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Roles of salt-inducible kinases in cancer (Review)

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Abstract. Salt inducible kinases (SIKs) with three subtypes SIK1, SIK2 and SIK3, belong to the AMP-activated protein kinase family. They are expressed ubiquitously in humans. Under normal circumstances, SIK1 regulates adrenocortical function in response to high salt or adrenocorticotropic hormone stimulation, SIK2 is involved in cell metabolism, controlling insulin signaling and gluconeogenesis and SIK3 coordinates with the mTOR complex, promoting cancer. The dysregulation of SIKs has been widely detected in various types of cancers. Based on most of the existing studies, SIK1 is mostly considered a tumor inhibitor, SIK2 and SIK3 are usually associated with tumor promotion. However, the functions of SIKs have shown contradictory in certain tumors, suggesting that SIKs cannot be simply classified as oncogenes or tumor suppressor genes. The present review provided a comprehensive summary of the roles of SIKs in the initiation and progression of different cancers, aiming to elucidate their clinical value and discuss potential strategies for targeting SIKs in cancer therapy.

Contents

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1. Introduction

Salt-inducible kinases (SIKs) are members of the AMP-activated protein kinase (AMPK) family, including three subtypes: SIK1, SIK2 and SIK3 (1). After being identified first in the adrenal glands of high-salt diet-fed rats in 1999 (2), this special kinase was named SIK1 and was initially described as a novel serine/threonine protein kinase (3). Subsequent studies identified the other two subtypes, SIK2 and SIK3 (4,5). In humans, SIK1 is abundantly expressed in the adrenal cortex, adipose and neural tissues (4,6,7), exhibiting the function of self-phosphorylation and regulating adrenocortical function under the stimulation of high salt or adrenocorticotropic hormone (ACTH) (2). SIK2 and SIK3 are constitutively expressed in tissues and are ubiquitous in humans. Among them, SIK2 is highly expressed in adipose tissues and is involved in the regulation of cell metabolism, including the control of insulin signaling (4,8) and gluconeogenesis (9), while the highest expression place of SIK3 is brain (10); it coordinates with the mTOR complex (11,12) and can be activated by inflammatory cytokines under stress, exerting a cancer-promoting effect (13).

The dysregulation of SIKs has been identified in various types of cancer, such as lung cancer, ovarian cancer, breast cancer, prostate cancer, gastric cancer and hepatocellular carcinoma (HCC) (14-17), which might be associated with tumorigenesis and tumor progression. A number of signaling molecules involved in cancer progression have been reported to regulate SIKs, including liver kinase B1 (LKB1) and protein kinase A (PKA). Additionally, downstream molecules such as cAMP response element-binding protein (CREB), hippo and β-catenin may also be regulated by multiple types of SIKs. Therefore, SIKs serve as intermediate links in the molecular signaling pathways involved in cancer development.

Existing studies indicate that SIKs play intricate roles in tumor progression. In most types of cancer, SIK1 is regarded as a tumor suppressor, whose expression is downregulated in malignant tumors (18-21). By contrast, SIK2 and SIK3 are considered candidate oncogenes endowing survival advantages to cancer cells for growth and correlating with the clinicopathological results of patients suffering from tumor (15), especially in breast cancer and ovarian cancer (6,13,22,23). However, the exact roles of SIKs in cancer development are still not well-characterized. The purpose of the present review

was to comprehensively summaries the roles of SIKs in the progression of different types of cancer, fully elucidate their clinical value and explore potential strategies for targeting SIKs for cancer therapy in clinical use.

2. The structure and regulatory molecules of SIKs

Structure and phosphorylation of SIKs. In humans, the SIK1 gene is located on chromosome 21, while genes encoding SIK2 and SIK3 are on chromosome 11 (24,25). All SIKs contain an N-terminal protein kinase domain, followed by a ubiquitin-associated (UBA) domain located inside a central sucrose non fermenting (SNF-1) homology (SNH) domain and a long C-terminal tail (5,26) (Fig. 1). The catalytic activity of SIKs relies on the phosphorylation of their threonine residues in the activation loop (T-loop, especially the binding sites of Thr182 in SIK1, Thr175 in SIK2 and Thr221 in SIK3) (25,27), which could be achieved by the kinase activity of LKB1 (27). Notably, the mutation of threonine to alanine could induce SIK inactivation (27). The phosphorylation threonine site of LKB1 is relatively conserved, located in the N-terminal protein kinase domain of SIK family. The SNH domain is distinct among SIKs: SIK2 and SIK3 share 70 and 37% similar sequences with SIK1, respectively (1). The C-terminal domain is highly conserved between SIK1 and SIK2, with multiple PKA phosphorylation sites. The two serine residues in SIK1, four in SIK2 and three in SIK3 can be phosphorylated by PKA to elevate intracellular cyclic AMP level (28). The elevated cyclic AMP induces the dephosphorylation of physiological substrates of the SIKs, indicating that the catalytic activity of SIKs could be inhibited by PKA phosphorylation (29-32). Another effect of PKA phosphorylation is to promote the nucleus translocation of SIK1 (28,32) to reduce its phosphorylation by LKB1, while SIK2 and SIK3 are localized predominantly within the cytoplasm (25). In addition, SIKs contain multiple motifs harboring PKA phosphorylation and 14-3-3 binding sites (10,31). Blocking these potential phosphorylation residues largely eliminates the binding of SIKs with 14-3-3, indicating that the combination of PKA phosphorylation and 14-3-3 protein binding is necessary for the inactivation of SIKs (11,25). In addition, the UBA domain is defined within the SNH domain (33) and mutations in this domain can interfere with the interaction between SIK and 14-3-3 adaptor protein and promote SIK nuclear transport, leading to the reduction in LKB1-mediated signaling pathways (33,34). Calcium-dependent protein kinase (CaMK) is another kinase for the activation of SIKs, which phosphorylates Thr322 residue in the SNH domain of SIK1 (26,35). However, in SIK2, the activity of CaMK is associated with its degradation (36). In addition, SIKs can also be activated by autophosphorylation. In the T-loop of SIK1 and SIK2, autophosphorylation sites exist in Ser186 and Ser179, respectively (37). The hypothesis for SIK autophosphorylation process was considered as follows: The autophosphorylation sites are located at the four amino acid C-terminal of the activated phosphor-threonine residue, creating a consensus motif for glycogen synthase kinase 3 (GSK3) phosphorylation (38). The formation of this motif allows the phosphorylation of SIK1 and SIK2 by GSK3 at Thr182 and Thr175, respectively, forming a positive feedback regulation on SIK activation.

Regulatory molecules of SIKs. In addition to the direct phosphorylation of binding sites, the expression of SIKs is also under the control of other extracellular signals and non-coding RNAs. SIK1 could be upregulated by high salt dietary intake (10), ACTH signaling (3), glucagon signaling (39), excitable cell depolarization (40) and circadian rhythms (41). Similarly, the synergistic effect of high salt and cytokine IL-17 also plays a role in stimulating SIK3 expression (13,42).

Non-coding RNAs constitute most of the human RNA, including microRNA, long non-coding RNA (lncRNA), circular RNA (circRNA) and enhancer RNA (43). They modulate cell physiology and functions, from epigenetic gene silencing to post-transcriptional regulation of mRNA stability (43). The expression level of SIK1 and SIK2 can be regulated by different non-coding RNAs. Based on existing studies, five microRNAs inside tumor cells promote tumor proliferation, migration and metastasis by suppressing the activity of SIK1: miR-17 affects the proliferation and migration process of human colorectal cancer (44), miR-203 plays a role in the progression of pancreatic cancer (45), miR-141 promote ovarian cancer proliferation (46) and the overexpression of miRNA-373 is associated with the migration of melanoma cells (47) (Fig. 2A). Only miR-103b-3p, as an exosomal RNA, affects SIK1 expression and shows a distinct role in tumor development (48). A total of six other miRNAs (miR-149-5p, miR-103a-3p, miR-526b, miR203, miR-654-5p, miR-874-3p and miR-874-5p) inhibit tumor development by repressing the expression of SIK2 (49-53) (Fig. 2B).

Other types of non-coding RNAs, including lncRNAs and circRNAs, indirectly control the activity of SIKs by interacting with microRNAs. LncRNA NR2F1-AS1 and TCONS 0029157 regulate SIK1-mediated tumor proliferation and migration. SIK1-adjusted tumor proliferation and migration are under the control of lnc RNA NR2F1-AS1 and TCONS 0029157 (54,55). Among them, TCONS 0029157 inhibits the progression of lung cancer, while lncNR2F1-AS1 prevents the development of cervical squamous cancer by sponging the suppressive effect of miR-17 on SIK1. SIK2 is controlled by lncRNA 00662 and UCA1, promoting the migration of various tumors (53,56). Single-stranded, covalently closed circRNAs frequently function as transcriptional regulators, miRNA sponges and protein templates (57). Circ 0078607 inhibits the progression of ovarian cancer by regulating miR-35-5p/SIK1 axis (58) and a similar mechanism was also detected in circEIF4G3 and miR-4449 in gastric cancer (59); while circAMOTL1 and circCELSR1 are regulators of SIK2 (49,50), playing a role in regulating cervical carcinoma and ovarian cancer, respectively. It is worth noting that the status of drug resistance could also be influenced by the effect of non-coding RNAs on SIK2 expression level. Studies focusing on ovarian and colon cancer have shown that SIK2 inhibition by miRNAs can effectively restore sensitivity in paclitaxel-resistant tumors, while lncRNAs and circRNAs that increase the activity of SIK2 can amplify tumor taxol resistance (49,51-53).

