

Structure and Function of Ceramide and Its Application in Diseases

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Abstract. About 50% of the lipid components in the human epidermis are ceramides, which, together with cholesterol and free fatty acids, constitute the lipid matrix in the stratum corneum. Ceramide plays an important role in skin barrier function, which can keep skin moist and protect skin from the external environment. Because of the diversity of long-chain bases and fatty acids in structure and chain length, there are many kinds of ceramides, which are often combined by two systems in naming. As an important sphingolipid in the human body, there are three main synthetic routes of ceramide: de novo synthesis, sphingomyelin hydrolysis and remedial route. Studies have shown that ceramide has complex functions in organisms. It is not only an important component of skin stratum corneum lipid but also the second messenger of the apoptosis-related signal pathway, and it also plays a certain role in metabolism and neurological function. Therefore, this paper sorts out the existing literature to help understand the relationship between ceramide and various diseases and hopes to provide new ideas for the prevention and treatment of diseases.

Keywords: ceramide; skin barrier function; disease; synthetic metabolism; ceramide nomenclature.

Sphingolipids (SLs) are important lipids in organisms, which generally exist on the cell membranes of animals, plants, fungi and other organisms and participate in many important life activities such as signal transduction and intercellular interaction. As a common precursor of sphingolipids, ceramide (Cer) is at the centre of a series of sphingolipid metabolism processes, and it is a star molecule in the sphingolipids family. Ceramide is formed by a long-chain base (LCB) and fatty acid (FA) through an amide bond, in which the structure and chain length of the long-chain base and fatty acid are diversified, which leads to the complexity of ceramide structure and function [1]. With the deepening of people's understanding of ceramide, it is found that ceramide has not only obvious effects in moisturizing skin and reducing inflammation but also has close ties with tumours, metabolic diseases and neurological diseases [2, 3]. For example, ceramide can promote the protein kinase C (PKC) and translocation to the Golgi apparatus, thus promoting the formation of a pro-apoptosis complex containing prostate apoptosis response-4 (PAR-4) [4]. This paper mainly expounds on the structure, function, nomenclature and application of ceramide in diseases.

1. Brief Introduction of Sphingolipids

In 1884, Thudichum J. discovered sphingolipids in brain tissue, but it was difficult to understand the biological function of sphingolipids at that time, so Thudichum named it the Sphinx (Sphinx, a monster who used riddles in Greek mythology) [5]. Based on the existing literature, sphingolipids are mainly composed of a polar head and two hydrophobic tails (sphingosine and long-chain fatty acids). N- acyl sphingosine, that is, ceramide, is produced when fatty acids are linked with amino groups on carbon atom 2 of sphingosine by amide bonds, so ceramide is the structural monomer of sphingolipids [6]. The structural classification of sphingolipids is mainly determined by their polar heads. When the head is combined with choline phosphate, it is sphingomyelin (SM), and when it is connected with sugar, it is sphingolipids. Among them, the sphingolipids with complicated sugar connections are also called gangliosides.

Sphingolipid is not only an important part of eukaryotic biofilm but also the site of many cell surface recognition processes. For example, sphingolipid is the determinant of human ABO blood group [3]. Among them, sphingomyelin mainly exists in the plasma membrane and myelin sheath, which plays an important role in maintaining membrane stability, maintaining cell cholesterol

homeostasis and lipid transport, and is also a key lipid that constitutes plasma lipoprotein [7, 8]. Studies have shown that sphingosine -1- phosphate (S1P) plays an opposite role to ceramide in cell apoptosis, which can promote cell survival and maintain the stability of ovarian follicles together with ceramide [3, 8]. As one of the most complex sphingolipids, ganglioside exists on the membrane of the human nervous system and plays an important role in biological processes such as cell apoptosis, cell proliferation, cell interaction, cell differentiation and intracellular signal transmission [9]. The metabolic disorder of ganglioside can induce many diseases, such as familial melanotic dementia. For patients with familial Alzheimer's disease, due to the lack of hexosamine lyase, the polar part of gangliosides can not be hydrolyzed, and gangliosides accumulate in their brains and spleen, which leads to patients' gradual nervousness and blindness, and they will die at the age of 3-4.[10].

