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REVIEW ARTICLE

Signaling roles of ceramide and its metabolites in cutaneous antimicrobial defense

Yoshikazu Uchida [1, 2, 3, 4, *], Young il Kim [1, 2, 3, 4], Kyungho Park [1, 2, 3, 4]

[1] Department of Dermatology, University of California, San Francisco, San Francisco, CA, USA
[2] School of Medicine, University of California, San Francisco, San Francisco, CA, USA
[3] Dermatology Service and Research Unit, Veterans Affairs Medical Center, San Francisco, CA, USA
[4] Northern California Institute for Research and Education, San Francisco, CA, USA

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ABSTRACT

The skin epidermis is a multipurpose barrier (i.e., against epidermal permeability disruption and oxidative/UV irradiation) as well as a mechanical barrier and antimicrobial barrier, to protect cells/tissues from external perturbants. When there is a normal barrier, function is restored and/or enhanced in the epidermis in response to external perturbations. Ceramide (Cer) is a well-known, key lipid constituent of the epidermal permeability barrier in the extracellular domain of the stratum corneum. Cer and its metabolites also serve as signaling lipids to regulate cellular function (e.g., proliferation, differentiation, and apoptosis). Recent studies from our laboratory demonstrate that the Cer metabolites, sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P), generate signaling transcriptionally to stimulate cathelicidin antimicrobial peptide (CAMP), and human beta-defensin (hBD) 2 and hBD3 production, respectively, in cells, including in epidermal keratinocytes. S1P and C1P production are increased by external perturbation-induced endoplasmic reticulum stress. These studies illuminate a mechanism through which external perturbations signal to stimulate antimicrobial peptides without evidence of microbial infections. In this work, we describe the signaling roles of Cer, S1P, and C1P in cells.

Introduction

Ceramide (Cer) is composed of long-chain aminoalcohol and amide-linked fatty acids, whose chain lengths are 18–20 and 16–24, respectively (Figure 1). Cer serves as a membrane constituent and also as the backbone of all complex sphingolipids. It is converted to metabolites, and Cer and its metabolites regulate cellular functions (Figure 2). In skin, Cer serves as a key component in the epidermal permeability barrier in the stratum corneum. We review the signaling roles of Cer and its metabolites in skin. To distinguish between Cer forming epidermal permeability barrier structures and Cer regulating cellular function, the former and the latter are referred to as “barrier Cer” and “signaling Cer,” respectively.

Ceramide for epidermal permeability barrier

An epidermal permeability barrier is required for survival of mammals living in dry terrestrial environments. Major barrier lipids consist of cholesterol, free fatty acid, and Cer, which localizes in the extracellular lipids in the stratum corneum and is a key permeability barrier constituent. At least nine molecular classes of Cer, in both bulk amounts and molecular heterogeneity, located in the stratum corneum are unique to skin.[1,2] Prior studies show that decreased contents of Cer and/or alteration of molecular species occur in some cutaneous diseases associated with permeability barrier abnormality, i.e., atopic dermatitis (AD), psoriasis, and certain ichthyoses.[3–5] Furthermore, it has been recently demonstrated that a minor Cer metabolite species, sphingosine, also contributes to form a competent permeability barrier structure.[6,7]

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dermatology Service (190) Veterans Affairs Medical Center, 1700 Owens Street, Room 326, San Francisco, CA 94158, USA.
E-mail address: uchiday@derm.ucsf.edu (Y. Uchida).

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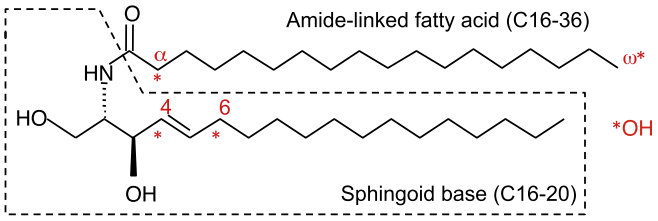

Figure 1 Ceramide structure.

Differences between Cer for epidermal permeability barrier and Cer for signaling

The differences between Cer responsible for permeability barrier formation in the stratum corneum and signaling Cer are summarized below.

