

Research and development

Shiseido elucidates cellular senescence mechanism underlying age spots through optical real-time FLIM analysis for the first time in the world

- Development of a unique triple active ingredients focusing on the "lifecycle of age spot," receiving the 2024 IFSCC top award -

Shiseido has uncovered a mechanism underlying the exacerbation of age spots through an innovative approach that challenges conventional knowledge in age spot research. Using FLIM^{*1}, which allows observation of the living human skin in real time, the company has established a method for evaluating cellular metabolism at the site of age spots for the first time in the world^{*2}. This led to capturing of the time frame of how age spots worsen, the "lifecycle of age spot," which has been difficult to observe until now. By utilizing this method, a cellular senescence occurring at the site of age spots was identified as the root cause of exacerbation of age spots, and unique triple active ingredients was developed to address the worsening of age spots (Figure 1). Focusing on the "lifecycle of age spot," we will devise innovative solutions to address the root cause of age spot exacerbation, challenging conventional knowledge in current age spot research.

The results of this groundbreaking research won the top award in the Podium Presentation Basic Research category at the IFSCC Congress^{*3}, the world's largest, prestigious research conference for cosmetics technology, achieving high acclaim as a next-generation cosmetic technology. The study was also presented at the 32nd Annual Meeting of the Japanese Society for Pigment Cell Research (2024/11/2-11/3). Moving forward, we will continue to aim for the development of innovative solutions through application of advanced research findings.

*1 FLIM: Fluorescence Lifetime Imaging Microscopy, an observation method for imaging based on fluorescence lifetime, which is an inherent property of fluorescent molecules.

*2 This is the world's first method to evaluate cellular metabolism at the site of age spots in the epidermis via a specific electron transport component using FLIM (as researched by Clarivate, September 2024)

*3 IFSCC: The International Federation of Societies of Cosmetic Chemists. Shiseido won Top Award for the results of this research at the 34th IFSCC Congress 2024 Brazil, Iguazu Falls (2024/10/14-10/17)

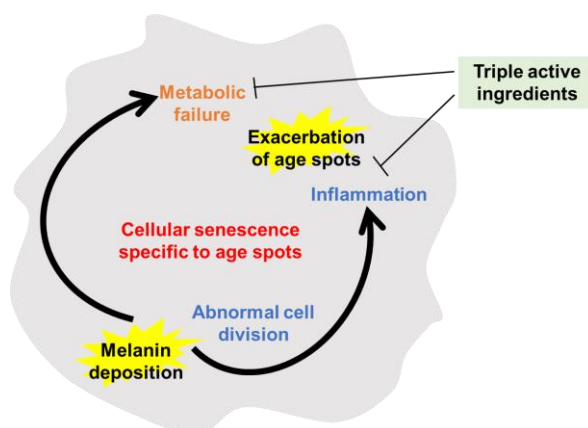


Figure 1. Cellular senescence mechanism specific to age spots and its solution

Research background

Through more than 100 years of skin research and advanced age spots research, Shiseido has revealed various factors related to the formation of age spots using multiple approaches to examine age-spot's microenvironment, where excessive melanogenesis and melanin-deposition occur. We came to think that the observation of the internal structure of the skin is important to elucidate age spots. To this end, we strived to

develop solutions by identifying factors specific to age spots: the condition of melanin deposition in age spots, abnormal capillary formation, darkening spiral that promotes excessive generation of melanin, and chronic micro-inflammation. Meanwhile, we have found that it is necessary to capture the dynamic changes occurring inside the skin, which are linked to these specific factors of age spots, at the cellular level in the same environment as the actual skin. However, it was difficult to analyze the inside of living age spots at the cellular level and in real time. In order to solve the fundamental problem of age spots, we needed to focus on the “lifecycle of age spot” and understand it as the activity state occurring within the lifecycle of skin cells, that is, metabolic changes in cells. This time, using FLIM, we established a new technique to observe the living skin, and observed mitochondrial metabolism in age spots for the first time in the world, taking on a challenge to verify the associated metabolic state.

