MedicalXpress

Investigators achieve important step toward treating Huntington's disease

January 19 2012

A team of researchers at the UC Davis Institute for Regenerative Cures has developed a technique for using stem cells to deliver therapy that specifically targets the genetic abnormality found in Huntington's disease, a hereditary brain disorder that causes progressive uncontrolled movements, dementia and death. The findings, now available online in the journal *Molecular and Cellular Neuroscience*, suggest a promising approach that might block the disease from advancing.

"For the first time, we have been able to successfully deliver inhibitory RNA sequences from stem cells directly into neurons, significantly decreasing the synthesis of the abnormal huntingtin protein," said Jan A. Nolta, principal investigator of the study and director of the UC Davis stem cell program and the UC Davis Institute for Regenerative Cures. "Our team has made a breakthrough that gives families affected by this disease hope that genetic therapy may one day become a reality."

Huntington's disease can be managed with medications, but currently there are no treatments for the physical, mental and behavioral decline of its victims. Nolta and other experts think the best chance to halt the disease's progression will be to reduce or eliminate the mutant huntingtin (htt) protein found in the neurons of those with the disease. RNA interference (RNAi) technology has been shown to be highly effective at reducing htt protein levels and reversing disease symptoms in mouse models.

"Our challenge with RNA interference technology is to figure out how to

deliver it into the human brain in a sustained, safe and effective manner," said Nolta, whose lab recently received funding from the California Institute for Regenerative Medicine to develop an RNAi delivery system for Huntington's disease. "We're exploring how to use human stem cells to create RNAi production factories within the brain."

Huntington's disease affects more than a quarter of a million Americans. The disorder can be passed down through families even if only one parent has the abnormal huntingtin gene. The disease is caused by a mutation in the gene, which is comprised of an abnormally repeating building block of DNA that appears on the fourth chromosome. While the building block pattern normally repeats up to 28 times on the chromosome, too many repeats cause an abnormal form of protein -- known as the huntingtin protein -- to be made. The huntingtin protein accumulates in the brain, causing the disease's devastating progression. Individuals usually develop symptoms in middle age if there are more than 35 repeats. A more rare form of the disease occurs in youth when the abnormal DNA pattern repeats many more times.

The UC Davis research team showed for the first time that inhibitory RNA sequences can be transferred directly from donor cells into target cells to greatly reduce unwanted protein synthesis from the mutant gene. To transfer the inhibitory RNA sequences into their targets, Nolta's team genetically engineered mesenchymal stem cells (MSCs), which were derived from the bone marrow of unaffected human donors. Over the past two decades, Nolta and her colleagues have shown MSCs to be safe and effective vehicles to deliver enzymes and proteins to other cells. She said finding that MSCs can also transfer RNA molecules directly from cell to cell, in amounts sufficient to reduce levels of a mutant protein by over 50 percent in the target cells, is a discovery that has never been reported before and offers great promise for a variety of disorders.

"Not only is finding new treatments for Huntington's disease a

worthwhile pursuit on its own, but the lessons we are learning are applicable to developing new therapies for other genetic disorders that involve excessive protein development and the need to reduce it," said Nolta, who recently received a prestigious Transformative Research Grant from the National Institutes of Health to study how mesenchymal stem cells can transfer microRNA and other factors into the cells of damaged tissues, and how that process can be harnessed to treat injuries and disease. "We have high hopes that these techniques may also be utilized in the fight against some forms of amyotrophic lateral sclerosis (Lou Gehrig's disease) as well as Parkinson's and other conditions."

Provided by University of California - Davis