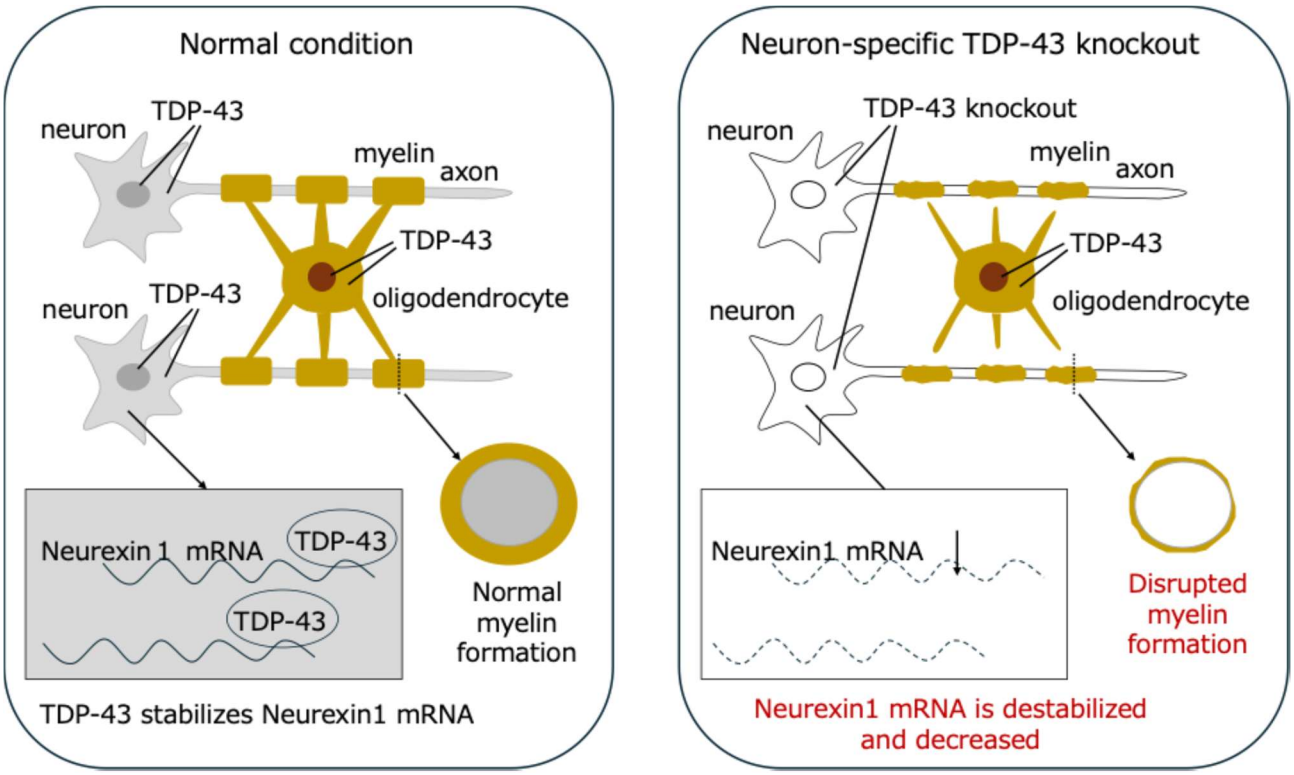
News Release

Neuronal TDP-43 regulates myelin formation by stabilizing Neurexin1 mRNA

Key Points

- Myelin formation is disrupted in neuron-specific TDP-43 knockout mouse
- TDP-43 promotes myelin formation by regulating Neurexin1 expression



Summary

A research group led by Research Fellow Jiayi Li, Associate Professor Yohei Iguchi, and Professor Masahisa Katsuno of the Department of Neurology, and Professor Hiroaki Wake of the Molecular Cell Biology, Nagoya University Graduate School of Medicine has demonstrated that Neuronal TDP-43 regulates myelin formation via Neurexin1 mRNA stabilization.

