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REVIEW

A Review of SIK2 in Ovarian Cancer: Function and Emerging Targeted Therapies

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Abstract: Ovarian cancer, a common gynecologic malignancy, is associated with a poor prognosis owing to difficulties in early detection, high recurrence rates, and frequent therapy resistance. Salt-inducible kinase 2 (SIK2), a serine/threonine kinase frequently overexpressed in ovarian cancer, has emerged as a potential key driver of tumor progression. It is implicated in diverse processes, including metabolic reprogramming, cell proliferation, DNA damage repair, metastasis, and chemoresistance. Consequently, SIK2 is increasingly recognized as a promising target for developing novel therapeutic strategies. Unlike previous reviews that broadly cover the SIK family or general ovarian cancer metabolism, this review provides a SIK2-centered perspective, comprehensively synthesizing its multifaceted oncogenic roles and systematically evaluating emerging targeted therapies—including ATP-competitive inhibitors (ARN-3261, MRIA9), a protein degrader (SIC-19), and a novel hydrogel delivery system (Gel Nap-S+HG). Despite these promising developments, it is important to note that most SIK2-targeted agents are still in preclinical stages, and several critical hurdles remain to be addressed before clinical translation—including off-target toxicity, limited selectivity, and the lack of validated predictive biomarkers for patient stratification. By integrating current mechanistic insights with an up-to-date evaluation of emerging therapies, this review provides a foundational framework for guiding future research and supporting the clinical development of SIK2-targeted strategies in ovarian cancer.

Keywords: salt-inducible kinase 2, ovarian cancer, molecular mechanisms, targeted therapy, kinase inhibitors

Introduction

Ovarian cancer is a leading cause of cancer-related mortality in women worldwide and exhibits the highest fatality rate among all gynecological malignancies. In 2022, there were an estimated 324,398 new cases and 206,839 deaths globally.[1] The current standard treatment for ovarian cancer involves cytoreductive surgery followed by platinum- and taxane-based chemotherapy, often supplemented with maintenance therapy to delay recurrence. However, this disease remains challenging due to a high recurrence rate and the frequent development of platinum resistance.[2] Consequently, the 5-year survival rate for patients with advanced disease remains low, underscoring the critical need to identify novel therapeutic targets to improve prognosis.[3] Salt-inducible kinase 2 (SIK2), a member of the adenosine monophosphate-activated protein kinase (AMPK)-related kinase family initially characterized for its roles in energy metabolism and adipose homeostasis,[4] has recently emerged as a key oncogenic driver in multiple malignancies. Notably, SIK2 is frequently overexpressed in ovarian cancer, where it promotes tumor progression by enhancing cancer cell proliferation and metastasis.[5–7]

Although SIK2 is the most extensively studied SIK family member in ovarian cancer, the distinct roles of SIK1 and SIK3 warrant consideration. SIK1 has been reported to function as a tumor suppressor in multiple malignancies, with its downregulation often associated with poor prognosis.[8–11] In contrast, the role of SIK3 in ovarian cancer appears more complex and remains poorly characterized. While SIK3 has been identified as a tumor-associated antigen that promotes

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cell proliferation when overexpressed,[12] another study linked its low expression to chemoresistance.[13,14] This limited and sometimes contradictory evidence underscores the need for further investigation into SIK3's function in ovarian cancer.

The opposing roles of SIK1 and SIK2 suggest that functional redundancy is unlikely to compromise SIK2-targeted therapy—in fact, pan-SIK inhibition that suppresses SIK1 could inadvertently counteract the antitumor effects of SIK2 targeting.[15] For SIK3, the very limited evidence in ovarian cancer precludes definitive conclusions about functional overlap with SIK2. However, recently developed SIK2-targeting agents with optimized kinome-wide selectivity (eg, MRIA9) and SIK2-selective protein degraders (eg, SIC-19) address this challenge: SIC-19 achieves selective SIK2 degradation with minimal activity against SIK1/3, while MRIA9 exhibits a markedly restricted off-target kinase profile despite its pan-SIK family activity.[16,17]

Given these considerations, this review focuses specifically on SIK2-centered mechanisms and therapeutic strategies in ovarian cancer, systematically elucidating its molecular roles in pathogenesis and progression while evaluating its potential as a therapeutic target and summarizing recent advances in SIK2 inhibitor development.

The Role of SIK2 in Driving Ovarian Cancer Progression

SIK2-Mediated Regulation of Metabolic Reprogramming

Metabolic reprogramming is an adaptive process in which cancer cells remodel their intracellular energy metabolism to meet the biosynthetic and energetic demands of rapid proliferation, invasion, and metastasis. This phenomenon represents a hallmark of malignant progression in ovarian cancer and has emerged as a major focus in oncology research and therapy development. As a member of the AMPK-related kinase family, SIK2 plays a pivotal role in reprogramming glucose and lipid metabolism in ovarian cancer cells.[18] By coordinately regulating pathways encompassing glucose metabolism, mitochondrial function, and lipid metabolism, SIK2 thereby drives tumor progression.

Rapidly proliferating cancer cells preferentially utilize glycolysis over the more efficient mitochondrial oxidative phosphorylation for energy production, even under aerobic conditions—a phenomenon known as the Warburg effect.[19] SIK2 remodels glucose metabolism by concurrently enhancing glycolytic activity and suppressing mitochondrial oxidative phosphorylation. This metabolic rewiring robustly fulfills the energetic and biosynthetic demands of ovarian cancer cells.

To enhance glycolysis, SIK2 activates the phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathway, leading to the upregulation of hypoxia-inducible factor 1α (HIF-1α). HIF-1α subsequently transactivates key glycolytic enzymes, including hexokinase 2 (HK2) and phosphofructokinase (PFKL), thereby promoting glucose uptake and lactate production.[20] Lactate serves as an oxidizable carbon source that contributes to maintaining systemic carbon metabolic homeostasis[21] and supplies both energy and biosynthetic precursors to support tumor cell proliferation.[22,23] Functional studies demonstrate that SIK2 knockdown in A2780 cells reduces glucose consumption by 40–50% and lactate production by 30%-40%, whereas SIK2 overexpression in SKOV3 cells markedly enhances glycolytic flux.[20] These findings substantiate the critical association between SIK2-driven glycolysis and malignant tumor progression. Furthermore, SIK2 phosphorylates the mitochondrial fission protein dynamin-related protein 1 (Drp1) at serine 616 (Ser616), thereby inducing excessive mitochondrial fission. This excessive fission impairs the activity of mitochondrial respiratory chain complexes I–V and lowers the oxygen consumption rate, collectively inhibiting oxidative phosphorylation.[20] Consequently, tumor cells are compelled to depend more heavily on glycolysis for energy, synergistically reinforcing metabolic reprogramming and sustaining their malignant phenotypes (Figure 1).

Aberrant lipid metabolism in ovarian cancer cells is hallmarked by enhanced fatty acid synthesis, cholesterol accumulation, and increased fatty acid oxidation. These alterations are primarily attributable to upregulated expression or activity of key lipogenic enzymes, including fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC),[24] and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR)—the rate-limiting enzyme in cholesterol synthesis.[25] By modulating the expression of these key enzymes, SIK2 orchestrates a dual regulatory role in lipid synthesis and oxidation, thereby supplying the essential biomaterials and energy required for tumor progression.

