Press Release

Keio University

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Discovery of Highly Toxic SOD1 Protein in Sporadic Amyotrophic Lateral Sclerosis —Expectations of a New Target toward the Development of Treatments for Intractable Neurological Diseases—

Keio University Faculty of Science and Technology Associate Professor Yoshiaki Furukawa and Research Associate Eiichi Tokuda (at the time of research; currently an assistant professor at Nihon University School of Pharmacy) conducted joint research with Vice Director Shinji Ohara of the National Hospital Organization Matsumoto Medical Center Department of Neurology (currently at the Iida Hospital Department of Neurology), Professor Isao Hozumi of the Gifu Pharmaceutical University Laboratory of Medical Therapeutics and Molecular Therapeutics, and Professor Noriko Fujiwara of the Hyogo College of Medicine Department of Biochemistry, discovering for the first time that cerebrospinal fluid collected from patients with amyotrophic lateral sclerosis (ALS), a neurodegenerative disease, contains SOD1 proteins with extremely high cytotoxicity. It was previously known that ALS develops when a mutation occurs in the *SOD1* gene that encodes the SOD1 protein, but even in sporadic ALS, for which the genetic background is unclear, it is suggested that abnormalities of the SOD proteins are involved in the onset of the disease. Because 90 to 95% of ALS cases are sporadic, the findings in this study are very important when considering the mechanisms that cause ALS and methods for its treatment.

The research was supported by the Ministry of Education, Culture, Sports, Science and Technology's Grant-in-Aid for Scientific Research on Innovative Areas for "Integrated Bio-metal Science", etc., and the outcomes of this research were presented in the online issue of the international scientific journal Molecular Neurodegeneration on November 19, 2019.

Amyotrophic lateral sclerosis (ALS) is an adult-onset neuromuscular disease in which motor neurons in the brain and spinal cord degenerate, and it is said that the disease affects approximately 2 out of every 100,000 people. The age of onset and duration of illness vary depending on the patient, but along with symptoms such as muscle weakness, muscle atrophy, and paralysis, breathing becomes difficult about 3 to 5 years after onset, making the use of a ventilator a necessity. There are only 2 drugs that have been approved to treat ALS, Riluzole and Edaravone, but their effectiveness is limited. Therefore, there is a need to understand the pathology of ALS and also for the early development of a fundamental treatment.

In this study, it was found that there are abnormalities in the structure of proteins known as SOD1 in the cerebrospinal fluid of patients with sporadic ALS, for which the responsible gene is unclear. In addition, although cerebrospinal fluid from ALS patients showed extremely high cytotoxicity, removing the structurally abnormal (called misfolded) SOD1 proteins from the cerebrospinal fluid significantly reduced the toxicity to cultured motor neuron-like cells.

Furthermore, misfolded SOD1 were also detected in some patients with other neurodegenerative diseases, suggesting that misfolded SOD1 are an important substance in understanding diseases other than ALS. However, further studies are required to confirm whether or not misfolded SOD1 are directly involved in the development of ALS and exacerbating the condition, or are only a product resulting from the disease. It is also necessary to figure out where and how SOD1 misfolds. For example, as a future step, it will be necessary to make clear whether SOD1 misfolded in the motor neuron of the spinal cord, which is the main region affected by ALS, is then discharged into the cerebrospinal fluid, or whether SOD1 discharged into the cerebrospinal fluid is subsequently misfolded within the fluid. If the mechanism by which misfolded SOD1 exert toxicity on neurons can be clarified, new advancements can be expected in the development of therapeutic medicine for ALS, a typical example of an intractable neurological disease.

＜Details of original paper＞

Title "Wild-type Cu/Zn-superoxide dismutase is misfolded in cerebrospinal fluid of sporadic amyotrophic lateral sclerosis"
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