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Not guility: Parkinson and protein phosphorylation

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Clues left at the scene of the crime don't always point to the guilty party, as EPFL researchers investigating Parkinson's disease have discovered. It is generally accepted that the disease is aggravated when a specific protein is transformed by an enzyme. The EPFL neuroscientists were able to show that, on the contrary, this transformation tends to protect against the progression of the disease. This surprising conclusion could radically change therapeutic approaches that are currently being developed by pharmaceutical companies. The research is to appear in an article in the *Proceedings of the National Academy of Sciences* (*PNAS*).

Parkinson's disease is characterized by the accumulation of a protein known as alpha-synuclein in the brain. If too much of it is produced or if it's not eliminated properly, it then aggregates into small clumps inside the neurons, eventually killing them. Several years ago scientists discovered that these aggregated proteins in the brain had undergone a transformation known as "phosphorylation"—a process in which an enzyme adds an extra chemical element to a protein, thus modifying its properties.

The investigators' conclusion that the enzyme's activity could be responsible for the disease seems eminently reasonable. If phosphorylation and protein aggregation go hand in hand, then it makes sense that one should cause the other. This is the assumption that researchers and pharmaceutical companies made as they tried to reduce the phosphorylation by deactivating an enzyme involved in the process. But they have been following a false lead, as the EPFL team was able to

show.

The scientists even discovered that the phosphorylation of the protein has positive effects. On the one hand, it considerably reduces the toxic aggregation of the protein, and on the other, it helps the cell eliminate the protein. "The two phenomena are undoubtedly related, and together could play a role in the reduction of alpha-synuclein toxicity, but we don't yet understand the impact of both processes at each stage of the disease," explains neurobiologist Abid Oueslati, first author on the study.

Going back to the beginning

To reach this conclusion, the biologists had to explore the initial disease conditions. They injected into rat neurons what were thought to be the elements needed to trigger the disease: an overexpression of alpha-synuclein and the enzyme that phosphorylates it (PLK2).

To their surprise, the group of animals subjected to both of the parameters—overproduction of the protein and phosphorylation—lost nearly 70% fewer neurons than another group in which only the protein was overexpressed. Consequently, they had fewer lesions, and less Parkinson symptoms.

"We owe this discovery to unique tools that we developed, in collaboration with the Aebischer group, in order to study the effect of this transformation at the molecular level. ," explains Hilal Lashuel, who directed the study. Our study revealed the limitations of the most commonly used approach, which uses genetic mutations to mimic this process.

Lashuel thinks it is highly probable that the phosphorylation of the proteins takes place after they are aggregated, that is to say once the disease is already established. Or it could be a defense mechanism of the

neurons, an attempt to try and slow down the progression of the disease from the beginning.

The scientists' research opens doors for the development of future drug therapies. "The lesson we learned from this research is that everything you find at the scene of a crime is not necessarily involved in the crime. By remaining fixated on that assumption, we may lose sight of the bigger picture."

More information: Polo-like kinase 2 regulates selective autophagic ?-synuclein clearance and suppresses its toxicity in vivo , www.pnas.org/cgi/doi/10.1073/pnas.1309991110

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