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REVIEW ARTICLE

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New insights into the roles and regulation of SphK2 as a therapeutic target in cancer chemoresistance

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Abstract

Chemoresistance is a complicated process developed by most cancers and accounts for the majority of relapse and metastasis in cancer. The main mechanisms of chemoresistance phenotype include increased expression and/or activated drug efflux pumps, altered DNA repair, altered metabolism of therapeutics as well as impaired apoptotic signaling pathways. Aberrant sphingolipid signaling has also recently received considerable attention in chemoresistance. Sphingolipid metabolites regulate main biological processes such as apoptosis, cell survival, proliferation, and differentiation. Two sphingosine kinases, SphK1 and SphK2, convert sphingosine to sphingosine-1-phosphate, an antiapoptotic bioactive lipid mediator. Numerous evidence has revealed the involvement of activated SphK1 in tumorigenesis and resistance, however, contradictory results have been found for the role of SphK2 in these functions. In some studies, overexpression of SphK2 suppressed cell growth and induced apoptosis. In contrast, some others have shown cell proliferation and tumor promotion effect for SphK2. Our understanding of the role of SphK2 in cancer does not have a sufficient integrity. The main focus of this review will be on the re-evaluation of the role of SphK2 in cell death and chemoresistance in light of our new understanding of molecular targeted therapy. We will also highlight the connections between SphK2 and the DNA damage response. Finally, we will provide our insight into the regulatory mechanisms of SphKs by two main categories, micro and long, noncoding RNAs as the novel players of cancer chemoresistance.

KEYWORDS
apoptosis, chemoresistance, DNA damage, SphK2

1 | INTRODUCTION

Innate and acquired resistances to chemotherapeutic agents are two categories of chemoresistance responsible for failure in cancer treatment and low response rate to therapy (Niederst, Engelman, & Hata, 2018; Yauch, Ye, & Ashkenazi, 2018). Due to the multifactorial nature of chemoresistance, despite much effort to produce novel therapeutic agents, improvement of cancer treatment is still not satisfactory. Numerous mechanisms can illustrate the molecular basis of drug resistance including increased expression of adenosine triphosphate (ATP)-dependent drug efflux pumps, which remove multiple drugs from the cytosol of cancer cells, gradually leading to multidrug resistance (MDR; Krishna & Mayer, 2000; Lage, 2016). Loss or altered p53-dependent apoptotic pathways upon DNA damage (Mogi & Kuwano, 2011), other hampered proapoptotic pathways induced by chemotherapeutic drugs; activation of antiapoptotic signaling pathways, as well as increased level of drug metabolizing enzymes, have been frequently recognized as major causes of resistance (Nonaka et al., 2012; Sineh Sepehr et al., 2014).

In the past two decades, sphingolipid metabolites also have been implicated to play crucial roles in resistance to various therapeutics in many cancer types (Antoon et al., 2011; Ogretmen, 2005). Apart from structural roles, sphingolipids, in particular, three close relative members, ceramide (Cer), sphingosine and sphingosine-1-phosphate (S1P), are considered as critical mediators of survival and cell death and regulate many cellular processes such as autophagy, angiogenesis, migration, differentiation, inflammation, and immune responses (Gao & Smith, 2011; Hannun & Obeid, 2008; Johnson, Becker, Facchinetti, Hannun, & Obeid, 2002; Maceyka, Harikumar, Milstien, & Spiegel, 2012; Neubauer & Pitson, 2013; Spiegel & Milstien, 2003). Two distinct sphingosine kinase isoforms, SphK1 and SphK2, convert the backbone of sphingolipids, sphingosine, a proapoptotic molecule to S1P, a prosurvival lipid mediator, and promote cell growth and cancer progression (Lewis, Voelkel-Johnson, & Smith, 2018; Neubauer & Pitson, 2013; N. J. Pyne et al., 2012; Qin, Kilkus, & Dawson, 2018). SphKs are also involved in cytotoxic drug-induced DNA damage response (DDR) pathway. Therefore, they have been considered as attractive targets for cancer therapy (Hait, Oskeritzian, Paugh, Milstien, & Spiegel, 2006).

Compelling studies have identified the role of SphK1 in cell survival, tumor progression, and resistance to therapeutics-induced apoptosis (Plano, Amin, & Sharma, 2014); however, the role of SphK2 in these processes is not firmly recognized. Previous studies have reported both discrepant, antiapoptotic and proapoptotic effects of this enzyme (Gao & Smith, 2011; Gao, Peterson, Smith, & Smith, 2012; H. Liu et al., 2003; Maceyka et al., 2005; Q. Wang et al., 2014). According to the finding of some studies, overexpression of SphK2 results in the induction of cell cycle arrest or cell death, elucidating a proapoptotic role for SphK2 (Igarashi et al., 2003; H. Liu et al., 2003; Maceyka et al., 2005). In contrast, others demonstrated that targeting SphK2 not only attenuated tumor progression in human tumor xenografts in mice (Chumanevich et al., 2010; Wallington-Beddoe et al., 2014), but also appears to inhibit cell proliferation more effectively than targeting SphK1 in several cancer cell lines (Gao & Smith, 2011; van Brocklyn et al., 2005). The existence of a relationship between the microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), two classes of noncoding RNAs (ncRNAs), and drug resistance have also received great attention in recent years (Askarian-Amiri, Leung, Finlay, & Baguley, 2016). The focus of this review is mainly on the role of SphK2 as a critical drug resistance factor in apoptosis and antiapoptosis signaling pathways and on molecular mechanisms for SphK2 regulation. Finally, the authors provide insight into crosstalk of SphK2 with other molecules that have been recently identified as crucial players of cancer chemoresistance, particularly with two main categories of ncRNAs, miRNA, and lncRNAs.

2 | SPHINGOLIPID SIGNALING

Ceramide, sphingosine, and S1P are considered as critical signaling molecules that regulate many cellular functions. S1P is antiapoptotic and progrowth, whereas its precursors, sphingosine, and ceramide are antiproliferative and proapoptotic (Takabe, Paugh, Milstien, & Spiegel, 2008). Based on the new concept of the rheostat, tumor outcome is determined not only by dynamic balance and interconversion between these two bioactive molecules but also by localized production and secretion of these metabolites as well as their involvement in numerous signaling pathways in the cell (Newton, Lima, Maceyka, & Spiegel, 2015). Ceramide which plays a central role in sphingolipid signaling is derived from sphingomyelin of the membrane by sphingomyelinases and de novo synthesis in response to inflammation and many cell stresses such as chemotherapy (Hannun & Luberto, 2000; Morad & Cabot, 2013; Mullen, Hannun, & Obeid, 2012).

In intestinal cells, insulin signaling is impaired by short-term palmitate or palm oil reservoir via ceramide production. The insulin-dependent protein kinase B (Akt) phosphorylation effects of ceramide in Caco-2/TC7 enterocytes are mediated by protein kinase C (PKC) but not protein phosphatase 2 (Tran et al., 2016). At primary basal cilia, binding of ceramide to Smad7 results in plasma membrane association of transforming growth factor-β receptor 1 and inhibition of its signaling pathway via sonic hedgehog signaling for migration. This role of ceramide shows the importance of ceramide synthase 4 and according to results of that study on ceramide synthases, only CerS4 was involved in cell migration and tumor metastasis (Gencer, Oleinik, Dany, & Ogretmen, 2016). The ceramidase catabolizes ceramide and liberates another bioactive sphingolipid, sphingosine, which is readily converted to S1P by the enzymatic activity of SphKs (Young, Kester, & Wang, 2013). In sharp contrast to ceramide, S1P has important established roles in cell survival, tumor growth, migration and angiogenesis (Spiegel & Milstien, 2011).

