Biochimica et Biophysica Acta 1841 (2014) 422–434

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Ceramide synthesis in the epidermis☆

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ARTICLE INFO

Article history:
Received 27 June 2013
Received in revised form 9 August 2013
Accepted 12 August 2013
Available online 27 August 2013

Keywords:
Ceramide synthesis
Epidermis
Skin barrier function
Autosomal recessive congenital ichthyosis (ARCI)
1-O-Acylceramides
Omega-esterified ceramides

ABSTRACT

The epidermis and in particular its outermost layer the stratum corneum provides terrestrial vertebrates with a pivotal defensive barrier against water loss, xenobiotics and harmful pathogens. A vital demand for this epidermal permeability barrier is the lipid-enriched lamellar matrix that embeds the enucleated corneocytes. Ceramides are the major components of these highly ordered intercellular lamellar structures, in which linoleic acid- and protein-esterified ceramides are crucial for structuring and maintaining skin barrier integrity. In this review, we describe the fascinating diversity of epidermal ceramides including 1-O-acylceramides. We focus on epidermal ceramide biosynthesis emphasizing its metabolic and topological requirements and discuss enzymes that may be involved in α- and ω-hydroxylation. Finally, we turn to epidermal ceramide regulation, highlighting transcription factors and liposensors recently described to play crucial roles in modulating skin lipid metabolism and epidermal barrier homeostasis. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier.

1. Introduction

Ceramide (Cer) is the central metabolite in sphingolipid metabolism and key intermediate for glycosphingolipid and sphingomyelin synthesis. Ceramides are essential components of the eukaryotic plasma membrane and are ubiquitously distributed throughout all mammalian tissues. However, the pattern of sphingolipid species is cell type and differentiation specific. Sphingolipids in general and ceramides in particular have been related to a myriad of cellular functions. Their role as structural components is well established as well as their importance as bioactive metabolites regulating cellular fate in processes like programmed cell death, ER stress and autophagy [1]. Their countless functions additionally include their involvement in cell to cell recognition, intercellular adhesion, motility and differentiation [2,3].

Although ceramides are minor components in most tissues, in the outermost epidermal layer, the stratum corneum (SC), ceramides account about half of the total lipid species by weight [4,5]. The specific importance of epidermal ceramides has been assigned definitely to their key role in maintaining epidermal barrier homeostasis. Most recently, the enzyme involved in the synthesis of all major epidermal ceramides has been elucidated. Deficiency of ceramide synthase 3 (CerS3) in mice revealed the lack of 90% of epidermal ceramides including all ω-esterified ceramides. Consequently, epidermal barrier is disrupted leading to premature death shortly after birth [6]. Our research documented that epidermal ceramides are not only essential for protection against desiccation but also for protection against microbial infections. These results explained the higher susceptibility for pathogenic infections in various human skin disorders like atopic dermatitis or harlequin ichthyosis characterized by reduced ceramide levels [7,8]. Excitingly, proof came from two recent studies identifying various mutations in the *CERS3* gene as a cause for autosomal recessive congenital ichthyosis (ARCI). In this rare skin disorder the cardinal features are collodion membrane at birth, generalized skin scaling with hyperkeratosis and acanthosis, mild erythroderma and repeated bacterial and fungal infections (Fig. 1A) [9,10]. Similar to patients, the phenotypic alterations in mice include persistence of periderm, hyperkeratosis, associated with persistence of peripheral and non-peripheral corneodesmosomes throughout SC, and enhanced susceptibility for *Candida* infection (Fig. 1B–F). In contrast to mutant mice, patients survive and present low ω-hydroxy ceramide (ωh-ceramide) levels, probably due to residual enzyme activity.

Abbreviations: ARCI, autosomal recessive congenital ichthyosis; CE, cornified envelope; Cer, ceramide; CerS1–6, ceramide synthase 1–6; CLE, corneocyte lipid envelope; ELOVL1–7, elongation of very long chain fatty acids 1–7; ER, endoplasmic reticulum; FA, fatty acid; FFA, free fatty acid; GCS, glucosylceramide synthase; GlcCer, glucosylceramide; LB, lamellar body; LC, long chain; LCB, long chain base; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptors; SB, stratum basale; SC, stratum corneum; SG, stratum granulosum; SM, sphingomyelin; SS, stratum spinosum; TAG, triacylglyceride; ULC, ultra long chain; VLC, very long chain; αh, α-hydroxy; ωh, ω-hydroxy

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http://dx.doi.org/10.1016/j.bbalip.2013.08.011

