

Sphingosine kinase I as an anticancer therapeutic target

Ying Gao^{1,*}

Fei Gao^{2,*}

Kan Chen^{3,*}

Mei-li Tian¹

Dong-li Zhao¹

¹Department of Radiotherapy Oncology, First Affiliated Hospital of Xi'an Jiaotong University,

²Department of Neurology, First Affiliated Hospital of Xi'an Medical University, Xi'an, ³School of Life Sciences, Zhejiang Sci-Tech University, Hangzhou, People's Republic of China

*These authors contributed equally to this work

Abstract: The development of chemotherapeutic resistance is a major challenge in oncology. Elevated sphingosine kinase 1 (SK1) levels is predictive of a poor prognosis, and SK1 overexpression may confer resistance to chemotherapeutics. The SK/sphingosine-1-phosphate (S1P)/sphingosine-1-phosphate receptor (S1PR) signaling pathway has been implicated in the progression of various cancers and in chemotherapeutic drug resistance. Therefore, SK1 may represent an important target for cancer therapy. Targeting the SK/S1P/S1PR signaling pathway may be an effective anticancer therapeutic strategy, particularly in the context of overcoming drug resistance. This review summarizes our current understanding of the role of SK/S1P/S1PR signaling in cancer and development of SK1 inhibitors.

Keywords: sphingosine kinase 1, S1P, S1PR, inhibitors, cancer, therapy

Introduction

Cancer is a prominent killer. Oncologists rely heavily on chemotherapy in the fight against cancer. However, some patients exhibit chemotherapeutic resistance, which makes chemotherapy ineffective, resulting in unrestrained metastasis and ultimately, death. Thus, there is a need to study the mechanisms underlying the development of chemotherapeutic resistance so that effective therapies can be developed for patients who show signs of chemotherapeutic resistance.

SKI and cancer transformation

Sphingosine kinase 1 (SK1) has well-established prosurvival functions in cancer cells. Indeed, the transformation potential of *SK1* suggests that it may function as an oncogene.¹ The SK1 enzyme is activated by an oncogenic form of eukaryotic elongation factor 1A lacking a GDP-GTP binding domain, called PTI-1, and SK1 activation is required for PTI-1-induced neoplastic transformation.²

SK1 activity is increased when it is phosphorylated on its Ser225 residue by ERK-2.³ Furthermore, phosphorylation of *SK1* at Ser225 is important for its expression in the plasma membrane, and targeting of SK1 to the plasma membrane increases *SK1*'s capacity to promote transformation.⁴ Indeed, artificial targeting of tagged S225A SK1 mutant protein to the plasma membrane promotes transformation. CIB1, aka calmyrin, has also been shown to facilitate *SK1* translocation to the plasma membrane through its involvement in a calcium-myristoyl switch.⁵ The Asn89 and Thr54 residues of *SK1* are also important contributors to SK1's selective affinity to the plasma membrane. Specific interaction with the phosphatidyl serines in these residues makes sphingosine available for generation of sphingosine-1-phosphate (S1P) by SK1. S1P released into the extracellular milieu engages with sphingosine-1-phosphate receptors

Correspondence: Ying Gao; Dong-li Zhao
Department of Radiotherapy Oncology,
First Affiliated Hospital of Xi'an
Jiaotong University, 277 Yan Ta
West Road, Xi'an city, Xi'an 710061,
People's Republic of China
Tel +86 029 8532 4029
Email togaoying@163.com;
jdyfy223@163.com

(S1PRs) to induce prosurvival functions.⁶ There are five G protein-coupled receptors (S1PR1–5), and these are activated in an autocrine/paracrine manner.

