HHS Public Access

Author manuscript

Adv Cancer Res. Author manuscript; available in PMC 2017 June 29.

Published in final edited form as:

Adv Cancer Res. 2013 ; 117: 201–235. doi:10.1016/B978-0-12-394274-6.00007-8.

Sphingosine Kinase 1 in Cancer

Linda A. Heffernan-Stroud[*,†,1] and **Lina M. Obeid**[*,‡,2,3]

[*]Molecular and Cellular Biology and Pathobiology Program, Medical University of South Carolina, Charleston, South Carolina, USA

[†]College of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

[‡]Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

Abstract

The role of sphingolipids as bioactive signaling molecules that can regulate cell fate decisions puts them at center stage for cancer treatment and prevention. While ceramide and sphingosine have been established as antigrowth molecules, sphingosine-1-phosphate (S1P) offers a progrowth message to cells. The enzymes responsible for maintaining the balance between these “stop” or “go” signals are the sphingosine kinases (SK), SK1 and SK2. While the relative contribution of SK2 is still being elucidated and may involve an intranuclear role, a substantial amount of evidence suggests that regulation of sphingolipid levels by SK1 is an important component of carcinogenesis. Here, we review the literature regarding the role of SK1 as an oncogene that can function to enhance cancer cell viability and promote tumor growth and metastasis; highlighting the importance of developing specific SK1 inhibitors to supplement current cancer therapies.

1. INTRODUCTION

While sphingolipids, along with cholesterol and other phospholipids, serve as critical structural components of cell membranes, their most interesting functions involve their roles as bioactive signaling molecules. Although there is still much to be elucidated about specific mechanisms involved in sphingolipid signal transduction, some themes have emerged. Ceramide is known to be involved in apoptosis, cell senescence, differentiation, and cell stress (Hannun and Luberto, 2000; Mathias et al., 1998; Perry and Hannun, 1998). Sphingosine has also been revealed as an antigrowth signaling molecule (Taha et al., 2006b). In contrast, however, sphingosine-1-phosphate (S1P) is known to promote proliferation, survival, and inhibition of apoptosis (Spiegel and Milstien, 2003) as well as having roles in cell migration, vascular development, and inflammation (Hla, 2004). Sphingosine kinase (SK) is a key enzyme in the sphingolipid pathway, as it regulates the levels of all three of the aforementioned lipids to influence cell fate. Furthermore, its activity is necessary for the clearance of sphingolipids, as once it produces S1P, the latter is hydrolyzed by S1P lyase in an irreversible reaction to produce hexadecenal and ethanolamine phosphate which marks the only exit point for the sphingolipid metabolic pathway.

[3]Corresponding author: lina.obeid@stonybrookmedicine.edu.

[1]Current Address: Department of Internal Medicine, Greenville Memorial Hospital, Greenville, South Carolina, USA

[2]Current Address: Department of Medicine, Stony Brook University, Stony Brook, New York, USA

1.1. S1P signaling

Unlike the antiproliferative effects of ceramide and sphingosine, S1P has been shown to play a significant role in proliferation, migration, survival, angiogenesis, inflammation, and lymphocyte egress (Spiegel and Milstien, 2003). S1P can exert its various effects by binding five distinct and differentially expressed cell surface S1P receptors; these G-protein-coupled receptors were formerly referred to as endothelial differentiation gene (Edg) receptors (Taha et al., 2004), further highlighting S1P's important prosurvival role.

S1P is capable of increasing cell survival and inhibiting the apoptotic process in a number of different cell types, including T cells (Goetzl et al., 1999; Kwon et al., 2001), and it has been also shown to induce a proliferative response in endothelial cells (Kimura et al., 2000) and vascular smooth muscle cells (Tamama et al., 2001). S1P, like potent angiogenic peptide growth factors such as VEGF and FGF-2, is now also considered one of the key regulators in angiogenesis. S1P acts on vascular endothelial cells via S1PR1 and S1PR3 receptors to stimulate migration and capillary-like tube formation *in vitro* (Kimura et al., 2000; Lee et al., 1999; Wang et al., 1999). This stimulatory activity of S1P on angiogenesis has recently been demonstrated *in vivo* in ischemic hindlimbs of mice (Oyama et al., 2008). Furthermore, siRNA-induced S1P receptor knockdown (Theilmeier et al., 2006) or FTY720-induced receptor downregulation has been shown to suppress tumor angiogenesis and tumor growth (LaMontagne et al., 2006; Nagaoka et al., 2008; Permpongkosol et al., 2002) as well as inhibit lymphocyte trafficking (Graler and Goetzl, 2004; Morris et al., 2005).

As S1P has been shown to be involved in cell survival, proliferation, and angiogenesis, it is easy to see how these S1P-mediated activities may contribute to the etiology of cancer (Olivera and Spiegel, 1993; Zhang et al., 1991). Interestingly, parenteral administration of S1P-specific antibodies has been shown to markedly slow human cancer xenograft progression and angiogenesis (Visentin et al., 2006). It is also important to note that S1P signaling has been implicated in the development of the drug resistant phenotype in cancer cells (Akao et al., 2006). Taken together, these findings implicate S1P as a very important signaling molecule in cancer biology that requires further study, and its manipulation may play a role in future anticancer therapies.

1.2. Sphingosine kinase

SK1 and SK2 are the enzymes responsible for catalyzing the conversion of sphingosine to S1P using adenosine triphosphate. Despite differences in structure (Okada et al., 2005) and cellular localization (Johnson et al., 2002) *in vivo* studies suggest that SK1 and SK2 may have some overlapping physiologic functions. For instance, although SK1 knockout (KO) mice and SK2 KO mice appear to develop normally, SK1/SK2 double KO mice suffer embryonic lethality due to inadequate angiogenesis and neurogenesis coupled with neuronal apoptosis (Mizugishi et al., 2005). SK1 and SK2 may in fact have some overlapping functions; however, a review of the current literature describes SK1 as being activated by several extracellular agonists and effecting extracellular S1P levels, whereas SK2 is considered to play more of a housekeeping role, and its function may be localized to the nucleus. Interestingly, it was recently shown that S1P produced by SK2 in the nucleus may regulate histone acetylation of the p21 promoter (Hait et al., 2009).

Further insights into the relative roles of SK1 and SK2 in S1P production have been complicated by the development of SK KO mice. Both the SK1 KO and SK2 KO mice show no abnormal gross or histological phenotypes and no compensation in message levels of the other SK isoform. However, SK1 KO mice show decreased S1P levels in their serum, while this was not detected in the sera of SK2 KO mice. To further investigate this, SK1 +/− mice were crossed with SK2 +/− mice. Interestingly, offspring lacking one to three SK alleles in any combination were indistinguishable from the wild type, but no animals lacking all four alleles were born, indicating that the SK1 KO SK2 KO genotype was embryonic lethal. These embryos had no detectable S1P and suffered hemorrhage and exencephaly due to vascular and neural tube defects (Mizugishi et al., 2005). It was also shown that SK1 KO SK2 +/− female mice were infertile due to defective decidualization with decreased cell mitosis, increased cell death, and defective decidual blood vessel formation (Mizugishi et al., 2007).

Despite the unclear consequences of SK1 KO on sphingolipid homeostasis, these mice have been useful for studying the oncogenic role of SK1. KO of SK1 was able to decrease the size but not the incidence of adenomas in Apc Min/+ mice by attenuating epithelial cell proliferation in the polyps. SK1 KOled to an elevation of sphingosine content and decreased expression of the G1/S cell cycle regulator CDK4 and c-myc in these adenomas, whereas S1P levels were not altered. Furthermore, this protection was not observed when Apc Min/+ mice were crossed with S1P receptor KOs. This highlights that the intracellular function of SK1, independent of the extracellular signaling of its product, S1P, is critical for the growth of intestinal adenomas (Kohno et al., 2006). Other studies have also shown that KO of SK1 can offer protection from chemically induced colon carcinogenesis (Kawamori et al., 2009; Snider et al., 2009).

The cancer preventative affects of SK1 KO are not confined to colon carcinogenesis but also apply to other chemically and genetically induced cancers. While 4-nitroquinoline-1-oxide (NQO) induced head and neck squamous cell carcinoma (HNSCC) in wild-type mice, genetic loss of SK1 prevented 4-NQO-induced HNSCC carcinogenesis with decreased tumor incidence, multiplicity, and volume. The SK1 KO mice showed decreased cell proliferation, increased caspase 3 activation, and decreased activation of AKT when compared with wild-type controls (Shirai et al., 2011). Work from our lab has shown that SK1 KO can protect p53 KO mice from developing their characteristic thymic lymphomas and increase their survival ~30%. Importantly, while KO of SK1 also protects p53 heterozygote mice from the development of lymphomas, it also protected them from the development of other tumor types including osteosarcoma and decreased tumor incidence while prolonging their survival (Heffernan-Stroud et al., 2012). Thus, studies with the SK1 KO mouse have confirmed the oncogenic character of SK1 *in vivo*.

2. SK1 IS AN ONCOGENE

Given its prime position in sphingolipid metabolism, SK1 expression affects the balance between prodeath and prosurvival sphingolipids to determine cell fate, a prime regulatory position for a potential oncogene. Likewise, screening of normal/tumor patient-matched thyroid and non-small-cell-lung cancer tissue, including carcinoid, squamous, and

adenocarcinoma, exhibited over-whelmingly positive immunostaining for SK1 as compared with patient-matched normal tissue (Guan et al., 2011a). Moreover, a twofold elevation of SK1 mRNA expression was observed in cancer versus normal tissue for several types of solid tumors including breast, uterus, ovary, colon, small intestine, and rectum in addition to lung (Johnson et al., 2005). Increased SK1 and S1P were also found in a mouse model of colon cancer, and remarkably SK1 KO mice were resistant to the azoxymethane induced colon cancer observed in mice expressing SK1 (Kawamori et al., 2009).

2.1. Increased expression of SK1 in cancer

The potent oncogene, Bcr/Abl, was shown to upregulate SK1 through various pathways leading to myeloid cell leukemia-1 (Mcl-1) expression in chronic myelogenous leukemia (Li et al., 2007a). In multiple myeloma cells, prokineticin-1, an endocrine gland-derived vascular endothelial growth factor, upregulates SK1 and Mcl-1 in addition to its activation of the MAPK, PI3K-AKT, and Jak-STAT3 pathways in order to protect cells from starvation-induced apoptosis (Li et al., 2010). Transcriptional upregulation of SK1 has also been associated with the tumorigenic phenotype of transgenic proerythroblasts in a mouse model of erythroleukemia (Le Scolan et al., 2005). It has also been shown in MKN1 gastric cancer cells that lysophosphatidic acid signaling through ERK-1 activation upregulates SK1 to exert its proliferative effects (Ramachandran et al., 2010). Increased SK1 expression has been shown to correlate with carcinogenicity in several other cancers including acute leukemia (Sobue et al., 2008), endometrial cancer (Knapp et al., 2010), prostate cancer (Malavaud et al., 2010), HNSCC (Facchinetti et al., 2010; Shirai et al., 2011; Sinha et al., 2011), and thyroid cancer (Guan et al., 2011a).

As for the possible mechanisms for this transcriptional upregulation of SK1 in cancer, in human glioblastoma cells, upregulation of SK1 transcription is induced by IL-1 and is mediated by a novel AP-1 element located within the first intron of the SK1 gene, and this upregulation of SK1 can be blocked by inhibition of JNK (Paugh et al., 2009). Rapidly growing tumors often undergo hypoxia, and this results in HIF-1α and HIF-2α production which has been shown to stimulate two putative hypoxia-inducible factor-responsive-elements in the SK1 promoter region (Anelli et al., 2008; Schwalm et al., 2008). Another pathway of SK1 upregulation has been found in rat pheochromocytoma cells in which nerve growth factor is able to upregulate SK1 expression in a pathway involving transcription factor specificity protein 1 (Sobue et al., 2005). Therefore, it seems that various transcription factors can promote SK1 expression for it to enact its oncogenic effects (Table 7.1).

2.2. SK1 as a prognostic indicator

The elevation of SK1 in various cancers implies that it could be a molecule of prognostic value. In fact, SK1 expression is higher in estrogen receptor (ER) negative breast tumors and its high expression correlates with worse survival and a higher chance of metastasis in patients, with carcinoma cells being the major source of SK1 expression in the tumors (Ruckhaberle et al., 2008). Furthermore, expression of SK1, but not SK2, in glioblastoma multiforme tissue correlated with short patient survival. Patients with low SK1 survived a median of 357 days, whereas those with high levels of SK1 survived a median of 102 days (Van Brocklyn et al., 2005). Also in glioblastoma multiforme, it was found that SK is

necessary for basal activity of the urokinase plasminogen activator system and glioma cell invasion (Young et al., 2009). High expression of SK1 in non-Hodgkin lymphomas (Bayerl et al., 2008), astrocytomas (Li et al., 2008), gastric cancer (Li et al., 2009), salivary gland carcinoma (Liu et al., 2010a), esophageal carcinoma (Pan et al., 2011), non-small-cell-lung cancer (Song et al., 2011), and head and neck squamous cell carcinoma (Facchinetti et al., 2010) also correlates with grade and shorter survival time. Thus not only is SK1 over-expressed in cancer, but it can also enhance tumor invasiveness and serve as a prognostic indicator.

