A new wrinkle in Parkinson's disease research

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The active ingredient in an over-the-counter skin cream might do more than prevent wrinkles. Scientists have discovered that the drug, called kinetin, also slows or stops the effects of Parkinson's disease on brain cells.

Scientists identified the link through biochemical and cellular studies, but the research team is now testing the drug in animal models of Parkinson's. The research is published in the August 15, 2013 issue of the journal *Cell*.

"Kinetin is a great molecule to pursue because it's already sold in drugstores as a topical anti-wrinkle cream," says HHMI investigator Kevan Shokat of the University of California, San Francisco. "So it's a drug we know has been in people and is safe."

Parkinson's disease is a degenerative disease that causes the death of neurons in the brain. Initially, the disease affects one's movement and causes tremors, difficulty walking, and slurred speech. Later stages of the disease can cause dementia and broader health problems. In 2004, researchers studying an Italian family with a high prevalence of early-onset Parkinson's disease discovered mutations in a protein called PINK1 associated with the inherited form of the disease.

Since then, studies have shown that PINK1 normally wedges into the membrane of damaged mitochondria inside cells that causes another protein, Parkin, to be recruited to the mitochondria, which are organelles

responsible for energy generation. Neurons require high levels of energy production, therefore when mitochondrial damage occurs, it can lead to neuronal death. However, when Parkin is present on damaged mitochondria, studding the mitochondrial surface, the cell is able to survive the damage. In people who inherit mutations in PINK1, however, Parkin is never recruited to the organelles, leading to more frequent neuronal death than usual.

Shokat and his colleagues wanted to develop a way to turn on or crank up PINK1 activity, therefore preventing an excess of cell death, in those with inherited Parkinson's disease. But turning on activity of a mutant enzyme is typically more difficult than blocking activity of an overactive version.

"When we started this project, we really thought that there would be no conceivable way to make something that directly turns on the enzyme," says Shokat. "For any enzyme we know that causes a disease, we have ways to make inhibitors but no real ways to turn up activity."

His team expected it would have to find a less direct way to mimic the activity of PINK1 and recruit Parkin. In the hopes of more fully understanding how PINK1 works, they began investigating how PINK1 binds to ATP, the energy molecule that normally turns it on. In one test, instead of adding ATP to the enzymes, they added different ATP analogues, versions of ATP with altered chemical groups that slightly change its shape. Scientists typically must engineer new versions of proteins to be able to accept these analogs, since they don't fit into the typical ATP binding site. But to Shokat's surprise, one of the analogs—kinetin triphosphate, or KTP—turned on the activity of not only normal PINK1, but also the mutated version, which doesn't bind ATP.

"This drug does something that chemically we just never thought was

possible," says Shokat. "But it goes to show that if you find the right key for the right lock, you'll be able to open the door."

To test whether the binding of KTP to PINK1 led to the same consequences as the usual ATP binding, Shokat's group measured the activity of PINK1 directly, as well as the downstream consequences of this activity, including the amount of Parkin recruited to the mitochondrial surface, and the levels of cell death. Adding the precursor of KTP, kinetin, to cells—both those with PINK1 mutations and those with normal physiology—amplified the activity of PINK1, increased the level of Parkin on damaged mitochondria, and decreased levels of neuron death, they found.

"What we have here is a case where the molecular target has been shown to be important to Parkinson's in human genetic studies," says Shokat. "And now we have a drug that specifically acts on this target and reverses the cellular causes of the disease."

The similar results in cells with and without PINK1 mutations suggest that kinetin, which is a precursor to KTP, could be used to treat not only Parkinson's patients with a known PINK1 mutation, but to slow progression of the disease in those without a family history by decreasing cell death.

Shokat is now performing experiments on the effects of kinetin in mice with various forms of Parkinson's disease. However, the usefulness of animal models in Parkinson's research has been debated, and therefore the positive results from the cellular data, he says, is as good an indicator as results in animals that this drug has potential to treat Parkinson's in humans. Initial human studies will likely focus on the small population of patients with PINK1 mutations, and if successful in that group the drug could later be tested in a wider array of Parkinson's patients.

More information: www.cell.com/abstract/S0092-8674%2813%2900901-X

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