Researchers reveal novel therapeutic strategy for ALS

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Researchers from the Institute of Neuroscience and their collaborators have revealed a new cellular mechanism for amyotrophic lateral sclerosis (ALS), suggesting a novel therapeutic strategy targeting the RNA degradation pathway, and identified an asthma drug as a potential medication for ALS.

In a study published online in *Brain* on April 1, researchers from Dr. XU Jin's lab at the Institute of Neuroscience of the Chinese Academy of Sciences and their collaborators revealed a new cellular mechanism for amyotrophic lateral sclerosis (ALS), suggested a novel therapeutic strategy targeting the RNA degradation pathway, and identified an asthma drug as a potential medication for ALS.

ALS is the most common motor neuron disease and one of the most devastating neurodegenerative diseases caused by progressive motor neuron degeneration. There is no cure for the disease, and current treatment options are very limited. Thus, the disease is characterized by fast progression and high lethality.

Recent genetic advances have identified a group of new genes whose mutations contribute to the development of ALS. Among these genes, C9orf72 is the most common genetic cause of familial ALS, and even contributes to sporadic ALS.

Unlike commonly seen point mutations and deletions, (GGGGCC)n hexa-nucleotide repeats expansion (HRE) in a non-coding region of

C9orf72 is the culprit. Intriguingly, these repeats could generate RNA and protein products and affect RNA metabolism as some other ALS-causing mutant proteins do, although the underlying mechanisms remain to be fully understood.

In this study, by coupling unbiased bioinformatic analysis of various transcriptome studies with validation experiments in multiple C9orf72 cellular and animal models, Dr. XU's team unveiled the inhibition of the nonsense-mediated mRNA decay (NMD) pathway as a conserved consequence of the C9orf72 HRE.

NMD is a type of RNA surveillance machinery vital for the removal of defective or harmful RNA generated from faulty transcription, alternative splicing or viral infection. Key protein components of NMD are found in cytoplasmic structures called processing bodies.

Interestingly, researchers found that HRE-derived neurotoxic dipeptide repeats (DPRs) could inhibit the NMD pathway by suppressing processing-body formation while promoting stress granule formation.

To test whether the NMD pathway could be a potential therapeutic target for ALS, they first genetically reactivated the NMD pathway and found that core NMD genes, such as UPF1, could effectively protect against C9orf72 DPRs neurotoxicity. Next, after evaluating several potential NMD-activating compounds, they identified Tranilast as the most promising NMD-activating drug and found that it could rescue cells and fruit flies from C9orf72 DPR-induced neurotoxicity.

Given that blood-brain barrier-permeable Tranilast has been clinically used to treat asthma with a great safety record since the 1980s, this study will prompt future pre-clinical and clinical investigations to test the therapeutic potential of Tranilast and other NMD-activating compounds in ALS patients with defective RNA metabolism.

More information: Wangchao Xu et al, Reactivation of nonsense-mediated mRNA decay protects against C9orf72 dipeptide-repeat neurotoxicity, *Brain* (2019). DOI: 10.1093/brain/awz070