

The Multifaceted Tumor Suppressor SASH1: From Molecular Scaffold to Clinical Biomarker and Therapeutic Target

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Abstract

SASH1 (SAM and SH3 domain-containing protein 1) is a tumor suppressor scaffold protein frequently downregulated in diverse cancers. Its loss, driven by epigenetic silencing, microRNAs, and altered protein interactions, promotes proliferation, epithelial–mesenchymal transition (EMT), invasion, and therapy resistance. Mechanistically, SASH1 integrates major oncogenic pathways, including PI3K/Akt/mTOR, TGF- β , Hippo/YAP, and CRKL/SRC signaling, while maintaining cell adhesion and cytoskeletal integrity. Clinically, reduced SASH1 expression is involved in advanced tumor stage, metastasis, and poor prognosis. Restoration of SASH1 expression, including pharmacological induction such as with chloropyramine, has shown anti-tumor effects in preclinical models and partial restoration of chemosensitivity, although evidence remains experimental. Overall, SASH1 represents a promising prognostic biomarker and potential therapeutic target that warrants further translational investigation.

Keywords: Cancer, SASH1, Tumor suppressor, Biomarker

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Introduction

Cancer progression is driven by the concerted dysregulation of core cellular circuits governing signal transduction, adhesive dynamics, and tissue architecture. Within this complex landscape, scaffold proteins have emerged as critical players due to their unique capacity to integrate disparate upstream cues and coordinate downstream cellular responses. SAM and SH3 domain-containing protein 1 (SASH1) exemplifies this class of regulatory molecules, having evolved from an initially identified differentially expressed gene to a multifaceted tumor suppressor and a central signaling hub in cancer pathology [1].

The initial discovery of SASH1 as a gene frequently silenced in epithelial malignancies hinted at its potential role in maintaining epithelial integrity [2]. Its modular architecture, featuring protein-interaction domains such as SH3 and SAM, prefigures a high capacity for forming dynamic protein-protein interaction networks [3, 4]. We now understand that this structural versatility underpins SASH1's ability to orchestrate seemingly discrete processes, including cytoskeletal organization, the stability of cell-cell and cell-matrix adhesions, and the modulation of key oncogenic signaling pathways [5, 6].

The role of SASH1 extends beyond that of a simple

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adhesion regulator. This protein operates at the nexus of several pivotal oncogenic pathways, including PI3K/Akt/mTOR, TGF- β , Hippo/YAP, and SRC-family kinase networks [7- 11]. In this capacity, SASH1 functions as a signal integrator, harmonizing the timing and amplitude of multiple pathway activations to determine the ultimate cellular output be it survival, migration, or differentiation. This strategic positioning establishes SASH1 as a guardian of tissue homeostasis, restraining epithelial-mesenchymal transition (EMT), invasion, and metastasis [11, 12].

The silencing or downregulation of SASH1 is a consistent finding across a broad spectrum of cancers and is frequently correlated with disease progression and poor patient prognosis. Notably, this loss of expression is seldom due to coding sequence mutations but is primarily enforced through dynamic epigenetic mechanisms, including promoter hypermethylation, regulation by oncogenic microRNAs and circular RNAs, and even intercellular communication via tumor-derived exosomes [13, 14]. These multi-layered regulatory controls underscore the critical importance of suppressing SASH1 for cancer cell fitness and highlight its emerging value as a biomarker.

Given these multifaceted roles, key questions come into focus: What are the precise protein interaction networks that position SASH1 as a central regulator? How are context-specific epigenetic mechanisms deployed to silence SASH1 expression in different tumor types? Most importantly, can the restoration of SASH1 function through genetic or pharmacologic means simultaneously dismantle multiple oncogenic programs and re-sensitize tumors to conventional therapies?

This comprehensive review synthesizes evidence from basic to clinical studies to solidify the position of SASH1 not only as a crucial tumor suppressor but also as a strategic therapeutic target and a promising prognostic biomarker across malignancies. By focusing on the integrative logic of SASH1 function and the translational potential of its restoration, we aim to chart a course for the development of novel therapeutic strategies in oncology.

Structure, Biology, and Fundamental Functions of SASH1

SASH1 is a multi-domain scaffold protein that integrates diverse cellular signals to regulate fundamental processes including cell adhesion, cytoskeletal organization, migration, and cell cycle progression [5, 6]. Its functional versatility stems from a modular domain architecture that facilitates specific protein-protein interactions [1], positioning SASH1 at critical nodal points within intracellular networks [3, 11].

Domain Architecture and Molecular Features

SASH1 is a member of the SH3 domain-containing expressed in lymphocytes (SLy) family of signal adapter proteins. It was first identified in 2003 as a candidate tumor suppressor gene located on chromosome 6q24.3 [1]. The human SASH1 gene spans approximately 201 kb, consists of 20 exons, and undergoes alternative splicing to generate distinct transcript isoforms [1, 4].