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) develop as spatial pathologies in which neurons and glial cells are interconnected. TAR DNA-binding protein 43 (TDP-43) is a major pathological protein that is inextricably associated with ALS and FTLD. In these diseases, TDP-43 is found to escape from the nucleus of degenerating neurons and accumulate in the cytoplasm as aggregates. Loss of TDP-43 function and aggregate toxicity in the cytoplasm are thought to be the primary causes of the neuronal death. Therefore, therapeutic strategies that suppress overall TDP-43 expression risk further reduction of TDP-43 function. No therapeutic strategy has been established that specifically reduces aggregation. The group investigated the roles of neuronal TDP-43 in neuron–oligodendrocyte interactions using neuron-specific TDP-43 knockout (TDP-43cKO) mice. TDP-43 depletion in neurons induced hypomyelination, which was confirmed by immunohistochemistry and ultrastructural analysis. In addition, conduction disturbance was revealed by electrophysiological analysis. The hypomyelination of TDP-43cKO mouse was restored by cytoplasmic TDP-43 supplementation in neurons. Neuron-specific transcriptome analysis revealed that Neurexin1 (NRXN1) is the regulatory target of TDP-43, which promotes myelin formation. The hypomyelination of TDP-43cKO mice was also restored by NRXN1b supplementation in neurons. We further confirmed that TDP-43 stabilizes *Nrxn1* mRNA by binding to the *Nrxn1* 3' UTR. Although TDP-43cKO exhibited impaired recognition memory, the supplementation of NRXN1 in the hippocampus recovered the memory disturbances. In conclusion, this study demonstrates the novel neuron-oligodendrocyte interaction mediated by neuronal TDP-43 by stabilizing *NRXN1* mRNA. These findings shed light on neuron–oligodendrocyte interaction in the disease mechanisms of ALS/FTLD. This study was conducted as a collaborative research project with National Institute for Physiological Sciences, Setsunan University, and Aichi Medical University.

Research Background

Most ALS patients develop the disease in middle age or later without any special triggers or prodromal signs. In the early stages of the disease, muscle weakness is restricted to a focal area, but gradually the entire body becomes weak, and in an average of 3 to 5 years, patients are unable to breathe on their own due to paralysis of the respiratory muscles. More than 90% of patients with ALS are sporadic, meaning that they have no relatives with the disease, and the cause of the disease has not been identified. However, pathological and biochemical analysis of the brain and spinal cord of ALS patients has revealed that TDP-43, a protein that normally resides in the nucleus, escapes from the nucleus and forms aggregates in the cytoplasm of ALS motor neurons (Fig. 1A). Since then, researchers including our own have conducted cell and animal studies and now ”loss of function” and ”aggregate toxicity” of TDP-43 have been considered to be the primary causes of neuron death. Ideally, normalizing the abnormal behavior of TDP-43 in ALS would be the most effective approach. However, because the underlying causes of TDP-43 dysfunction have not yet been fully identified, current therapeutic strategies are largely limited to compensating for the loss of TDP-43 function or reducing pathological TDP-43 aggregates.
This study proposes a novel therapeutic strategy aimed at compensating for TDP-43 loss of function, providing a new direction for the treatment of ALS.

