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

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Project Outline

Amyotrophic lateral sclerosis (ALS) is a neurological disorder that causes systemic muscle weakness and muscle thinning (atrophy) due to disorders of motor neurons. The effects of current marketing drugs are limited, and the development of more radical therapeutic agents is eagerly desired. In most ALS cases, it is known that a protein called TDP-43 is abnormally accumulated (deposited) mainly in the neurons at the lesion site, and some changes in the cell function of TDP-43 are indicated. It is considered that they are deeply involved in the onset of the disease. TDP-43 has the property of binding to messenger RNA (mRNA), which is a template required to make various proteins from genes in cells. Focusing on neurites, which are specific structures of neurons, especially axons, which are long neurites, we focus on mRNAs that encode multiple ribosomal proteins we identified as important mRNAs transported to axons by TDP-43. Ribosomal proteins are the skeleton that forms the ribosome, the apparatus involved in the synthesis of all proteins in the cell. If TDP-43 does not work well in neurons, the amount of ribosome protein mRNA transported to axons decreases, and the protein synthesis function by ribosomes there decreases, resulting in axon damage and eventually neuronal damage (Fig. 1). Actually, we confirmed that reducing TDP-43 in cultured neurons worsens axon elongation, while at the same time overexpressing several ribosomal proteins improves axon elongation (Fig. 2). This suggests that drug discovery targeting ribosomal proteins may lead to the development of new therapies for ALS. Therefore, in this project, we search for small molecule compounds and viral vectors that increase the expression of ribosomal proteins and related proteins, confirm the disease suppression effect of their administration to ALS model animals, and develop a novel ALS treatment strategy by improving the function of ribosomes.

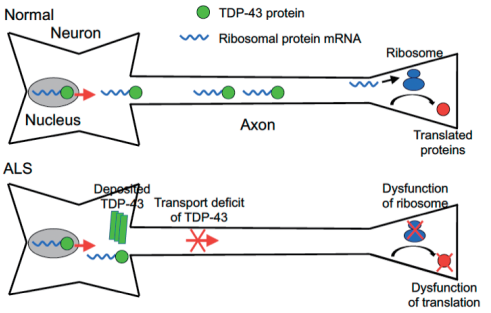

Fig. 1. Model of ALS pathogenesis by TDP-43 deposition

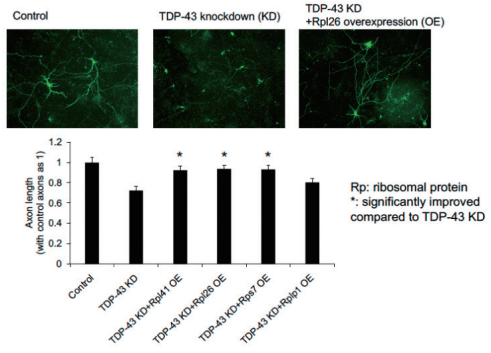

Fig. 2. Protective effects of Rp on axon outgrowth deficit by TDP-43 KD

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TDP-43 Proteinopathy Therapeutic Composition