Press Release

Shiseido Clarifies Underlying Mechanism of Age-Related Changes in Skin Immunity

Shiseido Company, Limited ("Shiseido") has collaborated with the Department of Dermatology (CBRC)*1 at Massachusetts General Hospital and found that the number of Langerhans*2 precursor cells*3 (hereafter, LC precursor cells) is reduced in the dermis of aged skin, and that decreased expression of CXCL14 that recruits LC precursor cells to the epidermis might result in the reduction of mature epidermal Langerhans cells.

This study has clarified an underlying mechanism by which epidermal Langerhans cells in the skin reduce with age. With these study results, it is expected that new technology will be developed to prevent age-related decrease of Langerhans cells and enhance the vitality of the skin to boost the innate power of the skin.

Going forward, Shiseido will apply the results of this study to the development of skincare research.

The study results were published in the Journal of Investigative Dermatology.

*1 Cutaneous Biology Research Center (CBRC): A comprehensive center for advanced research and development in dermatology. Established in 1989 by Harvard Medical University and Massachusetts General Hospital with the support of Shiseido. Shiseido dispatches personnel to conduct joint research with world-class researchers.

*2 Langerhans cells: Dendritic cells created in the bone marrow and exist in the epidermis to form a mesh network (Langerhans cells account for 2-5% of the total number of epidermal cells). Named after the medical scientist Paul Langerhans who discovered them in 1886.

*3 Precursor cells: Cells in the process of differentiation from a stem cell to another specific cell. LC precursor cells, which exist in the dermis, demonstrate immune functions as normal Langerhans cells once they migrate to the epidermis and differentiate.

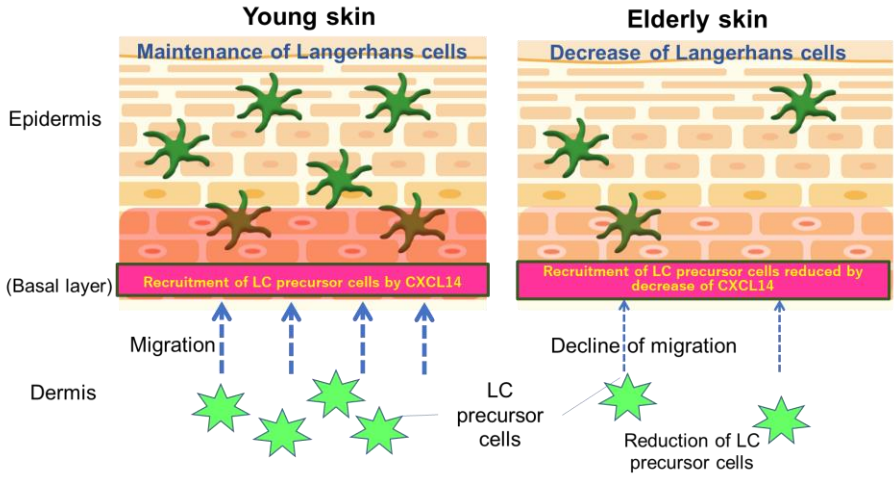

Figure 1. Mechanism of aged-related reduction of Langerhans cell suggested by this study.

Research background

In order to keep skin youthful and beautiful, it is important to elicit innate capacities of the skin and maintain homeostasis that enhances skin vitality. Langerhans cells play an important role in skin immunity, which is a function to maintain skin homeostasis, and on which Shiseido has conducted collaborative research with the CBRC for more than 30 years. In this joint research, we focused on aged-related changes in skin immune function and aimed to clarify the detailed mechanism under more stringent experimental conditions.

Langerhans cells, LC precursor cells, and LC precursor-recruiting factor are all reduced with age

We thoroughly analyzed the status of Langerhans cells, LC precursor cells, and the LC precursor-recruiting factors in sun-protected breast skin of young (16-28 years old, N=20) and elderly (53-74 years old, N=21) women, using techniques such as multiple immunostaining*4.

*4 Multiple immunostaining: A technique of dyeing multiple target factors in different fluorescent colors in a single sample. This technique has an advantage in that correlation between multiple factors can be clearly determined.

1. The number of epidermal Langerhans cells decreases with age

As in previous study results, it was confirmed that epidermal Langerhans cells were significantly reduced in aged skin (Figure 2).