The SASH1 protein comprises 1247 amino acids,

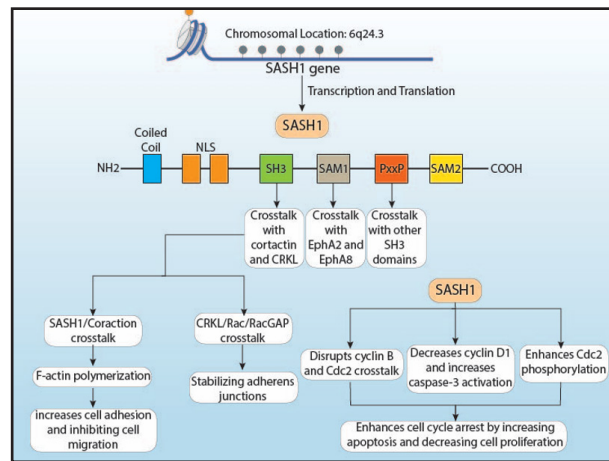


Figure 1. Chromosomal Location, Domains and Molecular Crosstalk of SASH1 in Cell Adhesion, Migration, and Cell Cycle Regulation.

making it the largest member of its family, and its primary structure includes several conserved functional motifs that confer its properties as a multifunctional scaffold (Figure 1) [1, 4]. Central to its architecture are two Src homology 3 (SH3) domains, which mediate critical protein-protein interactions by binding to proline-rich sequences in partner proteins such as cortactin and CRKL [11]. Flanking these are two Sterile alpha motif (SAM) domains. The N-terminal SAM1 domain (approximately amino acids 615-694) plays a particularly pivotal role by mediating heterotypic oligomerization with the SAM domains of Eph receptor tyrosine kinases, such as EphA2 [15] and EphA8 [3].

The protein also features extended N- and C-terminal regions containing a predicted coiled-coil motif, proline-rich regions that serve as docking sites for other SH3-domain containing proteins, and a second SAM domain in its C-terminal part [1, 5]. Furthermore, SASH1 possesses two bipartite nuclear localization signals (NLS1: aa 259-275; NLS2: aa 452-468) within its N-terminus [11]. These signals become functionally exposed following caspase-3-mediated cleavage during apoptosis, enabling the nuclear translocation of the C-terminal fragment of SASH1 and linking its function to cell death pathways [16].

This modular, multi-domain architecture equips SASH1 to function as a versatile signaling platform. It is capable of integrating and coordinating diverse inputs from cell adhesion receptors, growth factor pathways (such as those involving Eph receptors), and cellular stress-response mechanisms (including apoptotic signaling). This integrative capacity ultimately allows SASH1 to influence critical cell fate decisions, such as survival, migration, and death, in a highly context-dependent manner.

In addition to caspase-3-mediated cleavage, SASH1 regulation may involve alternative splicing and post-transcriptional and post-translational mechanisms, although these aspects remain incompletely characterized. The SASH1 gene gives rise to multiple transcript variants; however, the functional relevance of these

isoforms in cancer biology has not been established. Recent evidence suggests that SASH1 may participate in phosphorylation-dependent signaling within Hippo-related regulatory networks. In particular, a MAP4K4–LATS2–SASH1–YAP1 signaling cascade has been described in breast cancer, linking SASH1 to Hippo pathway activity and YAP1 regulation. However, the precise molecular mechanisms and whether SASH1 is a direct phosphorylation substrate of Hippo kinases remain to be fully elucidated [9, 10]. In contrast, limited information is available regarding additional post-translational modifications of SASH1, such as ubiquitination and proteasomal degradation, and their contribution to protein stability or signaling function. These gaps highlight important areas for future investigation into SASH1 regulation in cancer [16].

Role of SASH1 in Cell Adhesion and Cytoskeletal Dynamics

SASH1 plays a central role in maintaining epithelial architecture through regulation of both cell–matrix and cell–cell adhesion. Endogenous SASH1 localizes to the nucleus and cytoplasm, with prominent enrichment at dynamic, actin-rich membrane protrusions such as lamellipodia and membrane ruffles. Through direct interaction with cortactin a key regulator of actin nucleation and branching SASH1 enhances F-actin polymerization and stabilizes nascent adhesions. Experimentally, SASH1 overexpression increases cell adhesion to extracellular matrix components (fibronectin, laminin) while inhibiting random cell migration; conversely, SASH1 knockdown reduces adhesion and promotes a migratory phenotype [5].

Beyond peripheral adhesions, SASH1 forms a functional complex with IQGAP1 and E-cadherin at adherens junctions (AJs). This SASH1–IQGAP1–E-cadherin module is critical for stabilizing epithelial integrity. In breast cancer tissues, low levels of both SASH1 and IQGAP1 correlate with reduced E-cadherin expression and enhanced metastatic potential [17]. SASH1 contributes to AJ stability by scaffolding a regulatory complex containing CRKL, Rac, and RacGAP at cell–cell boundaries, thereby negatively regulating Rac activity. While transient Rac activation is necessary for initial AJ assembly, sustained Rac signaling disrupts junctional integrity. Thus, SASH1 acts as a molecular rheostat to balance Rac activity and maintain stable epithelial adhesion [6].

SASH1 in Neurodevelopment and Glial Cell Migration

Beyond its well-established role in epithelial biology and cancer, SASH1 performs critical functions in nervous system development. SASH1 is highly expressed in the mammalian central nervous system, particularly in glial cells, and shows conserved expression during zebrafish embryogenesis. Functional studies in zebrafish reveal that SASH1 knockdown (via morpholino oligonucleotides or CRISPR/Cas9) causes brain malformations and disorganized migration of gfap⁺ glial cells, while leaving motor neuron axonal growth unaffected. These morphological defects correlate with abnormal behavioral

trajectories in SASH1 morphants. Importantly, human SASH1 mRNA rescues these phenotypes, confirming functional conservation across vertebrates [18]. This highlights SASH1's role in orchestrating glial cell positioning during embryonic brain development, a function distinct from but potentially related to its regulation of cytoskeletal dynamics in epithelial cells.

