

Research and development

Research as a result of 30 years of collaboration between Shiseido and CBRC reveals a novel mechanism by which skin's immune cells eliminate senescent cells

Discovery of the possibility that skin's immune function may prevent aging,
published in journal *Cell*

Shiseido has collaborated with the Cutaneous Biology Research Center (CBRC)^{*1} at Massachusetts General Hospital to support research conducted at CBRC, which discovered as a new function of skin's immune cells the elimination of aged fibroblasts (senescent cells) and its mechanism. Advancing age alone does not correlate with the accumulation of senescent cells in the human skin. Among the potential mechanisms, Cytotoxic CD4⁺ T cell (CD4 CTL)^{*2}, a type of immune cells, are strongly associated with the inhibition of accumulation of senescent cells. In addition, as a mechanism by which CD4 CTL suppress the accumulation of senescent cells, it was discovered, for the first time in the world, that CD4 CTL recognize a part of human cytomegalovirus (HCMV)^{*3} as an antigen presented on the surface of senescent cells, which then leads to the selective elimination of senescent cells (Figure 1).

Shiseido, in collaboration with CBRC, has been engaged in research related to skin's immune function based on the idea of "preventing future skin problems with the power of the skin itself" for more than 30 years, making progress every step of the way on a continuous basis. Moving forward, the company aims to develop innovative values, such as that provided in this work relating to the suppression of accumulation of senescent cells through skin's innate immune system.

The results of the present study have been published in the journal *Cell*^{*4} issued on March 30, 2023.

*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 Cytotoxic CD4⁺ T cell (CD4 CTL): A type of T cell, it is also known to be an immune cell that is abundant in very long-lived people, who are considered models of ideal health and longevity.

*3 Most humans are infected with this virus in childhood, which causes latent infections throughout their lives but are mostly asymptomatic.

*4 One of the top academic journals in the world in the field of life science

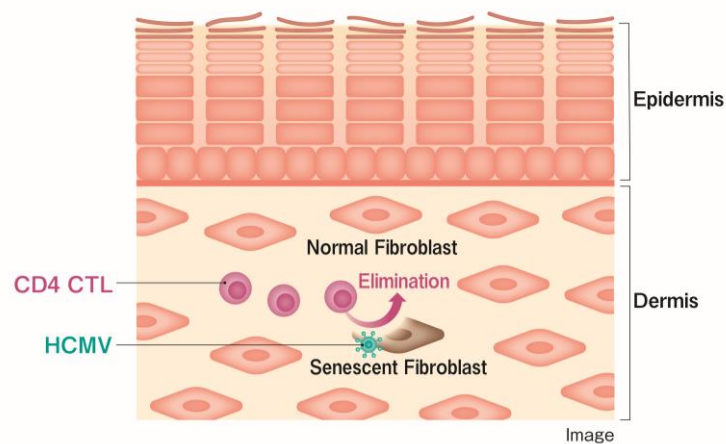


Figure 1. CD4 CTL eliminate senescent cells using HCMV as an antigen

Research background

It has been suggested that senescent cells gradually increase with age in the body, inducing and continuing to cause chronic inflammatory conditions and thereby promoting aging and aging-related diseases. However, much remains unknown regarding the conditions of senescent cell accumulation in various human organs, as well as the mechanism of how it is suppressed. In order to maintain the health of the skin, The reseachers thought it was important to investigate the physiological mechanism of senescent cell elimination in human skin and conducted the present study.

Discovery 1: There is age-independent increase in senescent cells in aged skin

First, the researchers investigated whether senescent cells accumulate with age in human skin tissue. The results showed that, compared with young skin, senescent cells were significantly increased in aged skin (Figure 2). On the other hand, looking at aged skin by itself, it was found that the number of senescent cells does not increase significantly with age from the 50s to the 70s (Figure 3). These findings suggest that the accumulation of senescent cells in old age may be suppressed by biological factors.

