Press Release

Keio University

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Keio University School of Medicine

Sjögren's Disease Pathophysiology by Autoantibody Profile: Paving the Way for Personalized and Precision Medicine

A research team at the Keio University School of Medicine's Division of Rheumatology has revealed at a single-cell level that the immune response and inflammation mechanisms in the salivary glands of patients with the autoimmune disorder Sjögren's disease differ according to the type of autoantibodies. The Keio team includes Jun Inamo (co-first author), Masaru Takeshita (co-first author), Yuko Kaneko, and Tsutomu Takeuchi, in collaboration with Immune-mediated Inflammatory Diseases Consortium for Drug Development—an industry–academia collaborative research organization led by Keio University School of Medicine—and the Laboratory for Regulatory Genomics (Team Director: Chung-Chau Hon) at the RIKEN Center for Integrative Medical Sciences (IMS).

This study employed an integrative approach combining cutting-edge methods, including single-cell analysis to comprehensively profile gene expression in individual salivary gland cells and spatial transcriptome analysis to assess cells in their tissue context. The results revealed three key findings: (1) expansion of cytotoxic GZMB+GNLY+CD8 positive T cells that directly attack the salivary glands, (2) distinct inflammatory pathways associated with different autoantibody types, and (3) THY1 positive fibroblasts functioning as a local "command center" orchestrating inflammation. These insights mark an important step toward developing fundamental treatments for Sjögren's disease, which until now has been managed primarily with symptomatic therapies, paving the way for therapies targeting both common and distinct disease pathways, tailored to each patient's specific condition.

These research findings were published in the international scientific journal *Nature Communications* on September 22, 2025 (London time).

1. Research Background

Sjögren's disease is an autoimmune disorder in which the body's immune cells attack exocrine glands, primarily the lacrimal and salivary glands, causing dry eye (keratoconjunctivitis sicca) and dry mouth (xerostomia). In Japan, the number of patients is estimated to be between 100,000 and 300,000. However, at present, there is no fundamental cure, and treatment is mainly symptomatic, aimed at alleviating symptoms.

Normally, our bodies have antibodies that bind to foreign invaders such as bacteria and viruses, working with immune cells to eliminate them and maintain health. However, patients with Sjögren's disease possess autoantibodies—antibodies that mistakenly target the body's own tissues. Representative examples include anti-SSA antibodies and anti-centromere antibodies, and clinical findings, such as arthritis and skin symptoms, vary depending on autoantibody type (Figure 1). However, the underlying mechanism explaining how differences in autoantibodies lead to differences in symptoms has remained unclear.

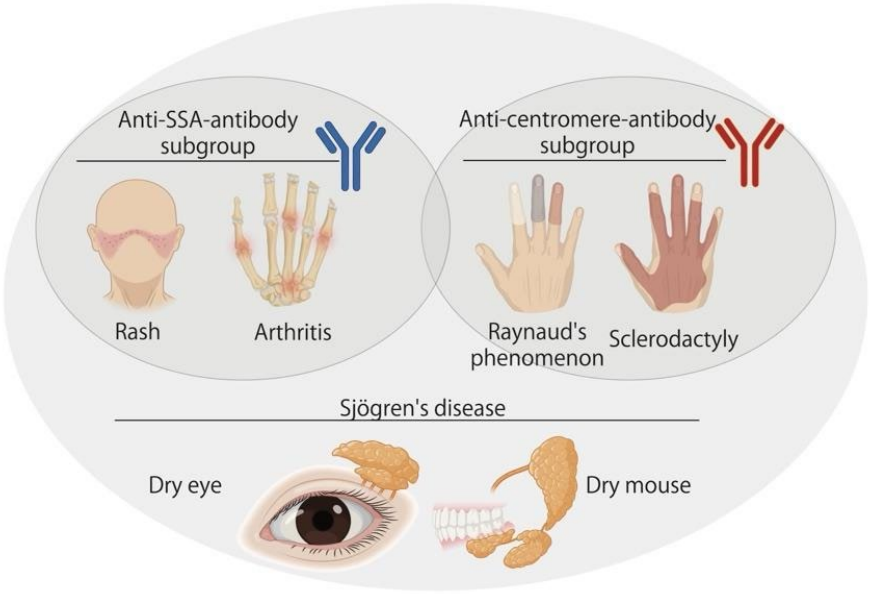

Figure 1: Clinical presentations in Sjögren's disease by autoantibody type

2. Research Significance

The research group obtained a total of 38 salivary gland tissue from two groups—those with Sjögren's disease who had different autoantibodies, and those with Sicca syndrome who lacked these autoantibodies—and compared the disease mechanisms at a molecular level (Figure 2).

