News Release

An unexpected reason why sensory neurons resist amyotrophic lateral sclerosis (ALS)

Key Points

- In amyotrophic lateral sclerosis (ALS), motor neurons degenerate owing to impaired proteolytic function, while sensory neurons are not affected.
- It is unclear why sensory neurons remain unaffected in ALS.
- Sensory neurons are spared from neurodegeneration by a lack of certain structures normally present in mature neurons.
- Damage-induced mechanisms involving proteolysis could provide new therapeutic targets.

Summary

Researchers at Nagoya University, Kyoto University, and the National Institutes of Natural Sciences have discovered an unexpected reason why sensory neurons are protected from degeneration in amyotrophic lateral sclerosis (ALS) using unique genetically engineered mice.

ALS is a progressive neurodegenerative disease characterized by motor neuron loss. However, it is not clear why motor neurons are selectively degenerated. ALS pathogenesis is thought to involve dysfunction of the proteasome, which plays a key role in protein degradation. In emergency situations, such as during neuronal damage, the proteasome actively degrades various proteins as part of the stress response to protect damaged neurons. One of the proteasome's targets is the axon initial segment (AIS). The AIS normally exists in mature neurons and acts as a gate for the selective transport of proteins and other materials to axons. In response to an emergency, the proteins comprising the AIS are disassembled by the proteasome. This results in the loss of gate function and an increased influx of mitochondria into the axon to ensure a sufficient supply of energy. Proteasome dysfunction in ALS motor neurons means they cannot activate this emergency response. However, sensory neurons are resilient to ALS pathology. The researchers found that sensory neurons lack the typical AIS structure at the beginning of the axon. This unique feature enables an increased mitochondrial supply to damaged axons in emergency states, even proteasome-deficient ALS conditions.

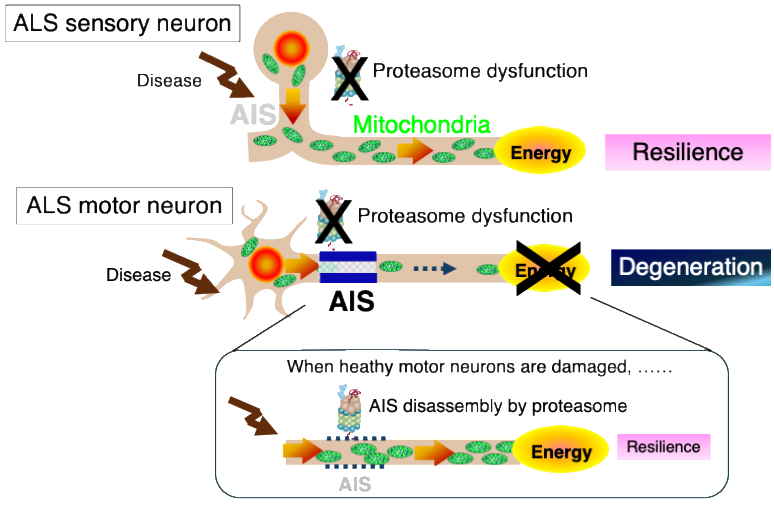
The team, led by Professor Kiryu-Seo and Emeritus Professor Kiyama from Nagoya University, expects that understanding the responses to disease-induced damage could provide new insight for early diagnosis and new clinical interventions. The study was published in the journal *Brain* on June 7, 2025.

Research Background

ALS is a degenerative disease characterized by the progressive loss of motor neurons. Effective treatments have not yet been established. Proteasome dysfunction in ALS is thought to cause the accumulation of protein aggregates, leading to motor neuron degeneration. However, the research team believes that the ability of motor neurons to resist ALS pathology might be impaired long before protein aggregates appear. In 2022, the researchers discovered a proteasome-dependent stress response in motor neurons that prevents axonal degeneration (Kiryu-Seo et al., EMBO J, 2022).

