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Takara Belmont Uses iPS Cells to Study Skin Aging

— Aiming to Develop Anti-aging Scalp Care Cosmetics —

Takara Belmont Corporation (headquarters: Osaka and Tokyo, Japan; Chairman & CEO: Hidetaka Yoshikawa), which provides barbershops, hair and nail salons, esthetic clinics, and dentist's and doctor's offices with their space designs and professional-use equipment, appliances and cosmetics, has collaborated with a research group led by Mikio Shimada and Yoshihisa Matsumoto, Assistant Professor and Associate Professor respectively at the Laboratory for Advanced Nuclear Energy, and Akitoshi Okino, Associate Professor at the Laboratory for Future Interdisciplinary Research of Science and Technology, the Institute of Innovative Research, Tokyo Institute of Technology to produce skin keratinocytes*1 from iPS cells (iPSCs) and generate pseudo-aged skin with radiation,*2 revealing the impact of aging on skin.

【Key points】

○ Skin keratinocytes produced from human iPSCs were used to unravel the details of cell response to pseudo-aging.

○ Difference in response between cells at different differentiation levels,*3 including stem and precursor cells, was clarified.

○ A ripple effect of the findings on various fields is expected, including the elucidation of the skin aging mechanism.

【Background】

DNA in body cells constantly incurs damage from both internal factors, including active oxygen, and external factors, including ultraviolet and radioactive radiation. Basically, such damage is quickly fixed by a DNA repair mechanism intrinsic to the body. In rare cases, however, some damage fails to be fixed and accumulates in the cells, causing them to age and rendering them cancerous. For example, when DNA damage causes hair follicle tissue,*4 an appendage to the skin, to run out of stem cells*5 that are supposed to develop into hair follicle cells, gray and thin hair results.

Few reports had been made on the study of DNA damage response*6 to radiation on keratinocytes derived from human skin. In this study, keratinocytes were produced from human iPSCs, and cells at different differentiation levels, from stem to precursor cells,*7 were compared in terms of DNA damage response. Also, response to radiation was analyzed with a skin model of a three-dimensional cell culture*8 similar to real skin.

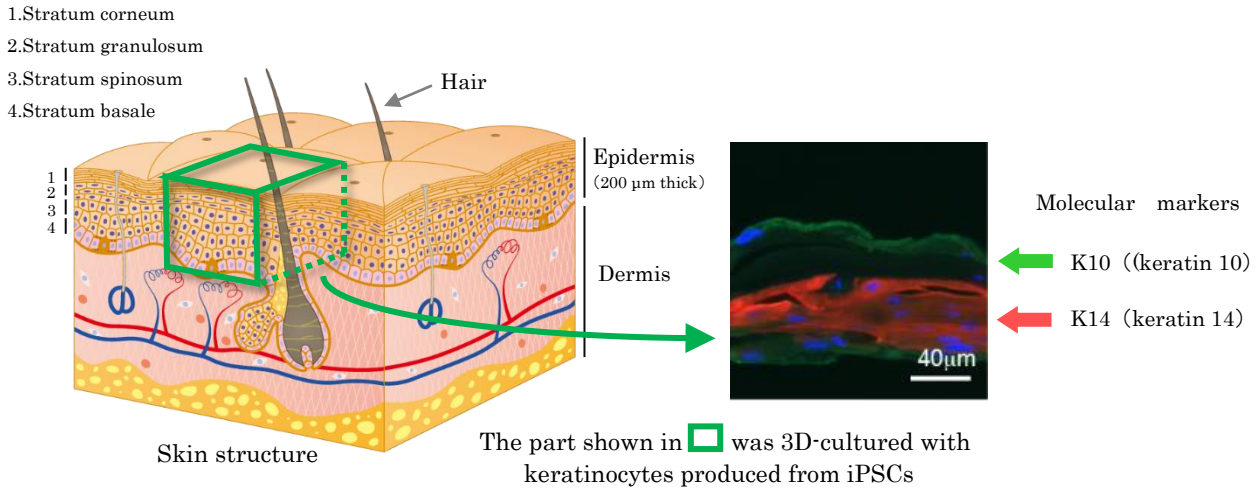

Fig. 1: Skin Structure and Overview of the 3D Cell Culture with Simulated Skin

【Results】

Skin keratinocytes were produced from iPSCs, and the difference in DNA damage response to radiation exposure was analyzed between the iPSCs and the skin keratinocytes derived from the iPSCs. This comparison revealed that iPSCs are more radiosensitive and more likely to cause apoptosis*9 than keratinocytes.

