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## Press Release

研究成果

June 16, 2023

Research field: Life science and medicine

Keywords: immunity, primary cilium, dendritic cell, epidermal keratinocyte, cutaneous immunity, atopic dermatitis, skin care

# World's first primary cilia found in human primary immune cells Clarified the functions for cutaneous immune responses

- Expected application for dermatological drugs and skin care agents focusing on primary cilia -

[Gist of the research]

- ◆ We discovered primary cilia present in human primary immune cells<sup>1</sup> for the first time in the world<sup>2</sup>.
- ◆ Primary cilia are organelles that project from a mammalian cell surface and function like antennas that transmit signals within the cell, as well as to other cells. However, it had been unclear if primary cilia exist in human primary immune cells.
- ◆ We found that primary cilia are increased by allergic factors, and that the number of immune cells with primary cilia actually increases in allergic diseases.
- ◆ We revealed that the number of cells with primary cilia also increased in epidermal keratinocytes under inflammatory conditions such as atopic dermatitis and psoriasis, suggesting that primary cilia are involved in cutaneous immune responses.
- ◆ Analyzing the functions of primary cilia in immune responses will help clarify the mechanism of inflammation-related diseases, and apply to anti-inflammatory agents, dermatological drugs, and skin care agents with a new approach focusing on primary cilia.

### ❖ Overview

Our research group, led by Guest Professor Fumitaka Fujita of the Laboratory of the Advanced Cosmetic Science Joint Research Program with Mandom at the Graduate School and School of Pharmaceutical Science, Osaka University; Guest Professor Ken Ishii (professor of the current Department of Microbiology and Immunology, the Institute of Medical Science, the University of

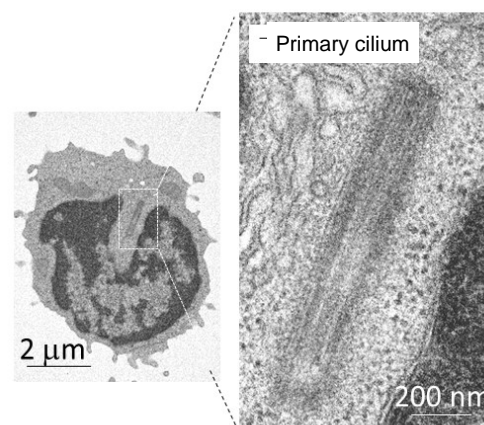


Figure 1. The world's first electron microscopic image of a primary cilium present in a primary human immune cell



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Tokyo) who is a former Guest Project Leader of the Mockup Vaccine Project of the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN); and Professor Akimichi Morita at the Graduate School of Medical Sciences and Medical School, Nagoya City University, discovered for the first time that organelles called primary cilia exist in primary human immune cells.

Primary cilia are organelles that project from a mammalian cell surface and function like antennas that transmit signals within the cell, as well as to other cells. Until now, it had been unknown if primary cilia exist in immune cells collected directly from human blood.

Our research group succeeded in observing that primary cilia exist in primary immune cells collected from human blood for the first time in the world. The group also found that cells with primary cilia increased when the dendritic cell, which is the control tower of immunity, was stimulated by allergenic factors. Our study found that the number of cells with primary cilia increased also in epidermal keratinocytes under inflammatory conditions such as atopic dermatitis and psoriasis, suggesting that primary cilia are involved in controlling skin inflammation.

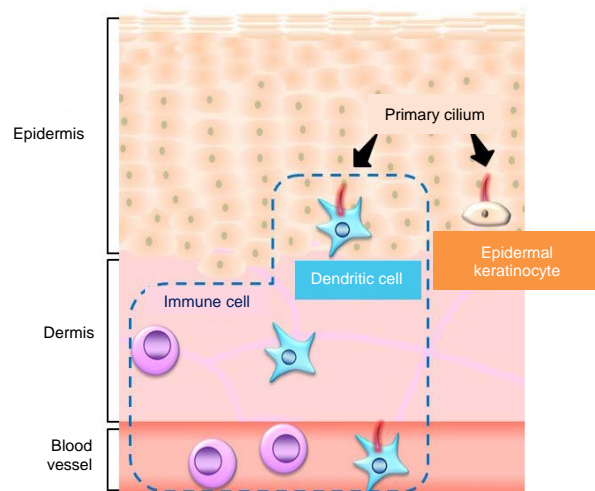
Analyzing the functions of primary cilia in immune responses will help clarify the mechanism of inflammation-related diseases, and it is expected that the outcome could be applied to the industrial field involving skin inflammation, including the manufacture of anti-inflammatory agents, dermatological drugs, and skin care agents with a new approach focusing on primary cilia.