SIK2 activates the PI3K/AKT signaling pathway to upregulate the expression and activity of sterol regulatory element-binding protein (SREBP) family members, thereby promoting the de novo synthesis of fatty acids and

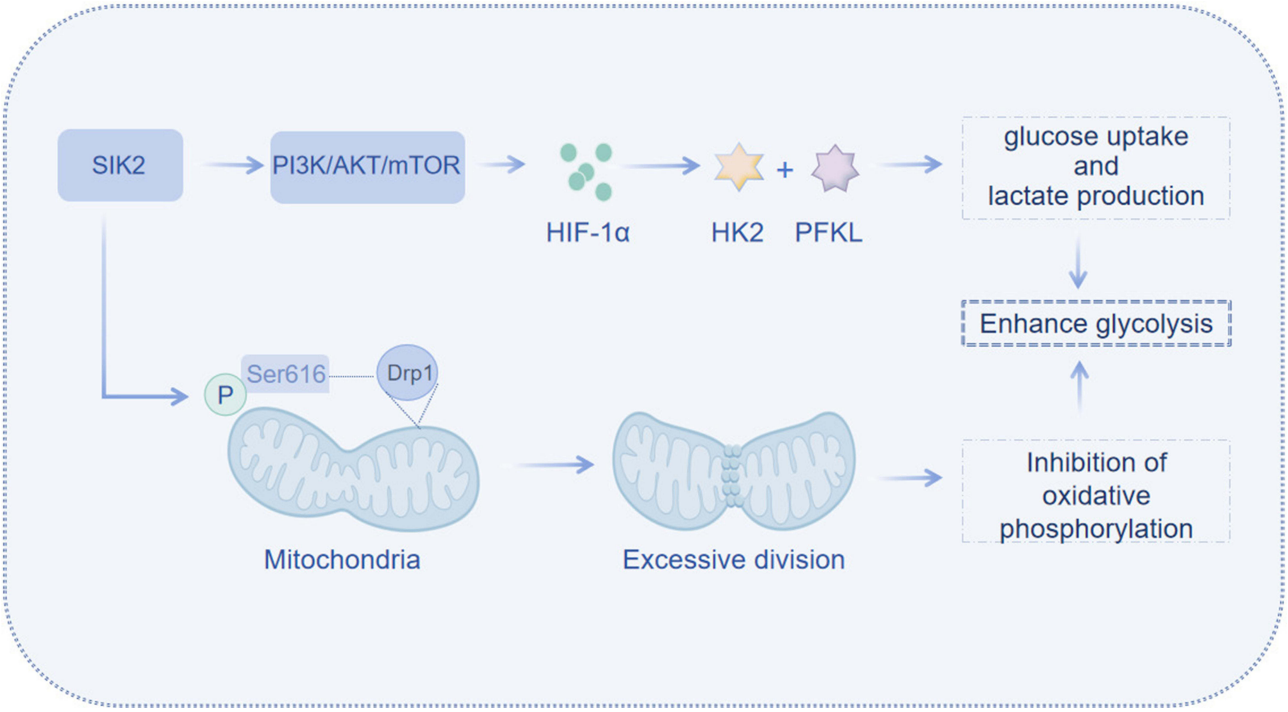

Figure 1 Schematic overview of the molecular mechanisms by which SIK2 regulates the Warburg effect and glucose metabolic reprogramming in ovarian cancer cells. SIK2 drives glycolytic enhancement and mitochondrial dysfunction via two parallel pathways: (1) SIK2 activates the PI3K/AKT/mTOR signaling axis, which upregulates HIF-1α and its downstream glycolytic enzymes HK2 and PFKL, ultimately promoting glucose uptake and lactate production to enhance glycolysis; (2) SIK2 directly phosphorylates the mitochondrial fission protein Drp1 at Ser616, which induces excessive mitochondrial fission, impairs mitochondrial respiratory function, and inhibits oxidative phosphorylation. These two pathways synergistically reinforce the Warburg effect to support the rapid proliferation of ovarian cancer cells.
Abbreviations: SIK2, Salt-inducible kinase 2; PI3K, phosphoinositide 3-kinase; HIF-1α, hypoxia-inducible factor 1α; HK2, hexokinase 2; PFKL, phosphofructokinase; Drp1, dynamin-related protein 1; Ser616, serine 616.

cholesterol. Specifically, SIK2 upregulates SREBP1c, which directly transactivates FASN to drive fatty acid synthesis. Concurrently, SIK2 upregulation of SREBP2 enhances the expression of HMGCR, resulting in intracellular cholesterol accumulation.[26] Analysis of clinical specimens reveals that SIK2 expression is significantly positively correlated with the levels of both FASN and HMGCR in ovarian cancer tissues. Moreover, high SIK2 expression is associated with poor patient prognosis,[26] collectively indicating that SIK2-mediated enhancement of lipid synthesis is closely linked to malignant tumor progression.

Conversely, SIK2 also contributes to enhanced fatty acid oxidation. Within the adipocyte-rich tumor microenvironment, free fatty acids released by adipocytes activate the phospholipase C (PLC) signaling pathway. This activation elevates intracellular calcium ion concentration, thereby inducing autophosphorylation and activation of SIK2 at serine 358 (Ser358). Activated SIK2 subsequently promotes the AMPK-mediated phosphorylation of ACC. Phosphorylated ACC exhibits reduced activity, leading to decreased malonyl-CoA production. The decline in malonyl-CoA relieves its inhibition of carnitine palmitoyltransferase 1A (CPT1A), a key enzyme in long-chain fatty acid β-oxidation, thereby enhancing fatty acid oxidation to fuel energy production for cancer cells within metastatic niches.[7,27] The dual regulatory role of SIK2 in lipid synthesis and oxidation, along with the underlying molecular pathways, is summarized above (Figure 2).

Regulation of Spindle Assembly and Cell Cycle Progression

The advancement of combination therapies incorporating cell cycle checkpoint inhibitors in clinical trials for ovarian cancer and other malignancies has spurred in-depth investigation into cell cycle regulatory mechanisms.[28] Understanding these key factors has become a pivotal direction in anti-tumor drug development. As a centrosome-localized kinase, SIK2 plays a critical role in cell division. Studies demonstrate that SIK2 colocalizes with γ-tubulin in the perinuclear region in approximately 70% of interphase cells. During mitosis, this colocalization becomes predominantly concentrated at the

