Review

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Changing the World of Cosmetics via Facial Aging R&D

Tomonobu Ezure*

Mirai Technology Institute, Shiseido Co., Ltd., Kanagawa, Japan

Skin care R&D has long been focused on skin surface issues, such as fine wrinkles, spots, and so on. However, people are actually mainly concerned with age-dependent changes of facial morphology, such as bulldog-like descending cheeks, loss of facial contour, and appearance of nasolabial folds. Thus, we tried to cultivate this novel field of facial aging in cosmetics. To develop effective skin care solutions for these issues, we first established a fundamental basis for research in this field by constructing definitions and evaluation systems for these morphological changes. Furthermore, to identify targets for intervention, we established a variety of novel approaches to study the internal structures and dynamics of aged skin, for example, digital reconstruction of skin in three dimensions (3D), using artificial intelligence (AI) technology. These approaches enabled us to identify novel facial aging mechanisms, such as the appearance of dermal cavitation, and to develop theoretical accounts, such as the adipo-aging theory. Then, building on those discoveries, we developed a variety of novel skin care solutions. Here, I am going to review the progress in the field of skin care to improve aged appearance, focusing on our cosmetics R&D work as well as discussing future prospects for this field.

Key words: skin care, anti-aging, 3D, AI, sagging, fat, rejuvenation, dermal cavitation, sweat gland, digital-3D skin, cytokine

1. Introduction

Facial morphology drastically changes with aging, and this is a matter of great concern to many people, especially in the current aging society. However, such changes have not been a major target of cosmetics, but have generally been targets for aesthetic surgery. We considered that age-related impairment of the properties of the skin contributes to these changes, and if this is so, cosmetics should be effective to ameliorate these age-dependent changes.

The skin forms the outermost layer of the body, serving to maintain the physiological condition of the body and to protect against invasion of harmful materials and microorganisms from the environment.[1,2] Another important function of the skin is to protect the internal organs from physical insults, such as collision or pressure, and to maintain them in their proper positions.[3] Therefore, it is plausible that changes in skin properties are associated with these facial morphological changes, and might be ameliorated by appropriate skin care. However, when we began our research, facial morphological changes were a novel field for cosmetics. Thus, to conduct anti-aging skin care R&D, we first needed to establish a fundamental basis from scratch.

*Corresponding author: Tomonobu Ezure (E-mail: tomonobu.ezure@shiseido.com)

Mirai Technology Institute, Shiseido Co., Ltd., 1-2-11, Takashima, Nishi-ku, Yokohama, Kanagawa 220-0011, Japan

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2. Establishment of a Fundamental Basis for Cosmetic R&D Targeting Facial Aging

2.1. Actual status of facial aging

Facial morphology changes in various ways with aging, but clear definitions and evaluation systems to establish how these changes progress with aging have been lacking. Thus, we observed a hundred female and male faces, and classified the morphological changes with aging. We found that, for example, cheek skin progressively sags down at three regions with aging.[4] Taking the upper cheek area as an example, this area initially shows smooth morphology, then a slightly convex region appears at the top of the area with the formation of a slightly concave area at the side, initiating sagging formation.[5] Subsequently, the convex area descends, and the concave area extends and forms a deep fold, called the nasolabial fold. Finally, the area becomes baggy and a ptotic morphology develops. Similar changes occur at the lower and outer parts of the cheek and the lower eyelids. In each area, various morphological changes occur at the top, sides, and bottom of the sagging region, such as marionette lines, hollow cheeks, and loss of facial contour. Thus, besides the aging appearance of sagging itself, sagging causes a variety of morphological changes in the surrounding areas.

