

## Press Release

## Research and development

**Shiseido discovers CCN2—the "definitive beauty gene"—which works on capillaries and increases components important for beautiful skin**

The study also led to the successful development of solutions to promote CCN2 gene expression

For more than 20 years, Shiseido has been conducting research on Serpin b3, a harmful factor that accelerates skin aging. This time, Shiseido revealed that the expression of the CCN2 gene, which is involved in the strengthening of the skin's tissue structure, is significantly decreased when Serpin b3 gene expression is increased. Moreover, CCN2 was identified as a "definitive beauty gene," with the discovery that it acts on pericytes—cells present in the capillaries<sup>\*1</sup> (Figure 1)—to increase the main component of collagen important for maintaining beautiful skin<sup>\*2</sup>, as well as a precursor of hyaluronic acid<sup>\*3</sup> (Figure 2). Furthermore, Green Tea Extract was found as an ingredient that promotes the CCN2 gene expression.

CCN2 expression has been shown to not correlate with age. Shiseido will utilize the results of this study with the aim of developing new solutions to achieve beautiful and healthy skin, regardless of age.

\*1 Cells that adhere to the vascular endothelial cells of capillaries and stabilize the structure of capillaries.

\*2 Hydroxyproline

\*3 N-acetylglucosamine-6-phosphate

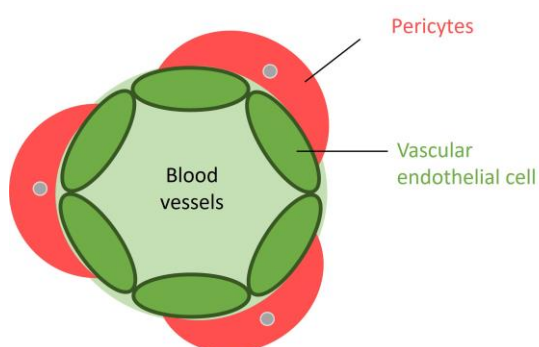


Figure 1. Capillary structure.  
Pericytes contribute to the stabilization of the capillary

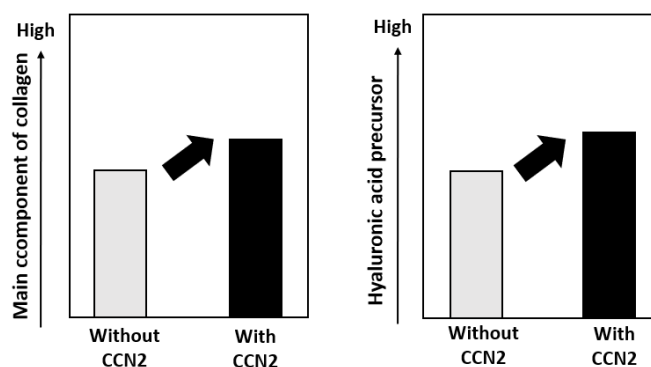


Figure 2. CCN2 increases the collagen component and hyaluronic acid precursor in pericytes

## Research background

Shiseido has elucidated the mechanism underlying accelerated skin aging<sup>\*4</sup>, including the accumulation of damage to the epidermis and adverse effects on the basement membrane and the dermis, which are brought about by the increased expression of harmful factor Serpin b3, which is induced by various factors inside and outside the body, such as UV irradiation, pollen, and sleep interruption. Based on an approach that aims to suppress the increase in Serpin b3 expression, Shiseido has been conducting research.

In addition, Shiseido has dedicated its efforts to research on capillaries that are closely related to the skin for more than 20 years and has clarified the mechanism by which capillaries produce skin elasticity. In our study, it was confirmed that the expression of APJ, a factor present in the capillaries, increases, and the capillaries become thicker, under the environment of adequate elasticity<sup>\*5,6</sup>. Furthermore, subsequent studies led to the discovery that pericytes that adhere to the outer layer of the capillaries undergo epidermal stem cell-like transformation, thereby potentially promoting the regeneration of the epidermis.<sup>\*7</sup>

This research combined our unique research conducted on the harmful factor Serpin b3 and our strength in vascular research to further elucidate the relationship between the inside of the skin and skin condition and apply the findings to the development of new solutions to achieve healthier and more beautiful skin.

\*4 Shiseido Discovers New Mechanism Accelerating the Aging of Skin (2011)

[https://corp.shiseido.com/en/newsimg/archive/0000000001278/1278\\_c8y20\\_en.pdf](https://corp.shiseido.com/en/newsimg/archive/0000000001278/1278_c8y20_en.pdf)

\*5 Shiseido Reveals the Relevance of Capillaries in Skin Elasticity (2019)

<https://corp.shiseido.com/en/news/detail.html?n=0000000002780>

\*6 Shiseido Elucidates Mechanism by Which Capillaries Maintain Skin Elasticity (2020)

<https://corp.shiseido.com/en/news/detail.html?n=0000000002911>

\*7 Shiseido Discovers that Capillaries Promote Epidermal Regeneration (2022)

<https://corp.shiseido.com/en/news/detail.html?n=0000000003494>

**Discovery of CCN2, the "definitive beauty gene," which fluctuates in conjunction with harmful factor Serpin b3**

Shiseido extensively examined genes that are affected when the expression of harmful factor Serpin b3 increases and confirmed that the expression of CCN2 gene decreases with an increase in Serpin b3 gene expression (Figure 3).