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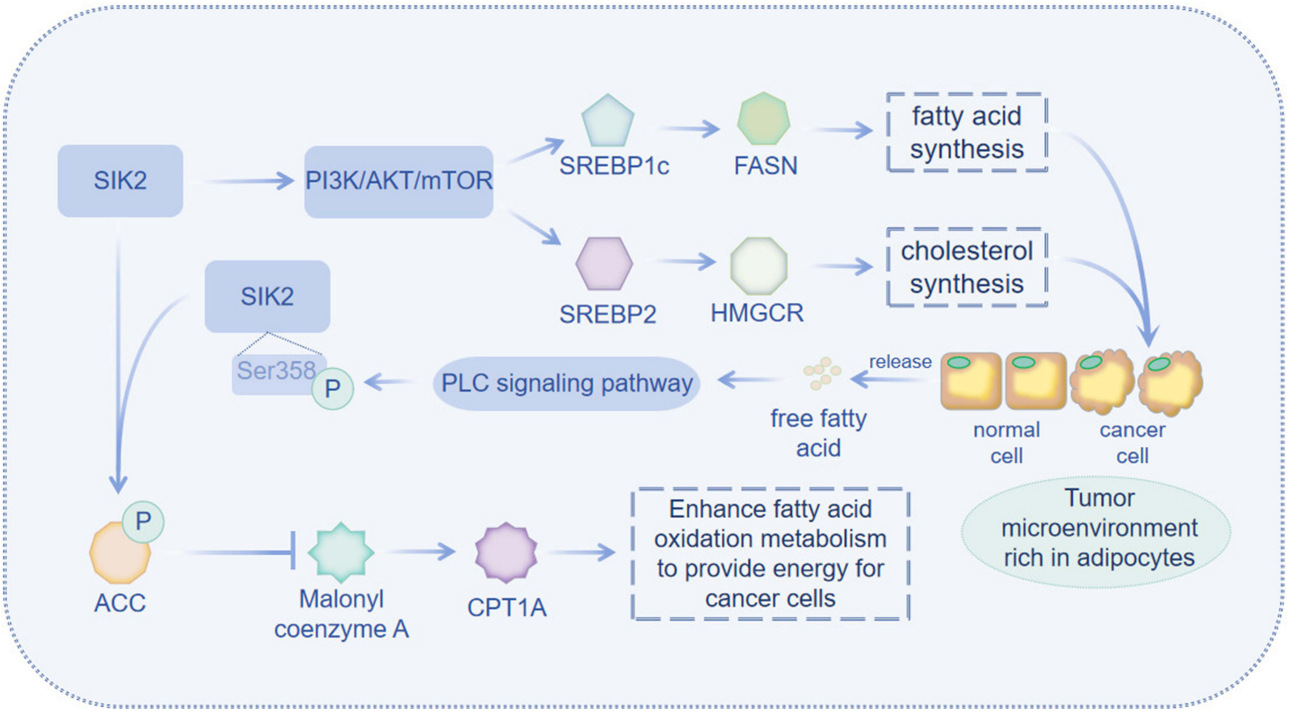

Figure 2 Schematic overview of the dual regulatory role of SIK2 in lipid synthesis and fatty acid oxidation in ovarian cancer. SIK2 orchestrates lipid metabolic reprogramming via two distinct axes: (1) The lipogenesis axis: SIK2 activates the PI3K/AKT/mTOR pathway to upregulate SREBP1c and SREBP2, which further drive the expression of FASN and HMGCR to promote de novo fatty acid synthesis and cholesterol synthesis, respectively; (2) The fatty acid oxidation axis: In the adipocyte-rich tumor microenvironment, adipocyte-released free fatty acids activate the PLC signaling pathway, which induces SIK2 autophosphorylation at Ser358. Activated SIK2 phosphorylates ACC to reduce its activity, which relieves the inhibitory effect of malonyl coenzyme A on CPT1A, ultimately enhancing fatty acid oxidation to supply energy for ovarian cancer cells in metastatic niches.
Abbreviations: SIK2, Salt-inducible kinase 2; PI3K, Phosphoinositide 3-kinase; SREBP, Sterol regulatory element-binding protein; FASN, Fatty acid synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; PLC, Phospholipase C; Ser358, Serine 358; ACC, Acetyl-CoA carboxylase; CPT1A, Carnitine palmitoyltransferase 1A.

spindle poles.[29] Proper centrosome separation is essential for bipolar spindle formation and the fidelity of mitosis. SIK2 regulates centrosome separation during mitosis by directly phosphorylating the centrosomal linker protein C-Nap1 at serine 2392 (Ser2392; Ser2394 serves as a secondary site). This phosphorylation event is a prerequisite for proper bipolar spindle assembly. Impairment of either SIK2 function or C-Nap1 phosphorylation leads to aberrant spindle formation and chromosome missegregation.[30]

Inhibition of SIK2 function, achieved through siRNA knockdown or the specific inhibitor ARN-3236, induces a dual cell cycle arrest. First, SIK2 deficiency causes centrosome separation defects during mitosis, resulting in prometaphase arrest. This arrest is characterized by a significant increase in monopolar or multipolar spindles and prolonged mitotic duration.[31] Second, SIK2 inhibition reduces AKT phosphorylation at serine 473 (Ser473) and threonine 308 (Thr308), thereby impairing the G1/S phase transition. Cell synchronization experiments confirm that a subset of cells consequently arrest in the G1 phase and fail to enter mitosis.[30] This dual arrest at both M phase and G1/S phase collectively promotes the massive accumulation of tetraploid and even octoploid (4n/8n) cells. Consequently, the division rate is significantly slowed, and the proliferative capacity of various ovarian cancer cell lines (eg, SKOV3, Hey, ES2) is substantially reduced.[30,31]

Notably, mitotic defects resulting from centrosome separation failure constitute an irreversible, core driver of proliferative arrest: even cells that bypass G1/S phase blockade will inevitably undergo mitotic catastrophe upon entering mitosis. In contrast, PI3K/AKT pathway inhibition acts as a secondary, synergistic mechanism that amplifies these anti-proliferative effects. Thus, based on current mechanistic evidence in ovarian cancer models, centrosome dysfunction and aberrant mitotic spindle formation appear to be the primary drivers of SIK2 inhibition-induced proliferation defects, with PI3K/AKT suppression providing a complementary contribution via impairment of the G1/S phase transition.[30,31]

Collectively, these findings demonstrate that SIK2 sustains the continuous proliferation of ovarian cancer cells by ensuring normal spindle assembly and orderly cell cycle progression, thereby driving malignant progression.

Regulation of Homologous Recombination Repair (HRR)

SIK2 contributes to the DNA damage response in ovarian cancer cells by regulating HRR and serves as a key mediator of resistance to chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors. DNA double-strand breaks (DSBs) represent the most severe form of DNA damage, induced by agents such as ionizing radiation, and constitute a primary basis for tumor radiotherapy.[32] The DNA repair protein RAD50 (hereafter referred to as RAD50) plays an indispensable role in recognizing and repairing DSBs.[33] SIK2 enhances HRR efficiency by phosphorylating RAD50 at serine 635 (Ser635), which promotes RAD50 nuclear translocation and facilitates nuclear filament assembly.[16] This mechanism is critical for maintaining DSBs repair capacity. Conversely, SIK2 inhibition impairs RAD50 phosphorylation, reduces nuclear filament assembly, and compromises HRR function. These defects lead to DNA damage accumulation and consequently sensitize tumor cells to DNA-damaging agents.

Histone deacetylases (HDACs) regulate gene expression through epigenetic mechanisms to influence tumor behavior and also participate directly in the DSBs repair process.[34] Through phosphorylation of class IIa HDACs (eg, HDAC4, HDAC5, HDAC7), SIK2 sustains the transcriptional activity of myocyte enhancer factor 2D (MEF2D). This promotes the expression of key DNA repair genes, including FANCD2, EXO1, and XRCC4, thereby ensuring efficient DSBs repair and ultimately facilitating ovarian cancer progression.[35] The core regulatory mechanisms of SIK2-mediated homologous recombination repair are detailed above (Figure 3).

