

## Shiseido Reveals Pressure Awakens Skin Regeneration Ability

**-New approach to stem cells dormant in reservoirs;  
beauty treatments entering era of regeneration-**

Shiseido Company, Limited (“Shiseido”) has revealed that the application of pressure to the skin stimulates the proliferation of stem cells stored in “stem cell reservoirs\*<sup>1</sup>”, suggesting a possibility of skin regeneration, through collaborative research with Kyoichi Matsuzaki, Chief of External Plastic Surgery, Faculty of Medicine at the International University of Health and Welfare, together with Jichi Medical University and the National Institute for Physiological Sciences. We will apply this finding, which will help improve the appearance of aging, into the development of beauty treatments and services.

A part of these research results was presented in the Podium Presentation of the IFSCC\*<sup>2</sup> Congress 2018 held in Munich, Germany and won the Congress Award.

\*<sup>1</sup> Stem cell reservoir: The area which stores stem cells, discovered and named in this collaborative research.

2018: Shiseido Clarifies “Propagation of Aging” in the Inner Skin <https://corp.shiseido.com/en/news/detail.html?n=00000000002569>

\*<sup>2</sup> IFSCC (The International Federation of Societies of Cosmetic Chemists): An international organization dedicated to the development of highly functional and safe cosmetic technology through the world-wide cooperation of cosmetic societies.

### **Exploring approach to “stem cell reservoirs”; skin regeneration breakthrough**

With age, the skin loses its elasticity resulting in facial aging such as wrinkles and sagging believed to be caused by the age-related deterioration of cells (dermal fibroblasts), which control skin elasticity.

In this collaborative research, the team has already discovered that stem cells which are the origin of these dermal fibroblasts are well-maintained around the sebaceous glands in the skin, and has named them “stem cell reservoirs”. Based on this breakthrough finding the team has begun to promote the development of useful drugs, targeting the reservoirs as a key factor for skin regeneration. Even more so, such finding has ultimately promoted research pursuant to our belief in the regenerative power of beauty treatments Shiseido has developed over many years.

### **Pressure stimulates proliferation of stem cells from stem cell reservoirs**

Beauty treatments consist of various mechanical stimulation elements such as “pressure”, “tapping”, “twisting”, “stretching”, etc., and combinations thereof. It is known that beauty treatments are effective for the skin; however, mechanism details such as what specific element acts on which part of the skin had not been clarified. Revealing this mechanism will lead to the development of particularly effective beauty treatments.

Thus, the team applied various stimuli imitating each element of beauty treatments to cultured skin (organ cultures) and observed the effect.

Results confirmed that applying pressure to the skin proliferated stem cells (stem cell marker-positive cells) in stem cell reservoirs (Fig. 1). The team then conducted further research, focusing particularly on the act of “pressure” among various stimulation elements.

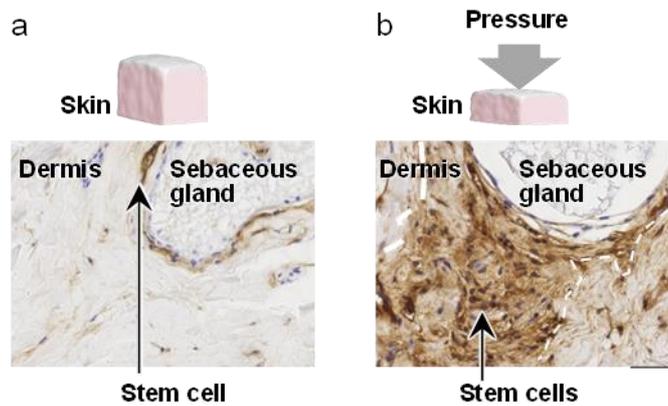


Figure 1. Pressure proliferates stem cells from stem cell reservoirs

a) Cultured skin with no pressure. A few stem cell marker-positive cells are found around the sebaceous gland (brown area indicated by arrow). This is similar to the state of the skin before culturing, and proliferation of stem cells is not observed. b) Comparatively, in cultured skin with pressure, the number of stem cell marker-positive cells is significantly increased.

### **Pressure reconstructs cellular network in proliferated cells**

Next, the team investigated whether the cells proliferated by pressure can actually function in the dermal layer. In order for the dermal cells to function properly, it is important that the cells connect to each other and reconstruct a network<sup>\*3</sup>. Therefore, the state of the cells was observed three-dimensionally with “Digital-3D Skin™<sup>\*4</sup>” technology that enables observation of this network (Fig. 2).

As a result, it was found that in pressurized skin, the proliferated cells connected to each other and reconstructed a network. This indicates that pressure promotes stem cell proliferation, leading to a functional state.