Substrates of SIKs. CREB-regulated transcriptional co-activators (CRTC), including CRTC1, CRTC2 and CRTC3, as well as Class 2a histone deacetylases (HDAC4, HDAC5, HDAC7 and HDAC9), have been identified as substrates of SIKs (25). The phosphorylation of CRTCs by SIKs induces

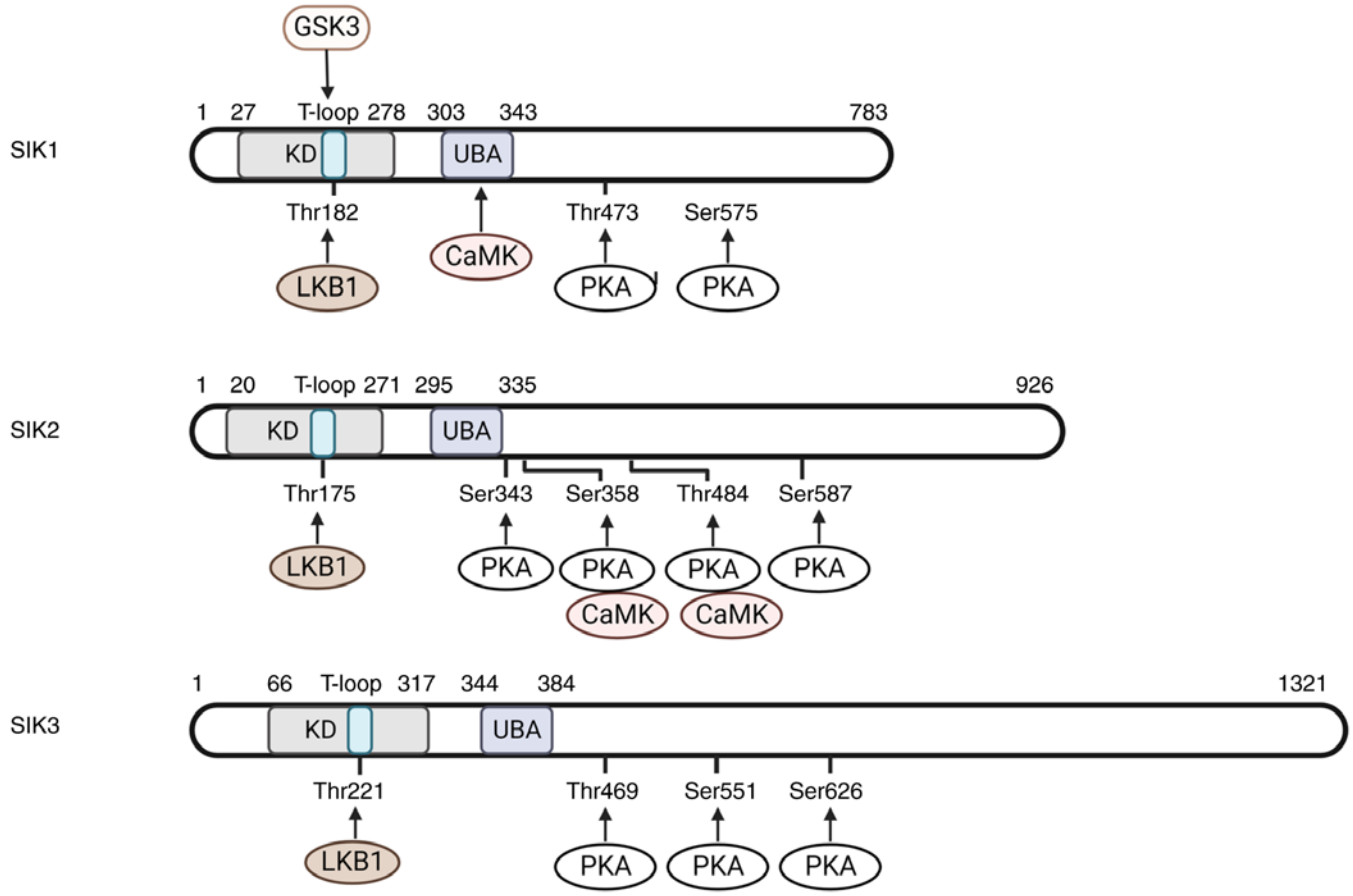

Figure 1. Structure and phosphorylation sites of SIKs. SIKs could be divided into three domains include KD, SNH domain and C-terminal domain. LKB1 phosphorylation sites are in KD, UBA domain is inside SNH, which was not shown in the figure. C-terminal domain contains multiple PKA phosphorylation sites. SIKs, salt inducible kinases; KD, kinase domain; SNH, sucrose non fermenting homology; LKB1, liver kinase B1; UBA, ubiquitin-associated; PKA, protein kinase A; CaMK, calcium-dependent protein kinase.

them to bind with 14-3-3 proteins in the cytosol, depriving their ability to activate nuclear transcription factor CREB (5,28,31). Conversely, SIK inhibition and CRTC dephosphorylation can activate CREB-dependent gene transcription59-63 (60-64). Phosphorylation of Class 2a HDACs by SIKs leads to their binding to 14-3-3 proteins and retention in the cytosol. When SIKs are inactivated, these proteins can enter the nucleus and bind to myocyte enhancer factor 2 (MEF2), repressing its target gene transcription (32,63,65,66).

3. Distinct roles of SIKs in cancer development

Roles of SIK1 in cancer progression

LKB1-SIK1 axis inhibits cancer progression. LKB1 has been identified as a critical barrier of cancer initiation and metastasis (27,67). As it widely regulates the AMPK family, the LKB1-SIK1 axis is a crucial pathway for LKB1 to suppress SIK-related cancers. Multiple tumor suppressors are under the control of this axis, including CRTC, HDAC, p53, ZEB1 (Fig. 3). In gastric adenocarcinoma, the LKB1-SIK1 axis could be activated by gastrin, inhibiting tumor metastasis by phosphorylating HDAC4 and enhancing the gastrin-induced transcription of c-fos and CRE-, SRE-, AP1- and NF-kB (21). In human breast cancer, SIK1 is required for the activation of p53 to promote tumor cell anoikis and loss of the function of either LKB1 or SIK1 is closely associated with tumor metastasis (19). Additionally, it has been found that the enhancement of aerobic glycolysis in breast cancer is dependent on p53 suppression induced by the lack of SIK1 (68). This is achieved by inhibiting glucose intake control gene Glut1 (69) and blunting the expression of LDHA to alleviate pyruvate-to-lactate conversion (68).

Another substrate of LKB1-SIK1 axis is TGFβ (70), which controls tumor development via positively stimulating the expression of two genes Zinc finger E-box-binding homeobox 1 (ZEB1) and SCN5. In ovarian carcinoma and non-small cell lung cancer (NSCLC) (18,71), ZEB1 can decrease the properties of epithelial cells and promote the expression of genes responsible for tumor metastasis (72,73). As for SCN5, its product voltage-gated sodium channel (Na_V)1.5 could be regulated by both SIK1 and TGFβ (74). Previous studies have shown that tumor cells are more permeable to Na^+ compared with normal cells (75). In breast cancer cells with significantly downregulated SIK1 levels, Nav1.5 overexpression has been observed, promoting Na^+-mediated invasiveness (76-78).

SIK1 blocks tumor epithelial-mesenchymal transition (EMT) via regulating the Wnt/β-catenin signaling pathway. Epithelial to mesenchymal transition is also a crucial process of tumor metastasis controlled by SIK1. It is characterized

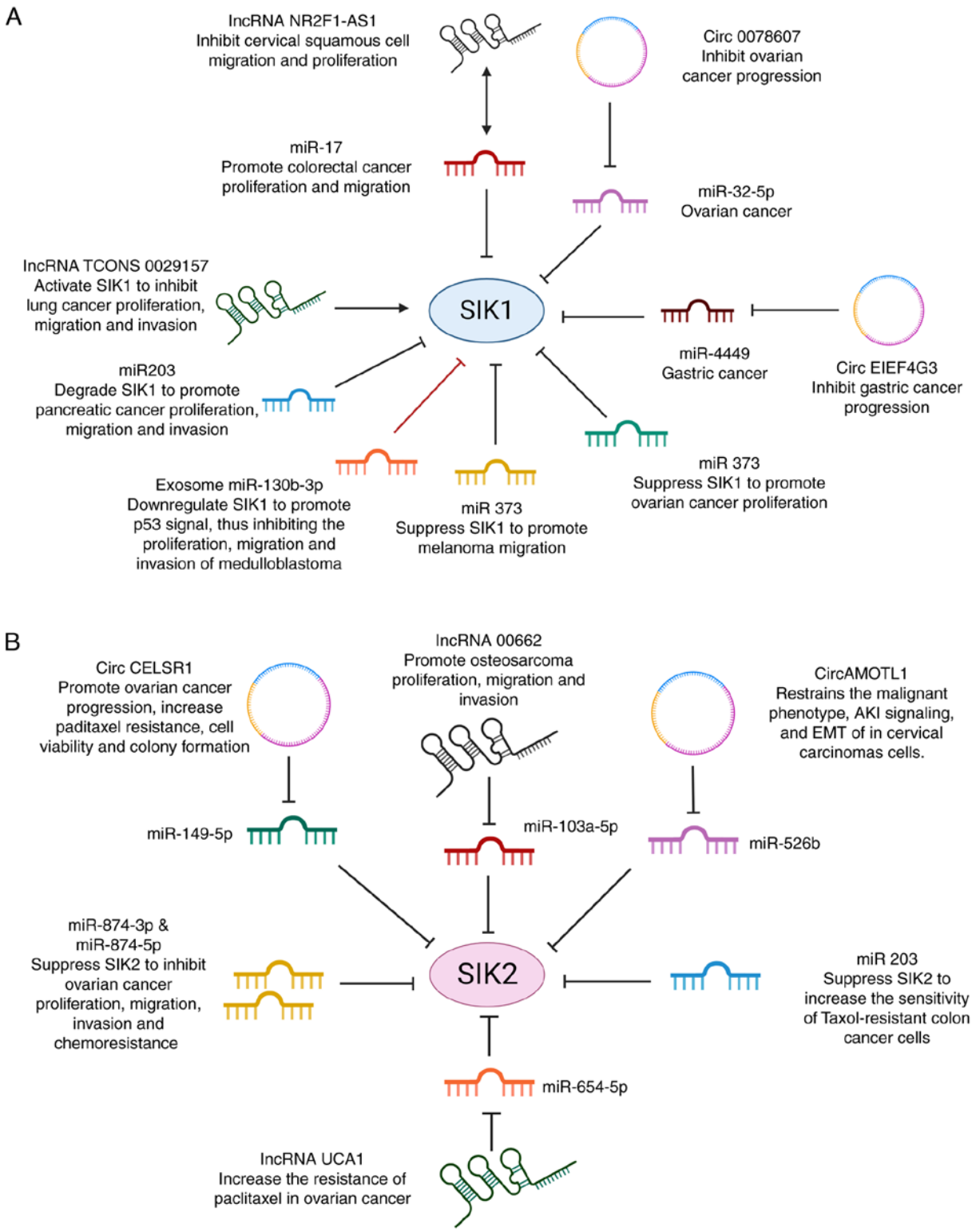

Figure 2. Non-coding RNAs regulate the expression of SIK1 and SIK2. (A) The activity of SIK1 could be regulated by six miRNAs, two lncRNAs and one circRNA. Among them, miR-17, miR-203, miR-141 miR-32-5p and miRNA-373 promote tumorigenesis by directly suppressing SIK1. LncRNA TCONS 0029157 activates SIK1 directly thereby inhibiting lung cancer progression. NR2F-AS1 and Circ 0078607 inhibit tumor development by inactivating the function of miRNA. Double arrow: NR2F-AS1 could interact with miR-17 to suppress tumor progression, but it cannot inhibit the expression of miR17. (B) The activity of SIK2 could be regulated by six miRNAs, two lncRNAs and two circRNAs. miRNAs inhibit tumor invasion by suppressing the activity of SIK2, while circRNAs and lncRNAs are associated with chemotherapeutic resistance by affecting SIK2 expression. SIKs, salt inducible kinases; miRNAs/miRs, microRNAs; lncRNA, long non-coding RNA; circRNA, circular RNA.