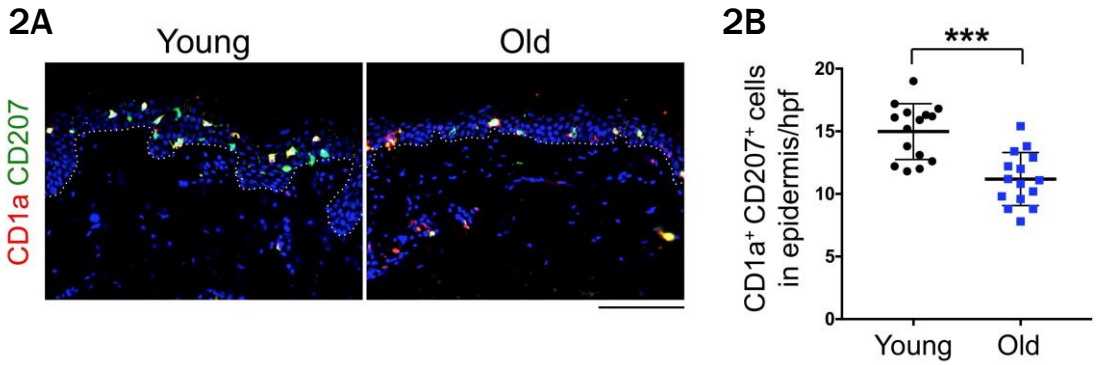

Figure 2A. Epidermal CD1a$^+$ CD207$^+$ Langerhans cells decrease with age (yellow-green in the image)

Figure 2B. The number of epidermal Langerhans cells in aged skin is reduced by approx. 20% compared with younger skin.

2. The number of dermal LC precursor cells decreases with age

Next, we quantified the number of CD14, CD207 and CCR6-positive cells, which are considered LC precursor cells, and found that there was a significant decrease in the dermis of aged skin (Figure 3).

3. LC precursor-recruiting factor CXCL14 is down-regulated in epidermis with age

Furthermore, we examined the expression of factors that can recruit LC precursor cells to the epidermis, and among these found that the expression level of CXCL14 in keratinocytes was significantly reduced in aged skin (Figure 4).

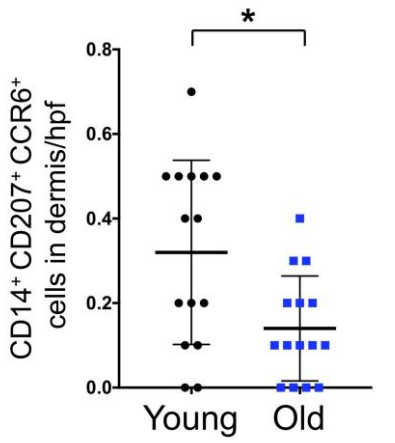

Figure 3. Comparison in the number of LC precursor cells in the dermis

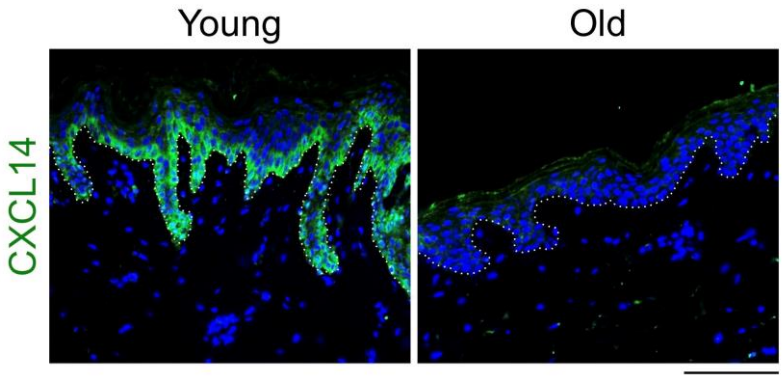

Figure 4. Comparison in the expression level of the LC precursor-recruiting factor CXCL14 between young and elderly skin.

The recruiting factor CXCL14 (green in the image) was clearly observed in young skin (left image) whereas only slightly in elderly skin (right image).

Movement (Migration) of LC precursor-like cells to the skin is significantly reduced with age

Furthermore, we performed an ex vivo migration assay using cultured LC precursor-like THP-1 cells.

As a result, it was confirmed that the migration of LC precursor-like THP-1 cells was significantly reduced in elderly skin compared to young skin (Figure 5).

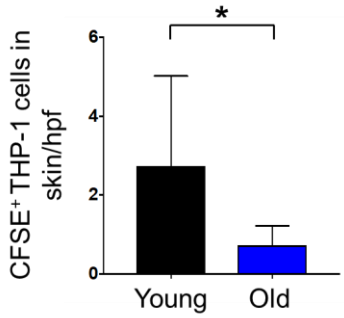

Figure 5. Comparison in the migration of LC precursor-like THP-1 cells between young and elderly skin. The migration was decreased in aged skin to about one-third of younger skin.