Regulation of Cell Cycle Progression

Emerging evidence positions SASH1 as a regulator of cell cycle checkpoints. In melanoma A-375 cells, SASH1 overexpression decreases cell viability primarily by inducing G2/M phase arrest, accompanied by accumulation of cells in S phase. Mechanistically, SASH1 disrupts cyclin B (CCNB1) and Cdc2 (CDK1) crosstalk and appears to enhance inhibitory phosphorylation of Cdc2 via the dual-specificity kinase Myt1. This modification may suppress Cdc2 catalytic activity or impede nuclear translocation of the cyclin B–Cdc2 complex, effectively blocking mitotic entry. Altered activity of Cdc25C phosphatase a positive regulator of Cdc2 may further contribute to G2/M arrest [19]. Similarly, in osteosarcoma MG-63 cells, SASH1 upregulation induces G0/G1 arrest, decreases cyclin D1 expression, and increases caspase-3 activation, collectively inhibiting proliferation and promoting apoptosis [20]. These findings across different cancer types suggest that SASH1 can modulate multiple cell cycle checkpoints depending on cellular context, adding another layer to its tumor-suppressive portfolio.

Regulation of SASH1 Expression and Epigenetic Control

Promoter Methylation of SASH1

Accumulating evidence suggests that epigenetic silencing through promoter methylation represents an important mechanism underlying SASH1 downregulation in cancer. Initial studies identified SASH1 as a candidate tumor suppressor gene and demonstrated its reduced expression in breast cancer tissues [1]. Subsequent investigations further showed that hypermethylation of the SASH1 promoter is associated with decreased gene expression in breast cancer, supporting the contribution of epigenetic regulation to tumor progression [21].

Regulation of SASH1 by microRNAs

miRNAs have emerged as crucial epigenetic regulators of gene expression, modulating various cellular processes including proliferation, apoptosis, migration, and invasion. Accumulating evidence indicates that several miRNAs exert their oncogenic or tumor-suppressive functions through direct regulation of the tumor suppressor gene SASH1 in diverse cancer types. Circ-ITCH, a circular RNA, has been reported to act as a tumor suppressor in glioma by sponging miR-106a-5p, thereby upregulating SASH1 expression. Functional studies demonstrated that circ-ITCH overexpression inhibited glioma cell proliferation and invasion both in vitro and in vivo, and rescue experiments confirmed that these effects were mediated through the miR-106a-5p/SASH1 axis, highlighting the critical role of this regulatory pathway

in glioma progression [13]. Similarly, in gastric cancer, exosomal miR-128-3p has been shown to promote angiogenesis by targeting SASH1 in endothelial cells. Serum exosomes from gastric cancer patients exhibited elevated levels of miR-128-3p, which facilitated endothelial cell proliferation, migration, and tube formation in vitro. Mechanistic studies confirmed that SASH1 is a direct target of miR-128-3p, suggesting that exosome-mediated transfer of this miRNA contributes to tumor angiogenesis and progression by suppressing SASH1 expression [14]. Endogenous miRNAs derived from transposable elements, such as HERV-H-derived miR-4454, have also been implicated in cancer regulation. Bioinformatic analyses and functional assays revealed that miR-4454 directly targets SASH1 and DNAJB4, two tumor suppressor genes, and promotes the progression of non-muscle invasive bladder cancer (NMIBC). Dual-luciferase reporter assays demonstrated a negative correlation between miR-4454 and these genes, supporting their direct regulation. These findings indicate that miRNAs originating from endogenous retroviral elements can influence cancer development by modulating SASH1 expression [22]. In osteosarcoma, both miR-17 and miR-128 act as oncogenic miRNAs by negatively regulating SASH1. miR-17 is upregulated in osteosarcoma cells and promotes proliferation, migration, and invasion while suppressing apoptosis through activation of the PI3K/AKT signaling pathway and downregulation of SASH1 [23]. Similarly, miR-128 is overexpressed in osteosarcoma tissues and cell lines, and its inhibition markedly reduces cell growth, induces apoptosis, and suppresses tumor growth in xenograft models. Mechanistic studies confirmed that SASH1 is a direct target of miR-128. Furthermore, miR-128 modulates apoptosis-related proteins, decreasing Bcl-2 levels while increasing Bax and caspase-3, highlighting its role in tumorigenesis and progression through the SASH1 pathway. Clinical data further demonstrated a correlation between elevated miR-128, reduced SASH1 expression, and aggressive osteosarcoma features, including tumor size, invasion depth, lymph node metastasis, and TNM stages [24]. Lastly, miR-130b has been reported as an oncogenic miRNA in esophageal squamous cell carcinoma (ESCC) by directly targeting SASH1. Overexpression of miR-130b promoted ESCC cell proliferation, aggressiveness, and tumor growth in vivo, whereas knockdown of miR-130b inhibited these processes. The direct interaction between miR-130b and the 3'UTR of SASH1 was confirmed, and functional assays demonstrated that the miR-130b/SASH1 axis plays a pivotal role in ESCC progression [25].

Multiple miRNAs have been shown to directly regulate SASH1 across different cancer types. These include miR-106a-5p, miR-128-3p, miR-4454, miR-17, and miR-130b. These miRNAs regulate SASH1 expression through direct targeting of its transcript. This regulation affects key cellular processes, including proliferation, apoptosis, migration, and invasion. miRNA-mediated regulation of SASH1 plays an important role in tumor progression and may serve as a potential therapeutic and biomarker target.

