version of SMA were treated with a high dose of Y-27632, a low dose or a placebo. The mice with the high dose

survived significantly longer, well into adulthood. By comparison, the other mice survived only to about four weeks. This is the greatest increase in survival ever demonstrated in this model of SMA, although the compound was still not able to fully restore lifespan or correct all the nerve problems associated with the disease.

"Our study is important because it opens up a promising new avenue for research into a devastating genetic disease," said Dr. Kothary. "Previous research has focused mainly on replacing the defective SMN gene, or replacing the nerve cells that are lost, but our study shows that targeting the biological problems in nerve cells may also be a valuable approach. I also want to emphasize that while these results are quite promising, this is just one study, using an experimental model of SMA, so we will need to do a lot more research to determine if this drug or a similar one might be a good candidate for testing in humans. Even if it is, I believe that SMA is a disease that will be best addressed by using multiple strategies together, including exercise, nutrition and possibly drugs, cells and gene therapies."

"This discovery by Dr. Kothary and his team is very exciting, although as he fully acknowledges, it must be replicated by other researchers, and replicated using FDA-approved drugs related to the one they used, at which point clinical trials in humans affected by SMA could be considered," said Dr. Rod McInnes, Scientific Director of the Institute of Genetics at the Canadian Institutes of Health Research. "At a minimum, however, this excellent research demonstrates that novel drugs, or novel uses of approved drugs, have the potential to alleviate devastating genetic disorders, even ones affecting the nervous system."

SMA affects approximately one in 10,000 births and more than 25,000 people in Canada and the U.S. are currently living with this disease. Severe forms of SMA will cause paralysis and death within the first few years of life, while milder forms can allow survival into adulthood with

less serious disabilities.

More information: Rho-kinase inactivation prolongs survival of an intermediate SMA mouse model. Bowerman M, Beauvais A, Anderson CL, Kothary R. Hum Mol Genet. E-pub Feb 16, 2010. hmg.oxfordjournals.org/cgi/content/abstract/ddq021

Provided by Ottawa Hospital Research Institute