

Shiseido Reveals that Downregulation of Epidermal Cell-Derived IL-34 Skews Macrophage Balance

- A new generation of beauty care focusing on “inflammaging” -

Shiseido Company, Limited (“Shiseido”) has found that the downregulation of interleukin 34 (IL-34)^{*1}, a protein secreted from the epidermis, skews the M1/M2 balance, a balance between two types of macrophages (M1 macrophages and M2 macrophages), which are known as immune cells (Figure 1). Furthermore, we also discovered that creeping thyme extract acts as an active ingredient that is expected to increase IL-34 production by epidermal cells and regulate the M1/M2 balance.

We have previously revealed that the skewing of the M1/M2 balance is involved in the development of “inflammaging”, in which chronic inflammation accelerates aging in the skin. Then, we also elucidated that the imbalance between M1 and M2 macrophages is associated with a series of collagen-related metabolic sequences. In this study, we clarified part of the mechanism that fundamentally regulates the M1/M2 balance, which is an important finding and expected to be applied to the development of new solutions. Some of these study results were presented at the 22nd Annual Meeting of the Japanese Society of Anti-Aging Medicine held from June 17 to 19, 2022, and the presenter, Shiseido researcher Satoshi Horiba, received the Best Presentation Award^{*2}.

This study is being conducted based on the Inside/Outside approach of Shiseido’s R&D philosophy “DYNAMIC HARMONY”. We will clarify the mechanism by which the balance of macrophages, a type of immune cell that is also attracting attention in the medical field, is related to skin aging and will provide new beauty care products to address various skin concerns.

^{*1} A type of interleukin, a protein secreted by immune cells. It is known to be involved in the maintenance of Langerhans cells, the immune cells in the skin.

^{*2} Shiseido MIRAI Technology Institute’s Researcher, Satoshi Horiba Won the Best Presentation Award at 22nd Annual Meeting of the Japanese Society of Anti-Aging Medicine

<https://corp.shiseido.com/en/news/detail.html?n=00000000003430>

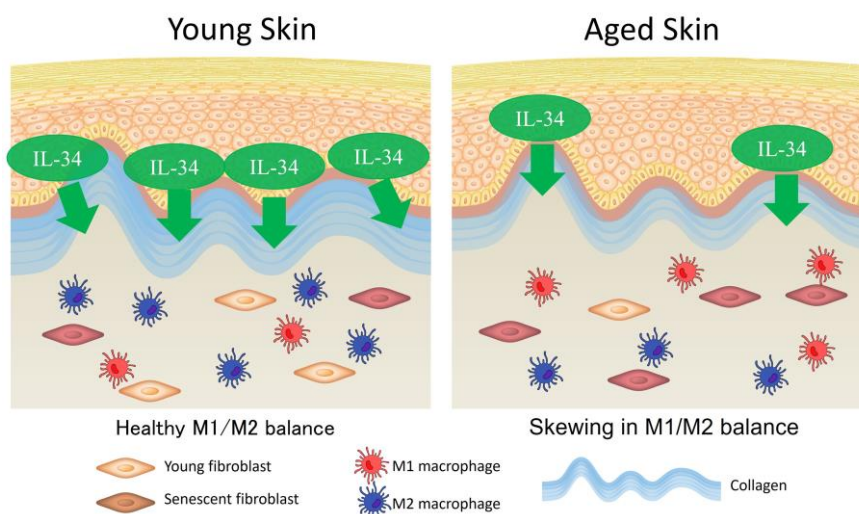


Figure 1. IL-34 downregulation skews macrophage balance.

Research Background: Relationship between macrophage balance and various skin-aging phenomena

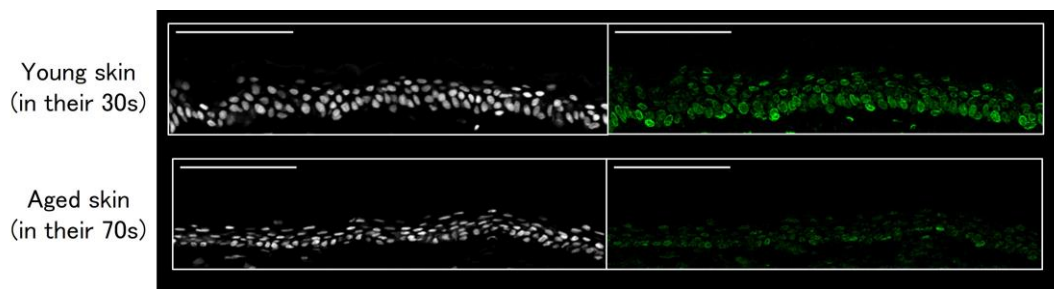
In 2020, Shiseido discovered that a skewing in the balance between M1 and M2 macrophages induces “inflammaging”, in which chronic inflammation accelerates aging in the skin. Furthermore, in 2022, we revealed that the skewing of the M1/M2 balance adversely affects a series of collagen metabolism, collagen production, fragmentation, degradation, and removal, and may cause a deterioration in skin firmness and elasticity. In this study, we carried out research to identify the causes of the skewing in the M1/M2 balance, which is related to skin aging phenomena, aiming to apply the findings to the development of new solutions.

