

Research and Development

## Shiseido Succeeds in 3D Visualization of Morphological Changes in Dysfunctional Lymphatic Capillaries

~Dysfunction of lymphatic capillaries induces the denaturation of dermal collagen~

Shiseido Company, Limited (“Shiseido”) has revealed for the first time in the world that significant morphological changes are observed in lymphatic capillaries\*1 inside the skin that exhibits reduced lymphatic function using its unique 3D technology to visualize the internal structure of the skin. It was also discovered that collagen in the dermis becomes denatured with a decrease in lymphatic function. Research results that cover the content of this study were presented at multiple academic meetings, including international conferences\*2.

The clarification of the relationship between lymphatic vessel dysfunction and morphological changes will lead to the establishment of innovative techniques for visual evaluation and diagnosis of cutaneous lymphatic vessel in the future. In addition, it was found that the dysfunction of lymphatic vessels with morphological changes causes changes in the properties of collagen, indicating a new mechanism that dermal lymphatic vessels affect the elasticity of the skin. Shiseido will continue to advance research from a holistic perspective regarding the association of the skin with the conditions of the inside of the skin, such as blood vessels, lymphatic vessels, immunity, and nerves, and open up a new world of dermatological research.

\*1 Present in the peripheral tissues, including the skin, and serve as a starting point for the collection of waste products and excess water.

\*2 The 46th Meeting of the Japanese Society of Lymphology (June 3–4, 2022), the 47th Annual Meeting of the Japanese Society for Investigative Dermatology (December 2–4, 2022), and International Societies for Investigative Dermatology (May 10–13, 2023)

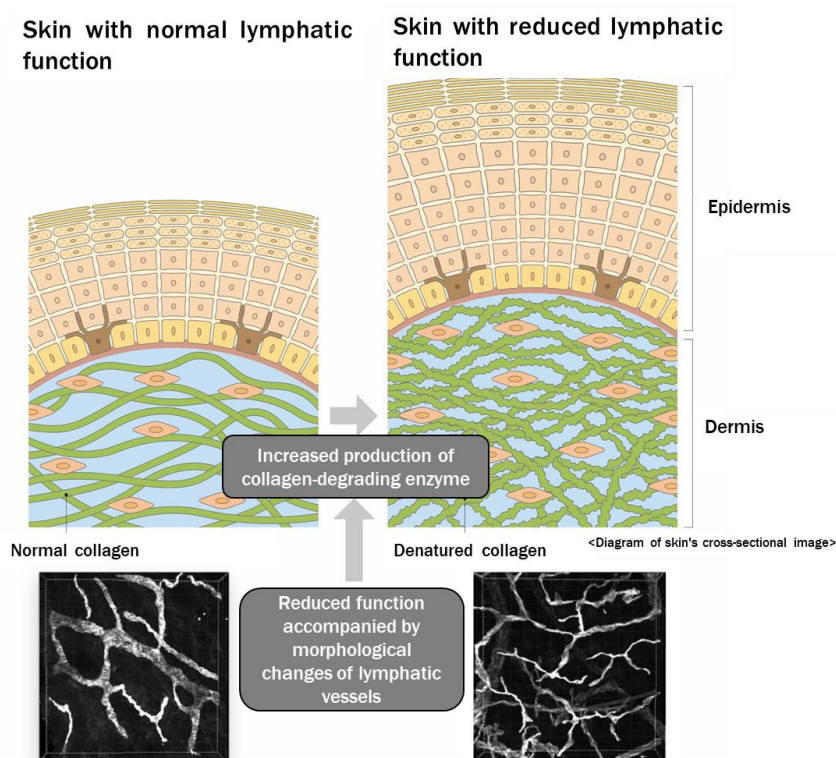


Figure 1. Reduced lymphatic function leads to denaturation of dermal collagen

## Research background

Shiseido believes that, in order to bring out the natural beauty of the skin, its relation to the inner body is important. Indeed, we were among the first to focus on dermatological research from the holistic perspective based on the relationship between the skin and the whole body. Lymphatic vessels are responsible for removing waste products in the body, and are known to be involved in, for example, swelling of the body. In our research focusing on lymphatic capillaries present in the skin, we have shown that reduced lymphatic function leads to wrinkle formation and sagging<sup>\*3,4</sup>, and clarified the mechanism of aging of lymphatic vessels, which is the root cause of their functional decline<sup>\*5</sup>. However, morphological characteristics of lymphatic vessels when their function is reduced, or what effects they have on dermal collagen that controls the elasticity of the skin, have not yet been fully elucidated. We therefore conducted joint research with Drs. Nobuyuki Mitsukawa and Shinsuke Akita of Chiba University Hospital to analyze the morphology of lymphatic capillaries in the lymphedema<sup>\*6</sup> skin which exhibits markedly reduced lymphatic function, and further examined its effect on dermal collagen.

