

Sphingolipids and DNA Damage Response

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Sphingolipids are essential structural components of biological membranes that mediate a wide array of physiological functions such as inflammation, cell proliferation, survival, senescence, and death. An emerging body of evidence suggests that bioactive sphingolipids modulate the DNA damage response (DDR) induced by genotoxic stress and therein determine cell fate.

sphingolipids

nuclear sphingolipids

DNA damage response

1. Definition

Sphingolipids are characterized by an amino-alcohol, sphingosine, backbone. They constitute major components of cell membranes. Sphingosine is synthesized in the endoplasmic reticulum from non-sphingolipid precursors [1]. Alterations in this basic structure give rise to different sphingolipid metabolites (sphingomyelin, ceramide (Cer), ceramide-1-phosphate (C1P), sphingosine-1-phosphate (S1P), glycosphingolipids...) that mediate various physiological and pathophysiological processes.

2. Introduction

Sphingolipids constitute a class of ubiquitous lipids that regulate the cell membranes' fluidity and subdomain structure [2][3]. Besides their structural role, research over the past few decades highlighted the importance of sphingolipids in modulating several cellular processes such as proliferation, differentiation, inflammation, senescence, and death [4]. These bioactive molecules mainly include sphingomyelin, ceramide, ceramide-1-phosphate, sphingosine, and sphingosine-1-phosphate. Several studies were conducted to unravel sphingolipids functions, along with the implications of their altered metabolic pathways in several pathological states such as cancer, atherosclerosis, angiogenesis, inflammation, and diabetes [4].

3. Sphingolipids Metabolic Pathway

Ceramide (Cer) is the central metabolite generated within the sphingolipid metabolic pathway through three different pathways. (i) Ceramide de novo synthesis: Palmitoyl-CoA is condensed with serine by the action of serine palmitoyl transferase, followed by a set of reduction and acetylation reactions to generate ceramide; (ii) Sphingomyelin (SM) catabolism: SM is catabolized by sphingomyelinases to generate ceramide; (iii) Salvage pathway: *N*-acylation of fatty acids with a sphingosine backbone produces ceramide through the action of ceramide synthases [5]. The generated pro-apoptotic Cer can be phosphorylated by ceramide kinase into ceramide-1-

phosphate (C1P) in trans-Golgi or plasma membranes. C1P plays an important role in inflammatory responses, cell survival and proliferation [1][4]. Afterwards, C1P can be dephosphorylated by C1P phosphatases or other unspecific lipid phosphate phosphatases (LPP family) [1][6]. Cer is also utilized to generate two major groups of complex glycosphingolipids. Glucosylceramide synthase generates glucosphingolipids by adding glucose as the first residue to Cer at C1 hydroxyl position, whereas galactosylceramide synthase generates galactosphingolipids by adding galactose to Cer [1]. Moreover, Cer can be catabolized by ceramidases into sphingosine which promotes cell cycle arrest and apoptosis. In its turn, sphingosine can be phosphorylated by sphingosine kinases into the pro-survival lipid sphingosine-1-phosphate (S1P) [7]. S1P can be dephosphorylated by S1P phosphatases [8][9] or unspecific LPP [10]. The generated sphingosine can be further used to produce Cer or S1P [9]. S1P lyase (SPL) is considered as the last enzyme in the sphingolipid catabolic pathway because it can irreversibly break down S1P into phosphoethanolamine and hexadecenal [11] (Figure 1).