Patients with ER-positive breast tumors that expressed high levels of both cytoplasmic SK1 and ERK-1/2 had significantly shorter recurrence times than those that expressed low levels of cytoplasmic SK1 and cytoplasmic ERK-1/2, with a difference in recurrence time of 10.5 years (Watson et al., 2010). In contrast, for patients with ER-positive breast cancer, a low HER1–3/SK1 expression ratio is correlated with improved prognosis compared to patients that have a high HER1–3/SK1 expression ratio. This is thought to occur since although the HER2 oncogene increases SK1 expression in these tumors, then SK1 limits HER2 expression in a negative-feedback manner, this phenomenon has been termed “oncogene tolerance” (Long et al., 2010).

Although treatment failure and Gleason score were found to correlate with tumor SK1 activity in prostate cancer patients (Malavaud et al., 2010), patients with prostate cancer were shown to have lower circulating levels of S1P and decreased SK1 activity in their erythrocytes when compared to healthy subjects. They found that decreased circulating S1P was an early marker of prostate cancer progression to hormonal unresponsiveness and correlated with prostate-specific antigen levels and lymph node metastasis as well as mortality (Nunes et al., 2012). Thus, implying that tumor versus serum SK1/S1P levels may have opposite prognostic indications in certain cancer patients.

2.3. Elevated SK1 confers resistance to chemotherapy

With increased SK1 correlated to poor prognosis in several cancers, it seems likely that overexpression of SK1 may confer resistance to current chemotherapeutics. In fact, imatinib-induced apoptosis in K562 human chronic myeloid leukemia (CML) cells involves an increase in C18-ceramide; however, imatinib-resistant cells have increased expression of SK1 which elevates their S1P to C18-ceramide ratio sixfold and prevents apoptosis (Baran et al., 2007). Furthermore, impaired SK1/S1P signaling enhanced the growth-inhibitory effects of nilotinib against 32D/T315I-Bcr–Abl1-derived mouse allografts, demonstrating SK1 inhibition as a potential chemosensitizer in CML (Salas et al., 2011).

Likewise, it has been found that camptothecin-resistant prostate cancer PC3 cells show higher expression of SK1 and S1PR1 and -3 receptors when compared to camptothecin-sensitive, LNCaP cells, and inhibition of SK1 or the S1P receptors can inhibit cell growth in PC3 cells (Akao et al., 2006). Increased SK1 also appears to be involved in cisplatin resistance in lung cancer cells (Min et al., 2005), daunorubicin resistance in leukemia cells (Sobue et al., 2008), *N*-(4-hydroxyphenyl) retinamide resistance in ovarian carcinoma cells (Illuzzi et al., 2010), oxaliplatin resistance in colon cancer cells (Nemoto et al., 2009), and doxorubicin, docetaxel, and tamoxifen resistance in breast cancer cells (Ling et al., 2009;

Nava et al., 2002; Sukocheva et al., 2009). Accordingly, inhibition or knockdown of SK1 has been found to increase drug efficacy in acute myeloid leukemia cells (Bonhoure et al., 2006), chronic myelogenous leukemia cells (Li et al., 2007a; Salas et al., 2011), colon cancer cells (Nemoto et al., 2009), and ovarian carcinoma cells (Illuzzi et al., 2010).

2.4. SK1 functions to suppress apoptosis of cancer cells

In vivo cells undergo apoptosis, cell cycle arrest, or senescence when their survival and growth no longer benefit the organism. When aberrant signaling overrides this response, these cells can become tumorigenic. Bioactive sphingolipids have been shown to be important signaling molecules for such cell fate decisions and SK is at crucial point for contributing to this since its product, S1P, is a prosurvival signaling molecule. Here, we review cell studies that illustrate the prosurvival role of the SK1/S1P pathway, in order to show how their functions at the cellular level might contribute to tumor initiation at the organismal level. For instance, in an elegant study by Le Scolan et al., they showed that overexpression of SK1 in erythroleukemic cells increased proliferation, clonogenicity, and resistance to apoptosis in reduced serum by a mechanism involving ERK1/2 activation and the PI3K/Akt pathway leading to increased tumorigenicity when engrafted *in vivo*. However, expression of a dominant-negative mutant of SK1 or treatment with a pharmacological inhibitor was able to reduce both cell growth and apoptosis-resistance in the tumorigenic erythroleukemia cells (Le Scolan et al., 2005). Furthermore, a novel hepatic growth factor that protects hepatocarcinoma cells, hepatopoietin Cn, was recently found to work through SK1 signaling to upregulate Mcl-1 expression to induce its antiapoptotic effects (Chang et al., 2010).

Work from our lab has shown in breast cancer cells, knockdown of SK1 causes cell cycle arrest and induces apoptosis involving effector caspase activation, cytochrome c release, and Bax oligomerization in the mitochondrial membrane, thus placing SK1 knockdown upstream of the mitochondrial pathway of apoptosis (Taha et al., 2006a). Knockdown or downregulation of SK1 has also been shown to lead to ceramide accumulation, decreased S1P, and apoptosis in other cancer cell lines including prostate cancer (Pchejetski et al., 2005), glioblastoma (Van Brocklyn et al., 2005), chronic myelogenous leukemia cell lines (Li et al., 2007a), and neuroblastoma cells (Gomez-Brouchet et al., 2007). (Table 7.2) Likewise, when SK1 is overexpressed in breast cancer cells, it results in enhanced proliferation and resistance to tamoxifen-induced growth arrest and apoptosis (Sukocheva et al., 2009) and it confers resistance to other anticancer drugs, sphingosine, and TNF-α (Nava et al., 2002). Interestingly, other studies in breast cancer cells have suggested that overexpression of SK1 stimulates autophagy. And it was shown that nutrient starvation stimulates SK1 activity and that SK1/S1P-induced autophagy can protect cells from apoptosis under nutrient-deplete conditions (Lavieu et al., 2006). Overexpression of SK1 was also shown to upregulate the Mcl-1 protein in multiple myeloma cells, leading to increased cell proliferation and survival. Furthermore, activation of SK1 was shown to mediate the suppressive effects of IL-6 on multiple myeloma cell apoptosis (Li et al., 2007b). Overexpression or activation of SK1 has been shown to suppress the apoptotic response in a variety of other cell lines including rat pheochromocytoma cells (Edsall et al.,

2001; Misasi et al., 2001) and Jurkat, U937, and HL-60 leukemia cells (Cuvillier and Levade, 2001) (Table 7.3).

SK1 status appears to be tightly linked with caspase-dependent apoptosis. KO of SK1, but not SK2, was shown to enhance caspase-3-mediated apoptosis induced by staurosporine (Hofmann et al., 2008). In several human leukemia cell lines (Jurkat, U937, and HL-60), S1P can inhibit caspase-3 activation by inhibiting translocation of cytochrome *c* and Smac/DIABLO from mitochondria to cytosol (Cuvillier and Levade, 2001). In addition to its prosurvival product S1P, SK1 also regulates the level of its proapoptotic substrate, sphingosine. Recent studies have shown that binding of sphingosine to 14-3-3 proteins renders them phosphorylatable at the dimer interface, an event that abolishes their prosurvival signaling. Thus by reducing the availability of sphingosine for interaction with 14-3-3, SK1 can inhibit cell death (Woodcock et al., 2010), underlining the important position of SK1 in balancing growth and death signaling sphingolipids.

2.5. SK1 affects apoptosis through controlling the cellular ceramide:S1P ratio

To illustrate this balancing act controlled by SK1, in noncancerous human endothelial cells, TNF activates sphingomyelinase and generates ceramide, but these cells are resistant to TNF-induced apoptosis since TNF also activates SK and increases S1P. However, in a transformed endothelial cell line (C11), TNF fails to activate SK and thus induces apoptosis, which treatment with S1P can prevent (Xia et al., 1999). Clearly, with its important role of regulating the balance between prodeath and prosurvival sphingolipids, modifications of SK1 could lead to aberrantly enhanced cell survival leading to tumorigenesis.

In fact, overexpression of SK1 in prostate cancer cells can increase resistance to chemotherapy by decreasing the ceramide:S1P ratio (Pchejetski et al., 2005). Furthermore, a significantly higher ceramide:S1P ratio was found in melanoma cells that are resistant to ceramide- and Fas-induced death than those sensitive to programmed cell death. Overexpression of SK1-reduced sensitivity of A-375 melanoma cells to Fas- and ceramide-mediated apoptosis while siRNA of SK1 decreased resistance of Mel-2a cells to apoptosis. Interestingly, overexpression of prosurvival protein Bcl-2 in A-375 cells stimulated SK1 expression and activity, and downregulation of Bcl-2-reduced SK1 expression (Bektas et al., 2005). Furthermore, it has been shown that Dasatinib (Gencer et al., 2011) and resveratrol (Kartal et al., 2011) induce apoptosis through downregulating SK1 and upregulating ceramide synthase genes to increase the ceramide:S1P ratio in K562 CML cells (Gencer et al., 2011; Kartal et al., 2011). This opposing regulation of ceramide synthases and SK1 has also been observed in breast cancer samples (Erez-Roman et al., 2009). Moreover, our work has shown that through KO of SK1, an increased ceramide:S1P ratio is protective from thymic lymphoma development and may initiate tumor cell senescence *in vivo* (Heffernan-Stroud et al., 2012) (Table 7.4).

2.6. SK1 inhibitors challenge cancer cell viability to enhance chemotherapy

Various studies have employed pharmacological inhibitors to show that inhibition of SK decreases cancer cell viability in neuroblastoma cells (Tavarini et al., 2000), glioblastoma cells (Bektas et al., 2009), and several types of leukemia cells (Cuvillier and Levade, 2001;

Paugh et al., 2008; Zhang et al., 2008) as well as in various solid tumor cell lines (French et al., 2003). SK inhibitors (outlined in Table 7.5). were found to be antiproliferative toward a panel of tumor cell lines, including lines with the multidrug resistance phenotype because of overexpression of either P-glycoprotein or multidrug resistance phenotype 1, and they could induce apoptosis (French et al., 2003). Furthermore, resistance to doxorubicin- or etoposide-induced apoptosis in acute myeloid leukemia cells was attributed to sustained SK1 activity and reduced ceramide accumulation; likewise, apoptosis could be restored in these cells by treatment with an SK inhibitor, F-12509a (Bonhoure et al., 2006). Later results using the same inhibitor suggest that SK1 regulates imatinib-induced apoptosis in primary cells from CML patients, as inhibition of SK1 could kill both imatinib-sensitive and -resistant cells. This work places SK1 downstream of the Bcr–Abl/Ras/ERK pathway inhibited by imatinib and upstream of Bcl-2 family members (Bonhoure et al., 2008).

Inhibition of SK was also shown to reduce cell colony formation and activate caspase-3 in temozolomide-resistant glioblastoma multiforme cells (Bektas et al., 2009). And inhibition of SK1 or the S1P receptors can inhibit cell growth in camptothecin-resistant prostate cancer cells (Akao et al., 2006). Interestingly, treatment with SK inhibitors SK1-I or SK1-II, can selectively induce apoptosis in T cell large granular lymphocyte leukemia cells but not in normal peripheral blood mononuclear cells (Zhang et al., 2008). Likewise, treatment with SK1-I potently induced apoptosis in leukemic blasts isolated from patients with acute myelogenous leukemia but again was relatively sparing of normal peripheral blood mononuclear leukocytes (Paugh et al., 2008). *In vivo*, treatment with SK1-I induced apoptosis and reduced tumor vascularization leading to a markedly decreased tumor growth rate of glioblastoma xenografts and enhancing the survival of mice harboring LN229 intracranial tumors (Kapitonov et al., 2009). Recently, production of an aspirinyl analog of SK1-I has been shown to increase its half-life for better *in vivo* delivery (Sharma et al., 2010).

