

News Release

Title

To understand the regeneration mechanisms of the skin:

Localization of dermal stem cells in the papillary dermis and involvement of collagen type 5 in their maintenance.

Key Points

○The localization of dermal stem cells in the dermis had been unclear, and was identified in this study.

○Dermal stem cells were localized in the papillary layer of the dermis, and the papillary layer is thought to be the site of dermis regeneration.

○Collagen type 5 was found to play an important role in maintaining an undifferentiated state of dermal stem cells.

○ Understanding of the regeneration mechanism of the dermis should lead to the improvement of wound treatment methods as well as health and beauty.

Summary

Nagoya University Graduate School of Medicine (Director, Kenji Kadomatsu), Nagoya University-MENARD collaborative research chair (Designated Lecturer, Yuichi Hasebe and Designated Associate Professor, Seiji Hasegawa) has been studying stem cells in the skin to apply the findings to medical, health, and cosmetic care in collaboration with Nippon Menard Cosmetic Co., Ltd. (President, Junichi Nonogawa), and Fujita Health University, Department of Applied Cells and Regenerative Medicine (Professor, Hirohiko Akamatsu) and Department of Dermatology (Professor, Kazumitsu Sugiura). Here, we report that our study showed the localization of dermal stem cells in the papillary dermis and suggested the involvement of collagen type 5 in the maintenance of the dermal stem cells.

Among various stem cells in the skin, epidermal stem cells have been the most extensively studied, and clinical application of cultured epidermis has already been achieved. Regarding dermal stem cells, their localization and the mechanisms of their maintenance and regeneration remained unknown. The whole regeneration mechanisms of skin including those of the dermis, subcutaneous adipose tissue, and hair follicles besides of the epidermis need to be understood to generate the skin *in vitro*, as well as for the future innovation in wound treatment methods, drug development, skin care and cosmetics.

In this study, we focused on the histological differences of the upper (papillary) and lower (reticular) dermis, and examined in detail cells and collagen fibers in each layer. We found that the stem cells (CD271-positive cells) were localized mostly in the papillary layer and in the same area collagen type 5 was highly expressed. We further analyzed the effect of collagen type 5 on the dermal stem cells, and showed that collagen type 5 play an important role in maintenance of an undifferentiated state of the dermal stem cells. These results suggest that in

the dermis, dermal stem cells are localized in the papillary layer and the papillary layer is the site of regeneration, supplying new dermal cells and constituents of the dermal tissue, such as collagen type 5, function of which in turn is important for the maintenance of the dermal stem cells.

The paper on the findings was published in *the Journal of Dermatological Science*. We will further continue to conduct research in our academic-industrial collaboration to develop new technologies of health-care and cosmetic products, as well as regenerative medicine.

Research Background

Stem cells in the skin have a long history of investigation compared to those in other tissues. Indeed, culturing methods of artificial epidermis were already established, and application to regenerative therapy (e.g. those against severe burn) has been started. As for other deeper skin tissues than the epidermis, including the dermis, subcutaneous adipose, and hair follicles, regeneration mechanisms of each tissue remain largely unknown, although existence of stem cells was reported. To achieve generation of the skin tissue including these lower layers *in vitro*, it is necessary to conduct research further on the stem cells in the dermis, subcutaneous adipose, and hair follicles and answering questions one by one should lead to innovation of technologies in wound treatment, drug development, and skin health and cosmetics.

We have been studying stem cells in the skin by isolating from skin tissues and culturing *in vitro* as well as generating 3D reconstructed epidermis, and showed the age-related changes and the role of stem cells in wound healing (Akamatsu et al., 2016; Iwata et al., 2017). In this study, we focused on the dermal stem cells, which had been less examined compared to other stem cells in the skin, to understand the maintenance and generation mechanisms of the dermis.

Research Results

The dermis is constituted of the upper papillary and lower reticular dermis. The papillary dermis has thin collagen fibers and is a sparse and soft tissue, on the other hand, the reticular dermis is composed of dense and solid tissue made up of thicker collagen fibers. We focused on these histological differences between the papillary and reticular dermis, and examined in detail cells and characteristics of collagen fibers in each layer. It was found that stem cells (CD271-positive cells) were mostly localized in the papillary layer (green in Figure). In addition, collagen type 5 was found to be highly expressed around the dermal stem cells (red in Figure), indicating that the dermal stem cells were localized in a collagen type 5-rich area of the papillary dermis.

Collagen type 5 was known to function in angiogenesis (Hering et al., 1983) and wound healing (Cuttle et al., 2005), but its effect on stem cells had not been studied. To understand the effect of collagen type 5 and the dermal stem cells, we cultured dermal stem cells with or without collagen type 5, and found that the stem cells required collagen type 5 to maintain their number, indicating that collagen type 5 plays an important role in maintaining an

undifferentiated state of the dermal stem cells.

The skin is exposed to various kinds of external stress, such as the ultraviolet and physical stimuli, and therefore required to have a high potential of tissue regeneration. In the dermis, the stem cells, which are required for regeneration, were found to be localized in the papillary dermis, and the papillary dermis is thought to be the site of regeneration where new dermal cells and constituents are supplied. It was also suggested that collagen type 5 functions to maintain the dermal stem cells.