Increased phosphorylation of sphingosine upon activation of SphKs by various stressors results in intracellular accumulation of S1P, which acts within the cells as the second messenger or secreted to outside the cell and signal from the extracellular side as a ligand through a family of five S1P-specific G protein-coupled receptors (GPCRs, $S1P_{1-5}$; Alshaker et al., 2012). This process has been termed the "inside-out" signaling by S1P which plays important roles in many diseases such as cancer, atherosclerosis, and autoimmune disorders (Takabe et al., 2008). In a very recent publication, it was suggested that the "sphingolipid rheostat" should be modified to include "inside-out" signaling, because the molecular roles of S1P in the rheostat and the mechanisms by which sphingolipid metabolites are involved in the control of cell fate have become more complex. Furthermore, many additional proteins have been identified to be involved in the regulation of sphingolipid metabolism (Newton et al., 2015). However, a novel role of sphingosine phosphorylation in regulating endocytic membrane trafficking and neurotransmission has been shown to occur by membrane recruitment of SphK1 and its direct interaction with the lipid bilayer (Shen et al., 2014). This novel function of S1P in endosomal signaling is beyond the established role of S1P in "inside-out" signaling and might influence current knowledge on "inside-out" signaling. The intracellular level of S1P is tightly determined by the equivalence between synthesis rate by SphKs and

TABLE 1 Identified intracellular targets of S1P

Name	Abbreviation	Enzyme produced	Roles	References
Tumor necrosis factor receptor-associated factor 2	TRAF2	SphK1	S1P, in response to TNF or interleukin-1, binds to TRAF2, an E3 ubiquitin ligase, and to cellular inhibitor of apoptosis 2 (cIAP2), respectively, and stimulates their lysine-63-linked polyubiquitylation activities binding of S1P to TRAF2 mediates K63 polyubiquitylation of RIP1, resulting in NF-kB activation	Melendez, Carlos-Dias, Gosink, Allen, and Takacs (2000)
Histone deacetylase 1/2	HDAC1/2	SphK2	Binds and inhibits the histone deacetylase (HDAC) 1 and 2 activity at the promoters of genes such as p21 and c-fos results in enhancing transcription of these genes	Neubauer et al. (2016)
Peroxisome proliferator-activated receptor γ	PPARγ	SphK1/SphK2	S1P directly interacts with PPARγ and enhances its ability to form the complex with PPARγ coactivator 1 (PGC1) β thereby increasing expression of PPARγ target genes in endothelial cells. S1P:PPARγ:PGC1β complex may be a useful target to therapeutically manipulate neovascularization.	Pitson (2011)
β-Site amyloid precursor protein (APP) cleaving enzyme-1	BACE1	SphK1/SphK2	S1P binds to the β-site amyloid precursor protein (APP) cleaving enzyme-1 (BACE1), the rate-limiting enzyme for amyloid-β peptide (Aβ) production, increasing its proteolytic activity, which was decreased by inhibition of SphK1/SphK2 or knockdown of SphK1 or SphK2 with opposing effect by overexpression of S1P degrading enzymes.	Xia et al. (2000)
Human telomerase reverse transcriptase	hTERT	SphK2	Binding of S1P to hTERT increases the stability of hTERT and maintains telomere integrity. Inhibition/depletion of SphK2 or mutation of the S1P binding site results in promotion of senescence. Pharmacological inhibition of SphK2 also decreases the tumor growth and expression of wild-type hTERT restores this effect.	S. Pyne et al. (2016)
Prohibitin 2	PHB2	SphK2	S1P in the mitochondria binds with PHB2 and regulates the assembly and function of respiratory complex IV (cytochrome *c* oxidase, COX) in the electron transport chain and mitochondrial respiration. Depletion of SphK2 or PHB2 results in a dysfunction in mitochondrial respiration through cytochrome *c* oxidase.	Heffernan-Stroud and Obeid (2013)

Note. NF-kB: nuclear factor-kB; S1P: sphingosine-1-phosphate; TNF: tumor necrosis factor.

cleavage by S1P lyase, S1P-specific phosphatases, and lipid phosphate phosphatases (Maceyka et al., 2012). S1P is transported out of cells through the ATP-binding cassette transporters, ABCA1 (Sato et al., 2007), ABCC1, ABCG2 (Mitra et al., 2006; Takabe et al., 2010) and a new S1P-specific transporter, identified as Spinster 2 (Spns2; Hisano, Kobayashi, Kawahara, Yamaguchi, & Nishi, 2011; Nagahashi et al., 2013). Recently, several novel intracellular targets for S1P were identified which are differentially regulated by SphK1 and SphK2 depending on S1P localized production (Table 1). SphK1-produced S1P, in response to tumor necrosis factor (TNF), binds to TNF receptor-associated factor 2 (TRAF2) and stimulates its lysine-63-linked polyubiquitylation activity. This binding was shown to be an essential component in the TRAF2-mediated K63 polyubiquitylation of RIP1, which is a key step in activation of nuclear factor-κB (NF-κB; Alvarez et al., 2010). However, in very recent studies TNF-α induced NF-κB activation and signaling was shown to be independent of either SphK1 (Etemadi et al., 2015; Xiong et al., 2013) or SphK2 (Xiong et al., 2013). Clearly, this contradiction needs to be further explored. It has been revealed that S1P directly interacts with the peroxisome proliferator-activated receptor γ and enhances the expression of its target genes in endothelial cells (Parham et al., 2015). S1P also affects the activity of BACE1, the rate-limiting enzyme of amyloid-β peptide production (Takasugi et al., 2011). Human telomerase reverse transcriptase, is another example of an intracellular target of S1P derived from SphK2 (Table 1; Panneer Selvam et al., 2015). Exit from the sphingolipid network is done by S1P lyase in irreversible cleavage of S1P to the 2-hexadecenal and phosphoethanolamine (Young et al., 2013).

3 | SPHINGOSINE KINASES

Human SphK1 and SphK2 are related to a family of lipid kinases conserved in all eukaryotes whose genes are located on chromosomes 17 and 19, respectively (Badalzadeh et al., 2015; Melendez et al., 2000). SphK1 and SphK2 share many common characteristics, however, they exhibit some different features including the number of amino acids (384 and 618 for SphK1 and SphK2, respectively) and subcellular localization.

SphK2 possesses additional amino acids at N-terminal and a central region that are not present in SphK1, which are responsible for additional roles such as regulation of membrane localization

(Evangelisti et al., 2016). For SphK1, three splice variants (a, b, and c) with various amino acid sequences at N-termini have been identified. Two isoforms for SphK2: short (SphK2-S or SphK2a) and long (SphK2-L or SphK2b) isoforms with 618 and 654 amino acids, respectively, have been identified. In comparison with SphK2-S, SphK2-L possesses 36 amino acids sequences extended at the N-terminal (Pitson, 2011). SphK2 in addition to cytosol and plasma membrane is localized predominantly to the nucleus and membrane of internal organelles such as mitochondria and the endoplasmic reticulum (ER). This enzyme can shuttle in and out of the nucleus in conformity with its nuclear localization and export signals (Hait et al., 2009; S. Pyne, Adams, & Pyne, 2016). However, SphK1 has never been shown to be localized in these compartments. SphK1 has been generally known to be a cytosolic enzyme which under various stressors and in response to stimulators, translocates to the plasma membrane (Johnson et al., 2002). These observations indicate that two isoforms of SphK have distinct biological roles. Both SphK1 and SphK2 have been demonstrated to be overexpressed in various types of human cancer and have been documented to be oncogenes that induce neoplastic transformation in vivo (Neubauer et al., 2016; Xia et al., 2000). Although the two SphKs exhibit some redundant and similar functions, they appear to play some separate roles. Where the role of SphK1 in cancer development is well characterized, with high SphK1 expression observed in different types of cancers, the roles of SphK2 and its involvement in cancer are much less understood (Heffernan-Stroud & Obeid, 2013).

4 | SPHINGOSINE KINASE 2 (SPHK2) REGULATION

4.1 | External effectors: SphK2 stimulators

Many stimulators and agonists have been reported to increase the catalytic activity of SphK1 (Pitson, 2011), which subsequently influence subcellular localization of SphK1 from cytosol to plasma membrane where it produces critical signaling molecule S1P. Many of these pathways trigger vast physiological processes in normal cells and pathophysiological responses in disease conditions (Maceyka et al., 2012). In contrast, external stimuli identified to stimulate SphK2 are much less than that of SphK1 and include epidermal growth factor (EGF; Hait et al., 2005), phorbol esters such as phorbol 12-myristate 13-acetate (PMA; Hait, Bellamy, Milstien, Kordula, & Spiegel, 2007) TNF-α (Mastrandrea, Sessanna, & Laychock, 2005), interleukin-1β (IL-1β; Mastrandrea et al., 2005), crosslinking of the immunoglobulin E receptor FcεRI (Olivera et al., 2006), hypoxia-inducible factor 1α signaling-independent hypoxia in A549 lung cancer cell line (Schnitzer, Weigert, Zhou, & Brune, 2009) and in vivo (Wacker, Park, & Gidday, 2009) as well as activated JNK/CREB pathway through direct binding of CREB with the 5′ promoter region of SphK2 in response to serum depletion leading to increased transcription and enzymatic activity of SphK2 in human colon cancer cells (Mizutani et al., 2015). As an important strategy for the regulation of protein function in diverse biologic processes, posttranslational modifications (PTMs) are commonly used by cells and phosphorylation is often the first wave of PTMs under various cellular stimuli. Like SphK1, SphK2 activation can occur via phosphorylation by extracellular signal-regulated kinase 1/2 (ERK1/2) at Ser351 and/or Thr578 on short isoform of SphK2 (SphK2a) and Ser387 and Thr614 on a long variant of SphK2 (SphK2b; Hait et al., 2007).