Researchers have examined the potential role of *SK1* in regulating neoplastic transformation in *SK1*-transfected NIH3T3 fibroblasts and found that *SK1* transfection increases the transformation rate of these fibroblasts into fibrosarcoma cells.⁴ These findings are consistent with the notion that SK1 supports cancer transformation and tumor cell survival.¹ SK1 is also required for Ras-mediated cell transformation. The messenger (m)RNA and protein expression levels of *SK1* are two- to eightfold greater in various cancer tissues (eg, breast, lung, ovarian, stomach, and colon cancers) than in noncarcinoma control tissues. Moreover, growing evidence suggests that increased expression of *SK1* is associated with enhanced metastasis, decreased survival, and poor prognoses,^{7–9} suggesting that SK1 may be useful as a biomarker of prognosis.^{8,9} Moreover, small interfering (si) RNA-mediated downregulation of SK1 has been reported to reduce migration of breast cancer cells, implicating SK1 as a potential therapeutic target.^{10,11}

SK1's role in cancer progression, metastasis, and apoptosis

S1P, the product of SK1, binds tumor necrosis factor receptor-associated factor, an E3 ubiquitin ligase that modulates tumor necrosis factor- α -induced activation of NF- κ B signaling and induces K63-mediated polyubiquitination of receptor-interacting protein 1, leading to I κ B degradation.¹² S1P regulation of NF- κ B signaling is consistent with the notion that SK1/S1P may be involved in cancer progression.

Growing evidence points to a role of SK1-derived systemic S1P in mediating tumor metastasis. A recent finding suggests that serum S1P (not tumor S1P) is important for metastasis to the lungs. In addition, the anti-S1P antibody SphingomabTM has been reported to suppress lung metastasis by neutralizing both circulating and systemic S1P, and upregulating breast cancer metastasis suppressor 1 levels. Expression of breast cancer metastasis suppressor 1 is upregulated in cancer cells under conditions of systemic SK1 deficiency, through activation of the S1PR2 signaling pathway.^{13,14} These findings suggest that the SK1 signaling pathway blockade may represent a promising strategy for inhibiting metastasis.

S1P stimulates fibrosarcoma cell migration via activation of GTPases (eg, RAC1 and CDC42).^{15,16} Interestingly, S1P facilitates the migration of *S1PR3*-expressing gastric cancer cells but suppresses the motility of cell lines with predominant *S1PR2* expression.¹⁷ Meanwhile S1PR1 and S1PR3 have

been implicated in ovarian cancer cell invasion, through activation of calcium mobilization and phospholipase C.¹⁸ S1P binding to S1PR3 was shown to stimulate the accumulation of phosphorylated ERK-1/2 into membrane ruffles/lamellipodia and promote the migration of MCF-7 breast cancer cells.¹⁹ Elimination of SK1 resulted in reduced S1PR3 expression and attenuated ERK-1/2 pathway stimulation, leading to a lesser cancer cell migration. These findings suggest that regulation of S1PR3 expression, in particular, may help control metastasis.

SK1 has also been shown to exert antiapoptotic effects through the BAD-BCL2 pathway, wherein mitochondrion-to-cytoplasm translocation of *Smac/DIABLO* and *cytochrome c*, which is important for apoptosis, is inhibited.²⁰ Additionally, SK1 has been reported to protect against the apoptotic effects of sphingosine/ceramide via a delayed BCL2-independent pathway.²¹ Thus, expressing high levels of SK1 appears to shield cancer cells from apoptosis.

SK1 and cancer prognosis

Elevation of SK1 in tumors suggests a potential prognostic application. Increases in SK1 protein and mRNA expression accompany breast cancer progression. By way of an apparent negative feedback process, HER2-induced increases in SK1 levels result in reduced HER2 expression in estrogen receptor (ER)-positive breast cancer cells, thereby preventing S1P-induced migration of these cells.¹⁹ Meanwhile, high *SK1* expression levels in ER-negative breast cancer tumors have been associated with tamoxifen resistance, a higher chance of metastasis, and reduced survival.^{19,22,23} Furthermore, patients with ER-positive breast cancer who had high ERK-1/2 and cytoplasmic SK1 levels were found to experience recurrence 10.5 years earlier, on average, than patients with low levels.²² Therefore, clinical phenotype is an important consideration for the clinical application of SK1 inhibitors.

