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Review article

Corneocyte lipid envelope (CLE), the key structure for skin barrier function and ichthyosis pathogenesis

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ABSTRACT

Research on the genetic abnormalities and pathogenetic processes of ichthyoses has progressed remarkably, and many causative genes and molecules have been identified in ichthyoses and ichthyosis syndromes. Most of the genes/molecules causative of ichthyosis are associated with the barrier function of the stratum corneum, and defects in the skin barrier play important roles in the pathogenesis of various ichthyosis phenotypes.

It has been elucidated that, of the ichthyosis-causative genes, *ABCA12*, *ALOXE3*, *ALOX12B*, *CYP4F22*, *CERS3*, *ABHD5*, *PNPLA1* and *ELOVL4* work in the formation of the corneocyte lipid envelope (CLE), a structure that is essential to sound skin barrier function. The CLE mostly consists of ultra-long-chain (ULC) ceramides derived from ULC-acylceramide (EOS; a combination of esterified ω-hydroxy fatty acids and sphingosines).

In this review, I shed light on the synthesis, metabolism and transport of epidermal ceramides, especially on ULC-acylceramide and the processes of CLE formation. In addition, I summarize the pathogeneses of various ichthyoses and ichthyosis syndromes from the aspects of abnormal synthesis of ULC-acylceramide and malformation of the CLE.

Investigations on the pathomechanisms of ichthyoses have provided novel knowledge on the synthesis and metabolism of ceramides in the epidermis. Conversely, research on the dynamics of epidermal ceramides has contributed to the elucidation of the pathogenesis of ichthyoses.

Advances in our understanding of the biology of epidermal lipids and the disease pathogeneses of ichthyoses and ichthyosis syndromes promise to provide clues for the development of effective therapies for ichthyosis patients in the near future.

Contents

Abbreviations: ABC, ATP-binding cassette; ABCA12, ATP-binding cassette sub-family A member 12; ABHD5, α/β-hydrolase domain-containing protein 5; ARCI, autosomal recessive congenital ichthyosis; CCE, cornified cell envelope; CERS, ceramide synthase; CIE, congenital ichthyosiform erythroderma; CLE, corneocyte lipid envelope; CYP4F22, cytochrome P450 4F22; ELOVL, elongation of very-long-chain fatty acid; eLOX3, lipoxygenase-3; ER, endoplasmic reticulum; FATP4, fatty acid transport protein 4; LI, lamellar ichthyosis; PNPLA1, patatin-like phospholipase domain-containing protein 1; TGase, transglutaminase; 12R-LOX, 12(*R*)-lipoxygenase; UGCG, UDP-glucose ceramide glucosyltransferase; ULC, ultra-long-chain.

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1. Introduction

The ichthyoses are a group of clinically and etiologically heterogeneous keratinization diseases that generally affect much or all of the skin [1]. Their clinical severity ranges from that of harlequin ichthyosis, the most severe form, to that of ichthyosis vulgaris, the mildest form [2]. For a long time, the pathogenetic mechanisms and causative genetic abnormalities of ichthyoses remained to be clarified. Recently, considerable advances have been achieved in our knowledge of the molecular basis of epidermal keratinization and skin barrier formation [3].

Many disease phenotypes of ichthyoses have primary causes and pathogenetic mechanisms associated with defective barrier function in the stratum corneum [1]. The barrier structure of the stratum corneum in human skin has four major components, from the inside of cornified cells to the outside: keratin/filaggrin and their degradation products filling the cytoplasm of cornified cells, the cornified cell envelope (CCE), the corneocyte lipid envelope (CLE) and the intercellular lipid layers (Fig. 1). Of these structures, the CLE and the intercellular lipid layers consist of essential epidermal lipid components. Ceramides are the most important components of the intercellular lipid layers in the stratum corneum. The CLE is mainly composed of ultra-long-chain (ULC) ceramide.

