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Spingolipid in Lung Cancer Pathogenesis and Therapy

Erhard Bieberich and Guanghu Wang

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Abstract

Recent genomic research has ranked sphingolipid metabolism as the top dysregulated pathways in lung cancer, demonstrating that these lipids and their metabolic enzymes play key roles in lung cancer pathogenesis. Hence, sphingolipid metabolism has become a forefront in lung cancer research. However, the function of the diverse sphingolipids and their metabolic enzymes and the underlying mechanism in lung cancer are still unclear. In this chapter, we will focus on ceramide and sphingosine-1-phosphate (S1P), the best characterized sphingolipids so far, to summarize the most recent studies and highlight the essential role of sphingolipids in lung cancer pathology, diagnosis, and treatment.

Keywords: lung cancer, NSCLC, sphingolipid, ceramide, sphingosine, sphingosine-1-phosphate (S1P), Spns2

1. Introduction

Lung (pulmonary) cancer is the leading cause of cancer-related death in the United States and worldwide. Its two major types are non-small cell lung cancer (NSCLC) and small-cell lung cancer, among which NSCLC is the most common form accounting for 85–90% of newly diagnosed cases [1, 2]. NSCLC can be further categorized into three major subtypes: large-cell lung cancer, squamous cell carcinoma, and adenocarcinoma.

Most lung cancer is diagnosed at a late stage; thus, chemotherapy is the most common approach for management [3]. However, the effectiveness of conventional chemotherapy for lung cancer has reached its plateau [3]. Multiple genes and signaling pathways have been associated with NSCLC, including the epidermal growth factor receptor (EGFR) family, mitogen-activated protein kinase (MAPK), mesenchymal-epithelial transition factor (c-MET), phosphatidylinositol 3-kinases (PI3K)-Protein Kinase B (PKB/Akt)-mammalian target of rapamycin (mTOR),

and vascular endothelial growth factor (VEGF) pathways [1, 2, 4]. Precision therapies have been designed to use inhibitors of these pathways such as gefitinib for EGFR mutations [5]. However, these drugs work for certain patients/for a while and the patients develop drug resistance, and the tumor develops to more aggressive metastatic cancer [2, 6].

Sphingolipid metabolism is among the pathways that show the highest abundance of dysregulation in lung cancer [7]. Yet the function of sphingolipids and underlying mechanism in lung cancer are still not clear, due in part to a lack of suitable *in vivo* models [8, 9]. Bioactive sphingolipids, including ceramide, ceramide-1-phosphate, sphingosine, and sphingosine-1-phosphate (S1P), regulate a wide range of cell signaling pathways that control cell proliferation, apoptosis, senescence, angiogenesis, and migration, key components of cancer pathology and progression. The roles of sphingolipids in general tumorigenesis have been reviewed extensively, and the readers are encouraged to resort to these resources [10–13]. In this chapter, we will focus on ceramide and S1P to discuss the essential functions of sphingolipids in lung cancer pathology, diagnosis, and treatment. Many enzymes in the sphingolipid metabolism are closely related to lung tumorigenesis. For the ease of discussion, we will first briefly introduce the sphingolipid metabolism pathways.

2. Sphingolipid metabolism

Sphingolipids are acyl derivatives of the amino alcohols sphingosine and dihydro sphingosine. They encompass sphingosine, ceramide, and ceramide derivatives such as ceramide-1-phosphate, S1P, sphingomyelin, and glycosphingolipids (**Figure 1**). These lipids are synthesized

