Role of SIK1 in tumors: Emerging players and therapeutic potentials (Review)

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Abstract. Salt-induced kinase 1 (SIK1) is a serine/threonine protein kinase that is a member of the AMP-activated protein kinase family. SIK is catalytically activated through its phosphorylation by the upstream kinase LKB1. SIK1 has been reported to be associated with numerous types of cancer. The present review summarizes the structure, regulatory factors and inhibitors of SIK1, and also describes how SIK1 is a signal regulatory factor that fulfills connecting roles in various signal regulatory pathways. Furthermore, the anti-inflammatory effects of SIK1 during the early stage of tumor occurrence and its different regulatory effects following tumor occurrence, are summarized, and through collating the tumor signal regulatory mechanisms in which SIK1 participates, it has been demonstrated that SIK1 acts as a necessary node in cancer signal transduction. In conclusion, SIK1 is discussed independent of the SIKs family, its research results and recent progress in oncology are summarized in detail with a focus on SIK1, and its potential as a therapeutic target is highlighted, underscoring the need for SIK1-targeted regulatory strategies in future cancer therapy.

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Contents

1. Introduction

The salt-induced kinase (SIK) family is one of the 14 members of the AMPK superfamily (1,2). The SIK subfamily comprises three kinases, namely SIK1, SIK2 and SIK3 (3), which are routinely expressed in humans. SIK1 is the founding member of this subfamily (4), and the induction of SIK1 expression was first demonstrated in the adrenal glands of rats fed on a high-salt diet (5). Although the members of the SIK subfamily possess a common domain in terms of their structure, the expression of SIK1 is regulated by external factors, unlike the other members of the subfamily, which are constitutively expressed (4). SIK1 features an extended C-terminal region, a sucrose non-fermenting protein (SNF-1) homologous (SNH) domain, and several phosphorylation sites (6). Furthermore, SIK1 is abundant in nerve tissue, fat and the adrenal cortex (7-9). Based on its special structure and high expression, SIK1 has been shown to regulate numerous physiological processes involved in energy production, gluconeogenesis (10-12) and lipid metabolism (10,13,14). SIK1 has also been found to be involved in apoptosis (15) and the regulation of circadian rhythms and sleep (16,17). Furthermore, SIK1 has been implicated in the development of diseases of the nervous system, including hypertension (18,19) and epilepsy (20-22). Cytokines involved in these processes create an extensive signaling network, featuring SIK1 as a central hub. Consequently, SIK1 exerts a crucial role in regulating both physiological and pathological processes, and, as a result, inhibitors targeting

SIK1 have been developed, ranging from broad-spectrum SIK inhibitors to those specifically targeting SIK1. The efficacy of these inhibitors has progressively improved both in terms of their sensitivity and their safety (23).

Moreover, accumulating evidence has suggested that SIK1 is involved in regulating the onset and progression of various types of tumors through cancer-associated signaling pathways. The expression of SIK1 was found to be downregulated in samples from patients with hepatocellular carcinoma, gastric cancer and colorectal cancer (24-29). This downregulated expression of SIK1 was found to be correlated with poor prognosis of the disease (27). Moreover, previous studies have shown that SIK1 inhibits the proliferation, invasion and migration of cancer cells in the majority of tumors (1,25,26,29); however, in certain tumors, the regulation of SIK1 has been revealed to have the opposite effect (30,31). This contradiction necessitates a further clarification of the association between SIK1 and cancer.

In the present review, the experimental studies that have been published on SIK1 over the course of the last 20 years are summarized, and the function of SIK1 is explained based on the experimental results and data that have been obtained. At the time of writing and preparing this review, the current state of knowledge on tumor signaling pathways in which SIK1 has been identified to participate is summarized, and this theme is developed with a discussion of the SIK1 regulatory factors in the second part of the review. Through analyses of the molecules, pathways and results of SIK1 research in different types of tumors, the present review highlights the independent effects of SIK1 that differentiate it from the other members of the SIK family, which should be of interest for researchers to refer to prior to designing further experiments, and which will aid scientists in terms of providing new ideas for research. Moreover, the present review provides robust evidence for the clinical development of drugs targeting SIK1, a novel class of molecules with great potential for future tumor therapeutic interventions.

2. Structure of SIK1 and its associated regulatory factors

Structure of SIK1 and its phosphorylation site. SIK1 is a member of the SIK subfamily of the AMPK-activated serine/threonine family of protein kinases (32). AMPK family members are activated by LKB1 phosphorylation (33). AMPK suppresses lung cancer through indirectly inhibiting the activation of mammalian target of rapamycin complex 1 oncogenic signaling via phosphorylating the downstream protein, tuberin complex subunit 2 (TSC2), to inhibit tumor growth pathways, including the fatty acid synthesis pathway that is required for cell proliferation. However, AMPK deficiency has been revealed to be detrimental to cancer cell survival in certain leukemia models (1). SIKs are a subfamily within the AMPK family. They share two key structural domains with other AMPK family members, one of which is the N-terminal serine/threonine kinase domain (KD), the other being the ubiquitin-associated (UBA) structural domain, which is responsible for the enzymatic activity of these proteins. The UBA domain fulfills a role in protein-protein interactions (32,34); however, unlike AMPK, which forms a complex with an ABC tetramer, SIKs are markedly simpler molecules (35). Each SIK consists of one monomer. Furthermore, the SIK family also has structural differences; for example, SIK2 and SIK3 share 70 and 37% sequence similarity in the SNH structural domain with SIK1, respectively (36). In addition to the common structural domain of the AMPK family, the SIK members also have a long C-terminal structure containing multiple cyclic AMP-dependent protein kinase A (PKA) activation sites (6). SIK1 was the first SIK to be identified in the adrenal cortical tissue of rats fed on a high-salt diet, thus becoming the founding member of this subfamily (5). The gene encoding SIK1 is located differently in different species; for example, it is located on chromosome 17 in mice, and on chromosome 21 in humans (17). SIK1 is a protein encoding 776 amino acids (32) (Fig. 1). The KD of SIK1 is located at residues 27-278 (2), and an activation loop (T-loop) has been identified in the KD (33) (Fig. 1). SIK activity is influenced by phosphorylation; specifically, phosphorylation at residue Thr-182 within the T-loop region is crucial for the enzymatic activity of SIKs (17). This phosphorylation may be triggered by LKB1, another kinase. The importance of LKB1 to SIK activation has been clearly demonstrated in cells lacking LKB1 activity or expression, such as HeLa cells or cells generated from LKB1-knockout mice (33,37,38). These cells exhibit significantly reduced SIK activity. Furthermore, SIK1 itself may have an additional autophosphorylation site within the T-loop, which is also essential for its activity (39). Glycogen synthase kinase 3 also phosphorylates SIK1 at the Thr-182 site, thereby forming a positive feedback regulation of SIK1 activation (36). Moreover, SIK1 contains an SNH structural domain at residues 301-354 (32). The Thr-322 residue located within this structural domain can be phosphorylated by Ca^{2+}/calmodulin-dependent protein kinase (CaMK) I (Fig. 1) (34,40). In addition, there is an UBA domain located in the SNH structural domains (41). The UBA domain participates in the activation of SIK1 mediated via LKB1 (42). Mutations in this structural domain have been shown to markedly reduce the SIK1 activity (41), thereby promoting SIK nuclear translocation through preventing SIK from interacting with the 14-3-3 adaptor protein (41,43). A structural domain containing a PKA-dependent phosphorylation site at residues 567-613 (32) is located at the C-terminus, which contains multiple PKA phosphorylation sites (32). PKA phosphorylation promotes the association of SIK1 and protein 14-3-3; moreover, SIK1 phosphorylation at Thr-473 and Ser-575 promotes both the relocalization of SIK1 to the cytoplasm, and its binding to protein 14-3-3 (17,44).