(1) Localization. As stated above, barrier Cer is localized in the extracellular spaces in the stratum corneum. In contrast, signaling Cer regulates cellular function on the plasma membrane or intracellular compartment in cells, including nuclear layers of epidermal keratinocytes.
(2) Content. Cer in the stratum corneum is present in millimolar quantities, which contribute to form the epidermal permeability barrier,[8] whereas plasma membrane or intracellular Cer has micromolar levels.
(3) Molecular species. Heterogeneous molecules of Cer are present in the stratum corneum, and such heterogeneity is required for formation of uniform lamellar membrane structures. It has been shown that Cer species that consist of N-nonhydroxyl fatty acid and sphingosine can regulate biological processes. Certain Cer species (chain lengths of amide-linked fatty acid 16) lack antimitogenic or proapoptotic features, which leads to increased apoptosis in squamous cell carcinoma cells in response to endoplasmic reticulum (ER) stress. However, the structure requirements of signaling Cer are largely unknown.

Ceramide metabolites

Cer is converted into four metabolic pathways (Figure 3).

(1) Choline phosphorylated to sphingomyelin by sphingomyelin synthase 1 or sphingomyelin synthase 2. The former is localized in the *trans* Golgi apparatus and latter is in the plasma membrane.
(2) Glycosylated to glucosylceramide by UDP-glucosyltransferase or galactosylceramide by UDP-galactosyltransferase to synthesize glucosylceramide and galactosyloceramide, respectively. Glucosylceramide, but not galactosylceramide, is synthesized in epidermal keratinocyte.
(3) 1-0-phosphorylated to ceramide-1-phosphate (C1P) by ceramide kinase.
(4) Hydrolyzed to aminoalcohol and fatty acid by ceramidase.

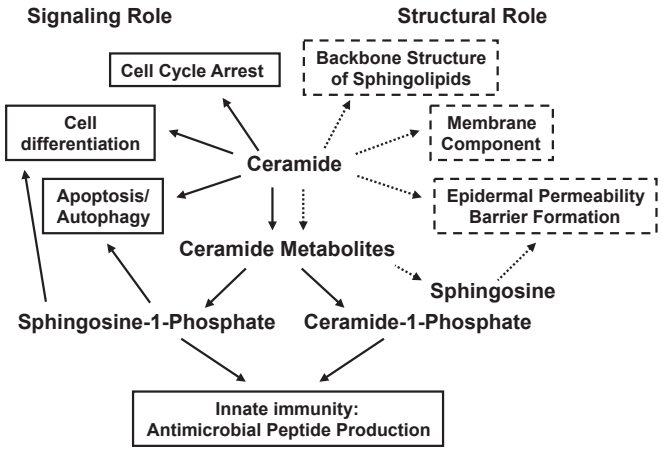

Figure 2 Roles of ceramide and its metabolites in epidermis.

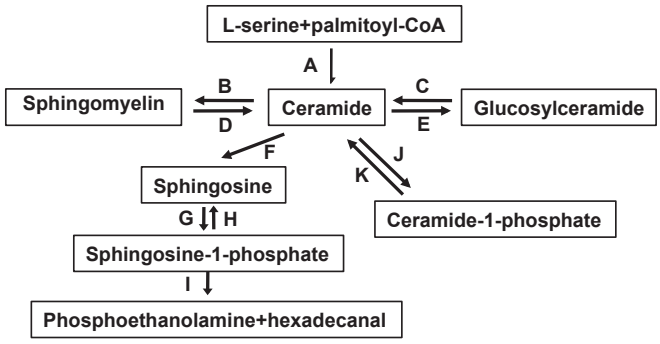

Figure 3 Ceramide (Cer) metabolic pathway. Cer is synthesized *de novo* pathway catalyzed by (A) serine palimoyltransferase, ceramide synthase, and desaturase, hydrolysis of sphingomyelin or glucosylceramide by (B) sphingomyelinase or (C) β-glucocerebrosidase, respectively. Conversely, sphingomyelin and glucosylceramide are synthesized from Cer by (D) sphingomyelin synthase and (E) UDP-glucosylceramide transferase, respectively. (F) Cer is hydrolyzed to sphingosine by ceramidase. (G) Sphingosine is phosphorylated to sphingosine-1-phosphate (S1P) by sphingosine kinase, and conversely, (H) S1Pis hydrolyzed to sphingosine by sphingosine-1-phosphate phosphatase. (I) S1P is dephosphorylated to phosphoethanolamine and hexadecanal by sphinosine-1-phosphate lyase. (J) Cer is phosphorylated to ceramide-1-phophosphate by ceramide kinase and conversely, (K) ceramide-1-phophosphate is dephosphorylated to Cer by ceramide-1-phosphate phosphatase.