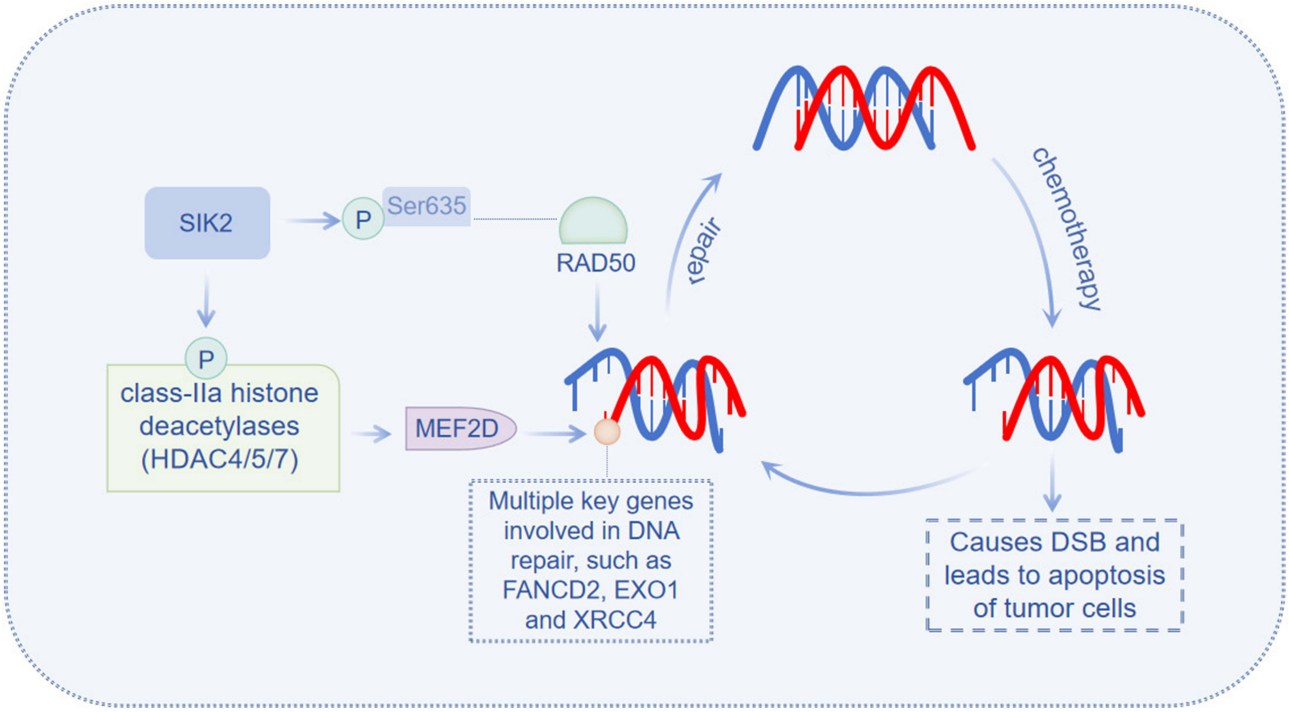

Figure 3 Schematic overview of the dual regulatory mechanisms by which SIK2 promotes HRR and chemotherapy resistance in ovarian cancer. SIK2 drives HRR proficiency via two parallel axes: (1) direct phosphorylation of RAD50 at Ser635 to promote RAD50-mediated DSBs repair; (2) phosphorylation of class-IIa HDACs (HDAC4/5/7) to sustain MEF2D transcriptional activity and upregulate HRR-related gene expression. These pathways converge to repair chemotherapy-induced DSBs, preventing tumor cell apoptosis and driving chemoresistance.

Abbreviations: SIK2, Salt-inducible kinase 2; HRR, Homologous recombination repair; Ser635, Serine 635; DSBs, DNA double-strand breaks; HDACs, Histone deacetylases; MEF2D, Myocyte enhancer factor 2D.

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Enhancement of Invasion and Metastasis

Ovarian cancer exhibits a high propensity for intraperitoneal implantation metastasis, frequently involving multiple sites including the omentum, pelvic organs, and peritoneal surface.[36] The invasion and metastasis process of cancer cells relies on enhanced cell motility, a cyclical process driven by three key steps: actin polymerization, cell adhesion, and actomyosin contraction.[37] Non-muscle myosin II (NMII), the primary contractile motor protein in cells, plays a pivotal role in cell migration by synergistically generating contractile force with actin filaments.[38] Multiple studies have established a close association between SIK2 and the migratory capacity of ovarian cancer cells.[20,39] Mechanistically, SIK2 phosphorylates myosin light chain kinase (MYLK) at serine 343 (Ser343), which activates the contractile function of its downstream substrate, myosin light chain (MLC). This activation significantly enhances the motility and migratory capacity of ovarian cancer cells. In vivo experiments using orthotopic xenograft models in nude mice further substantiate this mechanism, demonstrating that SIK2 knockdown significantly inhibits intraperitoneal metastasis of ovarian cancer.[40] These findings underscore the key role of SIK2 in promoting ovarian cancer invasion and metastasis.

Patients with epithelial ovarian cancer (EOC) frequently develop peritoneal metastases, with a striking predilection for the omentum—the dominant clinical site of ovarian cancer spread, involved in approximately 80% of serous ovarian cancer cases.[41] This metastatic tropism is driven by the omentum's unique adipocyte-rich peritoneal structure, which secretes a panel of soluble factors to form a microenvironment that potently promotes tumor growth, invasion, and chemotherapy resistance.[42] Adipocytes promote ovarian cancer cell invasion and metastasis through multiple mechanisms, including the release of adipokines, regulation of metabolic reprogramming, and modification of the immune microenvironment.[41,43,44] Recent studies indicate that SIK2 is a key signaling molecule secreted by tumor-associated adipocytes. It promotes the proliferation and invasion of ovarian cancer cells by modulating lipid metabolic reprogramming and directs their metastasis to lipid-rich tissues such as the omentum.[26] Compared to primary tumors, SIK2 expression is significantly upregulated in adipocyte-rich metastatic foci. The metastasis-promoting mechanisms of SIK2 involve two primary aspects. First, SIK2 enhances the fatty acid oxidation capacity of cancer cells, facilitating the efficient utilization of adipocyte-derived free fatty acids as an energy source. Second, SIK2 directly activates the PI3K/AKT signaling pathway to promote cancer cell proliferation and survival. Together, these mechanisms collectively drive the colonization and progression of ovarian cancer within lipid-rich niches.[7,45]

Collectively, this synthesis distinguishes complementary in vitro and in vivo findings of SIK2-driven ovarian cancer metastasis: in vitro motility assays delineate the cell-intrinsic mechanism by which SIK2 phosphorylates MYLK to enhance actomyosin contractility and cancer cell motility,[40] while in vivo omental metastasis models and clinical specimen analyses provide the most robust evidence. The highest-confidence, clinically relevant findings include: (1) SIK2 is significantly upregulated in patient omental metastatic foci compared to matched primary tumors;[7,26] (2) SIK2 knockdown potently suppresses intraperitoneal and omental metastasis in vivo;[40] and (3) SIK2 mediates metastatic niche adaptation via dual regulation of cell motility and adipocyte fatty acid oxidation,[7,45] a process unique to the in vivo peritoneal microenvironment. These findings represent the most robust evidence for SIK2 as a therapeutic target for metastatic ovarian cancer.

Role in Chemotherapy Resistance

The prognosis of patients with ovarian cancer is largely determined by their sensitivity to first-line chemotherapy, which primarily consists of platinum-based and taxane-based drugs. Although approximately 70% of patients exhibit an initial response to platinum-based agents, only about 40% achieve an objective response to taxane therapy.[46] Moreover, approximately 80% of patients experience disease recurrence within 6 months after completing primary treatment, with the majority developing platinum-resistant disease.[47,48] Studies have established SIK2 as a key regulator of taxane resistance in ovarian cancer, where it promotes the acquisition of a drug-resistant phenotype through the modulation of multiple signaling pathways. High SIK2 expression is significantly correlated with poor chemotherapy response and early disease recurrence, underscoring its critical role in ovarian cancer drug resistance.

Circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) are well-established key regulators of chemotherapy resistance in ovarian cancer, acting primarily through competing endogenous RNA (ceRNA) networks to modulate the expression of oncogenic drivers.[49,50] In the context of taxane resistance, two non-coding RNA axes converge on SIK2 as their critical downstream effector.