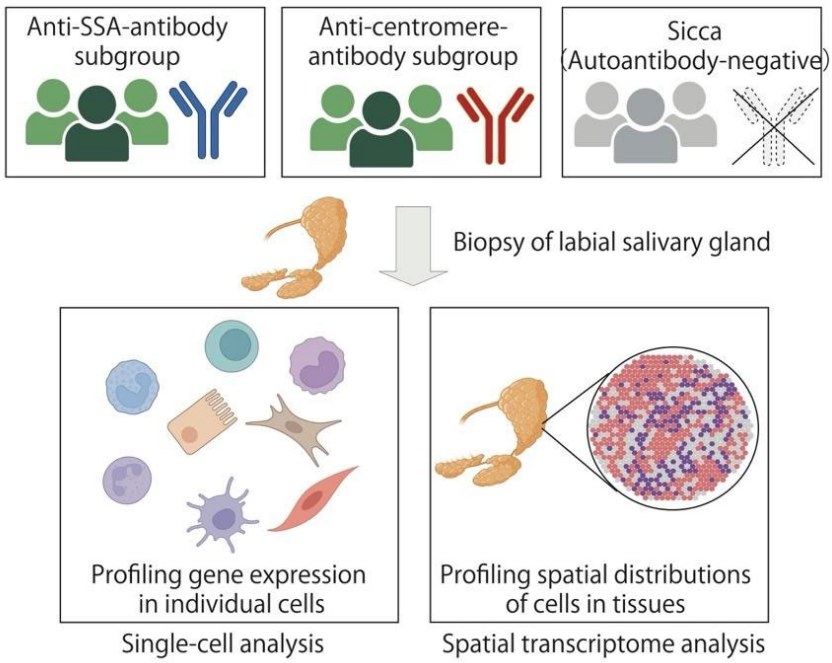

Figure 2: Research Methodology

(1) Discovery of a Common Pathogenic Mechanism Independent of Autoantibody Type

Regardless of the autoantibody type, a specific type of immune cell with high cytotoxic capability, the GZMB+GNLY+CD8 positive T cell, was consistently increased in the salivary glands of all Sjögren's disease patients (Figure 3). These cells are believed to directly attack the salivary gland cells, causing reduced saliva secretion.

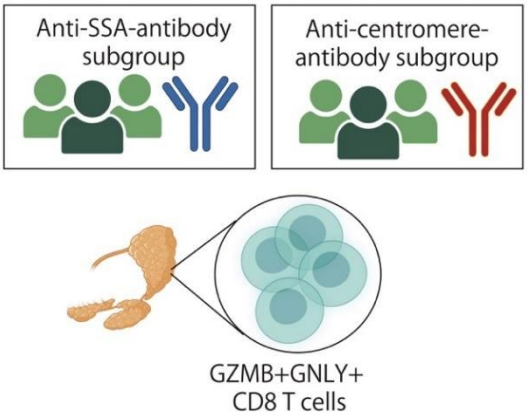

Figure 3: Expansion of GZMB+GNLY+ CD8 T cells in salivary glands of patients with Sjögren's disease

(2) Discovery of "Command Center" Cells at the Core of Inflammation
An analysis of the spatial distribution of cells in the salivary gland tissue showed that inflammatory signals from specialized cells called "THY1 positive fibroblasts" were dominant in all Sjögren's disease patients compared with Sicca syndrome patients (Figure 4). The study concluded that these fibroblasts act as a "command center," controlling inflammation by releasing chemokines that attract immune cells and complement that amplifies inflammation, thereby interacting with immune cells.

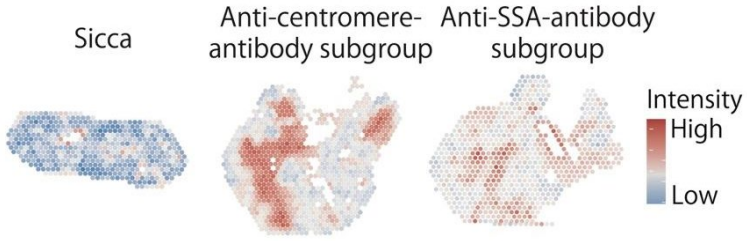

Figure 4: Inflammatory signals (e.g., chemokines and complement) from THY1-positive fibroblasts in salivary glands

(3) Identification of Different Main Inflammation Pathways for Each Autoantibody
Lastly, the underlying molecular networks differed by autoantibody type (Figure 5).

