Biochimica et Biophysica Acta 1841 (2014) 441–452

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

The role of sphingolipid metabolism in cutaneous permeability barrier formation☆

Bernadette Breiden, Konrad Sandhoff *

LIMES, Membrane Biology & Lipid Biochemistry Unit, c/o Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany

ARTICLE INFO

Article history:
Received 15 May 2013
Received in revised form 4 August 2013
Accepted 8 August 2013
Available online 15 August 2013

Keywords:
Stratum corneum
Ceramide
Acylceramide
Sphingomyelin
Glucosylceramide
Ultra long chain fatty acid

ABSTRACT

The epidermal permeability barrier of mammalian skin is localized in the stratum corneum. Corneocytes are embedded in an extracellular, highly ordered lipid matrix of hydrophobic lipids consisting of about 50% ceramides, 25% cholesterol and 15% long and very long chain fatty acids. The most important lipids for the epidermal barrier are ceramides. The scaffold of the lipid matrix is built of acylceramides, containing ω-hydroxylated very long chain fatty acids, acylated at the ω-position with linoleic acid. After glucosylation of the acylceramides at Golgi membranes and secretion, the linoleic acid residues are replaced by glutamate residues originating from proteins exposed on the surface of corneocytes. Removal of their glucosyl residues generates a hydrophobic surface on the corneocytes used as a template for the formation of extracellular lipid layers of the water permeability barrier. Misregulation or defects in the formation of extracellular ceramide structures disturb barrier function. Important anabolic steps are the synthesis of ultra long chain fatty acids, their ω-hydroxylation, and formation of ultra long chain ceramides and glucosylceramides. The main probarrier precursor lipids, glucosylceramides and sphingomyelins, are packed in lamellar bodies together with hydrolytic enzymes such as glucosylceramide-β-glucosidase and acid sphingomyelinase and secreted into the intercelullar space between the stratum corneum and stratum granulosum. Inherited defects in the extracellular hydrolytic processing of the probarrier acylglucosylceramides impair epidermal barrier formation and cause fatal diseases: such as prosaposin deficiency resulting in lack of lysosomal lipid binding and transfer proteins, or the symptomatic clinical picture of the "collodion baby" in the absence of glucocerebrosidase. 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. Guest Editors: Kenneth R. Feingold and Peter Elias.

1. Introduction

All land dwelling animals and plants are protected by a functional barrier between the organisms and their environment. The permeability barrier of mammals is localized in the stratum corneum (SC), the outermost cellular layer of the epidermis. This barrier protects the organisms against desiccation by transepidermal water loss and against the infiltration of pathogens and toxins.

The epidermis has a unique structure built of several layers mainly composed of differentiating keratinocytes. Keratinocytes of the stratum basale contain intact organelles and proliferate. During their migration through the adjacent outer epidermal layers, the stratum spinosum and the stratum granulosum (SG), they experience an increasing Ca^{2+} gradient and differentiate. The outer cell layer, the SC, is composed of terminally differentiated keratinocytes (corneocytes), which are dead flattened cells devoid of organelles but packed with keratin filaments. Corneocyte are embedded in a matrix of extracellular lipid lamellae, consisting mainly of ceramides, free fatty acids, and cholesterol [1,2]. These lipids form two lamellar phases with short and long periodicity of approximately 6 nm and 13 nm, respectively [3].

Human SC contains 12 free extractable ceramide fractions with different hydroxylation patterns in the sphingoid base and in the fatty acid (FA) moiety [4–8]. Two nomenclature systems are used for the description of SC ceramides. One is a numbering system based on the chromatographic migration (ceramide 1 to ceramide 8) and chronological arrangement of their publication (from ceramide 9 on). The other system is based on the molecular structure of the ceramides. It was proposed by Motta et al. [9] and modified by Robson et al. [5]. The last letter designates the sphingoid base: S (sphingosine), DS (sphinganine), P (phytosphingosine), and H (6-hydroxy sphingosine) and the front

Abbreviations: ABCA12, ATP binding cassette subfamily A member 12; ASM, acid sphingomyelinase; CE, cornified envelope; Cer, ceramide; CerS, ceramide synthase; ELOVL, fatty acid elongase; FA, fatty acid; GlcCer, glucosylceramide; LB, lamellar bodies; PPAR, peroxisome proliferator-activated receptor; Sap, saposin; SC, stratum corneum; SG, stratum granulosum; SM, sphingomyelin; SPT, serine palmitoyltransferase; VLC, very long chain; VLC-FA, very long chain FA (>C20); ULC-FA, ultra long chain FAs (≥C26)

☆ 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. Guest Editors: Kenneth R. Feingold and Peter Elias.

* Corresponding author. Tel.: +49 228 73 5346; fax: +49 228 73 7778.
E-mail address: sandhoff@uni-bonn.de (K. Sandhoff).

1388-1981/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbalip.2013.08.010

letter(s) designate the acyl chain: N (non-hydroxy FA), A (α-hydroxy FA), and EO (esterification of the ω-hydroxy FA with linoleic acid). Their structures and distribution in human SC are depicted in Fig. 1. In human SC, 342 different ceramide species belonging to eleven ceramide classes were identified by Masukawa et al. [10]. The analysis of sphingoid bases and fatty acids demonstrated carbon chain length in the range of 14–28 and 16–36, respectively [7,10]. Recently a new class of ceramides with four hydroxyl (OH) groups in the sphingoid base (T) has been identified in human epidermis by mass spectrometry [7], however, the position of OH-groups remains unknown. This new ceramide would be abbreviated as ceramide (NT).