High *SK1* expression has also been associated with poor prognosis in patients with a glioblastoma multiforme (aka grade 4 astrocytoma) diagnosis, and *SK1*-knockdown can reduce proliferation of glioblastoma cells.²⁴ Furthermore, SK is necessary for glioma cell invasion and basal activity of the urokinase plasminogen activator system in glioblastoma multiforme.²⁵ High expression of SK1 also correlates with higher grade and shorter survival time in non-small cell lung cancer, gastric cancer, non-Hodgkin lymphoma, salivary gland carcinoma, esophageal carcinoma, astrocytoma, and head and neck squamous cell carcinoma.^{26–32} Interestingly, exogenous SK1 has been reported to enhance tumor cell invasiveness despite the fact that it is already overexpressed in many cancers.

Importantly, the relationship between SK1/S1P levels and cancer progression may differ between different forms of cancer. Although Gleason score and treatment failure rate have been found to correlate with tumoral SK1 activity in prostate cancer, patients with prostate cancer were found to have lower circulating levels of S1P in their erythrocytes than healthy controls.^{33,34} Moreover, decreased circulating S1P has been implicated as an early marker of cancer progression to hormonal unresponsiveness, and circulating S1P levels have been shown to correlate inversely with prostate-specific antigen levels and lymph node metastasis.³⁴

Elevated SK1 and chemotherapeutic resistance

Overexpression of SK1 may confer the development of resistance to chemotherapeutics, whereas disruption of SK1/S1P signaling may restore or improve sensitivity. The multi-drug resistant phenotype is associated with an overexpression of P-glycoprotein 1 (aka multidrug resistance protein 1) in tumor cells. Elevated SK1 has been associated with pancreatic cancer cell resistance to gemcitabine and chronic myeloid leukemia (CML) resistance to imatinib.^{35,36} Conversely, SK1 inhibition can sensitize pancreatic cancer and CML cells to the proapoptotic effects of gemcitabine and imatinib, respectively, apparently by increasing the ceramide/S1P ratio and thereby enabling C18-ceramide-dependent apoptosis to proceed.³⁵⁻³⁷ Thus, the relationship between the SK1/S1P pathway and sensitivity of cancer cells to chemotherapeutics may be due to a direct relation between bioactive sphingolipid levels and drug resistance. Indeed, SK1 has been shown to alter imatinib-induced apoptosis in primary CML cells,³⁷ and resistance to etoposide- or doxorubicin-induced apoptosis can be restored with an SK inhibitor (eg, F-12509a), supporting the notion that chemotherapeutic resistance may be the result of reduced ceramide accumulation and sustained SK1 activity.³⁸ Attenuation of SK1/S1P signaling can also improve the growth-inhibitory effects of nilotinib.³⁹ SK1 elimination or inhibition has been shown to stimulate apoptosis, whereas overexpression of SK1 was shown to reduce caspase activity and reduce apoptosis in imatinib-sensitive cells.⁴⁰ Likewise, daunorubicin sensitivity has been associated with low S1P and high ceramide levels, and it can be restored in daunorubicin-resistant cells by inhibition of SK1 activity or siRNA repression of *SK1* expression.⁴⁰ Consistent with these findings, metastatic colon cancer biopsies have shown higher SK1 expression than nonmetastatic specimens, whereas SK1 expression is negligible to nondetectable in normal colon mucosa.⁴¹ Importantly, given that colon cancer