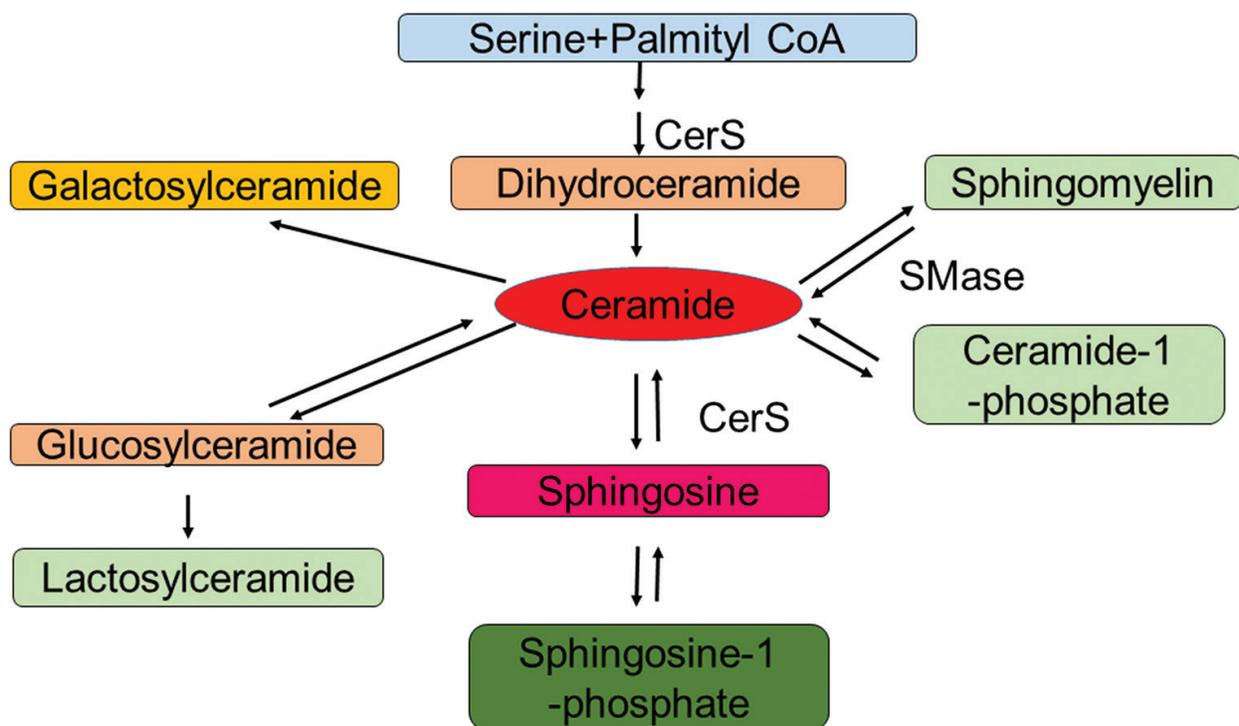


Figure 1. Schematics of ceramide synthesis.

in an interconnected network of enzymes, which is centered on ceramide (**Figure 1**). There are three pathways that produce ceramide, de novo, sphingomyelin cycle, and the salvage pathways [14–16]. In the de novo pathway, ceramide synthesis is initiated by serine palmitoyltransferase which condenses serine and palmitate to form ketosphinganine, followed by reduction of the ketone group to dihydrosphingosine. Dihydrosphingosine is then acylated by ceramide synthase (CerS) to generate dihydroceramides. A desaturation step, which is catalyzed by dihydroceramide desaturase, completes ceramide biosynthesis [14, 16]. In addition, ceramide can be generated by the salvage pathway in which CerS uses sphingosine as an acyl acceptor (**Figure 1**) [14, 16]. In a third pathway, ceramide is generated from sphingomyelin by sphingomyelinase (SMase) (**Figure 1**). The CerS enzymes, which currently encompass six enzymes (CerS1–6, also known as Lass1–6), and neutral SMase2 (nSMase2) are particularly interesting in lung cancer which will be discussed more in detail later. CerS enzymes use different chain lengths of acyl-CoAs and generate ceramide of varying lengths ranging from C14 to C32, while nSmase2 catalyzes sphingomyelin to generate ceramide.

S1P is synthesized intracellularly from sphingosine by the sphingosine kinases SphK1 and SphK2 (**Figure 2**). SphK1 is mainly cytoplasmic and can acutely translocate to the plasma membrane, whereas SphK2 is present predominately in the nucleus but also can be found in the cytoplasm [17]. Once formed, S1P is tightly regulated by three pathways to maintain intracellular homeostasis (**Figure 2**). Firstly, S1P is recycled to ceramide through CerS after dephosphorylation by S1P-specific ER phosphatases, S1P phosphatases 1 (SPP1) and S1P phosphatases 2 (SPP2) [18, 19], or lipid phosphatases. Secondly, S1P can be irreversibly