Sphingolipids can be produced by de novo synthesis, complex sphingolipid decomposition and circulation, and its metabolic centre is ceramide [7]. In de novo synthesis, serine and palmitoyl coenzyme A can be synthesized into 3- ketosphingosine catalyzed by serine palmitoyl transferase, and then ceramide can be generated through a series of enzymatic reactions. From ceramide, sphingosine, ganglioside and other sphingolipids, their metabolites can be synthesized [11]. Conversely, these complex sphingolipids can also be converted into ceramides through a series of enzymatic reactions, forming a whole cycle.

2. Structure of Ceramide 2

Ceramide is the hub of sphingolipid metabolism, and together with free fatty acids and cholesterol, it constitutes an important lipid component of human skin stratum corneum, in which ceramide accounts for as much as 50%, which is very important for the formation of stratum corneum needed by healthy skin [12]. Structurally, a molecule of ceramide is composed of a molecule of long-chain base and a molecule of fatty acid through an amide bond, and the diversity of these two components constitutes the complexity of ceramide.[1]. It is reported that there are five types of long-chain bases in mammalian ceramides: dihydrosphingosine (DS), sphingosine (S), phytosphingosine (P), 6-hydroxysphingosine (H) and 4,14- sphingosine (SD), and four types of fatty acids: non-hydroxyl (N) and α -hydroxyl (A). In addition, some omega-hydroxy fatty acids can also bind to protein (P-O), and the ceramide composed of omega-hydroxy fatty acids is called protein-bound ceramide, which can covalently attach to the surface protein (keratinized envelope protein) of terminally differentiated keratinocytes [13].

A study on ceramide showed that the chain length of long-chain bases constituting ceramide in the stratum corneum of human skin was mainly C16-26, of which C18(28.6%) took up the largest proportion, followed by C20(24.8%) and C22(12.8%) [13]. Relatively speaking, ceramides containing odd-numbered long-chain bases are obviously less, accounting for only 20.2% of all ceramides [13]. In addition, different types of fatty acids have the tendency to chain length. In the stratum corneum of human skin, the carbon chain length of N-type and A-type fatty acids is mainly C16-30, while O-type, EO-type and P-O-type fatty acids are concentrated in C30-36 [14].