Protein Regulators of SASH1

SASH1 is a tumor suppressor that plays a pivotal role in apoptosis, cellular proliferation, and tumor suppression, and its activity is tightly regulated by multiple proteins and signaling pathways. Caspase-mediated cleavage is a key regulatory mechanism: upon apoptotic stimuli such as UVC or staurosporine, caspase-3 cleaves SASH1 between amino acids 230–231, producing a C-terminal fragment that translocates to the nucleus and promotes NF- κ B pro-apoptotic activity. The removal of the N-terminal PARP-related domain likely disrupts membrane interactions, allowing nuclear relocation. SASH1 also acts as a scaffold for TRAF6, TAK1, and IKK subunits, facilitating NF- κ B activation. In addition, SASH1 inhibits the PI3K/Akt pathway and modulates EMT, highlighting its role as a central decision-making node in cell fate. Downregulation of SASH1, observed in many cancers, is associated with resistance to DNA damage-induced apoptosis, suggesting therapeutic potential for NF- κ B-targeted strategies in SASH1-deficient tumors [16]. Exosome-mediated regulation provides an additional layer of control. Exosomes derived from normal astrocytes (AS-EXOs) and glioma C6 cells (C6-EXOs) carry distinct protein cargos. While total protein profiles are broadly similar, unique exosomal proteins differ: glioma exosomes are enriched in PI3K-Akt signaling and actin cytoskeleton regulation, linked to proliferation and migration, whereas astrocytic exosomes are enriched in RNA processing, lysosomal, and proteasomal pathways. Functionally, AS-EXOs increase SASH1 expression in glioma C6 cells, an effect dependent on exosomal HMGB1. Interestingly, HMGB1 exerts opposing effects depending on its localization: exosomal HMGB1 promotes SASH1 expression, while extracellular HMGB1 suppresses SASH1 and upregulates TLR4, indicating context-dependent regulation through TLR4-mediated signaling [26]. Further epigenetic regulation of SASH1 has been reported in lung adenocarcinoma (LUAD). HMGB1 interacts with SET and HAT1 to form the HMGB1/SET/HAT1 complex, which suppresses H3K9 and H3K27 acetylation, leading to SASH1 repression [27]. This epigenetic silencing enhances glycolysis and promotes metastasis. Clinically, LUAD patients with high HMGB1 and low SASH1 expression exhibit poor prognosis. These findings highlight that, beyond apoptotic and exosomal mechanisms, SASH1 can be directly repressed by chromatin-modifying complexes, linking transcriptional and epigenetic regulation to tumor metabolism and progression [27].

Overall, SASH1 regulation involves a complex network of caspase-mediated cleavage, NF- κ B and PI3K/Akt signaling, exosome-mediated HMGB1 delivery, and epigenetic silencing via the HMGB1/SET/HAT1 complex. This integrated control ensures fine-tuned modulation of apoptosis, proliferation, and metabolic pathways, and its dysregulation contributes to cancer progression. Understanding these multifaceted protein-mediated mechanisms offers insights into potential therapeutic interventions for restoring SASH1 activity in tumors (Figure 2 and Table 1).

Table 1. Epigenetic and MicroRNA-Mediated Regulation of SASH1 in Cancer.

Regulator Type	Regulator	Cancer Type(s)	Effect on SASH1	Downstream Biological Impact	Reference (s)
DNA methylation	Promoter CpG hypermethylation	Breast	Downregulation	Suppresses transcription; reduces SASH1 mRNA and protein levels	[21]
Circular RNA	circ-ITCH	Glioma	Upregulation	Inhibits proliferation and invasion via miR-106a-5p/SASH1 axis	[13]
microRNA	miR-128-3p (exosomal)	Gastric cancer	Downregulation	Promotes angiogenesis, endothelial proliferation and migration	[14]
microRNA	miR-4454 (HERV-H-derived)	Bladder cancer (NMIBC)	Downregulation	Promotes tumor progression by targeting SASH1 and DNAJB4	[22]
microRNA	miR-17, miR-128	Osteosarcoma	Downregulation	Enhances proliferation, migration, invasion; suppresses apoptosis	[23]
microRNA	miR-130b	Esophageal squamous cell carcinoma (ESCC)	Downregulation	Increases proliferation, aggressiveness, tumor growth	[24, 25]
Protein/Exosome	HMGB1, HMGB1/SET/HA	Glioma, Lung adenocarcinoma	Downregulation	Epigenetic repression; promotes glycolysis, proliferation, metastasis	[16, 26, 27]

circ-ITCH: Circular RNA inhibitor of tumor, CpG: Cytosine-phosphate-Guanine dinucleotide, DNAJB4: DnaJ homolog subfamily B member 4, ESCC: Esophageal squamous cell carcinoma, HERV-H: Human endogenous retrovirus-H, HMGB1: High-mobility group box 1, miRNA: microRNA, NMIBC: Non-muscle invasive bladder cancer, SASH1: SAM and SH3 domain-containing protein 1.