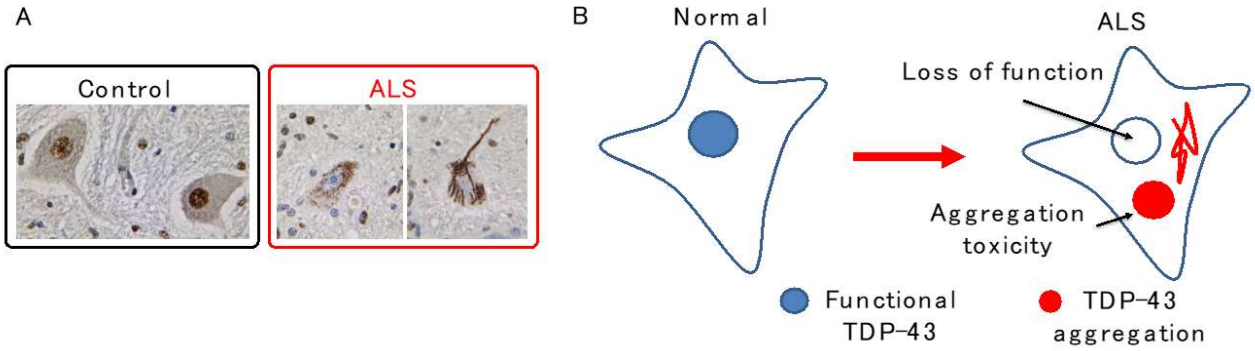


Figure 1. A. Immunostaining of spinal motor neurons. TDP-43 is normally predominantly localized in the nucleus, but forms aggregate in the cytoplasm in ALS pathology. B. “Loss of function” and “aggregate toxicity” of TDP-43 are considered the major causes of the degeneration of motor neurons in ALS.

Research Results

In this study, we closely examined the brains of mice in which TDP-43 was selectively deleted only in neurons (TDP-43cKO mice). We found that the structure known as myelin, which surrounds neuronal axons, was significantly reduced (Fig. 2). Myelin wraps around axons and plays a critical role in enabling fast and precise transmission of electrical signals in the nervous system. Importantly, in these mice, no obvious abnormalities were observed in the neurons themselves or in their axons. This suggests that the reduction in myelin was not a secondary consequence of neuronal or axonal degeneration. Myelin is produced by a type of glial cell distinct from neurons, called oligodendrocytes. However, in the TDP-43cKO mice, the number of oligodendrocytes was not reduced, indicating that the myelin abnormality was not due to a loss of these cells.

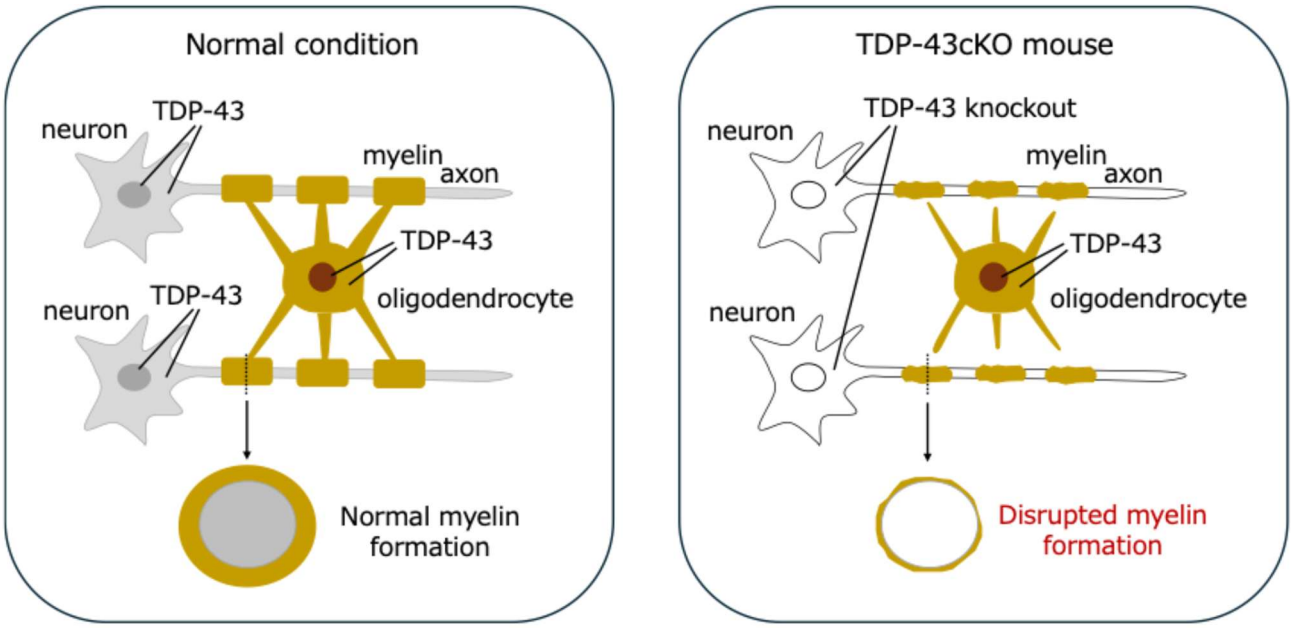


Figure 2. Pathological features of neuron-specific TDP-43 knockout (TDP-43cKO) mice. Although no significant reduction in neuronal number or axonal damage was observed in TDP-43cKO mice, myelin formation was markedly reduced, indicating impaired myelination.

