Synopsis of Original Research Paper

Skin barrier formation by the acyl-CoA synthetase ACSVL4

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Acylceramides are lipids that play an essential role in the formation of the permeability barrier in the skin, and the impairment of their synthesis causes the skin disorder ichthyosis. However, the acyl-CoA synthase (ACS) that converts ω-hydroxy fatty acid to ω-hydroxy acyl-CoA in the acylceramide synthesis pathway still remained unidentified. In the present study, we examined the possibility that *ACSVL4* (ACS very long-chain, member 4), which is the causative gene for ichthyosis prematurity syndrome, is the unidentified ACS involved in acylceramide production. *Acsvl4* knockout (KO) mice exhibited neonatal lethality and severe skin barrier defect phenotype. Histological analyses showed hyperkeratosis and abnormal lipid lamellar formation in *Acsvl4* KO mouse epidermis. The amount of acylceramides in *Acsvl4* KO mice was reduced to about 10% of that in wild-type mice. In addition to the role as an ACS, ACSVL4 has been implicated in a fatty acid transporter, and reduced fatty acid uptake has been assumed to be a cause of the ichthyosis pathogenesis. However, the amount of fatty acids and triglycerides were not decreased in the epidermis of *Acsvl4* KO mice. *In vitro* experiments revealed that ACSVL4 indeed exhibits ACS activity toward ω-hydroxy fatty acids. From these results, we conclude that the skin symptom of ichthyosis prematurity syndrome is not caused by decreased fatty acid uptake, but by impaired acylceramide synthesis. Our findings contribute to the elucidation of the molecular mechanism of skin barrier formation and the pathogenesis of hereditary ichthyosis.