Role of SASH1 in Signaling and Molecular Pathways in Cancer

PI3K/Akt Pathway

SASH1 acts as a scaffold protein that directly or indirectly regulates the PI3K/Akt signaling pathway, a central cascade controlling cell proliferation, survival, metabolism, and migration. SASH1 inhibits PI3K kinase activity, reducing PIP3 production and limiting AKT phosphorylation, which in turn modulates downstream mTOR signaling. By influencing both upstream and downstream components of this pathway, SASH1 plays a critical role in maintaining the balance of cellular signaling and preventing overactivation of oncogenic processes. In breast cancer cells, SASH1 enhances cell adhesion and suppresses migration. This effect is mediated through interactions with TRAF6/TAK1/IKK and MAP2K2/

MAP4K4 signaling components. These interactions ultimately lead to inhibition of ERK1/2 phosphorylation. Its regulation of PI3K/Akt/mTOR is evidenced by negative correlations between SASH1 expression and levels of p-PI3K, p-Akt, and p-mTOR, demonstrating that SASH1 can control proliferation, survival, and metabolic signaling through this pathway [8]. Under hypoxic conditions in pancreatic cancer, SASH1 expression is reduced, leading to increased phosphorylation and activation of PI3K and Akt. Overexpression of SASH1 counteracts this effect by suppressing HIF-1 α stabilization and PI3K/Akt phosphorylation, thereby limiting hypoxia-induced epithelial–mesenchymal transition (EMT), migration, and invasion. These observations highlight SASH1 as a critical modulator linking environmental stress to the PI3K/Akt signaling axis [28]. Similarly, in thyroid cancer, overexpression of SASH1 inhibits PI3K and Akt phosphorylation, resulting in increased epithelial markers (E-cadherin) and decreased mesenchymal markers (N-cadherin, Vimentin), which suppresses EMT, migration, and invasion [29]. Collectively, these findings across different cellular contexts demonstrate that SASH1 exerts its regulatory effects predominantly through the PI3K/Akt pathway, controlling key nodes of cell signaling that govern proliferation, survival, and motility.

TGF- β signaling pathway

Recent evidence indicates that SASH1 is a critical regulator of tumor progression through its interaction with the TGF- β signaling pathway. In melanoma models, SASH1 was shown to suppress cell proliferation, migration, invasion, epithelial–mesenchymal transition (EMT), and metastasis through negative regulation of the SASH1/THBS1/TGF- β 1 signaling axis. Mechanistically, SASH1 suppresses TGF- β 1 expression via regulation of THBS1, thereby inhibiting EMT and metastatic dissemination, while simultaneously promoting melanin

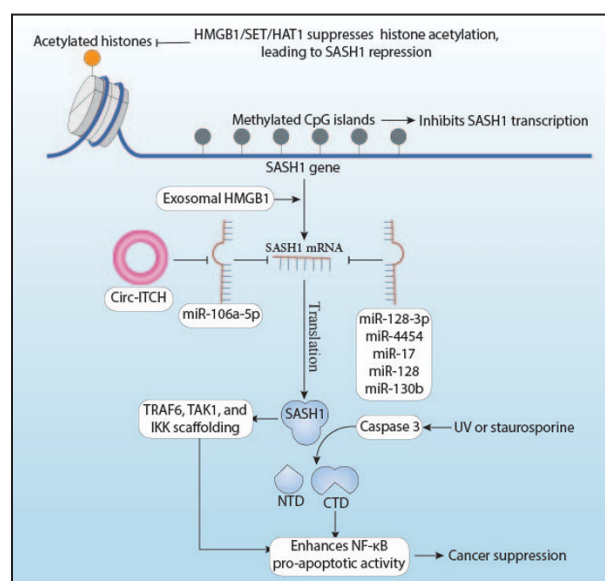


Figure 2. Epigenetic and Post-Transcriptional Regulation of SASH1 in Cancer Suppression.

synthesis. In vivo studies using SASH1-knockdown melanoma cells further confirmed that loss of SASH1 enhances tumor growth and metastatic potential through activation of TGF- β signaling [7]. A similar regulatory role of SASH1 within the TGF- β pathway has been demonstrated in gastric cancer. SASH1 is significantly downregulated in gastric cancer cells, and TGF- β stimulation further suppresses its expression. Functional studies revealed that SASH1 inhibits TGF- β -induced EMT by restoring epithelial markers such as E-cadherin while suppressing mesenchymal markers including N-cadherin. Consequently, SASH1 overexpression markedly attenuates TGF- β -mediated migration and invasion of gastric cancer cells, reinforcing its role as a key negative regulator of EMT [12]. Importantly, the inhibitory effect of SASH1 on TGF- β -driven EMT is mediated, at least in part, through suppression of the PI3K/Akt signaling pathway. TGF- β stimulation significantly increases phosphorylation of PI3K and Akt, whereas SASH1 overexpression effectively blocks this activation. This indicates that SASH1 acts as a molecular brake on TGF- β -induced oncogenic signaling by disrupting the crosstalk between TGF- β and PI3K/Akt pathways [7, 12]. Collectively, these findings establish SASH1 as a critical modulator of TGF- β -dependent EMT and metastasis across multiple tumor models and highlight its potential as a therapeutic target for interfering with TGF- β -driven cancer progression.