Furthermore, we examined how neural signals are transmitted between the left and right motor cortices of the brain and found that signal conduction was impaired in TDP-43cKO mice. In addition, detailed observation using electron microscopy revealed that the myelin sheath was thinner than normal (Fig. 3). Taken together, these findings suggest that neuronal TDP-43 plays a role in regulating myelin formation produced by oligodendrocytes, highlighting an unexpected mechanism by which neurons influence myelination.

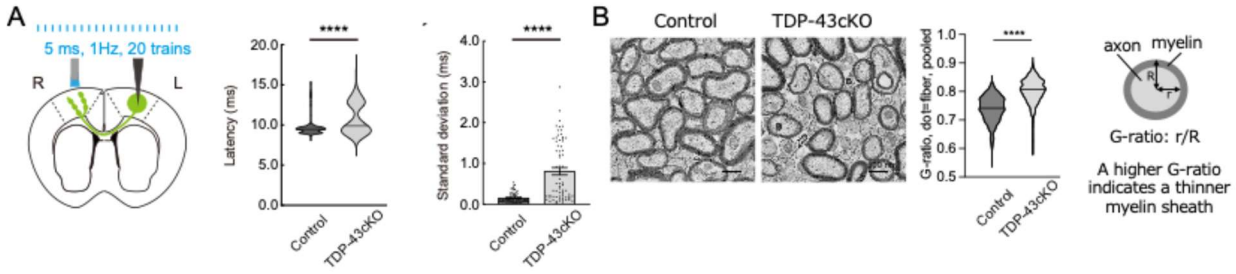


Figure 3. Electrophysiological and ultrastructural analyses in TDP-43cKO mice.
(A) Interhemispheric conduction between the left and right motor cortices was assessed. Neurons in the left motor cortex were rendered responsive to light, and optogenetic stimulation was applied to axon terminals in the right motor cortex, while evoked electrical signals were recorded in the left motor cortex. Latency was significantly prolonged in TDP-43cKO mice, and the standard deviation was also increased, indicating impaired axonal conduction. (B) Evaluation of myelin in the corpus callosum by electron microscopy revealed that the myelin sheath was significantly thinner in TDP-43cKO mice.

When we searched for molecules whose expression levels were altered in neurons lacking TDP-43, we found that Neurexin1 expression was reduced. Further analyses revealed that TDP-43 regulates the expression level of Neurexin1 by stabilizing its messenger RNA (mRNA) (Fig. 4).