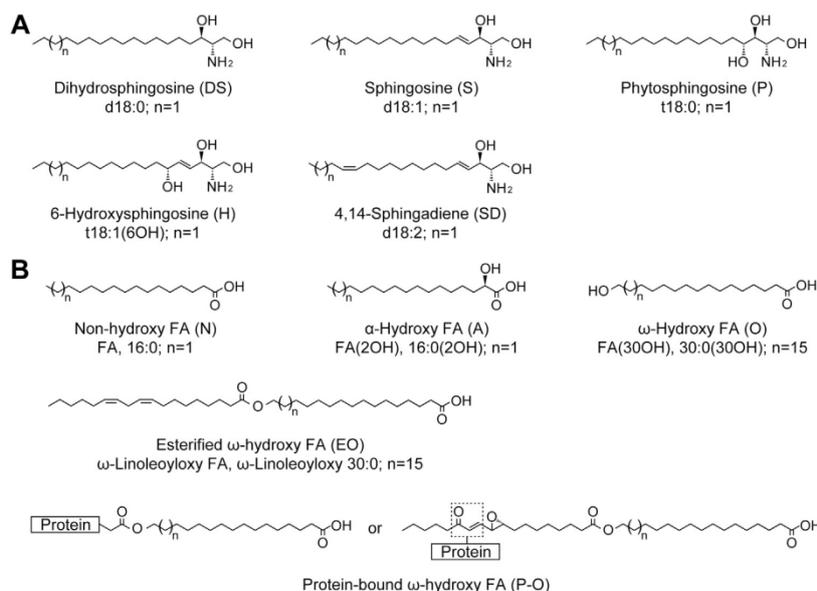


Figure 1. Structure and nomenclature of human ceramide. A: the structure and nomenclature of long-chain bases in human ceramide, which is named by English full name, abbreviation and expression of hydroxyl double bond number, and n is the number of -CH₂- omitted in the carbon chain. B: Structure and nomenclature of fatty acids in human ceramide. The first four labels are named by English full name, abbreviation, English abbreviation and expression of hydroxyl double bond number, and n is the number of -CH₂- omitted in the carbon chain. The fifth is a protein-bound fatty acid, abbreviated as (P-O).

3. The Naming of Ceramide

The naming of ceramide is closely related to its structure, which can be mainly divided into two types.

The first one is named after the abbreviations of fatty acids and long-chain base types. The fatty acid abbreviations come first, and the long-chain base comes last, so the non-hydroxyl fatty acid sphingosine can be named NS [13].

Second, according to the hydroxyl group (d, 2; t, 3) and the number of double bonds. For example, a sphingosine molecule has two hydroxyl groups and a double bond, so it is named d18:1. In this way, five long-chain bases with the carbon chain length of 18 can be renamed as d18:0 (DS), d18:1 (S), t18:0 (P), t18:1 (H) and d18:2 (SD). Under this set of rules, fatty acids can be named according to the number of carbon atoms and the position of hydroxyl groups. For example, a 30-carbon ω-hydroxy fatty acid can be named 30:0 (30OH). In this way, ceramide, composed of 16-carbon non-hydroxyl fatty acids and 18-carbon sphingosine, can also be represented by d18:1/16:0. It is worth noting that due to the diversity of fatty acid chains, there are often repetitions when describing fatty acids by this method. For example, both non-hydroxyl fatty acids and esterified ω-hydroxyl fatty acids have no hydroxyl groups, so it is difficult to distinguish them if the number of carbon atoms is the same, and abbreviations are often needed for assistance. In addition, the omega-hydroxy fatty acids bound to protein cannot be expressed in this way because of their complicated structures.

Table 1. Two Nomenclatures of 20+5 Human Ceramides. n in the Table representing the Number of Carbon Atoms of Fatty Acids

| FAs C LCBs Bs, ah | Non-hydroxyl group | α-hydroxyl group | ω-hydroxyl group | Esterification ω-hydroxyl (EO)n:0 | Protein-bound |
|----------------------|--------------------|------------------|------------------|-----------------------------------|---------------|
|----------------------|--------------------|------------------|------------------|-----------------------------------|---------------|

| | (N) n:0 | (A) n:0(2OH) | (O) n:0(nOH) | | ω - hydroxyl (P-O) |
|--------------------------------------|------------------|-----------------------|-----------------------|-------------------|---------------------------------|
| Dihydro-sphingosine (DS)d18:0 | NDS d18:0/n:0 | ADS d18:0/n:0(2OH) | ODS d18:0/n:0(nOH) | EODS d18:0/n:0 | P-ODS |
| Sphingosine (S) d18:1 | NS d18:1/n:0 | AS d18:1/n:0(2OH) | OS d18:1/n:0(nOH) | EOS d18:1/n:0 | P-OS |
| Plant sphingosine (P) t18:0 | NP t18:0/n:0 | AP t18:0/n:0(2OH) | OP t18:0/n:0(nOH) | EOP t18:0/n:0 | P-OP |
| 6- Hydroxysphingosine (H)t18:1 | NH t18:1/n:0 | AH t18:1/n:0(2OH) | OH t18:1/n:0(nOH) | EOH t18:1/n:0 | P-OH |
| 4,14-sphingosine (SD)d18:2 | NSD t18:2/n:0 | ASD t18:2/n:0(2OH) | OSD t18:2/n:0(nOH) | EOSD t18:2/n:0 | P-OSD |



