Medical & healthcare, Drug discovery

Development of therapeutic agents for amyotrophic lateral sclerosis by improving ribosome function

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurological disorder that causes muscle weakness and atrophy due to motor neuronal degeneration. In most ALS cases, TDP-43 is abnormally deposited mainly in neurons, but it was unclear how TDP-43 functions in neurons and how the deposition of TDP-43 causes ALS.

TDP-43 has been shown to bind to a large number of mRNAs and act on their intracellular maturation and transport. We focused on axons, which are the protruding structures of neurons, and identified mRNAs encoding ribosomal protein (ribosome protein mRNAs) as targets transported to axons by TDP-43. TDP-43 transports ribosomal protein mRNAs to axons to maintain the amount of ribosomal proteins produced in axons, which in turn maintains the number of ribosomes to translate various proteins in axons, which leads to maintaining the morphology and function of neurons (Figs. 1 and 2).

Background & Results

We established a method for collecting only the axon portion from cultured neurons, and used that method to search for mRNAs that are reduced in the axons of neurons in which TDP-43 was reduced by the microarray method. As a result, multiple ribosomal protein mRNAs were identified as a group of genes that were significantly reduced.

Ribosome proteins are proteins that constitute ribosome, which is an intracellular apparatus essential for translating proteins from mRNAs, and has a great influence on the translation efficiency of the entire protein by the ribosome. Analysis using cultured neurons revealed that ribosomal protein mRNAs co-localize with TDP-43 in a granular manner, ribosomal protein mRNAs and TDP-43 bind to each other, and the transport of granules containing ribosomal protein mRNAs to the axons was reduced due to a decrease in TDP-43. It was also found that ribosomal protein mRNAs transported to axons are translated into ribosomal proteins in axons by stimulation of neurons, and plays an important role in maintaining the translation function of ribosomes.

When TDP-43 is decreased in cultured neurons and neurons in mouse brains, axon elongation gradually deteriorates, but when each ribosomal protein mRNA is overexpressed at the same time, axon elongation was confirmed to improve (Fig. 2). Furthermore, when the motor neurons of the brain tissue of ALS patients with abnormal TDP-43 deposition were examined, it was found that multiple ribosomal protein mRNAs were decreased.

From the above, TDP-43 has the function of transporting ribosomal protein mRNAs to the axon in neurons, thereby supplying the ribosomal proteins in the axon to maintain the translation function by the ribosome. It was also clarified that the synthesis of various proteins in the axons was impaired and the elongation of the axons was inhibited, which were presumed to be associated with the onset of ALS (Fig. 1).

Significance of the research and Future perspective

In the future, it will be possible to develop a fundamental therapeutic method for ALS based on a new mechanism of action by transporting ribosomal protein mRNAs to axons, translating it there, and identifying drugs that increase the function of ribosomes in axons.

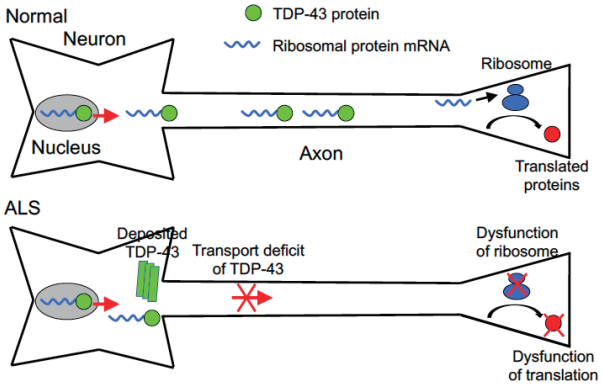

Fig. 1. Model of ALS pathogenesis by TDP-43 deposition

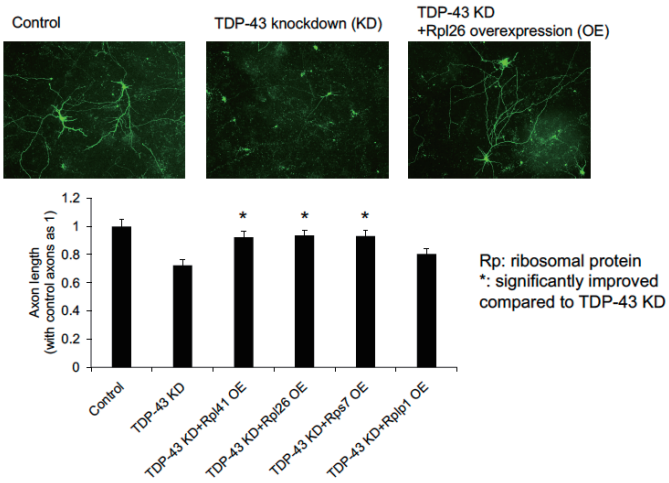

Fig. 2. Protective effects of Rp on axon outgrowth deficit by TDP-43 KD

Patent Japanese Patent Application No. 2016-087320, Japanese Unexamined Patent Publication No. 2017-197443

Treatise Nagano, Seiichi; Jinno, Junki; Abdelhamid, Rehab F. et al. TDP-43 transports ribosomal protein mRNA to regulate axonal local translation in neuronal axons. Acta Neuropathol. 2020; 140(5): 695-713. doi: 10.1007/s00401-020-02205-y

URL

Keyword amyotrophic lateral sclerosis, TDP-43, mRNA, axonal transport, ribosomal protein