Moreover, combining SK1-I and the proteasome inhibitor, bortezomib, synergistically increases apoptosis, decreases colony formation, and induces downregulation of BCR/ABL and Mcl-1 in human leukemia cells and was even effective in imatinib-resistant cells (Li et al., 2011). Whereas, SK1-II on its own has been shown to induce proteasomal degradation of SK1 in human pulmonary artery smooth muscle cells, androgen-sensitive LNCaP prostate cancer cells, MCF-7 and MCF-7 HER2 breast cancer cells (Loveridge et al., 2010). Although FTY720 has been reported to be more proficient at inhibiting SK2, some studies claim that FTY720 and its analogue (S)-FTY720 vinylphosphonate behave as typical SK1 inhibitors and induce proteasomal degradation of SK1 and apoptosis in breast and prostate cancer cells (Tonelli et al., 2010) as well as preventing S1P-stimulated rearrangement of actin in MCF-7 cells (Lim et al., 2011). Of note, it has also been reported that FTY720 inhibits SK1 to increase radiation sensitivity of prostate cancer tumor xenografts to reduce tumor growth and metastasis in mice (Pchejetski et al., 2010).

The first putative-SK inhibitor to enter phase 1 clinical trials for advanced solid tumor therapy was Safingol, 1-threo-dihydrosphingosine, in 2011, which was found to decrease plasma levels of S1P and prolong stable disease/inhibit cancer progression when used in combination with cisplatin in a small cohort of patients (Dickson et al., 2011). However, new

SK1 inhibitors with increased specificity are being developed. As the upregulation of SK1 in HNSCC cells correlates with their radioresistance, a group developed gold nanorod-SK1 siRNA nanocomplexes as a method of radiosensitization of head and neck cancer to achieve over 50% greater tumor regression as compared to controls (Masood et al., 2012).

Recently developed amidine-based SK1 nanomolar inhibitors were shown to significantly reduce S1P levels in human leukemia U937 cells (Kennedy et al., 2011). Two sphingoguanidine salts named LCL146 and LCL135 have been reported to be cytotoxic to cancer cells and decrease the migration rate of human prostate (DU145) cells through their inhibition of SK (Sharma, 2011). Interestingly, the anticancer agent resveratrol and its dimers, ampelopsin A and balanocarpol, have been shown to downregulate SK1 in MCF-7 human breast cancer cells (Lim et al., 2012). The AKT inhibitor, BI-69A11, was shown to reduce NF-κB signaling through its inhibition of SK1 to inhibit melanoma growth (Feng et al., 2011). All of these results indicate that an SK1 inhibitor could be a beneficial addition to the chemotherapeutic strategies employed for treating various types of tumors, leading to extensive review of the subject (Cuvillier, 2007, 2008; Edmonds et al., 2011; Gault and Obeid, 2011; Pallis, 2002; Pitman and Pitson, 2010; Pyne et al., 2011; Shida et al., 2008b; Uddin and Platanias, 2008).

3. SK1/S1P SIGNALS FOR TUMOR GROWTH AND SPREAD

Not only does SK1 protect cell survival, it also plays an important role in signaling for cell proliferation. It appears that SK1-dependent Akt activation plays a significant role in cell proliferation induced by TNF-α in 1321N1 glioblastoma cells (Radeff-Huang et al., 2007) and by 11,12-epoxyeicosatrienoic acid in human umbilical vein endothelial cells (Yan et al., 2008). SK1 has also been found to act as a proproliferative oncogenic kinase in thyroid cancer where it appears to activate the Akt/glycogen synthase kinase-3β/β-catenin pathway (Guan et al., 2011a). Moreover, various growth factors have been shown to function in part by upregulating SK1 expression and/or activity, these include PDGF (Francy et al., 2007), NGF (Edsall et al., 2001), IGF-BP3 (Martin et al., 2009), VEGF (Shu et al., 2002), and EGF (Doll et al., 2005). VEGF induces DNA synthesis in a pathway which sequentially involves protein kinase C, SK, Ras, Raf, and ERK1/2 (Shu et al., 2002). And epidermal growth factor both acutely and transcriptionally upregulates SK1 in a MAPK-, PKC-, and PI3K-dependent manner. Accordingly, when cells are depleted of SK1, but not SK2, by siRNA, EGF-induced proliferation and migration are drastically reduced (Doll et al., 2005). Also through the ERK1/2 and PI3K signaling pathways, glial cell line-derived neurotrophic factor induces transcription of SK1 which leads to neurite formation, GAP43 expression, and cell growth in TGW human neuroblastoma cells and growth and anchorage-independent colony formation in a model of multiple endocrine neoplasia type 2 tumor (Murakami et al., 2007).

3.1. Hormonal regulation of SK1

Hormones have also been shown to activate SK1. Progesterone induced SK1 expression (30-fold) in the rat uterus during pregnancy in the glandular epithelium, vasculature, and myometrium. Overexpression of SK1 in a rat myometrial leiomyoma cell line (ELT3) resulted in increased levels of the cell cycle regulator cyclin D1 and increased myosin light-

chain phosphorylation and increased proliferation rates (Jeng et al., 2007). Prolactin and 17-β estradiol were also shown to activate SK1, but not SK2, in MCF-7 breast adenocarcinoma cells both within minutes and within hours after STAT5-, PKC-, and MAPK-dependent promoter activation. Either inhibition of SK1 activation with glucocorticoids or direct knockdown of SK1 with siRNA could abolish the hormone-induced cell proliferation and migration observed in the breast cancer cells (Doll et al., 2007).

Interestingly, the SK1-II inhibitor binds the ER directly in the antagonist ligand-binding domain. SK1-II was shown to dose-dependently decrease estrogen-stimulated estrogen response element transcriptional activity and diminish mRNA levels of the ER regulated genes progesterone receptor and steroid derived factor-1 to block breast cancer viability, clonogenic survival, and proliferation (Antoon et al., 2011). In addition to hormonal regulation of SK1 in breast cancer, dihydrotestosterone was shown to signal for proliferation through an androgen receptor/PI3K/Akt-dependent stimulation of SK1 in hormone-sensitive prostate cancer cells (Dayon et al., 2009). This hormonal regulation of SK1 has even been shown to be important in neuroblastoma cell lines in which 17β-estradiol upregulates SK1 to protect from Tau hyperphosphorylation and glutamate toxicity (Lopez-Tobon et al., 2009).

3.2. SK1 functions to enhance proliferation of cancer cells

SK1 can signal to a cell to proliferate through its product S1P. For instance, in the presence of retinoic acid receptor alpha, retinoic acid upregulates neutral sphingomyelinase and downregulates SK1 to inhibit cell growth, but in the absence of that receptor, retinoic acid activates SK1 and promotes cell growth through S1P (Somenzi et al., 2007). Addition of S1P increases proliferation in neuroblastoma cells (Tavarini et al., 2000) and extracellular S1P is required for basic fibroblast growth factor-induced growth stimulation of astrocytes (Bassi et al., 2006). In a glioma cell line, S1P induces expression of early growth response-1, an essential transcription factor for fibroblast growth factor 2 (Sato et al., 1999). This was the first report of S1P acting as a transcription factor, and its role as a molecule capable of epigenetic regulation was more recently elucidated when it was shown to regulate histone acetylation (Hait et al., 2009). Clearly, SK1 and its product S1P could employ their potent proliferative signaling to enhance tumor growth.

3.3. SK1 can stimulate angiogenesis to increase blood supply to tumors

In order to maintain rapid growth, tumors require a sufficient vascular supply. As tumor cells rapidly proliferate, they undergo hypoxia which results in their signaling for new blood vessels to be formed. Hypoxia increases SK1 mRNA, protein, and activity in human glioma U87MG cells, followed by intracellular S1P production and S1P release and this could all be inhibited with knockdown of HIF-2α by siRNA (Anelli et al., 2008). Similar results were observed in endothelial cells themselves, where their production of HIF-1α and HIF-2α and their binding to two putative hypoxia-inducible factor and -responsive elements in the SK1 promoter led to increases in SK1 (Schwalm et al., 2008). Furthermore, our lab showed that conditioned medium from hypoxia-treated tumor cells results in neoangiogenesis in human umbilical vein endothelial cells in an S1P receptor-dependent manner (Anelli et al., 2008). Interestingly, inhibition of SK1 activity can prevent the accumulation of HIF-1α and its transcriptional activity in several human cancer cell lineages including prostate, brain,

breast, kidney, and lung (Ader et al., 2008). Thus, SK1 signaling appears to play an important role in creating new vasculature in order for oxygen and nutrients to be delivered to oxygen-starved tumors.

In addition to angiogenesis, SK1 has recently been shown to play a role in lymphangiogenesis. SK1 overexpression in HEK cells or its downregulation in glioma or breast cancer cells modulated extracellular S1P levels accordingly, which in turn increased or decreased both migration and tube formation in cocultured vascular or lymphatic endothelial cells. Furthermore, S1P initiated endothelial cell sprouting in three-dimensional collagen matrices (Anelli et al., 2010). Activation of SK1 has been shown to be necessary for the angiogenic effects of 11,12-epoxyeicosatrienoic acid, a product of cytochrome p450 epoxygenases (Yan et al., 2008), TNF-α (Xia et al., 1998), and VEGF (Kolmakova et al., 2009). Likewise, inhibition of SK has been shown to be responsible for the antiangiogenic properties of phenoxodiol (2H-1-benzopyran-7-0, 1,3-[4-hydroxyphenyl]), an anticancer drug undergoing clinical trials for its apoptotic properties (Gamble et al., 2006), and alphastatin, the potent antiangiogenic molecule that has been shown to inhibit gastric cancer angiogenesis (Chen et al., 2006; Li and Chen, 2009). In NIH3T3 cells with dominant negative CBF1, SK1 is required for FGF1 export and acceleration of cell growth to produce highly angiogenic tumors in nude mice (Kacer et al., 2011). Therefore, the angiogenic signaling properties of SK1 appear to be important for vascularization, and hence expansion, of tumors.

3.4. SK1 may enhance tumor metastasis

In addition to its angiogenic and lymphangiogenic properties, other aspects of SK1 signaling that could potentially contribute to tumor metastasis have been elucidated. For instance, upregulation of SK1 led to a migratory response in endothelial cells (Schwalm et al., 2008) and promotes migration of thyroid follicular carcinoma cells (Bergelin et al., 2009). Whereas, depletion of SK1 can inhibit EGF-induced (Doll et al., 2005; Sarkar et al., 2005), as well as hormone-induced migration of breast cancer cells (Doll et al., 2007), and it can abrogate migration toward EGF in HEK293 cells (Hait et al., 2005). SK1 was also shown to be required for nucleotide-induced migration of renal mesangial cells (Meyer zu Heringdorf and Jakobs, 2007). Moreover, the antimetastasis molecule KAI1 has been shown to suppress migration of pancreatic carcinoma cells through downregulation of SK activity (Guo et al., 2006), and it has been shown to downregulate hepatocyte growth factor induced activation of SK1 in order to impede migration of hepatoma cells (Mu et al., 2008). These results indicate that the regulation of SK1 is a crucial regulator of cell migration.

The ability to migrate as well as invasiveness and the aggressiveness of tumor cells is what distinguishes a benign mass from malignant cancer. Importantly, NIH3T3 fibroblasts overexpressing SK acquire a transformed phenotype, as determined by focus formation, colony growth in soft agar, and the ability to form tumors in NOD/SCID mice, and SK activity appears to be involved in transformation mediated by the potent oncogene, H-Ras (Xia et al., 2000). Furthermore, TGF-β's activation of SK and formation of S1P contribute to non-Smad signaling that could be important for progression of esophageal cancer (Miller et al., 2008), and S1P is able to induce invasion of glioblastoma cells (Bryan et al., 2008).

Studies show that hepatocellular carcinoma cell migration and invasion may also be promoted by SK1/S1P signaling through S1PR1 (EDG1) (Bao et al., 2011). Moreover, S1P has been shown to signal through S1PR2 for apoptotic cell extrusion, which because live cells can also be extruded, it is postulated that this may serve as a mechanism for the invasion of cancer cells (Gu et al., 2011). Other studies have suggested that SK1 is a convergence point of multiple cell surface receptors for LPA, EGF, and S1P, which have all been implicated in the regulation of motility and invasiveness of cancer cells (Shida et al., 2008a). Thus, it appears that SK1 signaling can contribute to the malignant transformation of tumors and their metastasis.

4. CONCLUSION

Through both regulating ceramide and sphingosine accumulation within the cell and producing S1P, increased expression of SK1 results in an oncogenic phenotype. Decreased ceramide and sphingosine levels can confer chemotherapeutic resistance to cancer cells and increased S1P can stimulate the proliferation, vascularization, and metastasis of tumors. Therefore, SK1 represents an important target for chemotherapy.

Acknowledgments

This work was supported, in part, by NIH/NCI P01 CA097132—project 3 (to L. M. O). NIH MSTP Training Grant (GM08716—to L. A. H. S), MUSC Hollings Cancer Center Abney Foundation Scholarship (to L. A. H. S), NIH/NIEHS TG T32 ES012878, and NIH-NIEHS/NRSA F30ES017379 (to L. A. H. S).