is considered to be a COX2-regulated cancer, knockdown of *SK1* expression with siRNA reduces expression of COX2 and production of the COX2 product prostaglandin E2 in colon cancer cells.⁴¹ PC3 (androgen-insensitive) prostate cancer cells been shown to have upregulated SK1 levels and S1PR1/S1PR3 signaling, and are resistant to camptothecin treatment. However, these cells were shown to become sensitive to camptothecin following inhibition of SK.⁴² Likewise, increased SK1 activity also appears to be related to daunorubicin resistance in leukemia cells, cisplatin resistance in lung cancer cells, oxaliplatin resistance in colon cancer cells, and *N*-(4-hydroxyphenyl)retinamide resistance in ovarian carcinoma cells, as well as to docetaxel, doxorubicin, and tamoxifen resistance in breast cancer cells.^{37,43-46} Accordingly, knockdown or inhibition of *SK1* has been reported to enhance drug efficacy in leukemia cells, ovarian cancer, and colon cancer.^{38,44,45} Hence, together, the aforementioned findings suggest strongly that *SK1* plays a biologically significant role in chemotherapeutic drug resistance.

Different S1PRs appear to play the dominant role in SK1/S1P-related chemoresistance across different cancers. *S1PR2* mRNA was found to be elevated in nephroblastoma tissue relative to levels in healthy kidney tissue.⁴⁷ Additionally, in nephroblastoma cells, it was shown that *S1PR2* overexpression resulted in increased mRNA and protein expression of *COX2* and, correspondingly, increased synthesis of its product prostaglandin E2, and these effects could be blocked by S1PR2 antagonism, demonstrating that S1PR2 signaling is a strong driver of renal cancer progression.⁴⁷ Meanwhile, cytoplasmic expression levels of S1PR1 and S1PR3 in ER-positive breast cancer tumors associate negatively with patient survival.²² The protective influence of SK1 on prostate cancer cells has been shown to involve S1PR2/3 receptors, whereas chemoresistance can be attenuated with FTY720, a sphingosine analog that inhibits S1PR signaling and induces proteasome-mediated degradation of SK1.⁴⁸

SK1/S1PR targeting in anticancer therapeutics

Oncological targeting of SK1/S1P is attractive due to the proapoptotic and antiproliferative potential of SK1 inhibition. Various SK1/S1P and/or S1PR agents have been developed, as elaborated below.

Pan-SK inhibitors

SK inhibition has been shown to reduce the viability of glioblastoma multiforme cells, neuroblastoma cells, several types of leukemia cells, and various solid tumor cell lines.⁴⁹⁻⁵³

Importantly, SK inhibitors can, not only inhibit growth of temozolomide-resistant⁴⁹ and camptothecin-resistant cancer cells⁵⁴ but also, can reduce proliferation and induce apoptosis in multidrug-resistant tumor cells,⁷ suggesting they may be able to convert chemotherapeutic-resistant tumors into chemosensitive tumors. *N,N*-dimethyl sphingosine (DMS) and *L*-threo-dihydrosphingosine (Safingol) are competitive SK inhibitors that have inhibitory influences on protein kinase C and ceramide kinase; they activate sphingosine-mediated targets, such as casein kinase 2 and PI3K.^{55,56} DMS, in particular, has been shown to suppress the growth of multiple cancer cell lines.⁵⁷ Reported off-target effects of DMS include hemolysis and hepatotoxicity.⁵⁸

Selective SK inhibitors

With the aim of minimizing the secondary effects of chemotherapy, researchers have sought and developed agents with more selective effects. The selective SK1 inhibitors SK1-I and SK1-II have each been shown to induce apoptosis in T-cell large granular lymphocyte leukemia cells but not normal cells.⁵³ Likewise, although SK1-I potently induces apoptosis in leukemic cells, normal leukocytes are relatively spared.⁵² SK1-I has been shown to have efficacy against xenograft glioblastomas as well as orthotopic or acute myeloid leukemia xenograft tumors.^{52,59} Additionally, SK1-I has been shown to decrease serum S1P levels, promote cancer cell apoptosis, and reduce lymph node and lung metastasis in a murine breast cancer model.¹⁴ Combining SK1-I with a proteasome inhibitor has been reported to yield synergistic antigrowth and proapoptotic effects in imatinib-resistant leukemia cells, and these effects have been associated with downregulation of Mcl-1 and BCR/ABL.⁶⁰ Meanwhile, SK1-II has been shown to induce proteasomal degradation of SK1 in androgen-sensitive prostate cancer, breast cancer, and human pulmonary artery smooth muscle cells.⁶¹