by the loss of epithelial markers including E-cadherin and γ-catenin and increased expression of mesenchymal markers such as N-cadherin, vimentin, Snail, Twist and ZEB (79,80). SIK1 regulates the EMT process by interacting with the Wnt/β-catenin signaling pathway (81) (Fig. 4). In normal cells, the silencing mediator of retinoic acid and thyroid hormone

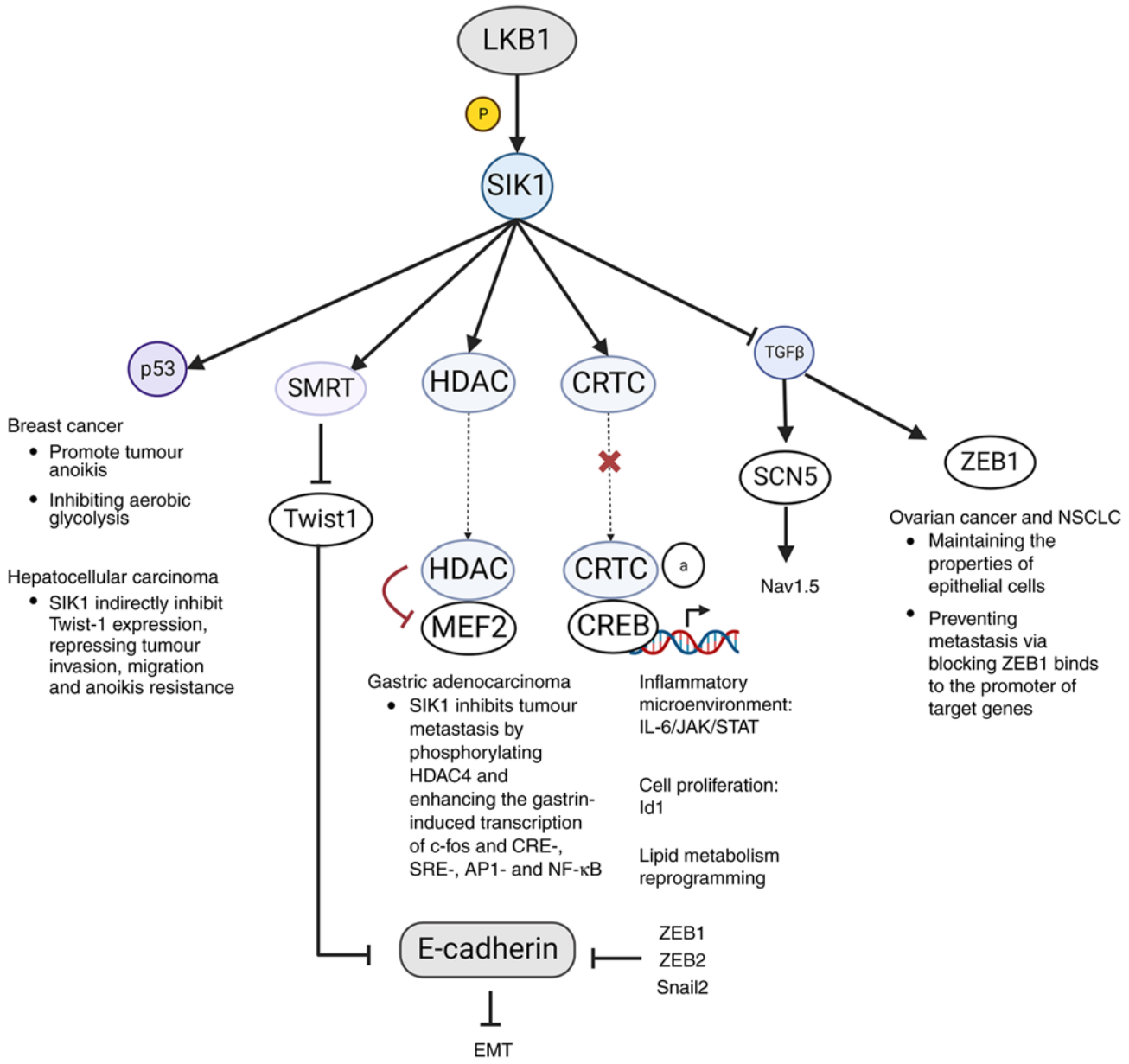

Figure 3. Roles of SIK1 in cancer progression. SIKs, salt inducible kinases; LKB1, liver kinase B1; HDAC, histone deacetylase; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; CRTC, CREB-regulated transcriptional co-activators; MEF2, myocyte enhancer factor 2; CREB, cAMP response element-binding protein; ZEB1, zinc finger E-box-binding homeobox 1; SCN5, sodium channel protein type 5; NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition; Snail2, snail family zinc finger 2.

receptor (SMRT) could be phosphorylated by SIK at threonine 1391. The activated SMRT is translocated into the nucleus and recruits transducin β-like protein 1 (TBL1)/TBL1-related protein (TBLR1) and NCoR/HDAC3 to β-catenin target gene Twist1 promoter region, thereby inhibiting the expression of Twist1 and intercepting the subsequent effects of β-catenin signal (81). In HCC cells, SIK1 is suppressed by its E3 ligase RNF2 (82), restoring β-catenin activity. The enhanced Twist-1 expression increases tumor invasion, migration and anoikis resistance (83,84), also binds to the E-box motif of the SIK1 promoter, relieving the restriction of SIK1 and SMRT on β-catenin signaling pathway (81).

Could SIK1 be identified directly as a tumor suppressor gene? As described above, most studies indicate that the effects of SIK1 on tumor cells are close to a tumor suppressor. Upon SIK1 activation by LKB1, it inhibits tumorigenesis and the EMT process, reducing cancer metastasis and promoting cancer apoptosis (1,25,85). However, controversy remains over SIK1: In medulloblastoma (MB), an uncovered novel effect of miR-130b-3p on SIK1 indicates that SIK1 might also be a tumor promoting protein (48). In 2020, Huang *et al* proposed that although miR-130b-3p is suppressed in MB cells, it is upregulated in the tumor-secreted exosomes in the plasma of MB patients and can be transferred to tumor cells (48). Of note, the inhibition of exosomal miR-130b-3p on SIK1 in transferred tumor cells produces anti-tumor effects, suggesting the potential oncogenic role of SIK1 (48). By contrast, in HCC the role of exosomal miRNA induced SIK1 inhibition remains to promote tumor progression (86). Additionally, the emerging

