

Researchers find chemical 'switches' for neurodegenerative diseases

November 27 2012

By using a model, researchers at the University of Montreal have identified and "switched off" a chemical chain that causes neurodegenerative diseases such as Huntington's disease, amyotrophic lateral sclerosis and dementia. The findings could one day be of particular therapeutic benefit to Huntington's disease patients.

"We've identified a new way to protect neurons that express mutant huntingtin proteins," explained Dr. Alex Parker of the University of Montreal's Department of Pathology and Cell Biology and its affiliated CRCHUM Research Centre. A cardinal feature of Huntington's disease – a fatal genetic disease that typically affects patients in midlife and causes progressive death of specific areas of the brain – is the aggregation of mutant [huntingtin protein](#) in cells. "Our model revealed that increasing another cell chemical called progranulin reduced the death of neurons by combating the accumulation of the mutant proteins. Furthermore, this approach may protect against [neurodegenerative diseases](#) other than Huntington's disease."

There is no cure for Huntington's disease and current strategies show only modest benefits, and a component of the [protein aggregates](#) involved are also present in other [degenerative diseases](#). "My team and I wondered if the proteins in question, TDP-43 and FUS, were just innocent bystanders or if they affected the toxicity caused by mutant huntingtin," Dr. Parker said. To answer this question, Dr. Parker and University of Montreal doctoral student Arnaud Tauffenberger turned to a simple genetic model based on the expression of mutant huntingtin in

the nervous system of the transparent roundworm *C. elegans*. A large number of human disease genes are conserved in worms, and *C. elegans* in particular enables researchers to rapidly conduct genetic analyses that would not be possible in mammals.

Dr. Parker's team found that deleting the TDP-43 and FUS genes, which produce the proteins of the same name, reduced neurodegeneration caused by mutant huntingtin. They then confirmed their findings in the cell of a mammal cell, again by using models. The next step was then to determining how neuroprotection works. TDP-43 targets a chemical called progranulin, a protein linked to dementia. "We demonstrated that removing progranulin from either worms or cells enhanced huntingtin toxicity, but increasing progranulin reduced cell death in mammalian neurons. This points towards progranulin as a potent neuroprotective agent against mutant huntingtin neurodegeneration," Dr. Parker said. The researchers will need to do further testing this in more complex biological models to determine if the same chemical switches work in all mammals. If they do, then progranulin treatment may slow disease onset or progression in Huntington's disease patients.

Provided by University of Montreal

Citation: Researchers find chemical 'switches' for neurodegenerative diseases (2012, November 27) retrieved 20 March 2024 from <https://medicalxpress.com/news/2012-11-chemical-neurodegenerative-diseases.html>

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