References

Ader I, Brizuela L, Bouquerel P, Malavaud B, Cuvillier O. Sphingosine kinase 1: A new modulator of hypoxia inducible factor 1alpha during hypoxia in human cancer cells. Cancer Research. 2008; 68:8635–8642. [PubMed: 18922940]

Akao Y, Banno Y, Nakagawa Y, Hasegawa N, Kim TJ, Murate T, et al. High expression of sphingosine kinase 1 and S1P receptors in chemotherapy-resistant prostate cancer PC3 cells and their camptothecin-induced up-regulation. Biochemical and Biophysical Research Communications. 2006; 342:1284–1290. [PubMed: 16516161]

Anelli V, Gault CR, Cheng AB, Obeid LM. Sphingosine kinase 1 is up-regulated during hypoxia in U87MG glioma cells. Role of hypoxia-inducible factors 1 and 2. The Journal of Biological Chemistry. 2008; 283:3365–3375. [PubMed: 18055454]

Anelli V, Gault CR, Snider AJ, Obeid LM. Role of sphingosine kinase-1 in paracrine/transcellular angiogenesis and lymphangiogenesis in vitro. The FASEB Journal. 2010; 24:2727–2738. [PubMed: 20335228]

Antoon JW, Meacham WD, Bratton MR, Slaughter EM, Rhodes LV, Ashe HB, et al. Pharmacological inhibition of sphingosine kinase isoforms alters estrogen receptor signaling in human breast cancer. Journal of Molecular Endocrinology. 2011; 46:205–216. [PubMed: 21321095]

Bao M, Chen Z, Xu Y, Zhao Y, Zha R, Huang S, et al. Sphingosine kinase 1 promotes tumour cell migration and invasion via the S1P/EDG1 axis in hepatocellular carcinoma. Liver International. 2011; 32:331–338. [PubMed: 22098666]

Baran Y, Salas A, Senkal CE, Gunduz U, Bielawski J, Obeid LM, et al. Alterations of ceramide/sphingosine 1-phosphate rheostat involved in the regulation of resistance to imatinib-induced apoptosis in K562 human chronic myeloid leukemia cells. The Journal of Biological Chemistry. 2007; 282:10922–10934. [PubMed: 17303574]

Bassi R, Anelli V, Giussani P, Tettamanti G, Viani P, Riboni L. Sphingosine-1-phosphate is released by cerebellar astrocytes in response to bFGF and induces astrocyte proliferation through Gi-protein-coupled receptors. Glia. 2006; 53:621–630. [PubMed: 16470810]

Bayerl MG, Bruggeman RD, Conroy EJ, Hengst JA, King TS, Jimenez M, et al. Sphingosine kinase 1 protein and mRNA are overexpressed in non-Hodgkin lymphomas and are attractive targets for novel pharmacological interventions. Leukemia & Lymphoma. 2008; 49:948–954. [PubMed: 18452097]

Bektas M, Jolly PS, Muller C, Eberle J, Spiegel S, Geilen CC. Sphingosine kinase activity counteracts ceramide-mediated cell death in human melanoma cells: Role of Bcl-2 expression. Oncogene. 2005; 24:178–187. [PubMed: 15637591]

Bektas M, Johnson SP, Poe WE, Bigner DD, Friedman HS. A sphingosine kinase inhibitor induces cell death in temozolomide resistant glioblastoma cells. Cancer Chemotherapy and Pharmacology. 2009; 64:1053–1058. [PubMed: 19597728]

Bergelin N, Blom T, Heikkila J, Lof C, Alam C, Balthasar S, et al. Sphingosine kinase as an oncogene: Autocrine sphingosine 1-phosphate modulates ML-1 thyroid carcinoma cell migration by a mechanism dependent on protein kinase C-alpha and ERK1/2. Endocrinology. 2009; 150:2055–2063. [PubMed: 19116345]

Bonhoure E, Pchejetski D, Aouali N, Morjani H, Levade T, Kohama T, et al. Overcoming MDR-associated chemoresistance in HL-60 acute myeloid leukemia cells by targeting sphingosine kinase-1. Leukemia. 2006; 20:95–102. [PubMed: 16281067]

Bonhoure E, Lauret A, Barnes DJ, Martin C, Malavaud B, Kohama T, et al. Sphingosine kinase-1 is a downstream regulator of imatinib-induced apoptosis in chronic myeloid leukemia cells. Leukemia. 2008; 22:971–979. [PubMed: 18401414]

Brizuela L, Dayon A, Doumerc N, Ader I, Golzio M, Izard JC, et al. The sphingosine kinase-1 survival pathway is a molecular target for the tumor-suppressive tea and wine polyphenols in prostate cancer. The FASEB Journal. 2010; 24:3882–3894. [PubMed: 20522783]

Bryan L, Kordula T, Spiegel S, Milstien S. Regulation and functions of sphingosine kinases in the brain. Biochimica et Biophysica Acta. 2008; 1781:459–466. [PubMed: 18485923]

Cakir Z, Saydam G, Sahin F, Baran Y. The roles of bioactive sphingolipids in resveratrol-induced apoptosis in HL60: Acute myeloid leukemia cells. Journal of Cancer Research and Clinical Oncology. 2011; 137:279–286. [PubMed: 20401667]

Chang J, Liu Y, Zhang DD, Zhang DJ, Wu CT, Wang LS, et al. Hepatopoietin Cn suppresses apoptosis of human hepatocellular carcinoma cells by up-regulating myeloid cell leukemia-1. World Journal of Gastroenterology. 2010; 16:193–200. [PubMed: 20066738]

Chen L, Li T, Li R, Wei B, Peng Z. Alphastatin downregulates vascular endothelial cells sphingosine kinase activity and suppresses tumor growth in nude mice bearing human gastric cancer xenografts. World Journal of Gastroenterology. 2006; 12:4130–4136. [PubMed: 16830360]

Cho SY, Lee HJ, Jeong SJ, Kim HS, Chen CY, Lee EO, et al. Sphingosine kinase 1 pathway is involved in melatonin-induced HIF-1alpha inactivation in hypoxic PC-3 prostate cancer cells. Journal of Pineal Research. 2011; 51:87–93. [PubMed: 21392092]

Cuvillier O. Sphingosine kinase-1–A potential therapeutic target in cancer. Anti-cancer Drugs. 2007; 18:105–110. [PubMed: 17159597]

Cuvillier O. Downregulating sphingosine kinase-1 for cancer therapy. Expert Opinion on Therapeutic Targets. 2008; 12:1009–1020. [PubMed: 18620522]

Cuvillier O, Levade T. Sphingosine 1-phosphate antagonizes apoptosis of human leukemia cells by inhibiting release of cytochrome c and Smac/DIABLO from mitochondria. Blood. 2001; 98:2828–2836. [PubMed: 11675357]

Dayon A, Brizuela L, Martin C, Mazerolles C, Pirot N, Doumerc N, et al. Sphingosine kinase-1 is central to androgen-regulated prostate cancer growth and survival. PLoS One. 2009; 4:e8048. [PubMed: 19956567]

De Luca T, Morre DM, Morre DJ. Reciprocal relationship between cytosolic NADH and ENOX2 inhibition triggers sphingolipid-induced apoptosis in HeLa cells. Journal of Cellular Biochemistry. 2010; 110:1504–1511. [PubMed: 20518072]

Dickson MA, Carvajal RD, Merrill AH Jr, Gonen M, Cane LM, Schwartz GK. A phase I clinical trial of safingol in combination with cisplatin in advanced solid tumors. Clinical Cancer Research. 2011; 17:2484–2492. [PubMed: 21257722]

Doll F, Pfeilschifter J, Huwiler A. The epidermal growth factor stimulates sphingosine kinase-1 expression and activity in the human mammary carcinoma cell line MCF7. Biochimica et Biophysica Acta. 2005; 1738:72–81. [PubMed: 16414307]

Doll F, Pfeilschifter J, Huwiler A. Prolactin upregulates sphingosine kinase-1 expression and activity in the human breast cancer cell line MCF7 and triggers enhanced proliferation and migration. Endocrine-Related Cancer. 2007; 14:325–335. [PubMed: 17639048]

Edmonds Y, Milstien S, Spiegel S. Development of small-molecule inhibitors of sphingosine-1-phosphate signaling. Pharmacology & Therapeutics. 2011; 132:352–360. [PubMed: 21906625]

Edsall LC, Cuvillier O, Twitty S, Spiegel S, Milstien S. Sphingosine kinase expression regulates apoptosis and caspase activation in PC12 cells. Journal of Neurochemistry. 2001; 76:1573–1584. [PubMed: 11238741]

Erez-Roman R, Pienik R, Futerman AH. Increased ceramide synthase 2 and 6 mRNA levels in breast cancer tissues and correlation with sphingosine kinase expression. Biochemical and Biophysical Research Communications. 2009; 391:219–223. [PubMed: 19912991]

Estrada-Bernal A, Lawler SE, Nowicki MO, Ray Chaudhury A, Van Brocklyn JR. The role of sphingosine kinase-1 in EGFRvIII-regulated growth and survival of glioblastoma cells. Journal of Neuro-Oncology. 2010; 102:353–366. [PubMed: 20938717]

Facchinetti MM, Gandini NA, Fermento ME, Sterin-Speziale NB, Ji Y, Patel V, et al. The expression of sphingosine kinase-1 in head and neck carcinoma. Cells, Tissues, Organs. 2010; 192:314–324. [PubMed: 20606403]

Feng Y, Barile E, De SK, Stebbins JL, Cortez A, Aza-Blanc P, et al. Effective inhibition of melanoma by BI-69A11 is mediated by dual targeting of the AKT and NF-kappaB pathways. Pigment Cell & Melanoma Research. 2011; 24:703–713. [PubMed: 21592316]

Francy JM, Nag A, Conroy EJ, Hengst JA, Yun JK. Sphingosine kinase 1 expression is regulated by signaling through PI3K, AKT2, and mTOR in human coronary artery smooth muscle cells. Biochimica et Biophysica Acta. 2007; 1769:253–265. [PubMed: 17482291]

French KJ, Schrecengost RS, Lee BD, Zhuang Y, Smith SN, Eberly JL, et al. Discovery and evaluation of inhibitors of human sphingosine kinase. Cancer Research. 2003; 63:5962–5969. [PubMed: 14522923]

French KJ, Upson JJ, Keller SN, Zhuang Y, Yun JK, Smith CD. Antitumor activity of sphingosine kinase inhibitors. The Journal of Pharmacology and Experimental Therapeutics. 2006; 318:596–603. [PubMed: 16632640]

Fuereder T, Hoeflmayer D, Jaeger-Lansky A, Rasin-Streden D, Strommer S, Fisker N, et al. Sphingosine kinase 1 is a relevant molecular target in gastric cancer. Anti-cancer Drugs. 2011; 22:245–252. [PubMed: 21360847]

Gamble JR, Xia P, Hahn CN, Drew JJ, Drogemuller CJ, Brown D, et al. Phenoxodiol, an experimental anticancer drug, shows potent antiangiogenic properties in addition to its antitumour effects. International Journal of Cancer. 2006; 118:2412–2420. [PubMed: 16353157]

Gault CR, Obeid LM. Still benched on its way to the bedside: Sphingosine kinase 1 as an emerging target in cancer chemotherapy. Critical Reviews in Biochemistry and Molecular Biology. 2011; 46:342–351. [PubMed: 21787121]

Gencer EB, Ural AU, Avcu F, Baran Y. A novel mechanism of dasatinib-induced apoptosis in chronic myeloid leukemia; ceramide synthase and ceramide clearance genes. Annals of Hematology. 2011; 90:1265–1275. [PubMed: 21455605]

Goetzl EJ, Kong Y, Mei B. Lysophosphatidic acid and sphingosine 1-phosphate protection of T Cells from apoptosis in association with suppression of bax. The Journal of Immunology. 1999; 162:2049–2056. [PubMed: 9973477]

Gomez-Brouchet A, Pchejetski D, Brizuela L, Garcia V, Altie MF, Maddelein ML, et al. Critical role for sphingosine kinase-1 in regulating survival of neuroblastoma cells exposed to amyloid-beta peptide. Molecular Pharmacology. 2007; 72:341–349. [PubMed: 17522181]

Graler MH, Goetzl EJ. The immunosuppressant FTY720 down-regulates sphingosine 1-phosphate G-protein-coupled receptors. The FASEB Journal. 2004; 18:551–553. [PubMed: 14715694]

Gu Y, Forostyan T, Sabbadini R, Rosenblatt J. Epithelial cell extrusion requires the sphingosine-1-phosphate receptor 2 pathway. The Journal of Cell Biology. 2011; 193:667–676. [PubMed: 21555463]

Guan H, Liu L, Cai J, Liu J, Ye C, Li M, et al. Sphingosine kinase 1 is overexpressed and promotes proliferation in human thyroid cancer. Molecular Endocrinology. 2011a; 25:1858–1866. [PubMed: 21940753]