\*3 Shiseido Reveals that Reduced Lymphatic Function Is the Cause of Wrinkle Formation (2008)

[https://corp.shiseido.com/jp/newsimg/archive/0000000000905/905\\_a5c92\\_jp.pdf](https://corp.shiseido.com/jp/newsimg/archive/0000000000905/905_a5c92_jp.pdf)(Japanese only)

\*4 Shiseido Becomes the First to Reveal the Relationship between Impaired Lymphatic Function and “Sagging” Skin (2015)

[https://corp.shiseido.com/jp/newsimg/archive/00000000001834/1834\\_a4z87\\_jp.pdf](https://corp.shiseido.com/jp/newsimg/archive/00000000001834/1834_a4z87_jp.pdf)(Japanese only)

\*5 Shiseido Reaches World's First Elucidation of Aging Mechanism of Lymphatic Vessels in the Skin (2020)

<https://corp.shiseido.com/en/news/detail.html?n=00000000002998>

\*6 Skin with lymphedema: Excess skin provided by patients with lymphedema at the time of treatment

## Visualization of morphological changes in lymphatic vessels with reduced function

In order to capture morphological changes, we used our unique technology that makes skin tissue transparent and allows visualization of specific structures in three dimensions<sup>\*7</sup>. This enabled us to three-dimensionally capture, for the first time, the images of lymphatic capillaries in the skin that exhibited reduced lymphatic function. Moreover, we were able to show that the volume of the lymphatic capillaries is large, and the vessels are thick and firm, in the normal skin, whereas in the skin with reduced lymphatic function, the volume of lymphatic capillaries is small, with changes in the appearance of the vessels, which are thinner and weaker (Figure 2).

\*7 Shiseido Establishes Lymphatic Vessel Visualization Technology(2020)

<https://corp.shiseido.com/en/news/detail.html?n=00000000002997>

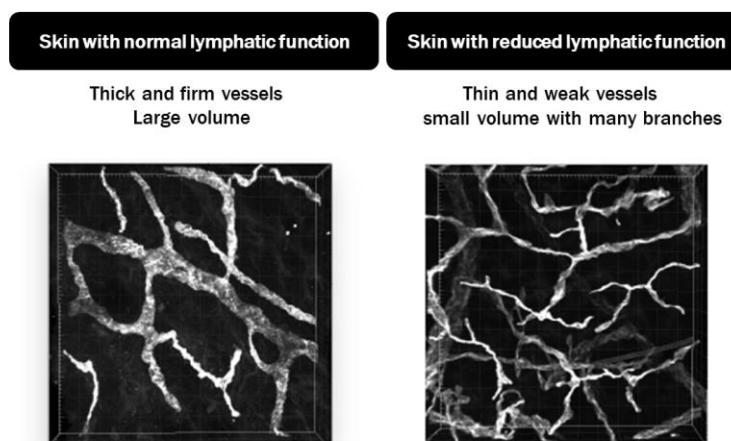


Figure 2. Phenotype of lymphatic capillaries in the skin with normal and reduced lymphatic function

## Denaturation of dermal collagen due to reduced lymphatic function

Collagen, which takes up a large portion of the dermis, plays a role in maintaining the structure and elasticity of the skin. The present study analyzed the dermis of skin that exhibited reduced lymphatic function, and as a result, it was confirmed that there was an excessive accumulation of collagen (Figure 3). Moreover, examination of the quality of the collagen revealed that it was mostly denatured (Figure 4). Denaturation of collagen, as in this case, is likely to affect the structure and elasticity of the skin. Furthermore, TGF- $\beta^8$ , which triggers the aging of lymphatic vessels, was found to enhance the production of MMP-2<sup>9</sup>, a factor contributing to collagen denaturation, in lymphatic endothelial cells (Figure 5). It has thus become clear that a decrease in the function of lymphatic vessels in the skin leads to denaturation of dermal collagen.

\*8 transforming growth factor  $\beta$ : It triggers the aging and transformation of lymphatic endothelial cells

\*9 Matrix metalloproteinase: A degrading factor of extracellular matrix components such as collagen and elastin

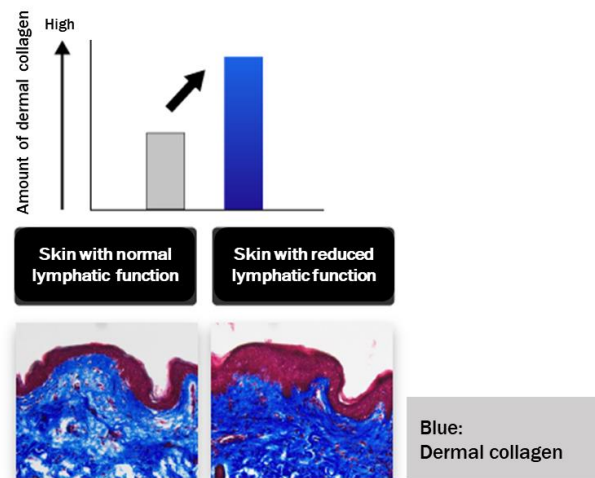


Figure 3. Excessive accumulation of dermal collagen in the skin with reduced lymphatic function