Figure 2. Three synthetic pathways of ceramide [15]. In the de novo synthesis route, L- serine and palmitoyl -CoA were synthesized from SPT to 3- ketosphingosine and then gradually synthesized into ceramide. In the sphingomyelinase (sphingomyelin hydrolysis) pathway, ceramide and sphingomyelin can be transformed into each other through SMase and SMS. In the remedial way, complex sphingolipids can be transformed into sphingosine and ceramide through CERS and CDase.

4. Synthesis of Ceramide

Changes in the structure, content or composition of ceramide in the stratum corneum will damage the skin barrier function. The change of ceramide content is mainly regulated by complex metabolic pathways. The research shows that the synthesis of ceramide can be divided into de novo synthesis, sphingomyelin hydrolysis and remedial pathway.^[16]

In de novo synthesis, the first step is to transfer serine residues to fatty acyl coenzyme A by Serine palmitoyltransferase (SPT) to form 18-carbon skeleton 3- ketosphingosine (3KDS), which is

then reduced to Dihydrosphingosine (DHS) by 3- ketosphingosine reductase. Then it is catalyzed by Ceramide synthases (CerS) to form dihydroceramide, and finally, it is converted into ceramide by dihydroamide desaturases (Des1, Des2) [16]. This ceramide synthesis pathway exists in mammals, plants and yeast, as shown in Figure 3.

The Sphingomyelinase (SMase) hydrolysis pathway mainly involves a small family, which can be divided into acidic, neutral or alkaline sphingomyelinase according to the optimal pH value or subcellular position, and can hydrolyze phosphatidylcholine groups in sphingomyelinase to ceramide [16]. Because the content of sphingomyelin varies greatly in different organisms, for example, mammals are rich in sphingomyelin, but this substance has not been found in plants, this pathway has different manifestations in different organisms. See Figure 3 for details [17].

Ceramide can also be catalyzed by other complex sphingolipids in an indirect way, which is called a remedial pathway. Higher-order sphingolipids (sphingolipids and sphingolipids) can be degraded by active enzymes (acidic SMase and acidic β -glucosidase 1) in acidic cells to form ceramides. Ceramide itself can be degraded into sphingomyelin and free fatty acids, thus entering the cytoplasm. In the cytoplasm, sphingosine can be converted into ceramide again by ceramidase to complete the cycle [16].