2.2. Sagging induces wrinkles

Moreover, we found that sagging also induces wrinkle formation. Wrinkles were formed in two stages: the first step is temporary formation of wrinkles due to movement of the skin, such as changes of facial expression, but these wrinkles disappear when the skin movement is reversed (transient wrinkle). The second step is retention of these wrinkles on the skin due to many repetitions of the same skin movement (fixed wrinkle). Although the first step is critical for wrinkle formation, most studies of wrinkles had focused on the second step, because of the difficulty of research, for example, asking volunteers to adopt precise facial expressions (such as a “30% smile”). Thus, we established the methodology to control facial expressions in a quantitative way, based on the angle of upward gazing, and used it to clarify the actual status and mechanism of temporary wrinkle formation.[6] We found that temporary winkle formation increases with aging, although the facial expression was the same. To clarify the mechanism, we analyzed the relationship of various facial parameters, and finally found that sagging at regions distant from the wrinkle area induces temporary wrinkle formation. For example, sagging of the upper eyelid interferes with vision, thus to pull up the eyelid to maintain vision, facial muscle activity increases, which causes transient wrinkles at the forehead. Thus, sagging is a critical target even for temporary wrinkle formation, which in turn leads to increases of permanent wrinkles.

2.3. Why do people perceive their face as younger than their actual age?

We found that sagging begins to occurs in the twenties and can be clearly seen in the thirties, but is only regarded as a concern by subjects in their forties. Thus, we tried to clarify people’s perception of facial appearance. Previous studies had used questionnaires,[7] which may be influenced by a variety of personal differences, such as interest in facial appearance and opinion of aged impression. Thus, we established an objective evaluation system using photograph-based grading criteria combined with two steps of evaluation of perception and confirmation of evaluation.[8] This work revealed that people perceive their facial appearance as 8.1 years younger than the actual status, on average. Furthermore, the reason for this perception gap is the difference in viewing angle of the face. Sagging is well recognized from the side view, at an angle of 45°, but people tend to see their own face from the front, from where it is hard to recognize facial sagging due to the lack of depth information.

2.4. Sagging is a critical target for facial aging

We further evaluated the actual status of facial morphological changes with aging, taking account of the differences in gender,[9] ethnicity, and so on, and concluded that sagging is a critical cause of facial aging. Thus, we set sagging as a target for improving a variety of facial morphological changes.

3. The Mechanism of Facial Aging

With the appropriate methodology in hand, we proceeded to investigate the precise mechanism of facial aging. We analyzed the relationship between facial morphological changes (sagging) and the physical parameters of the skin. We found that sagging increases with deterioration of the skin’s physical properties, namely, elasticity.[4] This was a critical finding, since it means that skin condition, the major target of cosmetics, is a causal factor of sagging, implying that cosmetics can contribute to improve sagging, or facial aging. Then, we tried to clarify the factors that lead to the loss of skin elasticity, to understand the mechanism of facial aging.

3.1. Establishment of "adipo-aging theory"

3.1.1. Increment of subcutaneous fat increases sagging

The skin consists of three layers: the epidermis, the dermal layer, and the subcutaneous adipose layer. The dermal layer contains abundant extracellular matrix molecules (ECMs), such as collagen, elastin, and hyaluronic acid.[10–12] Since these ECMs are hard or elastic materials, the dermal layer contributes to skin elasticity. Although the subcutaneous adipose layer is adjacent to the dermal layer, it had been considered as just a fat store, filled with adipocytes. The stereotypical image of subcutaneous fat, based on our questionnaire research, is that it is beneficial to prevent sagging, since it expands the skin. Thus, we measured the faces of volunteers with a wide range of subcutaneous fat amounts, in order to test the idea that subcutaneous fat might be a key skin care target. However, contrary to our expectation, subjects with larger amounts of fat showed greater sagging of the cheek.[13] We further found that increment of subcutaneous fat decreases skin elasticity. To establish the mechanism of this deterioration, we investigated the internal skin condition histologically, and found that the amount of elastic fibers in the dermal layer is decreased in skin with an increased amount of subcutaneous fat.[14] This suggests that physiological changes occur, instead of just descent of the skin under gravity due to the increased amount of cheek weight. Subcutaneous fat increases with aging due to inactivity or to menopause in women. Therefore, we designated this phenomenon as "adipo-aging", namely, an increment of subcutaneous fat induces skin and facial aging.