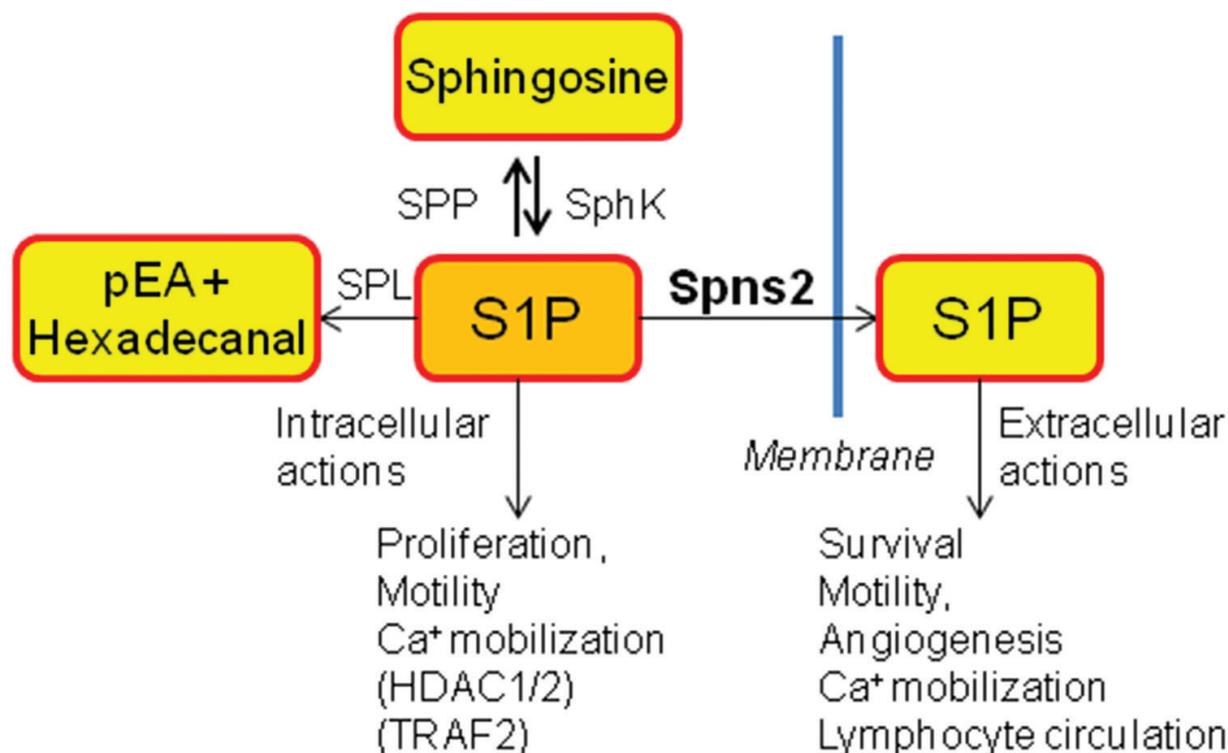


Figure 2. Schematics of S1P metabolism and function.

degraded by S1P lyase (SPL) into phosphoethanolamine (PEA) and hexadecenal [20]. In the third pathway, S1P is released to the extracellular space through transporter proteins, a process that is highly efficient in blood cells and endothelial cells [21, 22]. Several ATP-binding cassette (ABC) transporters are reported to transport S1P in blood cells. However, this notion is still being debated because knockout of the corresponding ABC transporters does not alter serum S1P level. A specific S1P transporter, Spns2, is responsible for S1P secretion in endothelial cells [23–26]. Spns2 gene deficiency in zebrafish and mice leads to significantly reduced extracellular S1P level and impaired egress of lymphocytes and migration of cardiomyocyte precursors [23–25, 27].

3. Ceramide in lung cancer

3.1. Ceramide and related enzymes in lung cancer pathology

Ceramide is generally believed to induce cell death and senescence. However, recent evidence has demonstrated that the roles of ceramide are concentration, cell context, and subcellular localization specific [8, 9, 28–30]. For example, C16 ceramide is shown to favor cancer cell proliferation and promote metastasis in lung cancer patients with CerS6 elevation [28, 29, 31–33]. On the other hand, C18 ceramide mediates cell death [28, 29, 31, 32]. These results emphasize the significance of concentration and cellular context in ceramide-mediated lung cancer cell death.

Most recently, CerS6, the enzyme that catalyzes C16:0 ceramide, was found to be overexpressed in advanced NSCLC patients and inversely correlated with clinical outcome [33]. C16:0 ceramide promotes NSCLC cell migration in vitro through formation of a RAC1-positive lamellipodia/ruffling structure in cells that escape C16 ceramide-induced apoptosis [33]. This notion is supported by data showing that CerS6 knockdown alters the ceramide profile, leading to decreased cell migration/invasion, reduced RAC1-positive lamellipodia formation in vitro, and attenuated lung metastasis in transplanted NSCLC cells in vivo [33].