The research achievements were published in *Frontiers in Molecular Biosciences* on April 26, 2023 and in *Experimental Dermatology* on January 17, 2021.

### ❖ Background of the research

Primary cilia are organelles that project from a mammalian cell surface and function like antennas that transmit information within the cell, as well as to other cells.

Primary cilia were first observed in 1867; however, their functions remained largely unknown. In the latter half of the 20th century, it attracted attention that primary cilia play an important role in living organisms, and that loss of primary cilia leads to serious genetic diseases such as visceral inversion, polydactyly, and kidney / liver dysfunction. Various studies on primary cilia have been conducted in domestic and overseas research institutes along with the development of microscopes; however, to date, the existence of primary cilia in human primary immune cells had been completely unknown.



Reference: Dermal Structure and Immune Cells

❖ Research content

Our research group has directly isolated the immune cells from human blood samples and observed primary immune cells. We have succeeded in depicting a clear image of the primary cilium and the characteristic microtubule, using an electron microscope that can provide high-resolution images (Fig. 1). This is the world's first image that depicts primary cilium present in human primary immune cells.

When our research group investigated the function of primary cilia, using dendritic cells, which are called the control towers of immunity, collected from human blood, we found that the number of cells with primary cilia increased when stimulated with allergenic factors (GM-CSF) (Fig. 2). Furthermore, the research group found that the number of immune cells with primary cilia significantly increased in patients with asthma and atopic dermatitis.

Next, the research group analyzed the relationship between skin inflammation and primary cilia. Using skin samples of atopic dermatitis and psoriasis, which are typical skin inflammatory diseases, we visualized the primary cilia of epidermal keratinocytes with a marker specific to primary cilia. As a result, it was revealed that epidermal keratinocytes with primary cilia increased in the skin of patients with atopic dermatitis and psoriasis compared to healthy skin (Fig. 3).

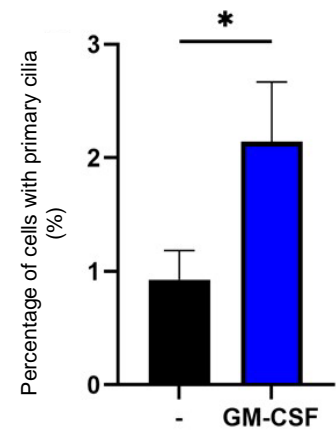


Figure 2. Increase in primary cilia of dendritic cells by allergenic factor (GM-CSF)