Four isoforms of ceramidase—(1) acidic ceramidase distributed in lysosome; (2) neutral ceramidase in plasma membrane and ER; (3) alkaline ceramidase 2 (so-called skin ceramidase) in ER and alkaline ceramidase 3 in Golgi apparatus; (4) phytoalkaline ceramidase (alkaline ceramidase 1) in ER—have been identified in mammals. Alkaline ceramidase 2 has been shown only in differentiated layers in the epidermis. Four ceramidase isoforms are present in keratinocytes, whereas both acidic and alkaline ceramidase 2 levels are increased and alkaline ceramidase 1 levels are decreased during keratinocyte differentiation.[1] The other three ceramidase levels are not changed in a differentiation-dependent manner. Moreover, glycosylceramides are further glycosylated to di- or polyglycosylceramide. In the epidermis, glucosylceramides are a major species. Sphingosine is phospholyated to sphingosine-1-phosphate (S1P) by sphingosine kinase 1 or 2.

Glucosylceramide is hydrolyzed to glucose and ceramide by β-glucocerebrosidase, whereas sphingomyelin is hydrolyzed to sphingosine and phosphorylcholine by sphingomyelinase.

Signaling Cer can be produced from hydrolyses of sphingomyelin or glucosylceramide, by sphingomyelinase or β-glucocerebrosidase, respectively, as well as *de novo* synthesis by activation of either serine-palimitoyltransferase or ceramide synthase.[1,9] In contrast to the sphingomyelin pathway that generates signaling Cer, the glucosylceramide pathway has not been elucidated. Our prior studies demonstrated that Cer production is increased following ultraviolet (UV) B irradiation or other oxidative stressors and results in increasing Cer-induced apoptosis in keratinocytes.[10] Both toxic (high doses) and subtoxic (low doses) increased ceramide, whereas toxic levels of irradiation sustained elevated Cer; however, Cer was restored toward normal levels in cells treated

with subtoxic levels of UVB because of its efficient conversion into nonapoptotic Cer metabolites,[10] suggesting that metabolic conversion contributes to protecting cells against Cer-induced apoptosis. Cer-induced apoptosis is in part a mechanism of chemotherapy, whereas accelerating metabolic conversion of Cer to glucosylceramide and S1P-attenuating chemotherapy has been shown in several types of tumor cells, including melanoma. In particular, the chemotherapy-resistant tumor cells often show increased enzyme production, which is responsible for the metabolic protective mechanism against Cer-induced apoptosis.[11,12]

Cer signaling roles that regulate cellular functions

The first demonstration of a Cer signaling role (to induce erythroblast maturation) was in 1974. The first barrier Cer studies, reported in 1975 by Gray and Yardley,[13] initiated the field of skin Cer research. In contrast, Cer signaling studies were not further developed for some time. In early 1990, it was shown that increasing cellular Cer levels by sphinomyelinase activation induced cell cycle arrest and differentiation in leukemia cells in response to vitamin D or phorbol ester.[14,15] A technical difficulty of Cer biological studies is the poor solubility of Cer in aqueous solution. The application of cell-permeable short-chain amide-linked fatty acid (C2–C8) containing Cer, which substantially increased hydrophilicity, has led to more signaling Cer studies. Although such short-chain Cer is not synthesized in mammalian cells, it can be used as a precursor to synthesize natural, long-chain Cer in cells.[16] Previous studies demonstrated that, in response to various stimuli, including ER stress, sphingomyelin hydrolysis by sphingomyelinase activation and/or *de novo* synthesis of Cer by ceramide synthase activation generate signaling Cer.[17–19]

Cer mechanisms that regulate cellular functions depend on cell types and/or stimuli.[12,20]

The following downstream mechanisms have been demonstrated in mammalian cells:

(1) Increased cellular Cer activates ceramide-activating serine/threonine phosphatases (CAPS)—i.e., protein phosphatase 1A (PP1A) and protein phosphatase 2A (PP2A),[21] protein kinase C (PKC) ζ,[22] cathepsin D,[23] and kinase suppressor RAS.[24]
(2) CAPS, PP1A, and PP2A inactivate PKCα,[25] and AKT [or protein kinase B (PFB)],[26] depending on cell and tissue types as well as stimuli.