Moderating factors

Upstream regulators. LKB1 activates AMPK *in vivo*, subsequently activating SIK1. LKB1 phosphorylates the Thr-182 site of SIK1, which induces the kinase activity of SIK1 (Fig. 2) (10). LKB1 encodes a serine/threonine kinase mediating the phosphorylation of downstream AMPK, and is considered a potent tumor suppressor gene (45,46). Hollstein *et al* (1) showed that LKB1-activated SIK1 and SIK3 are key targets for lung cancer. In addition, LKB1 is able to mediate SIK1 apoptosis and to regulate E-calmodulin (15), E-calmodulin expression and intercellular junction stability (47). Ca^{2+}/CaMK is also a major upstream regulator, although it operates in a stand-alone manner. Phospholipase C promotes the movement of Ca^{2+} ions from the endoplasmic

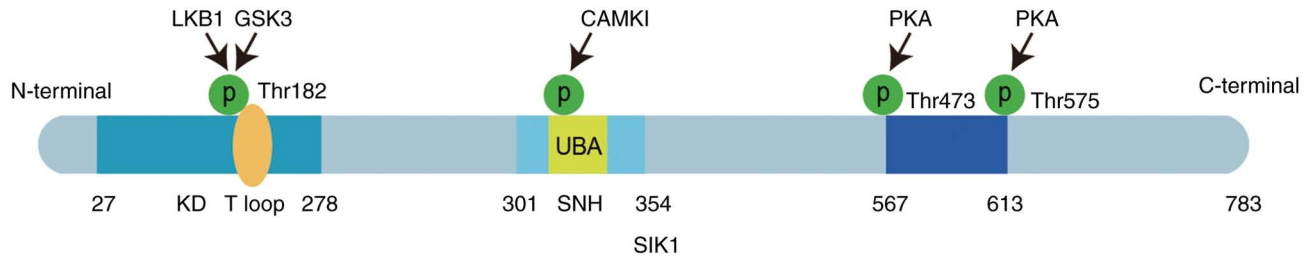

Figure 1. SIK1 structure and phosphorylation sites: SIK1 can be divided into three structural domains, namely: The KD structural domain, the SNH structural domain, and the C-terminal structural domain. From N-terminal to C-terminal, 27-278 amino acid residues have a KD structural domain, which contains an activation loop (T-loop) with phosphorylation sites. Amino acid residues 301-354 have an SNH structural domain, which contains a UBA structural domain with CAMP phosphorylation sites. Residues 567-613 have a structural domain containing multiple PKA phosphorylation sites. SIK1, salt-induced kinase 1; KD, silk-threonine kinase structural domain; SNH, sucrose nonfermentable homologous structural domain; UBA, ubiquitin-associated structural domain; LKB1, liver kinase B1; CaMKI, Ca^{2+}/calmodulin-dependent protein kinase I; PKA, protein kinase A; GSK3, glycogen synthase kinase 3.

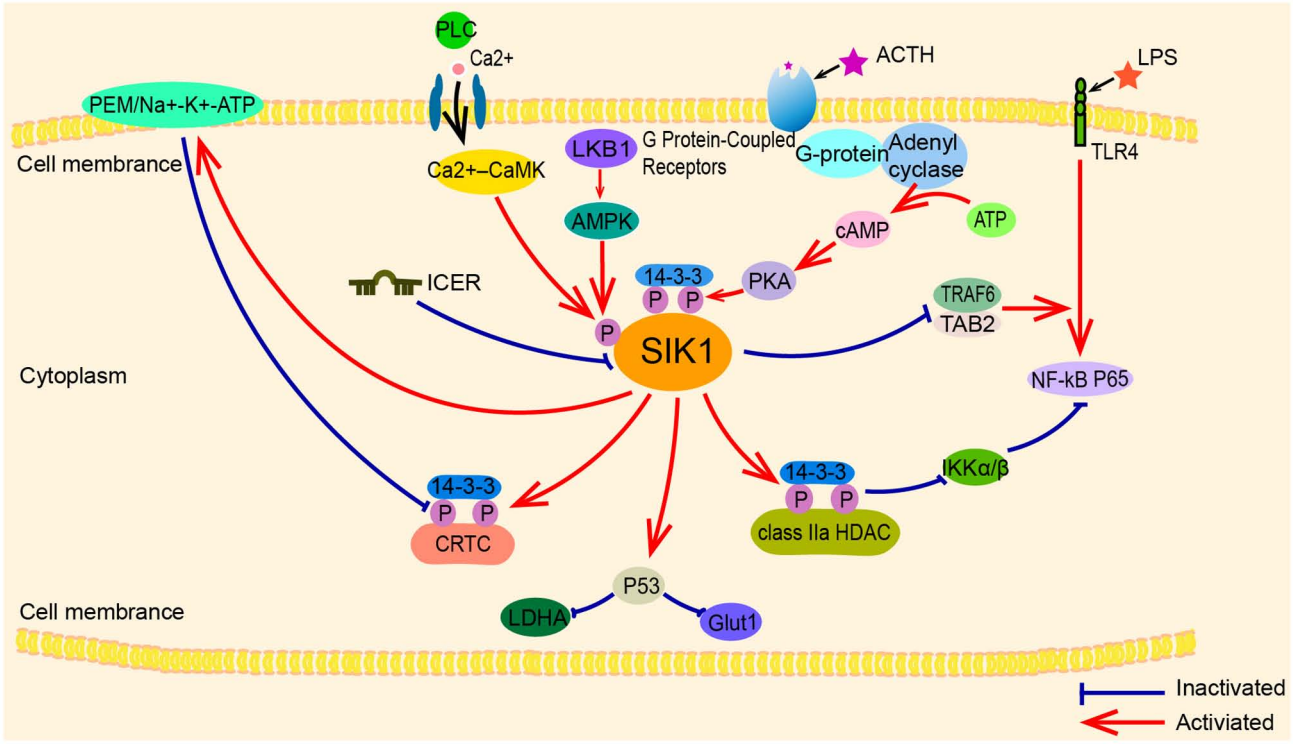

Figure 2. SIK1 upstream and downstream regulators: Upstream mainly includes LKB1, Ca^{2+} -CaMK, cAMP-PKA and some other regulators such as ICER; Downstream mainly identifies substrates such as CRTC and class IIa HDACs, and there are also some other signaling pathways such as PME-1/Na^{+}, K^{+}-ATP, NF-kB, P53 and other signaling pathways that play a regulatory role in tumor and other events. SIK1, salt-induced kinase 1; PLC, phospholipase C; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; LKB1, liver kinase B1; PKA, protein kinase A; ICER, inducible cAMP early repressor; CRTC, cAMP-responsive element-binding protein (CREB)-regulated transcription coactivators; HDAC, histone deacetylase; LDHA, lactate dehydrogenase A; ACTH, adrenocorticotropic hormone; LPS, lipopolysaccharide.

reticulum to the cytoplasm via the inositol trisphosphate receptor, especially in the central nervous system and during the regulation of T cells (48). This process activates CaMK, leading to phosphorylation of SIK1 within the UBA structural domains, thereby increasing SIK1 activity (49), followed by SIK1 activation of Na-K-ATPase (Fig. 2). SIK family members are induced by cAMP signaling (4). An increase in the concentration of cAMP increase is mediated by adenylate cyclase (AC), after which cAMP activates PKA (Fig. 2). PKA is another major upstream regulator of SIK1 that phosphorylates SIK1 at the Thr-475 site. SIK1 interacts with 14-3-3 following phosphorylation (50). SIK1 contains two PKA/14-3-3 sites, and its sensitivity to cAMP depends on these two PKA sites that mediate the interaction with 14-3-3 protein. Deletion of either of the 14-3-3 protein binding sites in SIK1 results in 14-3-3 protein binding failure, rendering it insensitive to cAMP (51). The absence of a single 14-3-3 binding site in SIK1 makes it insensitive to cAMP. There are several other upstream regulators, including the transcriptional repressor, inducible cAMP early repressor (ICER). ICER is induced by gastrin, which binds to the CRE promoter element and negatively regulates gene expression (52,53). The SIK1 promoter includes CRE binding sites (54), and SIK1 is a potential target gene for ICER. Selvik *et al* (55) demonstrated that ICER is a gastrin-induced factor that negatively regulates SIK1 expression.

Downstream regulators. SIK1 has two key groups of common substrates: cAMP-responsive element-binding protein (CREB)-regulated transcription coactivators (CRTCs) and class IIa histone deacetylases (HDACs). The CRTCs are regulated by CREB (17). SIKs proteins affect gene expression through phosphorylation. SIKs function as gene repressors in the nucleus by targeting another protein group: The class IIa HDACs, which act as gene repressors through binding to a protein called myoblast enhancer (51,54,56,57). When SIKs phosphorylate class IIa HDACs, this influences their ability to bind to DNA and to repress gene expression. As far as CRTCs are concerned, the mechanism via which these proteins operate is opposite to that of HDACs. They bind to CREB, and can also enhance the activity of bZIP transcription factors (4). Class IIa HDACs and CRTCs remain in the cytoplasm following phosphorylation due to their association with 14-3-3 protein in the cytoplasm (Fig. 2) (4,58). The dephosphorylated SIK substrates are transferred to the nucleus to participate in the regulation of gene expression (4). SIK1 controls the shuttling of these substrates between the cytoplasm and the nucleus through binding to 14-3-3. In a previous study, deletion of CRTC2 was shown to result in the complete inhibition of IL-6 production and SIK1 deletion-induced soft agar growth proliferation in non-small cell lung cancer (NSCLC), suggesting that CRTC2 is a major downstream target for LKB1 and SIK1/3-mediated inhibition of tumor formation (1).

