Press Release

Keio University

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Keio University School of Medicine

Mechanism of a "vicious cycle" of autoimmunity uncovered in Sjögren's disease

Discovery may enable development of therapies that selectively target disease-causing autoimmune responses

A research team at Keio University School of Medicine and JSR Corporation has uncovered a mechanism by which immune cells interact to sustain autoimmune responses in Sjögren's disease, as part of the JKiC Next-Generation Project. The team comprises Masaru Takeshita (Assistant Professor) and Yuko Kaneko (Professor) from the Division of Rheumatology at Keio University School of Medicine, Seiki Wakui (Chief Researcher) from JSR Corporation, among others.

In this study, the researchers investigated which molecules are recognized by $CD4^+$ T cells infiltrating the salivary glands of patients with Sjögren's disease. By combining single-cell analysis with T-cell reporter assays, they identified $CD4^+$ T cells that recognize peptides derived from the protein Ro60. Furthermore, many of these T cells exhibited characteristics of T follicular helper (Tfh) and T peripheral helper (Tph) cells, which support antibody production by B cells. The research group has previously reported that B cells infiltrating the salivary glands of patients with Sjögren's disease frequently produce antibodies against Ro60. Together with the present findings, these results indicate that $CD4^+$ T cells and B cells interact to amplify immune responses against Ro60, forming what can be described as a "vicious cycle" of autoimmunity.

These findings not only contribute to a better understanding of the mechanisms underlying Sjögren's disease but also provide important insights that may lead to the development of new therapies that selectively suppress disease-causing autoimmune responses.

The results of this study was published in the American scientific journal *Science Advances* on June 3, 2026 (ET).

1. Research Background

Sjögren's disease is an autoimmune disorder in which the body's immune system attacks exocrine glands such as the lacrimal and salivary glands, resulting in symptoms such as dry eyes and dry mouth. It is estimated that between 100,000 and 300,000 people in Japan are affected. Currently, no curative therapy exists, and treatment mainly relies on symptomatic therapy and systemic immunosuppressive treatments.

In healthy individuals, antibodies circulate in the bloodstream and bind to invading pathogens such as bacteria and viruses, helping immune cells eliminate them. In contrast, patients with autoimmune diseases are known to produce antibodies directed against self-antigens, termed "autoantibodies." For instance, approximately 70% of patients with Sjögren's disease possess anti-Ro60 antibodies.

The research group has previously analyzed immune cells infiltrating diseased tissues in Sjögren's disease and reported that B cells in the salivary glands frequently produce anti-Ro60 antibodies. However, it remained unclear which molecules other immune cells, particularly T cells, were responding to.

2. Research Findings

In this study, the researchers focused on CD4-positive T cells, which act as central coordinators of the immune system, and hypothesized that these cells, like B cells, might also respond to Ro60. To test this hypothesis, they performed single-cell analysis of CD4-positive T cells that accumulate in the salivary glands of patients with Sjögren's disease, examining the gene expression and functional properties of

individual cells in detail. Through this approach, they obtained the sequences of T cell receptors (TCRs)—which serve as the "eyes" that enable each T cell to recognize its target—and investigated whether these T cells respond to Ro60.

T-cell recognition occurs when antigen-presenting cells process proteins into short peptides and display them on their surface using molecules called HLA. T-cell receptors recognize the combination of the HLA molecule and the presented peptide, allowing T cells to determine whether an immune response should be triggered. Because HLA molecules vary greatly among individuals and identifying the peptides presented by them is technically challenging, determining T-cell targets has long been difficult.

In addition to samples collected from Japanese patients, the research group also incorporated T cell receptor (TCR) sequences derived from Caucasian patients with Sjögren's disease that have been reported in the scientific literature. In total, they identified more than 200 distinct TCRs, which were then expressed in engineered reporter cells for subsequent analyses (Figure 1, top panel). Artificial antigen-presenting cells expressing patient HLA molecules were then used to screen candidate peptides derived from Ro60 as well as immune complexes consisting of Ro60 bound to patient-derived autoantibodies (Figure 1, bottom panel). Through this comprehensive screening approach, the researchers identified 13 T-cell receptors that specifically recognize Ro60-derived peptides.

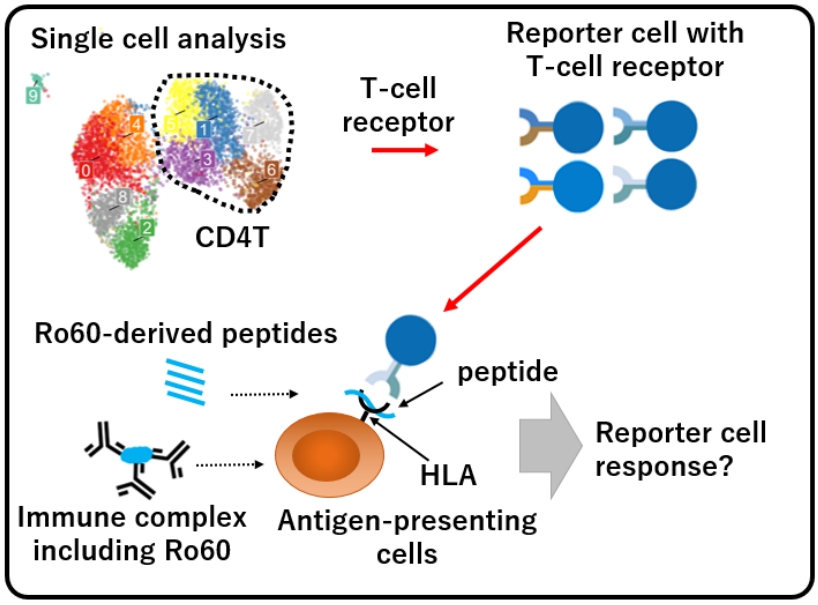

Figure 1: Overview of the experimental strategy used to identify Ro60-specific CD4⁺ T cells

