Role of repulsive guidance molecule A in amyotrophic lateral sclerosis

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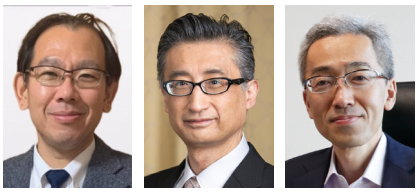

Abstract

The repulsive guidance molecule A (RGMa) is a potential therapeutic target for various neurological disorders. In this study, we investigated the role of RGMa in amyotrophic lateral sclerosis (ALS). Measurement of RGMa in the cerebrospinal fluid (CSF) of patients with ALS has shown a specific increase that correlates with respiratory function. Additionally, a neutralizing antibody against RGMa was effective in an animal model of ALS. The RGMa-neutralizing antibody also reduced abnormal protein aggregation in the anterior horn of the spinal cord in the ALS animal model, suggesting that RGMa promotes abnormal protein aggregation and exacerbates disease pathology in ALS.

Background & Results

ALS is a devastating neurodegenerative disease characterized by the accumulation of abnormal proteins in motor neurons. However, there is an unmet need to elucidate its pathology and develop effective treatments. RGMa was initially identified as an axon-guiding molecule that plays a critical role in the pathogenesis of several neurological diseases, including spinal cord injury and multiple sclerosis, positioning it as a promising therapeutic target. This study found that RGMa in the CSF was specifically increased in ALS and was correlated with the deterioration of respiratory function (Figure 1). Additionally, the expression of Neo1, a receptor for RGMa, increased in anterior horn motor neurons of the spinal cords of patients with ALS. Increased RGMa in the CSF and Neo1 expression have also been observed in a transgenic mouse model of ALS expressing mutant superoxide dismutase 1 (SOD1).

The treatment of ALS model mice with an anti-RGMa antibody resulted in prolonged survival, improved motor function, and decreased abnormal protein aggregation (Figure 2). RGMa alters the activity of small GTPases and actin dynamics. Consistent with the increase in RGMa and Neo1 levels, reduced levels of filamentous actin and phosphorylated cofilin were observed in the spinal cords of ALS mice, whereas treatment with an anti-RGMa antibody restored these changes. In in vitro experiments using primary cultured rat neurons, recombinant RGMa added to the culture medium enhanced the entry of mutant SOD1 into the neurons. This increased entry was inhibited by an anti-RGMa antibody, Neo1 knockdown by siRNA, and an actin depolymerization inhibitor. Previous reports have suggested that filamentous actin in neurons serves as a barrier preventing the intracellular entry of abnormal proteins, a concept termed as the “actin barrier.” RGMa likely destabilizes the actin barrier through the dephosphorylation of cofilin, enhancing the entry of abnormal proteins into neurons and contributing to the progression of ALS.

These results suggest that anti-RGMa therapy may strengthen actin polymerization via cofilin phosphorylation, thereby preventing the entry of abnormal proteins into neurons and ameliorating neurodegeneration in ALS.

Significance of the research and Future perspective

This study demonstrated that RGMa-induced disruption of the neuronal actin barrier in ALS promotes the intercellular transmission of pathogenic proteins, exacerbating disease pathology. The increase in RGMa in CSF appears to be specific to ALS, potentially serving as a biomarker for diagnosis and prognosis, in addition to being a therapeutic target. Such a pathology may not be specific to ALS but rather common to other neurodegenerative diseases involving protein aggregation, implying that RGMa inhibition therapy may also be applicable to Alzheimer’s disease, Parkinson’s disease, frontotemporal dementia, and other related conditions.

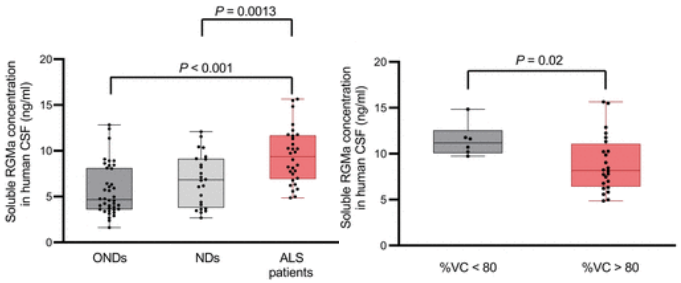

Figure 1: RGMa levels increase in CSF of patients with ALS (left)
Higher concentrations of RGMa in CSF are associated with lower vital capacity (%VC; right). This figure was reproduced from Shimizu et al.

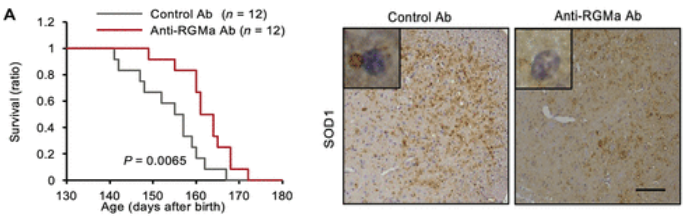

Figure 2: Administration of anti-RGMa antibody prolongs survival in ALS mice(left) and reduces SOD1-positive aggregate deposition(right). This figure was reproduced from Shimizu et al.

Patent
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