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Targeting sphingosine 1-phosphate and sphingosine kinases in pancreatic cancer: mechanisms and therapeutic potential

Khem Raj Limbu[1†], Rashmi Bhandari Chhetri[1†], Subin Kim[1], Jitendra Shrestha[2], Yoon Sin Oh[3], Dong Jae Baek[1*] and Eun-Young Park[1*]

Abstract

Pancreatic cancer is known to be the most lethal cancer. Fewer new treatments are being developed for pancreatic cancer as compared to other cancers. The bioactive lipid S1P, which is mainly regulated by sphingosine kinase 1 (SK1) and sphingosine kinase 2 (SK2) enzymes, plays significant roles in pancreatic cancer initiation and exacerbation. S1P controls many signaling pathways to modulate the progression of pancreatic cancer through the G-coupled receptor S1PR1-5. Several papers reporting amelioration of pancreatic cancer via modulation of S1P levels or downstream signaling pathways have previously been published. In this paper, for the first time, we have reviewed the results of previous studies to understand how S1P and its receptors contribute to the development of pancreatic cancer, and whether S1P can be a therapeutic target. In addition, we have also reviewed papers dealing with the effects of SK1 and SK2, which are kinases that regulate the level of S1P, on the pathogenesis of pancreatic cancer. We have also listed available drugs that particularly focus on S1P, S1PRs, SK1, and SK2 for the treatment of pancreatic cancer. Through this review, we would like to suggest that the SK/S1P/S1PR signaling system can be an important target for treating pancreatic cancer, where a new treatment target is desperately warranted.

Keywords Sphingosine 1-phosphate, Sphingosine kinase, Sphingosine1-phosphate receptor

Introduction

Pancreatic cancer (PC) is a lethal and aggressive cancer with a low survival rate. PC is difficult to diagnose and is often detected at an advanced stage, making it difficult to treat [1]. The standard treatment for PC is surgical resection; however, less than 15% of patients are eligible for surgery and the remaining patients need to undergo chemotherapy because of late diagnosis [2–6]. Although the causes are not entirely clear, older age, family history, smoking, alcohol use, diabetes, and obesity contribute to PC risk and development. PC is primarily caused by the activation of specific oncogenes and mutations in tumor suppressor genes. Activation of the Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) oncogene, which accounts for approximately 90% of pancreatic

†Khem Raj Limbu and Rashmi Bhandari Chhetri contributed equally to this work.

*Correspondence:
Dong Jae Baek
dbaek@mokpo.ac.kr
Eun-Young Park
parkey@mokpo.ac.kr
[1]College of Pharmacy, Mokpo National University, Joennam 58554, South Korea
[2]Massachusetts General Hospital Cancer Center, Boston, MA 02114, USA
[3]Department of Food and Nutrition, Eulji University, Seongnam 13135, South Korea

ductal adenocarcinomas (PDAC), is involved in the initial stages of PC. This is followed by a loss of function of tumor suppressor protein p53 and cyclin-dependent kinase inhibitor $p16^{INK4a}$ and inactivation of tumor suppressor genes, such as breast cancer gene 2, serine protease 1, liver kinase B1, mutL homolog 1, and suppressor of mothers against decapentaplegic 4 (*SMAD4*)/deleted in pancreatic cancer-4 [7–11]. PDAC often does not produce symptoms until it spreads to other organs. Owing to the difficulty in accessing PDAC, which is located deep in the retroperitoneum, its diagnosis is challenging. Therefore, adjuvant chemotherapy following surgical resection is possible in only some patients; however, the prognosis remains poor because of the high recurrence rate. The chemotherapeutic drugs used for treating PC include gemcitabine (the first Food and Drug Administration-approved PC treatment) and FOLFIRINOX drugs (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin), which are used in combination with gemcitabine and other anticancer drugs [12]. Other treatments include immunotherapy, hyaluronan inhibition, and targeted therapies (KRAS and p53, hedgehog pathway, interleukin-6 [IL-6], and Janus kinase/signal transducer and activator of transcription [JAK/STAT]) [13–17].

Sphingolipids represent a major class of membrane structural lipids in eukaryotic cells having a potential role in maintaining physical barriers and fluidity. Several studies have explored the importance of sphingolipids in health and disease over the past few decades and revealed their critical role in cell signaling [19]. Sphingolipids are regulated by various enzymes and metabolites, influence cellular metabolism, and are involved in post-translational modifications that affect enzymatic activity and cellular processes. Multiple genetic and multiomics studies have suggested that alterations in sphingolipid metabolism contribute to adverse conditions, such as cancer, neurodegenerative diseases, and autoimmune disorders [20, 21]. Sphingosine-1-phosphate (S1P) plays a key physiological role in cancer by regulating various cellular processes, such as proliferation, migration, angiogenesis, and immune cell trafficking [22]. S1P is produced through sphingosine phosphorylation, a process catalyzed by sphingosine kinase 1 and 2 (SK1 and SK2). It acts in an autocrine and paracrine manner to exert its effects by binding to G-protein–coupled receptors, which results in the stimulation of downstream pathways [23]. The roles of S1P and its receptors are related to cancer progression. Moreover, SK1 expression is associated with lymphatic invasion and poor prognosis in patients with PDAC, indicating the importance of the SK1/S1P signaling axis in PC progression [24]. In multiple cancer types, S1P is a key player in tumor progression and chemoresistance, making it an attractive therapeutic target for cancer. Recent studies have demonstrated that targeting the S1P signaling axis can modulate the tumor microenvironment (TME) and inhibit cancer cell survival, thereby underscoring its potential in anticancer strategies [25].

Understanding the regulation and function of S1P and S1P receptors (S1PRs) is crucial for the development of new therapeutic strategies for various diseases. Research on SKs that regulate S1P and S1P levels in various cancers is ongoing. Although the roles of S1P, S1PRs, and SKs have been explored in various cancers, their involvement in PC remains unclear. This review has summarized the potential of targeting S1P for PC therapy. In addition, we analyzed the role of SK, a key enzyme in S1P synthesis, and discussed several pharmacologic agents capable of modulating S1P and SK levels, thereby offering a therapeutic strategy for PC.

Sphingolipid metabolism and its role in cancer cell

Sphingolipids exist in various forms and are located in specific cellular compartments. Different enzymes controlling sphingolipid metabolism in a tightly regulated manner have been examined. Certain alterations in the expression or activities of these enzymes play an important role in cancer signaling and/or anticancer therapeutic approaches [26]. Bioactive sphingolipids, such as ceramides (N-acyl sphingosine), sphingosine, and S1P, act as key players and determine the fate of the majority of cancerous cells. Ceramide plays a central role in sphingolipid metabolism and may be produced *de novo* or through the breakdown of sphingomyelin and other complex sphingolipids. The biosynthesis of sphingolipids begins in the endoplasmic reticulum with the condensation of serine and palmitoyl-CoA via serine palmitoyl transferase to form 3-keto-dihydrosphingosine, which is reduced to dihydrosphingosine via 3-ketodihydrosphingosine reductase. Dihydrosphingosine is then acetylated via ceramide synthase to form dihydroceramides, which are subsequently converted into ceramides via dihydroceramide desaturase. Ceramide serves as a precursor for the synthesis of complex sphingolipids in the Golgi apparatus. Under the action of ceramidase, ceramide can undergo phosphorylation to form ceramide-1-phosphate or deacetylation to produce sphingosine. Sphingosine is then phosphorylated via SK1 and SK2 to form S1P (Fig. 1) [27]. Under normal conditions, after exerting its effect on target proteins, S1P is irreversibly degraded via S1P lyase or reversibly dephosphorylated via S1P phosphatase to form sphingosine [28]. Due to its polar head group, S1P requires transporters such as ABCC1, ABCG2, and Spns2 for movement across the plasma membrane [29]. Several transporters, such as the ATP-binding cassette (ABC) transporters ABCC1 and ABCG2 have been reported. Moreover, Spns2, a member of the major facilitator superfamily that lacks an ATP-binding site, is an S1P transporter in zebrafish [30–33]. In