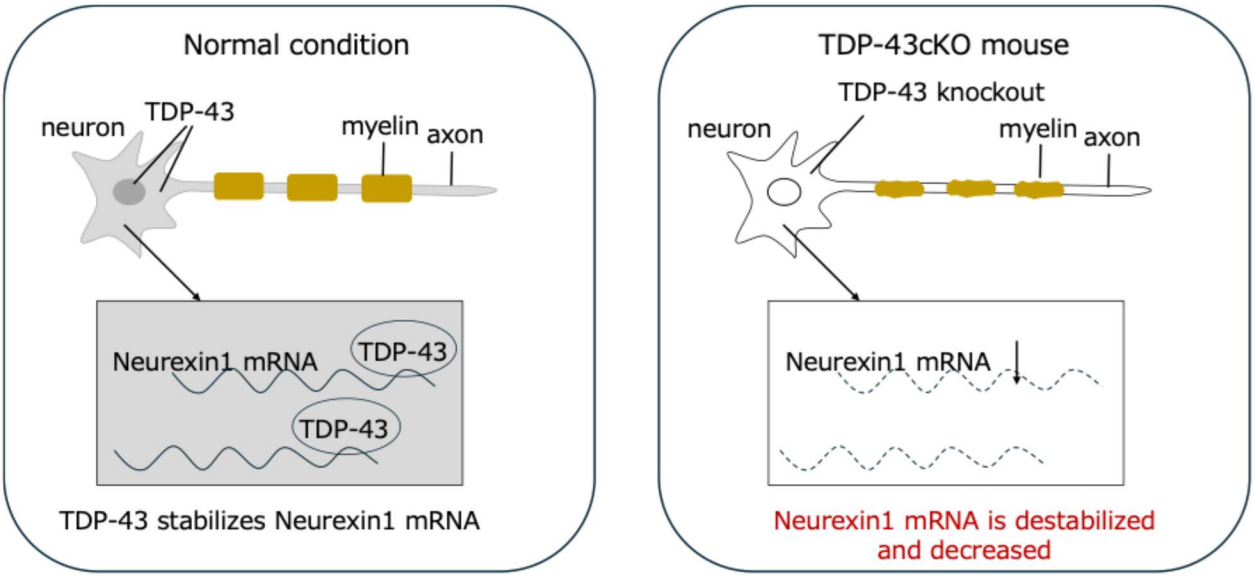


Figure 4. Regulation of Neurexin1 expression by TDP-43.Under normal conditions, TDP-43 stabilizes the messenger RNA (mRNA) of Neurexin1, thereby maintaining its expression. In contrast, in TDP-43–knockout neurons, the absence of TDP-43 leads to reduced Neurexin1 expression due to loss of mRNA stabilization.

We further found that restoring Neurexin1 expression in neurons of TDP-43cKO mice significantly rescued myelin formation (Fig. 5). In addition, although TDP-43cKO mice exhibited short-term memory impairment, this memory deficit was ameliorated when Neurexin1 was restored in neurons of both hippocampi (Fig.

6). Moreover, examination of postmortem brain and spinal cord tissues from patients with amyotrophic lateral sclerosis (ALS) revealed that Neurexin1 expression was also reduced within degenerating neurons.