LC precursor-recruiting factor CXCL14 is involved in the migration of LC precursor cells

Next, given that young skin recruits more LC precursor cells, we blocked the recruiting factor by treatment of an anti-CXCL14 antibody, and evaluated the effect. As a result, the migration of LC precursor-like cells was significantly reduced. On the other hand, when CXCL14 was added to aged skin, which recruits fewer LC precursor-like cells, the migration was markedly increased (Figure 6).

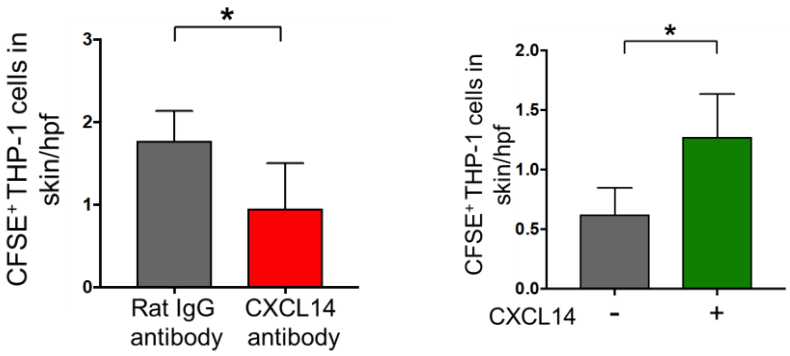

Figure 6. Effect of LC precursor-recruiting factor CXCL14 on the migration of LC precursor-like cells
Left: Effect of CXCL14 blockade on young skin. Right: Effect of CXCL14 treatment on aged skin.

Future outlook

While it has already been reported that the number of epidermal Langerhans cells is reduced by aging, this study data is considered to indicate a part of the mechanism.

Furthermore, this suggests that it is important to maintain the function of LC precursor-recruiting factor CXCL14 and the recruitment of LC precursor cells to the epidermis in order to hold mature Langerhans cells in the epidermis. With these findings, new technology development is expected with the aim to prevent the age-related decrease of Langerhans cells and keep skin youthful and beautiful by enhancing skin vitality and boosting the innate power of the skin.

Going forward, Shiseido will apply the results of this research to the development of skincare research.

[Reference]

Shiseido's research results on skin immunity

1. Research on skin immunity creates a new field of skin physiology. (1993)
   In 1993, Shiseido made a landmark discovery, scientifically proving that the skin and the nervous system are closely related, mediated by Langerhans cells, which are command the skin's immune system*5. With this discovery, Shiseido became part of creating a new field of skin physiology called Neuro-Immuno-Cutaneous-Endocrine – or the NICE theory. This finding came through a collaborative research effort with CBRC. It was this finding that inspired efforts to focus research on skin immunity.
   *5 Published in the scientific journal "Nature"; May 13, 1993

2. Discover: a new mechanism of skin trouble (2007)
   In 2007, Shiseido identified a mechanism of skin disorders, distinct from the known mechanism triggered by skin stress factors such as UV exposure and dryness. The new mechanism engages when the skin responds to stress or external stimuli, generating factors within cornified cells (keratinocytes) that make up the epidermis, and produce excessive skin damage factors, which can lead to various skin troubles*6. Meanwhile, another research institute had reported that Langerhans cells respond to stimuli response factors by attacking and sedating them, using their self-protection function to minimize skin troubles.
   Shiseido then conducted research to determine whether a relationship exists between aging and the self-protection function of Langerhans cells, and if so, to develop a skincare solution to address this mechanism.
   *6 Published in scientific journal "J Invest Dermatol" 2007; 127:362–371

3. Developing a multiple solution that acts directly on Langerhans cells and enhances skin immunity. (2014)
   In 2014, Shiseido discovered that the self-protection function that sedates stimuli response factors of Langerhans cells declines with age. When skin's self-protection function declines, it upsets the skin's homeostasis, resulting in roughness or decreased firmness caused by the degenerated barrier function of the horny cell layer, and degradation of collagen fibrosis in the dermis. To recover this self-protection function and heighten the immunity of the skin, Shiseido developed a multiple component that effectively combines three ingredients, including β-glucan, which directly influences Langerhans cells. When scientists used a prototype serum incorporating this multiple component, they were able to prove that the self-protection function of Langerhans cells can be heightened.