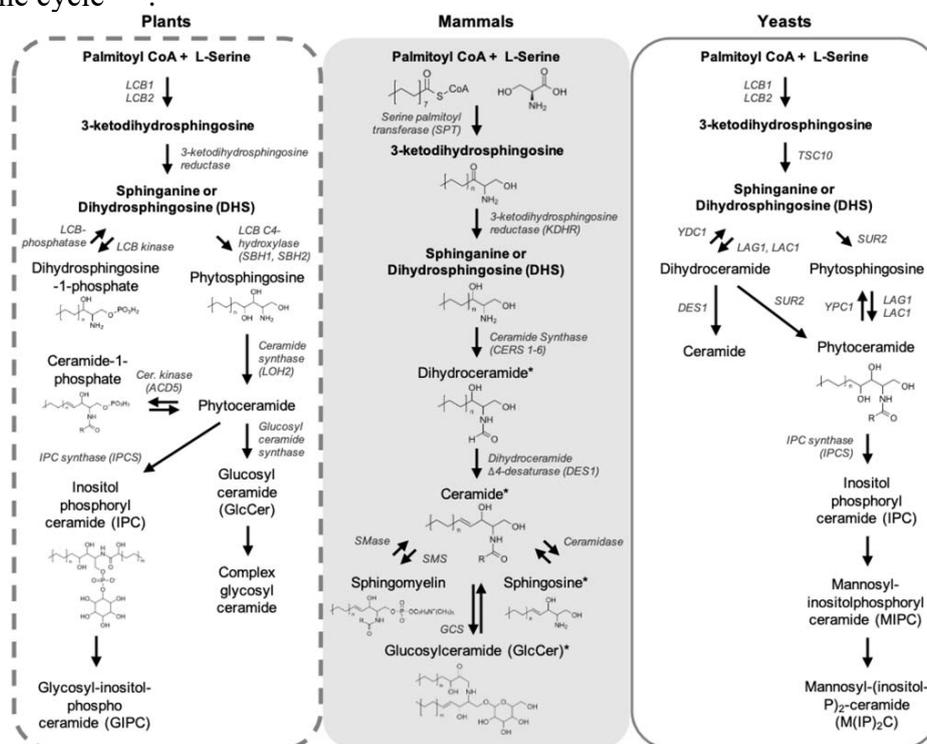


Figure 3. Main metabolic pathways of ceramide in plants, animals and yeast. Some sphingolipid complex structures were not exhibited because of their complexity [17]. Plant ceramides can be synthesized from L- serine and palmitoyl -CoA de novo and can be converted into sphingosine and DHS by ceramide kinase and ceramide -1- phosphate. Ceramide in mammals can be synthesized by de novo synthesis, sphingomyelin hydrolysis, and remedial pathways. Ceramide in yeast is mainly synthesized by de novo synthesis.

5. Function and Application of Ceramide

5.1 The effect of ceramide on skin

The stratum corneum is the outermost layer of the human epidermis, and its structure is usually described as a “brick wall structure” [18]. Brick is terminally differentiated keratinocytes, while mortar is intercellular lipid, which contains about 50% ceramide, 25% cholesterol, 15% free fatty acids and a very small amount of phospholipids [12, 19]. Among these lipids, ceramide is the most

effective in preventing transcutaneous water loss (TEWL) [20]. Ceramide not only has hydrophobic groups and hydrophilic groups at the same time, which helps the stratum corneum to retain water but also promotes the synthesis of skin barrier proteins such as filaggrin (FLG), which is of great significance to the skin barrier function [21]. A study on mice showed that CerS3-deficient mice died of TEWL shortly after birth, and their skin was more susceptible to infection by *Candida albicans* [22].

Studies have also shown that dermatoses such as psoriasis, Gaucher's disease and atopic dermatitis are all related to the abnormality of ceramide content and composition [23-25]. For example, in atopic dermatitis, compared with the control group of the same age, the ceramide level in patients' skin is significantly reduced [26]. In psoriasis, although the ratio of total ceramides to normal skin did not decrease, both long-chain ceramides containing ester-chain fatty acids and ceramides containing sphingomyelin in psoriasis patients' skin decreased [23]. Experiments show that supplementing or regulating ceramide can effectively alleviate related diseases. For example, the use of some emulsions with ceramide or ceramide analogues as the main components can reduce the severity of itching and TEWL in patients [2]. In addition, it has been reported that ceramide can also be used to treat rosacea and facial atopic eczema [2, 27].

Because of its moisturizing, whitening effects [28], anti-sensitivity [29], and anti-ageing [30], ceramide is also widely used in skin care products, cosmetics and other fields and is a star product in this field.

5.2 the role of ceramide in tumour

At the same time, ceramide participates in the signal transduction process in cells by relying on many kinds of protein kinases and transcription factors. It is an important second messenger in cells and participates in a series of signal pathways in cells, such as cell proliferation and apoptosis [31]. Different kinds of ceramides may mediate completely opposite physiological processes, such as C16-ceramide can promote the proliferation of tumour cells, while C18- ceramide can induce apoptosis [32]. Therefore, ceramide plays an important role in the occurrence of tumours. In some cases, ceramide can promote the abnormal activation of endothelial growth factor receptors, so that this pathway is abnormally activated and does not degrade, and constantly transmits proliferation signals, thus promoting the occurrence of cancer [33]. But more often, ceramide can rapidly and completely induce the dephosphorylation of B-cell lymphoma-2 (Bcl-2) protein by specifically activating mitochondrial protein phosphatase 2A (PP2A), thus promoting cell apoptosis and inhibiting the occurrence of most cancers [34].