Phosphorylation at each site exhibits a specific function, for example, phosphorylation by protein kinase D at either Ser419 or Ser421 within the nuclear export signal of SphK2 leads to its nuclear export for modulating subsequent cellular functions such as cell proliferation and survival. Shuttling of this molecule between the cytosol and the nucleus can be facilitated by phosphorylation depending on the regulation of its nuclear localization and export signals (G. Ding et al., 2007). An important result of phosphorylation of SphK2 by PKC following PMA treatment of the cells is activation and local production of S1P in the nucleus and inhibition of histone deacetylase (HDAC) 1/2 followed by enhanced histone acetylation and transcription re-expression of cyclin-dependent kinase inhibitor p21 and cell growth arrest in MCF-7 breast cancer cells. This finding suggests that SphK2 can inhibit cell proliferation and induce cell cycle arrest by its involvement in epigenetic modifications (Hait et al., 2009). Apart from phosphorylation, an alternative way of activation of SphK2 has also been reported by previous studies, which occurs upon the direct interaction with eukaryotic elongation factor 1A (eEF1A), a canonical molecule in polypeptide elongation during protein synthesis (Leclercq, Moretti, Vadas, & Pitson, 2008).

4.2 | SphK2 inhibitors

In addition to regulation by activation, SphK2 can also be regulated by inhibition with various chemical inhibitors and antagonists. Here, studies on SphK2 inhibitors and their application in relation to cell survival, growth and cancer drug resistance in various cancer types are reviewed. As mentioned, S1P is a crucial cell survival mediator and a second messenger in cell proliferation, inhibiting apoptotic pathways and the promoter of cell growth. Therefore, it is not surprising that SphK1 and SphK2, the only enzymes that generate S1P, are often altered in cancer (Spiegel & Milstien, 2000, 2002). SphK null mice, small interfering RNAs (siRNAs) and small molecule inhibitors are the three most-used approaches to further demonstrate the physiologic importance of these enzymes. To date, a number of selective SphK inhibitors with various specificities have been developed (Evangelisti et al., 2016). The earliest SphK inhibitors, including *N*,*N*-dimethyl-D-erythro-sphingosine (DMS), L-threo-dihydrosphingosine (DHS, also known as safingol), and *N*,*N*,*N* trimethylsphingosine were based on competitive inhibition of sphingosine. These first generation inhibitors had low-potency, specificity and selectivity in most cases (Neubauer & Pitson, 2013; Santos & Lynch, 2014). The well-characterized inhibitor in the last decade, SKI-II (also called SKi), is a nonlipid small molecule inhibitor which has been identified by high throughput screening (French et al., 2003). Despite being more described as a SphK1-specific inhibitor,

SKI-II inhibits SphK2 with slightly higher affinity than SphK1 (Ki 7.9 μM for SphK2 vs. 16 μM for SphK1; Gao et al., 2012). During the treatment of several cancer cell lines with SKI-II, the proteasome is activated as a result of SphK1 inhibition by this inhibitor which is followed by induction of degradation of SphK1 (Loveridge et al., 2010). Furthermore, there are some additional off-target effects reported for SKI-II, including inhibition of dihydroceramide desaturase (Cingolani et al., 2014) and enhancement of signaling via the transcription factor Nrf2 (Mercado et al., 2014). ABC294640 is the other nonlipid small molecule inhibitor analog of SKI-II, a first-in-class selective SphK2 inhibitor which was developed from structure–activity relationship studies (French et al., 2010). ABC294640 is the most studied SphK inhibitor in vivo that exhibits antiproliferative and antitumor effects in several cell lines and mice xenografts and is currently used in phase II clinical trials to treat advanced solid tumors (X. Ding et al., 2016). Some off-target effects of ABC294640 have been reported, which include partial inhibition of estrogen receptors in breast cancer cells as well as induction of the proteasomal degradation of SphK1 and dihydroceramide (McNaughton, Pitman, Pitson, Pyne, & Pyne, 2016; Venant et al., 2015), which may be responsible for, at least in part, its anticancer effects in vitro and in vivo (Table 2).

The immunomodulatory prodrug FTY720 that structurally possesses a backbone common in other sphingosine analog inhibitors is phosphorylated by SphK2, but not SphK1, to form FTY720-phosphate (FTY720-p). FTY720 is considered to be competitive; with sphingosine, an inhibitor of SphK1 (White, Alshaker, Cooper, Winkler, & Pchejetski, 2016). Minor modifications in the chemical structure of FTY720 convert it to (R)-FTY720-methyl ether ((R)-FTY720-OMe), and impart selectivity for SphK2 over SphK1 (Lim, Sun, Bittman, Pyne, & Pyne, 2011). The properties of this inhibitor are shown in Table 2. Second generation inhibitors are more drug-like than low potent and nonselective inhibitors, developed earlier. The amidine-based compounds have recently been introduced as SphK inhibitors and the most potent SphKs inhibitors at the time of their discovery (Raje et al., 2012). The trans isomers of a scaffold bearing small quaternary ammonium salts, Trans-12a and 12b, have been synthesized and demonstrated as compounds with low micromolar inhibitory activities to selectively inhibit SphK2 (Table 2; Raje et al., 2012). K145 has recently been shown to be a thiazolidine-based selective SphK2 inhibitor, which acts in a competitive manner with respect to sphingosine and inhibits the phosphorylation of FTY720, a SphK2 selective substrate, which confirms selectivity of inhibition for SphK2 over SphK1 (K. Liu et al., 2013). Continuous efforts to generate more potent and selective SphK2 inhibitors have led to the synthesis of guanidine-based compounds. SLR080811, a scaffold in which a cationic guanidine headgroup was featured instead of the amidine group, was shown to be a selective SphK2 inhibitor, which acts as a competitive inhibitor with sphingosine (Kharel et al., 2012). SLR080811 exhibited a reversed selectivity (about 10-fold) towards SphK2 as compared to 1a, an amidine-based inhibitor based on which SLR080811 was synthesized, and a 10-fold weaker affinity for SphK1 (Table 2; Kharel et al., 2012; Santos & Lynch, 2014). Surprisingly, in vivo characterization of SLR080811 demonstrated that administration of this inhibitor to wild-type mice has led to a rapid increase in S1P plasma concentrations in mice, which is in contrast to findings of those obtained by SphK1 selective inhibition in vivo (Kharel et al., 2012). This surprising finding of the unknown mechanism is reminiscent of works published on the genetics of SphK2 null mice (Olivera et al., 2007; Zemann et al., 2006).

The same group of researchers in understanding actual SphK functions continued their structure–activity relationship studies of guanidine-based SphK inhibitors by the same scaffold but altering a key methylene unit important to switch isoform selectivity. These studies resulted in the synthesis of SLP120701, a compound bearing an oxadiazole ring in the scaffold (Patwardhan et al., 2015). SLP120701 displayed an improved half-life in mice when compared with SLR080811 but had increased blood S1P levels (Congdon et al., 2015).

Subsequent modifications to further understand the in vivo function of SphK2 led to a scaffold that features a naphthalene ring where a benzyltrifluoromethyl "tail" results in the generation of SLC5091592, a selective SphK2 inhibitor over SphK1 with K_i value of 1.02 for SphK2 versus >20 μM for SphK1 (Congdon et al., 2016). This compound seems to be the most potent and selective SphK2 inhibitor, as reported earlier (Table 2). The adenosine analogs to target the ATP-binding site of kinases in the literature, have been used in conventional methods of kinase inhibition, as well. This strategy has been implicated by previous studies as a successful approach (Goldstein, Gray, & Zarrinkar, 2008). A very recent study using template-based modeling of the ATP-binding pocket of SphK1 has reported a first in-class ATP-binding site-directed SphK inhibitor, MP-A08. This small molecule inhibits both SphK1 and SphK2, with a somewhat higher affinity towards SphK2 over SphK1, and K_i value of 6.9 μM for SphK2 and 27 μM for SphK1 (Pitman et al., 2015). MP-A08 blocks proproliferative signaling pathways, induces intrinsic pathway of apoptosis, and reduces tumor growth in mice via induction of tumor cell apoptosis, reduction of tumor S1P as well as inhibiting tumor angiogenesis (Pitman et al., 2015). Unfortunately, current SphK2 inhibitors have moderate potency and selectivity, even though most of them exhibit therapeutic preclinical in vivo efficacy. Compared with SphK1, there are a limited number of SphK2 specific inhibitors described, with K_i values displaying by most of them in the micromolar range (Congdon et al., 2016). We are still far from understanding the structure and function of SphK2 and rational design of SphK2 inhibitors due to the lack of crystal structure of this isoform. Knowledge of the SphK crystal structure may help in the exploration of allosteric sites and generation of improved and specific molecules to modify SphK2 activity (Adams, Pyne, & Pyne, 2016; Hatoum, Haddadi, Lin, Nassif, & McGowan, 2017). To fully exploit the therapeutic potential of targeting SphKs, investigations on the structure–activity relationship of these molecules should be continued to find novel strategies for the efficient discovery of small molecule inhibitors for several disease states including cancer.