In addition to these mechanisms, Cer physically affect cellular functions. Cer permeabilizes mitochondrial outer membranes, leading to mitochondrial-mediated apoptosis.[27]

Signaling roles of Cer metabolites in regulation of antimicrobial peptide production

Skin deploys multiple barriers to protect cells and tissues from external perturbations—i.e., UV/oxidative stress, mechanical stress, and microbial infection. The antimicrobial peptide (AMP), an innate immune component, is a key constituent of the antimicrobial barrier. Microbial infection increases AMP production, whereas diverse types of external perturbations—such as epidermal permeability disruption, UV irradiation, and other types of oxidative stress—stimulate key epidermal AMP [cathelicidin antimicrobial peptide (CAMP), human beta-defensin (hBD) 1, hBD2 and hBD3 production]. Although all perturbations increase the risk of microbial infections, AMP production is increased in skin without infections following perturbations. Our recent studies demonstrate that acute epidermal permeability defects, as well as UVB/oxidative stress induce ER stress in keratinocytes.[28,29] The ER is an intracellular organelle that synthesizes protein and lipid, and is a major storage place for Ca^{2+}. ER stress occurs in cells when proteins are accumulated and Ca^{2+} is released from the ER. Three major transmembrane proteins—inositol-requiring enzyme 1 (IRE1 or ERN1, a kinase with ribonuclease activity), protein kinase RNA-like endoplasmic reticulum kinase (PERK; also known as PEK or EIF2AK3), and activating transcription factor 6—serve as sensors of ER stress and also induce rescue signals to restore cellular function, because ER stress causes deleterious cell effects, including apoptosis.[30] However, high levels of ER stress levels cause apoptosis. We found that ER stress stimulates both CAMP and hBD2 and hBD3, but not hBD1, production.[31,32] These studies demonstrate how different external perturbations can increase specific AMP production through one mechanism.

CAMP production

CAMP is a multifunctional AMP that is not only antimicrobial, but also accelerates cell growth, cell motility, angiogenesis, and certain cytokine production.[33,34] As discussed above, CAMP production is stimulated following external perturbation that can induce ER stress in parallel with increasing cellular Cer production. Prior studies characterized that a nuclear hormone receptor, vitamin D receptor (VDR), is dependent on the stimulation of CAMP production.[35] Microbial infection activates Toll-like receptor 2. Toll-like receptor 2 does not activate VDR, but does activate 25-hydroxy vitamin D_3 1-alpha-hydroxylase (CYP27B1), which synthesizes a VDR ligand 1α, 25-dihydroxy vitamin D_3, leading to stimulation of CAMP production. VDR binding sequence has not been identified on the promoter region of binding sequence on a murine CAMP (CRAMP) gene,[35] as opposed to the human CAMP gene. Importantly, we found that VDR transcription activity is suppressed in cells under ER stress, and VDR gene silencing does not alter increased CAMP production.[28] Recent studies further identified that a Cer metabolite, S1P, activates transcription factor nuclear factor-kappa B (NF-κB).[31] The NF-κB binding sequence is not identified on a CAMP promoter.[28,35] NF-κB then activates another transcription factor C/EBPα (by MAP kinase activation) that stimulates CAMP transcription[28] (Figure 4). S1P-mediated signaling of cellular functions is often dependent on prior binding to one or more of five known G-protein-coupled S1P receptors (S1P1–S1P5), located on the outer surface of the plasma membrane.[36] KC express all five receptors.[37] However, S1P activates NF-κB via the S1P receptor-independent pathway intracellular region.[31]

hBD2 and hBD3 production

Both hBD2 and hBD3 are stimulated by microbial infections, whereas upstream mechanisms to regulate these hBDs are different. Proinflammatory cytokines (interleukin-1β, tumor necrosis factor-α, interferon-γ) induce hBD-2 mRNA transcription by activation.[38] hBD3 production is induced by epidermal growth factor receptor activation.[39] Other transcriptional factors, signal transducer and activator of transcription (STAT) 1 and STAT 3, also serve as downstream signals to regulate hBD2 and hBD 3 transcription.[40,41] Recent studies have shown that C1P is increased following increased Cer production, in response to external perturbation and ER stress.[32]