The first well-characterized pathway is the circ_CELSR1/miR-149-5p/SIK2 axis. circ_CELSR1 is significantly overexpressed in taxane-resistant ovarian cancer tissues and cell lines, where it functions as a molecular sponge for miR-149-5p. This sequestration relieves the translational repression of SIK2, ultimately driving the acquisition and maintenance of the taxane-resistant phenotype.[51,52]

A second parallel, functionally conserved pathway is the lncRNA UCA1/miR-654-5p/SIK2 axis. lncRNA UCA1 is markedly upregulated in both taxane-resistant ovarian cancer cells and matched clinical specimens.[53] Consistent with the ceRNA regulatory paradigm, UCA1 sequesters miR-654-5p to abrogate its inhibitory effect on SIK2, with increased SIK2 expression consequently promoting taxane resistance and malignant progression.[54,55]

Collectively, these non-coding RNA regulatory axes primarily modulate SIK2 mRNA and protein expression at the post-transcriptional level, with no reported evidence to date that these pathways directly modify or regulate the intrinsic kinase activity of SIK2. Both axes share a conserved ceRNA mechanism: they sequester target microRNAs to block miRNA-mediated degradation or translational repression of SIK2 mRNA, resulting in increased SIK2 protein expression to drive taxane resistance. This convergent regulation establishes SIK2 as a central, non-redundant downstream effector of multiple non-coding RNA-mediated chemoresistance pathways, further validating its potential as a therapeutic target to reverse taxane resistance.

SIK2-Targeted Therapeutic Strategies for Ovarian Cancer

The preceding synthesis of SIK2's multi-dimensional oncogenic functions in ovarian cancer establishes a direct, mechanism-driven rationale for targeted therapeutic development, with each core oncogenic axis of SIK2 corresponding to a well-defined, unmet clinical opportunity for targeted inhibition. First and most clinically impactful, SIK2-mediated regulation of the HRR pathway directly supports the combination of SIK2 inhibitors with PARP inhibitors, a strategy designed to overcome both primary and acquired PARP inhibitor resistance in ovarian cancer.[15,35] Furthermore, SIK2's well-characterized role in spindle assembly and cell cycle progression underpins the robust synergism between SIK2 inhibitors and taxane chemotherapy, addressing the widespread clinical challenge of acquired taxane resistance in recurrent disease.[52,55] In addition, SIK2's regulatory control over adipocyte fatty acid oxidation in the omental metastatic niche identifies it as a high-priority target for suppressing peritoneal metastasis, the dominant pattern of ovarian cancer dissemination and a major driver of disease-related mortality.[26,56] Finally, the well-documented off-target toxicity and limited therapeutic window of first-generation pan-SIK inhibitors provide a clear biological imperative for the development of SIK2-selective agents and localized drug delivery systems.[57]

Based on this mechanistic framework and direct alignment with the core unmet clinical needs in ovarian cancer outlined above, all SIK2-targeted therapeutics and enabling technologies currently in development can be systematically stratified into four distinct translational tiers, organized by their core positioning, clinical readiness, and ability to resolve these clinical challenges. At the foundation of this development landscape sit HG-9-91-01 and its derivatives, classified as foundational research tools and lead compounds: this class of agents serves as the classical, widely used tool for SIK2 functional validation in ovarian cancer, and provides the core molecular scaffold for the future development of next-generation SIK2-selective agents.[58] Moving from foundational tools to near-term clinical translation, the near-term translational candidate tier is led by ARN-3261, an agent with completed comprehensive preclinical validation and ongoing Phase I clinical trial enrollment, prioritized for its ability to reverse chemotherapy resistance in recurrent ovarian cancer.[59] Building on this clinical foundation, the mechanism-validated preclinical candidate tier includes MRIA9 and SIC-19, two agents with optimized target selectivity or novel mechanisms of action, specifically designed to overcome PARP inhibitor resistance and minimize the off-target toxicity associated with earlier-generation inhibitors.[17] Finally, the enabling delivery technology tier is represented by Gel Nap-S+HG, a localized drug delivery system engineered to mitigate the systemic toxicity of earlier-generation SIK inhibitors, with particular clinical utility for suppressing

peritoneal metastasis.[57] Below is a systematic synthesis of each tier, aligned with their ability to resolve the core clinical challenges outlined above.

The Multi-Kinase Inhibitor HG-9-91-01 and Its Derivatives

HG-9-91-01 was initially designed as a broad-spectrum pan-SIK family inhibitor, with a primary translational direction of serving as a lead compound for the development of SIK2-selective agents, rather than a standalone clinical candidate for ovarian cancer monotherapy. Subsequent studies revealed that it also targets receptor-interacting protein kinase 3 (RIPK3), indicating its potential applicability for treating inflammatory and autoimmune diseases.[58,60,61] The original study on HG-9-91-01 did not report a half-maximal inhibitory concentration (IC_{50}) for SIK2 inhibition. However, it did demonstrate that 5 μM of the compound inhibited SIK2 kinase activity by 90% in vitro, with only weak effects on other AMPK family members, including AMPKα and SIK1. This profile indicates favorable subtype selectivity. Furthermore, HG-9-91-01 exhibited significant antitumor efficacy in ovarian cancer models. Treatment of SKOV3 cells with 5 μM HG-9-91-01 for 72 hours reduced cell viability to 45.2% and increased the apoptosis rate to 32%. Under the same conditions, the colony-forming capacity of OVCAR8 cells was reduced by 58%.[62]

Despite its preclinical efficacy and utility as a tool compound, HG-9-91-01 exhibits substantial off-target activity against a broad panel of unrelated kinases outside the AMPK family, including SRC, BTK, and FGFR1, as confirmed in large-scale kinase selectivity screens.[63] This broad off-target activity, combined with its non-selective pan-SIK inhibition, directly limits its clinical translational potential via three core mechanisms: (1) it introduces a high risk of dose-limiting systemic toxicity that narrows the therapeutic window; (2) it prevents definitive attribution of in vivo antitumor efficacy to SIK2-specific inhibition, complicating mechanistic interpretation and predictive biomarker development; (3) concurrent inhibition of the well-documented tumor-suppressive SIK1 may counteract the anti-tumor effects of SIK2 targeting.[8]

Using HG-9-91-01 as a lead compound, researchers developed YKL-05-099, a structurally optimized analog with enhanced potency for SIK family members and improved pharmacokinetic properties.[64] At well-tolerated doses, YKL-05-099 (biochemical IC_{50} = 40 ± 25 nM for SIK2, ~10 nM for SIK1, and ~30 nM for SIK3) maintains a serum concentration above its IC_{50} for SIK2 inhibition for over 16 hours and effectively suppresses the phosphorylation of established SIK substrates in vivo.[62] Further structural optimization yielded two additional derivatives, YKL-06-061 and YKL-06-062. Engineered with adjusted lipophilicity and molecular size, these analogs are better suited for local administration and for investigating other SIK-related pathologies.[65] Notably, these optimized derivatives retain non-selective pan-SIK inhibition and broad off-target kinase activity, and have not yet achieved SIK2 subtype selectivity to date, and no in vitro or in vivo studies have been conducted to validate their antitumor efficacy in ovarian cancer models as of the latest research progress.[64]

Collectively, while this compound class remains at the preclinical stage and is not suitable for direct clinical development in ovarian cancer due to the above limitations, its well-characterized scaffold and optimization potential offer a valuable foundation for the future development of next-generation SIK2-selective inhibitors.