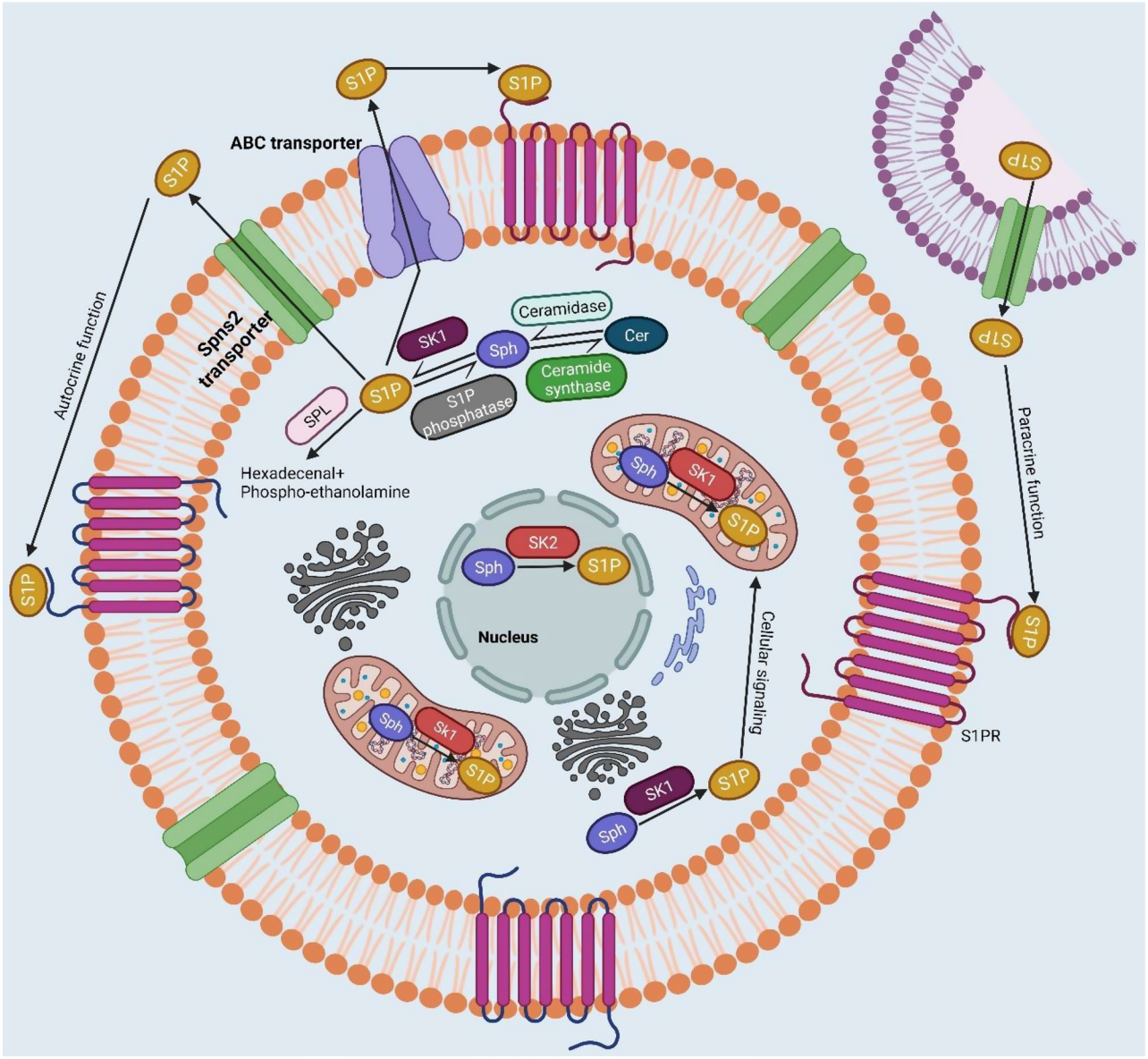

Fig. 1 Sphingolipid metabolism and sphingosine 1-phosphate production. S1P: Sphingosine 1-phosphate; Cer: Ceramide; Sph: Sphingosine; SK1 and SK2: Sphingosine kinase 1 and sphingosine kinase 2; SPL: Sphingosine 1-phosphate lyase; S1PR: Sphingosine 1-phosphate receptor and Spns2: Spinster homolog 2

addition, Kobayashi et al. identified MFSD2B as an S1P transporter in the mouse erythroid cell line MEDEP-E14 (Fig. 1) [22, 34]. Increased levels of S1P promote cell growth, viability, invasiveness, and motility, whereas higher levels of ceramides and sphingosine promote various cell death pathways, such as apoptosis, autophagy, and senescence in cancer.

The role of S1P and S1P receptors in cellular signaling and disease progression

S1P and S1PR are involved in various biological processes, including cell migration, survival, and proliferation. S1P is a sphingolipid signaling molecule that regulates various cellular functions by binding to specific G-protein-coupled receptors, which are known as S1PRs. There are five G-protein–coupled receptors for S1P, namely, S1PR1, S1PR2, S1PR3, S1PR4, and S1PR5 [35]. After its synthesis from sphingosine, S1P is released into the bloodstream where it binds to specific receptors on the target cell surface and activates downstream signaling pathways. S1P plays an important role in various diseases. For example, in the nervous system, S1P enhances olfactory neuronal cell proliferation both in vivo and in vitro through the S1PR1/RhoA/Yes-associated protein signaling axis, facilitating the formation of layers of olfactory nerves [36, 37]. S1P has also been implicated in various

neurological disorders, including multiple sclerosis and Alzheimer's disease [38, 39]. Similarly, S1P is known to enhance cancer, autoimmune diseases, and inflammation [22, 40, 41]. S1P is crucial for angiogenesis development in endothelial cells and matrigel plugs, whereas its depletion suppresses both tumor growth and neoangiogenesis in an in vivo model through inhibition of vascular endothelial growth factor-A (VEGF-A) [42, 43]. In immune cells, S1P aids in the migration of B cells and regulates their interaction with T cells, influencing the localization of natural killer cells and modulating their response to interferon-gamma, thereby indicating that it plays an important role in immune-mediated diseases [40]. In addition, in breast cancer, S1P promotes cancer stemness via a ligand-independent Notch activation mechanism through the S1PR3-mediated pathway. S1P not only facilitates the proliferation of several cancer stem cells (CSCs) but also substantially affects stem/progenitor cells and human embryonic stem cells, which are renewed by platelet-derived growth factors [44, 45]. Moreover, S1P/S1PRs activate various signaling pathways, such as mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) 1/2, Ras-related C3 botulinum toxin substrate 1, and protein kinase C, leading to drug resistance and cancer cell survival through the upregulation of antiapoptotic pathways [23, 46].