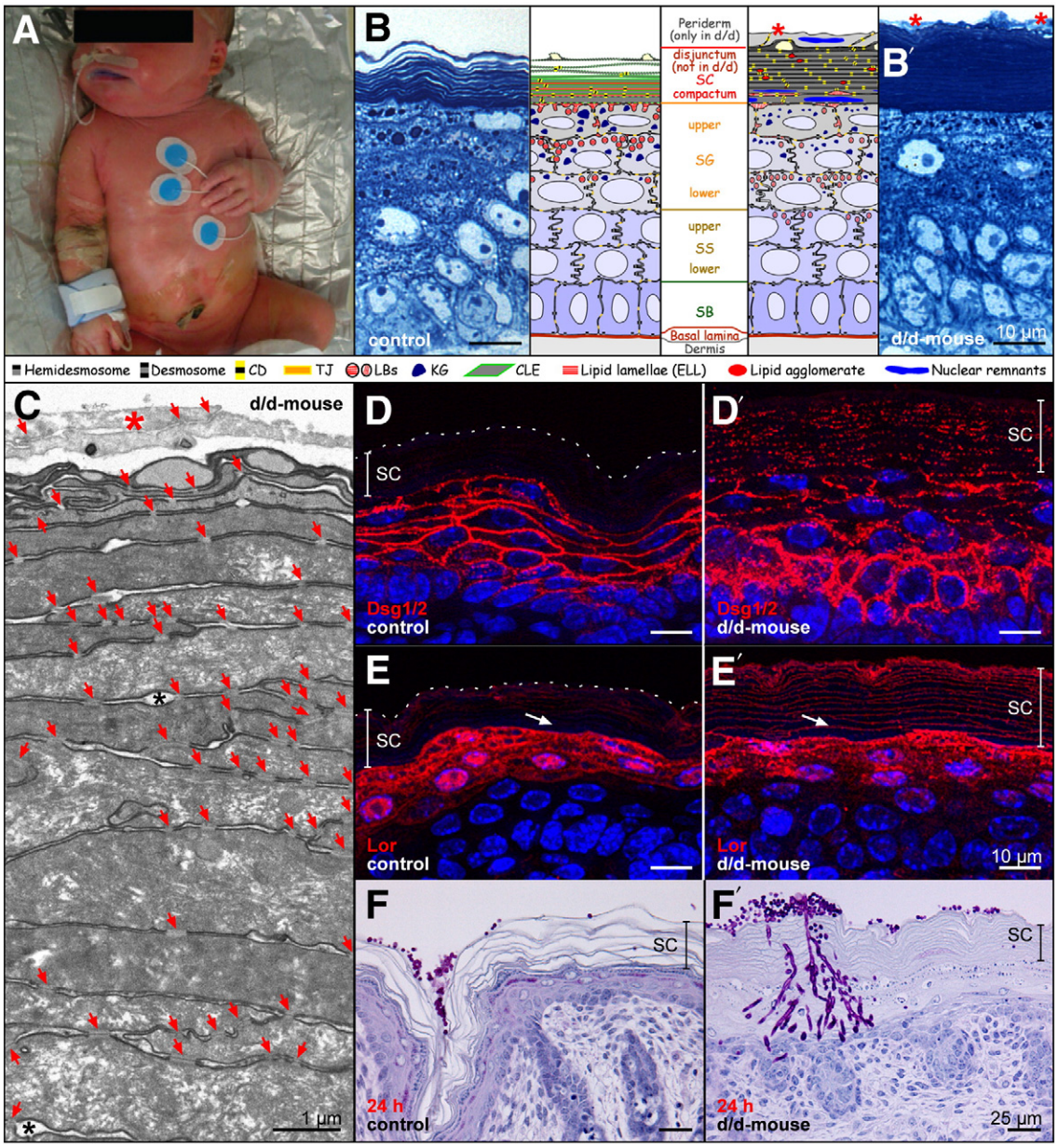

Fig. 1. Collodion baby with ARCI due to point mutation in CERS3 and epidermal phenotype of CerS3-deficient mice. A) Human ARCI patient with mutation in CERS3 at birth with collodion skin [9]. Light micrographs and corresponding schemes of control (B) and mutant (B′) mouse epidermis at birth. Note the larger keratohyalin granula in controls as well as the stratum disjunctum (upper SC part) containing the flaky uppermost corneocyte layers in controls. The latter is missing in the mutant, instead a thickened stratum compactum still carries a residual periderm (red asterisk). C) At the ultrastructural level persistence of peripheral and non-peripheral corneodesmosomes (red arrows) throughout the upper SC is striking in CerS3-deficient mice. Note lipid aggregates (black asterisk). Immunodetection of desmoglein 1/2 in control (D) and mutant (D′) skin. Note the persistence of desmoglein 1/2 labeling in mutant SC. Immunostaining of loricrin in control (E) and mutant (E′) skin. Note marking of CLE throughout mutant, but not control stratum corneum (white arrows). *In vitro* infection of control (F) and mutant (F′) skin cultures with *Candida albicans* after 24 h of infection [6]. Note the penetration of stratum corneum by pseudohyphae in mutant, but not in control skin.

Besides their crucial role in the formation and maintenance of skin barrier integrity, ceramides and their corresponding metabolites have been involved in cellular signaling and linked to cell proliferation, differentiation and apoptosis in human epidermis [11,12]. Ceramide levels conspicuously increase along with keratinocyte differentiation. Yet, ceramides are quickly derivatized into glucosylceramides (GlcCers) and sphingomyelins (SMs), thereby likely protecting keratinocytes from cytotoxic ceramide effects. Elevated ceramide levels by *de novo* synthesis have been shown as response to ultraviolet B-induced apoptosis in human keratinocytes as well as an up-regulation of GlcCer synthesis upon ceramide-induced stress [13,14].

The stratum corneum is composed of corneocytes embedded in a matrix of lipid-enriched lamellar sheets and provides the first line of defense against desiccation and pathogen invasion. Besides ceramides, these densely packed lamellar membranous structures are composed of free fatty acids (FFAs) and cholesterol in nearly equimolar ratios [15]. The adequate balance of these major components is imperative for a proper structure and maintenance of SC barrier competence [16]. Alterations to this ratio have been associated to various skin diseases, particularly to psoriasis, atopic dermatitis and several forms of ichthyosis [17–20] also reviewed in [21,22]. Deficiencies for minor components of the lipid matrix, namely cholesterol sulfate or free sphingoid bases, are also critical for preserving epidermal barrier homeostasis. Whereas defective hydrolysis of the former has been associated with X-linked ichthyosis leading to corneodesmosome retention and altered corneocyte desquamation, free sphingoid bases are required