Researchers explore PARIS; finds a key to Parkinson's

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Johns Hopkins scientists have discovered that PARIS -- the protein -- facilitates the most common form of Parkinson's disease (PD), which affects about 1 million older Americans. The findings of their study, published March 4 in *Cell*, could lead to important new targets for treatment.

Previous research has shown that a protein dubbed parkin protects brain cells by "tagging" certain toxic elements for natural destruction. Mutations in the parkin gene cause rare forms of PD that run in families, but its role remained unclear in sporadic late-onset PD, the prevalence of which is increasing as the population ages.

Using genetically alteredn mice as well as human brain tissue, the Hopkins team showed that another protein, PARIS, accumulates when the parkin gene is mutated and its protein degrading ability is blocked. Too much toxic PARIS tamps down the manufacture of a protective protein named PGC-1alpha. The less protection afforded to brain cells by this protein, the more they die and the greater the progression of PD.

"Of all the important changes that lead to the death of brain cells as a result of parkin inactivation, our studies show that PARIS is, without a doubt, a key player," says Ted Dawson, M.D., Ph.D., Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases and scientific director of the Johns Hopkins Institute for Cell Engineering.

To pin down the role of the PARIS protein, the researchers first knocked

out the parkin gene in embryonic mice. These animals, despite a 20-percent buildup of PARIS compared with wild-type mice, showed no significant change in the levels of the protective PGC-1alpha, and none of the neurodegeneration that is characteristic of PD, which the researchers measured by counting brain cells. In order to bypass the compensation that they suspected was at play in these young mice (which typically live about 2 years), the team next disabled the parkin gene in 8-week-old (adult) mice. By 10 months of age, these animals with the temporal loss of parkin showed three times the amount of PARIS accumulation in brain cells – similar to the amount in brain tissue from human patients who had mutations in the parkin gene or sporadic PD. Also, PGC-1alpha levels had decreased and a significant loss of neurons – known as neurodegeneration -- had occurred.

"Some might wonder why this same kind of compensation isn't occurring in humans," Dawson says. "Well, it is, but the difference is time. It usually takes us 60 or more years to get the most common form of PD. A body can compensate for only so long and so much. By disabling the gene in the brain cells of adult mice, we accelerated that process and thwarted compensation."

In a further experiment with PARIS, the team created a so-called double knock-out by disabling the gene for PARIS in those same mice in which the gene for parkin already was knocked out. The protective PGC-1alpha levels of these animals — which had no parkin or PARIS — were rescued, and no neurodegeneration occurred. The team then demonstrated that genetically altered mice with an abundance of PGC-1alpha were protected against the same significant loss of neurons.

When the scientists looked at human brain tissue, they also found evidence that PARIS is dependent on parkin function and a chief regulator of the protective PGC-1alpha. By comparing tissue of patients who died with Parkinson's disease with those who died of other causes,

they established that when parkin is shut down and PARIS, the "garbage" protein, accumulates, PGC-1alpha levels drop precipitously and neurons die en masse.

"No one has shown that neurons can be rescued by knocking out any of the other elements that parkin tags for destruction," Dawson says. "The fact that we can prevent parkin-associated brain cell death by blocking PARIS gives a promising new drug target that could someday enable us to slow or stop the progression of PD."

With people living longer, more people are developing this common, debilitating neurological disorder, according to Dawson, noting that one in 100 people are afflicted at the age of 60, and four times that many by the age of 80.

More information: *Cell*: www.cell.com/

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