Hippo/YAP Pathway

Recent studies have identified SASH1 as a key regulator of cell invasion through modulation of the Hippo/YAP signaling pathway. In triple-negative breast cancer (TNBC), SASH1 expression is significantly downregulated compared with other breast cancer subtypes. Functional analyses revealed that ectopic expression of SASH1 suppresses TNBC cell invasion, whereas SASH1 depletion enhances invasive behavior, accompanied by altered expression of MMP2 and MMP9. These findings were confirmed in both in vivo xenograft and chicken chorioallantoic membrane models, supporting the role of SASH1 as a tumor suppressor in TNBC [9]. Mechanistically, SASH1 exerts its anti-invasive effect through regulation of the Hippo core kinases MST1/2 and LATS1/2, as well as the Hippo pathway regulator Ajuba. Overexpression of SASH1 decreases the interaction between LATS1 and Ajuba, which is likely responsible for the modulation of YAP activity. SASH1 appears to specifically regulate YAP rather than TAZ in TNBC cells. Phosphorylation of SASH1 by LATS1 indicates a reciprocal feedback mechanism, whereby SASH1 both regulates and is regulated by Hippo signaling. Importantly, SASH1 depletion leads to reduced LATS1 and YAP phosphorylation, causing accumulation of active YAP and increased transcription of its downstream target CYR61. Conversely, SASH1 overexpression restores LATS1-mediated YAP phosphorylation and limits YAP nuclear activity [10]. Downstream of YAP, SASH1 influences the ARHGAP42-actin axis to modulate cytoskeletal organization and cell motility. Loss of SASH1

upregulates ARHGAP42 via YAP-TEAD transcriptional activity, enhancing actin cytoskeleton remodeling and promoting TNBC cell invasion. Pharmacological inhibition or knockdown of YAP reverses these effects, confirming the dependency of SASH1-mediated anti-invasive activity on YAP signaling. Collectively, these studies establish SASH1 as a critical modulator of Hippo/YAP signaling, linking its phosphorylation-dependent regulation to control of cell invasion and highlighting its potential as a therapeutic target in aggressive breast cancers [9, 10].

Other Pathways

SASH1 functions as a key regulator in multiple pathways influencing both tissue morphogenesis and cancer progression. In mammary epithelial cells, CEACAM1-induced lumen formation requires SASH1 and tightly controlled NOTCH1 signaling; loss of SASH1 disrupts apoptosis of central acinar cells and lumenogenesis [30]. In colorectal cancer, SASH1 down-regulation promotes EMT, enhancing migration, invasion, metastasis, and chemoresistance. Mechanistically, SASH1 inhibits CRKL-mediated signaling, preventing activation of small GTPases and SRC kinases that drive EMT. Clinical data confirm that reduced SASH1 and elevated CRKL correlate with poor prognosis [11]. These findings suggest that targeting the SASH1-CRKL axis or restoring SASH1 function may represent a promising therapeutic strategy across epithelial cancers (Figure 3 and Table 2).

Role of SASH1 Across Different Cancers

Although the molecular mechanisms of SASH1 signaling are largely shared across tumor types and are discussed in Section 4, extensive evidence supports a broad tumor-suppressive role for SASH1 in human malignancies. In most cancers, reduced SASH1 expression is associated with increased proliferation, EMT, invasion, metastasis, therapy resistance, and poor clinical outcome. Depending on tumor context, SASH1 dysregulation affects pathways including PI3K/Akt, TGF- β , Hippo/YAP, CRKL/SRC, FAK, and Hedgehog signaling. Restoration of SASH1 expression generally suppresses malignant phenotypes and improves therapeutic sensitivity (Table 2).

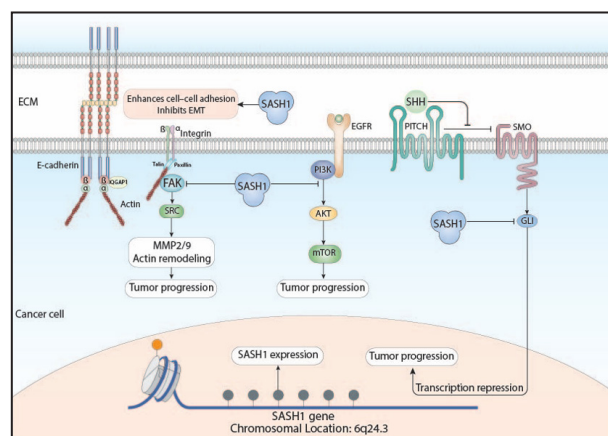


Figure 3. Role of SASH1 in Regulating Signaling Pathways.

Table 2. Summary of SASH1 Dysregulation and Functional Roles Across Different Cancers.

Cancer Type	SASH1 Expression Pattern	Key Functional Consequences of SASH1 Loss	Representative Pathways/Regulators*	Clinical Relevance	Reference (s)
Breast cancer	Downregulated	EMT, invasion, metastasis, endocrine resistance	PI3K/Akt/mTOR, Hippo/YAP, IQGAP1/E-cadherin	Poor survival and aggressive phenotype	[8-10, 17]
Gastric cancer	Downregulated	EMT, migration, angiogenesis	TGF- β , PI3K/Akt, exosomal miR-128-3p	Advanced TNM stage and poor prognosis	[12, 14, 31]
Lung cancer (NSCLC/LUAD)	Downregulated	Glycolytic reprogramming, metastasis, chemoresistance	HMGB1-SET-HAT1 axis	Poor prognosis and cisplatin resistance	[27, 33, 36, 37]
Colorectal cancer	Downregulated	EMT, invasion, metastasis, 5-FU resistance	CRKL/SRC signaling	Reduced overall survival	[2, 5, 11]
Cervical cancer	Downregulated	Increased proliferation and invasion	FAK signaling	Poor overall survival	[32, 38]
Hepatocellular carcinoma	Downregulated	EMT, proliferation, invasion	Sonic Hedgehog signaling	Tumor progression	[35]
Melanoma	Downregulated	Cell-cycle progression and metastasis	TGF- β signaling, cyclin B/Cdc2 regulation	Increased tumor aggressiveness	[7, 19]
Osteosarcoma	Downregulated	Proliferation, invasion, metastasis	miR-17/SASH1, miR-128/SASH1	Associated with metastatic disease	[20, 23, 24]
Glioma	Downregulated	Proliferation and invasion	circ-ITCH/miR-106a-5p, HMGB1 signaling	Higher tumor grade and poor prognosis	[13, 26, 39]
Pancreatic cancer	Downregulated under hypoxia	Hypoxia-induced EMT and invasion	HIF-1 α , PI3K/Akt	Enhanced metastatic potential	[28]
Thyroid cancer	Downregulated	EMT, proliferation, migration	PI3K/Akt signaling	Tumor progression	[29]
Bladder cancer	Functional suppression by miR-4454	Enhanced tumor progression	miR-4454-mediated regulation	Associated with oncogenic progression	[22]