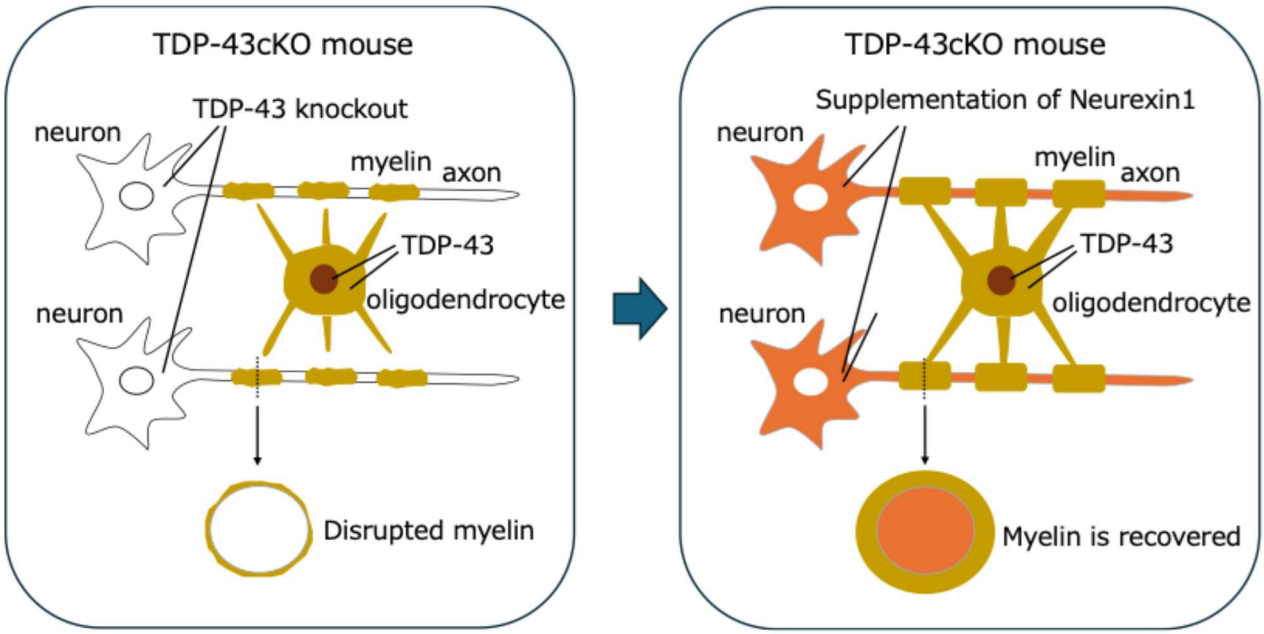


Figure 5. Restoration of Neurexin1 in neurons of TDP-43cKO mice.
Restoring Neurexin1 expression in hippocampal neurons of TDP-43cKO mice led to a significant recovery of myelin formation, indicating that Neurexin1 is sufficient to rescue the myelination deficit caused by neuronal TDP-43 loss.

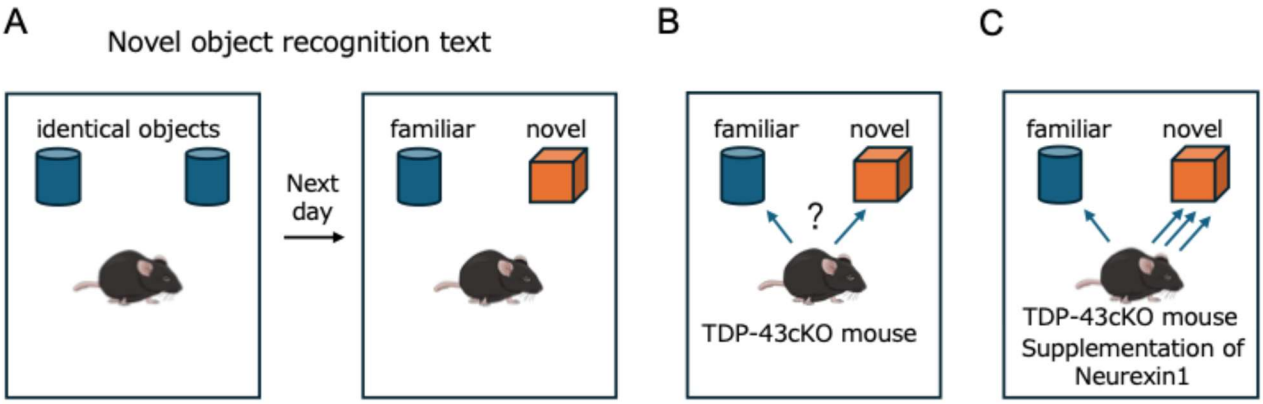


Figure 6. Short-term memory impairment in TDP-43cKO mice.
(A) Novel object recognition (NOR) test. Mice were first exposed to two identical objects during the training phase. On the following day, one of the objects was replaced with a novel object. Mice with intact memory typically show a preference for the novel object. (B) TDP-43cKO mice failed to show a preference for the novel object, suggesting short-term memory impairment. (C) TDP-43cKO mice in which Neurexin1 was restored in neurons of both hippocampi exhibited a renewed preference for the novel object, indicating rescue of the short-term memory deficit.

Future Perspective

In this study, we demonstrated that loss of TDP-43 function in neurons leads to reduced expression of Neurexin1, resulting in hypomyelination and associated functional impairments. These findings suggest that therapeutic strategies aimed at restoring Neurexin1 function may have the potential to ameliorate disease pathology in ALS and FTLD. In future studies, we plan to extend our analyses beyond TDP-43 knockout models to include ALS/FTLD disease models characterized by TDP-43 aggregation. By investigating Neurexin1-related pathologies in degenerating neurons in these models, we aim to further elucidate disease mechanisms and contribute to the development of novel therapeutic approaches.

Publication

Proceedings of the National Academy of Sciences
Neuronal TDP-43 regulates myelin formation via neurexin 1 mRNA stabilization

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DOI: 10.1073/pnas.2513642123

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