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Good cells gone bad: Scientists discover PINK-SNO

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A new study from The Scripps Research Institute (TSRI) is the first to show precisely how a process in nerve cells called the S-nitrosylation (SNO) reaction—which can be caused by aging, pesticides and pollution—may contribute to Parkinson's disease.

The leader of the study, TSRI Professor Stuart Lipton, M.D., Ph.D., is now investigating how new pharmaceuticals might counteract this harmful S-nitrosylation reaction.

"The new finding gives us a clue as to where to intervene," said Lipton, who holds a joint position at the University of California, San Diego, School of Medicine, where he is a practicing clinical neurologist involved in the care of Parkinson's patients.

The study was published today in the journal *Cell Reports*.

'PINK-SNO Man' Implicated in Parkinson's

The SNO reaction attaches a nitric oxide-like molecule to protein called PINK1, where the molecule attaches to a building block on PINK1 called a cysteine residue. This changes PINK1's activity—and its ability to do its job.

Since Lipton's group co-discovered the SNO reaction some 20 years ago, scientists have linked the reaction to protein misfolding and nerve cell

damage in cases of Alzheimer's, Huntington's, amyotrophic lateral sclerosis (ALS/Lou Gehrig's disease) and Parkinson's disease, as well as heart/cardiovascular disease and cancer.

In the new study, Lipton and his colleagues used human stem cell and mouse models to show exactly how SNO can trigger cell death in Parkinson's disease. They found that when SNO modifies PINK1, nerve cells cannot recruit another protein called Parkin to get rid of damaged mitochondria.

"Mitochondria are the energy powerhouses of the cell," explained Lipton. Because neurons need a lot of energy, Lipton said, it is especially crucial for them to use only healthy mitochondria and get rid of the damaged ones. Mitochondria can be damaged as people age and cells experience various forms of stress, and it is the job of PINK1 to help trigger a process called mitophagy to remove those dysfunctional mitochondria.

Previous studies had shown that inherited mutations to the gene that codes for PINK1 can stop a person from making working versions of the protein. This means their neurons cannot clear damaged mitochondria, and those cells eventually die—which can cause Parkinson's.

The SNO reaction seems to cause this same problem, but it is not inherited. Instead, cells start "SNO-ing" proteins when they get overwhelmed by reactive nitrogen molecules. "The quantities of these reactive chemical species get so high that cells start SNO-ing proteins, like PINK1, that would normally not be SNO-ed," said Lipton. The researchers call this the PINK-SNO complex, or a "PINK-SNO man."

"Formation of PINK-SNO is definitely harmful to nerve cells in the Parkinson's brain," said Lipton.

So where are these reactive nitrogen species coming from? The scientists noted that cells can generate excessive nitric oxide in response to pesticide exposure, other toxins, and possibly even air pollution.

"This is a scary thought, but also a hopeful thought," said Lipton. "if we can figure out how we're doing this to ourselves, we may be able to control it."

The new study adds to the evidence that some degenerative brain diseases appear to be caused by a combination of genetics and environment. Lipton explained that genetics may leave some people "predisposed" to be at risk for SNO-related Parkinson's.

Because humans inherit two copies (one from each parent) of the gene that encodes PINK1, we all have at least one copy of the gene if the other is mutated. Depending on the protein, this may or may not be sufficient for normal function.

"But, in any event, if the protein translated from the remaining good copy of the gene is then targeted by SNO, then you are stuck making dysfunctional PINK1 even from the remaining good copy of the gene," said Lipton. "The take-home message here is that the environment may affect you based on your individual genetics, and thus both are influential in causing diseases like Parkinson's."

Interestingly, Lipton's team found that SNO-ing appears to occur early in disease progression—early enough that intervention may be able to save brain function. He said the next step is to study how we can prevent these aberrant SNO reactions on particular proteins like PINK1.

Provided by The Scripps Research Institute

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