Role of S1P and S1PRs in PC

S1P is a bioactive lipid that exerts prosurvival effects in various cancers, including PC [47, 48]. S1P produced via SK2 binds to histone deacetylases 1 and 2 and participates in the activation of specific gene promoters. It also regulates histone acetylation, which is vital for gene transcription and gene expression regulation [48]. S1P influences PDAC in various ways such as promoting PC proliferation, chemotherapeutic resistance, migration and invasion of cancer cells, epithelial-mesenchymal transition (EMT), and immune escape [49]. It also modulates autophagy and pathways associated with cell death through the mammalian target of rapamycin pathway, a key regulator of autophagy [50]. In addition, S1P regulates autophagy by modulating antiapoptotic proteins B cell lymphoma 2 (Bcl-2) and B cell lymphoma extra-large as well as the S1P/S1PR pathway or by directly affecting lysosomal formation, which is necessary for the storage of lysosomal calcium and lysosome-associated membrane proteins. Thus, S1P plays a key role in the fusion of autophagosomes and lysosomes. Furthermore, it facilitates ceramide vesicular transport from the autolysosome to the Golgi apparatus and supplies sphingomyelin, which results in the synthesis of S1P [51]. Thus, S1P may play different roles in PC cells, and targeting sphingolipids may improve the prognosis of patients with PC.

After binding to S1PRs, S1P activates various downstream signaling pathways via heterotrimeric G proteins [52]. S1PR1 binds to G_i; S1PR2 binds to G_i, $G_{12/13}$, and G_q; S1PR3 binds to G_i, $G_{12/13}$, and G_q; S1PR4 binds to G_i; and S1PR5 binds to G_i and G_{12} [52–56]. In many cancers, S1P/S1PR1 activates the JAK/STAT3, AKT, and PI3K signaling pathways Similarly, S1P/S1PR2/3 and S1PR4 activate ERK, PI3K, Yes-associated protein, and AKT signaling pathways when coupled to G_i [57–60]. The focal adhesion kinase (FAK) signaling pathways are also activated by S1P/S1PR5 [61]. Thus, it is evident that S1P and S1PRs play important roles in cancer by regulating various signaling axes (Fig. 2) [62]. The effects of the S1P axis based on current research results are summarized along with several pathways associated with PC progression.

Effect of S1P on PC proliferation

S1P regulates cancer cell proliferation in PC by activating several signaling pathways. According to numerous studies [63–65], S1P levels are higher in PC patients than in healthy controls, and simultaneously elevated SK1 levels are associated with a poor prognosis for PDAC patients. S1P levels were found to be elevated in both in vitro and in vivo models of PC [63, 66]. In PC, elevated levels of S1P activate the G protein-coupled receptor S1PR1-5 and numerous signaling pathways, thereby promoting cell proliferation [67, 68]. S1P stimulates the growth of the PC cell lines Capan-1 and Panc-1 by activating the c-Src signaling pathway, which is accomplished by the phosphorylation of Tyr416 residue of c-Src through the action of S1PR1. Activated c-Src phosphorylates the Thr308 residue of AKT and p38MAPK, a signaling pathway involved in PC cell proliferation [69]. Additionally, the S1P generated by SK1 in PC has been observed to upregulate the proliferation marker Ki67 and the lymphocyte infiltration marker CD45, thereby enhancing the proliferation of PC in in vivo and in vitro studies [70]. Similarly, our previously conducted study has demonstrated that S1P enhances the proliferation of PC cells via activation of the JAK2/STAT3/Bcl-2 pathway [64]. Furthermore, S1P produced by SK1 overexpression in PC activates pancreatic stellate cells via the ERK/AKT pathway, promoting PC proliferation [71]. Besides these pathways, S1P is also known to promote PC proliferation by phosphorylation of AKT which leads to the activation of the NF-kB signaling pathway through the upregulation of p-IkBα [72, 73]. Thus, since S1P enhances the proliferation of PC through upregulation of various signal transduction pathways, the mechanism of inhibiting S1P has a good potential as a target for PC treatment.

Effect of S1P on angiogenesis in PC

Angiogenesis is a complicated process in which new blood vessels develop from pre-existing ones to supply

