News Release

Overexpression of ALS-linked TDP-43 in oligodendrocytes induces motor dysfunction in mice.

Key Points

• We established a novel mouse model overexpressing TDP-43, a product of an ALS-causative gene, specifically in oligodendrocytes.

• An excess amount of TDP-43 induced oligodendrocyte dysfunction and apoptosis.

• The oligodendrocyte dysfunction caused by excess TDP-43 led to motor dysfunction in the mice.

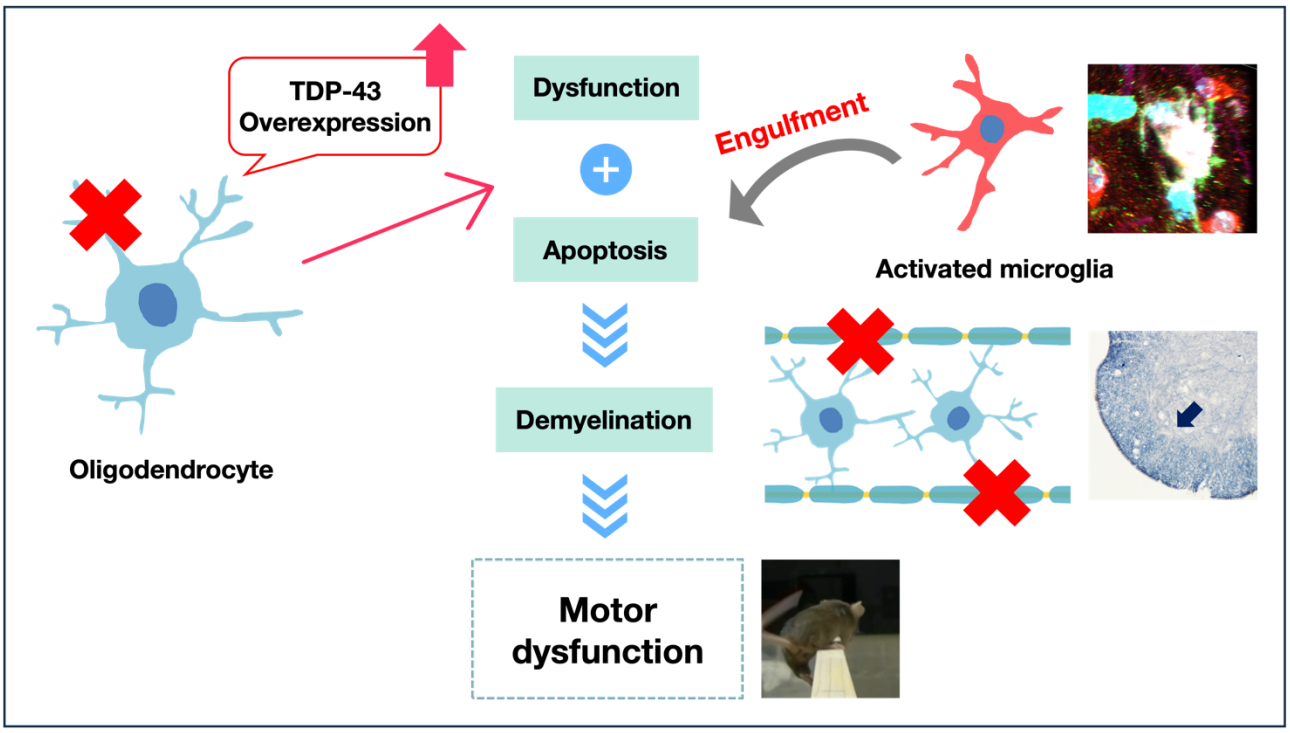

Figure. Schematic outline of this study

Summary

A research group led by Dr. Mai Horiuchi, Dr. Seiji Watanabe (co-first author), Prof. Koji Yamanaka (Department of Neuroscience & Pathobiology, Research Institute of Environmental Medicine (RIEM), Nagoya University), and their colleagues have identified that overexpression of TAR DNA-binding protein 43 (TDP-43), a product of an ALS-causative *TARDBP* gene, in oligodendrocytes induces oligodendrocyte dysfunction and motor dysfunction in mice.

Amyotrophic lateral sclerosis (ALS) is an intractable neurodegenerative disease that causes the gradual loss of muscle movement and strength due to motor

neuron death. TDP-43 protein aggregates in the cytoplasm in neurons and oligodendrocytes, a type of glial cells, and the aggregates are thought to be toxic to the cells in ALS patients. So far, various studies have reported impacts of TDP-43 aggregates on neurons. However, there are few studies focused on oligodendrocytes. In this study, the research group aimed to elucidate how TDP-43 induces oligodendrocyte dysfunction and how it contributes to the disease onset and/or progression in ALS.
To this end, the research group has established a novel mouse model overexpressing ALS-linked mutant TDP-43, specifically in oligodendrocytes. The model mouse exhibited motor dysfunction, such as whole-body tremors and gait abnormality. Reduced myelination and oligodendrocyte apoptosis were observed in the brain and spinal cord of the model mice, suggesting that the loss of myelinating oligodendrocytes induces motor dysfunction.
Our study has revealed that excess TDP-43 induces oligodendrocyte dysfunction and motor dysfunction. The model mouse established in this study is a promising tool for analyzing oligodendrocyte dysfunction in ALS. Further research focused on oligodendrocytes holds the potential to develop a new therapeutic strategy for ALS.

Publication

"ALS-linked mutant TDP-43 in oligodendrocytes induces oligodendrocyte damage and exacerbates motor dysfunction in mice"

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