Changes in fatty acid lengths of ceramides toward shorter chain dominance in human psoriasis skin

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Introduction

Background: Ceramides(CERs) are major component of the intercellular lipids, and average fatty acid(FA) chain length of the CERs correlate with the barrier function. Changes in skin lipid profiles have been associated with abnormal barrier function permeability in psoriasis. However, it is unknown how lipid synthetic enzymes affect the synthesis of ceramides.

Objective: We aimed to identify the alteration of FA chain length of CERs and lipid synthetic enzymes including elongases(ELOVLs) in human psoriasis skin.

Materials and Methods

- Subjects**
- **Human**
 - Psoriasis group(n=12, 9 men and 3 women; aged 22–91 years)
 - Control group: Age- and sex-matched healthy individuals without skin disorders
 - **Animal:** BALB/c female mice (5 weeks of age)
 - IMQ-induced psoriasis mimicking model: apply 62.5 mg of imiquimod 5% cream (Aldara®, 3M pharmaceuticals) on their shaved back skin and right ear once a day for 5 days (n=10)
 - Control group: treated with petrolatum in the same manner (n=5)
 - IRB approval: This study was approved by the ethical committee of Yonsei Wonju University of Medicine

- Evaluations**
- Stratum corneum(SC) sampling from lesional and non-lesional skin of patients or on the inner forearms of controls using film tape
 - Skin tissue sampling from lesional skin of human and back of mice
 - The unbound CERs in SC were quantified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.
 - The epidermal mRNA levels of following enzymes and transcription factors were measured by real-time quantitative PCR analysis
 - The epidermal protein levels of ELOVL and Ceramide synthase(CerS) were identified by Immunohistochemistry-staining.

Statistical analysis: All data were expressed as mean±SD. For comparisons, Student's t-test was used. Statistical significance is a p-value of less than 0.05.

Results

Fig 1. Amount of CER species in human epidermis
(A) CER[NS] with FAs shorter than C24 showed significantly increased level in lesional and non-lesional skin of psoriasis group
(B) CER[NP] with very long FAs (longer than C25) showed significantly decreased level in lesional and non-lesional skin of psoriasis group(*: P<0.05)

Fig 2. The mRNA levels of ELOVL1, ELOVL4 and CerS3 in mice epidermis. The mRNA level of ELOVL1, ELOVL4 and CerS3 showed significantly decreased in IMQ-treated group(*: P<0.05)

Fig. 3 (A) ELOVL1

(B) CerS3

Fig 3. The immunohistochemical staining for ELOVL1 and CerS3 in human epidermis.
(A) IHC staining showed decreased level of ELOVL 1 in lesional epidermis from psoriasis(a,b,c) than control(d,e,f)
(B) IHC staining showed decreased level of CerS 3 in lesional epidermis from psoriasis(a,b,c) than control(d,e,f)

Discussion and Conclusions

- **Profiles of FA lengths of CERs shifted toward shorter chain in lesional and non-lesional skin from psoriasis**
 - ✓ The unbound CERs ([NS],[NP]) with very long FAs (longer than C24) decreased whereas those with shorter FAs(shorter than C24) increased in psoriasis human skin.
- **The protein level of ELOVL1 and CerS3 were decreased in the IHC staining from psoriasis human skin**
 - ✓ The mRNA expression of ELOVL1, 4 and CerS3 were also decreased in psoriasis-like skin lesion in mice.
- **The down-regulation of ELOVL 1 and CerS3 might cause impairment in the synthesis of very long chain CERs.**
 - ✓ ELOVLs and CerSs play critical roles in regulating the length and degree of FAs.
 - ✓ELOVL1 are required for generation of long-chain fatty acids(FAs) longer than C22.
 - ✓CerS3 expression is associated with the appearance of the very long-chain fatty acids(FAs)

Thus, we suggest that the profile changes of FA lengths of CERs mediated by enzymatic changes, especially ELOVLs, can be associated in part with barrier dysfunction in psoriasis.

Fig 4. Schematic summary of the results

Acknowledgement

This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HN11C0048).

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