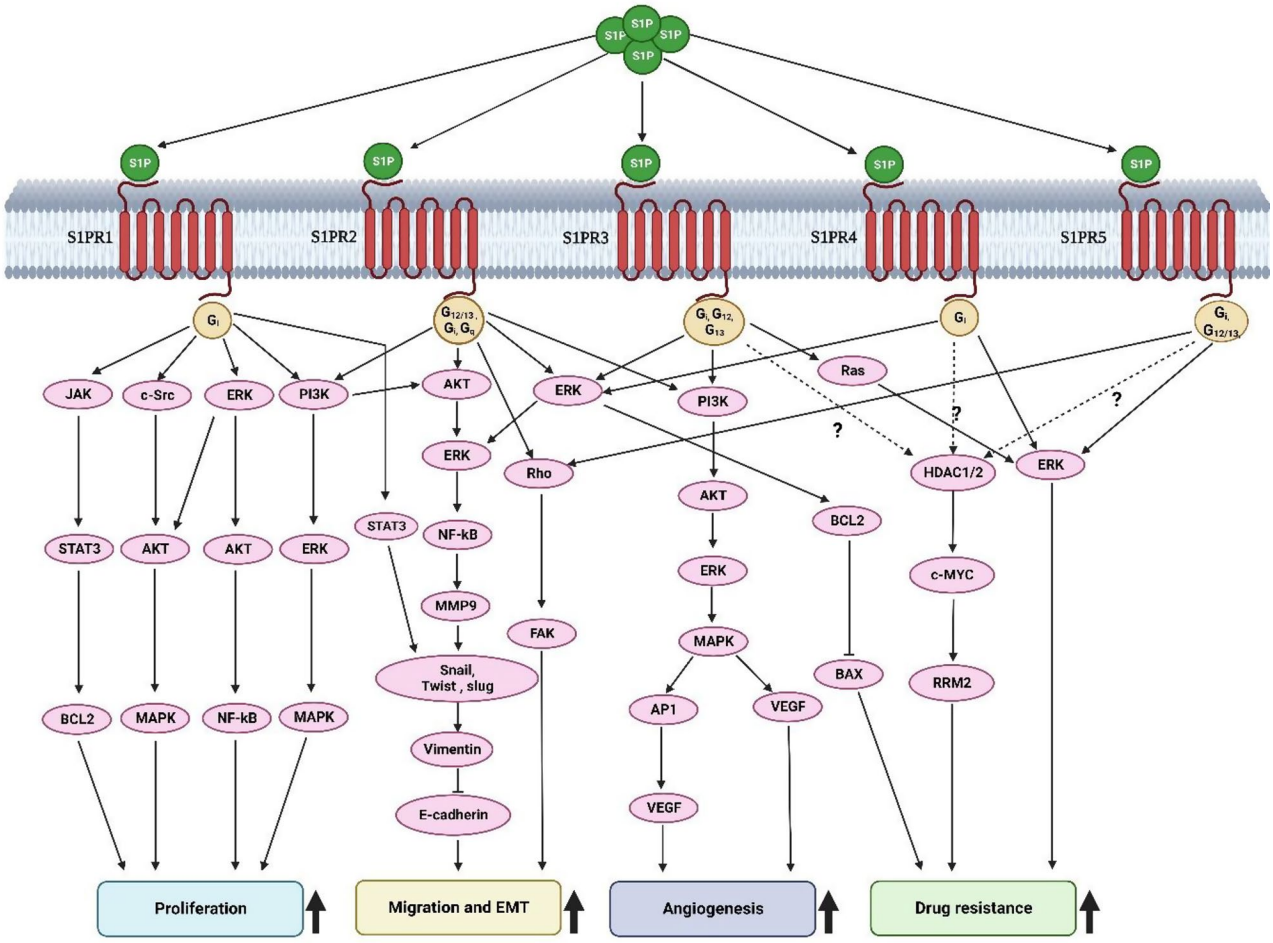

Fig. 2 S1P/ S1PR signaling pathways in pancreatic cancer

nutrition and oxygen to the tissue. The process of angiogenesis involves interactions between various biological factors, such as cell types, the upregulation of pro-angiogenic factors, and extracellular matrix components, which in turn promote cancer progression and metastasis. Angiogenesis involves degradation of the basement membrane by proteolytic enzymes followed by the activation and migration of endothelial cells, finally leading to the formation of capillary tubes, which eventually develop into new basement membranes, and all these steps take place sequentially [74] (Fig. 3). S1P acts as the main activator in the creation of vascular tubes and is also involved in vascular maturation [75] and permeability [76]. In conjunction with the S1PR1 receptor, S1P regulates vascular stability, stimulates microtubule polymerization in response to the Gi/Rac pathway, and activates the cell adhesion molecule N-cadherin thereby facilitating interactions between endothelial cells and mural cells. The phosphorylation of N-cadherin and p120-catenin catalyzed by S1P treatment resulted in development of cadherin/catenin/actin complexes and caused the transportation of N-cadherin to the polarized plasma membrane domain, thus strengthening cell-cell adhesions with mural cells [77]. Heo et al., investigated the effects of S1P on the induction of vascular endothelial growth factor (VEGF), known to be the most primary angiogenic factor and found that S1P rapidly increased VEGF mRNA by activating the VEGF promoter region in the presence of the G protein (alpha i/o)-mediated transcription factors such as phospholipase C, PI3K, ERK, p38 mitogen activated protein kinases (MAPK), and AP1 in endothelial cells. Activated VEGF promotes the formation of endothelial tubes and upregulates angiogenesis, indicating that S1P plays an important role in vasculogenesis [78]. Release of excessive VEGF leads to the formation of an abnormal tumor vascular network and causes instability in the tumor microenvironment [79, 80]. The overexpression of angiogenic factors such as VEGF and its associated receptor (VEGFR), promotes pancreatic neuroendocrine tumors to be hypervascular tumors, as evident in liver metastasis [81]. S1P has also been observed to stimulate platelet-derived growth factors (PDGF) alpha and beta via ERK/MAPK activation, which induces the proliferation of vascular smooth

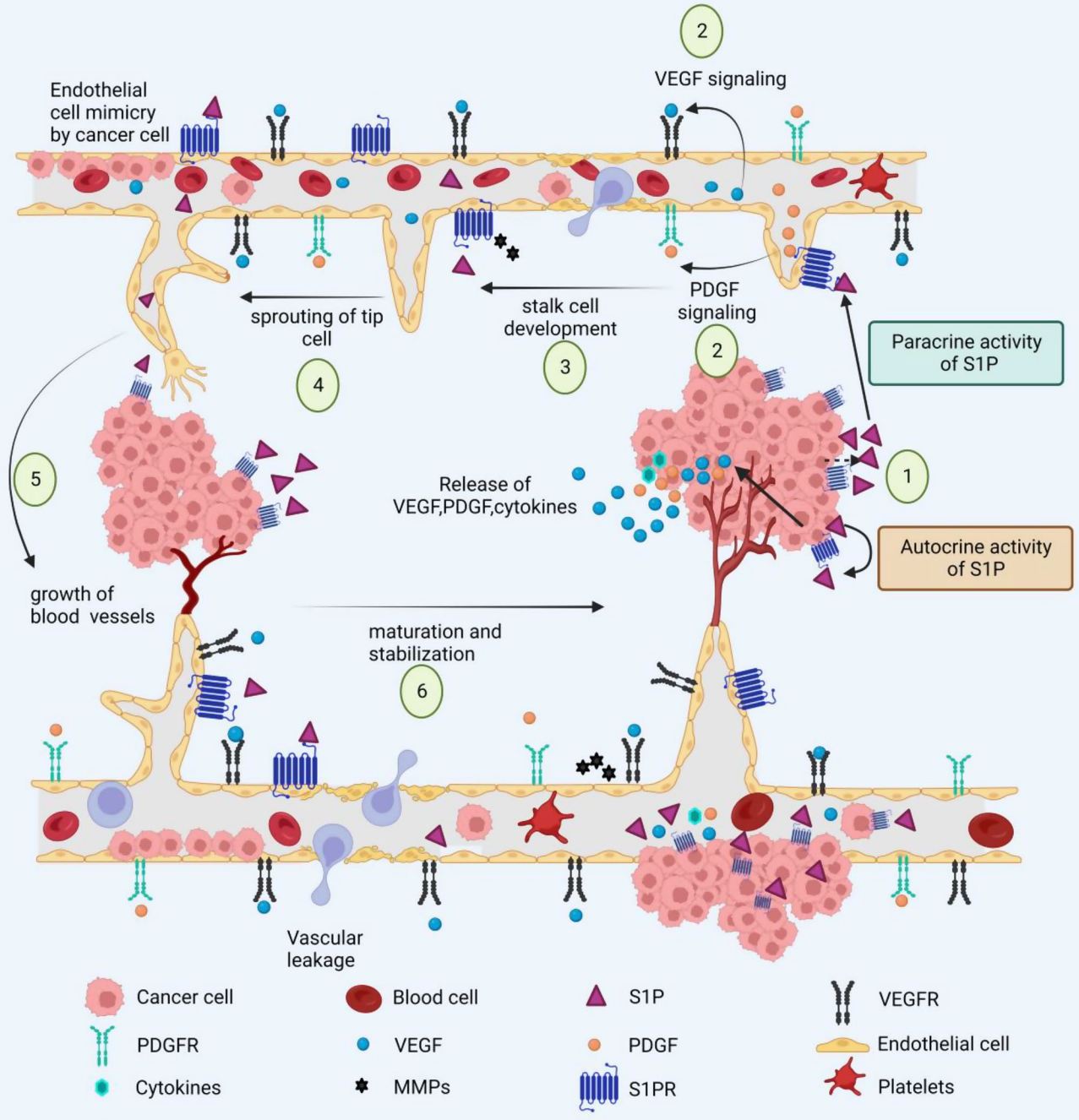

Fig. 3 S1P role in pancreatic cancer angiogenesis

muscle cells as well as pericytes, and allows them to participate in capillary formation during vascular growth [82]. Newly formed endothelial tubes are surrounded by pericytes which migrate when the PDGFR receptors are activated by PDGF-secreting endothelial cells. The VEGFR2/PDGFR complexes, derived from VEGF which has originated from vascular sprouts in endothelial cells inhibit PDGFR-signaling resulting in vascular instability by the elimination of pericytes covering endothelial sprouts [79]. As such, angiogenesis is an important factor in regulating the growth, microenvironment, and metastasis of PC. The mechanism by which S1P controls angiogenesis can serve as a good target for treatment of PC.

Migration and EMT regulation by S1P in PC

S1P plays an important role in increasing cancer cell metastasis and EMT in PDAC. Our recent study on PDAC revealed that S1P promotes EMT and cancer cell migration by increasing vimentin expression through S1P-mediated phosphorylation at Tyr397 of FAK [64].