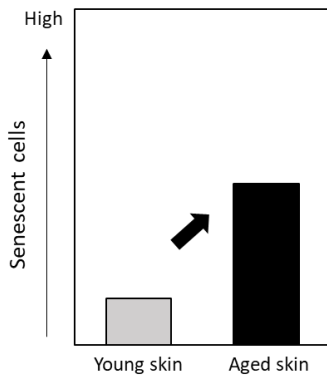


Figure 2. Senescent cells are more abundant in aged skin

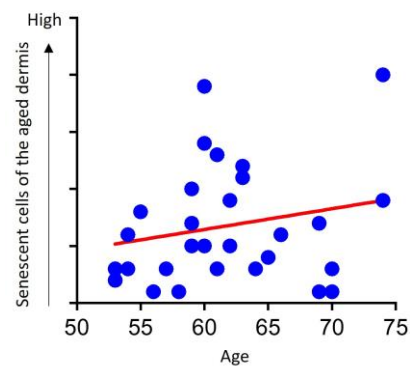


Figure 3. In aged skin, there is no correlation between senescent cells and age

Discovery 2: CD4 CTL, a type of immune cells, selectively eliminate senescent cells

The researchers then investigated factors that prevent the accumulation of senescent cells in aged skin. The researchers found that fewer senescent cells were present in aged skin with more CD4 CTL, a type of immune cells, suggesting the possibility that CD4 CTL may prevent the accumulation of senescent cells (Figure 4). Thus, in order to examine whether CD4 CTL can actually eliminate senescent cells, the researchers cultured normal fibroblasts (normal cells) and aged fibroblasts (senescent cells) together with immune cells isolated from human skin. The results confirmed that CD4 CTL do in fact selectively eliminate senescent cells (Figure 5).

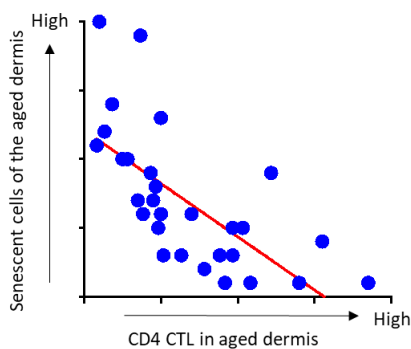


Figure 4: Skin with more immune cells (CD4 CTL) has fewer senescent cells

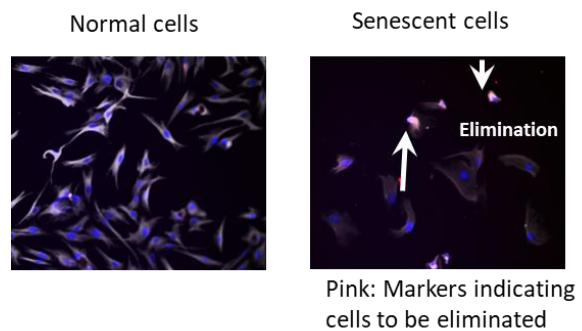


Figure 5: Immune cells (CD4 CTL) selectively eliminate senescent cells

Discovery 3: Human cytomegalovirus (HCMV) assists in the clearance of senescent cells by CD4 CTL

Next, the researchers investigated the mechanism by which CD4 CTL selectively eliminate senescent cells. The researchers discovered that a part (antigen) of the virus called HCMV, which establishes latency in human cells, appears on the surface of senescent cells, and CD4 CTL eliminate senescent cells by recognizing the antigen as a tag (Figure 6).

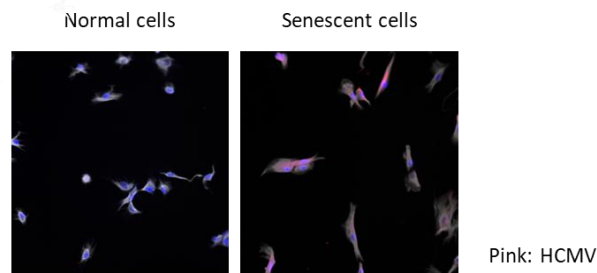


Figure 6: HCMV is reactivated in senescent cells

The present study clarified a novel function of immune cells in the skin, namely, the clearance of senescent cells. Based on these findings, Shiseido will create innovative values in the future that will help fundamentally approach aging with a focus on immune cells that prevent the accumulation of senescent cells in the skin.