Further gene expression analysis revealed that many of these T cells exhibit characteristics of Tfh/Tph cells, which are known to support antibody production by B cells. Together with previous findings showing that B cells infiltrating the salivary glands produce anti-Ro60 antibodies, these results suggest the following pathogenic mechanism:

- B cells in the salivary glands produce autoantibodies against Ro60
- These antibodies bind to Ro60 proteins released from dying cells, forming immune complexes
- Antigen-presenting cells take up these immune complexes and present Ro60-derived peptides via HLA molecules
- Ro60-specific CD4⁺ T cells recognize the HLA–peptide complex and become activated
- Activated T cells help B cells produce more antibodies

This process forms a self-reinforcing loop, sustaining autoimmune responses and contributing to chronic disease (Figure 2).

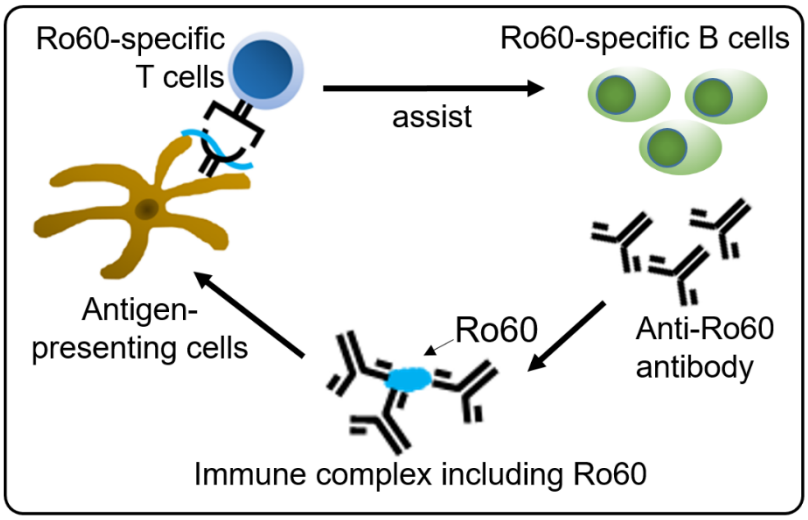

Figure 2: Proposed model of a self-reinforcing autoimmune loop in Sjögren's disease

3. Significance and Future Perspectives

This study demonstrates for the first time that $CD4^+$ T cells and B cells in the lesions of Sjögren's disease target the same autoantigen, Ro60, and interact to sustain autoimmune responses. These findings may have significant implications for future treatment strategies. Currently, therapies for Sjögren's disease suppress immune responses broadly, affecting both harmful and protective immune functions. If this pathogenic loop can be interrupted, it may become possible to selectively suppress disease-causing autoimmune responses without impairing normal immune function. Such approaches could potentially reduce the risk of infections and other complications associated with systemic immunosuppression.

Researchers at Keio University aim to further explore these mechanisms and translate these findings into the development of new therapies for Sjögren's disease and other autoimmune disorders, with the goal of improving quality of life for patients..

4. Notes

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5. Research Paper

Title: Identification of a shared antigen linking $CD4^+$ T and B cell pathology in Sjögren's disease
Authors: Masaru Takeshita, Jun Inamo, Seiki Wakui, Ryosuke Nagashima, Takahiro Nishino, Kazuyuki Tsunoda, Satoshi Usuda, Hajime Inokuchi, Kazuyoshi Ishigaki, Takashi Sasaki, Yuki Kagoya, Katsuya Suzuki, Yuko Kaneko
Publication: *Science Advances*
DOI: 10.1126/sciadv.aeb2491.

6. Glossary

(Note 1) Sjögren's disease: An autoimmune disease in which the immune system attacks the body's own exocrine glands, such as the lacrimal and salivary glands. It mainly causes dry eyes and dry mouth, but can also affect other organs and lead to symptoms such as arthritis, skin rashes, and interstitial lung disease.

(Note 2) $CD4^+$ T cells: A type of immune cell that regulates immune responses. Often referred to as the "command center" of the immune system, $CD4^+$ T cells help coordinate immune responses and support the functions of other immune cells, including antibody-producing B cells.

(Note 3) Single-cell analysis: A technology that analyzes gene expression in individual cells. By examining cells one by one, researchers can identify different cell types and determine their functional states within tissues.

(Note 4) T-cell reporter assay: An experimental method used to determine which antigens T cells recognize. Reporter cells are engineered to produce a detectable signal, such as fluorescence, when a T cell receptor recognizes a specific antigen.

(Note 5) B cells: A type of immune cell that produces antibodies against invading pathogens such as viruses and bacteria. In autoimmune diseases, B cells can produce antibodies that mistakenly target the body's own molecules.

(Note 6) Tfh/Tph cells: Specialized subsets of $CD4^+$ T cells that help B cells produce antibodies. Tfh (T follicular helper) cells mainly function in lymphoid tissues such as lymph nodes, while Tph (T peripheral helper) cells promote antibody production in inflamed tissues.

(Note 7) Autoantibodies: Antibodies that mistakenly recognize and bind to the body's own molecules. In this study, anti-Ro60 antibodies—commonly found in patients with Sjögren's disease—were examined.

(Note 8) HLA: Human leukocyte antigen molecules are proteins on the surface of cells that present peptide fragments to T cells. By recognizing peptides presented by HLA molecules, T cells determine whether an immune response should be activated.

(Note 9) Immune complex: A complex formed when antibodies bind to specific molecules (antigens). While normally involved in eliminating pathogens, immune complexes formed with self-antigens can trigger inflammation and contribute to autoimmune disease.

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