SASH1 as a Prognostic Biomarker

SASH1 has been identified as a potential prognostic biomarker in multiple cancers. In gastric cancer (GC), analyses of the Oncomine database and experimental validation revealed that SASH1 mRNA and protein levels were significantly downregulated in tumor tissues compared with adjacent normal tissues. Immunohistochemical staining showed primarily cytoplasmic localization of SASH1 in tumor cells. Low SASH1 expression was significantly associated with advanced TNM stage, higher T, N, and M classifications, poor differentiation, patient gender, and elevated preoperative CA19-9 levels. Kaplan–Meier survival analysis and multivariate Cox regression confirmed that reduced SASH1 expression was an independent predictor of poor overall survival in GC patient [31]. Similarly, in cervical cancer, SASH1 mRNA and protein levels were significantly lower in tumor tissues compared with normal cervical tissues. Low SASH1 expression correlated positively with higher FIGO stage, lymph node metastasis, and poor differentiation. Kaplan–Meier survival analysis showed that patients with low SASH1 expression had significantly worse overall survival, and multivariate analysis confirmed SASH1 as an independent prognostic factor [32]. In colorectal cancer, SASH1 expression was significantly downregulated in primary tumors and further reduced in liver metastases. Immunoblotting validated decreased SASH1 protein levels in most tumor samples. SASH1 downregulation was associated with the development of metachronous and synchronous metastases. Multivariate Cox regression revealed that SASH1 expression below the cutoff independently

predicted poorer overall survival, with a relative risk of 2.9 [2]. In non-small-cell lung cancer (NSCLC), SASH1 mRNA expression was significantly lower in tumor tissues compared to normal tissues. Kaplan–Meier survival analysis demonstrated that patients with high SASH1 expression had improved overall survival, especially in lung adenocarcinoma, while the effect was not significant in squamous cell carcinoma. Multivariate analysis indicated that low SASH1 expression independently predicted poor survival outcomes in NSCLC and lung adenocarcinoma [33]. Collectively, these findings suggest that reduced SASH1 expression is closely associated with tumor progression, metastasis, and poor patient outcomes across multiple cancer types (Table 3).

Therapeutic value of SASH1

SASH1 has been proposed as a tumor suppressor due to its association with favorable prognosis in multiple cancers and its inhibitory effects on cancer cell viability and invasiveness in vitro [33, 34]. Ectopic expression of SASH1 reduces breast cancer cell line viability, suggesting that restoring its expression could serve as a novel therapeutic strategy [34]. To identify potential drug candidates, in silico connectivity mapping using the CMap database highlighted chlorpyramine as a SASH1 inducer. Chlorpyramine treatment has been shown to increase SASH1 expression in multiple breast cancer cell lines and reduce cell viability, an effect that is at least partly SASH1-dependent, as siRNA-mediated knockdown of SASH1 partially rescues cell survival. Moreover, preclinical studies suggest that chlorpyramine can reduce breast cancer xenograft growth in vivo, though further

Table 3. Role of SASH1 in Clinical Outcomes, Prognosis, and Therapeutic Potential Across Different Cancers.

Cancer Type	SASH1 Expression	Associated Clinical Features / Prognostic Impact	Therapeutic Implications	Ref
Gastric Cancer (GC)	Downregulated	Advanced TNM stage, higher T/N/M classifications, poor differentiation, elevated CA19-9, poor overall survival	Potential prognostic biomarker, therapeutic target	[31]
Cervical Cancer	Downregulated	Higher FIGO stage, lymph node metastasis, poor differentiation, poor overall survival	Potential prognostic biomarker, therapeutic target	[32]
Colorectal Cancer	Downregulated	Reduced in primary tumors and liver metastases, metachronous/synchronous metastases, poor overall survival	Potential prognostic biomarker, therapeutic target	[2]
Non-Small-Cell Lung Cancer (NSCLC)	Downregulated	Poor overall survival, especially in lung adenocarcinoma, independent predictor of poor outcomes	Therapeutic target, chloropyramine increases SASH1 and sensitizes to cisplatin	[33]
Breast Cancer	Downregulated	Associated with tumor progression and poor outcomes	Therapeutic target, chloropyramine increases SASH1 and reduces cell viability; siRNA-mediated knockdown partially rescues	[34]

Abbreviations: CMap: Connectivity Map, NSCLC: Non-Small-Cell Lung Cancer, TNM: Tumor-Node-Metastasis, FIGO: International Federation of Gynecology and Obstetrics, CA19-9: Carbohydrate Antigen 19-9, siRNA: Small Interfering RNA.

investigation is needed [34]. Similarly, in non-small-cell lung cancer (NSCLC), chloropyramine increases SASH1 protein levels and enhances the sensitivity of NSCLC cells to cisplatin-induced apoptosis. SASH1 depletion using targeted siRNA partially rescues cell death, confirming that chloropyramine's cytotoxic effects are mediated, at least in part, through SASH1 [33]. Taken together, these findings highlight the therapeutic potential of SASH1, either by direct overexpression or pharmacological induction, and suggest that compounds such as chloropyramine could be repurposed as low-toxicity anticancer agents. Further preclinical studies and biomarker-driven clinical trials are warranted to validate the pharmacodynamic induction of SASH1 and its antitumor efficacy [33, 34].

