News Release

IL-17 axis and IL-36 signaling play critical roles in the pathogenesis of *Card14*-mutant pityriasis rubra pilaris model mice

Key Points

- **We report the establishment and analysis of the first mouse model of pityriasis rubra pilaris (PRP).**
- **Our findings demonstrate that the IL-17 axis and IL-36 signaling are essential inflammatory cytokines in the pathogenesis of PRP.**
- **Single-cell analysis allowed us to identify specific cell types pivotal to the development of this disease.**
- **The model mice responded favorably to treatment with anti-IL-17A antibodies.**

Summary

Prof. Masashi Akiyama (co-corresponding author), Dr. Takenori Yoshikawa (first author) and Dr. Takuya Takeichi (co-corresponding author) of the Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura, MD, PhD) have revealed that *Card14*-mutant pityriasis rubra pilaris model mice show hyperactivation of the IL-17 axis and IL-36 signaling in the skin.

Pityriasis rubra pilaris (PRP) is a chronic skin disease characterized by generalized erythematous scaling. It is classified into six types based on onset and clinical features, with type V PRP being severe and being characterized by abundant generalized erythematous scaling, intense itching, and pain from early childhood onward. In 2017, we reported that variants in *CARD14* cause type V PRP (*Takeichi et al. JAMA Dermatology 2017*). However, many aspects of this disease remain unclear.

We are the first in the world to have successfully generated a mouse model of type V PRP by introducing a *CARD14* variant. IL-17 and IL-36 are inflammatory cytokines in the skin, and by examining the gene expression in the skin of these mice, we found that the IL-17 axis and IL-36 signaling play a crucial role in the pathogenesis of this disease. Furthermore, using single-cell analysis, we identified specific cell populations that are essential for the development of this disease. We found that certain cells in the hair follicles exhibited the increased expression of the IL-17 receptor A protein and genes associated with hyperkeratosis, suggesting their involvement in the follicular hyperkeratosis characteristic of PRP. The administration of an IL-17A inhibitor significantly

ameliorated the symptoms in our model mice.

Based on these findings, we anticipate further advancements in the elucidation of the pathogenesis of PRP and the development of novel therapeutic strategies.

The results of this research have been published in the *Journal of Investigative Dermatology* (published online on 17 August 2024 in advance of print publication).

Research Background

PRP is a rare chronic skin disease characterized by generalized erythematous scaling. It is classified into six subtypes based on the onset and clinical features. Type V PRP is particularly severe, manifesting as generalized erythematous scaling with abundant scales even on the face, palms, and soles from early childhood and causing intense pruritic pain and a high risk of secondary bacterial infection. While we reported in 2017 that variants in *CARD14* are causative of this subtype (*Takeichi et al. JAMA Dermatology 2017*), the underlying pathogenesis remains poorly understood, and effective treatments have yet to be established. Thus, in order to develop novel efficient treatments for PRP, it was necessary to create a model mouse.

Research Results

Our research group generated a mouse model with a *CARD14* variant (Figure 1, right), which is associated with type V PRP in human patients (Figure 1, left and center).

Figure 1： Symptoms of type V PRP and model mouse.

IL-17 is secreted by immune cells, IL-36 is secreted by keratinocytes, and both of these cytokines are strongly associated with skin inflammation. Comprehensive gene expression analysis of the model mouse skin revealed that IL-17 and IL-36 play critical roles in the pathogenesis. To identify the key cell populations involved in the disease development, we performed single-cell RNA sequencing. This analysis revealed that outer root sheath cells of hair follicles, epidermal granular cells, and dermal fibroblasts exhibited upregulated expression of numerous inflammation-related genes. These findings suggest that reciprocal interactions among these cells contribute to the disease pathogenesis (Figure 2). Furthermore, outer root sheath cells showed increased expression of the IL-17 receptor A protein and genes associated with hyperkeratosis, such as *Krt16* and *Pla2g2f*, suggesting their involvement in follicular plugging, a feature of PRP (Figure 2). Treatment with anti-IL-17A antibodies significantly ameliorated the symptoms in the model mice. Additionally, the expression of *S100a7* and *Krt17*, genes, which are upregulated in psoriasis patients and mouse models, was normal in our PRP models, suggesting that these genes could serve as potential biomarkers to differentiate PRP from psoriasis.

