The structure, function, and importance of ceramides in skin and their use as therapeutic agents in skin-care products

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Ceramides (CERs) are epidermal lipids that are important for skin barrier function. Much research has been devoted to identifying the numerous CERs found in human skin and their function. Alterations in CER content are associated with a number of skin diseases such as atopic dermatitis. Newer formulations of skin-care products have incorporated CERs into their formulations with the goal of exogenously applying CERs to help skin barrier function. CERs are a complex class of molecules and because of their growing ubiquity in skin-care products, a clear understanding of their role in skin and use in skin-care products is essential for clinicians treating patients with skin diseases. This review provides an overview of the structure, function, and importance of skin CERs in diseased skin and how CERs are being used in skin-care products to improve or restore skin barrier function. (J Am Acad Dermatol 2014;71:177-84.)

Key words: ceramide; epidermal repair; skin barrier; skin care; skin disease.

Ceramides (CERs) are important structural components of the epidermis, which plays a key role in maintaining homeostasis of the human body.[1] Specifically, its outermost layer, known as the stratum corneum, forms a barrier between the external environment and the internal body.[2] This barrier function serves multiple purposes including prevention of water loss and protection from foreign insult. The structure of the stratum corneum is often referred to as "brick and mortar."[3] The "bricks" are terminally differentiated keratinocytes composed mostly of keratin filaments and filaggrin.[4] The "mortar" is composed of intercellular lipids arranged into lamellar layers consisting of CERs, free fatty acids, and cholesterol. CERs are the predominant lipid comprising approximately 50% of the intercellular lipid content by mass.[3] Stratum corneum lipids are essential for maintaining skin barrier function and preventing transepidermal water loss (TEWL). Disruptions or damage to the stratum corneum can impair skin barrier function and result in TEWL.

Abbreviations used:

CER:	ceramide
CERSyn:	ceramide synthase
FLG:	filaggrin gene
TEWL:	transepidermal water loss

CERs have been added to newer cosmetic products to improve skin barrier function and exogenously replenish skin CERs. Of the stratum corneum intercellular lipids, CERs are the most effective at restoring barrier function and increasing skin hydration.[5] Different CERs have been incorporated into cosmetic formulations, but understanding the differences between CERs used in formulations, or even identifying CERs in formulations can be complex. This is mostly because of an archaic nomenclature system that is fundamentally flawed based on current scientific evidence.[6]

The term "ceramide" may only be used in an International Nomenclature of Cosmetic Ingredients (INCI) name[7] to designate CERs identified in a 1985

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article by Wertz et al.[8] Newer more sensitive analytical techniques have identified additional classes of CERs and CER species in human skin that were not identified by Wertz et al.[8] However, because of the archaic INCI nomenclature, these CERs may not be called "ceramides" on ingredient labels. Until the INCI nomenclature is updated to reflect our current understanding of CERs, identifying CERs as ingredients may continue to be challenging.

Because of their importance in maintaining the skin barrier, much research has been focused on the roles of CERs in the stratum corneum in healthy and diseased skin and the use of CERs as therapeutic agents for improving skin barrier function. Understanding their role in skin and use in skin-care products may be important for clinicians as CERs become more ubiquitous. The aim of this review is to discuss the structure, function, and importance of skin CERs in diseased skin and how CERs are being used in skin-care products to improve or restore skin barrier function.

CAPSULE SUMMARY

- Ceramides (CERs) are an important class of molecules necessary for skin barrier function, and changes in skin CER content are associated with a number of diseases such as atopic dermatitis and psoriasis.
- CERs have been incorporated into skin-care product formulations, which aim to restore skin barrier function through exogenous application of CERs.
- It is important for clinicians to have an understanding of the importance of this class of molecules, and how they are being incorporated into skin-care products.

SKIN CER STRUCTURE

The basic CER is composed of a sphingoid base conjugated to a fatty acid via an amide bond (Fig 1). However, the composition of CERs within the human stratum corneum is very heterogeneous. The number of CER classes identified in human skin has grown to 12, and differ from one another based on the composition of the head group or esterification of the fatty acid (Fig 2).[9,10] There are currently 4 different sphingoid bases and 3 different types of fatty acids identified thus far. Within these 12 classes, chain length of the sphingoid base or fatty acid differentiates specific CERs. The number of CERs within human skin is extensive; over 340 CER species have been identified within the forearm stratum corneum.[11]

The length of CERs within human skin is quite variable.[9] Nonhydroxy fatty acid sphingosine CERs analyzed from human cheek skin and forearm skin contain 33 to 52 total carbon atoms. However, CER species with at least 42 carbons are more abundant in either skin sample compared with smaller CER species less than 42 carbons in size. A propensity for longer chain length is also reflected in stratum corneum free fatty acids.[12] Epidermal free fatty acid chain length ranges from 14 to 32 carbons, but those greater than 20 carbons predominate.

SKIN CER PRODUCTION

CERs are produced via 2 different pathways: a de novo pathway and a salvage pathway.[13] The de novo pathway is the route of CER production in the skin.[14,15] Serine and palmitoyl-coenzyme-A (CoA) are condensed to make 3-keto dihydrosphingosine, which is converted into dihydrosphingosine. Dihydrosphingosine is N-acylated using fatty acetyl-CoA by CER synthase (CERSyn) producing dihydro-CER. Dihydro-CER can be further modified through desaturation or hydroxylation to produce the various other sphingoid bases found in skin CERs. CERSyn can also N-acylate sphingoid bases other than dihydrosphingosine, such as sphingosine. Six CERSyns have been identified in human beings.[13] They differ in their preference for fatty acyl-CoA length and their expression is tissue specific.

De novo skin CER synthesis occurs in the suprabasal layers of the epidermis in the endoplasmic reticulum.[14,16] CERSyn3 is up-regulated in differentiated keratinocytes and has a preference for longer chained fatty acyl-CoA molecules, which correlates to higher length CERs in the stratum corneum.[17] Newly produced CERs are transported to the Golgi apparatus where they are either glucosylated or converted to sphingomyelin.[14] Glucosyl-CERs and sphingomyelins are transported through the Golgi apparatus into secretory vesicles that accumulate and increase in number as keratinocytes differentiate through the stratum corneum (Fig 3). When the keratinocytes reach the boundary between the stratum granulosum and the stratum corneum, the secretory vesicles fuse with the plasma membrane and deposit their content into the intercellular space of the stratum corneum. Once deposited into the stratum corneum, glucosyl-CERs and sphingomyelins are processed back to CERs by β-glucocerebrosidase and sphingomyelinase, respectively.[18-20]

SKIN CERS IN SKIN DISEASES

CERSyn

A study conducted in mice showed that CERSyn3 was essential for survival.[21] Mice deficient in