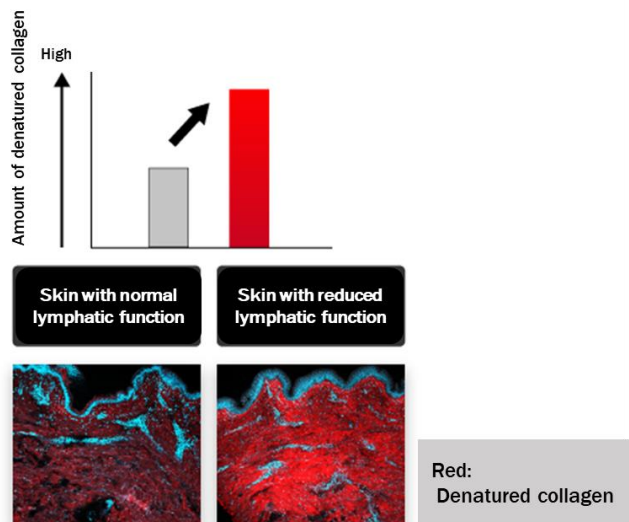


Figure 4. Denaturation of dermal collagen in the skin with reduced lymphatic function.

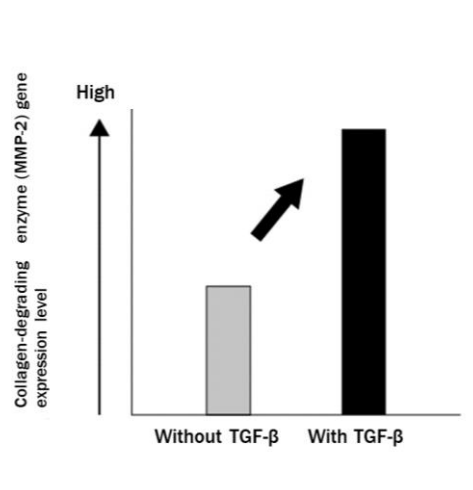


Figure 5. TGF-β increases collagen-degrading enzyme (MMP-2) gene expression

In our previous study, we have found that Mulberry White Bark extract inhibits the aging of lymphatic vessels induced by TGF-β<sup>5</sup>. Therefore, it is expected that Mulberry White Bark extract may suppress the denaturation of collagen due to reduced lymphatic function, as revealed in this study.

#### Future prospects

This time, Shiseido has clarified that the morphology of lymphatic capillaries inside the skin exhibiting reduced lymphatic function is markedly altered. Moreover, it was confirmed that denatured collagen accumulates in the dermis of skin with reduced lymphatic function, and as one of the underlying causes, the production of the collagen-degrading enzyme in lymphatic endothelial cells is enhanced by the aging factor of lymphatic vessels. These results clearly suggest the importance of maintaining the function of lymphatic vessels in order to create a healthy skin. As it works to realize its management strategic vision Personal Skin Beauty & Wellness Company, Shiseido takes up the challenge of beauty innovation that influences both the inside and outside of the skin, beyond conventional cosmetic products, and aims to bring out the original beauty of each and every person.

#### About our R&D strategies:

This study was conducted as a part of research in the area of skin foundation, which aims to elucidate the association of the skin with the conditions inside the skin, such as blood vessels, lymphatic vessels, immunity, and nerves, under Skin Beauty INNOVATION, one of the three pillars of Shiseido's R&D strategy.

- Integrated Report 2022 (Beauty Innovation)

[https://corp.shiseido.com/report/en/2022/value\\_creation/innovation/](https://corp.shiseido.com/report/en/2022/value_creation/innovation/)

- Keywords

Skin Beauty INNOVATION, Skin foundation, lymphatic vessel

<Reference>

### Researchers' challenges

#### ■ R&D Philosophy “DYNAMIC HARMONY” approach

Shiseido has been conducting the present research based on the Inside/Outside approach under the company's unique R&D philosophy, DYNAMIC HARMONY. Using our state-of-the-art technologies, we aimed to capture changes in the morphology and properties of lymphatic vessels inside the skin, and to clarify the effects of these changes on the skin.



Dr. Nao Itai, Researcher



Dr. Enkhtuul Gantumur, Researcher

#### ■ Inspired by the voices of consumers

“Where are the lymphatic vessels located inside the skin?” Consumers' questions such as this have led us to initiate our research on visualization of lymphatic vessels. After various hardships—which involved creating skin tissue samples with higher transparency and analyzing lymphatic vessels one by one with our own eyes, to name a few—we were finally able to achieve visualization of lymphatic vessels. We believe that this is a discovery that conveys how important the care for lymphatic vessels can be.

#### ■ Research from a holistic perspective

To realize a healthier and more beautiful skin, it is necessary to look not only at the skin but also into the conditions of our mind and body. We would like to deepen our research from a holistic perspective, being more conscious of the connection between the skin and the whole body, to explore how changes in the conditions of the skin, mind, and body affect the function of lymphatic vessels.

#### Shiseido's R&D Philosophy “DYNAMIC HARMONY”

Shiseido Formulates Its Unique R&D Philosophy “DYNAMIC HARMONY” (2021)

<https://corp.shiseido.com/en/news/detail.html?n=00000000003252>

DYNAMIC HARMONY website:

<https://corp.shiseido.com/en/rd/dynamicharmony/>