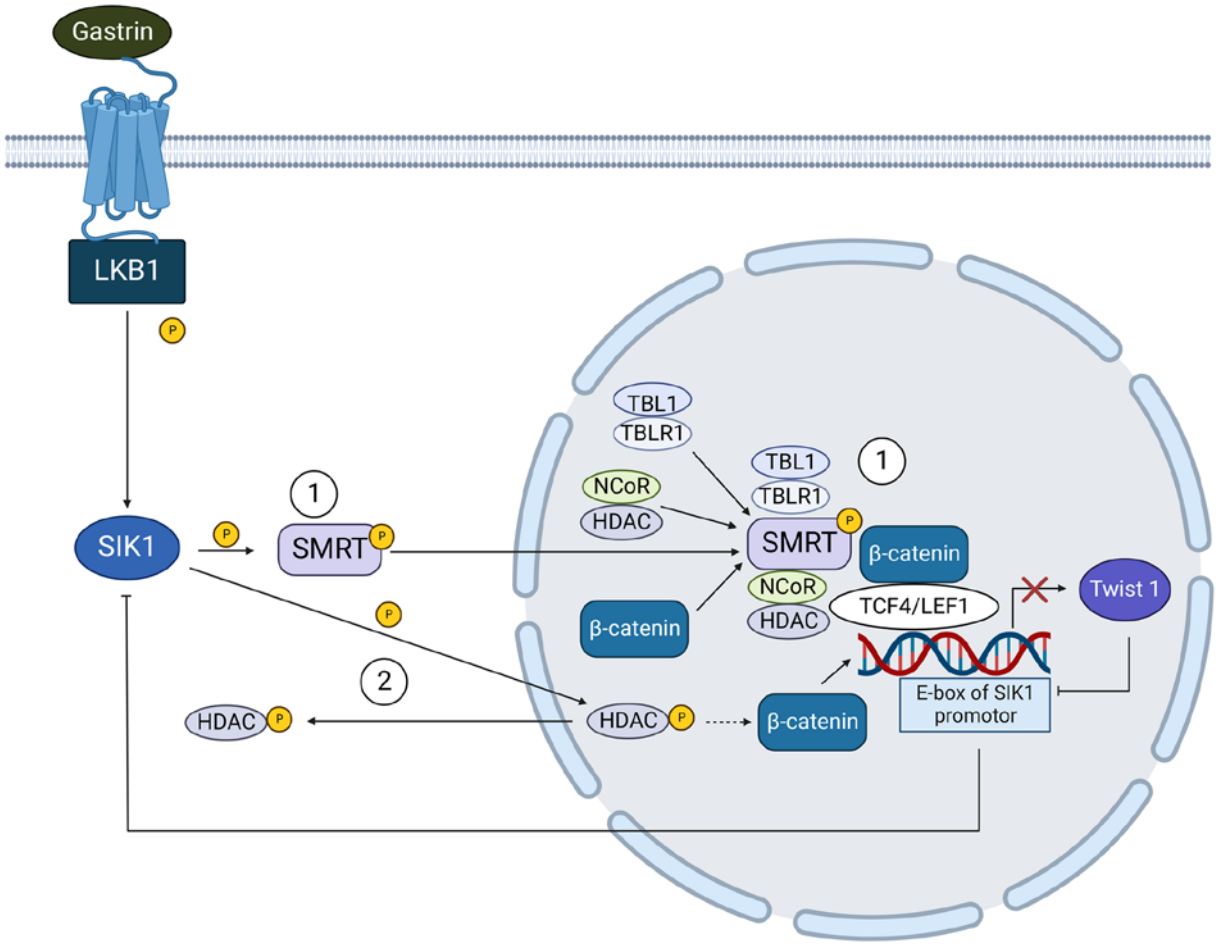

Figure 4. SIK1 inhibits tumor cell EMT by suppressing β-catenin signaling pathway and the expression of Twist 1. (1) In hepatocellular carcinoma, SIK1 phosphorylates SMRT, which forms complex withβ-catenin thereby inhibiting Twist1-associated EMT. Twist 1 could also negatively control the expression of SIK1 by binding to the E-box motif of the SIK1 promoter. (2) In gastric adenocarcinoma, SIK1 prevents tumor cell EMT by inducing the cytosolic translocation of HDAC, which in turn reduces the activity of β-catenin signaling pathway and blocks the tumor metastasis. Dashed arrow: This process was identified in human Uterine Fibroid, which is waiting for further verification in gastric adenocarcinoma cells. SIKs, salt inducible kinases; EMT, epithelial-mesenchymal transition; LKB1, liver kinase B1; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; HDAC, histone deacetylase; TBL1, transducin β-like protein 1; TBLR1, TBL1-related protein; NCoR, nuclear receptor corepressor.

oncogenic role of SIK1 has also been shown in the development of Desmoplastic small round cell tumor (DSRCT) (87): SIK1 can be activated by oncogenic transcription factor EWSR1, affecting DNA replication through regulating MCM DNA helicase (88). Consistently, the depletion of SIK1 leads to rapid growth arrest of DSRCT cells at the G_1/S phase, exhibiting a strong tumor repression effect (87). The results of these investigations suggest that the function of SIK1 may not be limited to a tumor suppressor, it could also exhibit stimulative function in some tumors. Further studies are required to validate the roles of SIK1 in distinct tumors.

Roles of SIK2 in cancer progression

SIK2 modulates tumor cell proliferation by regulating cell cycle. As aforementioned, uncontrolled mitosis is a hallmark of cancer cells. Therefore, anti-mitotic drugs such as the tubulin inhibitor paclitaxel have been developed for anticancer use (89). SIK2 is a centrosome kinase required for the initiation of mitosis and its inhibition induces the altered position of the mitotic spindle (90). Long-lasting suppression of SIK2 can lead to chromosomal instability (90). To accurately establish cell division plane, SIK2 orchestrates the centrosome alignment and spindle position during the cell division, maintaining the stability of chromosome (90). In ovarian cancer, the depletion of SIK2 induces decreased AKT phosphorylation and delayed G_1/S transition (89). The consequence of SIK2 induced PI3K/AKT activation is the upregulated expression of cell division regulator survivin (91), which affects microtubule dynamics, stability and mitotic progression (92,93). During mitosis, it serves as an interface between the centromere/central spindle and the chromosomal passenger complex (94). Survivin is overexpressed in multiple malignancies, inducing cell-cycle checkpoint bypasses and uncontrolled aberrant progression of transformed cells (95). Likewise, Bon *et al* (96) indicated that SIK2 knockdown could significantly reduce the growth rate of prostate tumor cells. This was accompanied by the arrest of G_1 cell cycle via up regulating p21 and p27 and downregulating Cyclin D1. Using SIK2 inhibitors on SIK2-overexpressed cancer cells could reduce the expression of survivin to a certain extent, providing evidence for the development of anticancer drugs.

Similar to SIK1, wild-type SIK2 could also impact tumorigenesis by phosphorylating CRTC1 and CRTC2 (96,97),

preventing their translocation and thus inhibiting the activation of CREB1. Theoretically, this effect is associated with tumor suppression. However, high levels of auto-antibodies against SIK2 were found in the plasma of patients with prostate cancer (96), transforming SIK2/CREB interaction into a tumor-promoting effect. Under the attack of these auto-antibodies, the kinase activity of SIK2 is lost, making it forms a complex with CRTC1 (96). This complex can be translocated into the nucleus, acting as a CREB trans-activator to trigger the activation of other transcription factors such as HSF, IRF and NFκB, resulting in endoplasmic reticulum stress response and cell apoptosis (96). These results indicated that wild type SIK2 remains a tumor promotor in prostate cancer, while loss of its kinase activity will accelerate tumor cell death (96). Therefore, it is reasonable to hypothesize that CREB exhibits diverse roles in prostate cancer; it serves as a tumor suppressor gene in Hodgkin's lymphoma and melanoma, directly binding to the promoter regions of cyclin D1, cyclin E1, CDK2 and CDK4 to disturb tumor proliferation (98,99). SIK2-induced downregulation promotes G_1/S phase transition, thereby promoting tumor cell cycle progression.

SIK2 is also an antagonist of the hippo signaling pathway, which is highly conserved from *Drosophila* to humans (100). Dysregulation of this signaling pathway has been detected in a wide variety of types of cancer. In humans, SIK2 dampens the Hippo signal by directly binding to and phosphorylating its partner, Sav, at Ser413 (85). This disrupts the interactions between mammalian STe20-like kinases (MST) 1/2 and large tumor suppressor homolog (LATS) 1/2 (homologous to hpo-warts in *Drosophila*), leading to increased expression of Yes kinase-associated protein (YAP) and its target genes, which confer growth advantages to cells. Thus, upon SIK2 activation, the Hpo signaling dependent-cell cycle exit and cell apoptosis are inhibited, resulting in tissue overgrowth. Notably, the effect of SIK2 inhibitors may enhance the Hpo pathway in ovarian tumor cells and this strategy might be less effective in tumors that are inherently rich in YAP expression (101) (Fig. 5).

SIK2 regulates tumor cell metabolic reprogramming. Metabolic reprogramming is an emerging hallmark of cancer, as cancer cells are defined as a 'metabolically abnormal system' (102). Cancer cell metabolism relies on oxidative glycolysis known as the Warburg effect. Hyperactive glycolysis is associated with the faster generation of ATP in malignancies, inducing the formation of metabolic intermediates macromolecules such as lipids and amino acids in rapidly dividing tumor cells (103). The rapid synthesis of these molecules significantly promotes the tumorigenesis process (103). In addition, the dysregulation of fatty acid metabolism also takes part in the malignant transformation in a number of different cancers (104,105). In most cases, oncogenic molecules trigger tumorigenesis by stimulating abnormal metabolism and SIK2 is a vital metabolic regulator. In ovarian cancer, it boosts the Warburg effect and tumor lipogenesis by activating PI3K/AKT-hypoxia-inducible factor-1α signaling pathway (103). SIK2 also inhibits oxidative phosphorylation by activating Drp-1 to promote mitochondria fission, then tumor cells rely on aerobic glycolysis for energy supply (103). In colorectal cancer, SIK2 enhances glycolysis by activating tripartite motif 28 (TRIM28) (106), whose

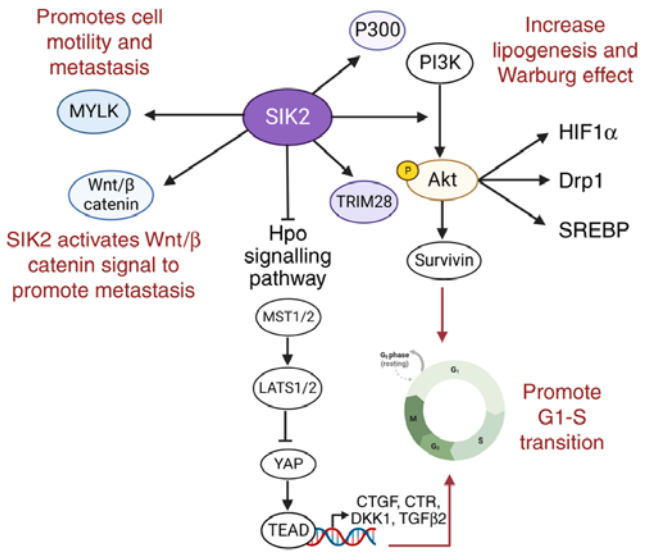

Figure 5. Roles of SIK2 in cancer development. SIKs, salt inducible kinases; MYLK, myosin light chain kinase; TRIM28, activating tripartite motif 28; MST, macrophage-stimulating protein; LATS1, large tumor suppressor homolog 1; YAP, Yes kinase-associated protein; TEAD, transcriptional enhanced associate domain; HIF1α, hypoxia-inducible factor-1α; Drp1, Dynamin-related protein 1; SREPB, sterol regulatory element-binding protein.

expression level is positively associated with poor overall survival and progression-free survival (106,107). The silencing state of SIK2 could be reversed by TRIM28 overexpression on tumor proliferation, migration, invasion and glycolysis, enhancing the tumorigenesis process.

As for the process of lipogenesis, AKT is a crucial molecule regulated by SIK2 in various types of cancer. In ovarian cancer, SIK2 enhances AMPK-induced phosphorylation of acetyl-CoA carboxylase, activating the PI3K/AKT pathway through p85a-S154 phosphorylation to promote tumor proliferation, survival and omental metastasis (108). Thus, upon SIK2 activation, the Hpo signaling dependent-cell cycle exit and cell apoptosis are inhibited, resulting in tissue overgrowth (109). The activation of AKT by SIK2 was also detected in the generation process of pancreatic cancer: SIK2 acts upstream in mTORC2/AKT signaling, regulating insulin-induced UPP-1 gene expression in brown adipocytes, thereby enhancing the metabolism of adipose tissue (110,111). Additionally, SIK2 also accelerates lipogenesis through other approaches. In the liver, SIK2 activates carbohydrate-response element-binding protein (ChREBP) by regulating histone acetyltransferase coactivator p300 (9), promoting lipogenesis and hepatic steatosis. ChREBP was identified as possessing the function of activating target genes favoring downstream tumorigenic pathways (112). Theoretically, steatosis accumulation and ChREBP activation significantly increase the risk of hepatocellular carcinoma. However, SIK2 is also reported to repress HCC by inhibiting the Wnt/β-catenin signaling pathway (14) (Fig. 6).

