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Studying hair follicle loss as a model of age-related organ decline

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Q Your research uses hair follicles as a model to study the mechanisms of tissue aging. Why did you choose hair follicles as a model system?

A: In mammals, most organs undergo a process called atrophy, where they become smaller (miniaturize) or thinner with age, and generally show reduced function and ability to regenerate over time. Also, if you look closely at aged organs, there is often obvious tissue damage. The hair follicle can be thought of as a "mini-organ" of the skin—like larger organs, it has its own stem-cell system to sustain cellular and tissue turnover. The hair follicle controls hair regrowth and, as we age, miniaturization of hair follicles leads to balding. Because of the relative simplicity of the hair follicle and the obvious physical manifestation of aging follicles, it is a good model system for studying the mechanisms of tissue aging.

Q You published a paper in *Science* on the mechanism of hair follicle aging. Can you explain the background and main findings of this research?

A: Stem cells, which renew themselves and also generate functionally differentiated cells, are important for adult tissue regeneration, and changes in stem cells are recognized as one of the hallmarks of aging. Hair follicle stem cells (HFSCs) generate all cell types needed for hair growth and are located in the hair follicle itself. However, we had not known what happens to aged HFSCs or what role stem-cell aging plays in the overall organ-aging process. In our study published in *Science*, we showed that DNA damage triggers a response in HFSCs that causes stepwise miniaturization of hair follicles, leading to hair loss. More specifically, DNA-damage response in HFSCs leads to the breakdown of type XVII collagen (or COL17A1), which is needed for HFSC maintenance. Instead of producing cell types that contribute to hair growth, those stressed HFSCs exclusively differentiate into terminally differentiated epidermal keratinocytes and are pushed to the skin surface and eliminated. With the other cell types being poorly produced, the hair follicles gradually become smaller until they disappear, resulting in hair loss.

Q Most of your work was carried out in mice—how can you be sure that it also reflects what happens in humans?

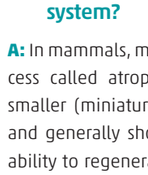
A: After defining the mechanism in mice, we decided to look at scalp tissue samples from women ranging from 22 to 70 years old. By staining these tissue sections with special markers for HFSCs such as COL17A1 and for DNA-damage response, we saw similar DNA-damage response in HFSCs, HFSC depletion and hair follicle miniaturization in tissues from the older women, confirming that our findings in mice are translatable to humans.

Q Your research involved both local and international collaboration. How does this fit into the overall goals of TMDU?

A: TMDU's vision emphasizes cutting-edge translational research that contributes to the health and well-being of society. Collaborating with other leaders in the field helps us achieve the goal of carrying out basic research with clinical applicability.

Q What are the clinical implications and future directions of your work?

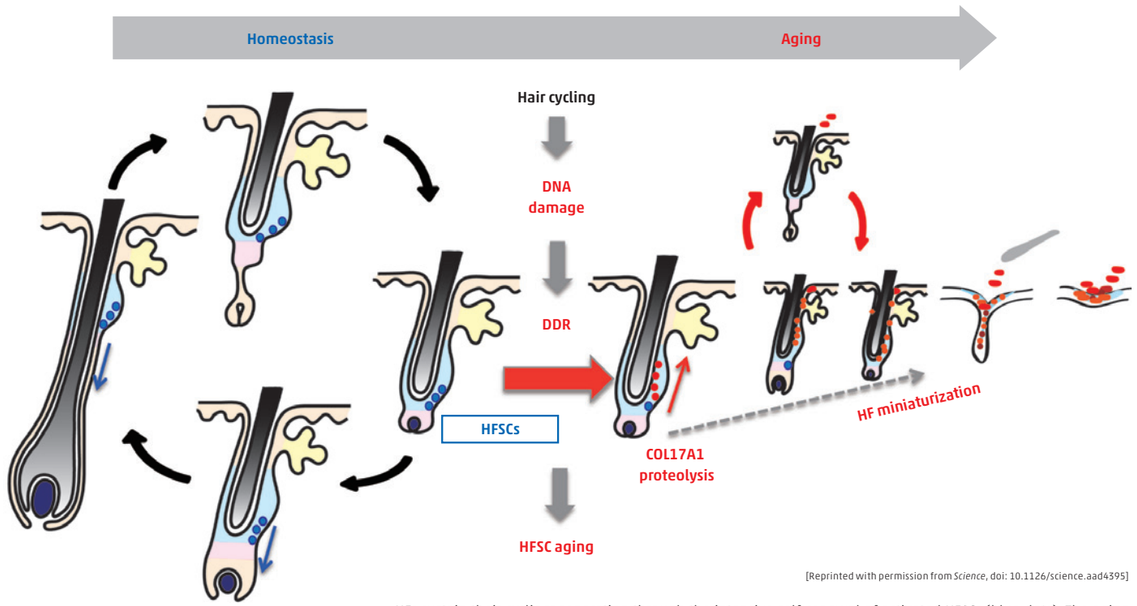
A: Our research uncovered several factors that are critical to the process of organ aging. First, we showed that DNA-damage response in stem cells is tightly linked to epithelial organ aging. Secondly, hair follicle aging could be prevented by controlling the expression of COL17A1, the type XVII collagen needed for maintenance of HFSCs. If levels of COL17A1 were maintained, we could prevent HFSCs from differentiating into epidermal keratinocytes. Age-related organ decline is expected to become an increasingly important health issue given the aging population. The hair follicle aging process is a good model of organ and tissue shrinkage and provides us with vital information for examining the functional decline of other organs. Understanding the key steps in the organ aging process provides exciting new avenues for the development of therapies that apply these processes to prevent and treat aging-associated diseases.



