Using Metalloendocrinology and quantum biology modeling, MITOL can be verified as an alternative designation for MARCH5 and DNAJB5; the enzyme for autophagy of lipids. The elemental constituents of this enzyme are copper - zinc in conjunction with the amino acids histidine - arginine - lysine.

Qualified bioinformatics professionals are encouraged to discuss these epigenetic factors as well as Parkin and PINK1 to verify their elemental constituents (elements and amino acids) in order to establish new treatment paths for PD.

https://neurosciencenews.com/parkinsons-protein-14034/?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+neuroscience-rss-feeds-neuroscience-news+%28Neuroscience+News+Updates%29

Researchers link new protein to Parkinson's

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Summary: *The MITOL protein has been implicated in Parkinson's disease.*

Source: *ASBMB*

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 the 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."

ABOUT THIS NEUROSCIENCE RESEARCH ARTICLE

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Journal of Biological Chemistry. doi:10.1074/jbc.RA118.006302

Abstract

Parkin recruitment to impaired mitochondria for nonselective ubiquitylation is facilitated by MITOL

PINK1 (PARK6) and PARKIN (PARK2) are causal genes of recessive familial Parkinson's disease. Parkin is a ubiquitin ligase E3 that conjugates ubiquitin to impaired-mitochondrial proteins for organelle degradation. PINK1, a Ser/Thr kinase that accumulates only on impaired mitochondria, phosphorylates two authentic substrates, the ubiquitin-like domain of Parkin and ubiquitin. Our group and others have revealed that both the subcellular localization and ligase activity of Parkin are regulated through interactions with phosphorylated ubiquitin. Once PINK1 localizes on impaired mitochondria, PINK1-catalyzed phospho-ubiquitin recruits and activates Parkin. Parkin then supplies a ubiquitin chain to PINK1 for phosphorylation. The amplified ubiquitin functions as a signal for the sequestration and degradation of the damaged mitochondria. Although, a bewildering variety of Parkin substrates have been reported, the basis for Parkin substrate specificity remains poorly understood. Moreover, the mechanism underlying initial activation and translocation of Parkin onto mitochondria remains unclear, as the presence of ubiquitin on impaired mitochondria is thought to be a prerequisite for the initial PINK1 phosphorylation process. Here, we show that artificial mitochondria-targeted proteins are ubiquitylated by Parkin, suggesting that substrate specificity of Parkin is not determined by its amino acid sequence. Moreover, recruitment and activation of Parkin are delayed following depletion of the mitochondrial E3, MITOL/March5. We propose a model in which the initial step in Parkin recruitment and activation requires protein ubiquitylation by MITOL/March5 with subsequent PINK1-mediated phosphorylation. As PINK1 and Parkin amplify the ubiquitin signal via a positive feedback loop, the low substrate specificity of Parkin might facilitate this amplification process.