Established a new technique for evaluating cellular metabolism at the site of age spots by applying FLIM, and elucidated the cellular senescence mechanism specific to age spots

FLIM-based analysis led to a finding that the mitochondrial metabolism in epidermal cells was reduced at the site of age spots in the living human skin compared with the no-age-spot site (Figure 2). It was also confirmed that this decrease in mitochondrial metabolism was caused by the excessive deposition of melanin (Figure 3), which further induced cellular senescence (Figure 4). These findings suggest that, at the site of age spots, mitochondrial metabolism is reduced because of the deposition of melanin, causing cellular senescence; this worsens age spots. In other words, there exists a source of age spot exacerbation, i.e., a vicious cycle of formation and spread of age spots.

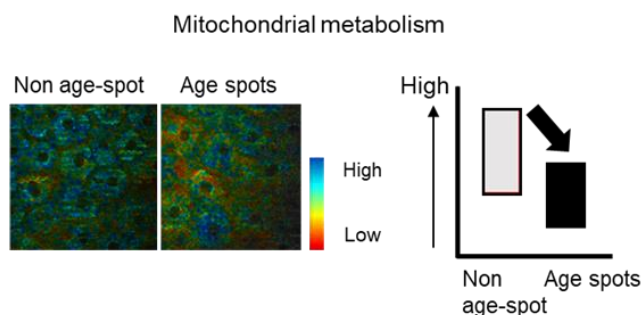


Figure 2. Mitochondrial metabolism in epidermal cells is reduced at the site of age spots compared with the non age-spot site

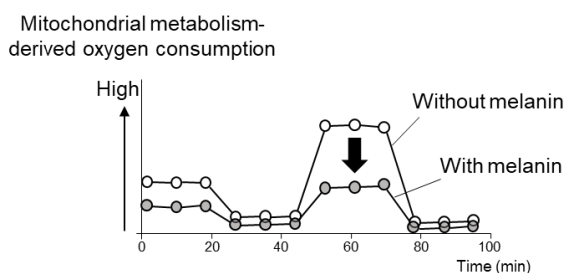


Figure 3. Excessive melanin deposition lowers mitochondrial metabolism

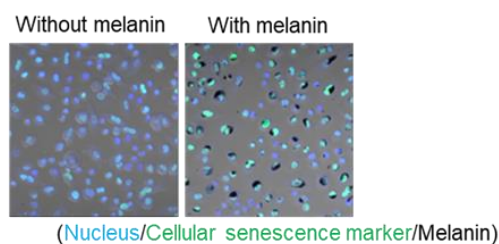


Figure 4. Excessive melanin deposition causes cellular senescence deposition lowers mitochondrial metabolism

Shiseido's unique triple active ingredients improves the cellular senescence mechanism specific to age spots

A formulation containing Shiseido's unique triple active ingredients was continuously applied to human skin for 6 weeks. As a result, we found that mitochondrial metabolism in age spots was enhanced with the application of the triple complex formulation (Figure 5). In addition to suppressing the decrease in mitochondrial activity, which is one of the major factors of cellular senescence, it also suppressed $GRO\alpha^{*4}$, a SASP factor^{*5} secreted by senescent cells that further exacerbates cellular senescence (Figure 6).

*4 One of SASP factors secreted by epidermal keratinocytes. It is also known to be involved in the process of melanocytes transformation to melanoma.

*5 General term for various factors including inflammatory factors secreted by senescent cells, called senescence-associated secretory phenotype (SASP).

At 6 weeks after continuous application

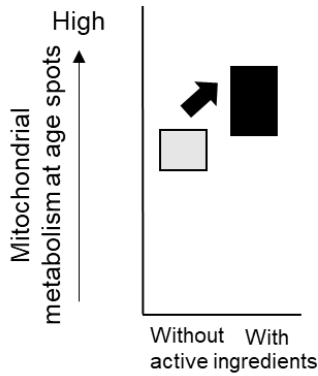


Figure 5. Continuous application of the triple active ingredients-containing formulation increases mitochondrial metabolism at age spots

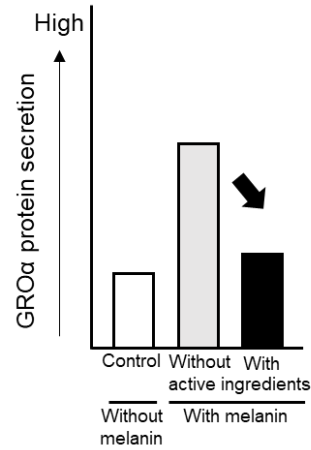


Figure 6. Triple active ingredients-containing formulation suppressed GROα

Future prospects

Shiseido aims to realize healthy beauty unique to each individual throughout his/her life under the company's vision toward 2030: "Personal Beauty Wellness Company." In order to respond to a variety of skin problems and support the pursuit of individual beauty, we will deepen our research toward a profound understanding of skin problems such as age spots and skin dullness and development of solutions.