Ceramide has been linked to cigarette smoking, the number one risk factor for lung cancer [8, 9, 34, 35]. Higher ceramide levels are reported in emphysema patients who are smokers, a subpopulation of patients greatly susceptible to lung cancer [34]. Just like ionizing radiation and chemotherapy drugs, cigarette smoking induces ceramide production which is mediated by nSMase2, an enzyme that hydrolyzes sphingomyelin to ceramide (**Figure 1**) [35]. Further evidence shows that during cigarette smoking, EGFR is favorably co-localized in ceramide-enriched regions of the plasma membrane, suggesting that nSMase2/ceramide plays a role in the aberrant EGFR activation, leading to augmented tumorigenic signaling and drug resistance [36]. Increased ceramide also triggers multidrug-resistant gene expression and synthesis of the pro-survival S1P and cell surface glycosphingolipids Gb3, which provide additional mechanisms for acquired drug resistance [8, 28, 37–39].

3.2. Ceramide as potential lung cancer treatment strategy and monitoring

Ceramide and related signaling is a promising target for lung cancer therapy. Based on the discovery that CerS6 is overexpressed in NSCLC, a combined treatment with

1- α -dimyristoylphosphatidylcholine (DMPC) liposome and the glucosylceramide synthase inhibitor *d*-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-PDMP) is used to induce cell apoptosis [33]. The combined treatment induced cell death in association with C16 ceramide accumulation and promoted cancer cell apoptosis and tumor regression in murine models.

Based on the observation that the C18 ceramide level is reduced and I2PP2A overexpressed in lung tumors, a study took advantage of FTY-720, an US Food and Drug Administration (FDA)-approved multiple sclerosis drug, which is a sphingosine analog of myriocin [40]. FTY-720 mimics C18 ceramide and binds to I2PP2A, leading to PP2A reactivation, lung cancer cell death, and tumor suppression in vivo [41].

To overcome the cisplatin resistance caused by the increased cell surface glycosphingolipid Gb3, the glucosylceramide synthase inhibitor DL-threo-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol (PPMP) has been tested. PPMP treatment substantially sensitizes cells to cisplatin cytotoxicity [39]. These data suggest that therapies targeting glucosylceramide synthase activity or Gb3 receptors may ameliorate acquired cisplatin drug resistance in lung cancer cells.

An additional exciting advance is that ceramide is a potential indicator of positive response after radiation therapy. Early biomarkers of lung tumor response are urgently needed to distinguish between responders and nonresponders to radiotherapy. A recent study shows that the plasma levels of total ceramide and four main subspecies are significantly higher in objective responders than in nonresponders of lung oligometastases [42]. In patients with increased total plasma ceramide levels, almost complete tumor control is achieved after 1 year, whereas the tumors continue to grow in half of the patients with lower ceramide levels [42]. This is intriguing since plasma ceramide is easily measurable and would enable early segregation of nonresponders so that additional more effective treatment options can be applied.

4. S1P and related signaling in lung cancer

Our understanding of the function of S1P and its signaling in lung cancer pathology is rather limited and fragmented when compared to other cancer types. SphK1, a major enzyme that generates S1P, was found to be overexpressed in lung patient samples [43]. The SphK/S1P pathway was shown to mediate the E2-induced transactivation of EGFR, which is associated with carcinogenesis in lung cancer cells [44]. It has also been reported that expression of the oncogenic K-Ras leads to plasma membrane localization of SphK1 and increased S1P level [45].

In a longitudinal study of 100 cases, plasma S1P level was found to be greater in lung cancer patients, implying that the level of extracellular S1P might contribute to the etiology of lung cancer or be a biomarker [46]. On the other hand, intracellular S1P was found to be increased in lung cancer cells going through epithelial mesenchymal transition, suggesting that intracellular S1P contributes to pathological epithelial mesenchymal transition, which is essential for lung cancer metastasis [47].

Consistent with this, knocking down the S1P transporter Spns2 enhanced migration in NSCLC cells partly due to increased intracellular S1P [26]. Pharmacological inhibition of S1P synthesis in Spns2 knockdown cells abolished the augmented cell migration mediated

by Spns2 knockdown, indicating that intracellular S1P plays a key role in migration. Cell signaling studies indicated that Spns2 knockdown increased GSK-3 β and Stat3-mediated pro-migration pathways [26]. More importantly, genetic studies showed that the Spns2 mRNA level was reduced in advanced lung cancer patients as quantified by using a small-scale Quantitative PCR (qPCR) array [26]. These data show that Spns2 plays key roles in regulating S1P homeostasis and the cellular functions in NSCLC cells and that Spns2 downregulation is a potential risk factor for lung cancer metastasis and drug resistance [26].