In addition, ceramide can also prevent tumour metastasis [35]. Osawa et al. reported that ceramide could be further hydrolyzed and phosphorylated into S1P, and S1P can induce macrophage aggregation, promote CD3⁺T cells to enter tumour and induce myofibroblasts in the liver to synthesize tissue inhibitor of metalloproteinase-1, which can inhibit liver metastasis of colon cancer [36].

5.3 The role of ceramide in metabolic diseases

In cellular autonomous systems and complex organisms, ceramide can change intracellular signal pathways to slow down anabolism, thus ensuring catabolism [16]. Specifically, both exogenous and endogenous ceramides can inhibit the phosphorylation activation of Serine-threonine kinase (Akt), an intermediate of insulin signal transduction, resulting in the decrease of glucose transporter 4 (GLUT4) expression and anabolic enzyme activity on the surface of skeletal muscle and adipocytes, thus inhibiting the synthesis of glycogen and protein and increasing the blood sugar content [37]. In addition, ceramide can also regulate mitochondrial function, which can increase the permeability of mitochondrial membrane structure and inhibit electron transfer complex, thus destroying electron transfer, leading to the increase of active oxygen content and inducing resistance to insulin function.[38]. In the study of pancreatic β cells, ceramide can also reduce the transcription level of proinsulin and promote the apoptosis of pancreatic β cells, thus limiting anabolism by changing the

hormone environment after meals [39, 40]. Therefore, ceramide is of great significance to metabolic diseases, such as diabetes and cardiovascular diseases. Literature shows that the contents of various 1- dehydroceramides (DoxCer) in patients with type 2 diabetes mellitus are significantly higher than those in normal people [41]. Another study on patients with myocardial infarction also found that the plasma ceramide level was significantly higher than that of the control group, and the higher the ceramide level, the higher the vulnerability of atherosclerotic plaques [42].

5.4 The effect of ceramide on nerves

The effect of ceramide on the nervous system and brain function is not clear. In some reports, C16-ceramide can improve the learning and short-term memory behavior of adult mice without affecting glucose metabolism, even for Alzheimer's disease model mice.^[43] However, another study found that ceramide can promote the production of reactive oxygen species (ROS) in nerve cells, trigger inflammatory reactions and induce apoptosis of nerve cells, which plays an important role in cognitive dysfunction^[44, 45]. In addition, ceramide may also be related to Parkinson's disease (PD). Studies have shown that plasma ceramide, glucose ceramide and lactose ceramide levels in PD patients are significantly higher than those in healthy controls^[46]. The disorder of ceramide metabolism may lead to the formation of Lewy bodies and α synuclein deposition, which may lead to PD^[47].

6. Conclusions

Ceramide is a simple sphingolipid, which is composed of long-chain bases and fatty acids. As an important part of human skin stratum corneum lipid, ceramide has the functions of moisturizing, anti-sensitivity and barrier. In addition, ceramide is an important second messenger in organisms, which can regulate physiological processes such as cell proliferation, differentiation, and apoptosis. It also has important research value for the occurrence and treatment of tumours. In terms of metabolism, ceramide can alleviate anabolism and promote catabolism, which is of great significance for metabolic diseases such as diabetes. Recently, some studies have shown that ceramide plays a certain role in many neurodegenerative diseases, but the complete mechanism needs to be further explored. In this paper, the related literature in the field of ceramide is sorted out, and the structure, nomenclature, synthesis, function and application of ceramide are mainly described, hoping to provide help for the research of related diseases.

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