Molecular mechanism triggering Parkinson's disease identified

28 July 2010

Scientists at the Stanford University School of Medicine have identified a molecular pathway responsible for the death of key nerve cells whose loss causes Parkinson's disease. This discovery not only may explain how a genetic mutation linked to Parkinson's causes the cells' death, but could also open the door to new therapeutic approaches for the malady.

In a study to be published July 29 in *Nature*, investigators used an animal model, the common fruit fly, to show that the mutation results in impaired activity of recently discovered molecules called microRNAs, which fine-tune protein production in cells. This impairment, in turn, leads to the premature death of nerve cells specifically involved in the secretion of the brain chemical dopamine. The degeneration of these so-called dopaminergic nerve cells in the brain is a hallmark of Parkinson's.

"MicroRNA, whose role in the body has only recently begun to be figured out, has been implicated in cancer, cardiac dysfunction and faulty immune response," said Bingwei Lu, PhD, associate professor of pathology and the study's senior author. "But this is the first time it has been identified as a key player in a neurodegenerative disease."

Parkinson's is a movement disorder characterized outwardly by tremor, difficulty in initiating movement, and postural imbalance and, in the brain, by a massive loss of the dopaminergic nerve cells in areas that fine-tune motor activity. It affects an estimated 1 million people in the United States. The incidence of Parkinson's, rare in younger people, increases dramatically with age, although nobody is sure why. Nor is it known why the most common mutation implicated in Parkinson's — LRRK2 G2019S, found in about one-third of all Parkinson's cases occurring among North African Arabs and North American Ashkenazi Jews — increases the likelihood of contracting the disease.

The new findings show that the LRRK2 mutation trips up the normal activity of microRNAs, resulting in the overproduction of at least two proteins that can cause certain cells, like brain cells, to die.

Understanding how microRNA can go wrong requires an understanding of its relationship to its much longer and better-known cousins, "messenger RNA" (or mRNA) molecules. The latter carry genetic recipes from a cell's DNA to specialized molecular machines that translate the instructions into the proteins that make up a cell. In contrast, a microRNA molecule is a very short string of RNA that doesn't contain instructions for making proteins but that can bind to parts of messenger RNA sequences that complement its own. As a result, the messenger RNA's sequence can no longer be read by the cell's protein-manufacturing apparatus, gumming up assembly of the protein it encodes.

It's only recently that scientists have started to understand microRNA's critical role.

The researchers in Lu's lab conducted their experiments in Drosophila, the fruit fly, which has previously proved itself a useful model for several neurodegenerative disorders, yielding substantial insights into Parkinson's, Alzheimer's and Huntington's diseases. They observed that certain proteins were being produced at higher-than-normal levels in the fly LRRK2 model of Parkinson's disease. What particularly drew their attention were two proteins that are important in regulating cell division. Mature nerve cells, which no longer divide, should not have high levels of these proteins; when they do, they are prone to premature cell death.

The researchers looked at the mRNAs containing the genetic recipes for the two overproduced proteins, and predicted that they would be bound by two specific microRNAs: let-7 and miR-184. When they then manipulated the activities of those two microRNA species in flies' brains, they had

results consistent with the damage associated with Parkinson's. Diminishing the activity of let-7 in dopaminergic nerve cells, for example, caused both the increased production of one of the suspect proteins and degeneration of the cells.

The researchers showed that toning down the levels of these two proteins, in itself, prevented dopaminergic nerve cell death in the flies. "The flies no longer got symptoms of Parkinson's," said Lu. "This alone has immediate therapeutic implications. Many pharmaceutical companies are already making compounds that act on these two proteins, which in previous studies have been shown to be associated with cancer. It may be possible to take these compounds off the shelf or quickly adapt them for use in non-cancer indications such as Parkinson's."

The researchers then went a step further, showing how the genetic mutation of LRRK2 caused interference of microRNA molecules' ability to inhibit their target mRNAs. It leads to the disruption of a huge complex of molecular machinery that must operate smoothly in order for microRNA to do its job. This link between the common Parkinson's-producing mutation and consequent microRNA malfunction is a new finding.

"The clinical impact of our findings may be five to 10 years down the road," Lu said. "But their impact on our understanding of the disease process is immediate. We can now start testing compounds in mammals and cultured human dopaminergic cells to see if they can inhibit overproduction of these proteins and stave off dopaminergic cell death." Currently available drugs for Parkinson's disease temporarily alleviate its symptoms but can have undesirable side effects, and they don't prevent dopaminergic cells from dying.

Provided by Stanford University