



Shiseido Discovers That Age-Induced Macrophage Imbalance Affects Collagen Metabolism

Shiseido Company, Limited (“Shiseido”) has revealed that the balance between two types of macrophages*¹ (the M1/M2 balance) is involved in a series of collagen metabolism, collagen production, fragmentation, and degradation*² in photoaged skin. Changes in the amount and properties of collagen in the skin due to adverse effects on collagen metabolism may cause a decrease in skin elasticity. We have been conducting research focusing on “inflammaging*³ (inflammatory aging)” in the skin. In our research, we already elucidated that the M1/M2 balance is skewed by photoaging, resulting in an increase in M1 macrophages and a decrease in M2 macrophages. Moreover, we also found that this kind of skewing in the M1/M2 balance induces aging of dermal fibroblasts*⁴.

This research is being conducted under the Inside/Outside approach of our unique R&D philosophy “DYNAMIC HARMONY”. We aim to offer a new approach to address various skin concerns by clarifying the relationship between age- and photo-induced skin aging and the balance of macrophages, a type of immune cell known to be involved in healing wounds in the skin. These research results were presented in part at the 46th Annual Meeting of the Japanese Society for Investigative Dermatology held from December 3 to 5, 2021.

*¹ A type of immune cell whose main function is to eliminate bacteria and waste products. M1 macrophages are mainly responsible for the inflammatory reaction and removing foreign materials, whereas M2 macrophages promote the anti-inflammatory reaction and repair of tissues damaged by inflammation.

*² The digesting and removal of materials at the cellular level in the body

*³ The inflammatory response is a necessary bodily defense reaction against external stimuli such as UV rays and dryness. However, it has been recently discovered that the inflammatory response does not fully disappear in the body, becoming more chronic, which has various adverse impacts on the body. The phenomenon of accelerated aging due to chronic inflammation is called inflammaging.

*⁴ Shiseido Discovers Relationship of Macrophage Balance to Skin Aging for the First Time in the World (2020)

<https://corp.shiseido.com/en/news/detail.html?n=00000000003038>

Research Background

It is said that collagen accounts for approximately 70% of the dermis layer in the skin and is considered to be one of the key factors that determine the morphological characteristics of the skin. Fibroblasts are known as the main cells that produce collagen. It is also known that UV-induced photoaging reduces collagen production by fibroblasts and causes excessive collagen fragmentation resulting in a loss of skin firmness and elasticity and a development of wrinkles and sagging. We have long been conducting research in this field focusing on various factors such as fibroblasts and have already revealed that in the sun-exposed areas, the total number of M1 and M2 macrophages does not change with aging but their balance (the M1/M2 ratio) does*⁵. In this round of experiments, we carried out research by using a new approach focusing on macrophage imbalance, which has been found to be involved in inflammaging.

*⁵ Horiba S et al. *JID Innov.* 2022

Relationship between the M1/M2 balance and collagen production/fragmentation

Recently, it has been reported that the M1/M2 balance plays an important role in controlling collagen metabolism during the process of healing wounds in the skin (wound healing). Thus, we examined the

effects of M1 and M2 macrophages on collagen production and fragmentation by fibroblasts. As a result, we confirmed a correlation between the M1/M2 balance and collagen expression in skin tissue. Furthermore, we found that the supernatant application of M1 macrophage culture*⁶ to fibroblasts suppresses collagen production and promotes its fragmentation, resulting in a significant decrease of collagen fibers (Figure 1). In addition, we found that the supernatant application of M2 macrophage culture promotes collagen production compared to the supernatant application of M1 macrophage culture through the evaluation using procollagen, a precursor of collagen as an indicator (Figure 2).

*⁶ Liquid collected from the surface of the culture solution when cells are being cultured. It contains secretions from cells.

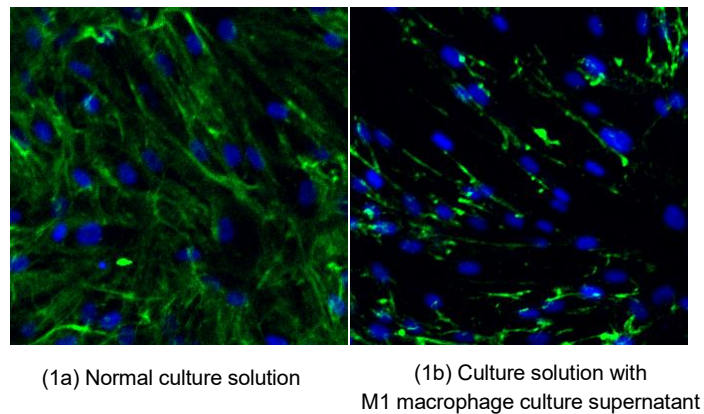


Figure 1. The effect of supernatant M1 macrophage culture on collagen fiber formation.
(Blue: fibroblast nuclei, Green: type I collagen)

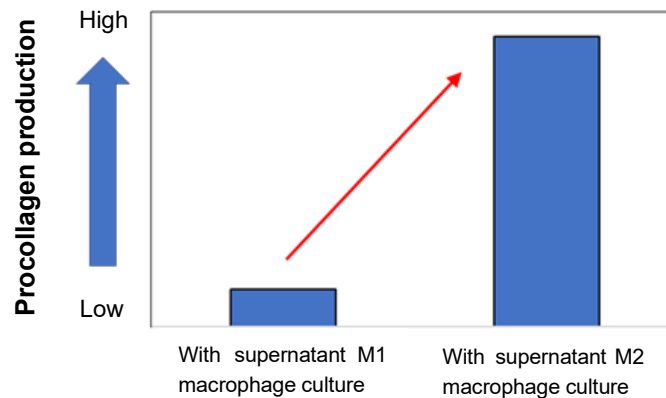


Figure 2. Promotion of collagen production by M2 macrophages

M2 macrophages remove fragmented collagen

Next, in order to clarify the relationship between the characteristic function of macrophages to collect, digest, and remove biological substances and collagen metabolism in the skin, we examined the functions of M1 and M2 macrophages and fibroblasts to degrade denatured (including fragmented) collagen*⁷. The results showed that M2 macrophages play the remarkable role of internalizing and degrading denatured collagen (Figure 3). As fibroblasts are known to produce more collagen when binding to collagen in the undegraded, healthy three-dimensional structure, proper removal of denatured collagen by M2 macrophages may promote collagen production.