TABLE 2 Inhibitory properties of selected SphK2 inhibitors

Inhibitors	Chemical name	*Ki* for SphK1 (μM)	*Ki* for SphK2 (μM)	Inhibitor application in vitro	Inhibitor application in vivo	References
ABC294640	3-(4-Chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-ylmethyl) amide	No inhibition detected up to 100 μM	9.8	Induction of cell death through both autophagy and apoptosis, via decreased S1P levels and increase in ceramide levels	Decreased circulating S1P levels in mice	Zemann et al. (2006); Olivera et al. (2007); Bartel (2004)
(R)-FTY720-OMe)	(2 *R*)-2-Amino-3-(*O*-methyl)-(2-(4′-n-octylphenyl) ethyl)propanol	Lacks activity against SphK1 up to 100 μM	16.5	Inhibits DNA synthesis and induces growth arrest of MCF-7 breast cancer cells, also induces the autophagic death of T-ALL cell lines and inhibits the phosphorylation of c-Myc and Akt in these cells	ND	Liang et al. (2017)
Trans-12a and 12b	[1r,4r]-*N*,N,*N*-trimethyl-4(4-octylphenyl) cyclohexanaminium iodide and [1r,4r]-*N*,*N*-dimethyl-4-(4-octylphenyl)-*N*-propylcyclohexanaminium iodide	60 and 47 for *trans*-12a and *trans*-12b, respectively	8	Reduce the production of FTY720-P, confirming selective inhibition of SphK2, there was no found change in S1P levels in U937 human leukemia cells	ND	Pitman et al. (2015)
K145	3-(2-Amino-ethyl)-5-[3-(4-butoxyl-phenyl)-propylidene]-thiazolidine-2,4-dione	No inhibition up to 10 μM	6.4	Suppresses the S1P levels and exhibits inhibitory effects on the growth of U937 cells, mainly through the inhibition of ERK and Akt signaling pathways and inhibits the phosphorylation of FTY720	Reduces tumor volume in nude mice through both intraperitoneal and oral administration without apparent toxicity	Hatoum et al. (2017)
SLR080811	(*S*)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboximidamide)	12	~1	Decrease in phosphorylation level of exogenously FTY720 in U937 cells	Much more half-life in mice than that of seen for lead compound 1a Rapid increase in S1P plasma concentrations in wild-type mice	White, Alshaker, Cooper, Winkler, and Pchejetski (2016); Adams et al. (2016)
SLP120701	(*S*)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboximidamide hydrochloride	>10	~1	Decreases S1P levels in U937 cells	Increases blood S1P levels, exhibits an improved half-life (about 8 hr) in mice compared with SLR080811	Yousefi et al. (2012); Congdon et al. (2015)
SLC5091592	Placement of a 4-trifluoromethylbenzyl group in SLR080811	>20	1	SLC5091592 displays increased selectivity (>20-fold) toward SphK2 when compared to SLR080811 Molecular docking studies emphasize the role of the tail region of the pocket on SphK selectivity	ND	Cheetham et al. (2013)

(Continues)

TABLE 2 (Continued)

Inhibitors	Chemical name	*Ki* for SphK1 (μM)	*Ki* for SphK2 (μM)	Inhibitor application in vitro	Inhibitor application in vivo	References
MP-A08	4-methyl-N-[2-[[2- [(4-methylphenyl) sulfonylamino] phenyl] iminomethyl] phenyl] benzenesulfonamide	27	6.9	Blocks proproliferative signaling pathways, induces intrinsic pathway of apoptosis	Reduces the growth of human tumor in a mouse xenograft model by inducing tumor cell apoptosis, reduction of tumor S1P as well as inhibiting tumor angiogenesis	Di Leva et al. (2014)

Note. ND: not determined.

4.3 | Internal regulators

4.3.1 | Epigenetic factors (ncRNAs)

The ncRNAs are conserved and endogenous RNA molecules that do not encode a protein, however, this definition does not reflect their emerging important roles and information that they have (Mattick & Makunin, 2006). Based on their differences in size, these RNA molecules are broadly categorized into two small and lncRNA categories (St. Laurent, Wahlestedt, & Kapranov, 2015). Small ncRNAs termed miRNAs: miRNAs are about 22 nucleotides in length and play essential roles in the regulation of gene expression by binding to the 3′-untranslated regions (3′-UTRs) of their target messenger RNA (mRNAs), resulting in inhibition of target genes (Bartel, 2004). MiRNAs are involved in a variety of biological and pathological states such as cancer (Liang et al., 2017). To date, more than 30 miRNAs have been discovered to play important roles in the regulation of lipid metabolism (Yousefi et al., 2012); however, studies investigating the role of miRNAs in regulation of sphingolipid metabolism and corresponding enzymes are few; therefore, the author's attention was turned to obtaining information on involvement of miRNAs in the roles and regulation of lipid kinases such as SphKs associated with induction of apoptosis and chemoresistance in various cancer types (Table 3).

LncRNAs refer to RNAs that have a length greater than 200 nucleotides (nt), which account for the largest class of noncoding transcripts in the human genome [100]. LncRNAs together with other transacting factors such as miRNAs and RNA-binding proteins (RBPs), mediate transcriptional and posttranscriptional regulatory processes and play important roles in the control of gene expression associated with cell cycle regulation, apoptosis, and DNA damage repair (Audic & Hartley, 2004; Cheetham et al., 2013; Di Leva et al., 2014; K. C. Wang & Chang, 2011). lncRNAs may be part of a broad epigenetic regulatory network and induce epigenetic modifications by binding to chromatin-modifying proteins in special chromatin remodeling complexes and recruiting their catalytic activity to specific chromatin sites, altering the chromatin structure and gene expression (Mercer & Mattick, 2013). As mentioned earlier, various external stimulators can potentiate the expression of SphK1 (Pitson, 2011); however, the internal modulators of SphK1 gene expression and molecular mechanisms by which transcription of SphK1 is controlled in response to these stimuli, are largely unclear. Recently, an antisense lncRNA named *Khps1* was reported to enhance SphK1 gene expression by recruiting the histone acetyltransferase p300/CBP to the SphK1 promoter, in an E2F1-dependent manner (Postepska-Igielska et al., 2015). Mechanistically, *Khps1* is tethered to the SphK1 promoter and forms a DNA-RNA triplex structure which in turn ensures binding of transcription factor E2F1 to this complex facilitating E2F1-dependent expression of SphK1; thereby, promoting cell proliferation as well as restriction of E2F1-induced apoptosis (Postepska-Igielska et al., 2015). Highly upregulated in liver cancer (HULC) is another lncRNA that upregulates SphK1 and contributes to the promotion of tumor angiogenesis in liver cancer (Lu et al., 2016). Mechanistically, HULC has been shown to activate

