News Release

Title
Innate immune adaptor TRIF confers neuroprotection in ALS mice by eliminating abnormal glial cells

Key Points
1. Glia and immune cells surrounding motor neurons are involved in the disease progression of amyotrophic lateral sclerosis (ALS).
2. Ablation of innate immune adaptor TRIF shortened survival times of ALS mice.
3. TRIF pathway plays an important role in protecting a microenvironment surrounding motor neurons by eliminating abnormally activated astrocytes.

Summary
There are compelling evidence that glial and immune cells contribute to the progression of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), an adult motor neuron disease. The adaptive immune response has been implicated in disease processes of ALS, but it remains unknown if innate immune signaling also contributes to ALS progression.

The research group led by Professor Koji Yamanaka in Research Institute of Environmental Medicine, Nagoya University (Director, Koji Yamanaka, MD, PhD) and Nagoya University Graduate School of Medicine (Dean, Kenji Kadomatsu, MD, PhD) revealed that deficiency of the innate immune adaptor TRIF, which is essential for certain Toll-like receptor (TLR) signaling cascades, significantly shortened survival time of ALS mice. While MyD88 is also a crucial adaptor protein for most TLR signaling pathways, MyD88 deficiency had only a marginal impact on disease course. They also found that aberrantly activated astrocytes were accumulated in the lesions of TRIF-deficient ALS mice, and that the number of aberrantly activated astrocytes was negatively correlated with survival time. To date, the fate of activated astrocytes in neurodegenerative disease was not known. These results suggest that TRIF pathway plays an important role in protecting a microenvironment surrounding motor neurons by eliminating aberrantly activated astrocytes.

Collectively, the current study reveals the novel roles of innate immunity in ALS pathomechanism and the researchers expect that their finding provides a clue to develop a new therapeutic approach for protecting ALS motor neurons. This work was published online in Cell Death & Differentiation on March 22, 2018.

Research Background
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease damaging motor neurons in brain and spinal cords. ALS patients show progressive muscle weakness and atrophy, leading to a fatal respiratory muscle paralysis. There are no effective therapies for ALS. About 10% of ALS patients are familial cases, and a dominant mutation in the gene for Cu/Zn superoxide dismutase gene (SOD1) is one of the frequent causes of familial ALS. The mice expressing SOD1 gene with human ALS mutation show ALS-like disease, and were frequently used for ALS research.

The recent research revealed that neuroinflammation, consisted of activated glial cells and infiltrating
immune cells in the lesion, contributes to the progression of ALS. Immune response is consisted of innate and acquired immunity. Innate immunity is the first line of defense for protecting the host from invading pathogens, while acquired immunity requires lymphocytes to enable highly specific and long-lasting protection to a particular pathogen. Although the previous studies showed the upregulation of innate immunity-related molecules in the lesion of ALS mouse and human ALS patients, the role of innate immune response in ALS was largely unknown.

**Research Results**

To test the role of innate immune response in the mouse model of ALS, the researchers focused on Toll-like receptors (TLR), which are important sensors for innate immunity. TLR signaling requires TRIF and MyD88, two critical adaptor proteins for transmitting signals. They found that ablation of TRIF significantly shortens survival time of ALS mice. While MyD88 is also a crucial adaptor for most TLR signaling pathways, MyD88 deficiency had no impact on disease course (Figure 1). In addition, they found that aberrantly activated astrocytes were accumulated in the lesions of TRIF-deficient ALS mice. Astrocytes, one type of glial cells are the supporting cells for survival and function of neurons in the brain by secreting many kinds of neuroprotective molecules. However, in the lesion of ALS, astrocytes change their shapes and some of them are abnormally activated to secrete the harmful molecules to the neurons (Figure 2). These aberrantly activated astrocytes overproduced toxic reactive oxygen. Researchers found TRIF signaling is able to eliminate these aberrantly activated astrocytes by apoptosis, a suicide program of the cells. In the absence of TRIF, these astrocytes were accumulated. Moreover, the number of aberrantly activated astrocytes was negatively correlated with survival time of ALS mice, suggesting that these astrocytes are toxic to the motor neurons (Figure 3).
Research Summary and Future Perspective

These results revealed for the first time that the TRIF pathway is involved in eliminating aberrantly activated astrocytes to maintain the microenvironment surrounding motor neurons in ALS mice. The current study reveals the new roles of innate immunity in ALS pathomechanism and provides a clue to develop a new therapeutic approach for protecting ALS motor neurons.

Publication

Innate immune adaptor TRIF deficiency accelerates disease progression of ALS mice with accumulation of aberrantly activated astrocytes

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