Mutations in a number of genes have been identified in ichthyoses [4] and ichthyosis syndromes [5]. Twelve causative genes have been identified in autosomal recessive congenital ichthyosis (ARCI) including lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE): *TGM1*, *ABCA12*, *ALOXE3* and *ALOX12B (two lipoxygenase genes)*, *NIPAL4*, *CYP4F22*, *CERS3*, *LIPN*, *PNPLA1*, *SLC27A4*, *SDR9C7* and *CASP14* [6,7]. In addition, a number of genes causative of ichthyosis syndromes have been identified. Not a few genes/molecules among them are involved in the synthesis and metabolism of epidermal lipids [8]. The recent identification of causative molecules of ARCI and ichthyosis syndromes has provided clues towards clarifying how ULC-ceramides and the CLE are closely associated with the pathogenesis of ichthyoses [8]. For a long time, little was known about the synthesis, metabolism and transport of epidermal ceramides. However, recently, we have obtained important information on ULC-acylceramide synthesis, metabolism and transport from the newly elucidated pathogenesis of ARCI and ichthyosis syndromes. In this context, the novel understanding of ichthyosis pathogenesis has opened up a new era of epidermal lipid biology. The elucidation of genetic causes of

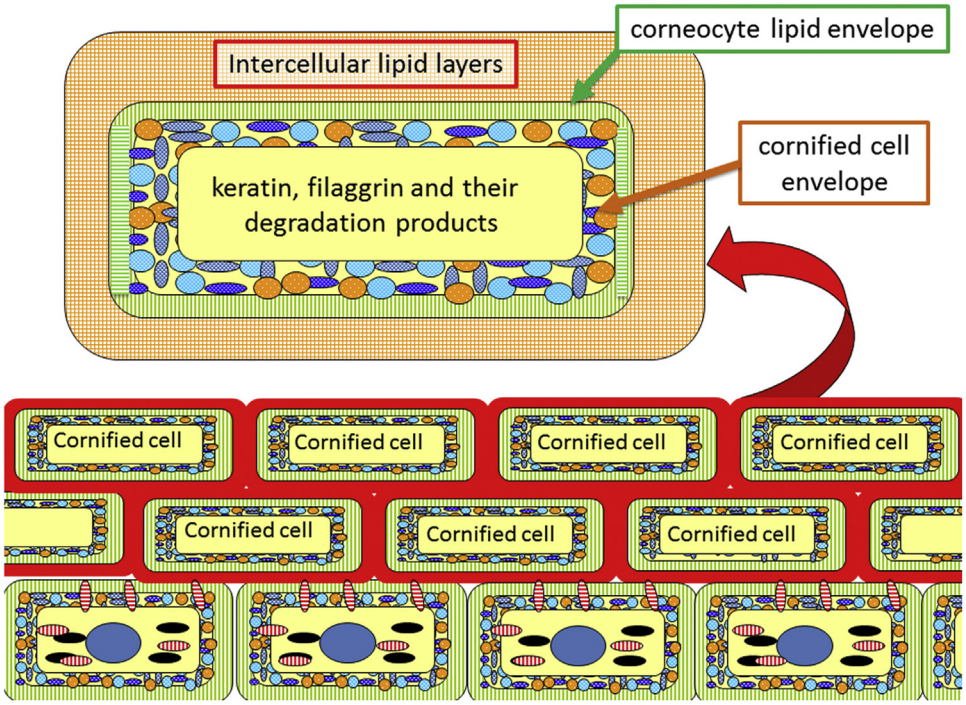

Fig. 1. The four major components of the skin barrier in the stratum corneum; 1) keratin, filaggrin and their degradation products, 2) cornified cell envelope (CCE), 3) corneocyte lipid envelope (CLE), 4) intercellular lipid layers. The CLE, a thin, single layer of ULC-ceramide or ULC fatty acid, is essential for sound skin barrier function.