TABLE 3 Selected miRNAs identified to influence SphKs regulation

miRNAs involved	Kinase regulated	Enzyme deregulation status	Cancer model	miRNA deregulation status	miRNA mechanism of action	Effects	References
miR-124	SphK1	Upregulated	Gastric cancer	Downregulated	– Directly targeting 3′-UTR of SphK1 – Induction of CDK inhibitors p21Cip1 and p27Kip1, – Enhancement of the transcriptional activity of FOXO1 and suppression of Akt activity	– Upregulation of miR-124 inhibited proliferation and tumorigenicity of gastric cancer cells both in vitro and in vivo	Tehrani, Karimian, Parsian, Majidinia, and Yousefi (2018)
miR-144–3p	SphK1	Upregulated	Papillary thyroid cancer	Downregulated	miR-144–3p directly targets fibronectin 1 (FN1) at the protein level	– Involving of the miR-144–3p-FN1 pathway in the pro-invasive role of SphK1 in PTC cells	Nowsheen and Yang (2012)
miR-515–5p	SphK1	Upregulated	Breast cancer	Downregulated	– miR-515-5p is transcriptionally repressed by ERα – miR-515-5p downregulation enhances estrogen-dependent SphK1 activity – Modulates cell proliferation by regulating Wnt pathway	– miR-515-5p inhibits proliferation and induces apoptosis – miR-515-5p levels are not altered in ERα-negative breast cancer cells after E2 and tamoxifen treatment – Estradiol (E2) downregulates miR-515-5p, the antiestrogen tamoxifen decreases SphK1	Majidinia et al. (2017)
miR-124	SphK1	Upregulated	Ovarian cancer	Downregulated	miR-124 directly targets SphK1 by binding the 3′-UTR of SphK1 mRNA	– Inhibition of migration and invasion of ovarian cancer cells by miR-124 targeting SphK1, as a promising target for rational cancer therapy	Majidinia and Yousefi (2017)
miR-101	SphK1	Enhanced activity	Colorectal cancer	Downregulated	miR-101 regulates SphK1 mRNA and protein expression	– Induces proapoptotic ceramide production in CRC cells – Increasing in vitro anti-CRC activity of chemoagents (paclitaxel and DOX)	Pan, Li, Lin, and Hung (2016)
miR-125b	SphK1	Upregulated	Bladder cancer	Downregulated	miR-125b directly targeted the 3′-UTR region of SphK1	– Inhibiting proliferation of T24 cells by miR-125b overexpression via targeting SphK1 – Induction of cell arrest at the G1 phase	Carroll, Donaldson, and Obeid (2015)
miR-506	SphK1	Upregulated	Liver cancer	Downregulated	miR-506 targets 3′-UTR of SphK1 and reduces the expression of SphK1 at the mRNA and protein levels	– Repression of the production of S1P in the supernatant of hepatoma cells resulting in the inhibition of tumor angiogenesis by the forced miR-506 expression	Carroll et al. (2015)

(Continues)

TABLE 3 (Continued)

miRNAs involved	Kinase regulated	Enzyme deregulation status	Cancer model	miRNA deregulation status	miRNA mechanism of action	Effects	References
miR-506	SphK1	Upregulated	Pancreatic cancer	Downregulated	miR-506 bounds to the 3′-UTR of SphK1 and reduces the SphK1 protein levels	– Activation of the Akt/NF-κB signaling pathway by SphK1 and affecting miR-506 mediated tumor suppression and enhanced chemosensitivity in pancreatic cancer	Reynolds et al. (2004)
miR-124	SphK1	Upregulated	Osteosarcoma (OS)	Downregulated	miR-124 could directly target SphK1	– Proliferation and invasion regulation of OS cells by miR-124 via SphK1 downregulation and the inhibition of Akt/NF-κB signaling pathway – The role of miR-124 as a possible diagnostic and predictive biomarker	Sathishkumar et al. (2005)
miR-613	SphK2	Upregulated	Papillary thyroid carcinoma	Downregulated	miR-613 blocks SphK2 expression by directly targeting its 3′-UTR	– Regulation of PTC cellular proliferation, migration, invasion and tumor growth by miR-613 through targeting SphK2	Heffernan-Stroud et al. (2012)
miR-338-3p	SphK2	Upregulated	Non-small-cell lung cancer	Downregulated	3′-UTR of SphK2 is a direct target of miR-338-3p	– Overexpression of miR-338-3p inhibits of SphK2 expression – miR-338-3p Serves as a potential target for the treatment of human lung cancer	Taha et al. (2004)
miR-K12-1	SphK2	Upregulated	KSHV-infected endothelial cells	Upregulated	SphK2 activity and SphK2 regulation of miR-K12-1 lead to NF-kB activation	– NF-kB activation by SphK2 in KSHV-infected cells – Pharmacologic blocking of SphK2, including dose-dependent repression of miR-K12–1 – Restoration of miR-K12–1 expression restores NF-kB activation and endothelial cell viability through SphK2 targeting	Reinhardt and Schumacher (2012)

Note. Akt: protein kinase B; CDK: cyclin-dependent kinase; CRC: colorectal cancer; KSHV: Kaposi's sarcoma-associated herpesvirus; mRNA: messenger RNA; miRNA: microRNA; 3′-UTR: 3′-untranslated region.

the promoter of SphK1 in hepatoma cells through sequestering of miR-107, which in turn upregulates transcription factor E2F1 through by targeting mRNA 3′-UTR of E2F1.

E2F1 was shown to be able to bind to E2F1 element in the SphK1 promoter (Lu et al., 2016). HULC promoted tumor angiogenesis through miR-107/E2F1/SphK1 signaling in HCC in vitro and in vivo. Levels of HULC were in accordance with levels of SphK1 and S1P in samples of patients with hepatocellular carcinoma (HCC) and knock-down of SphK1 abrogated HULC-enhanced angiogenesis. These findings provide new insights into the mechanism of regulation of SphK1 expression and tumor angiogenesis (Lu et al., 2016). H19, a maternally expressed lncRNA induced in human fibrotic/cirrhotic liver and bile duct ligated mouse liver was recently shown to play a critical role in the disease progression of cholestasis and to be leading cause of gender disparity of cholestatic liver injury in multidrug resistance 2 gene knockout (Mdr2$^{-/-}$) mice, a well-established model of cholestatic cholangiopathies (Li et al., 2017). Both bile acid taurocholate (TCA) and estrogen (17β-estradiol) via upregulation of S1P receptor 2 (S1PR2) and estrogen receptor alpha (ERα), respectively, activated significantly, the ERK1/2 signaling pathway and induced H19 expression mainly in cholangiocytes, but not hepatocytes. S1PR2-dependent activation of ERK1/2 subsequently increased protein level of SphK2 in female Mdr2$^{-/-}$ mice, which was blocked by short hairpin RNA-mediated H19 knocking down in cholangiocytes (Li et al., 2017). To the best of the author' knowledge, this is the first evidence of regulation of SphK2 by a lncRNA with a gap in knowledge on the mechanism by which H19 regulates SphK2 expression.

4.3.2 | Transcription factors

In a recent study, the regulatory mechanism of SphK2 expression and its involvement in the control of cell fate under various cellular stresses in human colon cancer cell lines was analyzed. Among the various cellular stresses tested, serum deprivation enhanced mRNA, protein, and activity of SphK2 but not SphK1. The rapid and transient activation of c-Jun N-terminal kinase followed by activation of CREB and direct binding as a candidate transcription factor to the CREB binding site of 5′ SphK2 promoter region was the major regulator of increased SphK2 transcription. Importantly, the role of SphK2 in serum-deprived cells was prosurvival but not cell cycle inhibitor or proapoptotic (Mizutani et al., 2015; Figure 1). To date, the exact mechanism of SphK2 transcription and possible involved transcription factors has not yet been reported. To the best of the author's knowledge, this is the first report describing the regulation of SphK2 expression via direct binding of a transcription factor to its promoter and modulation of its transcription.

5 | ROLE OF SPHK2 IN DNA DAMAGE RESPONSE AND CELL CYCLE

The DDR, a complex network of interconnected signaling pathways, is evoked in response to various stressors including chemotherapeutic agents and ionizing radiation. The ultimate goal of DDR is to preserve genomic integrity through different routes including cell cycle checkpoint activation, DNA repair and in a severe damage, initiation of apoptosis (Karimaian et al., 2017; Majidinia & Yousefi, 2017; Majidinia et al., 2017; Nowsheen & Yang, 2012; Su, 2006; Tehrani, Karimian, Parsian, Majidinia, & Yousefi, 2018). Disturbance of DDR may lead to a number of important pathological diseases such as cancer and defects in the DNA repair account for one of the main mechanisms by which human cancer cells develop chemoresistance (Carroll, Donaldson, & Obeid, 2015; Pan, Li, Lin, & Hung, 2016).

