MedicalXpress

Scientists make advancements that may lead to new treatments for Parkinson's

October 16 2015

More than one million people in the United States are afflicted with Parkinson's disease, a progressive disorder of the brain that affects movement and coordination. The cause is typically unknown, and presently there is no cure for the disease.

Scientists have discovered that the hallmark sign of Parkinson's disease is the intraneuronal accumulation and progressive spreading of clumps in certain areas of the brain, known as Lewy bodies. These Lewy body inclusions are formed mainly through the accumulation of a protein, called alpha-synuclein. Because of a correlation between the extent of Lewy body clumps and the severity of the Parkinson's clinical symptoms, it has been largely accepted that these inclusions accelerate the disease process. Therefore, identifying molecules and conditions which decrease or halt the formation of alpha-synuclein-containing toxic inclusions may be beneficial for Parkinson's disease patients.

A research team led by Assia Shisheva, Ph.D., professor of physiology in Wayne State University's School of Medicine, has made breakthrough advancements on a new molecular mechanism that may provide a means to "melt" these pathological clumps.

For nearly 15 years, Shisheva's laboratory has studied the cellular functions of two enzymes, PIKfyve and Sac3, and one accessory protein ArPIKfyve - the three proteins originally discovered by her group from 1999 to 2007 - and the role these proteins play in disease mechanisms. Previous work by Shisheva's team revealed that if the Sac3 enzyme is

not bound and protected by ArPIKfyve, it is prone to a quick demise inside the cell. In addition, they found that this double ArPIKfyve-Sac3 protein complex is a part of a bigger, triple assembly incorporating the PIKfyve enzyme as well. The triple complex controls the production and turnover of one rare phospholipid molecule that controls the traffic of membranes towards the digestive system of the cell.

It has remained a mystery why the Sac3 mutations are associated with neurodegeneration in humans, whereas the human mutations in PIKfyve are currently linked only to a relatively benign disease of the cornea. This led Shisheva's team to believe that the double ArPIKfyve-Sac3 complex has separate functions in the brain. Shisheva's group sought to identify brain-specific proteins that physically interact only with the double complex ArPIKfyve-Sac3.

In a recent paper, "The protein complex of neurodegeneration-related phosphoinositide phosphatase Sac3 and ArPIKfyve binds the Lewy-body-associated Synphilin-1 preventing its aggregation," published online in the *Journal of Biological Chemistry*, Shisheva and her research team characterized a novel interaction partner of the ArPIKfyve-Sac3 complex in the brain. The *Journal of Biological Chemistry* is the world's largest and most cited journal based on PageRank algorithm.

"We uncovered that the ArPIKfyve-Sac3 complex binds Synphilin-1, a protein already implicated in the pathogenesis of Parkinson's disease through its interaction with alpha-synuclein," said Shisheva. "As alpha-synuclein, Synphilin-1 is also entrapped in the abnormal Lewy body deposits. Our study revealed that the ArPIKfyve-Sac3 complex is an effective inhibitor of aggregate formation by Synphilin-1."

In addition, Shisheva's team found that excessive levels of Sac3 cause protein self-aggregation and further facilitate the clumping by Synphilin-1. Not surprisingly, researchers in Japan have recently found

that excessive Sac3 accumulates in Lewy bodies. Therefore, the ArPIKfyve-Sac3 complex may precipitate Parkinson's disease manifestation in two ways: when it is too low and when Sac3 is disproportionally high. These observations raise the possibility that increasing the levels of the ArPIKfyve-Sac3 complex may have a beneficial effect in Parkinson's disease.

According to Shisheva, the ArPIKfyve-Sac3 complex could shift Synphilin-1 distribution from a form of multiple aggregates towards the soluble form. Future attempts to block aggregate formation or to break down formed aggregates of Synphilin-1 and, possibly, of alpha-synuclein, based on the ArPIKfyve-Sac3 complex may prove beneficial as a therapeutic approach in reducing neurodegeneration in Parkinson's disease. The current study provides new insights into the neurodegeneration mechanisms and important clues about novel molecular means for reducing cytoplasmic aggregates in Parkinson's diseases.

Provided by Wayne State University