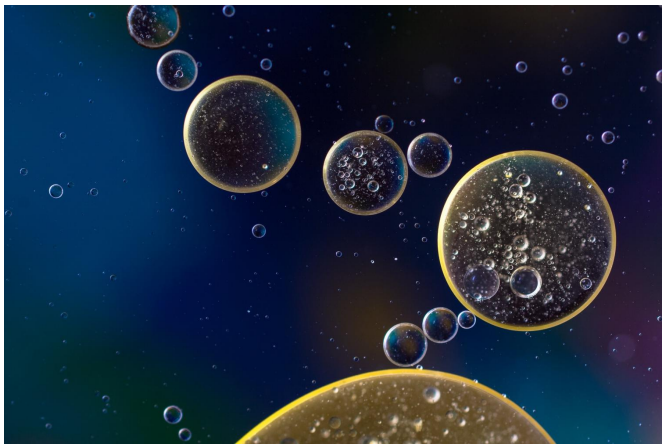
Study uncovers cause of cell death in Parkinson's disease

26 February 2018



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A University of Guelph researcher has discovered one of the factors behind nerve cell death in Parkinson's disease, unlocking the potential for treatment to slow the progression of this fatal neurodegenerative disorder.

Prof. Scott Ryan has found that cardiolipin, a molecule inside nerve cells, helps ensure that a protein called alpha-synuclein folds properly. Misfolding of this protein leads to protein deposits that are the hallmark of Parkinson's disease.

These deposits are toxic to nerve cells that control voluntary movement. When too many of these deposits accumulate, nerve cells die.

"Identifying the crucial role cardiolipin plays in keeping these proteins functional means cardiolipin may represent a new target for development of therapies against Parkinson's disease," said Ryan, a professor in U of G's Department of Molecular and Cellular Biology. "Currently there are no treatments that stop nerve cells from dying."

Parkinson's disease is the most common degenerative movement disorder in Canada, affecting about 100,000 people.

Published in the journal *Nature Communications*, the study used stem cells collected from people with the disease. Ryan's research team studied how nerve cells try to cope with misfolded alpha-synuclein.

"We thought if we can better understand how cells normally fold alpha-synuclein, we may be able to exploit that process to dissolve these aggregates and slow the spread of the disease," he said.

Funded by Parkinson Canada, the study revealed that, inside cells, alpha-synuclein binds to mitochondria, where cardiolipin resides. Cells use mitochondria to generate energy and drive metabolism.

Normally, cardiolipin in mitochondria pulls synuclein out of toxic protein deposits and refolds it into a non-toxic shape.

The U of G researchers found that, in people with Parkinson's disease, this process is overwhelmed over time and mitochondria are ultimately destroyed, said Ryan.

"As a result, the cells slowly die. Based on this finding, we now have a better understanding of why nerve cells die in Parkinson's disease and how we might be able to intervene."

He said understanding cardiolipin's role in protein refolding may help in creating a drug or therapy to slow progression of the disease.

"The hope is that we will be able to rescue locomotor deficits in an animal model. It's a big step towards treating the cause of this disease."

More information: Tammy Ryan et al, Cardiolipin exposure on the outer mitochondrial membrane

modulates ?-synuclein, *Nature Communications* (2018). DOI: 10.1038/s41467-018-03241-9