News Release

Title

Elucidating the mechanism of disrupted proteostatic stress response mediated by the mitochondria-associated membranes in amyotrophic lateral sclerosis (ALS)

Key Points

- Levels of active TANK-binding kinase 1 (TBK1), an ALS-causing gene product, were reduced in the affected tissues of ALS patients and mouse models.
- The reduced TBK1 activity in ALS was associated with disruption of the endoplasmic reticulum-mitochondrial contacts.
- MAM-dependent activation of TBK1 was crucial for neuronal stress responses, especially for protein homeostasis.

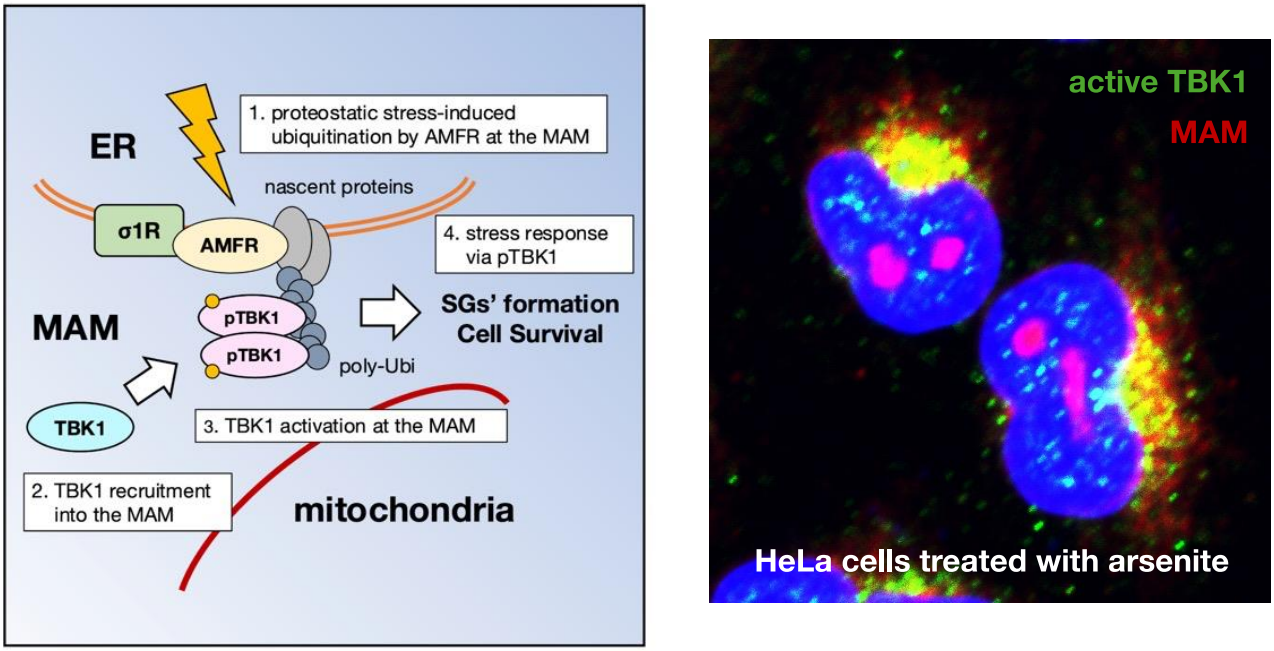

Figure. Schematic outline of this study (left) and activation of TBK1 at the MAM (B)

Summary

A research group led by Dr. Seiji Watanabe (first author), Prof. Koji Yamanaka (Department of Neuroscience & Pathobiology, Research Institute of Environmental Medicine (RIEM), Nagoya University), Prof. Tomoo Ogi (Department of Genetics, RIEM, Nagoya University), and Prof. Masahisa Katsuno (Department of Neurology, Graduate School of Medicine, Nagoya

University), and their colleagues have identified that disruption of the mitochondria-associated membranes (MAM) in amyotrophic lateral sclerosis (ALS) causes a reduction in the activity of TANK-binding kinase 1 (TBK1), leading to an abnormal stress response in motor neurons.
ALS is an intractable neurodegenerative disease that selectively affects the motor neurons. So far, the research group has shown that disruption of the MAM, a region where the endoplasmic reticulum and mitochondria contact each other, is essential for the development of ALS. However, the mechanism by which MAM disruption causes motor neuron degeneration was unclear.
The research group focused on TBK1, a key molecule in innate immunity and the product of the ALS-causative gene, and found that TBK1 activation was markedly reduced in brain and spinal cord tissues from ALS patients and mice in which MAM had been genetically disrupted. These results suggest that MAM disruption in ALS leads to a decrease in TBK1 activity. Moreover, motor dysfunction was observed in mice with disrupted MAM when treated with arsenite, which was associated with reduced TBK1 activity.
This study suggests that MAM contributes to the stress response of motor neurons via activation of TBK1 and that the decrease in TBK1 activity associated with MAM disruption leads to motor neuron degeneration in ALS. The results of this study are expected to lead to the development of new therapeutic strategies for ALS in the future.

Publication

“Mitochondria-associated membrane collapse impairs TBK1-mediated proteostatic stress response in ALS.”

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