ARN Series ATP-Competitive Inhibitors (ARN-3236 and ARN-3261)

The ARN series represents the first class of ATP-competitive small-molecule inhibitors targeting SIK2, developed by the research team at The University of Texas MD Anderson Cancer Center, with a primary therapeutic direction of reversing taxane and platinum chemotherapy resistance in recurrent ovarian cancer. Among them, ARN-3236 serves as the prototypical compound, whereas ARN-3261 is a structurally optimized derivative. Both inhibitors competitively bind to the ATP-binding pocket of SIK2, blocking phosphate transfer and thereby inhibiting the phosphorylation of downstream substrates. Of note, ARN-3261 has advanced to a first-in-human Phase I clinical trial, with ovarian cancer patients as the lead target population in the trial design, as formally reported in its preclinical development studies.[59]

Since the US FDA approved paclitaxel for advanced ovarian cancer in 1984, taxanes have become a cornerstone of ovarian cancer chemotherapy, primarily targeting microtubules;[66] the combination of paclitaxel and carboplatin remains the standard first-line chemotherapy for EOC, with ongoing research into its mechanism and clinical applications.[67] Against this clinical background, ARN series inhibitors have been developed to overcome chemoresistance and synergize with standard-of-care regimens. In vitro, ARN-3236 inhibited the proliferation of 10 ovarian cancer cell lines, with IC_{50}

values ranging from 0.8 to 2.6 μM; notably, these IC_{50} values correlated inversely with endogenous SIK2 expression levels.[31] ARN-3236 significantly enhanced sensitivity to paclitaxel in 80% of the ovarian cancer cell lines tested, with a synergistic interaction observed in at least three cell lines (SKOV3, OC316, and OVCAR8) as reported in the original study.[31] Both in vitro and in vivo experiments confirmed that the combination of ARN-3236 and paclitaxel exerted significantly superior tumor-suppressive effects compared to either agent alone.[31]

As an optimized derivative of ARN-3236, ARN-3261 circumvents P-glycoprotein-mediated drug efflux (a key mechanism of chemotherapy multidrug resistance), and exhibits improved absorption, distribution, metabolism, and excretion (ADME) properties as well as superior pharmacokinetic/pharmacodynamic (PK/PD) profiles. ARN-3261 has entered Phase I clinical trials, and inhibits the proliferation of eight ovarian cancer cell lines with IC_{50} values ranging from 0.8 to 3.5 μM.[59] In combination studies, ARN-3261 significantly sensitized 7 out of 8 ovarian cancer cell lines to carboplatin, with synergistic effects observed particularly in IGROV1, OC316, OVCAR8, and SKOV3 cells (combination index CI < 1). Notably, ARN-3261 retained sensitizing activity even in the carboplatin-resistant A2780-CP20 cell line, where ARN-3261 alone exhibited an IC_{50} of 2.4 μM (compared with 0.6 μM in the carboplatin-sensitive A2780-PAR cell line) and maintained synergistic interaction with carboplatin (CI < 1). Animal studies further validated the efficacy of this combination strategy: in an OVCAR8 intraperitoneal xenograft model, tumor weight was significantly lower in the ARN-3261 plus carboplatin group than in the carboplatin monotherapy group; in a SKOV3 subcutaneous xenograft model, both dual-drug (ARN-3261 with carboplatin or paclitaxel) and triple-drug (ARN-3261 + carboplatin + paclitaxel) regimens demonstrated superior tumor-suppressive effects.[59]

Beyond synergizing with standard chemotherapy, ARN series inhibitors also exhibit robust synthetic lethality in combination with PARP inhibitors, another core therapeutic modality for ovarian cancer. Several PARP inhibitors have been approved for treating homologous recombination deficiency (HRD)-positive ovarian cancer.[68,69] Preclinical studies have demonstrated that both ARN-3236 and ARN-3261 significantly sensitize ovarian cancer cells to the PARP inhibitor olaparib, with synergistic effects (CI < 1) observed across all 10 cell lines tested.[35] This synergistic effect extends to other PARP inhibitors (eg, rucaparib, niraparib, talazoparib), with no synergistic cytotoxicity detected in non-malignant ovarian epithelial cells at the tested concentrations.[35] In SKOV3 subcutaneous xenograft models, the combination of ARN compounds with olaparib resulted in significantly superior tumor suppression compared to either monotherapy; in the OC316 model, combination therapy significantly prolonged mouse survival, with tumor regression observed in 2 out of 10 tumor-bearing mice.[35]

In summary, ARN series inhibitors exert synergistic antitumor effects with paclitaxel, carboplatin, and PARP inhibitors, demonstrating efficacy in both chemotherapy-sensitive and -resistant contexts. The clinical translation of this inhibitor family offers a promising avenue for improving ovarian cancer outcomes and overcoming drug resistance. However, their full clinical potential and companion predictive biomarkers require further validation in prospective clinical trials.

The ATP-Competitive Inhibitor MRIA9

MRIA9 is a pyrido[2,3-d]pyrimidin-7-one-based pan-SIK ATP-competitive small-molecule inhibitor, developed via structure-based rational design with a primary translational direction of minimizing the broad off-target kinase activity associated with earlier-generation pan-SIK inhibitors, while retaining validated anti-tumor efficacy in ovarian cancer models via disrupting mitotic progression and PI3K-AKT signaling.[17,70] The antitumor mechanisms of MRIA9 in ovarian cancer are primarily attributed to its pan-SIK inhibitory activity: it interferes with SIK2-mediated centrosome function, disrupts mitotic spindle assembly and genomic stability, and downregulates the PI3K-AKT pathway, collectively impeding mitotic progression and inducing apoptotic cell death in ovarian cancer cells.[17] Cellular target engagement NanoBRET assays quantified the potency of MRIA9 against SIK family members, with a cellular IC_{50} of 180 ± 40 nM for SIK2, 516 ± 5 nM for SIK1, and 127 ± 23 nM for SIK3, confirming equipotent pan-SIK family activity with no SIK2 isoform selectivity.[70] In SKOV3 ovarian cancer cells, the combination of paclitaxel and MRIA9 significantly suppressed long-term cell proliferation in colony formation assays, enhanced growth inhibition in 3D spheroid models, and markedly increased apoptotic cell death compared with paclitaxel monotherapy, validating its chemosensitizing efficacy consistent with prior genetic knockdown studies of SIK2.[17,70]

The core advantage of MRIA9 over earlier-generation SIK inhibitors lies in its exceptional kinome-wide selectivity, rather than SIK2 isoform specificity. Earlier pan-SIK inhibitors exhibit broad off-target activity against unrelated kinases: HG-9-91-01 displays potent inhibition of SRC, BTK, and FGFR1 in addition to the SIK family;[63] YKL-05-099 non-specifically inhibits over 60 kinases at a concentration of 1 μM;[62] and ARN-3236 exhibits significant off-target activity against JAK2, LCK, and VEGFR2 despite limited selectivity profiling against 74 kinases.[71] In contrast, in a large-scale radiometric screen encompassing 443 human kinases at 1 μM concentration, MRIA9 displayed meaningful inhibitory activity only against SIK1–3 and PAK1–3, with no significant inhibition of other unrelated kinases. This markedly restricted off-target kinase profile substantially reduces the risk of dose-limiting systemic toxicity associated with earlier-generation non-selective SIK inhibitors, representing a key advancement for its preclinical development.[70]