2. The permeability barrier in the epidermis

Cellular membranes and lipid bilayers are permeable for water [11]. To avoid desiccation by excessive water loss, nature developed multilayered arrays of rather hydrophobic very long chain (VLC) and ultra long chain (ULC) nanostructured waxes (esters of ULC alcohols and ULC fatty acids (ULC-FAs)) on surfaces of plants (e.g. cacti) and insects, and extracellular lipid layers composed of ULC-FA, ceramides with ULC-FAs, and cholesterol on surfaces of the skin of land dwelling animals. The permeability barrier of mammalian epidermis is localized in the SC. The most important sphingolipids of keratinocytes are glucosylceramides (GlcCers) and ceramides containing a broad range of FA species. FAs are classified due to carbon chain length: FAs from C12 to C20 are long chain FAs, FAs >C20 are called VLC-FAs, and FAs ≥C26 are ULC-FAs [12].

Alterations in lipid composition of SC and their organization impair epidermal function resulting in disease. The scaffold for the lipid organization in the extracellular lipid matrix is made of ULC-sphingolipids, mainly ULC-ceramides, which are covalently attached to a three-dimensional network of cross-linked proteins (e.g. envoplakin and involucrin) of the cornified envelope (CE) [13,14]. They form a template on the surface of corneocytes to organize the extracellular lipid layers as a barrier in the interstices of the SC. Ceramides with ULC-FAs are major

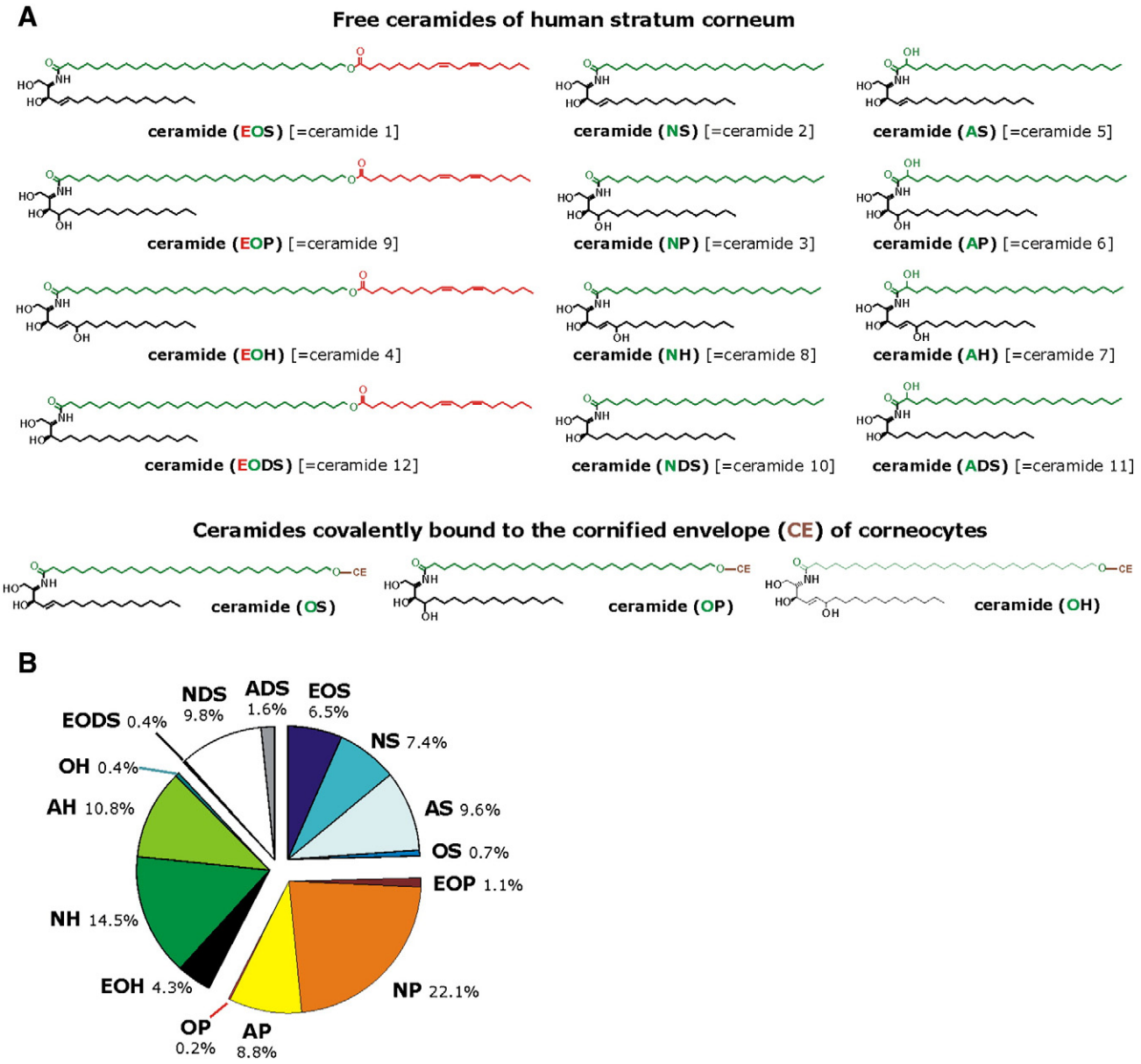

Fig. 1. Molecular structures and distribution of free and covalently-bound ceramides of the human SC. Structures (A) are shown in accordance with the terminology proposed by Motta et al. and modified by Robson et al. [5,9]. The structures are classified according to the sphingoid base (black, S: sphingosine, P: phytosphingosine, H: 6-hydroxysphingosine, DS: sphinganine) and the N-acyl residue (green, A: α-hydroxy-FA, O: ω-hydroxy-FA, N: no hydroxy-FA). E: acylated with linoleic acid (red) in ω-OH position. Panel B presents the distribution of different ceramide species in human SC modified from t'Kindt et al. [7].