Recently, ceramides, sphingosine, and S1P were shown to be critical regulators of the physiological response of the cell to DNA damage (Carroll et al., 2015). It has been widely accepted that ceramide increases in response to many cancer therapeutics or upon exposure of cells to radiation, and is also accumulated in the serum of irradiated patients due to catabolism of sphingomyelin, increased de novo synthesis or both, leading to interaction with multiple signaling

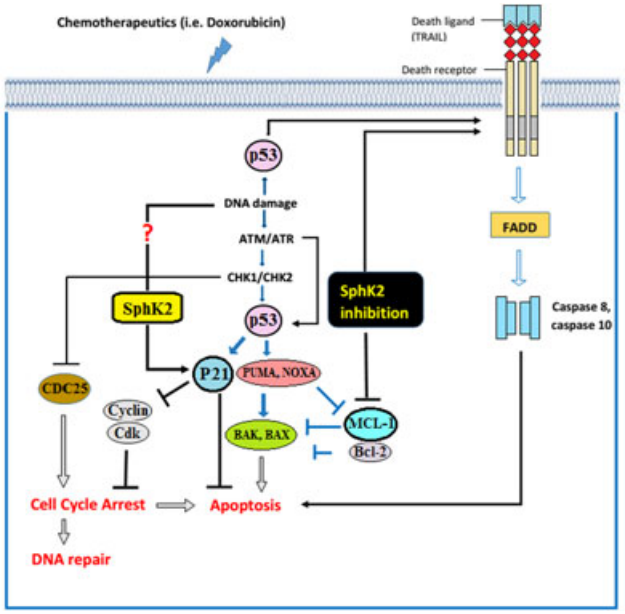

FIGURE 1 Role of SphK2 in the DNA damage response. DNA damage induces activation of ATM and ATR, leading to activation of CHK1 and CHK2 which in turn activate p53. CHK1 and CHK2 can signal through the inhibition of CDC25 to cause cell cycle arrest. Activated p53 signals an apoptotic pathway through PUMA/NOXA and BAK/BAX resulting in apoptosis. P53 also signals through p21, cyclin-CDK to cause cell cycle arrest. SphK2 can involve in p53-independent induction of p21 and cell cycle arrest by chemotherapeutics (i.e., DOX) leading to protection against apoptosis. Downregulation of SphK2 inhibits MCL-1 and leads to induction of apoptosis. Inhibition of SphK2 can also induce transcriptional upregulation and translocation of TRAIL death receptors, such as death receptor 4 and 5 (DR4 and DR5), to the plasma membrane through p53-independent mechanisms, linking intrinsic apoptotic pathway to extrinsic pathway and the decreasing threshold of apoptosis. DNA damage via both p53-dependent and p53-independent mechanisms can induce transcriptional upregulation of death receptors. CDK: cyclin-dependent kinase; MCL-1: myeloid cell leukemia-1 [Color figure can be viewed at wileyonlinelibrary.com]

pathways and in the final step, programmed cell death (Reynolds et al., 2004; Sathishkumar et al., 2005). Where sphingosine similar to ceramides induces cell growth arrest and apoptosis after DNA damage, S1P effectively promotes cell proliferation and survival (N. J. Pyne et al., 2012; S. Pyne et al., 2016). By phosphorylating sphingosine, the product of ceramide hydrolysis, SphKs was linked to DNA damage (Carroll et al., 2015). The regulation of SphK1 in response to DNA damage has been extensively elucidated. SphK1 is an essential downstream target of p53 in response to DNA damage and the inhibition of SphK1 is a necessary step in the p53-mediated induction of apoptosis (Heffernan-Stroud et al., 2012; Taha et al., 2004). Despite the fact that both enzymes catalyze the same reaction, most studies that utilized overexpression systems to examine SphK2 function in apoptosis and cancer chemoresistance found an opposite role for SphK1, which can promote cell cycle arrest and apoptosis (Igarashi et al., 2003; H. Liu et al., 2003; Maceyka et al., 2005). Although all the signaling pathways triggered by DNA double-strand breaks converge on the tumor suppressor p53 (Reinhardt & Schumacher, 2012), DNA damage can increase the expression of some death receptors, including FAS and death receptor 5 (DR5), via both p53-dependent and -independent mechanisms, leading to enhancement of cellular sensitivity to death-receptor ligands (Ashkenazi, 2002). Recently, Yang et al. (2015) showed that targeting SphK2 upregulated DR4 and DR5, and promoted translocation of these receptors from the cytoplasm to plasma membrane followed by enhancement of the sensitivity to tumor necrosis factor-related apoptosis inducing ligand (TRAIL) in NSCLC.

In another study by Sankala et al. it was demonstrated that endogenous SphK2 in response to doxorubicin (DOX) in a p53-independent manner induces p21 expression in MCF-7 breast cancer cells and showed that SphK2 knockdown reduces basal and DOX-induced p21 expression and G2/M cell cycle arrest in MCF-7 cells. Downregulation of SphK2 also markedly enhanced apoptosis induced by DOX. SphK2 was shown to be a regulator of balance between cytostasis and apoptosis of cancer cells (Sankala et al., 2007; Figure 1). Other studies also showed the involvement of SphK2 in the intrinsic pathway of apoptosis through an effect on components of this pathway. Downregulation of SphK2 by ABC294640 directed MCL-1 for proteasome degradation, enhanced expression of Noxa, a proapoptotic protein, and suppressed the growth of multiple myeloma cells in a mouse xenograft cancer model (Kummetha Venkata et al., 2014). These findings indicate that SphK2 by exhibiting the ability to link intrinsic and death receptor-mediated pathway of apoptosis can amplify the response of the cancer cells to various stimuli and this can be useful in increasing chemosensitivity in some cell types in which commitment to apoptosis needs augmentation of the death-receptor signal by the intrinsic pathway (Ashkenazi, 2002). SphK2 can also participate in cellular stress by localization in the ER in response to serum starvation. S1P produced at this site can promote a sphingosine salvage pathway of mammalian cells that finally leads to the production of ceramide by ER-localized S1P phosphatase and ceramide synthase (Maceyka et al., 2005; Figure 1).

TABLE 4 Discrepant roles of SphK2 in resistance to apoptosis (extrinsic pathway)

Types of modulation	Agent used	Cancer model/ cell line	Enzyme mechanism of action	Effects of modulation	References
Knockdown (siRNA), inhibition (ABC294640)	TRAIL	Lung cancer	– Negative regulation of the expression of death receptors (DR4 and DR5) – Negative regulation of translocation of death receptors from the cytoplasm to the cell membrane	– Enhances the sensitivity of TRAIL – Enhances apoptosis induced by TRAIL in resistant cells – Upregulates the expression of death receptors – Promotes the translocation of death receptors from cytoplasm to cell membrane	Nicholas, Rowsey, Priyadarsini, Mandal, and Karamichos (2017)
SiRNA-mediated knockdown	TNF-α	HEK293 cells	– Inhibition of DNA synthesis – Serum deprivation or drug resulted in the translocation of SphK2 into the nuclei	– Prevents serum deprivation or drug-induced apoptosis	Okada et al. (2005)
siRNA-mediated knockdown	TNF-α or ActD	Mouse embryonic fibroblasts	– Mediating BID induced BAK activation – The mitochondrial localization-dependent promoting MOMP and Cyt *c* release	– Resistance to apoptosis	Chipuk et al. (2012)

Note. ActD, actinomycin D; Cyt *c*, cytochrome *c*; MOMP, mitochondrial outer-membrane permeabilization; siRNA: small interfering RNA; TRAIL: tumor necrosis factor-related apoptosis inducing ligand; TNF-α: tumor necrosis factor α.

TABLE 5 Role of SphK2 in resistance to apoptosis (intrinsic pathway)

