

News Release

Title

SDR9C7 catalyzes critical dehydrogenation of acylceramides for skin barrier formation

Key Points

- In a patient with *SDR9C7* mutation and a mouse *Sdr9c7* knockout model, we showed loss of covalent binding of epidermal ceramides to protein, a structural fault in the corneocyte lipid envelope essential to the skin barrier.
- Recombinant SDR9C7 catalyzed NAD-dependent dehydrogenation of linoleate 9,10-*trans*-epoxy-11*E*-13-alcohol to the corresponding 13-ketone, while ichthyosis mutants were inactive.
- Our findings suggest a novel mechanism for coupling of ceramide to protein and provides important insights into skin barrier formation and ichthyosis pathogenesis.

Summary

Prof. Masashi Akiyama (corresponding author), Dr. Takuya Takeichi (first and corresponding author) at Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD), Prof. Alan R. Brash (corresponding author) at Department of Pharmacology and the Vanderbilt Institute of Chemical Biology, Vanderbilt University, and Dr. Tetsuya Hirabayashi at Laboratory of Biomembrane, Tokyo Metropolitan Institute of Medical Science, discovered that SDR9C7 catalyzes critical dehydrogenation of acylceramides for skin barrier formation.

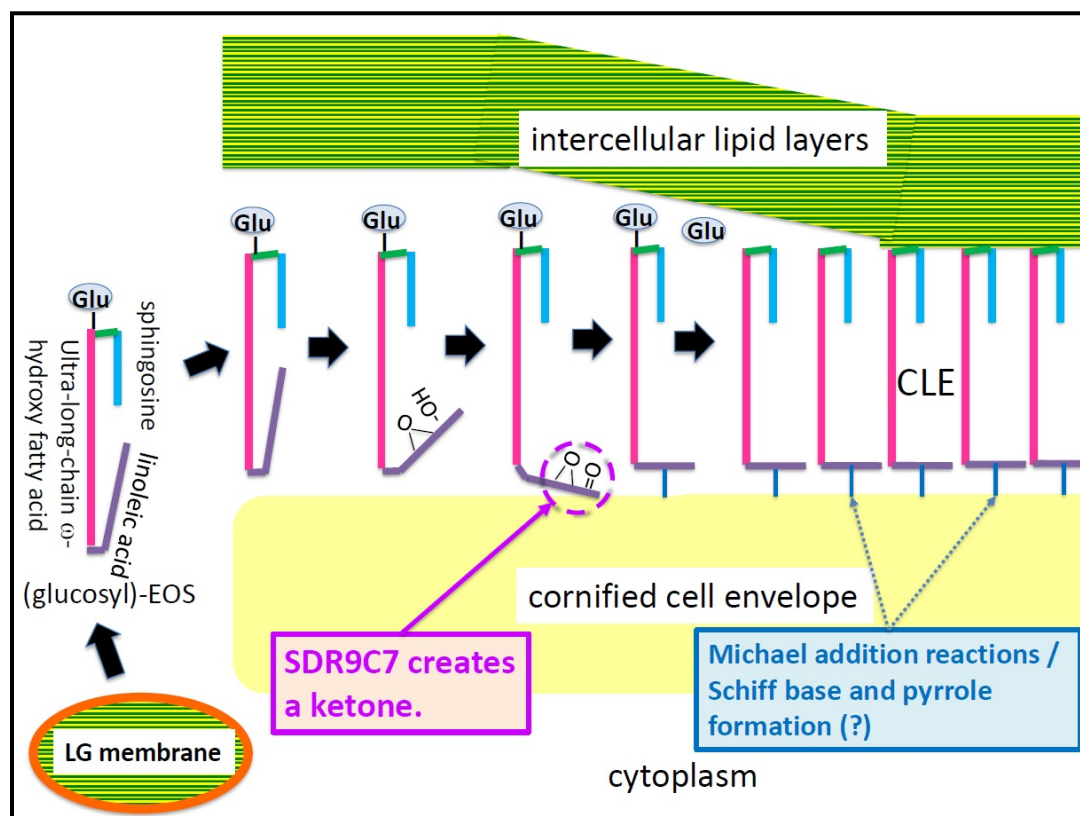
SDR9C7 encodes a short chain dehydrogenase/reductase family 9C member 7 (SDR9C7), recently found mutated in ichthyosis. In a patient with *SDR9C7* mutation and a mouse *Sdr9c7* knockout model, we showed loss of covalent binding of epidermal ceramides to protein, a structural fault in the corneocyte lipid envelope essential to the skin barrier. For reasons unresolved, protein binding requires lipoxygenase-catalyzed transformations of linoleic acid (18:2) esterified in ω -*O*-acylceramides. In *Sdr9c7*^{-/-} epidermis, quantitative LC-MS assays revealed almost complete loss of a species of ω -*O*-acylceramide esterified with linoleate-9,10-*trans*-epoxy-11*E*-13-ketone; other acylceramides related to the lipoxygenase pathway were in higher abundance. Recombinant SDR9C7 catalyzed NAD-dependent dehydrogenation of linoleate 9,10-*trans*-epoxy-11*E*-13-alcohol to the corresponding 13-ketone, while ichthyosis mutants were inactive. We propose, therefore, that the critical requirement for lipoxygenases and SDR9C7 is in producing acylceramide containing the 9,10-epoxy-11*E*-13-ketone, a reactive moiety known for its non-enzymatic coupling to protein. This suggests a novel mechanism for coupling of ceramide to protein and provides important insights into skin barrier formation and ichthyosis pathogenesis.

Research Background

The corneocyte lipid envelope composed of covalently bound ceramides and fatty acids is important to the integrity of the permeability barrier in the stratum corneum, and its absence is a prime structural defect in various skin diseases associated with defective skin barrier function. In 2016, two missense mutations in *SDR9C7* were identified in patients with autosomal recessive congenital ichthyosis (ARCI), and several more in 2018. *SDR9C7* encodes a short chain dehydrogenase/reductase family 9C member 7 (SDR9C7), and is highly expressed in the epidermis. Our ultrastructural observations of the skin lesion of an ARCI patient with *SDR9C7* mutations revealed disruption of the intercellular lipid layers in the stratum corneum.

Research Results

In a patient with *SDR9C7* mutation and a mouse *Sdr9c7* knockout model, we showed loss of covalent binding of epidermal ceramides to protein, a structural fault in the corneocyte lipid envelope essential to the skin barrier. For reasons unresolved, protein binding requires lipoxygenase-catalyzed transformations of linoleic acid (18:2) esterified in ω -*O*-acylceramides. In *Sdr9c7*^{-/-} epidermis, quantitative LC-MS assays revealed almost complete loss of a species of ω -*O*-acylceramide esterified with linoleate-9,10-*trans*-epoxy-11*E*-13-ketone; other acylceramides related to the lipoxygenase pathway were in higher abundance. Recombinant SDR9C7 catalyzed NAD⁺-dependent dehydrogenation of linoleate 9,10-*trans*-epoxy-11*E*-13-alcohol to the corresponding 13-ketone, while ichthyosis mutants were inactive.



Research Summary and Future Perspective

We propose that the critical requirement for lipoxygenases and SDR9C7 is in producing acylceramide containing the 9,10-epoxy-11 β -13-ketone, a reactive moiety known for its non-enzymatic coupling to protein. This suggests a mechanism for coupling of ceramide to protein and provides important insights into skin barrier formation and ichthyosis pathogenesis.

Publication

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