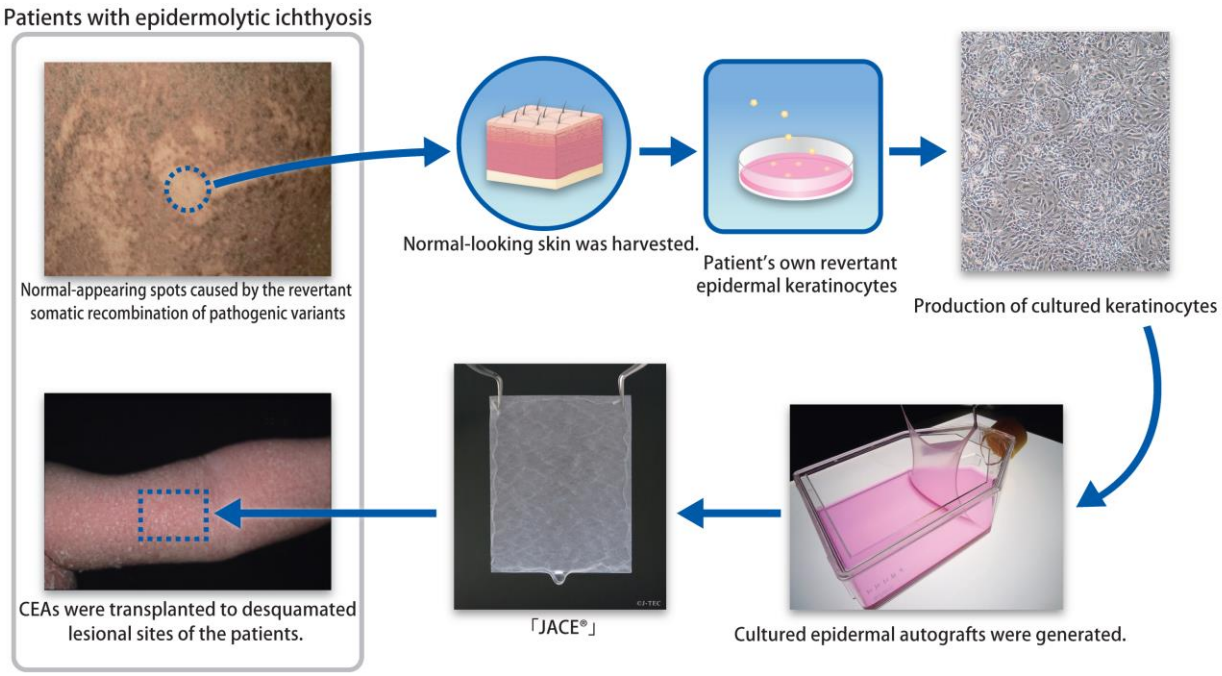
News Release

Title

Mosaic revertant skin-derived cultured epidermal autografts of keratinocytes carrying somatic revertant mutation as a potential treatment for epidermolytic ichthyosis.

Key Points

• We successfully produced cultured epidermal autografts (CEAs) from the genetically confirmed revertant skin of the two mosaic epidermolytic ichthyosis (EI) patients and one ichthyosis with confetti (IWC) patient, and genetically confirmed that CEAs mainly consist of revertant wild-type cells by amplicon sequencing and droplet digital PCR analysis.
• CEAs were transplanted to desquamated lesional sites of the patients.
• Four weeks after this transplantation, the rate of areas without the recurrence of ichthyosis lesions in the three cases was 39.52%, 100.0%, and 100.0% respectively, although the recurrence of ichthyosis lesions was seen at the site of CEA transplantation in all patients 24 weeks after transplantation.



Summary

Lecturer Kana Tanahashi, Prof. Masashi Akiyama, and Associate Prof. Takuya Takeichi of the Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura, MD, PhD), Prof. Michihiro Kono of the Department of Dermatology and Plastic Surgery, Akita University Graduate School of Medicine, and Dr. Masukazu Inoie of the Japan Tissue Engineering Co., Ltd. have produced CEAs from the genetically confirmed revertant skin of the two mosaic EI patients and one IWC patient and genetically confirmed that CEAs mainly consist of revertant wild-type cells.

No efficient treatment has been established yet for EI caused by pathogenic variants in *KRT1* or *KRT10*. Patients with IWC show multiple normal-appearing spots, caused by the revertant somatic recombination of pathogenic variants that occurs at each spot independently. Additionally, some patients with EI have large areas of normal skin due to revertant postzygotic mosaicism. To assess the feasibility of transplantation treatment of CEAs produced from revertant epidermal keratinocytes in patients with EI and IWC, we performed a clinical trial of treatment with CEAs produced from each patient's own revertant epidermal keratinocytes as a proof-of-concept study. This is a single-arm, open (masking not used), uncontrolled clinical study. The primary outcome was the rate of areas without the recurrence of ichthyosis lesions 4 weeks after the final transplantation (%). The secondary outcome was the rate of areas without the recurrence of ichthyosis lesions 24 weeks after initial transplantation (%).

We successfully produced CEAs from the genetically confirmed revertant skin of the two mosaic EI patients and one IWC patient and genetically confirmed that CEAs mainly consist of revertant wild-type cells by amplicon sequencing and droplet digital PCR (ddPCR) analysis. Single-cell RNA sequencing analysis confirmed the normal proliferation and safety profiling of CEAs. CEAs were transplanted to desquamated lesional sites of the patients. Four weeks after the transplantation, the rate of areas without the recurrence of ichthyosis lesions in the three cases was 39.52%, 100.0%, and 100.0% respectively, although the recurrence of ichthyosis lesions was seen at the site of CEA transplantation in all three patients at 24 weeks after transplantation. In conclusion, CEAs from normal skin have the potential to be a safe and local treatment option for EI and IWC.

Research Background

No efficient treatment has been established yet for EI caused by pathogenic variants in *KRT1* or *KRT10*. Patients with IWC show multiple normal-appearing spots, caused by the revertant somatic recombination of pathogenic variants that occurs at each spot independently. Additionally, some patients with EI have large areas of normal skin due to revertant postzygotic mosaicism.
On the other hand, CEAs have been used as a treatment option for severe burn injuries. Keratinocytes obtained from a skin biopsy of 3 cm^2 in area and cultured with feeder cells can be expanded more than 5,000- to 10,000-fold in 3 to 4 weeks.

Research Results

We successfully produced CEAs from the genetically confirmed revertant skin of the two mosaic EI patients and one IWC patient, and genetically confirmed that CEAs mainly consist of revertant wild-type cells by amplicon sequencing and ddPCR analysis. Single-cell RNA sequencing analysis confirmed the normal proliferation and safety profiling of CEAs. CEAs were transplanted to desquamated lesional sites of the patients. Four weeks after this transplantation, the rate of areas without the recurrence of ichthyosis lesions in the three cases was 39.52%, 100.0%, and 100.0% respectively, although the recurrence of ichthyosis lesions was seen at the site of CEA transplantation in all three patients at 24 weeks after transplantation.

Research Summary and Future Perspective

We successfully produced CEAs from the genetically confirmed revertant skin of two patients with mosaic EI and one patient with IWC, and genetically confirmed that the CEAs mainly consist of revertant wild-type cells by amplicon sequencing and ddPCR. CEAs from clinically normal skin consisting of genetically normal keratinocytes with revertant somatic mosaicism have the potential to be a safe and local treatment option for severe EI and IWC.

Publication

Journal: *British Journal of Dermatology*
Title: Treating epidermolytic ichthyosis and ichthyosis with confetti with epidermal autografts cultured from revertant skin
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