C1P directly activates cytosolic phospholipase A2 to rerelease arachinonate from glycerophospholipids, leading to increased eicosanoid production, including PGE2 and PGJ2. Prior study showed that C1P-mediated, elevated PGE2 levels increase inflammatory responses in cells.[42] C1P also increased PGJ2 production followed by stimulation of hBD2 and hBD3 production.[32] PGJ2 is an activator of nuclear hormone receptors, peroxisome proliferator-

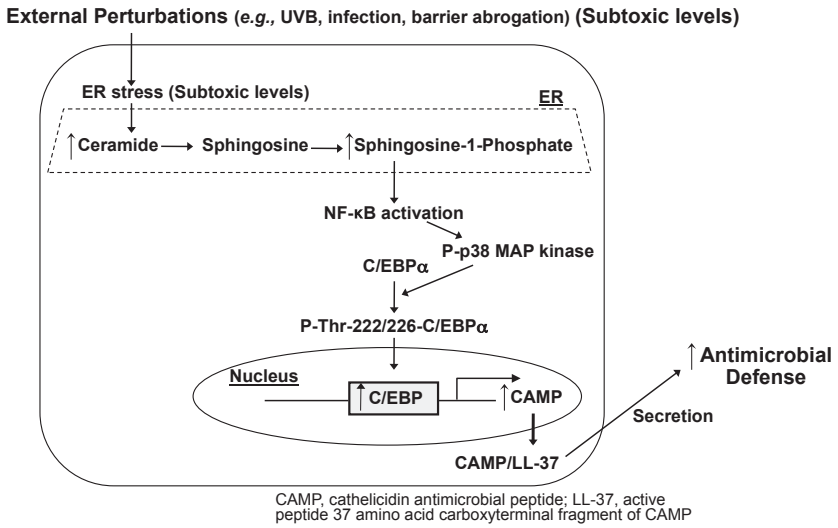

Figure 4 Ceramide metabolite, sphingosine-1-phosphate signals to stimulate cathelicidin antimicrobial peptide (CAMP) production.

activated receptors (PPAR) α, PPAR β/δ, and PPARγ.[43] C1P stimulates hBD2 and hBD3 production through PPARα and PPARβ/δ—but not PPARγ—activation.[32] Then, PPARα and PPARβ/δ activate STAT1 and STAT 3 via the activation of tyrosine Src kinase. STAT 1 and STAT 3 are activated by phosphorylation that binds to promoter sequences of hBD2 or hBD3, leading to hBD2 and hBD3 production[32] (Figure 5).

Pharmacological modulation and clinical implication of CAMP production

Recent studies have demonstrated that certain naturally occurring polyphenolic compounds, such as stilbenoid, resveratrol, and the soy-derived isoflavone, genistein, increase cellular levels of S1P that signal to stimulate production of the key epidermal AMP, CAMP.[44,45] Resveratrol and genistein increased S1P production via different signaling mechanisms (Figure 6): (1) resveratrol increased not only ceramide, but also its key metabolites, sphingosine and S1P; (2) genistein increased production of S1P (without changes in ceramide levels) by inhibiting the activity of S1P lyase, an enzyme catalyzing S1P breakdown to phosphoethanolamine and hexadecenal, as well as increasing expression of key enzymes—e.g., acidic/alkaline ceramidases and sphingosine kinase 1 (SPHK1), which convert ceramide to S1P. In addition to both naturally occurring compounds, our more recent studies suggested that direct activation of SPHK1 with a chemically synthesized compound, (*S*)-methyl 2-(hexanamide)-3-(4-hydroxyphenyl) propanoate (defensamide), can also stimulate CAMP production via our