S1P influences PDAC cell migration and invasion through S1PR1-mediated activation of c-Src signaling and upregulation of MMP9 and MMP2 (matrix metallopeptidase 9 and 2) in the PC cell lines Capan-1 and Panc-1, respectively [69, 83]. In addition to this, S1P increases c-Met, PI3K, and AKT-mediated cell migration in the Panc-1 and MIA Paca-2 cell lines [84]. In the in vivo/in vitro studies, S1P was observed to activate pancreatic stellate cells (PSCs) via S1PR2/AKT/ERK-mediated phosphorylation of ABL1 kinase (Tyr245 residues), which resulted in the activation of NF-kB transcription factor which binds to the promoters of matrix metalloproteinase-9 and enhance migration of PC cells [71, 85, 86]. The elevation in the levels of EMT transcription factors such as snails, twist1, and slug, that facilitates the overexpression of vimentin while downregulating E-cadherin to achieve cancer cell migration occurs through S1PR1-mediated phosphorylation of STAT3 [87]. In the PC cell lines Panc02-luc and AsPC-1, conjugated bile acids promote cancer cell migration in an S1PR2-dependent manner, which indicates that S1PR2 plays an important role in PC metastasis [67]. Another study on PC has demonstrated that lysophosphatidic acid (LPA) upregulates the SK1/2 mediated production of S1P, which in turn acts on S1PR1/4 to stimulate migration of PC [88]. SK1 and SK2 located in the cytoplasm and nucleus, respectively, enhance PDAC migration, proliferation and invasion through S1P/S1PR signaling pathways in pancreatic cancer. There exists a strong correlation between SK1/2 overexpression and cancer progression [89]. Taken together, the downstream signaling pathway of S1P/S1PR and the regulation of SK1 and SK2, which regulate the level of S1P, play an important role in PC migration and EMT, suggesting that each of these regulations can serve as a good target for PC treatment.

Regulation of autophagy by S1P in PC

Autophagy plays a dual role in PDAC, initially acting as a tumor-suppressive mechanism but later supporting tumor survival by providing metabolic substrates under nutrient-deficient conditions, thus contributing to cancer cell proliferation and chemoresistance [90]. To maintain iron homeostasis, cancer cells use the autophagy machinery to support mitochondrial function for the proliferation of PC cells. Autophagy dysfunction results in the production of IL-6 in cancer cells, which increases the level of ferritin and upregulates the expression of iron efflux protein ferroportin in cancer-associated fibroblasts (CAFs). This leads to the elevation of the labile iron pool to enhance the function of mitochondria and proliferation of PDAC cells [91]. Wang et al. found that the levels of S1P produced via SK1 were significantly elevated in chronic pancreatitis (CP), resulting in the activation of autophagy and pancreatic stellate cells (PSCs) through the modulation of 5′-adenosine monophosphate-activated protein kinase via S1PR2. This contributed to fibrogenesis and inhibited SK1 or S1PR2 to prevent fibrosis and PSC activation in CP. These findings indicate that S1P regulates PC progression through autophagy by activating PSCs [92]. Moreover, S1P regulates Bcl-2, which is a significant regulator of autophagy [64], Bcl-2, along with proteins such as JNK1 and ATG14L, competes for binding to the BH3 domain of Beclin-1 and disrupts the Beclin-1/Bcl-2 complex. This dissociation releases Beclin-1, which activates PI3KC-C1 and PI3KC-C2, facilitating autophagosome-lysosome fusion. The released Bcl-2 subsequently binds to proapoptotic proteins such as BAX and BAK, thereby preventing apoptosis and promoting the survival of PC cells. This mechanism indicates the critical role of Bcl-2 in regulating autophagy and apoptosis in PDAC, making it a key target for therapeutic interventions [93]. These findings underscore the important role of S1P in modulating autophagy within PC cells, demonstrating its regulatory influence on key cellular processes; however, the precise contribution of S1P to pancreatic tumorigenesis through autophagy remains unclear. This warrants further in-depth studies to elucidate the complex molecular mechanisms involved and their potential therapeutic applications.

Regulation of tumor microenvironment by S1P in PC

The formation and progression of PC are regulated by many genetic and epigenetic mechanisms that modify the TME by rearranging its components [94]. Cancer cells produce various cytokines, such as CCL5, CXCL5, neutrophil, and CSF-1, as well as some growth factors, such as TGFβ [95–97]. PC cells are surrounded by a stromal network of immune cells and CAFs, which contribute to an immunosuppressive microenvironment that supports tumor growth and chemoresistance [98]. Thus, activated PSCs and CAFs promote angiogenesis by increasing VEGF production, which contributes to immune suppression and chemoresistance in PC [99]. In addition, CAFs secrete TGF-β, which plays a role in enhancing PC progression, including metastasis, through mechanisms involving the EMT [100].

The interaction between PSCs and PC cells, with S1P reorganizing the actin cytoskeleton and upregulating profibrotic genes encoding proteins such as collagen and fibronectin, is important for shaping the fibrotic and immunosuppressive tumor microenvironment in PC. In PSCs, the binding of S1P to S1PR2 increases the expression of matrix metalloproteinase-9 (MMP-9) through the c-Abl pathway, which facilitates the migration and invasion of PC cells, thus contributing to the development of a TME [71]. TGF-β, a key profibrogenic cytokine, induces CAFs, and the cytokine activity is regulated by SK1 to support the TME [101]. CAF activation by

TGF-β induces thrombospondin 2 expression through the SMAD2/3 pathway, which interacts with the integrin receptors αvβ3/CD36, thereby activating the MAPK signaling axis to promote the proliferation and adhesion of PDAC cells in vitro and in vivo [102]. This evidence highlights the importance of S1P-mediated communication between cancer cells and stromal cells in shaping the TME; however, the precise mechanisms by which S1P influences the TME in PDAC remain unclear. Further studies are warranted to fully elucidate its role in disease progression.

S1P regulation on PC stemness

CSCs are a subset of tumor cells with self-renewal capacity and pluripotency. They contribute to tumor resistance to therapy and recurrence, making them a key focus of cancer treatment strategies [103]. Li et al. provided the first evidence of stem cell properties in PDAC by identifying a small subset of tumor cells expressing CD24+, CD44+, and epithelial-specific antigen, which exhibited significantly higher tumorigenic potential compared to the normal cancer cells [104]. Subsequently, Hermann et al. showed that CD133+CSCs in PC generated tumors within 3 weeks using only 500 CSCs; however, CD133−cells failed to cause malignancy within the same period, even when millions of cells were used. This finding underscores the enhanced tumorigenic capacity of CD133+cells compared with CD133−cells [105]. S1P plays a crucial role in promoting the expansion of CSCs. The study investigated the role of S1P in enhancing the proportion of aldehyde dehydrogenase–positive CSCs through S1PR3-mediated Notch signaling. The results revealed that CSCs overexpressing SK1 exhibited greater tumorigenic potential than wild-type CSCs [44]. Recent transcriptomic and lipidomic analyses in PDAC suggest that alterations in sphingolipid metabolism, particularly upregulation of SK1, are associated with the promotion of cancer stemness, highlighting the role of SK1 in driving stem-like characteristics in PC cells. Silencing SK1 in PC cells significantly reduced the expression of the CSC markers CD133, CD24, Sox2, and Nanog [106]. Furthermore, both STAT3 and NF-kB signaling pathways, which are modulated by S1P, are important regulators of PC stemness. This suggests that S1P drives stemness in PC via STAT3/NF-kB signaling [107, 108]. Although substantial evidence supports the role of S1P signaling in promoting cancer stemness across various malignancies, its specific involvement in PC remains underexplored, highlighting the need for further detailed studies to clarify the mechanisms underlying the SK/S1P/S1PR axis in PDAC stem cells.

S1P-mediated PC drug resistance

Cell fate is controlled by a delicate equilibrium between intracellular levels of the pro-survival factor S1P and the proapoptotic factor ceramide, and this equilibrium is often referred to as the ceramide/S1P rheostat. When the balance shifts toward ceramide accumulation, cancer cells are subjected to apoptosis, nonproliferation, and increased sensitivity to drugs, while a shift toward S1P exerts pro-survival and anti-apoptosis effects on cells, and they develop chemoresistance [18, 109]. SK/S1P protects cancer cells from drug-induced cell death, suggesting that the level of bioactive sphingolipids affects drug resistance. For instance, a study conducted by Guillermet-Guibert J et al., (2009) has reported that the resistance of Panc-1 to gemcitabine was due to the unbalanced ratio between ceramide and S1P caused by enhanced SK1 activity, demonstrating that PC cell resistance to gemcitabine could be correlated with SK1 activity [110].

