Synopsis of Original Research Paper

Development of a novel method for trans-epidermal delivery of cosmetics

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Claudin, a 24-kDa integral membrane protein with four transmembrane domains, plays a pivotal role in barrier-function of epithelial cell sheets. There are more than 20 members of the claudin family with different tissue-specific expression and barrier-function. The epidermis consists of several cell layers of strata corneum, granulosum and spinosum. Recently, Tsukita's group found that claudin-1 is expressed in the strata granulosum and is responsible for epidermal barrier. This finding indicates that a claudin-1 modulator may be a promising candidate for trans-epidermal delivery of cosmetics, such as anti-aging compounds and radical scavengers. However, a method to modulate claudin-1-barrier has never been developed.

A C-terminal fragment of Clostridium perfringens enterotoxin (C-CPE) is the only claudin modulator, and C-CPE disrupts barrier-function of claudin-4 in epithelial cells. We previously showed that modulation of claudin-4 is a novel strategy for intestinal absorption of drugs using C-CPE as a claudin modulator, and we also found that deletion of the C-terminal 16 amino acids of C-CPE lost its ability to modulate claudin-4. Taken together, we started to develop a claudin-1 modulator using C-CPE as a prototype. Previously, substitution of Tyr310 with Cys reduced binding of *Clostridium perfringens* enterotoxin to its receptor. Until now, we investigated roles of the tyrosines (Tyr306, Tyr310, and Tyr312) of the C-terminal 16 amino acids of C-CPE in claudin-4 binding and modulation of epithelial barrier by site-directed mutagenesis. Single mutations of Tyr306, Tyr310 and Tyr312 to alanine resulted in partial reduction of claudin-4-binding. Double mutants Tyr306Ala/Tyr310Ala and Tyr306Ala/Tyr312Ala lost the ability to bind to claudin-4 and to modulate epithelial barrier. These data provide us useful information in the development of claudin-1 modulator based on C-CPE.