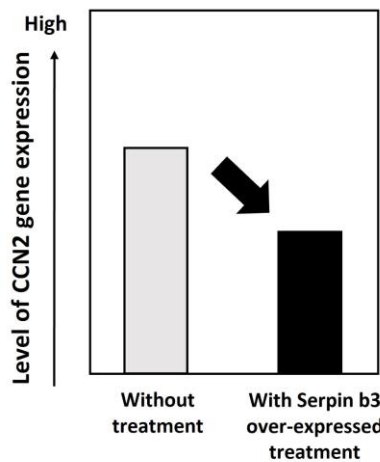


Figure 3. When Serpin b3 expression is increased, CCN2 gene expression is decreased

**Discovery of new findings, including the effect of CCN2 on capillaries as a mechanism to realize beautiful skin**

We conducted a study to investigate the relationship between CCN2 and pericytes, which are known to be deeply related to beautiful skin, and revealed that CCN2 acts on pericytes to strengthen the tissue structure of the dermis, increasing both the main component of collagen required to achieve firmness and the level of the hyaluronic acid precursor essential for retaining skin's moisture (Figure 2). These findings confirmed that CCN2 is also capable of approaching capillaries via pericytes.

In addition, it became clear that the level of CCN2 expression is not correlated with age, which makes this gene approachable in people of any age (Figure 4).

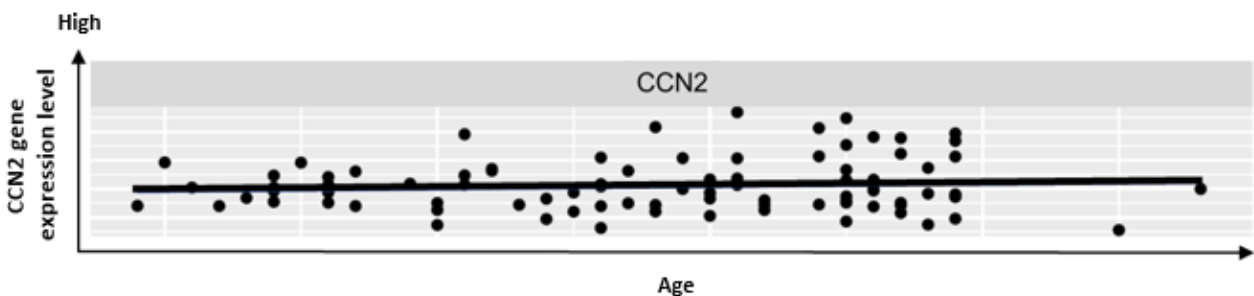


Figure 4. There is no correlation between the level of CCN2 expression and age

### Cosmetic ingredient that increases the gene expression level of CCN2: Green Tea Extract

Next, we searched for an active ingredient that can promote CCN2 gene expression and found that the Green Tea Extract increases CCN2 expression (Figure 5). Using this extract to approach the capillaries, dermis, and skin structure through the promotion of CCN2 expression, we will work toward achieving beautiful and healthy skin, regardless of age.

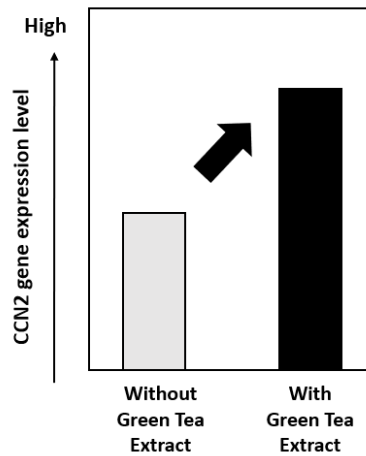


Figure 5. The effect of Green Tea Extract to promote CCN2 expression

### About our R&D strategy:

Under "Skin Beauty INNOVATION," one of the three pillars of Shiseido's R&D strategy, the present study was carried out as the brand's core science study by applying research in the area of skin foundation, the aim of which is to elucidate the relationship between the skin and conditions within the skin.

- 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, blood vessel

<Reference>

### Researchers' challenge

#### ■ R&D Philosophy "DYNAMIC HARMONY" approach

This research was carried out under the Inside/Outside approach of Shiseido's R&D philosophy, DYNAMIC HARMONY. We focused on CCN2, which functions as a messenger between cells, and tried to elucidate the mechanism connecting from the epidermis to the capillaries which is in the dermis. Our goal is to create new beauty approaches and solutions to achieve beautiful and healthy skin through blood vessels that circulate throughout the body.



Saori Yoneda, Researcher

#### ■ An approach unique to Shiseido, which has been researching Serpin b3 for more than 20 years

We have been independently researching the mechanism by which Serpin b3 promotes skin aging for more than 20 years. Serpin b3 is known to be increased due to various factors inside and outside the body, including UV irradiation, pollen, and sleep interruption. During the course of the study, we had one hypothesis that there may be another gene that fluctuates in conjunction with Serpin b3, and it was the beginning of the present study. To test this hypothesis, we focused on CCN2 that promotes wound healing in epidermal cells and collagen production in dermal cells, and found that this gene is not correlated with aging and is approachable in people of all ages, and that it has an effect of increasing ECM-related components in vascular cells that connect the skin and the whole body; this was a novel discovery. Moreover, as a solution, we also succeeded in identifying the effect of the Green Tea Extract, which has a strong connection to Japan.

#### ■ Challenge of a multi-faceted approach that goes beyond cell experiments

This time, our challenge was not only to perform cell experiments, but to conduct a study using global consumer data acquired over the course of eight years. The researchers directly visited the sites themselves and had repeated discussions with overseas members, acquiring data while flexibly adapting to changes in circumstances. In this manner, we realized discoveries regarding CCN2 through a multi-faceted approach, which ranged from cell experiments to global consumer surveys. We sincerely hope that this study will help consumer lead their own beautiful lives without being bound by age.

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=0000000003252>

- DYNAMIC HARMONY website:

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