One of the common causes of chemoresistance in PC cells is due to the ability of members of the ABC transporter family to efflux anticancer drugs from the cancer cells [111]. Enhanced levels of the ABC transporter family members such as P glycoprotein/ABCB1, breast cancer resistance protein (BCRP)/ABCG2, multidrug resistance protein 1 (MRP1)/ABCC1, and other members belonging to the ABCC subfamily contribute to PDAC chemoresistance [112]. ABCA8, a protein belonging to the subfamily of ABCA transporters, that is known to stimulate cholesterol and taurocholic acid efflux, contributes to the resistance of gemcitabine by activation of S1PR2/ERK signaling. Efflux of taurocholic acid (TCA) from ABCA8 led to the activation of ERK signaling via S1PR2, and conferred resistance to gemcitabine-induced apoptosis by upregulating the expression of antiapoptotic protein Bcl-2 and downregulating BAX (Bcl-2 associated protein X) in PC [113]. Change in nucleoside and gemcitabine metabolism following overexpression of the catalytic subunit of ribonucleotide reductase (RRM2) is known to be one of the major mechanisms of resistance to gemcitabine. S1P enhances the expression of other factors such as c-Myc and the RRM2. SK2-derived S1P activates HDAC activity, which results in the down regulation of p21 expression. The resulting inhibition of p21 renders it unable to bind with cyclin D and CDK complexes, allowing Rb to phosphorylate. Phosphorylated Rb activates the transcription of c-Myc and RRM2, after binding with the E2F-binding site [114]. Activated RRM2 results in an increase in the size of dNTP (deoxynucleotide triphosphate) pools, which competitively impedes the embodiment of gemcitabine triphosphate into DNA, thereby facilitating drug resistance in PC [115, 116]. As a result, the regulation of the S1P/S1PR signaling axis can

be used as a drug target point for lowering gemcitabine resistance.

Modulation of S1P/S1PR signaling as a promising target for PDAC treatment

S1P-targeted compounds under development

The activation of different signaling pathways by S1P and its receptors, which greatly boost chemotherapeutic drug resistance, proliferation, metastasis, and EMT, play a critical role in the advancement of PC. Treatment of PC becomes more challenging because of these changes [69]. Numerous S1PR modulators have been discovered, and are used for the treatment of diseases such as multiple sclerosis (MS) and ulcerative colitis (UC), and are currently being tested in multi-stage clinical trials. In PC, S1P/S1PR signaling is known to be involved in cancer development and deterioration, but unfortunately, only a few published pre-clinical trial studies focusing on S1PR modulators in PC are available [117]. Fingolimod gilenya (FTY720), a structural analog of sphingosine produced from the fungus *Isaria sinclairii*, is an immune suppressive medication for the treatment of MS and a modulator of S1PR1, S1PR3, and S1PR5 [118, 119]. Primary function of FTY720 is internalization of S1PR, which confines T cells in lymph nodes, thereby stopping them from triggering inflammatory and autoimmune responses [120]. The most important anticancer function of FTY720 is the inhibition of the conversion of sphingosine to active bio-lipid S1P [121]. Investigations regarding efficacy of FTY720 on different types of malignancies, including those of the breast, prostate, liver, bladder, gastric, colorectal, lung, and pancreas, revealed that it exerted strong anticancer effects, including cell cycle arrest, increased apoptosis, and prevention of migration, when tested both in vitro and in vivo [122–128]. In addition to FTY720, several analogs of FTY720 have also been reported to exert anticancer action through protein phosphatase 2 A (PP2A), a protein that dephosphorylates several signaling proteins, maintains cellular homeostasis and suppresses tumor progression in gastric and colorectal cancer cell lines [129–131]. FTY720 suppresses EMT and cancer cell proliferation and promotes apoptosis in PC by regulating multiple signaling pathways. For instance, treatment with FTY720 dramatically decreases phosphorylation of AKT and expression of anti-apoptotic protein Bcl-2, which ultimately affects the tumor cell survival by inducing apoptosis in PDAC cell lines through the activation of apoptotic proteins caspase-3 and caspase-9 [132]. FTY720 when used in combination with gemcitabine, significantly reduces EMT and promotes apoptosis through suppression of S1PR1/STAT-3-mediated NF-kB and Shh signaling. Additionally, FTY720 also suppresses myofibroblast activators CXCL12 and CXCR4, the downstream signaling molecules of NF-kB, which are responsible for PC stellate cell activation and ECM deposition respectively. When used in conjunction with gemcitabine in the treatment of PC, FTY720 alters gemcitabine-inactivating enzymes such as RRM1, RRM2, ABCC5, cytidine deaminase (hCDA), deoxycytidine kinase (hDCK), and deoxycytidine monophosphate deaminase (hDCTD), thereby enhancing the efficacy of gemcitabine [87]. Moreover, treatment with a combination of lapatinib and FTY720 increases lysosomal swelling and membrane permeability, leading to the depolarization of mitochondria, increased ER stress, and an imbalance in intracellular calcium that encourages PC cell death [133]. In summary, FTY720 is a promising molecule in the treatment of PDAC, and more in-depth research, including clinical trials, may be needed to ascertain its advantages (Table 1).

In addition to using S1PR modulators to treat PC, some studies on S1PR knock-down revealed a promising approach to PDAC treatment. The in vivo orthotopic PC model demonstrated that knocking out S1PR2 in PC stellate cells resulted in slower cancer metastasis and proliferation, and modulated the tumor microenvironment to inhibit cancer progression. These results imply that knocking out S1PRs and treatment with a combination of anticancer compounds could be a promising approach in PDAC management [71]. Furthermore, a study has previously reported that the conjugated bile acid TCA has demonstrated upregulation of S1PR2 expression to enhance the migration and proliferation of PC both *in vivo and in vitro*. The use of the S1PR2 inhibitor JTE-013 reversed the effect of TCA-induced PC cell proliferation and migration via the S1P/S1PR2/AKT/ERK signaling

Table 1 S1P inhibitors used in PDAC

S1PRs inhibitors used in pancreatic cancer study				
Compound name	**Mechanism**	**Experiment model**	**Receptors**	**Ref.**
FTY720	Induction of apoptosis through S1PR1 and S1PR1/STAT3 inhibition and AKT/BCL2/NF-kB inhibition	In vitro: MIA PaCa-2, BxPC-3, Panc-1, AsPC-1, Panc02-luc	S1PR1/2	[87]
JTE-013	Downregulation of cancer proliferation through inhibition of S1PR2/PI3K/AKT/ERK signaling pathway	In vitro: MIA PaCa-2, BxPC-3, AsPC-1, Panc02-luc In vivo: NOD.CB17-Prkdcscid/J mice and C57Bl/6 mice	S1PR2	[67, 135]

pathway [134]. According to another study of a similar nature, TCA upregulated the migration, proliferation, and invasion of cholangiocarcinoma through the S1PR2/PI3K/AKT/ERK-mediated signaling axis. The study also revealed that silencing S1PR2 using short hairpin RNA and JTE-013, suppressed cancer cell progression by inhibiting the S1PR2/AKT/ERK signaling pathway [135]. Overall, the development of S1P and S1PRs targeting compounds and S1PRs silencing could be promising strategies to control PC.

