News Release

Title

Novel function of sigma-1 receptor maintains ATAD3A as a monomer to prevent mitochondrial fragmentation in amyotrophic lateral sclerosis

Key Points

- Mitochondria-associated membrane (MAM), an ER contact site to the mitochondria, is disrupted in amyotrophic lateral sclerosis (ALS); however, the impact of MAM disruption on mitochondrial dynamics was unclear.
- We found that sigma-1 receptor (σ1R), a MAM-specific chaperone-like protein, maintained ATAD3A as a monomer to prevent mitochondrial fragmentation in ALS.
- Pharmacological activation of σ1R elongated mitochondrial network size *in vitro*.
- Targeting σ1R and ATAD3A axis may provide a novel therapeutic approach for ALS.

Summary

A research group led by Professor Koji Yamanaka, Assistant Professor Seiji Watanabe, and Graduate Student Mai Horiuchi of the Nagoya University, Research Institute of Environmental Medicine, Tokai National Higher Education and Research System, has discovered a mechanism by which the sigma-1 receptor (σ1R) regulates mitochondrial morphology in amyotrophic lateral sclerosis (ALS).

ALS is an intractable disease that causes selective degeneration of motor neurons and progressive atrophy of muscles throughout the body. The mitochondria are fragmented, and their function is impaired in ALS. However, the detailed mechanism of how mitochondria become fragmented remains unclear.

In this study, we found that σ1R, whose loss of function is causative for juvenile inherited ALS, interacts with ATAD3A on the mitochondrial

membrane to suppress mitochondrial fragmentation. In ALS model mice, impaired σ1R function was associated with mitochondrial fragmentation with abnormal ATAD3A dimerization.

Aberrant ATAD3A dimerization has also been reported in other neurodegenerative diseases such as Alzheimer's disease and Huntington's disease. Promoting the interaction between the σ1R and ATAD3A may lead to the development of a new strategy for neurodegenerative diseases, including ALS, in the future.

Publication

Sigma-1 receptor maintains ATAD3A as a monomer to inhibit mitochondrial fragmentation at the mitochondria-associated membrane in amyotrophic lateral sclerosis

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