News Release

Title

Metabolome and transcriptome analysis on muscle of sporadic inclusion body myositis

Key Points

- Sporadic inclusion body myositis (sIBM) is the most common inflammatory myopathy in the elderly, showing a slow progression.
- Although sIBM is characterized by skeletal muscle inflammation and degeneration due to protein accumulation, the disease is not responsive to conventional therapies that suppress inflammation. There is a need to elucidate the pathogenesis of the disease in order to develop new therapeutic targets.
- In this study, we found that the skeletal muscles of sIBM show increased histamine biosynthesis due to mast cell infiltration and impaired degradation of chondroitin sulfate, which accumulates in the interstitium.
- Mast cells and chondroitin sulfate are potential therapeutic targets for sIBM.

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine has revealed that the pathogenesis of sporadic inclusion body myositis (sIBM), the most frequent myositis among the elderly, is related to mast cells and chondroitin sulfate. This work was published online in *Annals of Clinical and Translational Neurology* in September 2022.

sIBM is a type of inflammatory myopathy characterized by inflammation of skeletal muscle, and the progression of the disease causes gait and swallowing disorders. There is no treatment to control the progression of the disease, so that patients cannot avoid the loss of mobility and aspiration pneumonia due to weakness of limb and pharyngeal muscles. sIBM is characterized by the presence of inflammatory infiltrates in skeletal muscle and protein accumulation in muscle fibers, but there are many unknowns about its pathogenesis, and more detailed pathophysiology is needed to develop treatment methods.

In this study, by combining two analytical methods, metabolomic analysis and transcriptomic analysis, Prof. Katsuno and his research team identified increased histamine biosynthesis and impaired chondroitin sulfate degradation in skeletal muscle in sIBM. Histopathological examination showed infiltration of mast cells and deposition of chondroitin sulfate in skeletal muscle samples, supporting the results of metabolomic and transcriptomic analyses.

The results of this study suggest that mast cells and chondroitin sulfate are involved in the pathogenesis of sIBM and may be new therapeutic targets.

Research Background

Sporadic inclusion body myositis (sIBM) is the most common inflammatory myopathy in the elderly, and the number of patients is gradually increasing worldwide. The main symptom of sIBM is a progressive weakness of the quadriceps and finger and wrist flexors, leading to loss of grip strength, gait disturbance, and eventual shortening of healthy life expectancy. Dysphagia due to bulbar palsy is reported in about half of patients, although respiratory failure is uncommon. Immunosuppressing therapies, including steroids, often fail to suppress progression, and no curative therapies have been identified for sIBM.

Research Results

In this study, we combined two methods, metabolomic analysis and transcriptomic analysis, to analyze the changes occurring in the skeletal muscles of sIBM patients (Figure 1).