SIK2 regulates tumor metastasis

SIK2 and Wnt/β-catenin signaling pathway. In contrast to SIK1, which exclusively inhibits Wnt/β-catenin signaling pathway by activating transcriptional co-repressor proteins

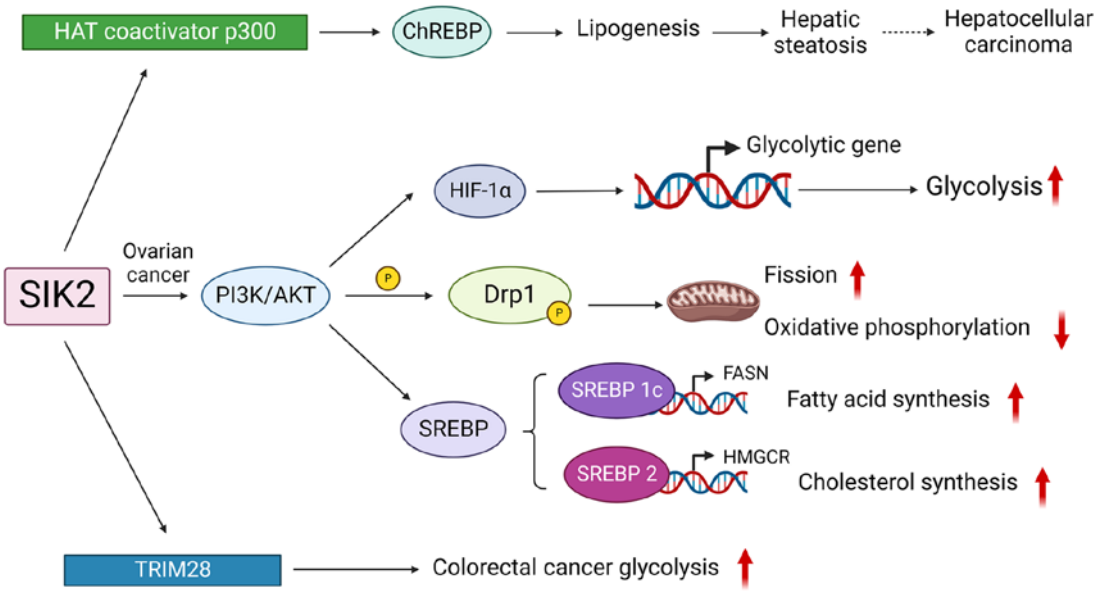

Figure 6. SIK2 promotes tumorigenesis by regulating cell metabolism. SIKs, salt inducible kinases; HAT, histone acetyltransferase; ChREBP, carbohydrate-response element-binding protein; TRIM, tripartite motif; SREBP, sterol regulatory element binding protein; FASN, fatty acid synthase; HMGCR, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; HIF1α, hypoxia-inducible factor-1α; Drp1, Dynamin-related protein 1; TRIM28, activating tripartite motif 28.

to prevent the binding of β-catenin to cellular DNA (81), the effects of SIK2 on β-catenin are different in distinct types of cancer. In gastric cancer and HCC, SIK2 promotes the activity of glycogen synthase kinase 3 (GSK3) by dephosphorylating AKT through the protein phosphatases PHLPP2 and PP2A (14,113). GSK3 effectively induces the degradation of β-catenin, enhancing Wnt/β-catenin transcription and tumor cell metastasis could be blocked (14,113). However, in breast cancer SIK2 acts as an oncogene to activate LPR6 receptor and enhance the Wnt/β-catenin signaling pathway, which contributes to maintaining the stemness of breast cancer stem cells (114). Cancer stem cells primarily drive tumor heterogeneity, contributing to breast cancer recurrence, metastasis and therapeutic resistance (115). By activating low density lipoprotein receptor-related protein 6, which is overexpressed in 20-36% of patients with breast cancer (116), SIK2 efficiently promotes the maintenance of stemness features of breast cancer stem cells (117,118). In addition, SIK2 could also restrict tumor autophagy to support the survival of triple-negative breast cancer (119) (Fig. 7).

SIK2 and myosin light chain kinase (MYLK). Tumor metastasis typically depends on lymphatic circulation and blood pathways, which are driven by increased cell motility involving cycles of actin polymerization, cell adhesion and actomyosin contraction (120,121). In addition to regulating intracellular signaling pathways, SIK2 can directly phosphorylate MYLK on Ser343 to further activate myosin light chain 2, which then facilitates cell contraction and motility, inducing alterations in the actin cytoskeleton (122). Rapid and dynamic changes in the cytoskeleton are required for cancer cell invasion and metastasis (123). This pathway is activated by omentum-derived adipocytes, which induce calcium-dependent activation and autophosphorylation of SIK2 (22).

Roles of SIK3 in cancer progression

SIK3 in tumorigenesis. As a cell cycle regulator, SIK3 controls tumor cell proliferation. Its activity significantly suppresses the Hippo signaling pathway, promoting the continuous progression of the cell cycle and preventing tumor apoptosis (100). In response to high salt stimulation, upregulated SIK3 enhances cell cycle progression by releasing G_1/S arrest, thereby bestowing growth advantages to breast cancers (13). More specifically, SIK3 upregulates the cyclin D and E and G_1/S-promoting CDK2 activity. These cell cycle arresting and apoptosis promotion effects were achieved by the interactions between SIK3 and Akt signaling pathway (124). Likewise, Charoenfuprasert *et al* (15) demonstrated that SIK3 enhances cell cycle progression in low-grade ovarian cancer through attenuating p21 Waf/Cip1 and p27 Kip activity, which are key effectors underlying the SIK3-mediated cell cycle regulation (125). Among them, c-Scr is the major signaling component responsible for SIK3-mediated downregulation of p21 in ovarian cancer, establishing a linkage between SIK3-Scr activation and p21 Waf/Cip1 gene regulation (125).

In addition, SIK3 can modulate tumor resistance to apoptosis by TNF-NFκB axis (23). It renders tumor cells susceptible to TNF secreted by tumor-activated cytotoxic T cells. Following TNF stimulation, SIK3 promotes nuclear translocation of NF-κB via the phosphorylation of IκBα. The accumulated nuclear NF-κB inhibits caspase-8/9 (23). Chromatin accessibility and transcriptome analyses from Sorrentino *et al* (23) indicated that SIK3 knockdown could disrupt the expression of pro-survival genes under the TNF-NF-κB axis, which exhibited the effect of SIK3 in regulating tumor cell survival. In addition, the phosphorylation of mTOR complex 1 (mTORC1) signaling also relies on SIK3 activity, conferring growth advantages to breast cancer cells by promoting aerobic glycolysis (126). After using clustered regularly interspaced short palindromic repeats (CRISPR) to

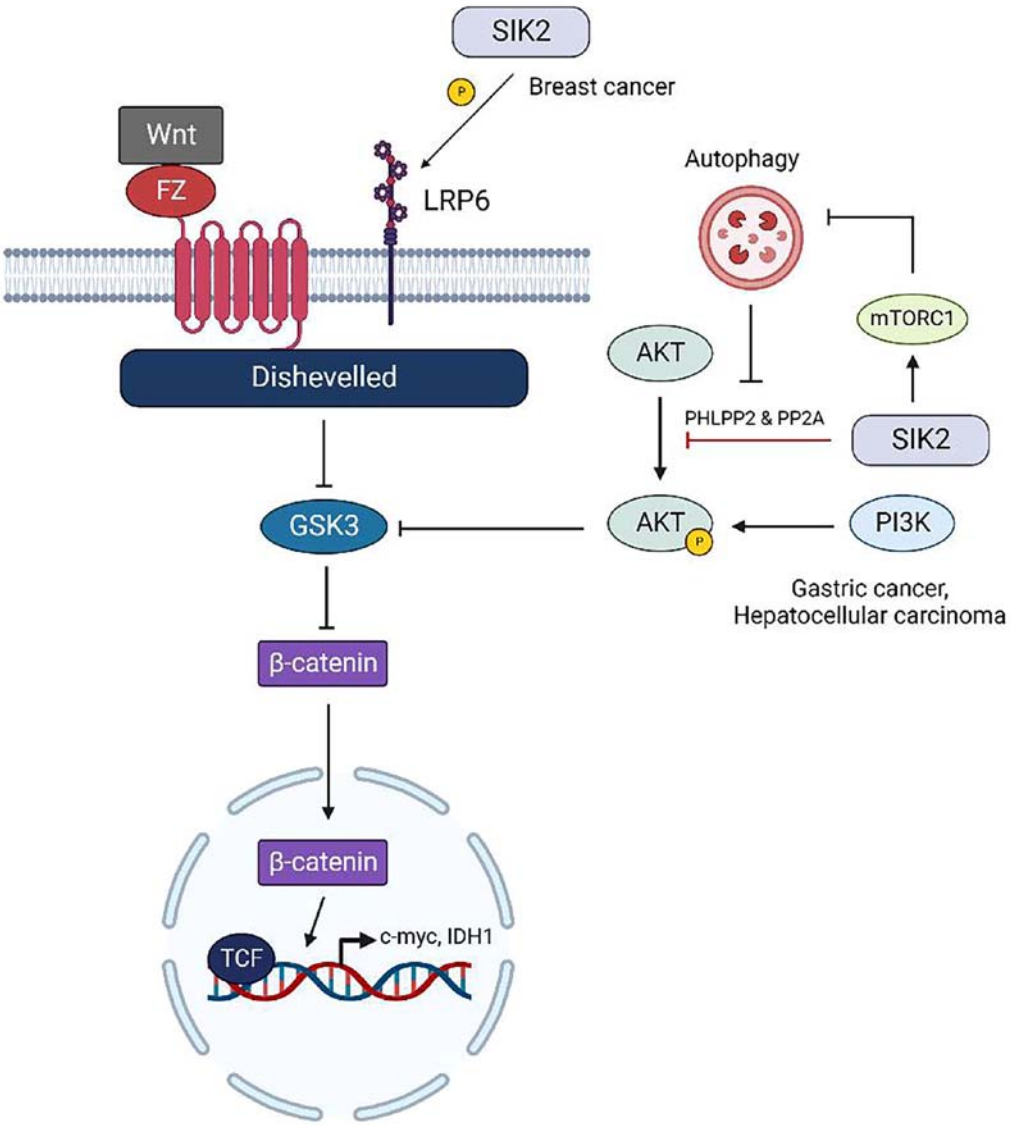

Figure 7. Effects of SIK2 on Wnt/β-catenin signaling pathway. SIKs, salt inducible kinases; Fz, Frizzled; GSK3, glycogen synthase kinase 3; LRP, low density lipoprotein receptor-related protein.

knockout SIK3, the phosphorylation levels of mTOR1 targeted molecules were decreased (124). In acute myeloid leukemia (AML), SIK3 regulates tumor proliferation under the control of LKB1 and HDAC4 is the downstream molecule participating in this process. When the catalytic activity of SIK3 is normal, HDAC4 is limited to the cytosol and MEF2-induced transcription maintains AML proliferation (127). The blockade of SIK3 releases HDAC4 into nucleus, thereby inhibiting the activity of MEF2 and suppressing AML development (128) (Fig. 8).