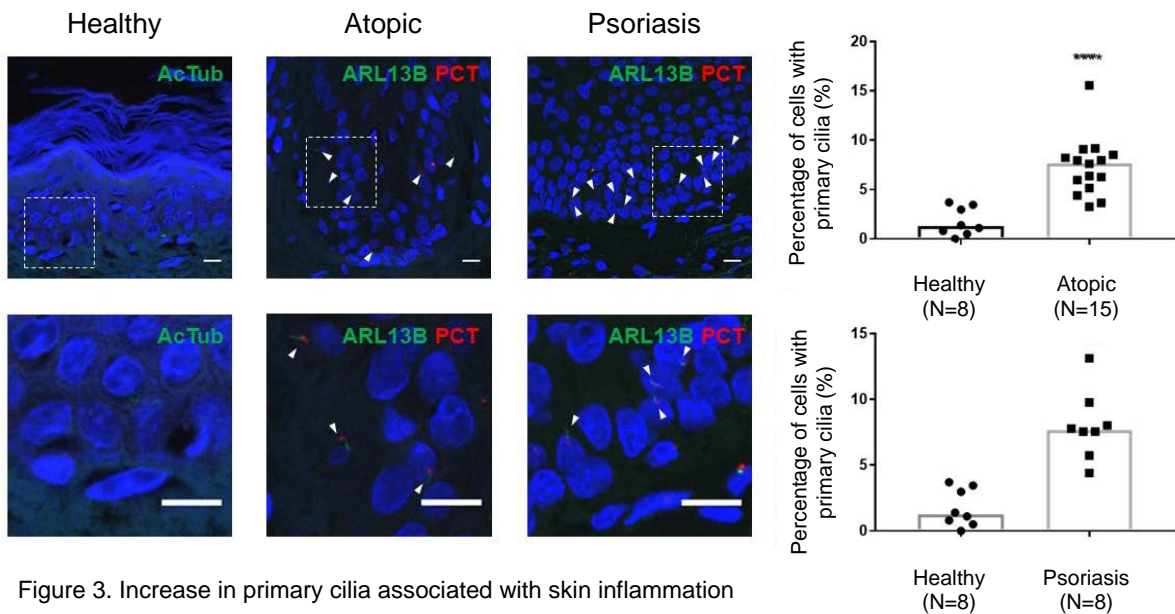


Figure 3. Increase in primary cilia associated with skin inflammation



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- ❖ Impact of this research achievement on society  
Inflammation is associated with various diseases. However, many aspects of the mechanisms that control inflammation remain unclarified. Our research demonstrated that primary cilia are present in primary immune cells extracted directly from human blood and that they are involved in immune responses. Further analyzing the functions of primary cilia in immune responses will help clarify the mechanism of inflammation-related diseases with unknown causes, and it could be applied to the development of anti-inflammatory agents, dermatological drugs, and skin care agents with a new approach focusing on primary cilia.

- ❖ Special notes

The research content was published in the following academic journals: *Frontiers in Molecular Biosciences* on April 26, 2023 and *Experimental Dermatology* on January 17, 2021.

### **Frontiers in Molecular Biosciences**

Title: Dendritic cell proliferation by primary cilium in atopic dermatitis

Authors: Manami Toriyama, Defri Rizaldy, Motoki Nakamura, Yukiko Atsumi, Michinori Toriyama, Fumitaka Fujita, Fumihiko Okada, Akimichi Morita, Hiroshi Itoh, Ken J Ishii

### **Experimental Dermatology**

Title: Increase in primary cilia in the epidermis of patients with atopic dermatitis and psoriasis

Authors: Defri Rizaldy, Manami Toriyama, Hiroko Kato, Runa Fukui, Fumitaka Fujita, Motoki Nakamura, Fumihiko Okada, Akimichi Morita, Ken J. Ishii

This research was partly supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (19K17797: Analysis of the mechanism of primary cilia in maintaining homeostasis of skin).

- ❖ Glossary

\*1 Primary immune cells

Immune cells extracted directly from living tissue. In this research, it was collected directly from human blood.

\*2 First time in the world

As of June 2023, we surveyed 35,772,281 academic literature and conference abstracts through Pubmed (a representative literature search system in the fields of medicine and biology provided by the US National Library of Medicine) but there was none applicable (investigated by Mandom).



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[Message from the specially appointed associate professor (full-time), Manami Toriyama, Graduate School and School of Pharmaceutical Science, Osaka University]

Although it had been assumed that almost all cells had the ability to form primary cilia since the discovery of primary cilium more than a hundred years ago, immune cells were considered to lack primary cilia. However, since the relationship between the onset of autoimmune diseases / allergic diseases and cilia dysfunction has been reported in recent years, elucidation of the physiological functions of primary cilia has been required in a wider range of research fields. We postulated that if there are primary cilia immune cells in the skin and if they are involved in the maintenance of skin homeostasis, it would be possible to take a different approach to developing technology for maintaining healthy skin.

Our research group found that changes in the properties of primary cilia can control the maturation and proliferation of skin keratinocytes and dendritic cells, which are a type of immune cell, and it suggested that the appropriate control of function and count of primary cilia will contribute to the maintenance of homeostasis. Therefore, we expect that technology for the control of primary cilia will be developed, leading to the elucidation of the pathogenesis of inflammatory skin diseases and the development of therapeutic methods and cosmetics that prevent the onset of these diseases.