Research Summary and Future Perspective

This study showed that dermal stem cells were localized in the papillary layer, and that collagen type 5 was highly expressed in the same area. This means that the dermal stem cells provide a special microenvironment (niche) in the papillary layer, which allows to maintain the stem cells themselves and also to regenerate the tissue. Based on these findings and by developing new technologies to regulate the niche function, we will try to increase the regeneration potential of the skin, which may lead to further insights into maintenance and improvement of skin health and cosmetics as well as application to regenerative medicine.

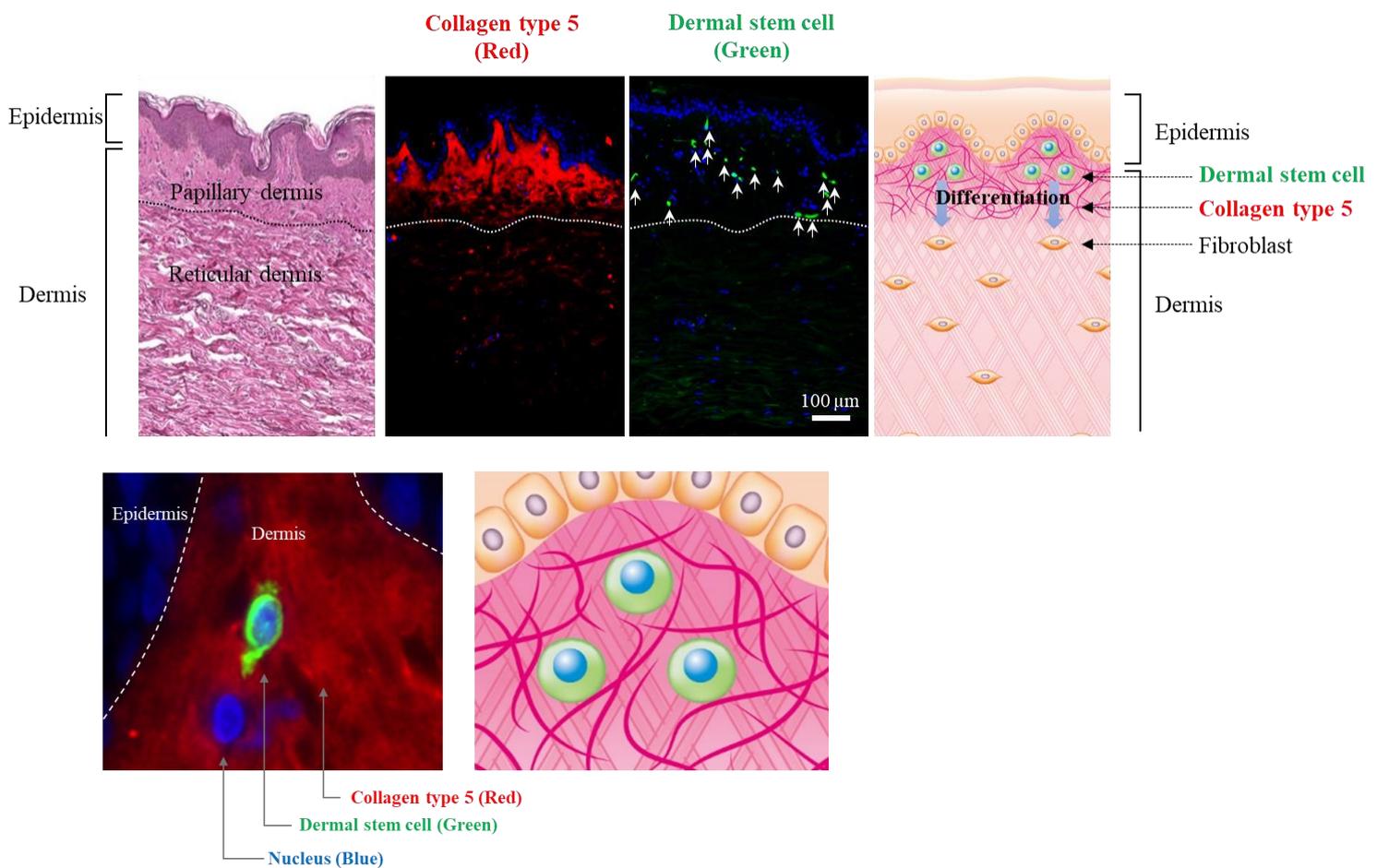


Figure. Localization of dermal stem cells.

H&E-stained histological section (top left), immunohistochemical images, and schematic drawing of human skin tissues. Red, collagen type 5; green, CD271; arrows, dermal stem cells;

dotted lines, the border of the papillary and reticular layer. Dermal stem cells were localized mostly in the papillary layer. Enlarged image of immunohistochemical staining against CD271 (bottom) showed that dermal stem cells were surrounded by collagen type 5.

Publication

Yuichi Hasebe, Seiji Hasegawa, Yasushi Date, Satoru Nakata, Akiko Yagami, Yohei Iwata, Kazumitsu Sugiura and Hirohiko Akamatsu.

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