3.1.2. Subcutaneous fat is a controller of dermal condition

To clarify the physiological influence of subcutaneous fat on to the dermal layer, we established an in vitro skin model, namely, a co-culture system of dermal fibroblasts with enlarged adipocytes, as a model of the skin of subjects with an increased subcutaneous adipose layer.[15] We found that enlarged adipocytes negatively influence the condition of dermal fibroblasts, causing a decrease of collagen and hyaluronic acid, major ECMs of the dermal layer, while matrix metalloproteinase 13 (MMP13), which degrades the collagen matrix, was increased. We further identified the factor that induces this reaction as palmitic acid, and established that the secretion of palmitic acid increases with increasing amount of subcutaneous fat. Moreover, a histological study of obese subjects indicated that enlarged adipocytes secrete MMP9, which degrades elastic fibers in the dermal layer.[14] By contrast, we found that adiponectin, secreted from normal, small adipocytes,[16] positively influences dermal fibroblasts, inducing an increase of collagen and hyaluronan secretion.[17] Thus, subcutaneous adipocytes control the dermal layer condition both positively and negatively depending on their size, namely, depending on the amount of subcutaneous fat. Subcutaneous fat had been considered as just quiescent cells storing fat, but our findings showed that in fact it is an active controller of the dermal cell condition.

3.1.3. Rejuvenation of facial appearance by targeting fat

Based on the adipo-aging theory and the discovery of subcutaneous fat as the dermal layer controller, subcutaneous fat appeared to be a novel target to improve aged appearance. One approach would be to reduce the size of enlarged adipocytes by means of reduction of body fat, namely, dieting. However, dieting is difficult for human beings, so we investigated a pharmaceutical route. We focused on the master regulator of the adipocyte condition, the proliferator-activated receptor gamma (PPARgamma). Activation of PPARgamma induces the formation of small adipocytes from precursor cells.[18] Furthermore, activation of PPARgamma also decreases enlarged adipocytes via acceleration of their turnover.[19] Thus, PPARgamma can completely change the condition of subcutaneous fat, from enlarged adipocyte-dominant to small adipocyte-dominant, without changing the total amount of subcutaneous fat. Based on the screening of natural plant extracts, we found that tiencha extract (*Rubus suavissimus S. Lee* extract) can induce PPARgamma in adipocyte precursors, leading to the generation of small adipocytes.[20]

3.1.4. Discovery of "dermal cavitation", and identification of sweat glands as a key target for facial rejuvenation

We also tried to clarify the mechanism of facial aging from a different viewpoint. Histological analysis of changes of skin condition is restricted to two-dimensional (2D) observation of skin slices. However, the internal skin structure is very complicated due to the presence of a variety of internal organs, such as hair follicles, sebaceous glands, and sweat glands. Furthermore, each of these organs also has a complicated structure, so that 2D observation is inadequate to understand the whole skin structure in detail.

3.2. Establishment of "dermal cavitation theory"

3.2.1. Establishment of skin visualization technology, "digital-3D skin"

To analyze the internal skin structures in 3D, we focused on X-ray microCT.[21] However, internal skin structures are difficult to detect using X-rays, and thus we tested a variety of contrast agents, pretreatments, and their combinations, and

finally established an observation technology called amplification of structure-associated X ray absorbance (ASAXA μ CT). To identify the internal structures in more than 1000 images per sample, we used artificial intelligence (AI)-based auto classification technology and reconstructed the whole skin as a 3D image on the computer. Since this 3D skin is digitally reconstructed, namely, each structure has independent spatial information, we can freely view and explore the internal structures on the computer. For example, we can digitally dissect it and separate and sort target structures within the 3D structure, which is impossible by conventional physical dissection. Moreover, we can quantify it at ultrafine resolution, and analyze the connections and distributions of structures to identify their relationships. Thus, we designated this skin as "digital-3D skin".

3.2.2. Dermal layer defects, designated as "dermal cavitation", are ubiquitous and become larger with aging

By examining digital-3D skin, we found that increasing numbers of defects appear in the deeper area of the dermal layer with aging.[22] These defects are filled with subcutaneous adipocytes. Before that, adipocytes had sometimes been observed in the dermal layer, but since they appeared to be isolated in the dermal layer based on 2D observation, they were considered to have differentiated from dermal cells in the dermal layer. However, our 3D observation revealed that these adipocytes are connected to the subcutaneous adipose tissue. Since, these dermal defects look like cavities, we called this feature "dermal cavitation". To analyze the influence of dermal cavitation on the facial condition, we measured the skin parameters and appearance of middle-aged female volunteers. We found that skin elasticity is significantly decreased with the progression of dermal cavitation. This seems reasonable since the highly elastic dermal layer is replaced by inelastic subcutaneous fat in dermal cavitation. Indeed, dermal cavitation increased sagging[23] and wrinkles.[24] Thus, dermal cavitation is a novel basis for facial rejuvenation. But, why does this happen?