Guan H, Song L, Cai J, Huang Y, Wu J, Yuan J, et al. Sphingosine kinase 1 regulates the Akt/FOXO3a/Bim pathway and contributes to apoptosis resistance in glioma cells. PLoS One. 2011b; 6:e19946. [PubMed: 21625639]

Guillermet-Guibert J, Davenne L, Pchejetski D, Saint-Laurent N, Brizuela L, Guilbeau-Frugier C, et al. Targeting the sphingolipid metabolism to defeat pancreatic cancer cell resistance to the chemotherapeutic gemcitabine drug. Molecular Cancer Therapeutics. 2009; 8:809–820. [PubMed: 19372554]

Guo XZ, Zhang WW, Wang LS, Lu ZZ, Wang H, Xu JH, et al. Adenovirus-mediated overexpression of KAI1 suppresses sphingosine kinase activation and metastasis of pancreatic carcinoma cells. Zhonghua Nei Ke Za Zhi. 2006; 45:752–754. [PubMed: 17166452]

Hait NC, Sarkar S, Le Stunff H, Mikami A, Maceyka M, Milstien S, et al. Role of sphingosine kinase 2 in cell migration toward epidermal growth factor. The Journal of Biological Chemistry. 2005; 280:29462–29469. [PubMed: 15951439]

Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, Singh SK, et al. Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science. 2009; 325:1254–1257. [PubMed: 19729656]

Hannun YA, Luberto C. Ceramide in the eukaryotic stress response. Trends in Cell Biology. 2000; 10:73–80. [PubMed: 10652518]

Heffernan-Stroud LA, Helke KL, Jenkins RW, De Costa AM, Hannun YA, Obeid LM. Defining a role for sphingosine kinase 1 in p53-dependent tumors. Oncogene. 2012; 31:1166–1175. [PubMed: 21765468]

Hla T. Physiological and pathological actions of sphingosine 1-phosphate. Seminars in Cell & Developmental Biology. 2004; 15:513–520. [PubMed: 15271296]

Hofmann LP, Ren S, Schwalm S, Pfeilschifter J, Huwiler A. Sphingosine kinase 1 and 2 regulate the capacity of mesangial cells to resist apoptotic stimuli in an opposing manner. Biological Chemistry. 2008; 389:1399–1407. [PubMed: 18783337]

Illuzzi G, Bernacchioni C, Aureli M, Prioni S, Frera G, Donati C, et al. Sphingosine kinase mediates resistance to the synthetic retinoid N-(4-hydroxyphenyl) retinamide in human ovarian cancer cells. The Journal of Biological Chemistry. 2010; 285:18594–18602. [PubMed: 20404323]

Jeng YJ, Suarez VR, Izban MG, Wang HQ, Soloff MS. Progesterone-induced sphingosine kinase-1 expression in the rat uterus during pregnancy and signaling consequences. American Journal of Physiology, Endocrinology and Metabolism. 2007; 292:E1110–E1121. [PubMed: 17164439]

Johnson KR, Becker KP, Facchinetti MM, Hannun YA, Obeid LM. PKC-dependent activation of sphingosine kinase 1 and translocation to the plasma membrane. Extracellular release of sphingosine-1-phosphate induced by phorbol 12-myristate 13-acetate (PMA). The Journal of Biological Chemistry. 2002; 277:35257–35262. [PubMed: 12124383]

Johnson KR, Johnson KY, Crellin HG, Ogretmen B, Boylan AM, Harley RA, et al. Immunohistochemical distribution of sphingosine kinase 1 in normal and tumor lung tissue. Journal of Histochemistry and Cytochemistry. 2005; 53:1159–1166. [PubMed: 15923363]

Kacer D, McIntire C, Kirov A, Kany E, Roth J, Liaw L, et al. Regulation of non-classical FGF1 release and FGF-dependent cell transformation by CBF1-mediated notch signaling. Journal of Cellular Physiology. 2011; 226:3064–3075. [PubMed: 21302306]

Kapitonov D, Allegood JC, Mitchell C, Hait NC, Almenara JA, Adams JK, et al. Targeting sphingosine kinase 1 inhibits Akt signaling, induces apoptosis, and suppresses growth of human glioblastoma cells and xenografts. Cancer Research. 2009; 69:6915–6923. [PubMed: 19723667]

Kartal M, Saydam G, Sahin F, Baran Y. Resveratrol triggers apoptosis through regulating ceramide metabolizing genes in human K562 chronic myeloid leukemia cells. Nutrition and Cancer. 2011; 63:637–644. [PubMed: 21500096]

Kawamori T, Kaneshiro T, Okumura M, Maalouf S, Uflacker A, Bielawski J, et al. Role for sphingosine kinase 1 in colon carcinogenesis. The FASEB Journal. 2009; 23:405–414. [PubMed: 18824518]

Kennedy AJ, Mathews TP, Kharel Y, Field SD, Moyer ML, East JE, et al. Development of amidine-based sphingosine kinase 1 nanomolar inhibitors and reduction of sphingosine 1-phosphate in human leukemia cells. Journal of Medicinal Chemistry. 2011; 54:3524–3548. [PubMed: 21495716]

Kimura T, Watanabe T, Sato K, Kon J, Tomura H, Tamama K, et al. Sphingosine 1-phosphate stimulates proliferation and migration of human endothelial cells possibly through the lipid receptors, Edg-1 and Edg-3. The Biochemical Journal. 2000; 348:71–76. [PubMed: 10794715]

Knapp P, Baranowski M, Knapp M, Zabielski P, Blachnio-Zabielska AU, Gorski J. Altered sphingolipid metabolism in human endometrial cancer. Prostaglandins & Other Lipid Mediators. 2010; 92:62–66. [PubMed: 20226264]

Kohno M, Momoi M, Oo ML, Paik JH, Lee YM, Venkataraman K, et al. Intracellular role for sphingosine kinase 1 in intestinal adenoma cell proliferation. Molecular and Cellular Biology. 2006; 26:7211–7223. [PubMed: 16980623]

Kolmakova A, Rajesh M, Zang D, Pili R, Chatterjee S. VEGF recruits lactosylceramide to induce endothelial cell adhesion molecule expression and angiogenesis in vitro and in vivo. Glycoconjugate Journal. 2009; 26:547–558. [PubMed: 19219548]

Kwon YG, Min JK, Kim KM, Lee DJ, Billiar TR, Kim YM. Sphingosine 1-phosphate protects human umbilical vein endothelial cells from serum-deprived apoptosis by nitric oxide production. The Journal of Biological Chemistry. 2001; 276:10627–10633. [PubMed: 11134047]

LaMontagne K, Littlewood-Evans A, Schnell C, O'Reilly T, Wyder L, Sanchez T, et al. Antagonism of sphingosine-1-phosphate receptors by FTY720 inhibits angiogenesis and tumor vascularization. Cancer Research. 2006; 66:221–231. [PubMed: 16397235]

Lavieu G, Scarlatti F, Sala G, Carpentier S, Levade T, Ghidoni R, et al. Regulation of autophagy by sphingosine kinase 1 and its role in cell survival during nutrient starvation. The Journal of Biological Chemistry. 2006; 281:8518–8527. [PubMed: 16415355]

Le Scolan E, Pchejetski D, Banno Y, Denis N, Mayeux P, Vainchenker W, et al. Overexpression of sphingosine kinase 1 is an oncogenic event in erythroleukemic progression. Blood. 2005; 106:1808–1816. [PubMed: 15890687]

Lee MJ, Thangada S, Claffey KP, Ancellin N, Liu CH, Kluk M, et al. Vascular endothelial cell adherens junction assembly and morphogenesis induced by sphingosine-1-phosphate. Cell. 1999; 99:301–312. [PubMed: 10555146]

Li T, Chen L. Alphastatin inhibits tumor angiogenesis in nude mice bearing human gastric cancer xenografts. Zhonghua Wei Chang Wai Ke Za Zhi. 2009; 12:61–64. [PubMed: 19145507]

Li QF, Huang WR, Duan HF, Wang H, Wu CT, Wang LS. Sphingosine kinase-1 mediates BCR/ABL-induced upregulation of Mcl-1 in chronic myeloid leukemia cells. Oncogene. 2007a; 26:7904–7908. [PubMed: 17599053]

Li QF, Wu CT, Duan HF, Sun HY, Wang H, Lu ZZ, et al. Activation of sphingosine kinase mediates suppressive effect of interleukin-6 on human multiple myeloma cell apoptosis. British Journal of Haematology. 2007b; 138:632–639. [PubMed: 17686057]

Li J, Guan HY, Gong LY, Song LB, Zhang N, Wu J, et al. Clinical significance of sphingosine kinase-1 expression in human astrocytomas progression and overall patient survival. Clinical Cancer Research. 2008; 14:6996–7003. [PubMed: 18980995]

Li W, Yu CP, Xia JT, Zhang L, Weng GX, Zheng HQ, et al. Sphingosine kinase 1 is associated with gastric cancer progression and poor survival of patients. Clinical Cancer Research. 2009; 15:1393–1399. [PubMed: 19228740]

Li QF, Zhu HY, Yang YF, Liu J, Xiao FJ, Zhang QW, et al. Prokineticin-1/endocrine gland-derived vascular endothelial growth factor is a survival factor for human multiple myeloma cells. Leukemia & Lymphoma. 2010; 51:1902–1912. [PubMed: 20795791]

Li QF, Yan J, Zhang K, Yang YF, Xiao FJ, Wu CT, et al. Bortezomib and sphingosine kinase inhibitor interact synergistically to induces apoptosis in BCR/ABl+cells sensitive and resistant to STI571

through down-regulation Mcl-1. Biochemical and Biophysical Research Communications. 2011; 405:31–36. [PubMed: 21195056]

Lim KG, Tonelli F, Li Z, Lu X, Bittman R, Pyne S, et al. FTY720 analogues as sphingosine kinase 1 inhibitors: Enzyme inhibition kinetics, allosterism, proteasomal degradation, and actin rearrangement in MCF-7 breast cancer cells. The Journal of Biological Chemistry. 2011; 286:18633–18640. [PubMed: 21464128]

Lim KG, Gray AI, Pyne S, Pyne NJ. Resveratrol dimers are novel sphingosine kinase 1 inhibitors and affect sphingosine kinase 1 expression and cancer cell growth and survival. British Journal of Pharmacology. 2012; 166(5):1605–1616. [PubMed: 22251058]

Ling B, Chen L, Alcorn J, Ma B, Yang J. Sphingosine-1-phosphate: A potential therapeutic agent against human breast cancer. Investigational New Drugs. 2011; 29(2):396–399. [PubMed: 20041340]

Liu G, Zheng H, Zhang Z, Wu Z, Xiong H, Li J, et al. Overexpression of sphingosine kinase 1 is associated with salivary gland carcinoma progression and might be a novel predictive marker for adjuvant therapy. BMC Cancer. 2010a; 10:495. [PubMed: 20846391]

Liu XY, Yang YF, Wu CT, Xiao FJ, Zhang QW, Ma XN, et al. Spred2 is involved in imatinib-induced cytotoxicity in chronic myeloid leukemia cells. Biochemical and Biophysical Research Communications. 2010b; 393:637–642. [PubMed: 20153728]

Long JS, Edwards J, Watson C, Tovey S, Mair KM, Schiff R, et al. Sphingosine kinase 1 induces tolerance to human epidermal growth factor receptor 2 and prevents formation of a migratory phenotype in response to sphingosine 1-phosphate in estrogen receptor-positive breast cancer cells. Molecular and Cellular Biology. 2010; 30:3827–3841. [PubMed: 20516217]

Lopez-Tobon A, Cepeda-Prado E, Cardona-Gomez GP. Decrease of Tau hyperphosphorylation by 17beta estradiol requires sphingosine kinase in a glutamate toxicity model. Neurochemical Research. 2009; 34:2206–2214. [PubMed: 19543831]

Loveridge C, Tonelli F, Leclercq T, Lim KG, Long JS, Berdyshev E, et al. The sphingosine kinase 1 inhibitor 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole induces proteasomal degradation of sphingosine kinase 1 in mammalian cells. The Journal of Biological Chemistry. 2010; 285:38841–38852. [PubMed: 20926375]

Malavaud B, Pchejetski D, Mazerolles C, de Paiva GR, Calvet C, Doumerc N, et al. Sphingosine kinase-1 activity and expression in human prostate cancer resection specimens. European Journal of Cancer. 2010; 46:3417–3424. [PubMed: 20970322]

Marfe G, Di Stefano C, Gambacurta A, Ottone T, Martini V, Abruzzese E, et al. Sphingosine kinase 1 overexpression is regulated by signaling through PI3K, AKT2, and mTOR in imatinib-resistant chronic myeloid leukemia cells. Experimental Hematology. 2011; 39(653–665):e6.