SIK3 affects tumor microenvironment via inducing inflammation. The activity of SIK3 is closely associated with chronic inflammation, tumor formation and proliferation (129). Unlike acute inflammation, which effectively eliminates pathogen or disease, chronic inflammation is the initiation of several molecular cascades, such as reactive nitrogen and oxygen species (RNS/ROS), resulting in DNA damage and tumor formation (13). Simultaneously, chronic inflammation can activate a range of signaling transcription factors, contributing to uncontrolled cell growth and tumor progression (13). In addition, cell stress is also related to inflammation, which then promotes the release of growth factors to increase tumor angiogenesis. These newly formed blood vessels provide access for tumor cells to metastasize to various parts of human body (130).

The roles of SIK3 in inflammation have been established: It induces pro-inflammatory arginine metabolism and RNS release. In breast cancer cells treated with high salt and IL-17, the formation of RNS, nitric oxide and citrulline were significantly higher than basal control conditions and the expression of pro-inflammatory inducible nitric oxide synthetase (iNOS) and arginosuccinate synthetase (ASS-1) was also enhanced (13). As an important enzyme for converting arginine into nitric dioxide (NO), the expression level of iNOS could directly affect RNS level in the tumor microenvironment (13). Noticeably, the downregulation of anti-inflammatory arginase-1 and ornithine decarboxylase was also detected in the experiments, indicating that the roles of tumor promotion in SIK3 are closely associated with inflammatory reactions (13).

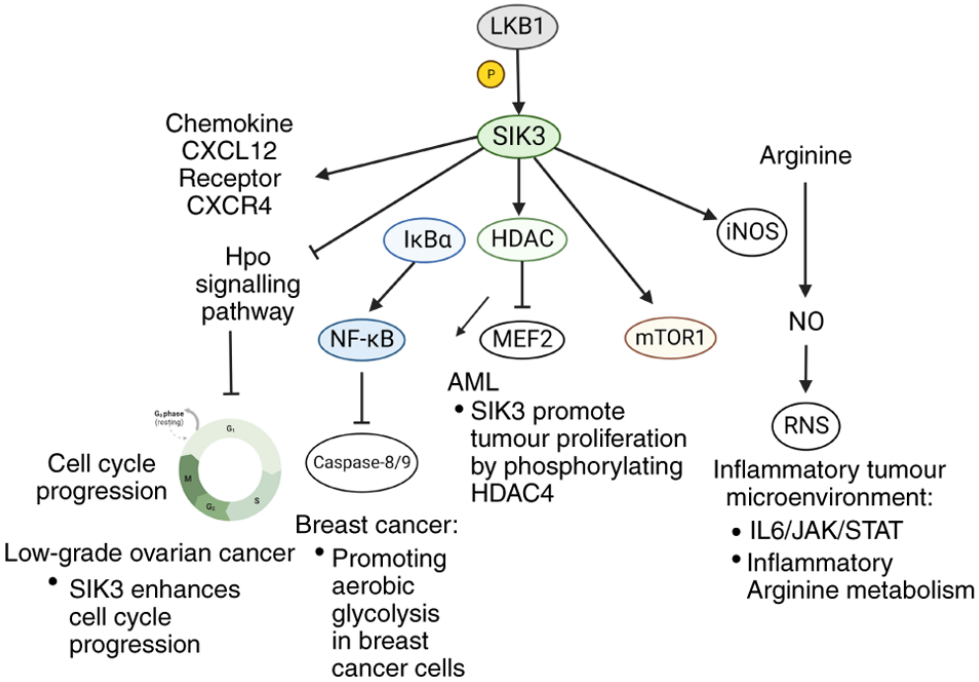

Figure 8. Roles of SIK3 on tumorigenesis. SIKs, salt inducible kinases; LKB1, liver kinase B1; HDAC, histone deacetylases; MEF2, myocyte enhancer factor 2; iNOS, inducible nitric oxide synthase; RNS, reactive nitrogen species; CXCL12, C-X-C motif chemokine 12; CXCR4, C-X-C motif chemokine receptor 4.

The mediators and cellular effectors of inflammation are important constituents of the tumor environment. In some types of tumors, inflammation can be considered a precursor to the occurrence of malignancy (131-133). By contrast, the oncogenic change could also induce an inflammatory microenvironment to promote tumor development (134). Regardless of its origin, the consistent existence of inflammation in tumor microenvironment contributes to the development of malignancies, promoting angiogenesis and metastasis, subverting adaptive immune responses and altering responses to hormones and chemotherapeutic agents (134).

The tumorigenic potency of SIK3 is also reflected in the metastatic hallmark of breast cancer. Several lines of evidence have reported that chemokine CXCL12 and its specific receptor CXCR4 expressed on cancer cells contribute to the metastatic property of malignant tumors (135). Amara *et al* (13) also showed that SIK3 can induce a pronounced increase in these metastatic markers in breast cancer. Consistently, SIK3 inhibition by prostratin also exerts anti-cancer effects partially through attenuating the expression of CXCR4 on breast cancer as anticipated (42).

Interactions between SIKs in cancer development. As aforementioned, most of the current studies indicate that SIK1 and SIK2 exhibit antagonistic effects in the process of tumorigenesis progression. However, although the research on SIK3 is still very limited, the function of SIK3 has shown synergistic effects with both SIK1 and SIK2 and occasionally three subtypes of SIKs can exhibit similar effects.

SIK1 and SIK3 show synergistic effects in tumor inhibition and inflammation. As the substrates of LKB1, SIK1 and SIK3 have exhibited synergistic roles in KRAS-driven tumors (17). By using CRISPR, Hollstein *et al* (17) indicated that the tumorigenesis process is accelerated in KRAS mutated lung cancer with concomitant loss of SIK1 and SIK3. This tumor growth promoted ability is comparable to those loss of LKB1 expression. The tumorigenesis process is closely associated with the effect of SIKs on pro-inflammatory cytokines, which might be achieved by two pathways including the direct phosphorylation of the substrates of SIKs and the indirect influence on Toll-like receptor 4 (TLR4) mediated cytokine production. It has been reported that the overexpressed SIK1 and SIK3 repress the expression of NF-κβ which is one of the downstream signals of TLR4 (136). Under the tumor microenvironment, NF-κβ mediates the expression of a number of pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 (137-139), which can be enhanced when SIK1 and SIK3 are suppressed in tumor cells. Simultaneously, after the phosphorylation level of CRTC2 is reduced, IL-6 signal is upregulated in the tumor microenvironment, which increases tumor proliferation via activating Ras/Raf/MEK/MAPK, PI3K/AKT and JAK/STAT signaling pathways (140). IL-6 has the function of facilitating the repair and induction of countersignaling pathways, including antioxidant and anti-apoptotic/pro-survival signaling and protecting cancer cells from therapy-induced DNA damage, oxidative stress and apoptosis (140). In addition, it has been reported that SIK inhibitor elevates IL-10 production by inducing the dephosphorylation of CRTC3 (60). Although IL-10 has been identified as an immunosuppressive cytokine, it has been thought to promote tumor immune escape by diminishing anti-tumor immune response in the tumor microenvironment (141). Conversely, the recovery of either LKB1 or SIK1/3 function can significantly reduce the expression level of cytokines (17), supporting the synergistic roles of SIK1 and SIK3 in inflammatory regulation.

SIK2 and SIK3 show synergistic effect in regulating metabolism and T cell activity. With respect to cancer development, studies on the synergistic effect of SIK2 and SIK3 are relatively limited. However, their similar roles in other aspects have been reported. It is well-established that SIK2 is the major type of SIK in human adipose tissue (142) and stimulates tumorigenesis by upregulating the abnormal synthesis of metabolites. The expression levels of SIK2 and SIK3 in adipose tissue are consistent and can be downregulated by TNFα in patients with insulin resistance (142), indicating that these two types of SIKs might act synergistically in regulating metabolism. In addition, T cell dysregulation is also a crucial feature of tumorigenesis (143). Knockout of SIK3 is associated with the reduced formation of peripheral T cells and the constitutive knockout of SIK2 and SIK3 in the haemopoietic cells can accelerate this reduction (144). Although the synergistic effects of SIK2 and SIK3 in cancer formation and development have not been extensively reported, their combined roles in processes related to tumorigenesis have been found.