Phosphatase methyl esterase-1(PME-1)/Na^+ and K^+-ATPases provide another set of downstream substrates of SIK1 (Fig. 2). PME-1/Na^+ and K^+-ATPases are predominantly found in cell membranes, and are able to regulate intracellular electrophysiological homeostasis by transporting Na^+ and K^+ ions. PME1 alone demethylates and inactivates protein phosphatase 2A (PP2A) (59), and when SIK1 is activated by CaMK, it phosphorylates PME-1. This phosphorylation event causes PME-1 to dissociate from the PP2A-Na^+, K^+/ATPase complex, leading to activation of PP2A, which ultimately influences how the Na^+/K^+-ATPase pump functions in the cell (40,60,61). SIK1 also regulates important signaling pathway factors, such as NF-kB and p53. Under inflammatory conditions, an increased expression of SIK1 interferes with protein interactions in the NF-κB pathway that are triggered by immune cells by preventing the phosphorylation of IKKα/β (62). Through activating the tumor suppressor protein p53, SIK1 reduces the expression of the glucose transporter Glut1 and lactate dehydrogenase A, which both participate in aerobic glycolysis, a process that is important for cancer cell proliferation. Additionally, SIK1 can inhibit the proliferation of breast cancer cells under conditions when the supply of nutrients is limited (24).

SIK1 inhibitors. SIK1 inhibitors also regulate SIK1. Given that current pan-SIK inhibitors target SIK isozymes, these are valuable for understanding the role of SIK1. The inhibitor HG-9-91-01, a 4,6-diaminopyrimidine derivative, has become an important tool for studying the specific role of SIK1 (63), and this highly selective inhibitor specifically targets the SIK family without inhibiting other AMPK family members (22,23,64). A pathophysiological model that exploited the selectivity of HG-9-91-01 revealed that SIK inhibition induces the production of IL-10 through macrophage-like cells, while downregulating IL-6, IL-12 and TNF-α (63). In another study, upon converting the 2,4-diaminopyrimidine derivative KIN-112 into HG-9-91-01, the activity of SIK1 was found to be significantly enhanced (~10-fold) without significantly changing its selectivity (Fig. 3) (63). Given that HG-9-91-01 showed promising effects *in vitro*, but poor outcomes *in vivo*, the HG-9-91-01 analogues YKL-05-099, YKL-06-061 and YKL-06-062 (Fig. 3) were subsequently developed for *in vivo* studies (17). Studies on two other inhibitors, MRT-67307 and MRT-199665 (63,65) (Fig. 3), primarily explored their regulatory effects on IL-10 and its functions, as well as the kinase selectivity of both these compounds and HG-9-91-01. The microtubule affinity-regulating kinases (MARKs)1-4, and NUAK family SNF1-like kinases (NUAKs)-1 and -2, are other members of the AMPK family. In contrast to HG-9-91-01, the MRT-67307 and MRT-199665 inhibitors target several other AMPK-associated kinases. Although these inhibitors can inhibit all the kinases MARK1-4 and NUAK1 and NUAK2, MRT-67307 has been shown to have greater potency against MARK3, whereas MRT-199665 is more effective against MARK1, MARK2 and MARK4 (63). In a separate study, Peng *et al* (22) investigated the limitations of pan-SIK inhibitors through developing selective inhibitors targeting only SIK1 and SIK2. These inhibitors were designed to be safer than HG-9-91-01. Notably, key differences were identified in the amino acid sequences of these new inhibitors compared with other similar kinases, as the focus was on specific residues such as threonine 'gatekeepers' and the nearby glutamate residue (Glu-103). Using this information and structure-based drug-design techniques, JRD-SIK 1/2 i-3 and JRD-SIK 1/2 i-4, selective inhibitors for SIK1 and SIK2, were developed (23). These SIK1/2-specific inhibitors were found to hold promise for treating inflammatory bowel disease through promoting the production of the anti-inflammatory factor IL-10, while simultaneously inhibiting pro-inflammatory factors by interfering with SIK1/2-dependent signaling pathways. In addition, endogenous proteins in the body are able to significantly inhibit SIK; for example, 14-3-3 proteins modulate SIK1 inhibition through the cAMP-mediated regulation of gene expression in vertebrate cells. Camp-mediated phosphorylation of PKA inhibits SIK family dephosphorylation, thereby promoting 14-3-3 protein release and causing nuclear translocation of the CRTCs (51).

3. SIK1 regulates tumor progression

Role of SIK1 in inflammation. Inflammation is closely associated with cancer (66). The majority of the experimental and population-based studies that have been published have confirmed that chronic inflammatory mediators promote tumor initiation, development and progression, thereby mediating tumorigenesis (67). The causes of chronic inflammation, such as infectious agents, immune-mediated diseases and allergies, have been shown to create a cancer-triggering microenvironment (66).

SIK1 is able to act as a key molecular switch in the occurrence of inflammation. The dephosphorylation of CRTC3 enables the transformation of classically activated macrophages (M1 macrophages) into regulatory macrophages (M2 macrophages) through the inhibition of SIK1, which leads to the production of higher levels of the anti-inflammatory molecule IL-10 and lower levels

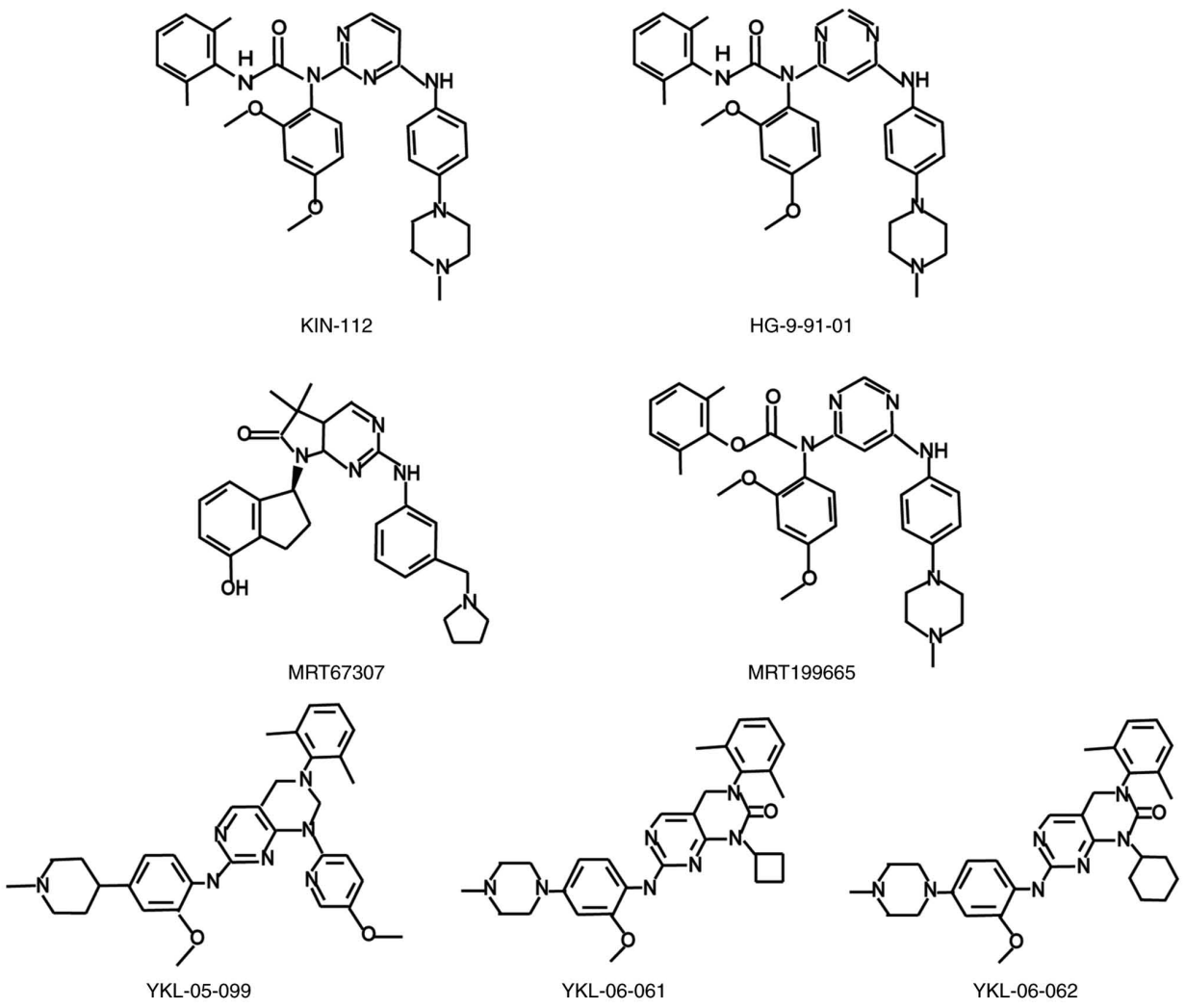

Figure 3. Structure of compounds that inhibit SIK1: HG-9-91-01 is a highly selective SIK family inhibitor derived from KIN-112; MRT-67307 and MRT-199665 can inhibit other members of AMPK family, and it is possible to inhibit SIK family. YKL-05-099, YKL-06-061 and YKL-06-062 are analogues of HG-9-91-01, and they can function better *in vivo* cell experiments than HG-9-91-01. SIK, salt-induced kinase.