About our R&D strategy:

We conducted this research under "Skin Beauty INNOVATION," one of the three pillars of Shiseido's R&D strategy, to elucidate the causes of "permanent skin concerns", including age spots/skin dullness, wrinkles, sagging, and pores, that our customers have been expressing for many years and develop solutions.

- Integrated Report 2023 (Beauty Innovation)

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

- Keywords

Skin Beauty INNOVATION, age spots/skin dullness, lifecycle of age spots

References: Related major news releases

- Shiseido discovers that the division of melanin deposited keratinocytes is reduced at the site of age spots (2008) https://corp.shiseido.com/jp/newsimg/archive/0000000000956/956_w6q94_jp.pdf (Japanese)
- Development of new skin brightening technology to suppress the vicious cycle of age spots (2010) https://corp.shiseido.com/jp/newsimg/archive/0000000001225/1225_g5j21_jp.pdf (Japanese)
- Elucidation of a new mechanism promoting an increase in age spots from deep inside the skin (2012) https://corp.shiseido.com/jp/newsimg/archive/0000000001438/1438_n8i43_jp.pdf (Japanese)
- Success in visualizing capillaries without cutting the skin (2017) <https://corp.shiseido.com/jp/news/detail.html?n=0000000002265> (Japanese)
- Discovery of involvement of abnormal capillary network in the formation of age spots (2017) <https://corp.shiseido.com/jp/news/detail.html?n=0000000002264> (Japanese)
- Shiseido succeeds in 3D visualization of vascular malformation in pigmented skin (2018) <https://corp.shiseido.com/en/news/detail.html?n=0000000002498>
- Discovery that the density of blood vessels at the site of age spots affects the improvement of pigmentation (2020) <https://corp.shiseido.com/jp/news/detail.html?n=0000000002975> (Japanese)
- Confirmation of new factors that lead to blood vessel-mediated age spot formation (2020) <https://corp.shiseido.com/jp/news/detail.html?n=0000000003009> (Japanese)
- Discovery that the cell adhesion molecule E-cadherin is involved in the generation and fixing of age spots (2022) <https://corp.shiseido.com/jp/news/detail.html?n=0000000003497> (Japanese)
- Shiseido discovers that aging increases the risk of hyperpigmentation under UV light exposure during daytime hours, leading to the development of suppression methods (2024) <https://corp.shiseido.com/en/news/detail.html?n=0000000003759>

<Reference>

Researchers' Challenges

■ R&D Philosophy "DYNAMIC HARMONY" approach

This research is being conducted based on the Inside/Outside approach of Shiseido's unique R&D philosophy "DYNAMIC HARMONY." Using a noninvasive observation technique, we identified a phenomenon of excessive melanin deposition hidden inside age spots exacerbating age spots, and developed an effective combination of active ingredients.

■ An innovative approach that challenges conventional knowledge in age spot research, with a focus on the "lifecycle of age spot"

As we age, age spots change in a variety of ways; they spread, darken and increase in number. This research was initiated with the idea that the problems related to age spots in one's lifetime may be addressed by perceiving these various age-related changes as the "lifecycle of age spot." In order to do so, it was necessary to constantly explore the viewpoint and technology needed to capture the universal phenomena occurring inside various kinds of age spots. Mitochondrial metabolism and cellular senescence are becoming common research categories, but within these, there was a hidden essence specific to the site of age spots. This discovery also led to the development of a combination of active ingredients to fundamentally approach age spots. The first chapter of our research and development has just begun. By observing and understanding the lifecycle of age spot, we will provide customers with new approaches and reliable solutions to tackle age spots.



Daigo Inoue, Ph.D.,
Researcher

What is research and development (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>

•The DYNAMIC HARMONY special website

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