Type of SphK2 modulation	Drug/agent used	Cancer type	Enzyme mechanism of action	Effects of modulation	References
Inhibition	Gemcitabine	Pancreatic cancer cells	– Negative expression of ribonucleotide reductase (RRM2) and c-Myc thereby influencing phosphorylation of Rb – Role in E2F and c-Myc mediated transcription through alteration of histone acetylation and p21 expression	– Synergistic cytotoxic effect (of ABC294640) with gemcitabine	Lewis, Voelkel-Johnson, and Smith (2016)
siRNA-mediated knockdown	Doxorubicin	Breast and colon cancer cells	Increase in basal and doxorubicin-induced p21 expression without affecting p53 expression	– -Decreased G2-M arrest, enhanced apoptosis	Sankala et al. (2007)
siRNA-mediated knockdown	Gefitinib	NSCLC	Unknown mechanism	– Decreasing chemoresistance in vitro, – Inhibition of disease progression and improving the survival rate of NSCLC patients	W. Liu et al. (2016)
Downregulation (siRNA)	Sodium butyrate	Colon cancer cells	– NaBT-induced cytoplasmic localization of SphK2 – ERK regulates the export of SphK2 and apoptosis of HCT116 cells by modulating PKD – NaBt induces apoptosis via mitochondrial pathways not involving TNF-α	– Downregulation of SphK2 facilitated sodium butyrate-induced apoptosis and decreased the resistance of cells to NaBT-induced apoptosis – PKD-mediated cytoplasmic accumulation of SphK2 results in inhibition of apoptosis	Xiao, Liu, and Zou (2012); Xiao, Liu, Zou, and Zou (2014); Wang, Luo, and Xia (2009)
Inhibition	Doxorubicin, etoposide	MCF-7TN-R and MDA-MB-231 cells	Targeting NF-kB signaling pathway through decreased activation of the ser536 phosphorylation site on the p65 subunit	– Inducing intrinsic apoptosis pathway – enhancement of efficacy of drugs used – decreasing tumor growth in chemoresistant breast cancer in vivo	Nonaka et al. (2012)
Inhibition	Sorafenib	Cholangiocarcinoma	– STAT3 phosphorylation	– Inhibition of cell proliferation and clonogenicity – induction of apoptosis – induction of autophagy	Olivera et al. (2007)
Enhanced activity by hypoxia	Etoposide	A549 lung cancer cells	Promotion of synthesis and release of S1P which binds to S1P1/S1P3 receptors and activates p42/44 mitogen-activated protein kinase	– Protection of A549 cells from etoposide-induced cell death. – Knockdown of SphK2 relieved chemoresistance	French et al. (2003)
Inhibition, siRNA-mediated knockdown	Oxaliplatin (l-OHP)	Colon (RKO and HCT116) cancer cells	– By controlling ceramide formation – By a decrease in phosphorylated Akt levels in resistant RKO cells	– Suppressed cell viability – Increased caspase activity	Nemoto et al. (2009)
Inhibition	Paclitaxel	Ovarian cancer cells	– Potentiation of bcl-2-associated X-protein and caspase-9 transcription levels when using inhibitor alone – Activation of caspase-9 as in combination with chemotherapeutic	– Inhibition of clonogenic survival and cell viability – Increase apoptotic cell death	White, Chan, Antoon, and Beckman (2013)

(Continues)

TABLE 5 (Continued)

Type of SphK2 modulation	Drug/agent used	Cancer type	Enzyme mechanism of action	Effects of modulation	References
Inhibition/silencing	Temozolomide	Glioblastoma cells and primary culture of human glioblastoma	The constitutive and efficient release of S1P into the extracellular milieu in glioblastoma stem-like cells (GSCs)	– Decreases the proliferation rate of glioblastoma cells and prevents their entry into the cell cycle – Restores the sensitivity of glioma stem cells to temozolomide	H. Liu et al. (2003); Riccitelli et al. (2013); Zhang et al. (2012)

Note. NF-kB: nuclear factor-kB; NSCLC: non-small cell lung cancer; PKD: Polycystic kidney disease; S1P: sphingosine-1-phosphate; STAT3: signal transducer and activator of transcription 3; TNF-α: tumor necrosis factor α.

The involvement of SphKs has also shown in some intracellular functions of insulin-like growth factor (IGF) binding proteins (IGFBPs) such as regulation of cell growth, survival, and DNA damage repair (Granata et al., 2004). In addition to their endocrine role in IGF transport, the six members of the IGFBP family have many actions within the nucleus, including induction of apoptosis and DNA damage repair which are, indicative of their involvement in tumor progression and chemoresistance. In endothelial cells, SphK activation can be potentiated by stimulatory effects of IGFBP-3 on this enzyme which in turn results in S1P production and signaling through IGF1R, EGFR and potentially, other tyrosine kinase receptors. S1P can act within the cells as the second messenger or transactivate a number of growth factor receptors, at least partly, via a mechanism so-called "criss-cross" also known as "inside-out" signaling, which was discussed earlier (Baxter, 2014; Chua et al., 2015). Furthermore, inhibiting SphK1 and SphK2 by DMS hampers the protective effect of IGFBP-5 against ceramide-induced cell death (Baxter, 2014; McCaig et al., 2002). The above-mentioned studies have only just begun to show that SphKs regulate and are regulated in response to various cell stresses such as DNA damage. Although the effects of SphK2, either alone or in combination with chemotherapeutics on the DDR has been shown over the past two decades, none of them has shown upstream and downstream components of DDR affected by this isoform (Carroll et al., 2015). There is only one exception in this regard, as mentioned earlier, the study that demonstrated that SphK2 is involved in the induction of p21 by DOX, which is p53-independent (Sankala et al., 2007). Interestingly, SphK2 in combination with other therapeutics other than DOX (i.e. TRAIL) also acts as p53 independently (Yang et al., 2015). To further explore the function of SphK2 in the DDR, more studies are required.

6 | DEVELOPMENT OF RESISTANCE BY SPHK2 VIA ABERRANT REGULATION OF APOPTOSIS

In initial publications, a proapoptotic role was considered for SphK2 both in studies that utilized overexpression systems and others that showed the same role for endogenous SphK2 (Igarashi et al., 2003; Maceyka et al., 2005; Okada et al., 2005). Nevertheless, there is now an emerging body of evidence indicating that SphK2, similar to SphK1, mediates oncogenesis and plays a role in promoting survival and proliferation (Neubauer et al., 2016; Ogretmen, 2005), and also accounts for greater anticancer effect than SphK1. Downregulation of SphK2 with siRNA inhibited proliferation of glioblastoma cells more potently than that observed for SphK1 knockdown (van Brocklyn et al., 2005), suggesting that SphK2 is a more viable candidate for chemotherapeutic targeting. Based on previous studies, SphK2 has the differential ability to be involved in either extrinsic or intrinsic pathway of apoptosis, depending on the type of cell line studied, presence or absence of serum, growth factors and glucose, the type of chemotherapeutic/agent used, as well as other stressors such as hypoxia (Kreitzburg et al., 2018; Mizutani et al., 2015; Okada et al., 2005).

6.1 | Extrinsic pathway

The "extrinsic pathway" of apoptosis is generally engaged by death receptors including CD95, TNFR1, DR4, and DR5 and two nonfunctional decoy receptors, DcR1 and DcR2 (Ashkenazi, 2002; Giussani, Tringali, Riboni, Viani, & Venerando 2014; Yousefi et al., 2015). Apo2 ligand also called TRAIL, which binds to DR4 and DR5, exhibits a selective toxicity against cancer cells and a low toxicity towards normal cells; therefore, it is not surprising for it to be an attractive anticancer agent in cancer research area (Leili, Nasser, Nadereh, Siavoush, & Pouran, 2018). In a recent study, induction of apoptosis by SphK2 inhibition and its connection with TRAIL efficacy in two groups of NSCLC cells, resistant (A549 and H1299) and sensitive (H460) cells to TRAIL cytotoxicity, were shown with high expression of SphK2 in resistant cancer cells. TRAIL in