of the pro-inflammatory factor IL-12, thereby preventing and alleviating chronic inflammation and autoimmune diseases (38). Alcohol consumption is known to increase the likelihood of developing neuroinflammatory diseases. Microglia are significantly associated with alcohol-induced neuroinflammation and apoptosis. An increased expression of SIK1 has been demonstrated to occur in the primary microglia of alcohol-consuming mice (62). SIK 1 inhibits microglial inflammation through the NF-κB signaling pathway (62). SIK1 participates in the process of epithelial-mesenchymal transition (EMT) as well as inflammation; in addition, SIK1 is a marker of the transition from acute kidney injury (AKI) to chronic kidney disease (CKD). SIK1 overexpression inhibits Wnt/β-catenin signaling and its downstream transcription factor, Twist1, leading to an attenuation of the inflammatory response and slowing the transition from AKI to CKD (68). NLR family pyrin domain-containing 3 (NLRP3) inflammasomes are protein complexes that promote inflammation through producing cytokines and triggering cellular pyroptosis. A recent study suggested that SIK1, when phosphorylated, has a role in regulating NLRP3 (69). This regulation appears to involve reducing the mRNA expression levels of the protein absent in melanoma 2, which prevents the development of autoimmune uveitis in the eye. Similarly, Pirie *et al* (70) observed that reducing SIK1 expression in healthy C57B16/J mouse primary splenocytes from mice enhanced their acute inflammatory responses, with acute inflammation being a healthy physiological response associated with tissue recovery or reconstruction (67). However, elucidating the precise details of the association between chronic inflammation and tumorigenesis requires further studies. SIK1 inhibitors can also exert anti-inflammatory effects. Lombardi *et al* (71) demonstrated that SIK inhibition (through the use of the inhibitors HG-9-91-01 and ARN-3236) significantly reduced the production of pro-inflammatory factors (such as TNF α and IL6) in human bone marrow cells, and increased the secretion of anti-inflammatory factor IL-10 thereby preventing and mitigating the development of inflammation (71). Timely blockade of SIK is able to effectively prevent disease progression to tumors from occurring. Although HG-9-91-01 has a high selectivity for SIK1, it has poor pharmacokinetic and pharmacodynamic characteristics, including a fast clearance rate, a slow exposure rate *in vivo*, and a high binding rate with plasma proteins. Cai *et al* (72) designed and synthesized several pyrimidine-5-carboxamide derivatives, where compound 8h was shown to have favorable activity and selectivity for SIK1,

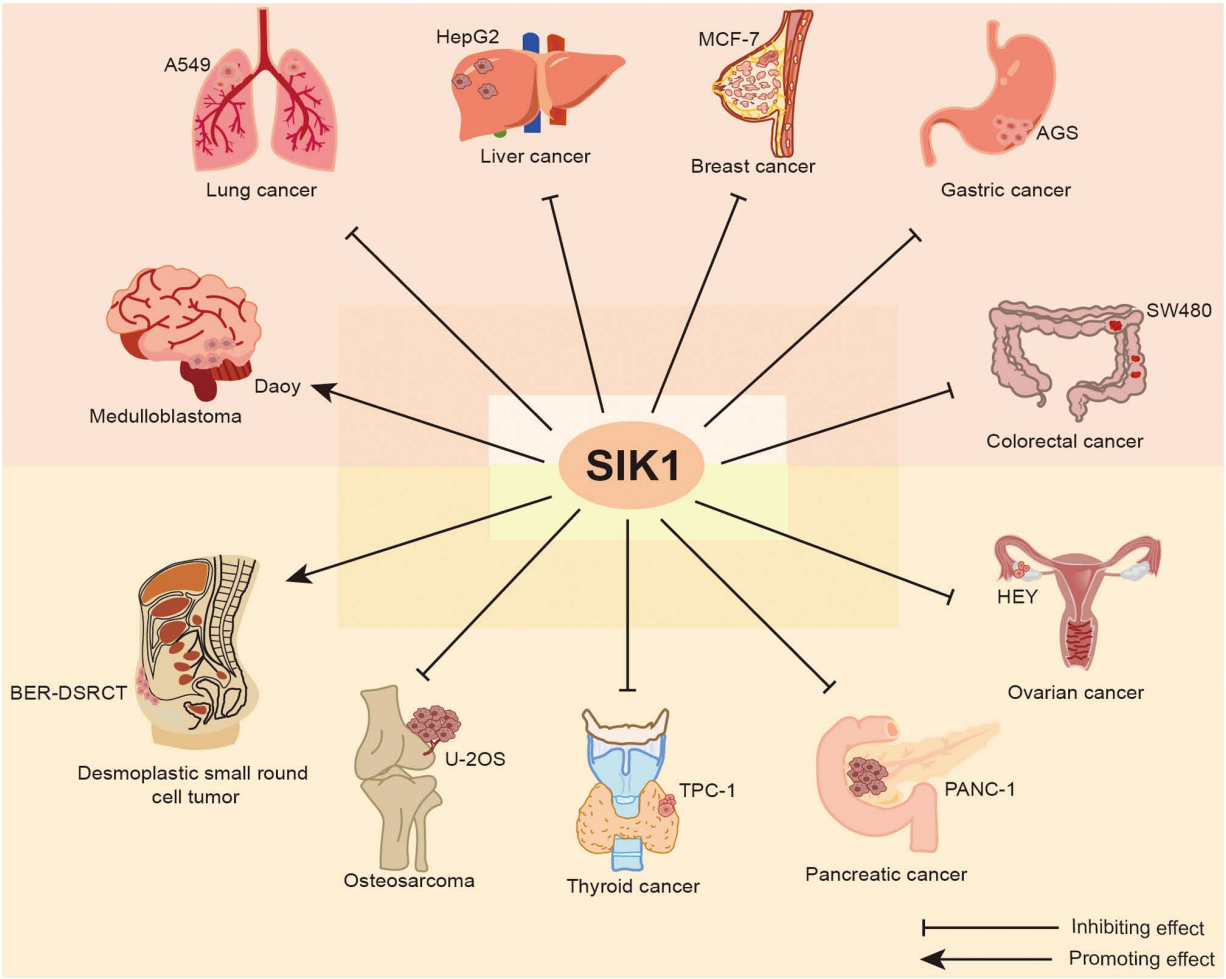

Figure 4. SIK1 plays two general roles in the proliferation of different tumor cells in different experiments: Inhibition and promotion. For example, in lung cancer A549 cells and hepatocellular carcinoma HepG2 cells, SIK1 inhibits the proliferation of tumor cells; in medulloblastoma Daoy cells, SIK1 promotes the proliferation of tumor cells. SIK 1, salt-induced kinase 1.

avoiding the aforementioned shortcomings of HG-9-91-01. This compound had the capability of increasing the anti-inflammatory effects of IL-10, while significantly reducing the pro-inflammatory effects of IL-12; in addition, compound 8h was shown to exert favorable effects on colitis models.

Expression of SIK1 in clinical samples. Several studies have been performed to explore the influence of SIK1 in tumorigenesis and development. The downregulation of SIK1 was shown to promote tumor enlargement and distant metastasis in liver cancer cells (P<0.001) (25). In addition, SIK1 downregulation is associated with shorter overall survival (OS) rates and worsened disease-free survival rates. Moreover, SIK1 is an independent predictor of OS. SIK1 expression was found to be significantly decreased in all the studied liver cancer cell lines compared with normal liver cell lines (25). Another study has shown that SIK1 levels are reduced in liver cancer tissues (73); the level of SIK1 was higher in normal liver tissues compared with that in liver cancer tissues (73) (5.15±0.41 vs. 3.12±0.29; P<0.006). In addition, survival analysis identified that low SIK1 expression was positively associated with a poor prognosis (73). Similarly, survival analysis of the prognosis of patients with breast cancer showed that the high expression of SIKs was positively associated with OS and recurrence-free survival (RFS) (26). Moreover, the Klein score of SIK1 in patients with breast cancer was found to be higher in ER-positive patients compared with ER-negative patients (26). Ponnusamy and Manoharan (24) revealed that low expression of SIK1 is associated with breast carcinogenesis. Based on an analysis of the Oncomine data, SIK1 expression was found to be lower in breast cancer tissues compared with normal tissues, and the most prominent subtype of breast cancer present was the luminal subtype (24). Compared with paraneoplastic non-tumor tissues, SIK1 was shown to be downregulated in 36 pairs of gastric cancer tissues (29). SIK1 is also downregulated in colorectal cancer cell lines; the downregulation of SIK1 was found to be an independent risk factor of patients with colorectal cancer (27). Notably, SIK1 is also downregulated in patients with pancreatic cancer, suggesting that SIK1 may be a tumor suppressor in pancreatic cancer (28).

Functions of SIK1 in tumors. The roles of SIK1 in tumor growth may be divided into two broad categories (Fig. 4): One is the inhibition of cancer (Table I), and the other is promotion of cancer (Table I). These two opposite effects have been verified in a large number of experiments.