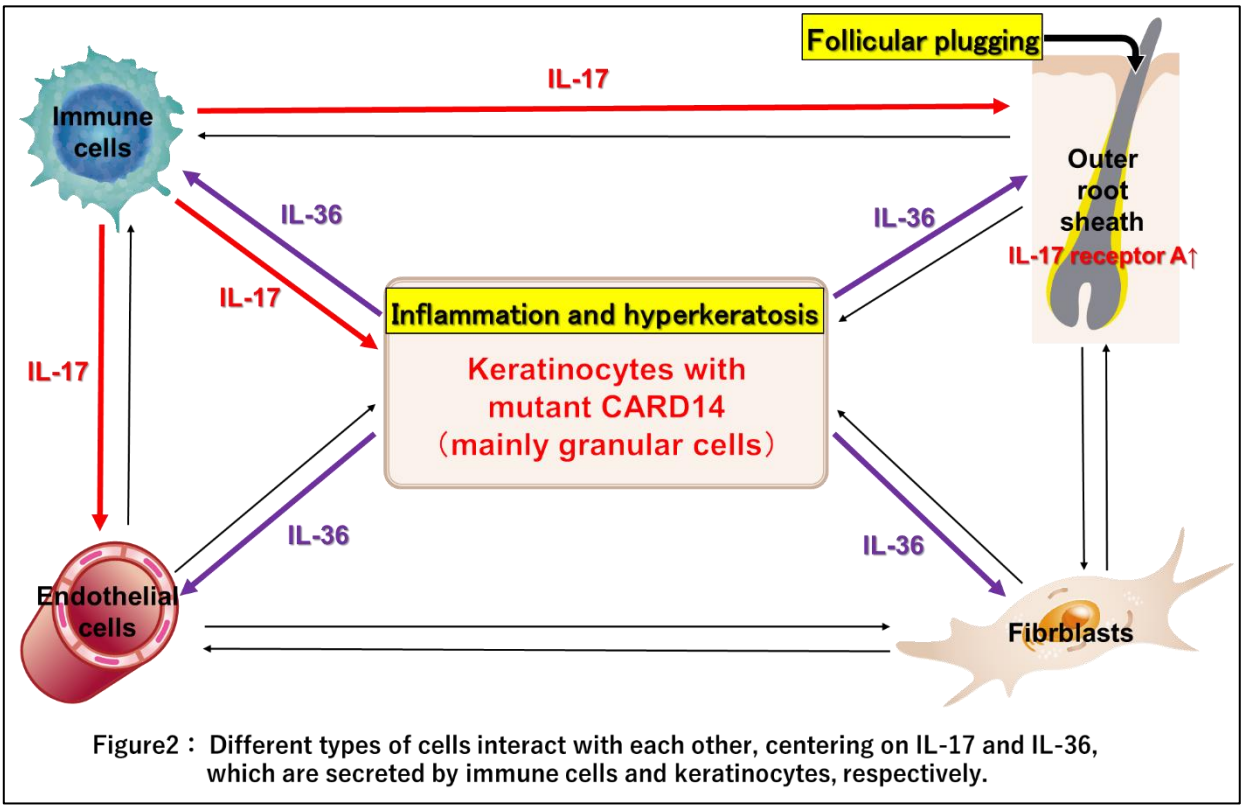

Figure2： Different types of cells interact with each other, centering on IL-17 and IL-36, which are secreted by immune cells and keratinocytes, respectively.

Research Summary and Future Perspective

In this study, we have established a model mouse that reproduces type V PRP and have elucidated part of the pathogenesis of type V PRP. We anticipate that this model mouse will facilitate further investigations into the pathogenesis of PRP and the development of novel therapeutic strategies for PRP.

Publication

Takenori Yoshikawa, Takuya Takeichi, Tetsuya Hirabayashi, Yoshinao Muro, Yuki Miyasaka, Tamio Ohno, Masashi Akiyama
Hyperactivation of the IL-17 axis and IL-36 signaling in *Card14*-mutant pityriasis rubra pilaris model mice. *Journal of Investigative Dermatology*, Published online on 17 August 2024, before print publication.
DOI: 10.1016/j.jid.2024.04.036

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Jou_240930.pdf