Dr. Nishimura obtained her MD in 1994 and did her Dermatology residency at Kyoto University Hospital. She then obtained her PhD at Kyoto University and did her postdoctoral training at the Dana Farber Cancer Institute, Harvard Medical School. She then started her own group as an Associate Professor at Hokkaido University in 2004, and became a Professor at Kanazawa University the following year. Her laboratory moved to TMDU in 2009. She is currently a Professor at the Medical Research Institute of TMDU. She identified melanocyte stem cells in 2002 and revealed that the exhaustion or depletion of stem cells in hair follicles underlies the graying and thinning of hair in aging. Her group is currently focusing on epidermal stem cell aging and the mechanisms of skin homeostasis, aging-associated decline of the skin, and cancer development.

Science, doi: 10.1126/science.aad4395

The mechanism of hair follicle aging and associated hair loss



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HFs sustain their cyclic regeneration through the intensive self-renewal of activated HFSCs (blue dots). The aging of HFSCs is triggered by DNA-damage response (DDR)-induced COL17A1 proteolysis. Once aged HFSCs (red dots) are activated during the hair cycle, they leave the niche and terminally differentiate into epidermal keratinocytes and are then eliminated from the skin surface. HF, hair follicle; HFSC, hair follicle stem cell.

TMDU Research NEWS

TMDU,UCSD and USC held joint symposium

In September 2018, TMDU hosted the "1st TMDU-UCSD-USC Joint Symposium," providing the three universities with a vital opportunity to deepen relationships and exchange cutting-edge information and experience regarding medical and dental research.

The first symposium featured the research theme, "Frontiers in Liver Research and Global Medicine." After opening remarks from TMDU President Yasuyuki Yoshizawa, three speakers from each university gave lectures on the research theme.

The nine speakers were all well-known, active researchers in their respective fields of liver research: from UCSD, Vice Chancellor David Brenner, Health Sciences, Assistant Vice Chancellor Mounir Soliman, Health Sciences, and Associate Prof. Tatiana Kisseleva, Department of Surgery; from USC, Prof. Hidekazu Tsukamoto, Department of Pathology, Associate Prof. Kinji Asahina, Department of Pathology, and Associate Prof. Keigo Machida, Department of Molecular Microbiology and Immunology; and from TMDU, Prof. Hiroshi Nishina, Department of Developmental and Regenerative Biology, Prof. Shinji Tanaka, Department of Molecular Oncology, and Associate Prof. Sei Kakinuma, Department of Liver Disease Control.

Some 100 participants enjoyed the lectures and participated in question and answer sessions. The symposium concluded with remarks by Vice Chancellor David Brenner from Health Sciences, UCSD.

TMDU looks forward to continuing a wide variety of exchanges with UCSD and USC in the future.