Communication breakdown: What happens to nerve cells in Parkinson's disease

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A new study from The Montreal Neurological Institute and Hospital - The Neuro - at McGill University is the first to discover a molecular link between Parkinson's disease and defects in the ability of nerve cells to communicate. The study, published in the prestigious journal *Molecular Cell* and selected as Editor's Choice in the prominent journal *Science*, provides new insight into the mechanisms underlying Parkinson's disease, and could lead to innovative new therapeutic strategies.

Parkinson's, a neurodegenerative disease affecting approximately 100,000 Canadians and over 4 million people worldwide, a number expected to double by the year 2030, causes muscle stiffness and tremor and prevents people from controlling their movements in a normal manner. The disease is characterized by the degeneration and death of dopamine neurons in specific regions of the brain, causing neurological impairment. It is not known exactly what causes the death of these neurons.

Mutations in the parkin gene are responsible for a common inherited form of Parkinson's disease. By studying defects in the genes and proteins of patients with inherited forms of Parkinson's, principal author of the study at The Neuro, Dr. Edward Fon, is learning about the molecular mechanisms involved in the death of dopamine neurons.

The function of the parkin protein is not yet well defined. Scientists learn about the function of a protein by studying normal and mutated forms as well as investigating what the protein binds to. These kind of

studies provide clues as to what processes the protein may be involved in. It is known that parkin is involved in the degradation of other proteins. However, how defects in this function are linked to Parkinson's remains unclear. To further understand how a mutated parkin protein causes Parkinson's, Dr. Fon and his colleagues looked at where mutations are found on the gene and focused on understanding the function of region that is commonly mutated and searched for proteins that bind to this particular domain of the protein.

They identified that parkin binds to a protein called endophilin-A, a protein discovered at The Neuro in 1997 by Dr. Peter McPherson, a co-investigator on the current study. Endophilin-A is central to the process of synaptic transmission, specifically synaptic vesicle trafficking. Synaptic transmission is the process whereby one nerve cell communicates with another. It involves the release of neurotransmitters from a synaptic vesicle at the surface of the cell. The neurotransmitter travels across the gap or synapse and is brought into (or endocytosed) the communicating neuron. Synaptic vesicles are spheres that transport and release neurotransmitters, the 'signal' required for the propagation of nerve cell signals across the synapse. The binding protein, endophilin-A plays an important role in regulating synaptic vesicle endocytosis, that is the formation, as well as recycling of synaptic vesicles.

"One of the most consistent and intriguing findings associated with both dominant and recessive forms of Parkinson's, including those due to parkin mutations, have been defects in synaptic transmission, possibly related to altered synaptic vesicle endocytosis, recycling or release," says Dr. Fon. "Yet, until now, the molecular mechanisms involved have remained completely unknown. Thus, by linking parkin to endophilin-A, a protein at the heart of synaptic vesicle endocytosis and recycling, our findings provide a molecular link between recessive Parkinson's genes and defects in synaptic transmission. This now gives us a whole new set of potential treatment targets."

"This provides a novel and critical molecular link between the parkin gene and synaptic regulation," says Dr. Jean-Francois Trempe, post-doctoral student in Dr. Kalle Gehring's lab at McGill, who studied the structural biology of the binding of the two proteins."The strength and specificity of the interaction makes it a very clear and interesting finding, and indicates that we are heading in the right direction."

"Our next studies will investigate the function of the parkin-endophilin-A interaction, adds Dr. Fon. "We believe that, if the parkin is mutated then the proper functioning of endophilin-A will be affected as it binds parkin, thereby disrupting synaptic vesicle recycling. This could potentially lead to the death of dopamine neurons by depriving neurons of neurotransmitters necessary for neuronal survival and functioning."

"Dr. Fon's new findings will improve our understanding of the defects in the genes and proteins of people who suffer from Parkinson's disease," says Dr. Anthony Phillips, Scientific Director at the Canadian Institutes of Health Research (CIHR) Institute of Neurosciences, Mental Health and Addiction. "CIHR is proud to support research that may pave the way to innovative new therapeutic strategies to cure Parkinson's, which affects too many Canadians."

There is as yet, no known cure for Parkinson's disease. A number of drugs and clinical treatments have been developed which can help to control or minimize the symptoms of this disabling and debilitating disease.

As a world-class academic medical centre and a designated National Parkinson Foundation (NPF) Center of Excellence, The Neuro not only delivers first class clinical care but, also conducts innovative research that leads to important discoveries about the disease and significant advancements in medical care and treatments for patients.

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