The role of SK1 and SK2 in PDAC and the development of SK1/2 inhibitors

The levels of S1P are regulated by SK1 and SK2; however, the roles of SK1 and SK2 in PC remain unclear [136]. SK1 exerts well-known prosurvival effects in various cancers, and its overexpression is correlated with the low survival rate of patients with enhanced tumor grades [137, 138]. The evaluation of various in vitro and in vivo studies and human pancreatic tumor tissue revealed that the expression level of SK1 is higher in pancreatic tumor tissue than in adjacent normal tissue [71]. As SK1 produces S1P, its function is critically dependent on its specific intracellular localization, enabling it to regulate the sphingolipid signaling pathways involved in cell survival and proliferation, rather than acting as a general housekeeping enzyme [139]. S1P generated by SK1 is an important cofactor for the E3 ubiquitin ligase activity of TRAF2, which facilitates lysine-63-linked polyubiquitination of receptor-interacting protein kinase 1 and subsequent activation of the NF-kB pathway. This process occurs independently of S1PRs and is essential for promoting cancer progression through inflammatory and antiapoptotic signaling pathways [140, 141].

Transplantation of PC cells into SK1 knockout (SK1 KO) mice demonstrated that cancer cell proliferation and PC progression were inhibited in the SK1 KO mice compared to normal mice, suggesting that SK1 is responsible for PC progression [70]. In contrast, Yuza et al. reported that SK1 KO enhanced the proliferation and migration of PC cells, whereas SK2 KO reduced their proliferation and migration. Moreover, mice injected with SK1 KO cells exhibited a dramatically shorter survival period than those injected with wild-type cells. These results highlight the complex and context-dependent roles of SK1 and SK2 in PC progression [66]. Although the ablation of SK1 or SK2 individually does not induce substantial complications in murine models, the deletion of both enzymes results in embryonic death and disrupts key processes such as neurogenesis and angiogenesis, as observed in a developmental study [142]. Activation of SK1 in PC cells is induced by various external stimuli, particularly phorbol 12-myristate 13-acetate, through the ERK1/2-mediated pathway. This results in the phosphorylation of SK1 at serine 225, which activates SK1 and facilitates its translocation from the cytosol to the plasma membrane. At the membrane, SK1 converts sphingosine into S1P, which acts on S1PRs on the cell surface, inducing downstream oncogenic signaling pathways [65, 143]. The overexpression of *HAS2* and *SK1* is strongly linked to PC development and has been observed at higher levels in PC cell lines, such as AsPC-1, PANC-1, Capan-1, and HDPE6C7, than in normal cells [144] Overexpression of *SK1* in PDAC results in the activation of the AKT/NF-kB signaling pathway to promote cancer cell proliferation and invasion. This upregulation is significantly associated with poor prognosis and contributes to the progression of PC [72]. In addition, *SK1* overexpression promotes the movement and invasion of PC through the activation of MMP-9 via the S1P/S1PR2-mediated pathway [69, 71]. In PC, although the role of S1P produced via SK2 is less understood compared with that of S1P produced via SK1, a study suggested that SK2 plays an important role in cancer progression. Inhibition of SK2 using specific inhibitors, such as ABC294640, has shown promising antitumor effects, including reduced cell proliferation and induced apoptosis. This highlights the potential of SK2 as a therapeutic target in PC [145]. Thus, above studies indicate that SK1 and SK2, which modulate S1P levels in PC cells, serve as therapeutic targets in PC. Compounds that directly or indirectly inhibit these kinases have been developed and their effectiveness has been verified at several stages (Table 2).

The increased expression of SK1 is correlated with higher tumor grades, lower rates of patient survival, and chemoresistance to anticancer agents. Inhibition of SK1 suppresses intracellular S1P expression and increases ceramide levels, thereby promoting apoptosis and reducing cancer cell proliferation. The SK1 inhibitor RB005 is a structural analog of FTY720 that contains a heterocyclic ring with a hydroxyl group. It reduces the accumulation of S1P by inhibiting SK1 activity. When tested in an experimental model of colorectal cancer, RB005 reduced S1P levels by inhibiting SK1 activity while increasing the levels of ceramide, a pro-apoptotic factor [146]. Shrestha et al. evaluated RB005 as an anticancer agent in colorectal cancer and revealed that it decreased both SK1 activity and S1P expression but increased ceramide levels. RB005 also activated PP2A and markedly reduced the proliferation of colorectal cancer cells through Bax, Bcl-2 cytochrome-c, and caspase 3-mediated intrinsic apoptotic pathways [147]. Moreover, RB005 significantly suppresses SK1/S1P, which inhibits the proliferation and migration of PC cells [64]. To evaluate the efficacy of selective structure-specific SK1 inhibitors and optimize the efficacy of RB005, several RB005 analogs have been synthesized, with modifications introduced in the tail, polar head group, and linker domains. For example,

Table 2 SK1 and SK2 inhibitors used in PDAC study

SK1 inhibitors used on PDAC.				
Compound name	**Mechanism**	**Experiment model**	**Receptors**	**Ref.**
PF-543 derivatives (Compounds 5 and 10)	Inhibition of SK1, activation of cleaved caspase 3 and PARP and apoptosis, PP2A activation	In vitro: MIA PaCa2, PANC-1 and H6C7	(-)	[152]
SKI-II	Increased ceramide production by inhibition of SK1 and induced apoptosis through JNK activation	In vitro: MIA PACa2 and PANC-1	(-)	[153]
FTY720	Enhanced effect of gemcitabine, increased apoptosis, suppressed NF-kB and STAT3 pathway, Activation of PP2A, Inhibition of epithelial-mesenchymal transition	In vitro: BxPC-3, AsPC-1, MIA PaCa-2 and PANC-1 and PAN 02 cell lines In vivo: NOD.CB17-Prkdcscid/J mice and C57Bl/6 mice	S1PR1	[74]
RB005	Inhibition of PDAC proliferation and migration through inhibition of SK1	In vitro: PANC-1, Capan-1 and MIA PaCa-2	(-)	[64]
PF543	Inhibition of PDAC proliferation and migration through inhibition of SK1	In vitro: PANC-1, Capan-1 and MIA PaCa-2	(-)	[64]
SK2 inhibitors used in PDAC.				
ABC294640	Inhibition of SK2 and HDAC1/2 to downregulates c-MYC and RRM2 gene in pancreatic cancer	In vitro: MIA PaCa-2, BxPC-1, Panc-1	(-)	[114]
ABC294640		Clinical trial: human PADC patients	(-)	[155]
ABC294735	Inhibition of SK1/2 with activation of caspase3/7 to induce apoptosis along with suppression of ERK phosphorylation Activation of caspase3/7 leading to apoptosis together with suppression of ERK phosphorylation by SK1/2 inhibition	In vitro: BxPC-3 In vivo: SCID mice	(-)	[154]
PF543 derivative (Compound 10)	Inhibition of SK2 and AKT/ERK pathway to induce apoptosis, Activation of PP2A	In vitro: MIA PaCa-2, Panc-1, H6C7	(-)	[151]

replacing hydroxyl group with an azido group in RB029 and RB030 and replacing the 4-hydroxyl group with an amino group in RB032 significantly reduced the inhibitory effect of SK1. Moreover, replacing the 4-hydroxyl group in RB005 with a fluoro (RB034) or methoxy (RB036) group decreased the inhibitory activity against SK1, whereas substitution of the 4-hydroxyl group with a keto group enhanced the inhibition of SK2 [148]. These findings indicate that changes in the structures of anticancer compounds improve their anticancer activity; however, further studies are warranted to develop selective SK1 and SK2 inhibitors and verify their therapeutic effects in PC.