Macrophage balance is skewed by downregulation of epidermal cell-derived IL-34

In order to conduct a comprehensive search for factors that skew the M1/M2 balance in the skin, we conducted a bioinformatics analysis^{*3} using human skin data of approximately 200 individuals (in their 60s) listed in the international database “GTEx Portal”^{*4}. We sought for factors that showed significant differences in gene expression between sun-exposed and sun-protected skin areas and that were strongly associated with macrophages, and consequently, we found IL-34, which made us wonder if IL-34 might strongly affect the M1/M2 balance. Given that our previous research results have already showed that IL-34 is a factor that plays an important role in maintaining healthy skin, we actually compared the IL-34 gene expression between the young skin (in their 30s) and the aged skin (in their 70s) (sun-exposed skin). As a result, it was confirmed that IL-34 expression was markedly decreased in the aged skin (Figure 2). In addition, after examining its relationship with M1/M2 balance in human skin tissue, we found that skin with a larger number of IL-34-positive epidermal cells had a M1/M2 balance similar to that in the young skin (Figure 3), and that by applying IL-34 to macrophages, the polarization into M2 macrophages was accelerated in a concentration-dependent manner (Figure 4).

^{*3} A data analysis technique mainly for biological data through information science such as statistics and programming skills.

^{*4} International database that provides comprehensive information on genes expressed in each of the various tissues of the human body.



IL-34 expression decreases in the aged skin. Left: epidermal cells (white) Right: IL-34-positive cells (green)

Figure 2. IL-34 downregulated by the accumulation of UV damage with aging.

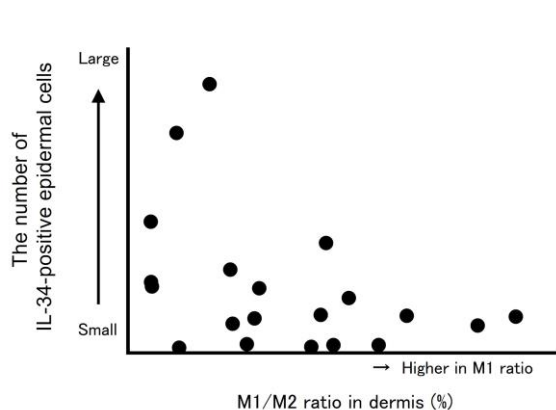


Figure 3. Relationship between the number of IL-34-positive epidermal cells and the M1/M2 balance.

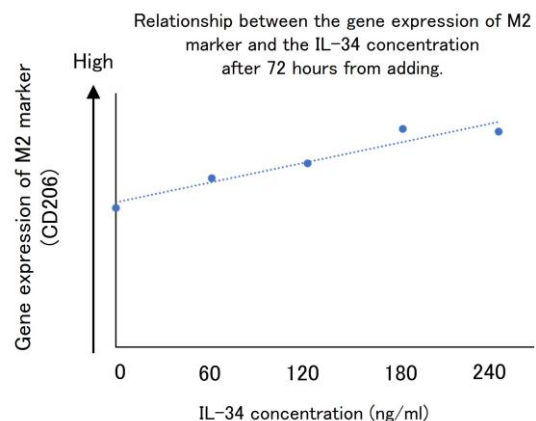


Figure 4. Differentiation into M2 macrophages is accelerated by addition of IL-34.

Creeping thyme extract promotes IL-34 production in epidermal cells

In this study, we searched for ingredients that promote IL-34 production, which was confirmed to be associated with the skewing in the M1/M2 balance, and found creeping thyme extract as an active ingredient with particularly excellent effects among several candidate ingredients (Figure 5).

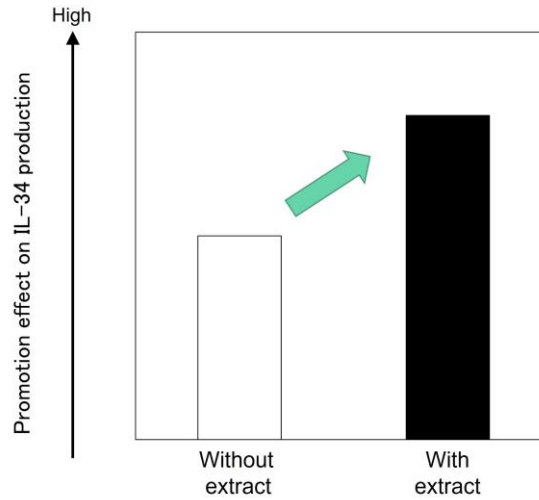


Figure 5. Creeping thyme extract promotes IL-34 production

Future prospects

Shiseido has been leading research focusing on the importance of M1/M2 macrophage balance in beauty. Going forward, we will continue to actively deepen our knowledge on the relationship between macrophages and various skin problems, and strive to propose new solutions.

<Reference>

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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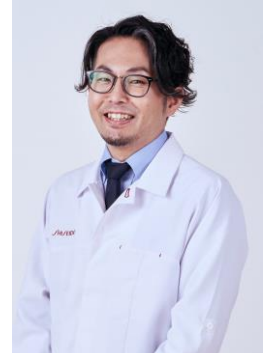
Shiseido Discovers That Age-Induced Macrophage Imbalance Affects Collagen Metabolism (2022)

<https://corp.shiseido.com/en/news/detail.html?n=0000000003374>

Researchers' challenges

- Seek for research methods by utilizing bioinformatics analysis and objective evaluation

In order to find out what is involved in macrophage differentiation and shows particularly significant differences in the sun-exposed areas, we investigated a large number of factors using bioinformatics analysis, and found IL-34. In pursuing our research, we always try to ensure our scientific credibility through asking for technical guidance from professors who are the authority on macrophage research and presenting our research at academic conferences twice a year to receive objective evaluations from outside parties.



Researcher, Satoshi Horiba

- Contribute to the realization of ideal skin conditions for each user

As society ages, as a result of medical advances, we believe that cosmetics can provide significant value in helping people enjoy long lives comfortably, happily, and positively. Especially in a society of longevity, chronic inflammation, which has become a priority target in medicine, is a major problem associating with various issues in maintaining healthy skin. Thus, we hope to contribute to the realization of the best skin conditions for each user by providing scientifically supported solutions to chronic inflammation and various skin problems.