Martin JL, Lin MZ, McGowan EM, Baxter RC. Potentiation of growth factor signaling by insulin-like growth factor-binding protein-3 in breast epithelial cells requires sphingosine kinase activity. The Journal of Biological Chemistry. 2009; 284:25542–25552. [PubMed: 19633297]

Masood R, Roy I, Zu S, Hochstim C, Yong KT, Law WC, et al. Gold nanorod-sphingosine kinase siRNA nanocomplexes: A novel therapeutic tool for potent radiosensitization of head and neck cancer. Integrative Biology: Quantitative Biosciences from Nano to Macro. 2012; 4:132–141. [PubMed: 22159374]

Mathias S, Peña LA, Kolesnick RN. Signal transduction of stress via ceramide. The Biochemical Journal. 1998; 335:465–480. [PubMed: 9794783]

Meyer zu Heringdorf D, Jakobs KH. Renal mesangial cells: Moving on sphingosine kinase-1. British Journal of Pharmacology. 2007; 150:255–257. [PubMed: 17200675]

Miller AV, Alvarez SE, Spiegel S, Lebman DA. Sphingosine kinases and sphingosine-1-phosphate are critical for transforming growth factor beta-induced extracellular signal-regulated kinase 1 and 2 activation and promotion of migration and invasion of esophageal cancer cells. Molecular and Cellular Biology. 2008; 28:4142–4151. [PubMed: 18426913]

Min J, Van Veldhoven PP, Zhang L, Hanigan MH, Alexander H, Alexander S. Sphingosine-1-phosphate lyase regulates sensitivity of human cells to select chemotherapy drugs in a p38-dependent manner. Molecular Cancer Research. 2005; 3:287–296. [PubMed: 15886300]

Misasi R, Sorice M, Di Marzio L, Campana WM, Molinari S, Cifone MG, et al. Prosaposin treatment induces PC12 entry in the S phase of the cell cycle and prevents apoptosis: Activation of ERKs and sphingosine kinase. The FASEB Journal. 2001; 15:467–474. [PubMed: 11156962]

Mizugishi K, Yamashita T, Olivera A, Miller GF, Spiegel S, Proia RL. Essential role for sphingosine kinases in neural and vascular development. Molecular and Cellular Biology. 2005; 25:11113–11121. [PubMed: 16314531]

Mizugishi K, Li C, Olivera A, Bielawski J, Bielawska A, Deng CX, et al. Maternal disturbance in activated sphingolipid metabolism causes pregnancy loss in mice. The Journal of Clinical Investigation. 2007; 117:2993–3006. [PubMed: 17885683]

Mora R, Dokic I, Kees T, Huber CM, Keitel D, Geibig R, et al. Sphingolipid rheostat alterations related to transformation can be exploited for specific induction of lysosomal cell death in murine and human glioma. Glia. 2010; 58:1364–1383. [PubMed: 20607862]

Morris MA, Gibb DR, Picard F, Brinkmann V, Straume M, Ley K. Transient T cell accumulation in lymph nodes and sustained lymphopenia in mice treated with FTY720. European Journal of Immunology. 2005; 35:3570–3580. [PubMed: 16285007]

Mu Z, Wang H, Zhang J, Li Q, Wang L, Guo X. KAI1/CD82 suppresses hepatocyte growth factor-induced migration of hepatoma cells via upregulation of Sprouty2. Science in China. Series C, Life Sciences. 2008; 51:648–654. [PubMed: 18622748]

Murakami M, Ichihara M, Sobue S, Kikuchi R, Ito H, Kimura A, et al. RET signaling-induced SPHK1 gene expression plays a role in both GDNF-induced differentiation and MEN2-type oncogenesis. Journal of Neurochemistry. 2007; 102:1585–1594. [PubMed: 17555548]

Nagahashi M, Ramachandran S, Kim EY, Allegood JC, Rashid OM, Yamada A, et al. Sphingosine-1-phosphate produced by sphingosine kinase 1 promotes breast cancer progression by stimulating angiogenesis and lymphangiogenesis. Cancer Research. 2012; 72:726–735. [PubMed: 22298596]

Nagaoka Y, Otsuki K, Fujita T, Uesato S. Effects of phosphorylation of immunomodulatory agent FTY720 (fingolimod) on antiproliferative activity against breast and colon cancer cells. Biological & Pharmaceutical Bulletin. 2008; 31:1177–1181. [PubMed: 18520051]

Nava VE, Cuvillier O, Edsall LC, Kimura K, Milstien S, Gelmann EP, et al. Sphingosine enhances apoptosis of radiation-resistant prostate cancer cells. Cancer Research. 2000; 60:4468–4474. [PubMed: 10969794]

Nava VE, Hobson JP, Murthy S, Milstien S, Spiegel S. Sphingosine kinase type 1 promotes estrogen-dependent tumorigenesis of breast cancer MCF-7 cells. Experimental Cell Research. 2002; 281:115–127. [PubMed: 12441135]

Nemoto S, Nakamura M, Osawa Y, Kono S, Itoh Y, Okano Y, et al. Sphingosine kinase isoforms regulate oxaliplatin sensitivity of human colon cancer cells through ceramide accumulation and Akt activation. The Journal of Biological Chemistry. 2009; 284:10422–10432. [PubMed: 19240026]

Nunes J, Naymark M, Sauer L, Muhammad A, Keun H, Sturge J, et al. Circulating sphingosine-1-phosphate and erythrocyte sphingosine kinase-1 activity as novel biomarkers for early prostate cancer detection. British Journal of Cancer. 2012; 106(5):909–915. [PubMed: 22315056]

Okada T, Ding G, Sonoda H, Kajimoto T, Haga Y, Khosrowbeygi A, et al. Involvement of N-terminally extended form of sphingosine kinase 2 in serum-dependent regulation of cell proliferation and apoptosis. Journal of Chemical Biology. 2005; 280:36318–36325.

Olivera A, Spiegel S. Sphingosine-1-phosphate as second messenger in cell proliferation induced by PDGF and FCS mitogens. Nature. 1993; 365:557–560. [PubMed: 8413613]

Oyama O, Sugimoto N, Qi X, Takuwa N, Mizugishi K, Koizumi J, et al. The lysophospholipid mediator sphingosine-1-phosphate promotes angiogenesis in vivo in ischaemic hindlimbs of mice. Cardiovascular Research. 2008; 78:301–307. [PubMed: 18187460]

Pallis M. Sphingosine kinase inhibitors in the apoptosis of leukaemia cells. Leukemia Research. 2002; 26:415–416. [PubMed: 11839389]

Pan J, Tao YF, Zhou Z, Cao BR, Wu SY, Zhang YL, et al. An novel role of sphingosine kinase-1 (SPHK1) in the invasion and metastasis of esophageal carcinoma. Journal of Translational Medicine. 2011; 9:157. [PubMed: 21936950]

Park SR, Cho HJ, Moon KJ, Chun KH, Kong SY, Yoon SS, et al. Cytotoxic effects of novel phytosphingosine derivatives, including N, N-dimethylphytosphingosine and N-monomethylphytosphingosine, in human leukemia cell line HL60. Leukemia & Lymphoma. 2010; 51:132–145. [PubMed: 20001229]

Paugh SW, Paugh BS, Rahmani M, Kapitonov D, Almenara JA, Kordula T, et al. A selective sphingosine kinase 1 inhibitor integrates multiple molecular therapeutic targets in human leukemia. Blood. 2008; 112:1382–1391. [PubMed: 18511810]

Paugh BS, Bryan L, Paugh SW, Wilczynska KM, Alvarez SM, Singh SK, et al. Interleukin-1 regulates the expression of sphingosine kinase 1 in glioblastoma cells. The Journal of Biological Chemistry. 2009; 284:3408–3417. [PubMed: 19074142]

Pchejetski D, Golzio M, Bonhoure E, Calvet C, Doumerc N, Garcia V, et al. Sphingosine kinase-1 as a chemotherapy sensor in prostate adenocarcinoma cell and mouse models. Cancer Research. 2005; 65:11667–11675. [PubMed: 16357178]

Pchejetski D, Doumerc N, Golzio M, Naymark M, Teissie J, Kohama T, et al. Chemosensitizing effects of sphingosine kinase-1 inhibition in prostate cancer cell and animal models. Molecular Cancer Therapeutics. 2008; 7:1836–1845. [PubMed: 18644996]

Pchejetski D, Bohler T, Brizuela L, Sauer L, Doumerc N, Golzio M, et al. FTY720 (fingolimod) sensitizes prostate cancer cells to radiotherapy by inhibition of sphingosine kinase-1. Cancer Research. 2010; 70:8651–8661. [PubMed: 20959468]

Permpongkosol S, Wang JD, Takahara S, Matsumiya K, Nonomura N, Nishimura K, et al. Anticarcinogenic effect of FTY720 in human prostate carcinoma DU145 cells: Modulation of mitogenic signaling, FAK, cell-cycle entry and apoptosis. International Journal of Cancer. 2002; 98:167–172. [PubMed: 11857403]

Perry DK, Hannun YA. The role of ceramide in cell signaling. Molecular and Cell Biology of Lipids. 1998; 1436:233–243.

Petak I, Vernes R, Szucs KS, Anozie M, Izeradjene K, Douglas L, et al. A caspase-8-independent component in TRAIL/Apo-2L-induced cell death in human rhabdomyosarcoma cells. Cell Death and Differentiation. 2003; 10:729–739. [PubMed: 12761581]

Pewzner-Jung Y, Brenner O, Braun S, Laviad EL, Ben-Dor S, Feldmesser E, et al. A critical role for ceramide synthase 2 in liver homeostasis: II. Insights into molecular changes leading to hepatopathy. The Journal of Biological Chemistry. 2010; 285:10911–10923. [PubMed: 20110366]

Pitman MR, Pitson SM. Inhibitors of the sphingosine kinase pathway as potential therapeutics. Current Cancer Drug Targets. 2010; 10:354–367. [PubMed: 20370685]

Pyne S, Bittman R, Pyne NJ. Sphingosine kinase inhibitors and cancer: Seeking the golden sword of Hercules. Cancer Research. 2011; 71:6576–6582. [PubMed: 21940750]

Radeff-Huang J, Seasholtz TM, Chang JW, Smith JM, Walsh CT, Brown JH. Tumor necrosis factor-alpha-stimulated cell proliferation is mediated through sphingosine kinase-dependent Akt activation and cyclin D expression. The Journal of Biological Chemistry. 2007; 282:863–870. [PubMed: 17114809]

Ramachandran S, Shida D, Nagahashi M, Fang X, Milstien S, Takabe K, et al. Lysophosphatidic acid stimulates gastric cancer cell proliferation via ERK1-dependent upregulation of sphingosine kinase 1 transcription. FEBS Letters. 2010; 584:4077–4082. [PubMed: 20804754]

Raymond MN, Bole-Feysot C, Banno Y, Tanfin Z, Robin P. Endothelin-1 inhibits apoptosis through a sphingosine kinase 1-dependent mechanism in uterine leiomyoma ELT3 cells. Endocrinology. 2006; 147:5873–5882. [PubMed: 16959847]

Ren J, Dong L, Xu CB, Pan BR. Expression of sphingosine kinase gene in the interactions between human gastric carcinoma cell and vascular endothelial cell. World Journal of Gastroenterology. 2002; 8:602–607. [PubMed: 12174364]

Ren S, Xin C, Pfeilschifter J, Huwiler A. A novel mode of action of the putative sphingosine kinase inhibitor 2-(p-hydroxyanilino)-4-(p-chlorophenyl) thiazole (SKI II): Induction of lysosomal sphingosine kinase 1 degradation. Cellular Physiology and Biochemistry. 2010; 26:97–104. [PubMed: 20502009]

Ricci C, Onida F, Servida F, Radaelli F, Saporiti G, Todoerti K, et al. In vitro anti-leukaemia activity of sphingosine kinase inhibitor. British Journal of Haematology. 2009; 144:350–357. [PubMed: 19036099]

Ruckhaberle E, Rody A, Engels K, Gaetje R, von Minckwitz G, Schiffmann S, et al. Microarray analysis of altered sphingolipid metabolism reveals prognostic significance of sphingosine kinase 1 in breast cancer. Breast Cancer Research and Treatment. 2008; 112:41–52. [PubMed: 18058224]

Salas A, Ponnusamy S, Senkal CE, Meyers-Needham M, Selvam SP, Saddoughi SA, et al. Sphingosine kinase-1 and sphingosine 1-phosphate receptor 2 mediate Bcr-Abl1 stability and drug resistance by modulation of protein phosphatase 2A. Blood. 2011; 117:5941–5952. [PubMed: 21527515]

Sarkar S, Maceyka M, Hait NC, Paugh SW, Sankala H, Milstien S, et al. Sphingosine kinase 1 is required for migration, proliferation and survival of MCF-7 human breast cancer cells. FEBS Letters. 2005; 579:5313–5317. [PubMed: 16194537]

