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Elucidation of the roles of MITOL in the formation of mitochondria-associated membrane (MAM) and relationship between MAM disruption and diseases

Roles of
Membrane Contact Sites in
Organelle Dynamics and
Diseases

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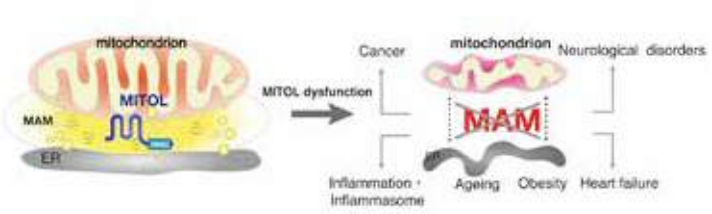
Research summary

The mitochondrion plays an important role in exchanging Ca2+ or metabolizing lipids by positioning at sites situated close to the endoplasmic reticulum (ER), which is called MAM. Mitofusin2 (Mfn2) is a mitochondrial fusion factor which is localized in the endoplasmic reticulum as well as in mitochondria and play a role in the attachment of these organelles to each other. Although a previous study indicates that Mfn2 is required for MAM formation, the mechanisms regulating this process remain unknown. Recently we have demonstrated that MITOL ubiquitinates Mfn2 and induces MAM formation through Mfn2 oligomerization. However, the regulatory mechanism for MITOL-induced MAM formation and the involvement of disrupted MAM in disease pathology are still obscure. In this project, we will explore the roles of MITOL in the MAM formation and MAM-associated diseases such as Alzheimer disease.

Figure

A model of the mechanism by which MITOL regulates MAM formation

MITOL ubiquitinates mitochondrial Mfn2 on its lysine residue in position 192 in a K63-dependent manner, thereby activating Mfn2. In turn, activated Mfn2 binds to Mfn2 localized in the ER, resulting in mitochondria-ER tethering by oligomerization of Mfn2.



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