In conclusion, SASH1 has emerged as a pivotal tumor suppressor across a wide array of malignancies, including breast [8], colorectal [5], gastric [31], lung [33], hepatocellular [35], cervical [32], melanoma [19], osteosarcoma [23], and glioma [13]. Its tumor-suppressive effects are multifaceted, encompassing inhibition of EMT, suppression of proliferation, induction of apoptosis, cell cycle arrest, and stabilization of both cell–cell and cell–matrix adhesion. Downregulation or loss of SASH1 mediated by genetic alterations, promoter hypermethylation, oncogenic miRNAs (e.g., miR-17 [23], miR-128 [14], miR-130b [24, 25], miR-4454 [22]), circRNAs [13], or exosomal signals (e.g., miR-128-3p [14], HMGB1 [26]) promotes tumor progression, metastasis, therapy resistance, and poor clinical outcomes. Clinically, low SASH1 expression consistently correlates with advanced TNM stage, higher grade, lymphovascular invasion, metastasis, and reduced overall survival across multiple cancer types, establishing SASH1 as a robust prognostic biomarker [2, 25, 31–34]. Mechanistically, SASH1 is involved in multiple signaling networks that integrates multiple oncogenic and tumor-suppressive pathways. In breast cancer, SASH1 interacts with the IQGAP1–E-cadherin axis [17] and modulates PI3K/Akt/mTOR [8] and Hippo/YAP [9] pathways to suppress invasion and endocrine resistance. In colorectal cancer, SASH1 inhibits the CRKL/SRC axis [11], preventing cytoskeletal remodeling and EMT-driven metastasis. In lung adenocarcinoma, epigenetic repression via the

HMGB1–SET–HAT1 complex [27] drives glycolytic reprogramming and metastatic behavior, which can be reversed by restoring SASH1. Additionally, SASH1 regulates TGF- β -induced EMT in gastric [12] and melanoma cells [7], and modulates FAK signaling in cervical cancer [32]. Its interactions with cytoskeletal proteins such as cortactin and actin-rich structures further highlight its role in maintaining adhesion and inhibiting motility [5]. Collectively, these studies reveal SASH1 as a signaling hub that integrates intrinsic tumor-suppressive programs with microenvironmental cues, including exosomal regulation and hypoxia-induced signaling, to restrain malignancy.

Future research should focus on elucidating the precise molecular mechanisms governing SASH1-mediated tumor suppression. Detailed mapping of its protein–protein interactions, including partners such as CRKL, IQGAP1, cortactin, and EphA receptors, could uncover context-specific regulatory networks. Structural studies, employing approaches like X-ray crystallography, cryo-EM, or NMR, could provide high-resolution insights into the functional interfaces of SASH1 domains (SAM and SH3) with key partners, facilitating rational design of modulators that restore or mimic SASH1 function. Additionally, the role of SASH1 in coordinating tumor-intrinsic and tumor-extrinsic processes, including its regulation by exosomal microRNAs and circRNAs, warrants further exploration. Investigating these regulatory circuits in orthotopic and metastatic models could reveal novel strategies to counteract metastasis and therapy resistance. Finally, pharmacologic induction of SASH1, exemplified by compounds such as chloropyramine, should be systematically evaluated in preclinical models to establish safety, efficacy, and mechanistic dependence on SASH1. Collectively, advancing our understanding of SASH1 biology holds significant potential to inform prognostic assessment and develop targeted therapies, offering a promising avenue to improve cancer management.

From a therapeutic perspective, restoration of SASH1 function has shown potential preclinical effects. Pharmacologic inducers such as chloropyramine have been reported to increase SASH1 expression,

suppress tumor growth, and enhance chemosensitivity in breast and lung cancer models. In addition, targeting upstream repressors including HMGB1, MAP4K4, and oncogenic miRNAs may provide alternative strategies to restore SASH1-mediated tumor suppression. However, several important limitations should be acknowledged. Most current mechanistic evidence is derived from overexpression or knockdown studies in established cancer cell lines, which may not fully reflect the complexity and heterogeneity of human tumors. Moreover, relatively few investigations have validated these findings in patient-derived samples, organoid systems, or genetically engineered in vivo models. Therefore, the context-dependent functions and translational relevance of SASH1 across different tumor microenvironments and disease stages remain incompletely understood. Future studies should focus on defining the molecular networks regulated by SASH1 in a context-specific manner, validating its prognostic and predictive significance in large multicenter cohorts, and developing clinically relevant pharmacologic or genetic strategies to restore SASH1 activity. Integration of patient-derived models, single-cell analyses, and in vivo genetic approaches will be essential for advancing SASH1-based precision medicine strategies aimed at limiting tumor progression, metastasis, and therapy resistance across diverse cancers.

Declarations

Ethics approval

This manuscript does not encompass any research involving animals or people.

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Conflict and interest

The authors assert no conflict of interest in this work.

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