Sato K, Ishikawa K, Ui M, Okajima F. Sphingosine 1-phosphate induces expression of early growth response-1 and fibroblast growth factor-2 through mechanism involving extracellular signal-regulated kinase in astroglial cells. Brain Research. Molecular Brain Research. 1999; 74:182–189. [PubMed: 10640689]

Sauer L, Nunes J, Salunkhe V, Skalska L, Kohama T, Cuvillier O, et al. Sphingosine kinase 1 inhibition sensitizes hormone-resistant prostate cancer to docetaxel. International Journal of Cancer. 2009; 125:2728–2736. [PubMed: 19521959]

Schwalm S, Doll F, Romer I, Bubnova S, Pfeilschifter J, Huwiler A. Sphingosine kinase-1 is a hypoxia-regulated gene that stimulates migration of human endothelial cells. Biochemical and Biophysical Research Communications. 2008; 368:1020–1025. [PubMed: 18261991]

Sharma AK. Sphingo-guanidines and their use as inhibitors of sphingosine kinase (WO2010078247). Expert Opinion on Therapeutic Patents. 2011; 21:807–812. [PubMed: 21457086]

Sharma AK, Sk UH, Gimbor MA, Hengst JA, Wang X, Yun J, et al. Synthesis and bioactivity of sphingosine kinase inhibitors and their novel aspirinyl conjugated analogs. European Journal of Medicinal Chemistry. 2010; 45:4149–4156. [PubMed: 20598402]

Shida D, Fang X, Kordula T, Takabe K, Lepine S, Alvarez SE, et al. Cross-talk between LPA1 and epidermal growth factor receptors mediates up-regulation of sphingosine kinase 1 to promote gastric cancer cell motility and invasion. Cancer Research. 2008a; 68:6569–6577. [PubMed: 18701480]

Shida D, Takabe K, Kapitonov D, Milstien S, Spiegel S. Targeting SphK1 as a new strategy against cancer. Current Drug Targets. 2008b; 9:662–673. [PubMed: 18691013]

Shirai K, Kaneshiro T, Wada M, Furuya H, Bielawski J, Hannun YA, et al. A role of sphingosine kinase 1 in head and neck carcinogenesis. Cancer Prevention Research (Philadelphia, Pa.). 2011; 4:454–462.

Shu X, Wu W, Mosteller RD, Broek D. Sphingosine kinase mediates vascular endothelial growth factor-induced activation of ras and mitogen-activated protein kinases. Molecular and Cellular Biology. 2002; 22:7758–7768. [PubMed: 12391145]

Sinha UK, Schorn VJ, Hochstim C, Chinn SB, Zhu S, Masood R. Increased radiation sensitivity of head and neck squamous cell carcinoma with sphingosine kinase 1 inhibition. Head & Neck. 2011; 33:178–188. [PubMed: 20848438]

Snider AJ, Kawamori T, Bradshaw SG, Orr KA, Gilkeson GS, Hannun YA, et al. A role for sphingosine kinase 1 in dextran sulfate sodium-induced colitis. The FASEB Journal. 2009; 23:143–152. [PubMed: 18815359]

Sobue S, Hagiwara K, Banno Y, Tamiya-Koizumi K, Suzuki M, Takagi A, et al. Transcription factor specificity protein 1 (Sp1) is the main regulator of nerve growth factor-induced sphingosine kinase 1 gene expression of the rat pheochromocytoma cell line, PC12. Journal of Neurochemistry. 2005; 95:940–949. [PubMed: 16135093]

Sobue S, Nemoto S, Murakami M, Ito H, Kimura A, Gao S, et al. Implications of sphingosine kinase 1 expression level for the cellular sphingolipid rheostat: Relevance as a marker for daunorubicin sensitivity of leukemia cells. International Journal of Hematology. 2008; 87:266–275. [PubMed: 18283525]

Somenzi G, Sala G, Rossetti S, Ren M, Ghidoni R, Sacchi N. Disruption of retinoic acid receptor alpha reveals the growth promoter face of retinoic acid. PLoS One. 2007; 2:e836. [PubMed: 17786207]

Song L, Xiong H, Li J, Liao W, Wang L, Wu J, et al. Sphingosine kinase-1 enhances resistance to apoptosis through activation of PI3K/Akt/NF-kappaB pathway in human non-small cell lung cancer. Clinical Cancer Research. 2011; 17:1839–1849. [PubMed: 21325072]

Spiegel S, Milstien S. Sphingosine-1-phosphate: An enigmatic signalling lipid. Nature Reviews Molecular Cell Biology. 2003; 4:397–407. [PubMed: 12728273]

Sukocheva OA, Wang L, Albanese N, Pitson SM, Vadas MA, Xia P. Sphingosine kinase transmits estrogen signaling in human breast cancer cells. Molecular Endocrinology. 2003; 17:2002–2012. [PubMed: 12881510]

Sukocheva O, Wadham C, Holmes A, Albanese N, Verrier E, Feng F, et al. Estrogen transactivates EGFR via the sphingosine 1-phosphate receptor Edg-3: The role of sphingosine kinase-1. The Journal of Cell Biology. 2006; 173:301–310. [PubMed: 16636149]

Sukocheva O, Wang L, Verrier E, Vadas MA, Xia P. Restoring endocrine response in breast cancer cells by inhibition of the sphingosine kinase-1 signaling pathway. Endocrinology. 2009; 150:4484–4492. [PubMed: 19706837]

Taha TA, Argraves KM, Obeid LM. Sphingosine-1-phosphate receptors: Receptor specificity versus functional redundancy. Biochimica et Biophysica Acta. 2004; 1682:48–55. [PubMed: 15158755]

Taha TA, Kitatani K, El-Alwani M, Bielawski J, Hannun YA, Obeid LM. Loss of sphingosine kinase-1 activates the intrinsic pathway of programmed cell death: Modulation of sphingolipid levels and the induction of apoptosis. The FASEB Journal. 2006a; 20:482–484. [PubMed: 16507765]

Taha TA, Mullen TD, Obeid LM. A house divided: Ceramide, sphingosine, and sphingosine-1-phosphate in programmed cell death. Biochimica et Biophysica Acta. 2006b; 1758:2027–2036. [PubMed: 17161984]

Tamama K, Kon J, Sato K, Tomura H, Kuwabara A, Kimura T, et al. Extracellular mechanism through the Edg family of receptors might be responsible for sphingosine-1-phosphate-induced regulation of DNA synthesis and migration of rat aortic smooth-muscle cells. The Biochemical Journal. 2001; 353:139–146. [PubMed: 11115407]

Tavarini S, Colombaioni L, Garcia-Gil M. Sphingomyelinase metabolites control survival and apoptotic death in SH-SY5Y neuroblastoma cells. Neuroscience Letters. 2000; 285:185–188. [PubMed: 10806317]

Theilmeier G, Schmidt C, Herrmann J, Keul P, Schafers M, Herrgott I, et al. High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. Circulation. 2006; 114:1403–1409. [PubMed: 16982942]

Tonelli F, Lim KG, Loveridge C, Long J, Pitson SM, Tigyi G, et al. FTY720 and (S)-FTY720 vinylphosphonate inhibit sphingosine kinase 1 and promote its proteasomal degradation in human pulmonary artery smooth muscle, breast cancer and androgen-independent prostate cancer cells. Cellular Signalling. 2010; 22:1536–1542. [PubMed: 20570726]

Uddin S, Platanias LC. Sphingosine kinase is an attractive target for novel pharmacological interventions in non-Hodgkin lymphomas. Leukemia & Lymphoma. 2008; 49:850–851. [PubMed: 18464106]

Van Brocklyn JR, Jackson CA, Pearl DK, Kotur MS, Snyder PJ, Prior TW. Sphingosine kinase-1 expression correlates with poor survival of patients with glioblastoma multiforme: Roles of sphingosine kinase isoforms in growth of glioblastoma cell lines. Journal of Neuropathology and Experimental Neurology. 2005; 64:695–705. [PubMed: 16106218]

Visentin B, Vekich JA, Sibbald BJ, Cavalli AL, Moreno KM, Matteo RG, et al. Validation of an anti-sphingosine-1-phosphate antibody as a potential therapeutic in reducing growth, invasion, and angiogenesis in multiple tumor lineages. Cancer Cell. 2006; 9:225–238. [PubMed: 16530706]

Wang F, Van Brocklyn JR, Hobson JP, Movafagh S, Zukowska-Grojec Z, Milstien S, et al. Sphingosine 1-phosphate stimulates cell migration through a G(i)-coupled cell surface receptor. Potential involvement in angiogenesis. The Journal of Biological Chemistry. 1999; 274:35343–35350. [PubMed: 10585401]

Watson C, Long JS, Orange C, Tannahill CL, Mallon E, McGlynn LM, et al. High expression of sphingosine 1-phosphate receptors, S1P1 and S1P3, sphingosine kinase 1, and extracellular signal-regulated kinase-1/2 is associated with development of tamoxifen resistance in estrogen receptor-positive breast cancer patients. The American Journal of Pathology. 2010; 177:2205–2215. [PubMed: 20889557]

Woodcock JM, Ma Y, Coolen C, Pham D, Jones C, Lopez AF, et al. Sphingosine and FTY720 directly bind pro-survival 14-3-3 proteins to regulate their function. Cellular Signalling. 2010; 22:1291–1299. [PubMed: 20403428]

Xia P, Gamble JR, Rye KA, Wang L, Hii CS, Cockerill P, et al. Tumor necrosis factor-alpha induces adhesion molecule expression through the sphingosine kinase pathway. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95:14196–14201. [PubMed: 9826677]

Xia P, Wang L, Gamble JR, Vadas MA. Activation of sphingosine kinase by tumor necrosis factor-alpha inhibits apoptosis in human endothelial cells. The Journal of Biological Chemistry. 1999; 274:34499–34505. [PubMed: 10567432]

Xia P, Gamble JR, Wang L, Pitson SM, Moretti PA, Wattenberg BW, et al. An oncogenic role of sphingosine kinase. Current Biology. 2000; 10:1527–1530. [PubMed: 11114522]

Yan G, Chen S, You B, Sun J. Activation of sphingosine kinase-1 mediates induction of endothelial cell proliferation and angiogenesis by epoxyeicosatrienoic acids. Cardiovascular Research. 2008; 78:308–314. [PubMed: 18192241]

Young N, Pearl DK, Van Brocklyn JR. Sphingosine-1-phosphate regulates glioblastoma cell invasiveness through the urokinase plasminogen activator system and CCN1/Cyr61. Molecular Cancer Research. 2009; 7:23–32. [PubMed: 19147534]

Zhang H, Desai NN, Olivera A, Seki T, Brooker G, Spiegel S. Sphingosine-1-phosphate, a novel lipid, involved in cellular proliferation. The Journal of Cell Biology. 1991; 114:155–167. [PubMed: 2050740]

Zhang R, Shah MV, Yang J, Nyland SB, Liu X, Yun JK, et al. Network model of survival signaling in large granular lymphocyte leukemia. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105:16308–16313. [PubMed: 18852469]

Table 7.1

Consequences of upregulation of SK1 in cancer

Cancer type	Inducer (reference)	Result	Cell line
Breast adenocarcinoma	Prolactin or 17-β estradiol (Doll et al., 2007)	Proliferation and migration	MCF-7
	Estrogen (Sukocheva et al., 2006)	Release of S1P activates S1P3 receptor resulting in transactivation of enhanced growth factor receptor in a MMP-dependent manner	MCF-7
	EGF (Doll et al., 2005)	Proliferation and migration	MCF-7
	HER2 (Long et al., 2010)	Limits p21-activated protein kinase 1 and ERK1/2 signaling and desensitizes the S1P-induced formation of a migratory phenotype through negative feedback	ER+MCF-7 HER2
Esophageal adenocarcinoma	TGF-β (Miller et al., 2008)	ERK1/2 activation and progression of cancer through non-Smad signaling	OE33
Glioma	Hypoxia and HIF-2α (Anelli et al., 2008)	Neoangiogenesis	U87MG
	EGF and EGFRvIII (Estrada-Bernal et al., 2010)	Proliferation	U-1242, U-251, and U-251-E18
Hepatocellular carcinoma	Hepatopoietin Cn (Chang et al., 2010)	Increases cell viability, decreases trichostatin A-induced apoptosis, and upregulates myeloid cell leukemia-1	SMMC7721 and HepG2
Leukemia and lymphoma	PI3K/AKT2/mTOR (Marfe et al., 2011)	Imatinib resistance	K652
	12-Ootetradecanoyl-phorbol-13-acetate (Cuvillier and Levade, 2001)	Inhibits cytochrome *c* and Smac/DIABLO release	Jurkat, U937, HL-60
	BCR/ABL (Li et al., 2007a)	Upregulation of Mcl-1	BaF3
Multiple myeloma	IL-6 (Li et al., 2007b)	Protection from apoptosis	XG-7, SKo-007, U266
Neuroblastoma	17β-Estradiol (Lopez-Tobon et al., 2009)	Protects from glutamate-induced Tau hyperphosphorylation	SH-5Y5Y
Pheochromocytoma	Prosaposin Misasi et al., 2001	DNA synthesis and protection from apoptosis	PC12
Prostate adenocarcinoma	Dihydrotestosterone (Dayon et al., 2009)	Reestablishes cell proliferation of androgen-deprived cells	LNCaP