There is great interest in the anticancer potential of the synthetic sphingosine analog FTY720 (2-amino-2-[2-(4-octylphenyl)]-1,3-propanediolhydrochloride), aka fingolimod. FTY720 is a competitive sphingosine inhibitor of SK1, and its analog (S)-FTY720 vinylphosphonate is a noncompetitive inhibitor of SK1. FTY720 and (S)-FTY720 vinylphosphonate have been reported to stimulate relocalization of actin away from the lamellipodia of breast cancer cells, suggesting these inhibitors' possible application for prevention of tumor metastasis.^{19,62}

Although the mechanism of FTY720's anticancer effects has not been clarified, evidence suggests that it may work through both caspase-dependent and caspase-independent

apoptotic pathways. FTY720 has been found to inhibit breast and colon cancer cell lines through S1PR-independent effects.²⁰ Binding of FTY720-phosphate on T-lymphocytes to S1P1 was shown to induce S1P1 downregulation and lymphopenia.⁶³ Both FTY720 and its analog (S)-FTY720 vinylphosphonate were shown to induce proteasomal degradation of SK1 and apoptosis in prostate and breast cancer cells.⁴⁸ They also prevented S1P-stimulated actin rearrangement in MCF-7 cells.⁶² FTY720 has been reported to increase prostate cancer sensitivity to radiation, and to reduce tumor growth and metastasis.⁶⁴ Meanwhile, SEW2871 (a S1PR1-specific antagonist) has been shown to suppress angiogenesis, indicating a receptor-dependent function.^{64,65} Other S1PR1 and S1PR1/3 receptor antagonists, such as VPC2309, VPC4416, W146, and VPC25239, have shown promising results *in situ*.^{66,67}

FTY720 is currently Food and Drug Administration (FDA)-approved for use as an immunosuppressant in patients with multiple sclerosis.⁶³ However, a great deal more research is required to delineate the receptor-dependent and -independent functions of FTY-720 in the context of its reported inhibitory effects on cancer cell proliferation. Synthetic SK1-specific inhibitors, such as 9ab, 6ag, and 12aa, have shown promising effects *in vitro*, but their efficacy has yet to be validated *in vivo*.⁶⁸

Anti-S1P antibodies

Anti-S1P monoclonal antibodies that specifically neutralize and target S1P have been reported to be effective against breast MDA-MB-231, lung A549, ovarian SKOV3, and melanoma F16/B10 cancer models *in vivo* and *in situ*. Anti-S1P antibodies, which function somewhat like a molecular sponge to neutralize S1P signaling, have been reported to favor tumor regression and inhibit lung metastasis in xenograft and allograft models. Spingomab (LT1002) and its humanized form (LT1009), not only neutralize VEGF- and bFGF-induced angiogenesis but also, block S1-induced endothelial cell tube migration and formation in numerous assays.⁶⁹

Conclusion

An accumulation of evidence indicates that the SK/S1P/S1PR signaling pathway plays a crucial role in various cancers and in sphingolipid-mediated drug resistance. Elevated expression of SK1 leads to an oncogenic phenotype, through SK1 effects on S1P production, and sphingosine and ceramide accumulation. Conversely, administration of SK1 inhibitors induces proteasomal degradation. Therefore, SK1 represents

a particularly interesting target for cancer therapy. Targeting the SK/S1P/S1PR signaling pathway may be an effective anticancer therapeutic strategy, particularly for overcoming drug resistance.

Acknowledgments

This study was supported by The National Natural Science Foundation of China (grant number 81301937) and by the International Cooperation Foundation of Shaanxi Province of China (grant number 2013KW-27-03).

Disclosure

The authors report no conflicts of interest in this work. This paper has not been published previously.

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