Table I. Model types and functional characteristics of SIK1 used in different tumors.

First author, year	Tumors	Model types	Functional characteristics	(Refs.)
Hollstein *et al*, 2019	Lung cancer	KP ($Kras^{LSLG12D/+}$; $p53^{fl/fl}$; $R26^{LSL;\ luc/luc}$) mice induced by sgSIK1	SIK1 inhibits lung cancer growth.	(1)
Murray *et al*, 2019		$Kras^{LSL\text{-}G12D}$, $p53^{flox}$, $Lkb1^{flox}$, $H11^{LSL\text{-}Cas9}$ and $Rosa26^{LSL\text{-}tdTomato}$ mice	SIK1 is a downstream gene of the oncogene LKB1, which is regulated by LKB1 to inhibit lung cancer growth.	(74)
Qu *et al*, 2016	Liver cancer	Nude mice orthotopic liver cancer cell model overexpressing SIK1 and HepG2 model silencing SIK expression.	SIK1 inhibits invasion and lung metastasis of liver cancer cells.	25
Fu *et al*, 2017		Nude mice injected with siSIK1 Hep3B and siSIK1 Huh-7	SIK can inhibit the proliferation and apoptosis of liver cancer cells.	(76)
Qu *et al*, 2017		MHCC97H cells treated with siRNF2, shRNF2 and shSIK1 respectively	SIK1 is the target of RNF2 E3 ligase, which can reverse RNF2's promotion of liver cancer growth.	(73)
Ponnusamy and Manoharan, 2021	Breast cancer	MCF-7, ZR-75-1 and MCF-10A transfected with siSIK1	SIK significantly inhibits the proliferation of breast cancer, promotes oxidative phosphorylation and inhibits aerobic glycolysis.	(24)
Xin *et al*, 2021		MDA-MB-231 and MCF-7 treated with SIK1 si/shRNA	SIK1 inhibits chemotherapy resistance of breast cancer more obviously than other subtypes.	(26)
Zang *et al*, 2022	Gastric cancer	Human gastric cancer cell lines (AGS, HGC-27, MKN-45 and SGC-7901) and siSIK1 transduced AGS and HGC-27 cell lines	SIK1 is an intermediate molecule that circEIF4G3 regulates gastric cancer cells and inhibits gastric cancer growth when it exists alone.	(29)
Selvik *et al*, 2014		AGS-GR cells transfected with siSIK1	SIK1 participates in the migration of gastric adenocarcinoma cells induced by gastrin.	(55)
Gao *et al*, 2023	Colorectal cancer	RKO and SW480 cell lines of OE-SIK1; HCT116 cell line of KD-SIK1; Female BALB/c nude mice (6-8 weeks old) injected with HCT116shSIK1.	SIK1 inhibits metastasis and chemotherapy resistance of colorectal cancer.	(77)
Jin *et al*, 2022	Ovarian cancer	HEY and ES-2 cell lines of pc-DNA overexpression vector	SIK1 inhibits the migration and invasion of ovarian cancer cells and promotes apoptosis.	(78)
Ren *et al*, 2016	Pancreatic cancer	Gemcitabine-resistant cells (PANC-1, Hs766T, ASPC-1, MiaPaCa-2 and MPanc96 cells) and gemcitabine-sensitive cells (HPAC, L3.6pl, CFPAC, BxPC-3 and SU86.86 cells)	SIK1 inhibits gemcitabine resistance and inhibits DNA synthesis in pancreatic cancer cells.	(28)
Kou *et al*, 2022	Thyroid cancer	LKB1 overexpressed TPC-1 and BCPAP	SIK1 as the main downstream regulator of LKB1 has an inhibitory effect on thyroid cancer.	(79)

Table I. Continued.

First author, year	Tumors	Model types	Functional characteristics	(Refs.)
Wang *et al*, 2022	Osteosarcoma	Transfected 143B and U-2OS cells with different siRNA (siRNA#1 and siRNA#2)	SIK1 inhibits the proliferation and migration of osteosarcoma cells.	(82)
Huang *et al*, 2020	Medulloblastoma	Specific siRNA knocks down Daoy cells; 6-week-old nude mice implanted with Daoy cells stably expressing sh-SIK 1	SIK1 is an intermediate molecule connecting miR-130b-3p and p53, which promotes medulloblastoma growth when it exists alone.	(30)
Hartono *et al*, 2022	Desmoplastic small round cell tumor	Dox-inducible shSIK1 stable JN-DSRCT-1 (JN) and BER-DSRCT (BER) cells; Stable injection of JN- and BER-shSIK1 and sh-Renilla Mice with immune-deficient NOD.SCID/IL2Rγ-null (NSG) mice	SIK1 may mediate the regulation of desmoplastic small round cell tumor by EWSR1-WT1 and participate in DNA replication of tumor cells.	(31)

SIK1, salt-induced kinase 1.

Anticancer effects of SIK1

Lung cancer. Human A549 lung adenocarcinoma cells with LKB1 deleted have been used for colony formation on soft agar plates to explore the role of SIK family members in KRAS-dependent lung tumors. The results obtained showed that only SIK family members were able to restore the soft agar colonies after the inhibition of recombinant colonies by LKB1 (1). Lung tumor size was found to be significantly higher in SIK1-disrupted mice compared with the control mice. Furthermore, H&E staining of lung tissue from mice transfected with sgSIK1 revealed that the lung tumor size of virus-treated mice carrying sgRNA targeting SIK1 was significantly increased, consistent with floating Sik1 allele analysis (1). Another experiment investigating the effect of the LKB1-SIK axis pair in lung cancer showed that the tumor load was increased in mice transduced with vectors carrying sgSik1 or sgSik1+3. In another study, genes downstream of SIK were found to be highly enriched when LKB1 was re-expressed, thereby confirming that SIK1 is a downstream gene of LKB1, and is regulated by LKB1 to inhibit tumor growth (74).

Liver cancer. Liver cancer cells are able to stably express SIK1. SIK1 significantly reduces growth efficiency; however, SIK1 deletion led to an increased efficiency of lesion formation, a larger number of colonies as shown by soft-agar colony formation assay, and an increased liver cancer growth rate (25). In nude mouse orthotopic MHCC97H liver cancer cells, SIK1-overexpressing cells were found to have a smaller tumor volume compared with control cells. By contrast, SIK1 silencing led to a marked promotion of the proliferation of liver cancer cells *in vivo* (25). These experiments also investigated the presence of metastatic cancers (25), such as bone metastases, which are common in lung cancer (75); however, in liver cancer, lung metastasis is frequently detected. Fewer lung metastases and smaller metastatic foci of liver cancer were found in nude mice compared with the control mice following hydrostatic injection of MHCC97H-SIK1. These experiments confirmed that SIK1 inhibits the invasion and metastasis of liver cancer (25). MicroRNA (miR)-25 inhibitors have also been shown to attenuate tumor metastasis and proliferation in mice, and to promote apoptosis in liver cancer cell lines; however, SIK1 silencing is able to reverse these effects (76). The E3 ubiquitin ligase RNF2 regulates downstream SIK1 activity (73). Downregulation of RNF2 can induce restoration of the levels of SIK1, which thereby leads to the inhibition of liver cancer cell proliferation and promotion of apoptosis of liver cancer cells, both changes of which were found to be significant (73). Moreover, the presence of SIK1 following RNF2 knockdown reduced the ability of cells to migrate ($P<0.01$); however, knocking down SIK1 led to a reversal of the aforementioned effects (73).

Breast cancer. Ponnusamy and Manoharan (24) transduced SIK1-specific siRNA into the malignant breast cancer cell lines MCF7, ZR-75-1 and MCF10A, revealing that SIK1 knockdown (SIK1-KD) is able to promote cancer cell proliferation based on MTT assays. SIK1-KD also led to significant increases in energy expenditure, inhibition of ATP production, and promotion of the proliferation of the luminal subtypes of breast cancer cells. Another experiment also showed that high SIK1 expression is positively correlated with RFS ($P=0.0026$). Furthermore, an *in vitro* stromal cell invasion assay was

performed to reveal that SIK1-KD can increase the invasive potential of breast cancer cells. Further studies found that SIK1 knockdown can increase the resistance of breast cancer cells to chemotherapeutic drugs paclitaxel (IC_{50}: SIK1-KD, 18.62 μM vs. 5.279 μM). Notably, the resistance of the breast cancer cell lines to chemotherapy was more pronounced when the three SIK family members were simultaneously knocked down (26). Furthermore, The Cancer Genome Atlas database showed that the patients who responded better to chemotherapy with paclitaxel had a higher expression level of SIK1 (P=0.019).