*⁷ Collagen protein that has lost its inherent three-dimensional structure.

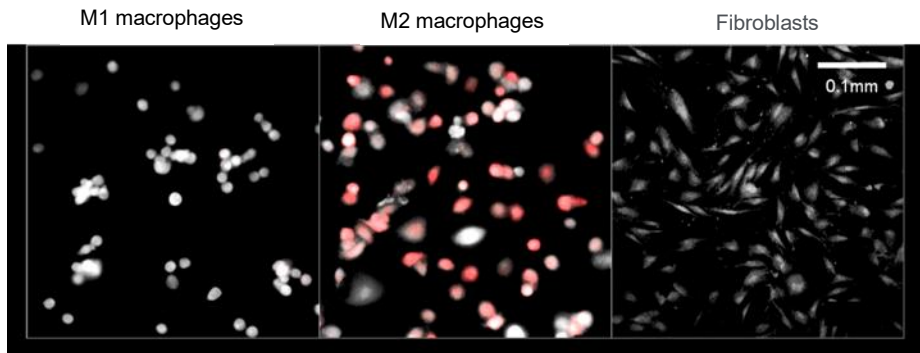


Figure 3. Various cells internalizing and degrading collagen.

Hypericum erectum extract, an agent that inhibits differentiation into M1 macrophages

M1 macrophages are known to function by differentiating from immature macrophages, and thus, we searched for an agent that inhibits differentiation into M1 macrophages. As a result, we found that Hypericum erectum extract has the effect of inhibiting this differentiation pathway (Figure 4). It is expected that the inhibition of differentiation into M1 macrophages will create an environment in which M2 macrophages can easily increase.

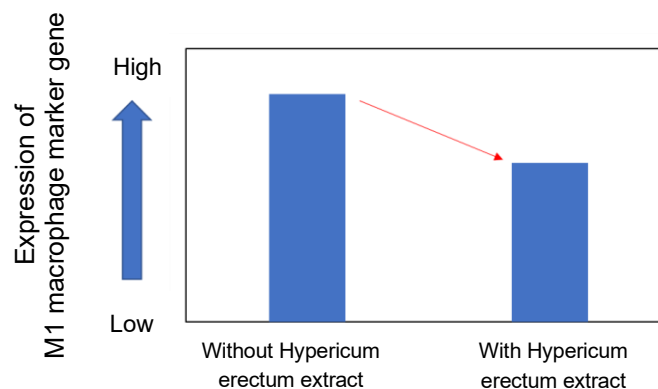


Figure 4. Hypericum erectum extract inhibits M1 macrophage differentiation.

Future Prospects

Previously, we found that the skewing of M1/M2 balance in the skin causes a failure in curbing chronic inflammation and induces inflammaging, and in this research, we revealed that macrophage imbalance affects collagen metabolism. Maintaining a healthy macrophage balance may support inherent collagen metabolism in the skin by encouraging the degradation of collagen after fragmentation, while serving the existing effects of maintaining and promoting collagen production. We at Shiseido will continue our research into the relationship between various skin conditions and the latest findings such as inflammaging and others that are attracting attention in the medical field and will create new beauty approaches that go beyond consumers' expectations.

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>

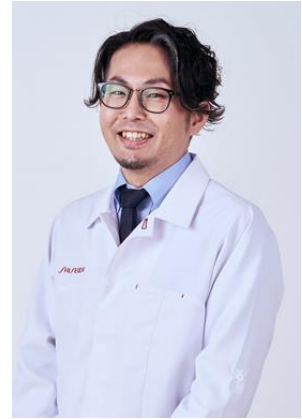
The DYNAMIC HARMONY special website: <https://corp.shiseido.com/en/rd/dynamicharmony/>

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Researchers' Challenge

■ Research inspired by medical approach

Diabetes and metabolic syndrome are thought to be partly attributed to chronic inflammation, a condition in which the body is in a constant state of low-grade inflammation, and recently, there has been an urgent need to develop treatments for such chronic inflammatory diseases in the medical field. The aging phenomenon due to chronic inflammation is called “inflammaging”, and we conducted research with a focus on inflammaging in the skin. In order to improve the chronic inflammation, it is important to remove the causes of inflammation such as waste products and normalize the function to suppress inflammation. It is well known that the M1/M2 balance plays an important role in healing wounds in the skin, but little was known about its relationship with aging. Thus, we focused on the M1/M2 balance to confirm the function of macrophages in skin aging. This was the first research focusing on the M1/M2 balance in skin aging inside and outside the company, we had so many trials and errors starting with the establishment of experimental methods, such as staining and counting of macrophages in skin, and finally were able to achieve the results through many discussions among researchers in various fields of expertise.



Researcher, Satoshi Horiba

■ Versatile and fundamental approaches to skin problems

Macrophages digest and remove foreign substances such as invading bacteria in the body. It is becoming clear that macrophages also support the normal functions of other tissues such as fibroblasts, epidermal cells, and blood vessels in normal skin. Skin problems vary between people, such as spots, dullness, wrinkles, or sagging, but by applying our findings regarding macrophages, we may be able to create versatile, fundamental approaches to these skin concerns.