<sup>\*3</sup> 2020: Shiseido Reveals Network of Dermal Fibroblasts

<https://corp.shiseido.com/jp/news/detail.html?n=00000000002898> (Japanese)

<sup>\*4</sup> 2020: Shiseido Develops New AI-based Skin Analysis Technology “Digital-3D Skin™”

<https://corp.shiseido.com/jp/news/detail.html?n=00000000002897> (Japanese)

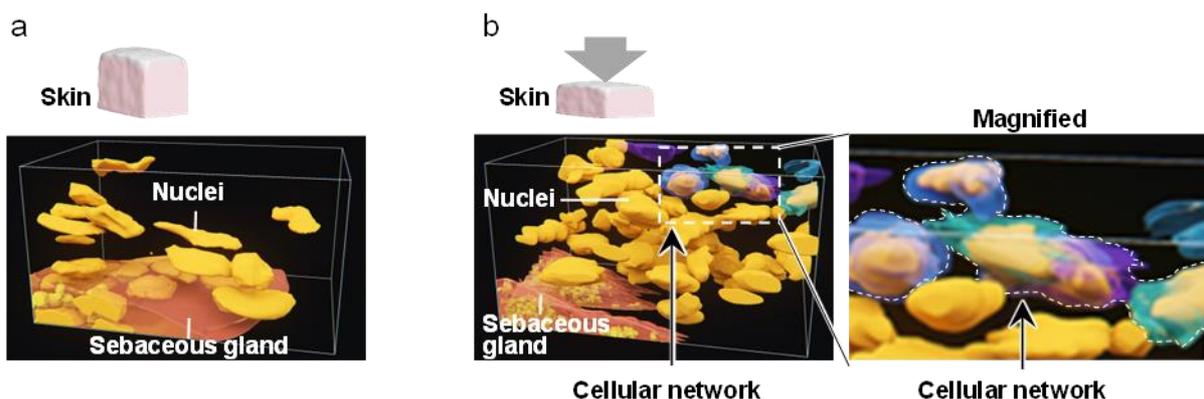


Figure 2. Reconstruction of cell network by pressure

Three-dimensional observation of the cultured skin with Digital-3D Skin™. a) Skin before applying pressure. b) Cultured skin with pressure. The number of cells around the sebaceous gland is significantly increased (this can be confirmed by the increase of cell nuclei). In further expanded cells, the network structure (indicated by arrow) can also be identified (colored for better visibility).

### **Collagen production of cells that reconstruct a network by pressure**

Furthermore, the team examined whether the cells that became functional with the application of pressure could regenerate the dermis. Collagen in the skin significantly decreases with age, resulting in the deterioration of skin elasticity. On the other hand, cells that have reconstructed a network produce collagen, and the production of collagen allows the dermis to regain its elasticity.

By observing the pressurized skin by method of detecting newly produced collagen (through immunohistochemistry), the team confirmed the production of collagen (Fig. 3). This result suggests that pressure induces regeneration of the dermis.

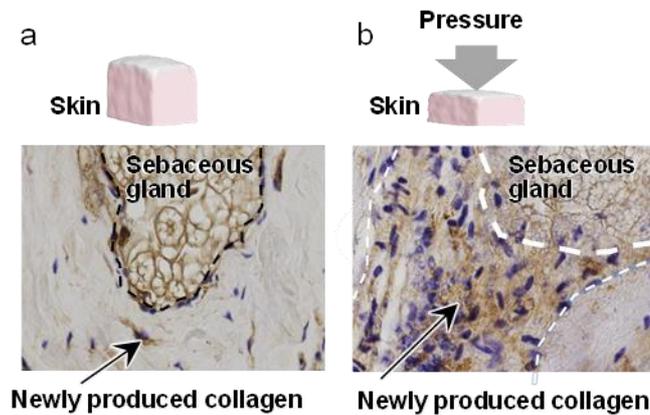


Figure 3. Increase of collagen by pressure

Analysis of newly produced collagen in cultured skin. a) In skin before applying pressure, newly produced collagen (brown area indicated by arrow) is slightly confirmed. b) Comparatively, in cultured skin with pressure, newly produced collagen is significantly confirmed.

### **Possibility of pressure to induce skin rejuvenation**

This series of studies suggests that pressure promotes the proliferation of stem cells released from stem cell reservoirs, and those cells reconstruct a dermal cell network resulting in the production of collagen, which ultimately result in regeneration of the skin (Fig. 4). At the same time, results have revealed great potential for beauty treatments to lead to skin rejuvenation. By utilizing this knowledge, first with beauty treatments and beauty devices, we will promote the development of various services.

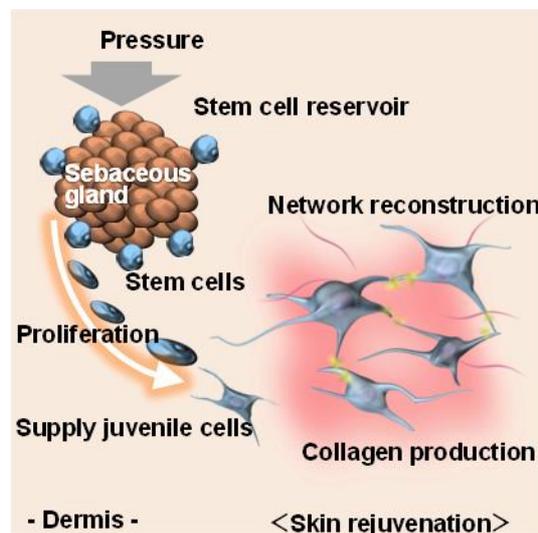


Figure 4. Pressure resulting in skin regeneration

When pressure is applied to the skin, stem cell marker-positive cells in the stem cell reservoir (around sebaceous gland) increase and supply juvenile cells to the surrounding area. These cells reconstruct the network structure and produce collagen, which leads to the improvement of skin elasticity and aged appearance.