About our R&D strategy:

This study was conducted under "Skin Beauty INNOVATION," one of the three pillars of Shiseido's R&D strategy, to clarify the relationship between the skin and its internal condition such as blood vessels, lymph vessels, immunity, and nerves.

- Integrated Report 2023 (Beauty Innovation)

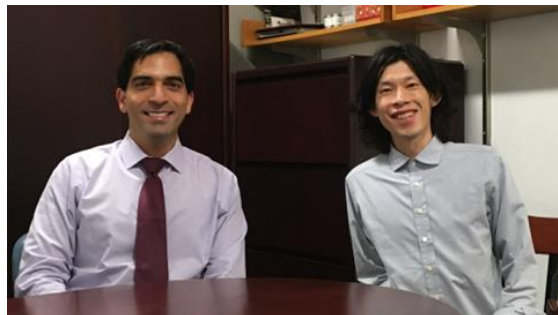
<https://corp.shiseido.com/report/en/2023/message/cmio>

- Keywords

Skin Beauty INNOVATION, skin immunity

Research efforts related to "skin immunity" at Shiseido

Shiseido has been working with CBRC on studies related to skin's immune function for over 30 years. The results of collaborative research with CBRC have received very high acclaim worldwide, including those published in the journal *Nature* in 1993. Shiseido's skin immunity research continues to evolve, and with the discovery of the senescent cell removal mechanism by immune cells this time, our innovative skin immunity research will take a leap even further to bring out the natural beauty of the skin beyond the boundaries of age.



Dr. Shadmehr Demehri at CBRC (left) with Dr. Tatsuya Hasegawa at Shiseido (right)

Shiseido Innovation Conference 2023

12:15 The latest findings from Shiseido's more than 30 years of skin immunity research
(Kentarō Kajiyā, Shiseido MIRAI Technology Institute)

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

References: The company's past research results on immunity

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<https://corp.shiseido.com/jp/news/detail.html?n=00000000003696> (Japanese)

<Reference>

Researchers' challenges

■ R&D Philosophy "DYNAMIC HARMONY" approach

This research has been conducted with the Inside/Outside approach under Shiseido's unique R&D philosophy, "DYNAMIC HARMONY." By elucidating the new mechanism of relationship between the skin and immunity, we aim to approach the essence of the root causes of aging to realize healthy and beautiful skin with the power of the skin itself.

■ Our skin immunity research is in a constant state of evolution

For more than 30 years, Shiseido has been advancing its research focusing on the importance of immunity for skin health. In order for immune cells to function correctly and eliminate foreign substances such as pathogens, it is first important that immune cells recognize foreign substances accurately by distinguishing them from self (as "non-self"). In the present study, The researchers led our investigation with a focus on the possibility that immune cells in the skin might recognize senescent cells as non-self and eliminate them, and made a groundbreaking discovery of a new fact, which was exactly as we had anticipated, that immunity was involved in the prevention of skin aging.

Shiseido's immunity research has previously led to a discovery of the connection between the skin and the nervous system (mind). This time, The researchers discovered that aging is prevented through the relationship between the skin and viruses—microorganisms living symbiotically in the skin. Indeed, we have identified and demonstrated that some unexpected invisible elements, such as the mind and microorganisms, are linked to immunity in a variety of ways. We believe that this is the strength of Shiseido's immunity research, which actively promotes fusion with various research fields. Going forward, we will continue to elucidate the ability of immunity, which has great potential to improve skin health, by understanding it from diverse perspectives while promoting fusion with different fields, with the aim of realizing the innate beauty of the skin free from aging and skin concerns in our customers.

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>