- **Anti-SSA antibody-positive patients:** Molecular networks related to interferon (IFN), a substance known for its role in antiviral responses, were highly active in both immune cells and salivary gland cells. An excessive interferon response is thought to drive the immune system out of control.
- **Anti-centromere antibody-positive patients:** Molecular networks related to TGF-β, which promotes tissue hardening (fibrosis), and IL6, which induces inflammation, showed elevated activity. TGF-β is also a hallmark of another autoimmune disease, systemic sclerosis, characterized by the hardening of the skin and other organs.

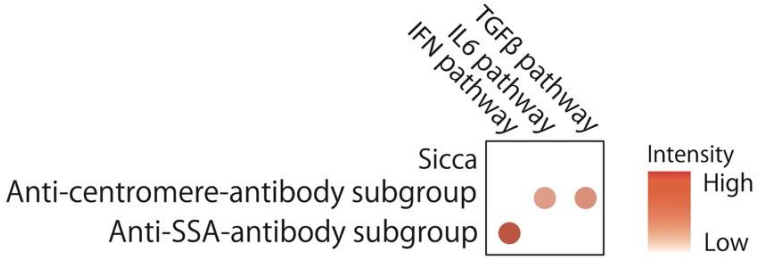

Figure 5: Distinct Inflammatory Pathways for Each Autoantibody Type

3. Future Development
This study has clarified that Sjögren's disease involves both cell populations shared across autoantibody types and distinct molecular mechanisms specific to each type. These insights have the potential to transform future treatment strategies. In particular, suppressing the activity of the inflammatory command center—the THY1 positive fibroblasts—may enable the development of entirely new treatment methods independent of autoantibody type. Furthermore, progress toward more effective, lower-side-effect precision and

personalized medicine is anticipated, such as treatments that inhibit interferon activity in anti-SSA antibody-positive patients or TGF-β activity in anti-centromere antibody-positive patients.

Building on these findings, the research team will continue to advance research aimed at elucidating the pathology of autoimmune diseases, including Sjögren's disease, and developing new therapies that improve patients' quality of life.

4. Notes

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5. Research Paper

Title: Comparative single-cell and spatial profiling of anti-SSA-positive and anti-centromere-positive Sjögren's disease reveals common and distinct immune activation and fibroblast-mediated inflammation
Authors: Jun Inamo, Masaru Takeshita, Katsuya Suzuki, Kazuyuki Tsunoda, Satoshi Usuda, Junko Kuramoto, Jonathan Moody, Chung-Chau Hon, Yoshinari Ando, Takashi Sasaki, Kazutoshi Yoshitake, Susumu Mitsuyama, Shuichi Asakawa, Yae Kanai, Tsutomu Takeuchi, Yuko Kaneko
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6. Glossary

- **Sjögren's disease:** An autoimmune disorder in which the immune system attacks the lacrimal and salivary glands. The main symptoms are dry eyes and dry mouth, but the disease can also affect the whole body, causing arthritis, skin rashes, and interstitial lung disease.
- **Autoantibody:** An antibody that mistakenly targets the body’s own cells. Anti-SSA and anti-centromere antibodies, the focus of this study, are also used in diagnosing Sjögren's disease.
- **Single-cell analysis:** A technique that involves separating the individual cells that make up a tissue and comprehensively analyzing each cell’s gene expression information (RNA). This provides detailed insight into the types of cells present in the tissue and their states.
- **Spatial transcriptome analysis:** A technology that comprehensively examines which genes are expressed in specific locations while preserving the positional relationships of cells in the tissue. This enables the creation of a "disease map" showing where specific cells are located and how they interact with neighboring cells.
- **Interferon (IFN):** A molecule that plays a central role in the body's defense against viral infections. In autoimmune diseases, excessive interferon responses can cause persistent inflammation.
- **TGF-β:** A molecule that regulates cell growth and differentiation. While it plays an important role in processes like wound healing, excessive activity can cause fibrosis (hardening of tissues), leading to a decline in organ function.
- **Fibroblast:** A major cell type in connective tissue that produces extracellular matrix components such as collagen. Recent studies have shown that they are not only structural support cells but also active regulators of inflammation in cancers and autoimmune diseases.

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