Neurons require large amounts of energy to maintain their structural and functional integrity. They have a unique morphology in which a single, long axon extends from the cell body. Mitochondria are critical for supplying energy, so neurons have developed an effective system to deliver healthy mitochondria from the cell body to the axon. The junction between the cell body and axon, the AIS, normally functions as both an action potential generator and a gate for the selective transport of cargo such as mitochondria. In response to axonal injury, AIS proteins in motor neurons undergo proteasome-mediated disassembly, resulting in the loss of their gate function. This increases the influx of mitochondria from the soma into the axon, satisfying the energy demand of the axon and preventing motor neuron degeneration.

The reason why motor neurons selectively degenerate in ALS remains unclear. Neuroanatomically, the axons of both motor and sensory neurons co-exist, forming the spinal nerves. Inflammation around the spinal nerves exacerbates ALS pathology. However, it is unclear why sensory neurons remain unaffected in ALS. This study attempted to clarify why sensory neurons exhibit greater resilience to damage despite proteasome dysfunction.



Why do sensory neurons have greater resilience to ALS pathological damage?

Research Results

The researchers first examined whether ALS damages sensory neurons using mouse models of the disease. They found that ATF3 expression is induced in both motor and sensory neurons during disease progression. ATF3 is a stress-responsive transcription factor induced in neurons after disease or nerve injury, and a well-known marker of damaged neurons. This result indicates that sensory neurons are also damaged by ALS. Next, the researchers addressed why sensory neurons are resilient to the disease, despite being damaged. It was hypothesized that sensory neurons may have a mechanism that provides resistance to the effects of proteasome dysfunction, a hallmark of ALS.

To address this issue, the researchers used a sciatic nerve injury model. This is because diseased and injured neurons share many common stress responses, making nerve injury a simple, appropriate, and reproducible experimental model for analyzing damage response mechanisms. The sciatic nerve is a spinal nerve consisting of motor and sensory axons. When the sciatic nerve is cut, both types of neurons are damaged simultaneously and exhibit various responses. Alongside the sciatic nerve injury model, the researchers used *Atf3*:bacterial artificial chromosome transgenic (BAC Tg) mice. In these mice, the induction of Cre recombinase and GFP labelling of mitochondria are under the control of an *Atf3* gene regulatory element, and therefore only occur in damaged neurons. Using these BAC Tg mice as Cre driver mice, the researchers generated a line in which the proteasome is specifically deleted in damaged neurons.

Surprisingly, injury-induced proteasome-deficient sensory neurons survived after sciatic nerve injury. In contrast, injury-induced proteasome-deficient motor neurons degenerated quickly; this is because of their lack of a proteasome-mediated stress resilience mechanism. Previously, the research team identified an AIS protein, AnkG, as a crucial proteasome target after motor axon injury. The proteasome-dependent breakdown of the AIS would be beneficial for damaged motor neurons to supply mitochondrial energy to axon. Thus, the researchers examined the morphological distribution of AIS proteins and mitochondria in sensory neurons before and after nerve injury. They found unexpected result that no AIS-related proteins were detected at the initial segment of the sensory neuron even before injury, while mitochondria were evenly distributed in the region. Owing to the mutually exclusive relationship between AIS proteins and mitochondria, the researchers concluded that sensory neurons lack a typical AIS.

Finally, researchers examined this damage-induced mechanism in ALS model mice. ALS motor neurons respond to pathological damage. However, pathologically damaged ALS motor neurons fail to disassemble the AIS due to proteasome dysfunction, restricting mitochondrial entry into the axon. In

contrast, the absence of the AIS in sensory neurons facilitates an increase in damage-induced mitochondrial influx into the axon, with or without activity of the proteasome. This may explain how sensory neurons resist ALS pathology.

Research Summary and Future Perspective

The AIS is a hallmark of mature neurons, and its absence in sensory neurons is an unexpected protective mechanism against neurodegeneration. The regulation of AIS degradation is a key to resisting pathological damage in ALS. There might be additional unknown proteasome-dependent or -independent mechanisms that affect resilience to pathological damage before protein aggregation becomes apparent in ALS. Understanding the response to disease-induced damage could provide new insights for early diagnosis and clinical intervention.

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Japanese ver.
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