Gastric cancer. Overexpression of the circular RNA (circRNA) circEIF4G3 inhibits the proliferation of malignant cells in gastric cancer. However, SIK1-KD was found to attenuate this inhibition. Moreover, cells of the circEIF4G3-transfected HGC-27 gastric cancer cell line exhibited inhibited tumor growth with an increasing level of SIK1. These findings suggested that circEIF4G3 can inhibit the proliferation of gastric cancer cells via regulating SIK1 (29). In another study, SIK1 was demonstrated to affect gastrin-induced migration of gastric adenocarcinoma cells; notably, SIK1-KD gastric cancer cell line AGS exhibits stronger cell migration (55).

Colorectal cancer. A recent study showed that SIK1 is downregulated in colorectal cancer tissues (P<0.001), with a reduced migratory capability (P<0.001) and a reduced capacity for trauma healing (P<0.01) in two cell lines RKO and SW480 with OE-SIK1. However, the opposite trend was observed in SIK1-KD strain HCT116 (both migratory capability and capacity for trauma healing, P<0.01) (77). Lentiviral transfection of HCT116 cells with downregulated SIK1 led to a significant increase in the chemotherapy resistance of nude mice, thereby decreasing the efficacy of the therapy. Furthermore, H&E staining and Ki67 immunohistochemistry experiments showed that the SIK1 + oxaliplatin (OXA) chemotherapy group had an increased rate of proliferation, as indicated by higher Ki67 values compared with the short hairpin (sh) NC + OXA chemotherapy group. Taken together, these findings suggested that SIK1 may be useful as an *in vivo* colorectal cancer chemotherapeutic drug-binding target (77).

Ovarian cancer. In an investigation of the regulatory mechanism of ovarian cancer, upon transfection of circ_0078607 into the HEY and ES-2 cell lines, overexpression of circ_0078607 led to a significant promotion of the expression of SIK1 in HEY and ES-2 cells (P<0.001), although the expression of miR-32-5p was inhibited. Furthermore, an overexpression vector, pc-DNA SIK1, was constructed. Overexpressed SIK1 was revealed to significantly inhibit the migration (P<0.01) and invasion (P<0.01) of HEY and ES-2 cells, and to promote cell apoptosis (P<0.001). A series of experiments were performed, including reverse transcription-quantitative PCR experiments, which confirmed that overexpressed circ_0078607 inhibited the progression of ovarian cancer via targeting miR-32-5p to upregulate SIK1 (78).

Pancreatic cancer. In a study which explored the resistance of SIK1 to gemcitabine, the 10 pancreatic cancer cell lines employed in the study were divided into two categories: The PANC-1, Hs766T, ASPC-1, MiaPaCa-2 and MPanc96 cell lines, which were resistant to gemcitabine, and the HPAC, L3.6pl, CFPAC, BxPC-3 and SU86.86 cell lines, which were sensitive to gemcitabine. Western blot analysis identified that the expression of SIK1 in gemcitabine-resistant cells was lower compared with that in gemcitabine-sensitive cells. Through quantitative image analysis again, it was shown that SIK1 was downregulated in gemcitabine-resistant pancreatic cancer. Finally, according to a bromodeoxyuridine incorporation test, SIK1 was able to significantly inhibit DNA synthesis in pancreatic cancer cells (28).

Thyroid cancer. High expression of LKB1 inhibits the growth of thyroid cancer (79). Using OE-LKB1 cell lines TPC-1 and BCPAP, it was found that the upregulation of LK1 increased the levels of p-SIK1 and SIK1 proteins (79). Moreover, SIK1 inhibitors can eliminate the inhibition of proliferation caused by LKB1 overexpression (P<0.05) and reverse the elevation of E-Cadherin (79). These findings demonstrated SIK1's role as a key downstream inhibitor of LKB1 in thyroid cancer. Western blot analysis of nude mice injected with TPC-1 or OE-LKB1 cells revealed significant reductions in thyroid tumor mass and volume in the LKB1 overexpression group. Furthermore, levels of p-SIK1, SIK1 and E-Cadherin proteins were elevated (79).

Osteosarcoma. The proto-oncogene B lymphoma Mo-MLV insertion region 1 (BMI 1) is a transcriptional repressor that is known to modulate tumorigenesis (80,81). In osteosarcoma, BMI1 was found to promote osteosarcoma cell proliferation, migration and invasion *in vitro*. Bioinformatics analysis of osteosarcoma lines with BMI using chromatin immunoprecipitation sequencing data revealed the presence of the target gene SIK1 in BMI. The levels of SIK1 mRNA were increased in osteosarcoma cells treated with PTC-209 (BMI1-specific inhibitor). SIK1-KD in osteosarcoma cell lines 143B and U-2OS enhances the proliferation (P<0.001) and migration (P<0.001) of tumor cells (82). Taken together, these studies have shown that various means of inhibiting SIK1 can lead to an enhancement of the proliferation and migration of osteosarcoma cells.

Pro-cancer effects of SIK1.

Medulloblastoma. Transfection with siSIK1 led to an inhibition of the migration (P<0.05) and invasion (P<0.05) of medulloblastoma cell Daoy (30). In addition, six downstream candidate target genes (SIK 1, SIK 3, ESR 1, SMAD 4, MAP 2 and TSC1) were also detected in medulloblastoma cells transfected with miR 130b 3p. Among these six genes, the SIK1 gene demonstrated the most pronounced level of downregulation (P<0.01). Further studies reported that miR-130b-3p upregulation and SIK1 downregulation in medulloblastoma cells led to an increase in the activity of the p53 oncogenic pathway (30). Injection of medulloblastoma cells with a SIK1-KD vector caused a significant decrease in the average tumor volume and tumor weight of mice inoculated with shSIK1 cells at week 8 compared with sh-GFP mice (P<0.05), demonstrating that SIK1 was able to promote medulloblastoma formation (30).

Desmoplastic small round cell tumor. Desmoplastic small round cell tumor is a rare and aggressive type of cancer that is caused by a specific genetic abnormality (31). This abnormality involves a chromosomal translocation, where two portions of chromosomes 11 and 22 swap positions (31). The resulting fusion gene creates a protein called EWSR1-WT1, which acts as an oncogenic transcription factor, causing an abnormal promotion of cell proliferation, ultimately leading to cancer (31). Researchers have found that SIK1 is expressed at

markedly higher levels in desmoplastic small round cell tumor compared with other types of sarcomas (cancers that arise in connective tissues). This suggests that SIK1 may be a regulatory factor which acts downstream of EWSR1-WT1, potentially fulfilling a role in mediating the effects of EWSR1-WT1 on desmoplastic small round cell tumor (31). Later, under the induction of DOX, the levels of SIK1 protein in JN and BER of shSIK1 stable desmoplastic small round cell tumor cells decreased, thus reducing or inhibiting DNA replication in cancer cells (P<0.0001). Injection of desmoplastic small round cell tumor cells stably expressing shSIK1 in immunodeficient mice revealed that SIK1 deficiency could inhibit the growth of xenograft tumors (P<0.001). Intraperitoneal injection of EdU into mice before euthanasia revealed that the deletion of SIK1 gene could reduce the number of EdU cells in xenograft tumors (P<0.0001), which indicated that SIK1 was necessary for DNA replication of tumor cells *in vivo* (31).

4. SIK1 regulates tumor progression through different signals

SIK1 is expressed in diverse types of tumors, either promoting or inhibiting tumor growth by participating in tumor signaling pathways and influencing upstream or downstream molecules (Table II). Therefore, SIK1 is a potential target in the treatment of solid tumors, and SKI participates in different signaling pathways that are associated with each other to jointly regulate tumorigenesis (Fig. 5).

LKB1-SIK1 signaling pathway. LKB1 kinase is an important tumor suppressor in human cancers (1,83). LKaB1 can target and regulate SIK1 and its downstream factors (Fig. 5A), thereby exerting inhibitory effects in numerous tumors (1,74,79,83). Through constructing the radiation-resistant cell lines A549R and H1299R, Yao *et al* (84) showed that an attenuation of LKB1-SIK1 signaling led to an upregulation of the expression of the EMT driver ZEB1, which promotes EMT and radiation-resistance in NSCLC. Murray *et al* (74) also demonstrated that tumor growth inhibition occurs through the LKB1-SIK axis in lung cancer growth and differentiation.

Role of the transforming growth factor-β (TGF-β) signaling pathway. TGF-β induces multiple signaling pathways, and is integrated into different signaling regulatory pathways (85). TGF-β is a downstream substrate of LKB1-SIK1 (86), which stimulates the downstream genes ZEB1 and α-subunit of the channel protein called Nav1.5 (SCN5) to control tumor progression (87-89). SIK1 can also inhibit Smad7 (90) and other targets of the TGF-β pathway in colorectal cancer, thereby inhibiting colorectal cancer metastasis (77). Furthermore, SIK1 inhibits EMT by regulating the level of ZEB1 and reversing oxaliplatin resistance in colorectal cancer (Fig. 5A) (77). An elevated level of ZEB1 expression was shown to promote EMT development and tumor metastasis in both ovarian cancer and NSCLC (84,91). In metastatic breast cancer, lower levels of SIK1 protein are associated with an increase in the level of Nav1.5. This channel protein, encoded by the SCN5A gene, is a voltage-gated Na^+ channel that fulfils a crucial role in nerve and muscle cells. In cancer cells, Nav1.5 also has a role in cell adhesion and movement. When Nav1.5 levels are high due to

Table II. The signaling pathways and regulatory mechanisms of SIK1 in tumors.

