Synopsis of Original Research Paper

# Synthetic pathway and physiological function of human-specific epidermal ceramides

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The stratum corneum, which constitutes the outermost layer of the epidermis, consists of corneocytes and lipid lamellae. The lipid lamellae, comprising a multi-layered lipid structure, are important for the skin permeability barrier that protects against the invasion of pathogens and foreign substances and prevents water loss through the skin. Ceramides account for approximately 50% of the lipid lamellae (by weight) and play a pivotal role in the skin permeability barrier function. In contrast to most tissue, a variety of ceramides exist in the stratum corneum. Ceramides containing a 6-hydroxy long-chain base (H-ceramides) are unique to the human stratum corneum and are the predominant ceramides. However, the biosynthetic pathway and physiological function of H-ceramides remain unclear.

In this study, we demonstrated that H-ceramide production increases in a keratinocyte-differentiation-dependent manner, and treatment with ascorbic acid enhances its production. Meanwhile, treatments with cosmetic ingredients that have antioxidant properties, such as kojic acid, coenzyme $Q_{10}$, and astaxanthin, did not enhance the production of H-ceramides, indicating that antioxidative effects are not involved in the H-ceramide production. By comprehensive expression analysis using RNA sequencing, we identified i) 1073 genes increased (≥2-folds) during keratinocyte differentiation, ii) 159 genes increased (≥2-folds) by a treatment with ascorbic acid, and iii) 87 genes increased in both conditions. Among them, we cloned 16 genes and investigated their activity to produce H-ceramides by an overexpression assay using HEK 293T cell. However, H-ceramides were not produced at least in our assay condition. Therefore, further analyses, including to establishment *in vitro* and *in vivo* assay systems, are required to identify the gene responsible for H-ceramide synthesis. Our finding contributes to future studies identifying an H-ceramide synthase, elucidating the mechanisms of its production, and developing novel cosmetic materials/products.