PF543 inhibits SK1 with a half maximal inhibitory concentration (IC_{50}) of 2.0 nM, and is more than 100 times selective for SK1 as compared to SK2. Treatment with PF543 inhibited S1P, increased the accumulation of ceramides and induced apoptosis of PC cells [64]. Despite its strong SK1 inhibitory effect, high sphingosine levels were probably the reason for reduced anticancer activity of PF543 in PC cell lines [149, 150]. To overcome the low anticancer potency of PF543 in PC, various analogs of PF543 with various modifications, such as variations in the aromatic or aliphatic tails of the triazole group, have been synthesized, and their inhibitory effects have been tested in PC cell lines. The study indicated that compounds with aliphatic tails have a stronger anticancer potency than those with aromatic tails. In contrast to an aliphatic tail-containing compound, this aromatic tail-containing compound was found to selectively inhibit SK1. The aliphatic tail-containing compound 10 demonstrated significant inhibition of S1P levels and upregulated ceramide levels, and it also inhibited the AKT/ERK pathway through the activation of PP2A, resulting in apoptosis [151]. In addition to this, the dual SK inhibitor SKI-II and SKI-IV in combination with bortezomib treatment on PC cell lines Panc-1 and MIA PaCa-2 upregulated ceramide production and enhanced apoptosis of PC cells via ASK1/JNK-mediated signaling [152]. In addition, the anthelmintic drug mebendazole reduced S1P production through SK1 inhibition, suppressing its downstream signaling systems, S1P/JAK2/STAT3/Bcl-2 and S1P/FAK/vimentin pathways, respectively, thereby restricting the growth and movement of PDAC [64].

Apart from the use of SK1 inhibitory compounds to control PC, some studies suggest that silencing SK1 using Sh-RNA or Si-RNA by the CRISPR/Cas9 gene editing method, in combination with other anticancer compounds, helps control cancer progression [66]. Similarly, another study has demonstrated a significant reduction in cancer progression, migration, and metastasis in SK1 ablation mice compared with wild-type mice [70]. It has also been reported that overexpression of long non-protein-coding RNAs TSV1 and TSV2 demonstrate reduced AKT/NF-KB signaling through the inhibition of SK1 expression, in which further results in the inhibition of

PC cell growth and increased apoptosis, which suggests that SK1 inhibition may be an effective target for PC treatment [73].

The SK2 inhibitor ABC294640 possesses widespread anti-tumor effect, and depletion of SK2 affects tumor growth more deeply than the depletion of SK [153]. Inhibition of SK2 by ABC294640 brought about an increase in the sensitivity of gemcitabine in human PC cell lines through downregulation of the catalytic subunit of ribonucleotide reductase and MYC. Acetylation of H3-K9 and p21 levels increased with ABC294640 treatment, thereby suppressing c-Myc protein and phosphorylation of Rb at S780, which ultimately prevented the transcription activity of E2F, resulting in inhibition of cancer cell growth [114]. A study investigating the anticancer activities of ABC294640 and dual SK1/SK2 inhibitor ABC294735 was carried out along with the co-administration of sorafenib in human pancreatic adenocarcinoma and kidney carcinoma. Combination treatment with both agents, ABC294735 and sorafenib or ABC294640 and sorafenib demonstrated synergistic cytotoxic effects in Bxpc-3 and A-498 cell lines by reducing proliferative MAPK signaling and increasing pro-apoptosis-related caspase 3/7 activity. Also, p-ERK levels were found to be lower in tumor tissues extracted from mice treated with the combination treatment. Moreover, delay in tumor growth was observed in xenograft models with oral administration of ABC294640 or ABC294735 plus sorafenib than with the treatment with sorafenib alone, suggesting the significant role of the SK inhibitors in the treatment of PC patients [154]. In addition to this, SK2 KO by using CRISPR/Cas9 gene editing in PC cell lines showed reduced proliferation and metastasis of cancer cells [66]. Therefore, these results suggest that sphingosine kinase inhibitors and combination therapies which enhance the efficacy of existing treatments can be used as treatment modalities in PC and further research should be conducted to develop more SK inhibitors.

Conclusion

Determining the molecular processes that regulate S1P metabolism, regulatory enzymes, and receptor-mediated signaling pathways in cancer and mapping sphingolipid–protein interactions are important for understanding the proliferation of PC cells. Numerous studies have been conducted on the roles of S1P, produced via SK1 or SK2, and its receptors in PC. Studies have described various functions of S1P, interactions of S1P and its receptors with signaling pathways, role of S1P in the proliferation and metastasis of PC cells, and chemotherapeutic resistance. This review summarized the recent advances in targeting sphingolipid metabolism and associated genes and evaluated them as promising therapeutic strategies for PC. This review emphasized the critical role of S1P signaling in cancer progression, indicating that modulating this pathway can significantly enhance drug discovery and therapeutic interventions. Despite this progress, studies on the anticancer effects of S1P, SK1, SK2, and S1PRs in PC are still in their early stage. Moreover, newly synthesized compounds with structural modifications that target S1P, SK1, and SK2 have demonstrated significant anticancer activity, offering opportunities for the development of effective treatments. In conclusion, the discovery of selective compounds targeting SK, S1P, and S1PR and their evaluation in clinical studies are necessary to improve PC treatment.

Abbreviations

ABC	ATP-binding cassette
ABL1	ABL proto-oncogene 1
AKT	Protein kinase B
AP1	Activator protein 1
ATP	Adenosine Tri-phosphate
BAX	Bcl-2 associated protein X
BCL2	B-cell lymphoma 2
BCRP	Breast cancer resistance protein
BRCA2	Breast Cancer gene 2
CDA	Cytidine deaminase
c-MYC	Cellular myelocytomatosis oncogene
c-Src	Proto-oncogene tyrosine-protein kinase Src
CXCL12	C-X-C motif chemokine 12
CXCR4	C-X-C chemokine receptor 4
DCK	Deoxycytidine kinase
DCTD	dCMP deaminase
DNA	Deoxyribonucleic acid
dNTP	Deoxynucleotide triphosphate
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinase
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
FOLFIRINOX	Folinic acid, 5-fluorouracil, irinotecan, oxaliplatin
FTY720	Fingolimod gilenya
HAS2	Hyaluronan synthase 2
HDCA	Histidine decarboxylase
IC_{50}	Half maximal inhibitory concentration
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
KRAS	Kirsten rat sarcoma viral oncogene homolog
LKB1	Liver kinase B1
LPA	Lysophosphatidic acid
MAPK	Mitogen activated protein kinases
MFSD2B	Major facilitator superfamily domain containing 2B
MLH1	MutL homolog 1
MMP	Matrix metalloproteinases
MRP	Multidrug resistance protein
MS	Multiple sclerosis
NF-kB	Nuclear factor Kappa-Beta
PC	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinomas
PDGF	Platelet derived growth factors
PDGFR	Platelet derived growth factors receptor
PI3K	Phosphatidylinositol – 3 kinase
PP2A	Protein phosphatase 2 A
PRSS1	Protease serine 1
PSCs	Pancreatic stellate cells
RNA	Ribonucleic acid
S1P	Sphingosine 1-phosphate
S1PR	Sphingosine 1-phosphate receptor
SK1 KO	SK1 knockout
SK1	Sphingosine kinase 1
SK2	Sphingosine kinase-2

SMAD 4	SMAD family member 4
Spns2	Spinster homolog 2
STAT	Signal transducer and activator of transcription
TCA	Taurocholic acid
UC	Ulcerative colitis
VEGF	Vascular endothelial growth factor
VEGFR	VEGF and its associated receptor
YAP	Yes-associated protein

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