First author, year	Signaling pathways	Tumors	Regulatory mechanisms	(Refs.)
Yao *et al*, 2016	LKB1-SIK1	NSCLC	Suppression of EMT and radiation resistance in NSCLC.	(84)
Murray *et al*, 2019		Lung cancer	Inhibits the growth of lung cancer cells.	(74)
Gao *et al*, 2023	TGF-β	Colorectal cancer	SIK1 inhibits TGF-β pathway and metastasis of colorectal cancer, inhibits EMT, and reverses drug resistance.	(77)
Gradek *et al*, 2019		Brest cancer	Downregulated SIK1 upregulates Nav1.5 to increase EMT and cancer cell invasiveness.	(89)
Qu *et al*, 2016	Wnt/β-catenin	Hepatocellular carcinoma	SIK1 inhibits hepatocellular carcinoma cell invasion, migration, and EMT through inhibition of β-catenin and Twist1.	(25)
Huang *et al*, 2020	p53	Medulloblastoma	miR-130b-3p inhibits medulloblastoma by downregulating SIK1 factor through the p53 pathway.	(30)
Ponnusamy and Manoharan, 2021		Brest cancer	SIK1 activates p53 to inhibit glycolysis and suppress breast cancer cell proliferation.	(24)
Sun *et al*, 2023	PI3K-AKT	Brest cancer	Inhibits SIK1 binding to JAK2-STAT3 after activation of AKT signaling to promote breast carcinogenesis.	(95)

SIK1, salt-induced kinase 1; EMT, epithelial-mesenchymal transition; NSCLC, non-small cell lung cancer.

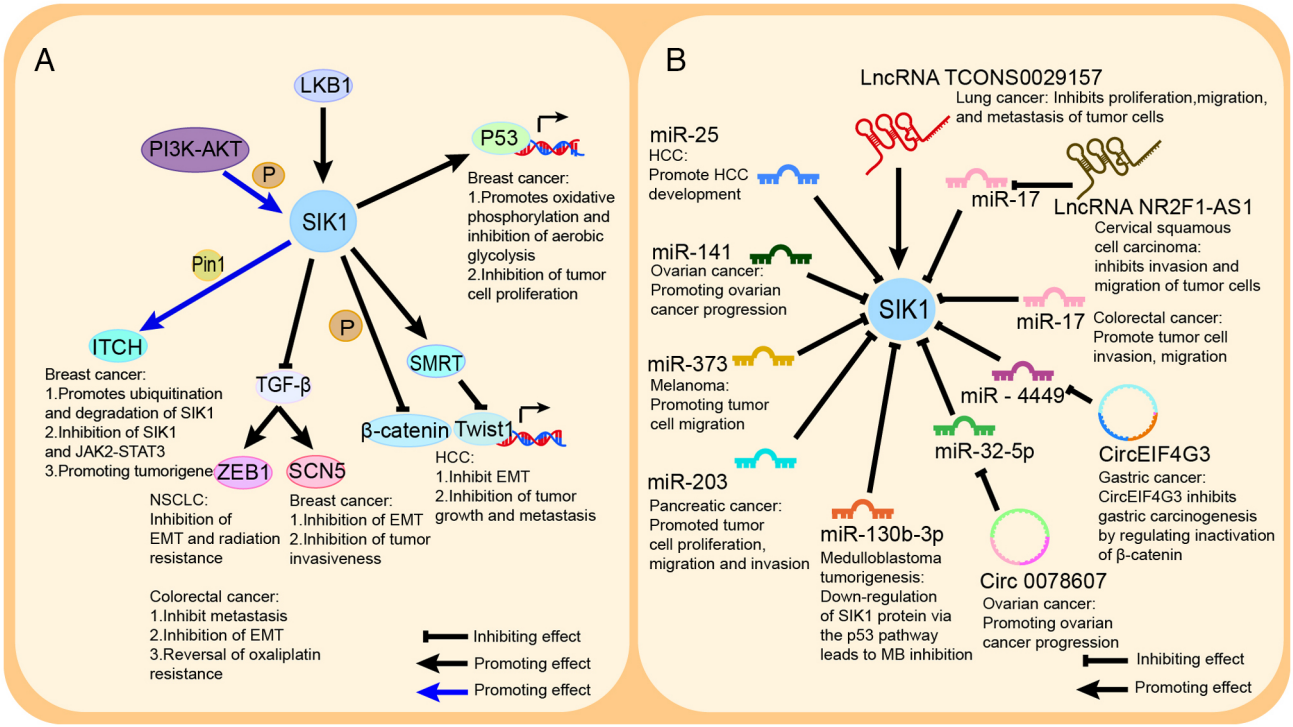

Figure 5. SIK1 regulates tumor development through different signaling pathways: (A) PI3K-AKT phosphorylates SIK1, which interacts with ITCH under the action of Pin1 to promote the occurrence and development of breast cancer; LKB1 activates SIK1 to target and regulate different downstream pathways; SIK1 inhibits the TGF-β pathway and participate in NSCLC and colorectal cancers; SIK1 inhibits β-catenin pathway and inhibits Twist transcription factor by phosphorylating SMRT in HCC; and SIK1 promotes p53 transcription and plays an inhibitory role in breast cancer. (B) Non-coding RNAs are involved in regulating SIK1 expression. miR-130b-3p, miR-141, miR-25, miR-17, miR-373 and miR-203 directly inhibit SIK1 to promote tumor development; lncRNA NR2F1-AS1, Circ0078607 and CircEIF4G3 inhibit SIK1 to promote tumor development by regulating downstream miR to inhibit SIK1 to promote tumor development; lncRNA TCONS0029157 activates SIK1 to inhibit tumor development. SIK 1, salt-induced kinase 1; LKB1, liver kinase B1; NSCLC, non-small cell lung cancer; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; HCC, hepatocellular carcinoma; miR, microRNA; lncRNA, long non-coding RNA; circ-, circular; EMT, epithelial-mesenchymal transition.

a reduction in the level of SIK1, cancer cells become more aggressive. This happens as increased Nav1.5 activity triggers increases in the levels of two other proteins, SNAI1 and ZEB1, which are known to be involved in EMT. EMT allows cancer cells to lose their original form and become more motile, contributing to their spread (89,92). Nav1.5 overexpression has also been shown to promote Na^+-mediated invasiveness, since the tumor cells are sensitive to Na^+ (93).

Role of the Wnt/β-catenin signaling pathway. SIK1 suppresses EMT by inhibiting the transcriptional activity of β-catenin, thereby inhibiting tumor growth and metastasis in liver cancer (25). Twist1 is a protein that functions as a brake on gene expression. When Twist1 levels are high, this protein is able to promote cancer cell invasion, migration and resistance to cell death signals (94). In liver cancer, SIK1 and β-catenin have been revealed to work together to regulate Twist1. They phosphorylate the co-repressor, silencing mediator of retinoic acid and thyroid hormone receptor (SMRT), which then inhibits Twist1 activity (Fig. 5A). This pathway inhibits the growth and spread of liver cancer. Interestingly, researchers have also found that Twist1 can target the SIK1 gene directly *in vivo*. Through binding to the SIK1 promoter, Twist1 can suppress SIK1 production: This creates a negative feedback loop, where high Twist1 levels can lead to lower SIK1 levels, which partially counteracts the initial inhibitory effect of SIK1 on Twist1. A low SIK1 expression in liver cancer has been shown to be suggestive of a poor prognosis, indicating that SIK1 may be a valuable biomarker for liver cancer (25).

Role of the p53 signaling pathway. p53 is also a signaling molecule that lies downstream of the LKB1-SIK1 axis with its own associated regulatory pathway. Studies have shown that SIK1 inhibits breast cancer cell proliferation through activating p53 transcriptional activity, which promotes oxidative phosphorylation and inhibits aerobic glycolysis (Fig. 5A) (24). SIK1 also connects LKB1 with p53-dependent anoikis, thereby suppressing breast cancer metastasis (15). Furthermore, p53 participates in the regulation of medulloblastoma tumorigenesis mediated by SIK1. miR-130b-3p was identified to inhibit medulloblastoma tumor progression by downregulating the expression of SIK1 factor via p53 targeting (Fig. 5B) (30).

Role of the PI3K-AKT signaling pathway. Overactive ATK signaling has been found to contribute towards breast cancer. In breast cancer, SIK1 functions as a downstream target of PI3K-AKT, acting as the bridge between AKT and STAT3. SIK1 binds AKT and is phosphorylated at Ser-435. Following phosphorylation, SIK1 interacts with 14-3-3 proteins, and is translocated to the cytoplasm. The presence of the prolyl isomerase Pin1 promotes the interaction between SIK1 and the E3 ubiquitin-protein ligase ITCH, which enhances SIK1 ubiquitination and degradation (Fig. 5A). Considered overall, these factors have been shown to ameliorate the inhibitory

effect of SIK1 on STAT3, thereby promoting breast cancer development (95).