SIC-19: A Ubiquitination-Mediated SIK2 Degrader

SIC-19 represents a novel degrader-based class of SIK2 inhibitor that operates through a mechanism distinct from traditional ATP-competitive inhibitors like ARN-3236. Rather than merely inhibiting kinase activity, SIC-19 directly induces the degradation of the SIK2 protein via the ubiquitin-proteasome pathway, thereby ablating its biological functions. Its primary therapeutic direction is to induce durable functional HRD in HRP ovarian cancer, thereby overcoming primary PARP inhibitor resistance. Notably, it is the first agent reported to achieve complete SIK2 degradation.[16] SIC-19 exhibits antiproliferative activity across a panel of solid tumor cells, including models of ovarian cancer, triple-negative breast cancer, and pancreatic cancer. In ovarian cancer cell lines specifically, it inhibits proliferation with IC_{50} values ranging from 2.13 to 9.74 μM, and its potency (IC_{50}) shows an inverse correlation with endogenous SIK2 expression levels, underscoring the target-dependent nature of its effect.[16,72]

The breast cancer susceptibility gene (BRCA) proteins are essential for high-fidelity repair of DSBs through HRR. Consequently, loss-of-function mutations in BRCA1 or BRCA2 result in HRD, which confers sensitivity to PARP inhibitors.[73] PARP inhibitors trap the PARP enzyme on DNA, impeding the repair of single-strand breaks (SSBs). These unrepaired SSBs are converted into DSBs during replication. In HRD cells, which lack proficient HRR, this accumulation of DSBs leads to "synthetic lethality". In contrast, homologous recombination-proficient (HRP) cells can repair these lesions, thus remaining insensitive to PARP inhibition.[74,75]

By disrupting the SIK2-RAD50-nuclear filament axis, SIC-19 impairs SIK2-mediated HRR and compromises high-fidelity DSBs repair. This effect effectively induces a state of "functional" HRD in otherwise HRP ovarian cancer cells, thereby sensitizing HRP cells—which are normally resistant—to PARP inhibitors. The clinical importance of this synthetic lethal strategy is underscored by the long-term success of PARP inhibitors in BRCA-mutated ovarian cancer: the SOLO1 trial demonstrated that 2 years of maintenance olaparib led to a 45% reduction in the risk of death (Hazard Ratio 0.55) and a 7-year survival rate of 67.0%.[15] Extending such benefits to HRP patients through SIK2 inhibition represents a major therapeutic opportunity. The combination of SIC-19 and a PARP inhibitor synergistically enhances DNA damage accumulation, ultimately triggering apoptotic cell death. In vitro experiments demonstrated that the IC_{50} values for the combination of SIC-19 with either olaparib or niraparib were significantly lower than for any single agent alone in SKOV3, OVCAR8, and A2780 cells (combination index CI < 1, indicating synergistic effects). Flow cytometry confirmed that the combination regimens induced the highest levels of apoptosis, with rates increasing approximately 2-3-fold compared with single-agent treatment, most notably in SKOV3 cells. In vivo studies using SKOV3 and OVCAR8 xenograft models corroborated these findings: the SIC-19 and olaparib combination significantly inhibited tumor growth, extended median survival, and was well-tolerated with no significant toxicity observed.[16] Immunohistochemical (IHC) analysis of tumor tissues revealed that the combination treatment group exhibited the most intense γH2AX staining (indicating DNA damage) concurrent with the weakest Ki67 signal (indicating proliferation), consistent with the proposed mechanism.[72] Currently, SIC-19 remains in the preclinical evaluation stage. Future work should focus on optimizing its druggability, conducting thorough toxicity assessments, and systematically evaluating its clinical translation potential.

A SIK2-Responsive Supramolecular Hydrogel for Localized Drug Delivery (Gel Nap-S+HG)

As emerging biomaterials for drug delivery, hydrogels enable localized administration that enhances drug concentration at the target site, improves the stability of therapeutic molecules, and minimizes systemic toxicities and off-target accumulation in organs such as the liver and kidneys.[76] To overcome the challenges of low bioavailability and pronounced off-target toxicity associated with HG-9-91-01, a SIK2-responsive supramolecular hydrogel delivery system, termed Gel Nap-S+HG, was developed. This system facilitates the localized and sustained release of HG-9-91-01 at the tumor site, a strategy anticipated to enhance therapeutic efficacy while minimizing systemic exposure and toxicity.

In vitro release studies demonstrated that Gel Nap-S+HG achieved a cumulative release of 42.5% for HG-9-91-01 over 64 hours in SKOV3-SIK2 cells, exhibiting a stable release profile and confirming its favorable sustained-release characteristics. Pharmacodynamic assessment revealed that the hydrogel system induced significantly greater inhibition of proliferation and induction of apoptosis in SKOV3-SIK2 cells compared to the free drug. It also markedly suppressed cell migration and invasion. In a Balb/c nude mouse model of ovarian cancer peritoneal metastasis, treatment with Gel Nap-S+HG elicited significant antitumor effects, characterized by reduced tumor burden, fewer intraperitoneal metastatic nodules, and diminished ascites volume. Safety evaluation indicated no significant hydrogel-induced pathological damage to vital organs (heart, liver, spleen, lungs, kidneys). Furthermore, animal body weight fluctuations remained within 5%, collectively indicating favorable biocompatibility and in vivo safety.[57]

Targeted drug delivery systems, which enable precise drug localization to tumors, offer a promising solution to the limitations of current adjuvant chemotherapy for ovarian cancer, including poor targeting, suboptimal efficacy, and systemic toxicity. As such, they have emerged as a pivotal strategy for enhancing treatment efficacy and safety.[77] Future development of delivery systems for SIK2 inhibitors should explore diverse platforms—such as drug-carrier conjugates, nanoparticle encapsulation, and intelligent hydrogels—to achieve more precise, efficient, and safe therapeutic outcomes in ovarian cancer. The core characteristics of all the aforementioned SIK2-targeted therapeutic strategies, encompassing both small-molecule inhibitors and delivery systems, are summarized in Table 1.

Table 1 SIK2-Targeted Therapeutic Strategies in Ovarian Cancer: Clinical Development and Synergistic Efficacy

Agent Name	Agent Class	Selectivity Profile	Key in vivo Ovarian Cancer Models	Clinical Trial Identifier & Development Status	Synergy & Key Preclinical Findings	References
HG-9-91-01 and derivatives	Pan-SIK ATP-competitive inhibitor	Pan-SIK inhibitor; no direct biochemical IC_{50} for SIK2 reported, with 90% SIK2 inhibitory activity observed at 5 μM in vitro; off-target activity against SRC, BTK, FGFR1 and other unrelated kinases	No validated in vivo ovarian cancer models for HG-9-91-01 derivatives; only in vitro cell line assays reported for the parent compound HG-9-91-01	Preclinical development, no trial initiated	Exhibits anti-proliferative activity in ovarian cancer cell lines via SIK2 inhibition; no in vivo antitumor efficacy or synergistic data in ovarian cancer models reported for its derivatives	[63,64]
ARN-3236	SIK2-selective ATP-competitive inhibitor	SIK2-selective (IC_{50}: 20 nM for SIK2, >100-fold selectivity over SIK1/3)	Ovarian cancer subcutaneous CDX model (athymic nude mice); intraperitoneal metastasis model	Preclinical development, no trial initiated	Synergizes with paclitaxel/carboplatin, reverses chemotherapy resistance; suppresses intraperitoneal metastasis	[31,35]

(*Continued*)

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Table 1 (Continued).