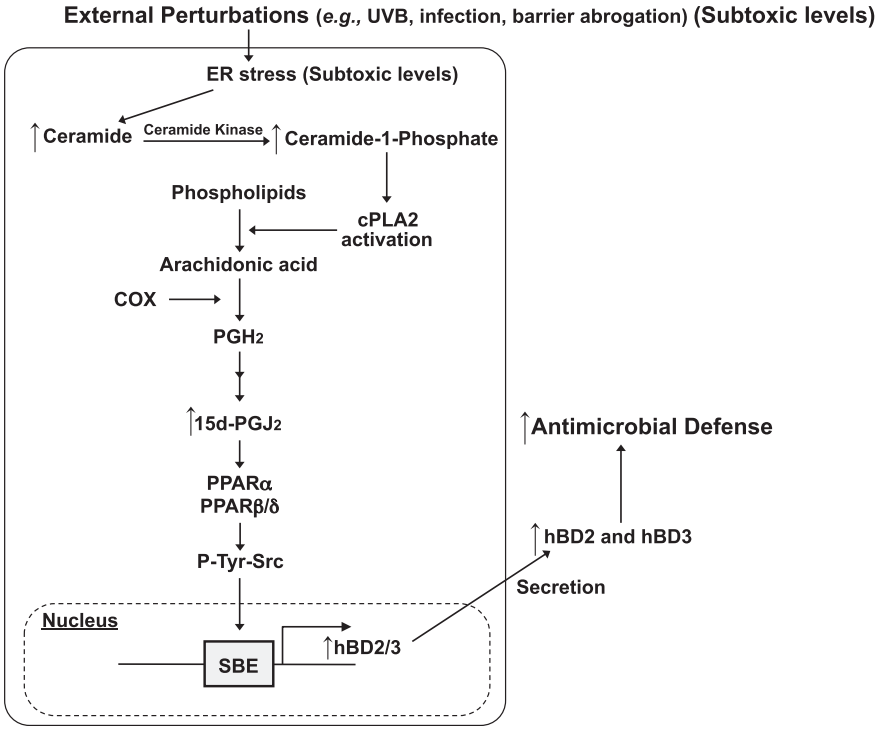

Figure 5 Ceramide metabolite, ceramide-1-phosphate signals to stimulate human beta-defensin (hBD) 2 and hBD3 production.

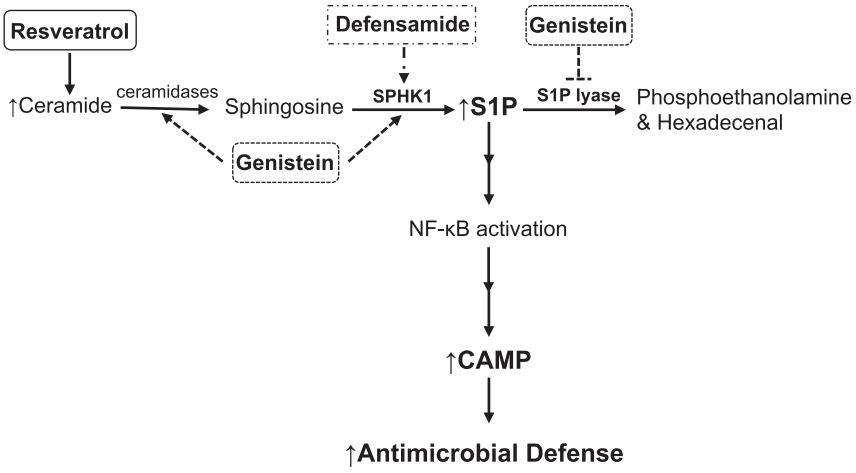

Figure 6 Pharmacological enhancement of cathelicidin antimicrobial peptide (CAMP) production.

identified S1P-dependent mechanism (unpublished data) (Figure 6). These studies indicate multiple target points whereby naturally occurring or chemically synthesized compounds increase production of S1P that could enhance antimicrobial defense through the stimulation of CAMP production.[44,45]

In addition, curcumin stimulates CAMP production via the VDR-independent pathway.[46] Because patients with AD do not produce enough CAMP in response to microbial pathogens, bacterial infections are a serious and frequent complication of AD patients. Therefore, these individual compounds, which can stimulate CAMP production, are potentially useful for the development of novel potential therapeutic agents and/or cosmetic products to enhance antimicrobial defense in AD.

Conclusion

Cer and its metabolites exhibit multifunctions in mammalian cells, including keratinocytes. In contrast to barrier Cer, even a 1/1000 part of Cer concentration will suffice to generate signals to alter cellular function. Because such a small change occurs in certain cellular compartment(s) and/or basal Cer, S1P, and C1P levels are low, increased levels of Cer or its metabolites could have a great impact on cells. A rescue mechanism, metabolic conversion, against Cer-induced apoptosis enhances innate immunity through AMP production. Hormesis shows that low levels of external perturbations, including radiation, and oxidative stress, enhance the cellular antioxidant system (superoxide dismutase) and thioredoxin, a tumor suppressor gene p53, and heat shock proteins.[47] Similarly, low levels of Cer and its metabolites could enhance defense against these external perturbants in cells.

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