Table 7.2

Consequences of downregulation of SK1 in cancer

Cancer type	Inhibitor (reference)	Result	Cell line
Cervical adenocarcinoma	NADH (De Luca et al., 2010)	Antiproliferative	HeLa
Hepatocellular carcinoma	KAI1/CD82 overexpression, Sprouty2 (Mu et al., 2008)	Reduces migration induced by hepatocyte growth factor	SMMC-7721
Leukemia	Dasatinib (Gencer et al., 2011)	Apoptosis	K562 Meg-01
	Spred2 (Liu et al., 2010b)	Inhibits proliferation, induces apoptosis, and enhances imatinib-induced cytotoxicity	K652
	AKT2 suppression (Marfe et al., 2011)	Increased sensitivity to imatinib-induced apoptosis	K652
Leukemia and breast cancer	Resveratrol (Cakir et al., 2011; Kartal et al., 2011) and its dimers Ampelopsin A and Balanocarpol (Lim et al., 2012)	Apoptosis PARP cleavage	HL60, K562 MCF-7
Melanoma	AKT inhibitor BI-69A11 (Feng et al., 2011)	Antiproliferative	UACC 903 SW1
Neuroblastoma	Amyloid-β peptide (Gomez-Brouchet et al., 2007)	Apoptosis	SH-SY5Y
Pancreatic carcinoma	KAI1 overexpression (Guo et al., 2006)	Inhibits migration	PANC1
Prostate adenocarcinoma	Inhibition of PI3K/Akt pathway (Dayon et al., 2009)	Prevents neuroendocrine differentiation/transformation	LNCaP
	Docetaxel (Pchejetski et al., 2005)	Decreased tumor volume, reduced occurrence and number of metastases in a mouse model	PC-3
	Docetaxel (Sauer et al., 2009)	Apoptosis	PC-3 and DU145
	Gamma irradiation (Nava et al., 2000)	Apoptosis	TSU-Pr1
	Dietary polyphenols (Brizuela et al., 2010)	Apoptosis and decreased tumor growth	PC-3 and C4-2B

Table 7.3

Consequences of SK1 overexpression in cancer

Cancer type (reference)	Result of SK1 overexpression	Cell line
Breast adenocarcinoma (Sukocheva et al., 2003, 2009)	Prevents cell death and enhances proliferation and resistance to tamoxifen-induced growth arrest and apoptosis	MCF-7
Esophageal adenocarcinoma (Pan et al., 2011)	Increases the invasiveness of cells *in vitro* and cell growth and spontaneous metastasis *in vivo*	EC9706
Fibrosarcoma (Xia et al., 2000)	Leads to transformation and tumor formation	NIH3T3
Glioma (Guan et al., 2011b)	Protects cells from UV- or adriamycin-induced apoptosis through PI3K-dependent activation of Akt, inactivation of FOXO3a, and downregulation of Bim	U87MG and LN-382
Leukemia (Marfe et al., 2011)	Imatinib resistance	K562
Multiple myeloma (Li et al., 2007b)	Increases proliferation and survival, inhibits dexamethasone induced apoptosis, and upregulates Mcl-1	XG-7, SKo-007, U266
Non-small-cell-lung cancer (Song et al., 2011)	Inhibits doxorubicin- or docetaxel-induced apoptosis through activation of the PI3K/Akt/NF-κB pathway	95D and A549
Ovarian carcinoma (Illuzzi et al., 2010a, 2010b)	Induces *N*-(4-hydroxyphenyl) retinamide (HPR) resistance	A2780
Pheochromocytoma (Edsall et al., 2001)	Protects from apoptosis in response to trophic factor withdrawl or C2-ceramide treatment	PC12
Prostate adenocarcinoma (Pchejetski et al., 2005)	Increases tumor volume and resistance to docetaxel in a mouse model	PC-3

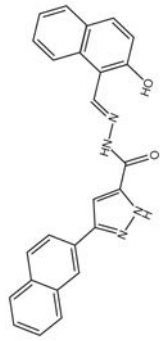
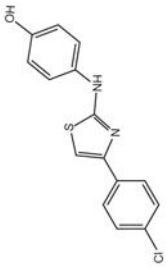
Table 7.4

Consequences of SK1 knockdown in cancer

Cancer type (reference)	Result of SK1 knockdown	Cell line
Bladder carcinoma (Shu et al., 2002)	Blocks VEGF-induced DNA synthesis and Ras-GTP and p-ERK accumulation	T24
Breast adenocarcinoma (Sukocheva et al., 2009; Sarkar et al., 2005)	Restores cell growth arrest and apoptosis in tamoxifen-resistant MCF-7 cells	MCF-7
	Reduced EGF and serum stimulated growth; enhanced sensitivity to doxorubicin	MCF-7
Colon adenocarcinoma (Nemoto et al., 2009)	Restores chemosensitivity to oxaliplatin including increased C16-ceramide, decreased pAkt, increased p53 and p21 protein levels and PARP cleavage	RKO
Gastric cancer (Fuereder et al., 2011)	Increases apoptosis, inhibits growth by 50%, and increases sensitivity to doxorubicin treatment	MKN28 and N87
Glioma (Radeff-Huang et al., 2007; Van Brocklyn et al., 2005)	Decreases TNF-α-stimulated Akt phosphorylation, cyclin D expression, and DNA synthesis	1321N1
	Decreases proliferation rate and prevents cells from exiting G1	U-1242 MG, U87MG
Glioma and breast adenocarcinoma (Anelli et al., 2010)	Decreased migration and tube formation in cocultured vascular or lymphatic endothelial cells	U87MG, MDA-MB-231
Head and neck squamous cell carcinoma (Shirai et al., 2011; Sinha et al., 2011)	Prevents 4-nitroquinoline-1-oxide-induced head and neck squamous cell carcinoma (HNSCC)	Mouse model
	Reduces xenograft tumor proliferation and volume synergistically with radiation treatment	SCC-15 in Mouse model
Leukemia (Salas et al., 2011; Bonhoure et al., 2008; Marfe et al., 2011; Li et al., 2007a; Sobue et al., 2008)	Reduces Bcr–Abl1 stability	K562/IMA-3 MEFs
	Apoptosis of imatinib-sensitive and resistant cells	Primary CML
	Increases sensitivity to imatinib-induced apoptosis in resistant cells and returns BCR–ABL to baseline levels	K562
	Enhances STI571-induced apoptosis	K562
	Increases daunorubicin sensitivity	K562
Non-small-cell-lung cancer (Song et al., 2011)	Increases doxorubicin- or docetaxel-induced apoptosis through decreased activation of the PI3K/Akt/NF-κB pathway	95D and A549
Prostate cancer (Cho et al., 2011)	Blocked expression of HIF-1α during hypoxia, decreased phospho-Akt and VEGF production	PC-3
Thyroid cancer (Guan et al., 2011a)	Leads to dephosphorylation of protein kinase B and glycogen synthase kinase-3β and subsequent inactivation of β-catenin-T-cell factor/lymphoid enhancing factor transcriptional activity and decreases cell proliferation	WRO, FRO, SW579
Various tumors (Heffernan-Stroud et al., 2012)	Protects p53 KO mice from thymic lymphoma and p53 heterozygote mice from sarcoma development to increase life span ~30%	Mouse model

Table 7.5

Effects of SK1 inhibitors in cancer

Inhibitor	Mechanism of action
 SKI-I (French et al., 2003)	Induces apoptosis and suppresses tumor growth rate and vascularization of glioblastoma xenografts (Kapitonov et al., 2009)
	Sensitizes pancreatic cancer cells to gemcitabine induced death (Guillermet-Guibert et al., 2009)
	Decreases growth and survival while enhancing apoptosis and Bcl-2 cleavage in leukemia cells (Paugh et al., 2008)
	Suppresses lysophosphatidic acid mediated proliferation in gastric cancer cells (Ramachandran et al., 2010)
	Suppressed S1P levels, decreased hemangiogenesis and lymphangiogenesis, reduced metastases to lymph nodes and lungs, and decreased overall tumor burden in murine model of breast cancer (Nagahashi et al., 2012)
	Blocked cell proliferation and induced apoptotic cell death in glioblastoma multiforme neurosphere cell line (Estrada-Bernal et al., 2010)
	Increases oxaliplatin-induced cytotoxicity in colon cancer (Nemoto et al., 2009)
	Increases sensitivity of non-small-cell-lung cancer cells to doxorubicin- or docetaxel-induced apoptosis (Song et al., 2011)
	Rescues daunorubicin sensitivity in leukemia cells (Sobue et al., 2008)
	Enhances ability of imatinib mesylate to inhibit cell growth, survival, and clonogenic potential in leukemia cells (Ricci et al., 2009)
	Sensitizes prostate and breast cancer cells to docetaxel (Sauer et al., 2009) (*as does B-5354c*)
	Reduces proliferation and sensitizes ovarian cancer cells to cytotoxic effect of *N*-(4-hydroxyphenyl) retinamide (Illuzzi et al., 2010a, 2010b)
	Impedes DHT-induced cell proliferation, DNA synthesis, and PSA secretion in prostate cancer cells (Dayon et al., 2009)
 SKI-II (French et al., 2003)	Blocks expression of urokinase plasminogen activator and its receptor to inhibit glioma cell invasion (Young et al., 2009)
	Prevents accumulation and transcriptional activity of HIF-1α in prostate, brain, breast, and lung cancer cells (Ader et al., 2008)
	Reduces cell colony formation and activates of caspase-3 in glioblastoma cells (Bektas et al., 2009)
	Antimigratory and toxic effects on human glioma and glioma stem cells (Mora et al., 2010)
	Blocks breast cancer viability, clonogenic survival, and proliferation and dose-dependently decreases estrogen-stimulated estrogen response element transcriptional activity (Antoon et al., 2011)
	Sensitizes HNSCC to radiation-induced cytotoxicity (Sinha et al., 2011)
	Induces proteasomal degradation of SK1 and apoptosis in androgen-sensitive prostate cancer cells Loveridge et al., 2010
	Triggers lysosomal degradation of SK1 rather than direct inhibition of SK1 in HEK293 cells and lung cancer cells (Ren et al., 2010)
	Increases Tau hyperphosphylation by glutamate in neuroblastoma cells (Lopez-Tobon et al., 2009)
SKI-I and SKI-II	Induce apoptosis of T-LGL leukemia PBMCs but not normal PBMCs (Zhang et al., 2008)
SKI-I, SKI-II, and SKI-V	Reduce rate of solid tumor growth when JC mammary adenocarcinoma cells injected into BALB/c mice (French et al., 2006)
SKI-I, SKI-II, SKI-III, SKI-IV, and SKI-V	Induce apoptosis of bladder cancer cells (French et al., 2003)
SKI-II and DMS	Decreases TNF-α-stimulated DNA synthesis in glioma cells (Radeff-Huang et al., 2007)
DMS	Sensitizes prostate cancer cells to gamma-irradiation (Nava et al., 2000)

Inhibitor	Mechanism of action
	Enhances cytochrome *c* and Smac/DIABLO release in leukemia cells (Cuvillier and Levade, 2001)
	Inhibits proliferation of Gastric Carcinoma cells (Ren et al., 2002)
	Increases sensitivity to imatinib-induced apoptosis in resistant chronic myeloid leukemia cells and returns BCR–ABL to baseline levels (Marfe et al., 2011)
DMS and DHS	Enhance apoptosis of leiomyoma cells in response to serum starvation by antagonizing the effects of endothelin-1 (Raymond et al., 2006)
DHS	Protects rhabdomyosarcoma cells from from TRAIL-induced apoptosis (Petak et al., 2003)
Phytosphingosine derivatives	Methylphytosphingosine induces apoptosis, decreases phophorylation of ERK, and inhibits daunorubicin-induced ERK activation in leukemia cells (Pewzner-Jung et al., 2010)
	Dimethylphytosphingosine suppresses cell growth and induces apoptosis in human leukemia cells; decreases phophorylation of ERK and inhibits daunorubicin-induced ERK activation to enhance its cytotoxicity in leukemia cells (Park et al., 2010)
F-12509a	Enhances imatinib-induced apoptosis in leukemia cells (Bonhoure et al., 2008)
B-5354c	Induces apoptosis and sensitizes prostate cancer cells to docetaxel and camptothecin to reduce tumor size *in vivo* (Pchejetski et al., 2005, 2008)