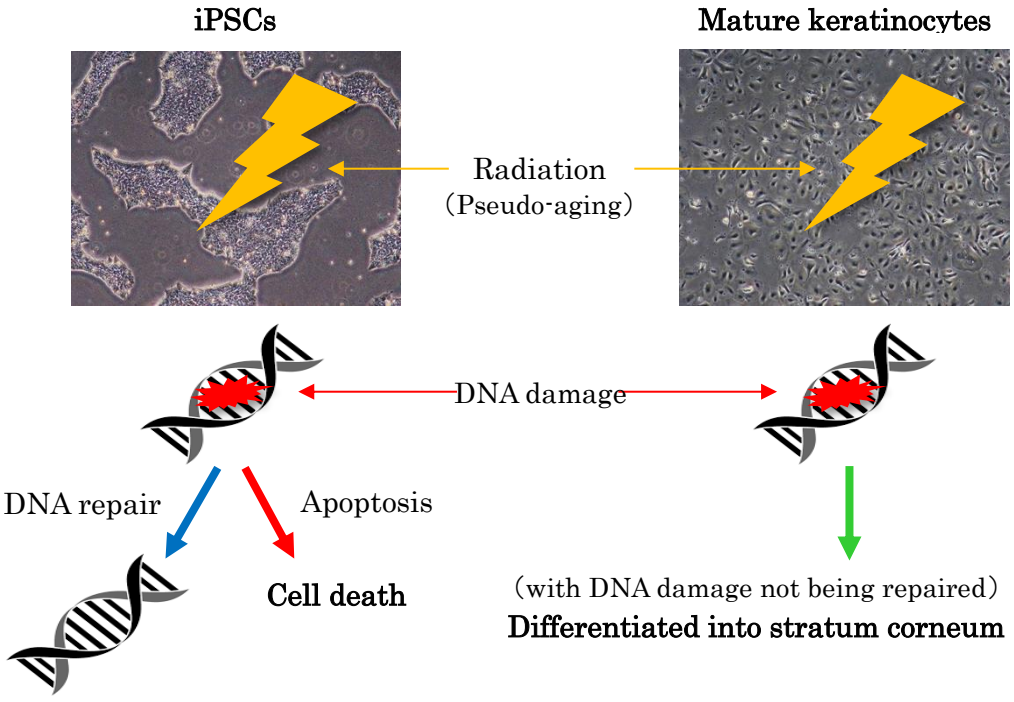

Fig. 2: Difference in Response to Radiation between iPSCs and Keratinocytes

When iPSCs, which are undifferentiated cells, suffer any damage to their DNA, they seem to choose either complete repair or apoptosis, thereby eliminating the DNA damage. Compared to iPSCs, mature keratinocytes showed a lower speed and percentage of DNA repair. As keratinocytes mature, they change from live cells into hard stratum corneum to protect the body as the outermost barrier of the

skin. Since they are destined to peel away in the end, a decline in their DNA repair function seems unimportant.

【Prospects】

This study has established a system of generating pseudo-aging with three-dimensionally cultured skin cells. With this system, Takara Belmont is planning to further elucidate the skin aging mechanism, analyze the anti-aging effect of cosmetic ingredients, and develop scalp and hair care products based on the findings of such research.

【Publication】

The results of this study appeared on May 11 in the electronic version of the International Journal of Radiation Oncology Biology Physics, a magazine published by the American Society for Radiation Oncology.

Article title: “DNA Damage Response After Ionizing Radiation Exposure in Skin Keratinocytes Derived from Human-Induced Pluripotent Stem Cells”

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≪Terminology≫

＊1 Keratinocytes: Also called keratinized skin cells, keratinocytes make up approx. 95% of the cells found in the epidermis. The stratum corneum, or the outermost layer of the skin, is formed by cornified keratinocytes and plays an important role in protecting the body from external stimuli.

＊2 Generate pseudo-aged skin with radiation: Pseudo-aged cells can be generated by giving damage to DNA in cells directly and indirectly using radiation, such as gamma rays. In the direct method, the radiation energy breaks the DNA strands. In the indirect method, the radiation enhances the energy of the water molecules in the cells, and free radicals, which are highly reactive, damage the DNA strands.

＊3 Differentiation levels: Stem and precursor cells of keratinocytes are found in the stratum basale of the epidermis. As keratinocytes mature, they change into cells that form stratum spinosum, then stratum granulosum, and then stratum corneum while migrating toward the outermost layer of the skin. Differentiation refers to changes in cells caused by this maturation, and the differentiation level indicates the phase the cells are currently in.

＊4 Hair follicle tissue: Refers to the tissue that wraps around the hair roots. It protects the hair roots, and the hair grows through it. A hair follicle consists of an epithelial root sheath, a grassy membrane, and a connective tissue root sheath. The upper part of a hair follicle has an opening called a “sebaceous gland,” which secretes sebum to render the skin and hair surface smooth and moisturized.

＊5 Stem cells: Refer to special cells with two abilities: to make copies of themselves and to differentiate into various cells (“multipotency”). With these abilities, stem cells are considered to play the role of genesis and anagenesis. Stem cells are divided into several types, including

embryonic stem (ES) cells, adult stem cells, and iPSCs.

＊6 DNA damage response: When genomic DNA in cells is damaged, for example by radiation, the body responds by mobilizing a DNA damage response mechanism, a defense system to efficiently repair the DNA damage.

＊7 Precursor cells: Refer to cells halfway through the process whereby stem cells are differentiated into specific somatic cells or germ cells.

＊8 Three-dimensional cell culture: The recent development of culture technologies and the progress of tissue engineering, including iPSCs, have made it possible to replicate the three-dimensional structures of various organs in vitro. Monolayer culture was the mainstream of in vitro culture, but three-dimensional culture has been contributing to the elucidation of molecular networks between different cells, and has also been used in pharmaceutical tests.

＊9 Apoptosis: Refers to cell death actively induced to maintain the body in better condition. Also called programmed cell death, apoptosis plays an important role in genesis and homeostasis.