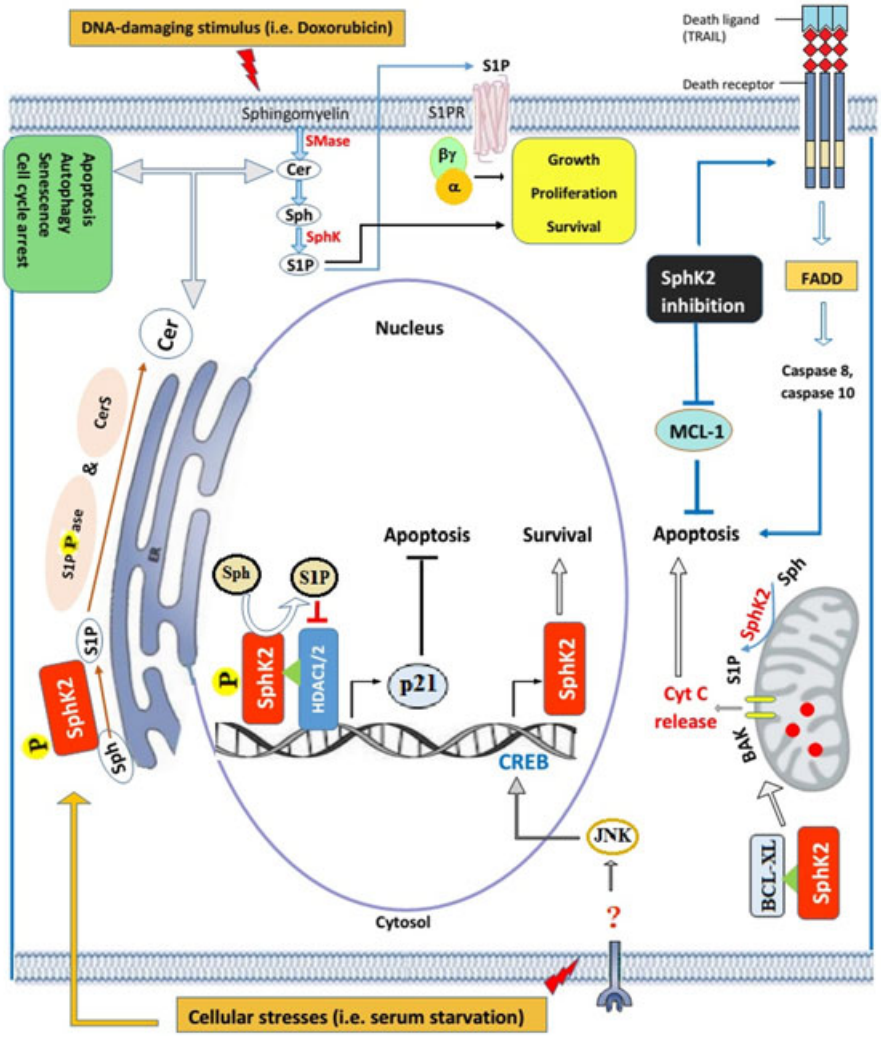

FIGURE 2 Proposed scheme for the role of SphK2 in exhibiting the dual antiapoptotic and proapoptotic effects in response to cell stresses. Chemotherapeutic drugs can induce ceramide production through the activity of acid sphingomyelinase. The ceramide production may lead to cell cycle arrest, autophagy and cell death, however, some cancer cells convert ceramide to sphingosine and activate sphingosine kinases including SphK2 to produce S1P, which can act within the cells as second messenger or secrete to outside of the cell and signal from extracellular side as a ligand through S1P-specific GPCRs resulting in survival and proliferation. SphK2 can also act as a proapoptotic protein when localized to the endoplasmic reticulum, through producing S1P which is channeled into the biosynthesis of proapoptotic ceramide. At the mitochondria, SphK2-derived S1P has been reported to activate and cooperate with the mitochondrial protein, BAK, to promote mitochondrial outer membrane potential and cytochrome c release leading to cytochrome c release and apoptosis. SphK2 due to possessing a BH3 domain can sequester and inhibit the prosurvival Bcl-2 family member, Bcl-xL, which results in apoptosis. In response to serum starvation, SphK2 transcription can be increased via rapid and transient JNK activation followed by CREB activation. The direct binding of activated CREB as a candidate transcription factor to the CREB binding site of 5′ SphK2 promoter region, results in enhancement of both nuclear and cytoplasmic SphK2 activity. The role of SphK2 in serum-depleted cells is prosurvival but not cell cycle inhibitor or proapoptotic. The nuclear localization and activation of the SphK2 can induce cell cycle arrest and protect apoptosis by its involvement in the induction of p21 as a result of HDAC1/2 inhibition by localized SphK2-derived S1P. Downregulation of SphK2 can inhibit MCL-1 and induce upregulation and translocation of TRAIL death receptors, DR4 and DR5, to the plasma membrane, linking intrinsic and extrinsic apoptotic pathways. CREB: cAMP response element binding protein; GPCRs: G-protein-coupled receptors; HDAC: histone deacetylase; JNK: c-Jun N-terminal kinase; MCL-1: myeloid cell leukemia 1; TRIAL: tumor necrosis factor-related apoptosis inducing ligand [Color figure can be viewed at wileyonlinelibrary.com]

combination with SphK2 inhibitor, ABC294640, reduced proliferation and survival of A549 and H1299 cancer cells (Yang et al., 2015). Our recent study also showed similar results, in which ABC294640 enhances doxorubicin-induced apoptosis of NSCLC cells via altering Survivin expression (Leili et al., 2018). Knockdown of endogenous SphK2 in HEK293 cells or mouse embryonic fibroblasts prevents the induction of apoptosis by TNF-α , as well (Chipuk et al., 2012; Okada et al., 2005; Table 4). There are few studies on the involvement of SphK2 in drug-induced mitochondria-independent apoptosis in human cancer. Knowledge of Sphk2 in drug resistance is still poorly understood; therefore, further investigation of the role of SphK2 in altering apoptotic threshold of cancer cells to specific therapeutics is required.

6.2 | Intrinsic pathway

Another pathway that controls apoptosis is an intrinsic pathway, a mitochondrial-initiated event, which involves a number of non-receptor-dependent stimuli including radiation, chemotherapeutics, hypoxia, and free radicals (Elmore, 2007). The final goal of both extrinsic and intrinsic pathways involves caspases and lead to apoptotic cell death (Giussani et al., 2014). Targeting SphK2 can restore sensitivity to chemotherapeutics through the intrinsic pathway of apoptosis and could be a useful approach for resensitization of tumors to standard therapy. As shown in Table 5, SphK2 can counteract the final goal of therapy in favor of cell survival and also show an opposite role for SphK2 in cancer chemoresistance in some instances.

7 | THE INTERPLAY OF SPHK2 WITH SIGNALING PATHWAYS INVOLVED IN DRUG RESISTANCE

The interactions of Sphk1 and the signaling pathways often activated in malignancies have been previously explored in cancer cells (Song et al., 2011); however, there are few studies on the role of Sphk2 in these signaling pathways. As the phosphorylation and activation of Sphk2 are achieved by ERK1/2, it can be placed downstream of all signaling cascades that activate ERK1/2 pathways such as Ras, B-Raf, and MEK1/2 (Hait et al., 2007; Saliani et al., 2013).

The discrepant roles of this less-known isoform, when compared with its counterpart (SphK1) in the cell cycle, survival and apoptotic cell death is illustrated in a figure (Figure 2) to further show how SphK2 participates in these processes under various cell stressors and different conditions. SphK2 has been shown to play a role in the regulation of signaling pathway of IL-12, an immunoregulatory cytokine that promotes T helper 1 (Th1) differentiation. It was identified that mouse SphK2 is associated with the cytoplasmic region of receptor β1 of IL-12 and transient expression of wild-type SphK2 potentiates IL-12-induced STAT4-mediated transcriptional activation in T-cell hybridoma. In Th1 cell clone, ectopic expression of dominant-negative SphK2 reduced IL-12 induced production of IFN-γ, while that of wild-type SphK2 enhanced it (Yoshimoto et al., 2003). It has been shown that Sphk2 inhibition can attenuate the NF-κB survival signaling and blockade of both viability and survival in the endocrine therapy-resistant MDA-MB-231 and chemoresistant MCF-7TN-R as well as induction of the intrinsic pathway of apoptosis (Antoon et al., 2011). A very recent study has unraveled the interplay of sphingolipids and transforming growth factor-β (TGF-β) signaling in the human corneal fibroblasts (HCFs). Exogenous S1P in HCFs reduced cellular migration and downregulated SphK1, SphK2, and S1PR3. In contrast to high dose, low dose of S1P upregulated both TGF-β1 and TGF-β3. It was suggested that sphingolipids cross-talk with TGF-β signaling pathway in human cornea exhibit different functions based on the cell type (Nicholas, Rowsey, Priyadarsini, Mandal, and Karamichos, 2017).

8 | CONCLUDING REMARKS

There are contradictory results regarding the role of SphK2 in cell death and cancer progression. SphK2 is present in several subcellular compartments. Spatial and temporal changes in SphK2 subcellular localization render this enzyme the ability to switch between proapoptotic and prosurvival under specific states of the cell. It is still unclear whether selective inhibition of SphK2 is beneficial or detrimental; therefore, there is difficulty in targeting SphK2 in "rheostat" modulation therapies. SphK2 exhibits some nonoverlapping functions with SphK1 and there is lack of crystal structure of SphK2 to develop specific ligands to allosteric sites to modulate SphK2 activity and show the exact molecular mechanism of this protein in cell fate. Hence, rational design of potent and selective SphK2 inhibitors is necessary so that, the results obtained from their application can reflect the direct result of modulating enzyme activity. On the contrary, in the literature, there is a scarcity of dedicated studies on the role of SphK/S1P in epigenetic regulation such as DNA methylation, chromatin modification, and ncRNAs. The connection points between sphingolipid metabolism and epigenetic factors are just emerging either in physiological or pathophysiological states such as cancer. So, it would be of great interest to further explore the regulation of expression of genes associated with drug resistance such as SphK2, under the influence of epigenetic events.

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CONFLICTS OF INTEREST

The authors declared that there are no conflicts of interest.

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