4.1. Targeting S1P for potential lung cancer therapy

S1P functions to enhance survival, proliferation, and angiogenesis; thus, removal of extracellular S1P and the use of SphK inhibitors to reduce S1P biosynthesis are major approaches for lung cancer therapy targeting S1P [48–50].

To remove S1P, an antibody was developed to physically sequester extracellular S1P. In animal models, the S1P-specific monoclonal antibody reduced lung tumor growth [51]. Sequestering extracellular S1P by using this antibody also attenuates lung metastasis of tumor cells from multiple other organs [50, 52].

Although SphK1 is elevated in lung cancer patients suggesting a potentially important role for this enzyme in lung tumor cell proliferation and survival [43, 53], results with novel, highly potent, and selective inhibitors to SphK1 in tumor cells did not affect their growth in vitro or in vivo, suggesting that tumor SphK1 may not be an efficacious therapeutic target for cancer [54, 55]. Hence, inhibitors of SphK2 are developed and tested for inducing lung cancer cell death, among which ABC294640 is a first-in-class drug [56]. One recent study demonstrates that ABC294640 suppressed growth of primary and A549 human lung cancer cells but sparing SphK2-low lung epithelial cells [56]. Inhibition of SphK2 by ABC294640 increased ceramide and decreased S1P levels, leading to lung cancer cell apoptosis. Another study shows that ABC294640 sensitized NSCLC cells to cell death induced by TNF-related apoptosis-inducing ligand (TRAIL) [56]. Compared with TRAIL alone, the combination therapy enhanced the apoptosis induced by TRAIL, and knockdown of SphK2 by siRNA presented a similar effect [57].

5. Concluding remarks

Exciting advances have been made regarding the roles of ceramide and its signaling in lung cancer in the past few years. Excess ceramide clearly has a critical function in inducing cell death in lung cancer cells, although those that escape this verdict are more prone to metastasis, as one important study shows [33]. Further increasing ceramide levels in these cells using combined drug treatment successfully induced apoptosis and reduced tumor size in vitro and in vivo [33]. This kinetic response opens new avenues to treat lung cancer by using ceramide-based therapies, the efficiency of which depends on the successful fine-tuning of ceramide metabolism, by using ceramide-inducing drugs such as fenretinide, and D-PDMP. Another exciting approach is to use ceramide mimics and short-chain ceramide or to increase the sensitizer proteins of ceramide, such as I2PP2A and Par-4, which are found to be reduced in lung cancer patients [41, 58, 59].

In terms of targeting S1P in lung cancer, aside from the antibody, using SphK2 inhibitors and its combination with SphK1 inhibitors seem to be promising approaches that merit further discovery [60]. In addition, agents such as transporter Spns2 [26] have shed new insights into the biology of S1P signaling. Such mechanistic insights have revealed additional control points for potential lung cancer therapeutic intervention. Even though receptor modulators have become the mainstream of current drug discovery [61], only one drug that targets the SphK/S1P axis (FTY-720, Fingolimod) is approved by FDA. And, the precise function of FTY-720 is very complicated and context/concentration dependent [41].

One important way that lung cancer cells overcome ceramide-induced cell death and senescence is to generate S1P, the pro-survival sphingolipid. Therefore, compounds that prevent S1P conversion from ceramide or further metabolize S1P to other derivatives which potentially sensitize cells to chemotherapy-induced tumor cell death are becoming an important approach for treating patients with lung cancer [62, 63].

In summary, growing evidence suggests that targeting sphingolipid metabolism is essential in improving lung cancer therapy and overcoming drug resistance. Due to the complexity and ubiquity of the sphingolipid metabolism and signaling, it is likely that a combined therapy employing conventional or novel targeted drugs and strategies based on chemical compounds or genetic approaches to modulate ceramide and S1P metabolism can be more beneficial than monotherapy. However, some important caveats should be considered in order to allow the development of more specific drug targets and inhibitors, in particular, the complexity of biological events that involve sphingolipids and the redundancy of the functions of the different enzymes.

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Abbreviations

S1P	Sphingosine-1-phosphate
CerS	Ceramide synthase
SMase	Sphingomyelinase
nSMase2	Neutral sphingomyelinase2
SphK	Sphingosine kinase
SPP1 and SPP2	S1P phosphatases 1 and 2

SPL	S1P lyase
PEA	Phosphoethanolamine
NSCLC	Non-small cell lung cancer
DMPC	Dimyristoylphosphatidylcholine
TRAIL	TNF-related apoptosis-inducing ligand

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