Three subtypes of SIKs exhibits synergistic roles in regulating macrophage phenotype. Tumor-associated macrophages (TAM) are a part of the tumor microenvironment and are usually controlled by tumor cells to promote their growth, immune escape, angiogenesis and metastasis (145). The roles of M2 macrophage are similar to TAM and their polarization is under the control of diverse cytokines in the tumor microenvironment (145). SIK2 is the major contributor of overall SIK activity in macrophages. Its knockout in mice model is associated with the upregulation of macrophage-secreted IL-10 in the tumor microenvironment and macrophages are more prone to polarize into the M2 phenotype (146). This process is mediated by the activity of CREB target gene Nur77. However, the use of SIK2 inhibitors alone is insufficient to fully convert macrophages to the M2 phenotype. Only the simultaneous blockade of SIK1, SIK2 and SIK3 can induce mouse macrophages to be polarized into stable anti-inflammatory phenotype and simultaneous knockout of SIK2 and SIK3 showed a significantly stronger effect on IL-10 expression stimulation than single knockout, indicating that three subtypes of SIKs represent synergistic effects on the determination of macrophage phenotype (146).

4. SIKs as the target of anti-cancer agents

Potential applications of SIK1 activator. As SIK1 can be identified as a tumor suppressor in most types of cancers, it is reasonable to consider that its activator with the potential of becoming new agents for cancer treatment. Although current studies suggest that LKB1 is the natural SIK1 activator (1,25,85), extra SIK1 activators can remain to be developed to inhibit tumor development and metastasis. Based on existing investigations (1,25,85), it is reasonable to consider that exogenous SIK1 activators can take a variety of forms, including the direct activation of SIK1, enhancing the function of LKB1, or lncRNA or CircRNA that reduce the degree of miRNA inhibition of SIK1 in tumor cells. However, there are currently no cellular experiments or preclinical studies focusing on additional SIK1 activators, indicating that this could be the direction of future research on the relationship between SIK and cancer.

Potential applications of SIK2 inhibitor. As aforementioned, SIK2 is an important cell cycle regulator affecting tumor proliferation and metastasis (89,147). Using SIK2 inhibitors to block its downstream signal is a theoretically feasible cancer treatment strategy. Several SIK2 inhibitors with sharing mechanisms have been already investigated in preclinical studies. Among them, the effects of MRIA9 are being tested in cell lines; the single use of HG-9-91-01, ARN3236, ARN3261, as well as their combination with traditional chemotherapeutics are undergoing pre-clinical trials in animal models. Additionally, the roles of combining ARN3261 (GRN300) with paclitaxel for cancer treatment are evaluated in clinical trials (Tables I and II). The updating progress or promising strategies of these drugs are described following:

MRIA9. MRIA9 is a potent pan-SIK inhibitor with a high selectivity against SIK2 at the concentration of 1 μM (148). MRIA9-induced SIK2 inhibition interferes with the complete separation of centrosome in ovarian cancer cells, leading to malfunctioning mitotic spindle assembly and G_2-M transition block (90). In line with this, the mitotic indices are significantly reduced in SKOV-3 cells treated with MRIA9 of 1 μM compared with the control group (8 vs. 37.7%) (90). Additionally, after a three-week continuous treatment of low dose MRIA9 (0.5 μM), the mean number of chromosomes was observed to increase from 47.54-76.86% in SKOV-3 cells and 58.83-71.26% in OVCAR3 cells (90). This suggests that MRIA9-dependent long-lasting SIK2 inactivation can also enhance the chromosomal instability, which might be attributed to failure in accurate positioning and aberrant transmission of genomic materials (90). All these findings indicate that MRIA9 has shown favorable anti-tumor mechanisms in preclinical studies and has a promising future prospect.

ARN3236 and ARN3261. ARN-3236 and ARN 3261 are newly developed SIK2 inhibitors with similar tumor-suppressive mechanisms summarized as follows: i) promoting centrosome uncoupling from nucleus; ii) inhibiting centrosome splitting in cells undergoing mitosis; iii) inducing cell cycle arrest, apoptosis and the formation of tetraploid; and iv) attenuating SIK2/AKT/survivin pathway (149,150). These anti-tumor effects have been validated in ovarian and breast cancer cell lines, as well as in female athymic nude mice models, yet transposing into clinical practice remains a challenge.

NaP-S+HG. HG-9-91-01 is a SIK2 inhibitor with a remarkable therapeutic effect on ovarian cancer in preclinical trials. However, its significant off-target effects limit the clinical utility. To deal with this, an emerging compound Nap-S+HG with SIK2 responsiveness was rationally designed as a vector for HG-9-91-01 and is undergoing pre-clinical trials in animal models. Upon the activation of SIK2, Nap-S is phosphorylated and disassembled from HG. Then, the SIK2-responsive release of HG in turn downregulates the overactivation of SIK2, exhibiting a stronger anti-tumor effect in Balb/c nude mice intraperitoneally injected with SKOv3-SIK2 ovarian cancer cells (151). Consistently, the tumor weight and ascites volume are significantly decreased in the Nap-S+HG mice at day 8 compared with the other three groups treated with PBS, Nap-S and HG, respectively (151). These encouraging results

Table I. Pre-clinical data of SIKs inhibitors in cell and animal models.

Agent	Type	Targeted cancers	Stage	Effects
ARN-3236	SIK2 inhibitor	Serous ovarian cancer; breast cancer	Pre-clinical trials in animal models (mice)	ARN-3236 inhibits tumor growth and boosts the sensitivity of ovarian cancer cells to paclitaxel; ARN-3236 enhances the olaparib-mediated inactivation of PARP enzyme, sensitizing breast and ovarian cancer cells.
ARN-3261	SIK2 inhibitor	Ovarian cancer; breast cancer	Phase I clinical trial	ARN-3261 inhibits tumorigenesis and sensitizes ovarian cancer cells to carboplatin; ARN-3261 increases the sensitivity of ovarian and breast cancer to PARP inhibitors.
HG-9-91-01	SIK2 inhibitor	Ovarian cancer	Pre-clinical trials in animal models (mice)	HG inhibits ovarian tumor growth and metastasis; Nap-S+HG is a SIK2-responsive compound with less systemic toxicity.
MRIA9	SIK2 inhibitor	Ovarian cancer	Pre-clinical trials in cell lines	MRIA9 induces cell apoptosis and enhances paclitaxel sensitivity in ovarian cancer cells.
Berberine and Emodin	SIK3 inhibitor	Breast cancer	Pre-clinical trials in cell lines	Berberine and Emodin exert synergistic cytotoxic potential against breast cancer cells via SIK3 kinase.
OMX-0370	SIK3 inhibitor	Colorectal cancer, breast cancer, renal carcinoma, pancreatic carcinoma	Pre-clinical trials in cell lines	Abating the TNF-driven NF-κB activity in tumors and enhancing the sensitivity to TNF-induced cell death.
OMX-0407	SIK3 inhibitor	Colorectal cancer, breast cancer; lung cancer	Phase I clinical trial	OMX-0407 blunts TNF-mediated HDAC4/ NF-κB activity in a dose-dependent manner.
Prostratin	SIK3 inhibitor	Breast cancer	Pre-clinical trials in cell lines	Prostratin exerts its anti-tumor effect by inhibiting SIK3/HDAC4-mediated cell proliferation.
YKL-05-099	SIK3 inhibitor	Acute myeloid leukemia	Pre-clinical trials in animal models (mice)	YKL-05-099 treatment abrogates AML progression and extends survival in two mouse models of MLL-AF9 AML.

SIKs, salt inducible kinases; PARP, poly ADP-ribose polymerase; HDAC, histone deacetylases; AML, acute myelocytic leukemia.

indicated that NaP-S+HG with the potential of maximizing the therapeutic effects of SIK2 inhibitor and deserves to transpose into practice in future.

Combination therapy of SIK2 inhibitors. In breast cancer and ovarian cancer, Poly ADP-ribose polymerase (PARP) inhibitors, paclitaxel and platinum are the most common agents. All of them kill tumor cells by disturbing tumor DNA structure and mitosis stabilization. Direct using chemotherapeutic drugs in cancer cells can induce a number of lesions including bulky platinum-DNA adducts and DNA double-strand breaks (DSBs) (152). Currently, an increasing number of studies place a high premium on combinational strategy of SIK2 inhibitors and have preliminarily demonstrated that the combination treatment is viable and effective in preclinical settings.

MRIA9, ARN-3261 and ARN-3236 have been investigated to increase paclitaxel sensitivity in ovarian cancer cell lines by interfering with mitotic progression (90,149,150). Of these, ARN-3261 (GRN300) is currently being assessed in a clinical phase I trial to find its maximum tolerated dose or the effects when combining with paclitaxel (153) (Table II).

ARN-3261 and ARN-3236 can boost the sensitivity of ovarian cancer to carboplatin treatment by enhancing carboplatin-mediated DNA damage (150). In addition, these two drugs enhance the PARP inhibitor (Olaparib) synergistically in ovarian cancer and triple-negative breast cancer in mice models (154). The inactivation of Class-IIa HDAC/MEF2D pathway appears to be a key event in the synergistic effect observed between SIK inhibitors and Olaparib: ARN-3261 and ARN-3236 reduce the phosphorylation of Class-IIa HDACs and promote the activity of MEF2 transcription factors, repressing the transcription of genes involved in DNA DSB repair (150,154). Consequently, this malfunction of DNA repair machinery contributes to chromosomal instability and form 'synthetic lethality' with Olaparib (150).

Table II. Currently ongoing clinical trials of oncolytic adenovirus for the treatment of prostate cancer.

Responsible Party, year	Study title	Official title	Clinical trials ID	Intervention	Study description	Phase	Status	(Refs.)
Green3Bio, Inc, 2020	First-in-Human Evaluation of GRN-300 in Subjects with Recurrent Ovarian, Primary Peritoneal and Fallopian Tube Cancers.	Ph 1/1B Evaluation of the Safety, Pharmacokinetics and Efficacy of GRN-300, a Salt-inducible Kinase Inhibitor, Alone and in Combination With Paclitaxel, in Recurrent Ovarian, Primary Peritoneal and Fallopian Tube Cancers.	NCT04711161	GRN-300 and Paclitaxel	This study is divided into two parts; In Part 1, the tolerability of continuous twice-daily oral GRN-300 will be assessed with each cycle consisting of 28 days of treatment. Monitor the tolerability at each dose level and incidence of dose-limiting toxicities to adjust the number of dosing cycles. Part 2 will test the tolerability of continuous 28-day cycles of GRN-300 in combination with weekly paclitaxel given 3 of 4 weeks per month (x3).	I	Active	(153)
iOmx Therapeutics AG, 2023	A Study of OMX-0407 in Patients With Previously Treated Solid Tumors That Can't be Removed Surgically	A Phase I Dose Escalation Study of OMX-0407 a Salt-inducible Kinase Inhibitor in Patients With Previously Treated Unresectable Solid Tumors	NCT05826600	OMX-0407	Identify the maximum tolerated dose and recommended dose for Phase II based on adverse events of each dose level; Assess the safety and tolerability of OMX-0407: Occurrence and severity of toxicities at each dose level; Pharmacokinetics: Maximum observed plasma concentration; Time of maximum observed plasma concentration; Area under the plasma concentration-time curve from time of dosing to the last quantifiable timepoint; Area under the plasma concentration-time curve from time of dosing to infinity and its percentage; Terminal elimination half-life	I	Recruiting	(159)

Taken together, combination strategy is of considerate interest for maximizing the therapeutic benefits and further assessing the combination of SIK2 inhibitors with these therapies should be prioritized to optimize the clinical utility of these drugs in the near future.