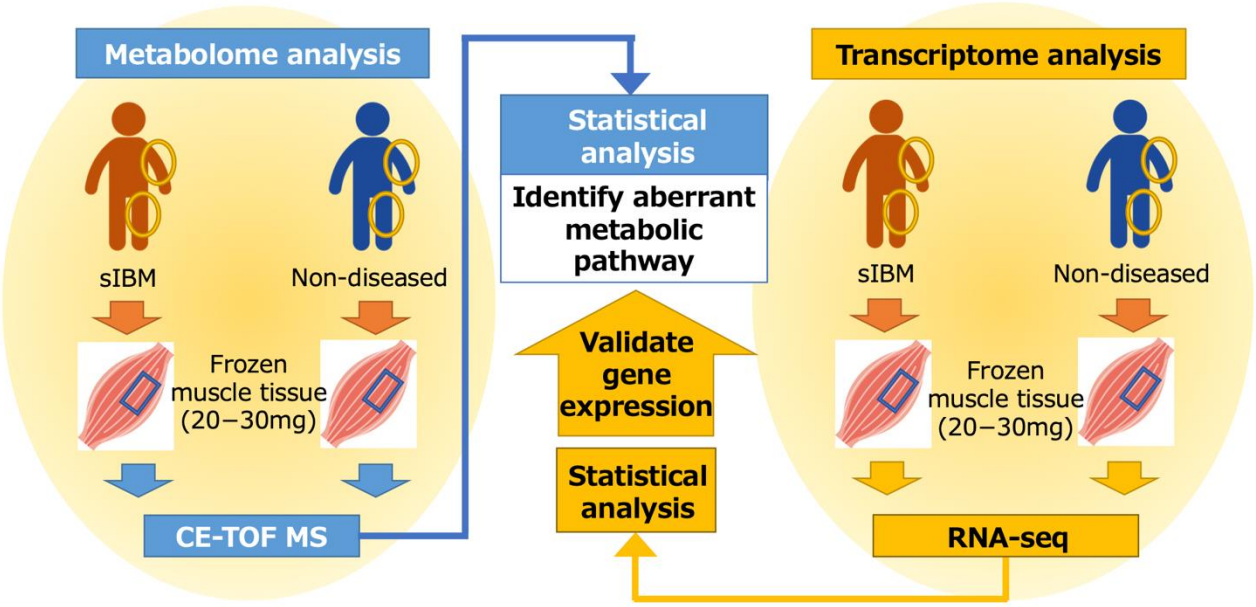

Figure1. Patients and methods

By metabolome analysis, we found that the levels of histamine and sugar nucleotides (materials for glycosaminoglycans, including chondroitin sulfate) were increased in the skeletal muscles of sIBM patients (Figure 2).

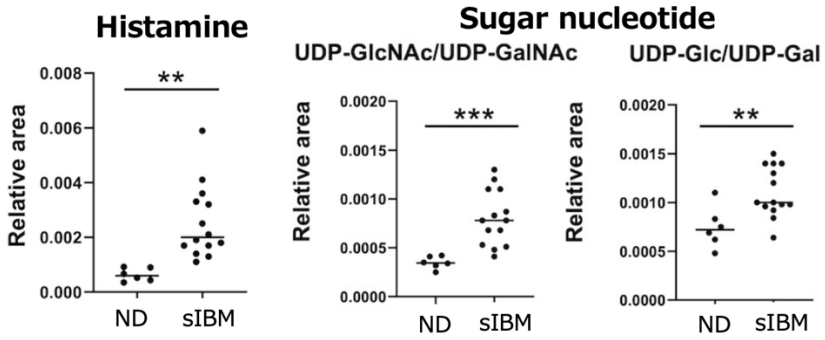

Figure2. Results of metabolome analysis

Transcriptome analysis was performed to confirm gene expression. The results showed that (1) expression of genes involved in histamine biosynthesis was enhanced, and (2) expression of genes involved in chondroitin sulfate biosynthesis was enhanced, but expression of genes related to degradation was insufficient. Next, we investigated the number of mast cells in the skeletal muscles of sIBM patients and found that the number of mast cells was higher than in non-diseased subjects (Figure 3A). Immunohistochemistry confirmed that chondroitin sulfate deposited in the skeletal muscles of sIBM patients, especially in the interstitium (Fig. 3B).

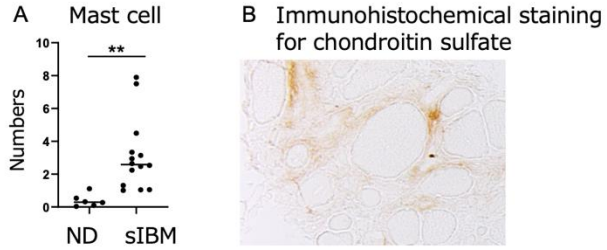

Figure3. Mast cells and chondroitin sulfate in patients with sIBM

Research Summary and Future Perspective

The results of this study suggest that mast cells and chondroitin sulfate are involved in the pathogenesis of sIBM. In the future, we would like to confirm that these changes are reproduced using animal models, and to verify whether therapeutic agents that suppress mast cell infiltration and/or chondroitin sulfate accumulation improve symptoms of sIBM.

Publication

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