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Biochemistry shows how the protein MITOL kicks off Parkin activity

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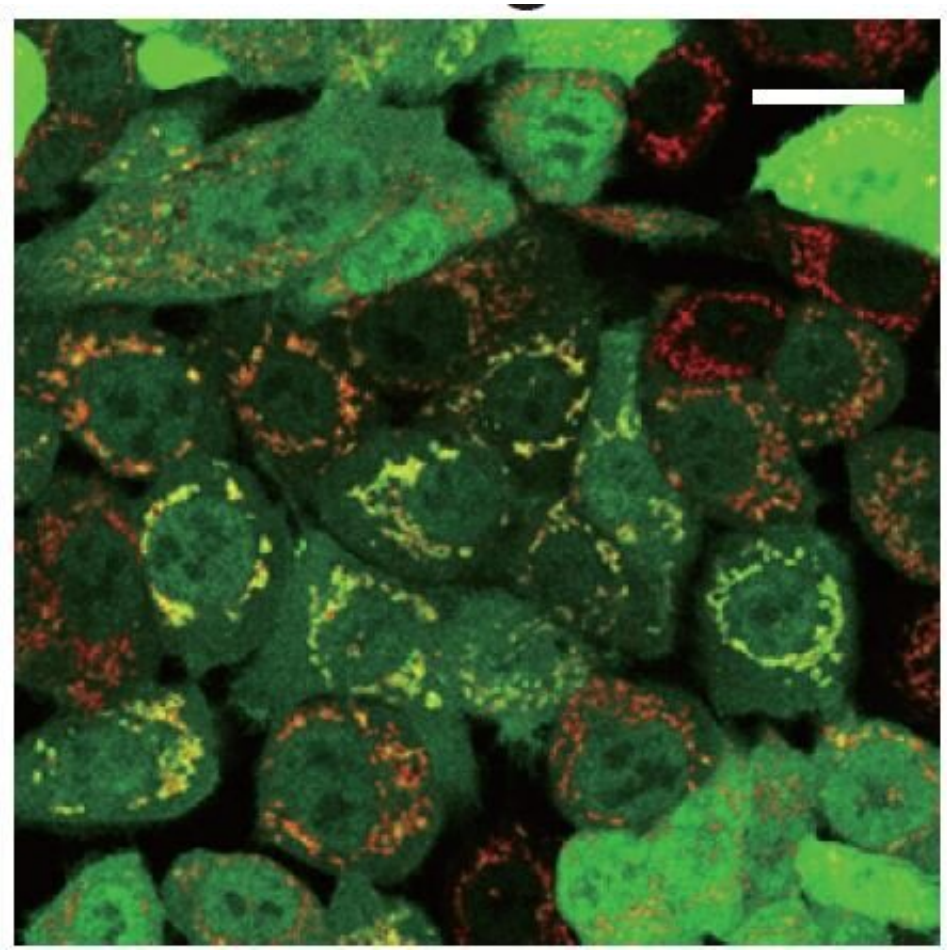

The protein Parkin, which is mutated in some forms of Parkinson's disease, helps cells clear damaged mitochondria. In this image of cells, taken 60 minutes after the cells' mitochondria were damaged with a poison, there is strong overlap (yellow) between fluorescently labeled Parkin (green) and mitochondria (red). Researchers at Tokyo Institute for Medical Sciences found that without a protein called MITOL, Parkin accumulated more slowly at damaged mitochondria. Credit: Koyano et al., JBC 2019

Researchers at Tokyo Metropolitan Institute of Medical Sciences are reporting new insight into how the Parkinson's disease-associated protein Parkin selects its targets. Cells depend on Parkin to help get rid of damaged mitochondria. This new work, which appears in the *Journal of Biological Chemistry* on Monday, May 20, suggests that Parkin depends on other proteins, including one called MITOL that has not previously been linked to Parkinson's disease, to direct it to those damaged mitochondria. The finding might help improve experimental therapies for Parkinson's that aim to boost Parkin activity.

Parkin is attracted to damaged mitochondria, where it adds a degradation tag called ubiquitin to proteins on the mitochondrial surface. In some patients with familial Parkinson's disease, Parkin activity is disrupted and bad mitochondria cannot be destroyed. Harmful byproducts from those bad mitochondria can damage neurons. By understanding how Parkin works and what goes wrong when it's mutated, researchers hope to help patients with other forms of Parkinson's disease, too.

While other ubiquitin tagging proteins, known as E3 ligases, recognize specific amino acid sequences on their substrates, Parkin has many known substrates that don't seem to share a sequence in common. While studying how Parkin chooses its substrates, a group of scientists led by Fumika Koyano in Noriyuki Matsuda's lab at the Tokyo Metropolitan Institute of Medical Science discovered that Parkin can tag any lysine-containing protein with ubiquitin—even a bacterial protein that is not ordinarily found in the cell—as long as it's present at the surface of the mitochondria.

"Parkin is not regulated by its substrate specificity," Koyano said of the finding. Instead, she added, control of Parkin activity comes from how it is recruited and activated by other proteins.

The discovery that activated Parkin is not terribly selective led Koyano and her colleagues to take a closer look at Parkin's recruitment and activation. Some details of that process are well known; for example, a protein called PINK1 is known to boost Parkin activity. But Koyano and colleagues discovered a new step that has to happen before PINK1 can contribute to Parkin activation. They found that Parkin acts much more rapidly when a first ubiquitin molecule is already present, acting as a "seed" for addition of more ubiquitins. In most cases, the researchers found, this seed ubiquitin is added by a protein called MITOL, which has not previously been linked to Parkinson's disease.

The research could help contribute to drug-design initiatives, some of which aim to boost Parkin activity to slow the advance of Parkinson's disease. "If we achieve upregulation of 'seed' ubiquitylation on mitochondria," Koyano said, "it might accelerate Parkin recruitment and Parkin activation to eliminate damaged mitochondria more efficiently."

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