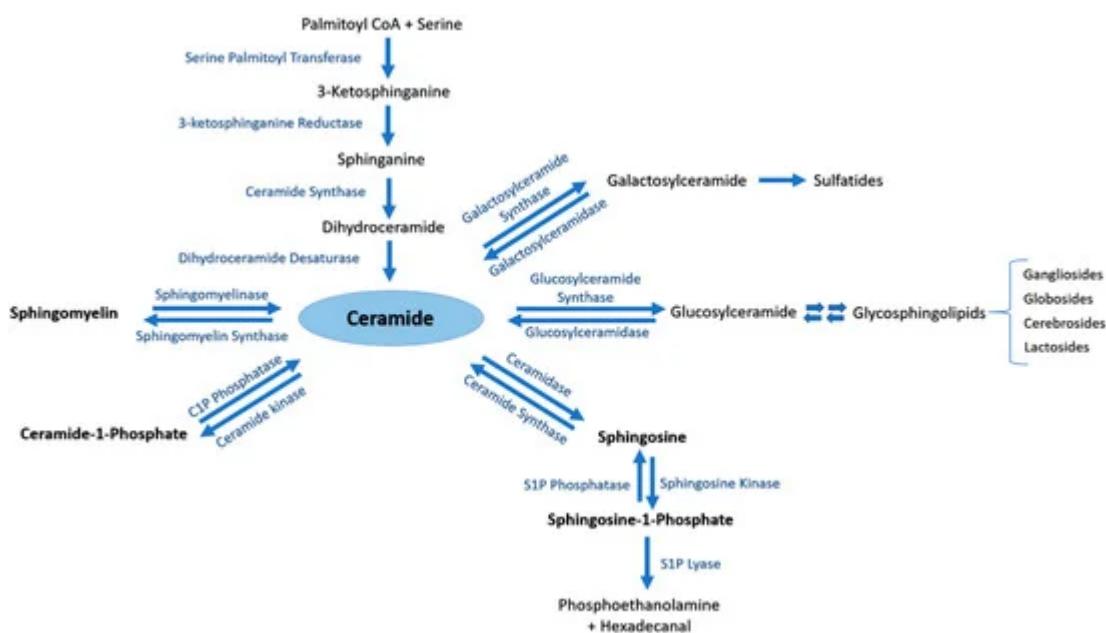


Figure 1. The sphingolipid metabolic pathway. Ceramide is the central metabolite generated in the sphingolipid metabolism by three distinct pathways. Ceramide de novo synthesis consists of Palmitoyl-CoA condensation with serine by the action of serine palmitoyl transferase, followed by a set of reduction and acetylation reactions to generate ceramide. Sphingomyelin (SM) catabolism generates ceramide through the action of sphingomyelinases. The salvage pathway involves N-acylation of fatty acids with a sphingosine backbone to produce ceramide by ceramide synthases. Ceramide can be further phosphorylated to ceramide-1-phosphate (C1P) by ceramide kinase, or converted into complex glycosphingolipids by glucosylceramide or galactosylceramide synthases. Ceramidase is responsible of catabolizing ceramide into sphingosine, which may be further metabolized by sphingosine kinases to generate sphingosine-1-phosphate (S1P).

4. Nuclear Sphingolipids

Many studies have identified sphingolipids as important modulators of key nuclear processes. So far, various subnuclear compartments including the nuclear envelope, nuclear matrix, nucleolus, and chromatin have been

described to host various sphingolipid species [12][13][14][15][16][17][18][19][20]. Although nuclear pores should permit the nucleo-cytoplasmic exchange of sphingolipids, many of these nuclear metabolites are in a dynamic state and undergo turnover. Nuclear localization of sphingolipid metabolizing enzymes has been demonstrated. To this end, the utilization of several analytical, biochemical, and microscopic techniques led to the identification and quantification of various nuclear sphingolipid species along with their metabolizing enzymes [21]. In fact, sphingomyelin (SM) is the dominant nuclear sphingolipid variant [22]. Through its metabolism, SM gives rise to ceramides, sphingosine, and S1P, which in turn give other metabolites (table 1).

Table 1. Nuclear sphingolipid metabolites and metabolizing enzymes. This table recapitulates the various nuclear sphingolipid metabolites and enzymes detected in the nuclear compartment with a brief description of their important nuclear functions. NE: nuclear envelop, dsRNA: double stranded RNA.

Nuclear Sphingolipid Metabolites	Nuclear Sphingolipid Producing Enzymes	Nuclear Sphingolipid Degrading or Converting Enzymes	Main Nuclear Functions
<i>Sphingomyelin</i>	Sphingomyelin synthase	Reverse sphingomyelin synthase Neutral sphingomyelinase	Maintenance of NE and nucleoplasm structure Regulation of NE permeability and Fluidity Stabilization of DNA and dsRNA
<i>Ceramide</i>	Ceramide synthase Ceramide desaturase Neutral sphingomyelinase	Ceramidase Ceramide kinase	Regulation of Cell cycle arrest, Senescence, and Apoptosis
<i>Ceramide-1-phosphate</i>	Ceramide kinase	C1P phosphatase	Regulation of cell growth and survival
<i>Sphingosine</i>	Ceramidase	Ceramide synthase Sphingosine kinase 2	Regulation of gene transcription and apoptosis

<i>Sphingosine-1-phosphate</i>	<i>Sphingosine kinase 2</i>	S1P lyase S1P phosphatase	Epigenetic modulation of gene transcription Regulation of cell cycle progression and apoptosis Stabilization of human telomerase
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5. Role of Sphingolipids in DNA Damage Response

Various chemotherapeutic drugs and DNA damaging agents target sphingolipid metabolizing enzymes. Strong evidence suggests that lipids are involved in DDR and determining cell fate [5]. Most cancer treatments lead to Cer generation which is implicated in cell death response [23]. However, cancer cells tend to develop survival strategies like generating the pro-survival sphingolipid metabolite S1P after the phosphorylation of sphingosine generated by Cer hydrolysis [24]. Hence, the regulation of these metabolites production is of significant importance in determining the cells' fate in response to DNA damage [5].

All non-surgical cancer therapies aim to eradicate tumor cells while sparing normal tissues through complex cell signaling pathways. Research over the past few decades confirmed that the stress induced by these therapies involves the accumulation of ceramide. However, any dysregulation in this process, due to either decreased generation or increased metabolism of ceramide, confers resistance against these therapies [25]. From this perspective, emerging therapeutic and clinical interventions are under investigation to maximize the positive outcomes of these therapies by a combinatorial approach. For instance, as recombinant human acid sphingomyelinase (rhASM) was previously evaluated in patients with Niemann-Pick disease, the idea of its administration in cancer therapies flourishes. rhASM might be used to induce pro-apoptotic ceramide levels beyond the tolerance of cells. This treatment is more likely to affect tumors than normal tissues [26]. Moreover, a recent study reported that gentamicin, a commonly used anti-microbial drug, can potentially play a role in cancer therapies. The administration of gentamicin highly upregulated acid sphingomyelinase and induced apoptosis in human gastric cancer cells [27]. As cancer cells can develop survival strategies like generating the pro-survival S1P, inhibitors for both SK1 and SK2 were developed. However, sphingosine kinase inhibitors exhibited some downstream off-target effects such as inhibiting ERK and Akt pathways [28]. Hence, further studies should address the development of more specific sphingosine kinase targets for possible clinical trials. Interestingly, the total plasma levels of ceramide, measured in early days after the combined treatment of radio-chemotherapy, can

predict tumor responses in patients with liver and lung metastases of colorectal cancer. It allows the identification of patients with high risks of metastases [29]. Therefore, successful discoveries of sphingolipid therapeutic targets and biomarkers will potentially enhance the standard of care therapies by overcoming tumor resistance and developing new effective diagnostic and prognostic sphingolipidomic-based tests.

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