Agent Name	Agent Class	Selectivity Profile	Key in vivo Ovarian Cancer Models	Clinical Trial Identifier & Development Status	Synergy & Key Preclinical Findings	References
ARN-3261	SIK2-selective ATP-competitive inhibitor	SIK2-selective (IC_{50}: <50 nM for SIK2, >50-fold selectivity over SIK1/3)	Subcutaneous/ intraperitoneal CDX models (athymic nude mice); carboplatin-resistant xenograft model	Ongoing Phase I clinical trial (details not yet publicly disclosed)	Circumvents P-glycoprotein-mediated drug efflux; sensitizes 7/8 ovarian cancer cell lines to carboplatin, retains activity in platinum-resistant models	[35,59]
MRIA9	Pan-SIK ATP-competitive inhibitor with optimized kinome-wide selectivity	Pan-SIK activity (cellular IC_{50}: 180 nM for SIK2, 516 nM for SIK1, 127 nM for SIK3); no SIK2 isoform selectivity; exceptional kinome-wide selectivity with inhibitory activity restricted to SIK1-3 and PAK1-3 at 1 μM	No in vivo ovarian cancer CDX/PDX model data reported; only in vitro 3D spheroid model (SKOV3) validation	Preclinical development, no trial initiated	Sensitizes ovarian cancer cells to paclitaxel via disrupting mitotic spindle assembly; inhibits PI3K-AKT signaling to suppress ovarian cancer cell proliferation; minimal off-target kinase activity reduces systemic toxicity risk	[17,70]
SIC-19	First-in-class selective SIK2 protein degrader	Selective SIK2 degradation (DC_{50}: ~0.5 μM for SIK2; no significant SIK1/3 degradation at working concentrations)	Subcutaneous/ intraperitoneal CDX models (athymic nude mice); PARP inhibitor-resistant xenograft model	Preclinical development, no trial initiated	Induces durable functional HRD in HRP ovarian cancer; synergizes with olaparib/niraparib to overcome PARP inhibitor resistance	[16]
Gel Nap-S +HG	Localized hydrogel delivery system (HG-9-91-01 loaded)	Retains the selectivity profile of parent compound HG-9-91-01	Ovarian cancer intraperitoneal dissemination model (athymic nude mice)	Preclinical development, no trial initiated	Local sustained drug release; suppresses peritoneal tumor growth with minimal systemic toxicity	[57]

Abbreviations: SIK, Salt-inducible kinase; IC_{50}, half-maximal inhibitory concentration; CDX, Cell Line-Derived Xenograft; PDX, Patient-derived xenograft; PI3K, phosphoinositide 3-kinase; DC_{50}, half-maximal degradation concentration; PARP, Poly (ADP-ribose) polymerase; HRD, Homologous recombination deficiency; HRP, Homologous recombination-proficient.

Conclusions

Ovarian cancer remains one of the most lethal gynecological malignancies worldwide, limited by high rates of recurrence, widespread acquired chemoresistance, and a lack of effective targeted options for patients with HRP disease. Against this unmet clinical backdrop, this systematic review synthesizes over 15 years of peer-reviewed research on SIK2 in ovarian cancer, establishing a robust, evidence-based framework for its multifaceted oncogenic functions and translational therapeutic potential. SIK2 is a validated, multi-functional oncogenic driver in ovarian cancer, with consistent overexpression documented in patient tumor specimens and a causal role in five core hallmark processes of disease progression: metabolic reprogramming, cell cycle dysregulation, HRR proficiency, metastatic dissemination, and chemotherapy resistance. Of these oncogenic roles, its direct regulatory control over the HRR pathway carries the greatest clinical weight, as it serves as the core mechanism driving SIK2-mediated resistance to both platinum-based

chemotherapy and PARP inhibitors. In line with this well-validated mechanistic rationale, targeted inhibition of SIK2 emerges as a biologically grounded strategy to address two of the most intractable unmet clinical needs in ovarian cancer: reversing acquired platinum and taxane chemotherapy resistance, and extending the well-documented survival benefits of PARP inhibitors to patients with HRP disease. The translational potential of this strategy is supported by a growing pipeline of investigational agents with promising preclinical and early clinical activity: the near-term translational candidate ARN-3261, which has completed comprehensive preclinical validation and advanced to an ongoing Phase I clinical trial, has consistently demonstrated robust chemosensitizing activity across a panel of ovarian cancer models, while the first-in-class SIK2-selective protein degrader SIC-19 achieves complete, sustained ablation of SIK2 protein—rather than the transient, reversible kinase inhibition of ATP-competitive agents—to induce durable functional HRD and superior synergism with PARP inhibitors in HRP ovarian cancer models. Further, the collective body of literature confirms that targeted modulation of SIK2, with minimization of off-target kinase activity and careful consideration of SIK1/3 activity, is critical to maximizing therapeutic efficacy: this is driven by the well-documented tumor-suppressive function of SIK1, as well as the poorly characterized, context-dependent role of SIK3 in ovarian cancer, where non-selective pan-SIK inhibition may inadvertently counteract the anti-tumor effects of SIK2 targeting. Notably, the optimized kinome-wide selectivity of MRIA9, despite its pan-SIK activity, provides a valuable preclinical tool to deconvolute the roles of SIK family members in ovarian cancer, while minimizing the confounding effects of broad off-target kinase inhibition.

Despite these well-established consensus findings and promising preclinical advances with lead agents including ARN-3261 and SIC-19, several critical, unresolved hurdles stand in the way of successfully translating SIK2-targeted strategies into routine clinical care for ovarian cancer. The functional heterogeneity of SIK2 across ovarian cancer histological subtypes remains largely uncharacterized, as nearly all preclinical studies of SIK2 function and inhibitor efficacy have been conducted exclusively in high-grade serous ovarian carcinoma models, creating a critical gap in our understanding of its role in less common but clinically aggressive subtypes such as clear cell carcinoma. Compounding this challenge, there are currently no validated predictive biomarkers for patient stratification in SIK2-targeted therapy, with no consensus across the field regarding whether SIK2 expression level, HRD status, metastatic site, or other molecular features represent the optimal predictive marker—a barrier that will directly impact the design, interpretability, and ultimate success of future clinical trials. Additionally, the long-term toxicity profile of sustained SIK2 inhibition in humans remains largely unknown, as nearly all preclinical studies have only assessed short-term toxicity in immuno-compromised mouse models, with no robust data available on the impact of chronic SIK2 inhibition on normal tissue homeostasis or endogenous anti-tumor immune function.

Addressing these barriers will require targeted, prioritized research efforts closely aligned with the most pressing unmet clinical needs in ovarian cancer, and we define three high-priority directions to advance the field toward clinical translation. The highest immediate priority is to conduct head-to-head comparative studies of ATP-competitive SIK2 inhibitors (represented by ARN-3261) and SIK2 protein degraders (represented by SIC-19) in patient-derived xenograft (PDX) models of chemotherapy and PARP inhibitor-resistant ovarian cancer, to define the optimal therapeutic modality, dosing schedule, and combination partner for each clinical setting, providing rigorous, clinically relevant preclinical data to support downstream clinical trial design. Alongside this, there is an urgent need to validate predictive biomarkers for SIK2-targeted therapy in large, well-annotated clinical cohorts of ovarian cancer patients, to establish a standardized, evidence-based patient stratification system that enables precise, personalized application of these therapies. Finally, a key long-term priority is to evaluate the safety and efficacy of SIK2-selective inhibitors in combination with standard-of-care regimens in early-phase clinical trials, with a dedicated focus on ovarian cancer-specific patient enrollment, to accelerate the translation of preclinical findings into tangible clinical benefit for patients with this devastating disease.

In summary, SIK2 is a pivotal kinase driving multiple malignant processes in ovarian cancer, rendering it a target of substantial scientific and clinical relevance. As our understanding of its multifaceted oncogenic mechanisms deepens and drug discovery efforts advance, SIK2-targeted therapy is poised to become an integral component of the precision oncology paradigm for ovarian cancer, offering new, promising avenues for improving long-term patient outcomes.

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The authors report no conflicts of interest in this work.

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