3.2.3. Sweat gland deforms with aging, which leads to dermal cavitation

To clarify the mechanism of dermal cavitation, we analyzed the interior of dermal cavitation areas via digital-3D skin. We found that sweat glands exist in areas of cavitation with a high probability. Although the sweat gland function is known to deteriorate with aging, the underlying mechanism has not been clear, partly due to the difficulty of analyzing the complex sweat gland structure with conventional observation technology. Whereas sweat glands are generally considered to decrease in number or volume with aging, our digital 3D analysis revealed no significant difference between young and aged skin regarding the density of sweat glands per skin area, or the volume of sweat glands, whether the total volume or the volume of each part (secretory coil and secretory duct).[25] However, we found that the morphology of sweat glands drastically changed with aging, with a shift towards the skin surface of the skin due to tangling and rotation of the secretory duct. This shift of sweat glands was accompanied with expansion of the dermal cavitation toward the skin surface. Moreover, based on gene expression analysis of micro-dissected sweat glands, we found that matrix metalloproteinase is highly expressed in the sweat gland. These results suggest that sweat glands shift toward the skin surface with aging, inducing dermal cavitation due to the degradation of the dermal layer (or collagen) by matrix metalloproteinase, and adipocytes move into the vacated spaces, resulting in loss of skin elasticity, which in turn leads to sagging.

3.2.4. Sweat gland is a novel target for anti-aging skin care

Our study revealed that dermal cavitation occurs beneath the sweat gland, and thus indicates that the sweat gland could be a novel target of anti-aging skin care. As the sweat gland is well known to serve a drug delivery route, we could employ sweat glands for effective delivery of an active ingredient directly to the cavitated area. Subcutaneous fat contains adipocyte precursor cells, generally called adipose tissue-derived stem cells (ADSCs), and ADSCs or exosomes secreted by them are already targeted to enhance wound healing or for aesthetic treatment.[26] Thus, ingredients that can activate ADSCs in dermal cavities or attract ADSCs from subcutaneous adipose tissue connecting to cavitated areas, just as hair follicles attract ADSCs during the hair cycle, might be effective. We considered that this could be an impactful solution for regeneration of the cavitated dermal layer to rejuvenate the face.

4. Future Perspective

Our extensive investigations revealed that sagging is the critical factor in age-dependent changes of facial morphology. Sagging occurs due to the effect of gravity pulling down the skin, and although the body has internal systems to resist gravity, such as anti-gravity muscles and the skeletal system, the nature of the anti-gravity system of the skin has not been clarified. However, current technology cannot easily address this, because to study it we need to observe the dynamics (deformation and recovery processes) of the whole skin and its internal structures, namely, 4D analysis technology is needed. This faces two difficulties, namely, observing the skin in an intact state without chemical treatment, and analyzing an astronomic volume of data. However, we believe that clarifying the anti-gravity machinery of skin will provide a deeper insight into facial morphology, and could provide a new target for anti-aging skin care R&D.

5. Conclusion

In order to conduct cosmetics R&D in the novel field of facial morphology, we first established a fundamental basis for research by developing suitable definitions and quantitative methodologies to clarify the actual status of morphological changes. This enabled us to identify the critical target for facial rejuvenation, namely, sagging. Next, we focused on the mechanisms of facial aging. One of them is an increment of subcutaneous fat, which controls skin condition. Another is dermal cavitation, which we discovered using our novel technology, digital-3D skin, enabling analysis of complex internal skin structures in 3D. These studies provided a variety of novel skin care targets, such as adipocytes and sweat glands, which had not previously been a focus for anti-aging skin care. These breakthroughs in cosmetic R&D, based on novel research technology, leading to the identification of new mechanisms and theories of facial aging, as well as discovery of targets for novel solutions, have contributed to opening up a new era of skin care.

Conflict of interests: The authors declare no conflicts of interest associated with this manuscript.

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