Regulation of SIK1 via other signaling mechanisms. In addition to the aforementioned molecular pathways, several other molecules have also been reported to regulate SIK1, among which miRs are the most extensively investigated (Fig. 5B). Through the previous research articles on SIK1, the inhibitory effects of eight miRs on SIK1 and tumor growth have been summarized (Table III). miR-141 was shown to downregulate SIK1 protein, which led to the promotion of cancer cell proliferation (96). Increased miR-17 levels were also identified to enhance the aggression and mobilization of colorectal cancer cells. Dual-luciferase reporter gene assay demonstrated that SIK1 directly targets miR-17. Consequently, the upregulation of miR-17 may exert oncogenic effects via targeting SIK1. The SIK1 protein presents itself as a potential therapeutic target for colorectal cancer (27). miR-25 targets SIK1 to downregulate the expression of SIK1 protein, which consequently increases the activity of the Wnt/β-catenin signaling pathway, promoting the progression of liver cancer and potentially providing a novel therapeutic strategy for the targeted therapy of liver cancer (76). miR-373 has been found to inhibit SIK1 expression to enhance melanoma cell migration (97). Moreover, inhibition of SIK1 by miR-203 promoted the proliferation, migration and invasion of pancreatic cancer cells (28). Other types of non-coding RNAs, such as long non-coding RNAs (lncRNAs) and circRNAs, have been shown to mediate the regulatory effects of SIK1 on tumor growth (Fig. 5B). Among them, circEIF4G3, circ0078607 and the lncRNA NR2F1-AS1 indirectly inhibit SIK1 expression through regulating miRs (29,78,98); the lncRNA TCONS 0029157 directly targeted SIK1 to modulate tumor development (99). circEIF4G3 was found to regulate the miR-4449-SIK1 signaling axis, thereby inhibiting the β-catenin signaling pathway and tumor growth (29). Eventually, circEIF4G3 was also shown to stimulate the β-catenin signaling pathway, thereby inhibiting gastric carcinogenesis (29). A recent study on ovarian cancer showed that circ0078607 may act as an miR-32-5p 'sponge' to modulate the expression of the SIK1 protein, thereby suppressing ovarian cancer progression (78). NR2F1-AS1 inhibits the migration and invasion of cervical squamous cell carcinoma through modulating the miR-17-SIK1 axis (98). Finally, activation of SIK1 by TCONS 0029157 was shown to inhibit the proliferation, migration and metastasis of lung cancer (99).

5. Discussion

SIK1 phosphorylates the Thr-1391 site of SMRT, thereby promoting nuclear localization, inhibiting the Wnt/β-catenin/Twist1 signaling pathway, and silencing the progress of liver cancer (25). Under identical conditions, SIK2 and SIK3 do not exhibit these effects. The structural differences among the three SIK proteins, particularly in their C-terminal domains, contribute to their varied roles in tumor development. The potential for further distinguishing and deepening the understanding of these differences, especially associated with the C-terminal long carbon chain and UBA domain in the SIK family, may be explored through X-ray crystallization analysis of the SIK structures. The three members of the SIK family have different functions in tumor regulation. The overexpression of SIK2/3 leads to progression of the cell cycle (promoting the G1/S phase), which provides tumor cells with the capability of rapid reproduction (100-104). By contrast, SIK1 exerts an inhibitory role in the majority of tumor types. An enhanced understanding of the structure of the SIK family members would be helpful in terms of understanding the reasons why SIK exerts different roles in tumor regulation. Additionally, SIK1 has been found to promote cell proliferation in mouse neuro-endothelial cells (105) under conditions of oxygen and glucose deprivation, as well as in hypoglycemic mouse neuro-endothelial cells (30). This situation is similar to the roles that have been identified for SIK1 in medulloblastoma and desmoplastic small round cell tumor cells. These results suggest that the functions of SIK1 may be cell-specific, and further research is required to delineate fully the mechanisms of SIK1 in tumorigenesis. SIK1 has been shown to influence the progression of breast cancer through the PI3K/AKT and P53 signal-transduction pathways (24,95). Via the same P53 signal pathway, SIK1 is able to inhibit the development of breast cancer and promote medulloblastoma proliferation (24,30). In addition, the SIK1 gene may be utilized as a downstream target of various regulatory RNA species, fulfilling regulatory roles in the occurrence of different types of cancer; for example, targeting SIK1 with miR-17 can regulate both colorectal cancer and cervical squamous cell carcinoma (27,98). In the future, all types of RNA that are targeted to regulate the SIK1 gene should be investigated; at the same time, larger studies enrolling more patients with cancer are required to evaluate more comprehensively the potential biological functions of RNAs in terms of their regulation of SIK1.

6. Conclusion and future prospects

SIK1 is a member of AMPK kinase family, which contains multiple domains and phosphorylation sites. These special structures ensure that SIK1 can be easily phosphorylated and activated, and it can be used as an intermediate component for connecting various cytokines, thus playing a connecting role in signal molecular networks. In the present review, it is considered that SIK1 has inhibitory effects on lung, liver, breast, gastric, colorectal, ovarian, pancreatic and thyroid cancers, as well as osteosarcoma. By contrast, it can promote medulloblastoma and desmoplastic small round cell tumor with adhesion and proliferation, although it is not known whether the inhibitory function comes from the difference of genes themselves or from the difference of tumor cells, which needs further experimental verification. SIK1 is involved in most classical tumor signaling pathways, including TGFβ, Wnt/β catenin and PI3K/AKT pathways. In addition, different types of RNA, such as miRs, lncRNAs and circRNAs, also indirectly participate in the regulation of SIK1 in tumor signaling pathway, or they directly affect the expression of SIK1. Moreover, most of the recent studies on SIK1 are related to RNA, and the combination of SIK1 with various RNA molecules is expected to make a further breakthrough in targeted regulation. In conclusion, the present review provides novel insights into the intricate regulatory mechanisms of SIK1 and its diverse implications in cancer progression. By elucidating the multifaceted functions of SIK1, the way is paved for the development of precision

Table III. Summary of eight miRs regulated by SIK1.

First author, year	Name	Targeted cancer	Action on SIK1	Functions	(Refs.)
Chen *et al*, 2016	miR-141	Ovarian cancer	Inhibitory effect	MiR-141 can promote the proliferation of ovarian cancer cells by inhibiting the expression of SIK1 protein.	(96)
Huang *et al*, 2019	miR-17	Colorectal cancer	Inhibitory effect	MiR-17 can inhibit the invasion and migration of colorectal cancer cells by targeting the inhibition of SIK1.	(27)
Peng *et al*, 2020		Cervical squamous cell carcinoma	Inhibitory effect	NR2F1-AS1 inhibits the invasion and migration of cervical squamous cell carcinoma by regulating the miR-17/SIK1 axis.	(98)
Fu *et al*, 2017	miR-25	Liver cancer	Inhibitory effect	MiR-25 targets SIK1 and promotes liver cancer development by decreasing the expression of SIK1.	(76)
Bai *et al*, 2018	miR-373	Melanoma	Inhibitory effect	MiR-373 inhibits the expression of SIK1 and promotes the migration of melanoma cells.	(97)
Ren *et al*, 2016	miR-203	Pancreatic cancer	Inhibitory effect	The inhibition of SIK1 by miR-203 promotes the proliferation, migration and invasion of pancreatic cancer cells.	(28)
Huang *et al*, 2020	miR-130b-3p	Medulloblastoma	Inhibitory effect	SIK1 promotes the development of medulloblastoma, and miR130b-3p downregulates SIK1 to inhibit the migration and invasion of medulloblastoma cells.	(30)
Zang *et al*, 2022	miR-4449	Gastric cancer	Inhibitory effect	CircEIF4G3 can inhibit the development of gastric cancer by regulating the miR-4449/SIK1 axis to inactivate β-catenin signaling.	(29)
Jin and Wang, 2022	miR-32-5p	Ovarian cancer	Inhibitory effect	Circ0078607 acts as a molecular sponge of miR-32-5p to regulate the miR-32-5p/SIK1 axis and thus inhibit the progression of ovarian cancer.	(78)

SIK1, salt-induced kinase 1; miR, microRNA; circ-, circular.

medicinal approaches that leverage SIK1 as a strategic target for cancer intervention. The current findings emphasize the importance of understanding the complex roles of SIK1 in cancer, which may lead to the discovery of more effective therapies and improved patient outcomes.

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Availability of data and materials

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Authors' contributions

JC received funding, designed and directed the study. YS, DXA and YZ reviewed the references. XRZ and CYZ wrote the manuscript. JC, QQY, XCP and JYX revised the manuscript. ZXR and JL contributed to the figures and diagrams. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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