Potential applications of SIK3 inhibitors. As the role of SIK3 in cancer is being continuously clarified, insights from emerging evidence contribute to the development of SIK3 inhibitors. Several drugs have been tested in pre-clinical and clinical trials. The single use of prostratin, photochemicals and OMX-0370 are tested in tumor cell lines; YKL-05-099 and the combination of OMX-0407 with immunotherapeutic agents are undergoing pre-clinical trials in animal models; while the roles of OMX-0407 are being examined in a clinical trial (Tables I and II). These trials will further provide a rationale for advanced clinical validations and studies in patients.

Prostratin. Prostratin, a phorbol ester natural plant compound, was identified with the function of suppressing tumor metastasis by targeting SIK3 (42). In a pre-clinical study, it suppressed SIK3, HDAC4 and CXCL4 simultaneously, completely blocking the SIK3 signaling pathway in breast cancer cell lines (42). It has been established that SIK3 can upregulate CXCR4 to promote tumor invasion and metastasis (155). Investigation from Alotaibi *et al* (42) also confirmed this role, in which prostratin showed higher cytotoxicity in highly-metastatic breast cancer cell lines. Therefore, the SIK3 inhibitor prostratin could be considered a promising anti-cancer chemotherapeutic regimen to restrain tumor metastasis.

Photochemicals. Photochemicals are also identified as anticancer agents. They modulate deregulated signaling pathways involving various cellular events including cell growth, metabolism and death (156). Berberine and Emodinare are two photochemicals targeting SIK3 in breast cancer cells. Their combination effectively downregulates the mTOR signaling pathway and Akt signaling pathway, blocking aerobic glycolysis and cell cycle progression; therefore, it is considered a promising anti-breast cancer regimen (124).

OMX-0407 and OMX-0370. OMX-0407 and OMX-0370 as first-in-class SIK3 inhibitors, has exhibited similar tumor-suppressive effects mainly by perturbing the SIK3-HDAC4/5-NF-κB axis, which has been validated in tumor cell lines MC38, MC38 NF-κB-luc lines, RENCA, EMT-6 and human PANC1 (157,158). As aforementioned, the loss of SIK3 function results in decreased phosphorylation of HDACs, preventing its nuclear retention and abating NF-κB mediated pro-survival gene transcription in response to TNF. Besides the inhibitory effect on TNF-driven pro-tumorigenic NF-κB activity in MC38 NF-κB-luc lines, SIK3 inhibitors can also re-sensitize MC38 and PANC1 tumor cells to TNF-mediated caspase activation and apoptosis. Notably, it has been demonstrated that the tumor suppressive capacity of OMX-0307 could be superior to anti-PD-1 antibody therapy in RENCA and EMT-6 cell lines (158). Additionally, both OMX-0407 and -0370 can remodel the tumor microenvironment (TME) from an immunosuppressed to a pro-inflammatory setting by reducing regulatory T cells (T-regs) and increasing activated cytotoxic T lymphocytes (157,158). This suggests that SIK3 inhibitors harbor tremendous clinical potentials for monotherapy. A phase I clinical trial of OMX-0407 is ongoing to identify the maximum tolerated dose and profile its pharmacokinetics (159) (Table II).

YKL-05-099. YKL-05-099 is a chemosynthetic pan-SIK inhibitor with *in vitro* 50% inhibitory dose of SIK3 being 30 nM (160). Currently, the therapeutic effects of YKL-05-099 are being tested in mice: YKL-05-099-dependent SIK3 inhibition suppresses the AML progression by abolishing SIK3/HDAC4/MEF2C signaling pathways (128). In addition, both YKL-05-099-treated animals and SIK3-knockdown mice showed favorable viability and limited toxic responses, which might be attributed to the minimal on-target effects on the growth of normal tissues. All these findings indicate that pharmacological inhibition of SIK3 could harbor great clinical significance in AML treatment. However, to achieve its therapeutic significance, two imperative problems remain to address: i) Off-target activity of YKL-05-099 for other important cellular kinases obscures the correlation between MEF2C addiction and the sensitivity to YKL-05-099; ii) Considering a tumor-suppressive role of SIK3 in the context of lung cancer, whether sustained SIK3 inhibition may play a tumorigenic role in non-hematopoietic tissues yet requires further investigations.

Combination therapy of SIK3 inhibitors with immunotherapy. Although the potent anti-cancer effects of OMX-0407 as a monotherapy regimen have been demonstrated, the coadministration of these drugs with other therapies also has a promising future. A recent study has suggested that OMX-0407 can act synergistically in combination with anti-PD/PD-L1 immunotherapy by sensitizing tumor cells to apoptosis and reshaping the immunosuppressive TME in immune checkpoint inhibitor-resistant breast cancer and lung cancer animal models (157). These two models were established by implanting EMT6 tumor cells into the mammary fat pad of BALB/c mice and subcutaneously injecting KLN205 tumor cells into DBA/2 mice (157). This combinational strategy might particularly benefit patients with resistance to currently available immune checkpoint inhibitors, thereby possessing great clinical significance.

Combination therapy of SIK3 inhibitors with antimitotic drugs. A previous study has shown that the depletion of SIK3 by using siRNA exhibited the effect of prolonging mitotic duration (100). Therefore, it is reasonable to consider that specific SIK3 inhibitors might act synergistically with conventional antimitotic drugs. If the inactivation of SIK3 allows the lower doses of antimitotic drugs to be prescribed, patients will suffer fewer side effects of the drugs. Chen *et al* (161) conducted SIK3 depletion in HELA cells and indicated that the downregulation of SIK3 could enhance the mitotic arrest and cell apoptosis effects of spindle poisons, including nocodazole and Taxol. In addition, the depletion of SIK3 promotes mitotic arrest induced by emerging types of antimitotic drugs, including those targeting AURKA, AURKB, PLK1 and Eg5 (161).

However, SIK3 inhibitor is not suitable for all cancers with high levels of SIK3 expression. Although the preferential expression of SIK3 has been found in ovarian cancer (15),

trying to repress its activity has been shown to be associated with a poor prognosis in patients with advanced ovarian cancer: Liang *et al* (162) reported that stage III/IV epithelial ovarian cancer patients with high SIK3 levels benefit more from chemotherapy than those with lower expression levels. This was specifically related to the upregulation of ATP-binding cassette protein ABCG2. In addition, in NSCLC, the simultaneous downregulation of SIK1 and SIK3 in KRAS mutant tumors accelerates lung tumorigenesis comparably to those with loss of LKB1 (17). The most appropriate conditions for its use remain to be explored.

As the role of SIK in cancer is being continuously clarified, insights from emerging evidence contribute to the development of more potent drugs. Nevertheless, most of the present research on SIK-targeted drugs is still in the pre-clinical trial stage and their effects have been initially investigated, which means further studies for SIK-targeted agents are required.

5. Conclusion and future directions

The roles of SIKs are distinct in the context of different cancers. Under most circumstances, SIK1 acts as a tumor suppressor, inhibiting tumorigenesis and the EMT process, thereby reducing cancer metastasis and promoting cancer apoptosis. SIK2 serves as an oncogene, promoting tumorigenesis by regulating cell cycle and metabolism of tumor cells and enhancing the Warburg effect. Upregulated SIK3 is mainly detected in breast cancer and ovarian cancer and accelerates tumorigenesis by preventing cell cycle arrest and increasing inflammatory response. However, with the continuous in-depth exploration of SIKs, their roles in certain tumors are in contrast to their traditional effects, indicating that SIKs cannot be simply defined as tumor suppressors or oncogenes. Despite the fact that the roles of SIKs are distinct in cancer regulation, their upstream and downstream signaling molecules have shown strong associations, suggesting that SIKs are not the initial regulators of tumor metastasis but are located in the central of this signaling pathway. Their targeted agents might be a feasible option to inhibit tumor metastasis. Currently, the inhibitors of SIK2 and SIK3 are still in the preclinical stage. Considering their synergistic effects with chemotherapy drugs, adding SIK inhibitors into chemotherapeutic regimens is a promosing strategy to improve the therapeutic effect.

However, the questions about the roles of SIKs in cancer development are not fully resolved. First, although most studies indicated that SIK1 is a tumor suppressor, its tumor promoting effects were also reported in MB and DSRCT (48,87). This might be related to the difference in the occurrence and progression of these two tumors and other cancers. The roles of SIK1 in other neuroendocrine neoplasms similar to MB needs to be further explored, which may improve the definition of the function of SIK1 in tumor development. Second, SIK2 has exhibited controversial effects in the same cancer by interacting with different molecules. Its ultimate effect on tumor cells requires further determination and developing new drugs to amplify its tumor suppressive effects is a possible strategy for cancer treatment. Third, p300 has been identified as a target of SIKs (163). Its effects on inhibiting tumor progression and enhancing chemotherapeutic drugs have been discussed (164,165). However, p300 was only reported as a downstream molecule of SIK2 for metabolic regulation. Whether SIKs can regulate cancer progression by affecting the activity of p300 requires further investigation. Last, although the clinical use of SIK inhibitors is theoretically possible in cancer treatment, their defects, such as low bioavailablity, remain unresolved and warrant further study.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Author contributions

SF, DH and LL were responsible for conceiving and designing the present study; SF and FW drafted the manuscript. SF, FW, HS, SC, and BW revised the manuscript critically for important intellectual content. SF, FW, HS, SC, BW, DH and LL gave final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. 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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