


SNHG16: A Novel Long-Non Coding RNA in Human Cancers

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Abstract: Long noncoding RNAs (lncRNAs) have recently been considered as central regulators in diverse biological processes controlling tumorigenesis. Small nucleolar RNA host gene 16 (*SNHG16*) is an important tumor-associated lncRNA mainly involved in tumorigenesis and progression by competing with endogenous RNA (ceRNA) which sponges tumor-suppressive microRNA (miRNA), and by its recruitment mechanism. *SNHG16* is overexpressed in tumor tissues and cell lines of different kinds of cancers, and its presence is associated with a poor clinical prognosis. Reviewing all publications about *SNHG16* revealed that it plays a key role in the different hallmarks that define human cancer, including promoting proliferation, activating migration and invasion, inhibiting apoptosis, affecting lipid metabolism and chemoresistance. This review highlights the role that the aberrant expression of *SNHG16* plays in the development and progression of cancer, and suggests that *SNHG16* may function as a potential biomarker and therapeutic target for human cancers.

Keywords: long noncoding RNA, biomarker, cancer, *SNHG16*

Plain Language Summary

Studies have shown that the long non-coding RNA *SNHG16* plays a functional role in various human cancers and is closely associated with tumor growth, metastasis and poor prognoses.

SNHG16 is upregulated in hepatocellular carcinoma, osteoblastoma, lung cancer, colorectal cancer, glioma, ovarian cancer, bladder cancer, breast cancer, gastric cancer, retinoblastoma, cervical cancer, and thyroid cancer.

SNHG16 is overexpressed in several types of cancer and is implicated in multiple different hallmarks that define human cancer.

In order to have a deeper comprehension of this novel biomarker for prognosis and therapy in cancers, more studies are need for further analysis.

Introduction

Cancer is a group of malignant diseases in which cell growth, migration, and invasion are uncontrolled. The high mortality and disability rates associated with cancer are a cause of distress and burden on patients and society as a whole.¹ Surgical treatment, chemotherapy, and radiation therapy are currently the main treatments for cancer. However, the therapeutic effects of these primary treatments remain limited.² Therefore, early diagnostic markers and new treatments are urgently needed.

About 70–90% of the human genome is transcribed into RNA, but only 2% of the total RNA is translated into protein. The remaining RNA that is not translated into

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protein is called noncoding RNA (ncRNA).³ An ncRNA that is 200 nucleotides in length or shorter is categorized as a short ncRNA, whereas an ncRNA longer than 200 nucleotides is considered a long ncRNA (lncRNA).⁴ It was previously thought lncRNA did not play a role during transcription.⁵ However, studies have shown that lncRNAs can regulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels. A number of lncRNAs are involved in biological processes, including genomic imprinting, histone modification, chromatin remodeling, and cell cycle regulation.^{6–8} Furthermore, studies have found a clear correlation between lncRNAs and tumorigenesis.⁹ Differences in lncRNA expression in tumor tissues and adjacent tissues, as well as in cancer cell lines and corresponding normal cells, have also been reported in various types of cancer. This differential expression may promote angiogenesis and induce metastasis by affecting the cell cycle and cytological behavior of tumors, thus promoting tumor development.^{10,11}

Small nucleolar RNA host gene 16 (*SNHG16*), which is encoded by a 7571-bp region at chromosome 17q25.1, has recently been recognized as a cancer-related lncRNA.¹² The *SNHG16* was initially discovered in neuroblastoma.¹³ The dysregulation of *SNHG16* has been detected in various types of cancer, including colorectal cancer (CRC),¹⁴ hepatocellular carcinoma (HCC),¹⁵ osteosarcoma,¹⁶ and glioma.¹⁷ Recent studies have demonstrated that *SNHG16* expression is upregulated in multiple types of tumors. Furthermore, downregulation of *SNHG16* in cancer cells inhibits cell proliferation, invasion, and migration; induces apoptosis; and results in decreased N-cadherin and increased E-cadherin,^{15,18–23} suggesting that *SNHG16* also acts as an oncogenic lncRNA in cancer.

Understanding the role of *SNHG16* may provide a new perspective to study the mechanisms of cancer development. This paper reviews current studies on the expression, function, mechanism, and clinical significance on tumor development of *SNHG16* and highlights its impact on the hallmarks of cancer.

Mechanisms of *SNHG16* in Human Cancers

Further evidence shows that *SNHG16* promotes tumor development by acting as a competitive endogenous RNA (ceRNA).^{24,25} The ceRNA hypothesis states that various RNA species, including mRNAs encoding proteins and RNAs without protein-encoding capabilities

(eg, pseudogenes, lncRNA, and circular RNA), share miRNA binding sites, allowing for competitive binding to common miRNAs with pro- or anti-cancer effects. Thus, the inhibition of miRNAs on other targets can be alleviated. In this manner, lncRNAs can have tumor-promoting or -inhibiting abilities. The ceRNA model is a very important biological pathway and, through this pathway, lncRNAs can participate in the entire process of tumorigenesis.²⁶ It is evident from previous literature that *SNHG16* acts as a ceRNA to regulate mRNA by sponging corresponding miRNAs in multiple cancers.^{17,27} Argonaute-crosslinking and immunoprecipitation (AGO-CLIP) analysis led to the hypothesis that *SNHG16* heavily binds to AGO. It has 27 AGO/miRNA target sites along its length and may act as a ceRNA for miRNA in cancer.¹⁴ In addition to the ceRNA mechanism, *SNHG16* can also play a role in promoting cancer through other mechanisms. p21, a cell cycle-dependent protein kinase inhibitor belonging to the kinase inhibitory protein/cyclin-dependent kinase (CDK) -interacting protein (KIP/CIP) family, can form a cell cycle G1 checkpoint with p53. If DNA damage is not repaired, the cell cannot progress through the cell cycle, which reduces the replication and accumulation of damaged DNA, thus reducing the risk of oncogenesis.²⁸ *SNHG16* can directly inhibit the expression of p21 by enriching enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2), thereby promoting proliferation and inhibiting apoptosis in bladder cancer cells.²⁹ The function of *SNHG16* in various biological processes is conferred primarily by binding with miRNAs as sponges or by interacting with proteins, including those active in cell proliferation, migration, invasion, and apoptosis.

Overexpression of *SNHG16* and Clinical Significance in Cancer

It has been shown that *SNHG16* expression is significantly upregulated in tumor tissues and cell lines, such as hepatocellular carcinoma (HCC), lung cancer (LC), colorectal cancer (CRC) and glioma.^{15,17,30,31} In addition, overexpression of *SNHG16* indicates poor prognosis and is usually correlated with tumor size, lymph node metastasis, tumor grade, disease-free survival, and overall survival (OS). For example, to gain more in-depth knowledge of tumor biology, nine co-expression modules were identified in the Cancer Genome Atlas database after screening and analysis. These modules identified four important

prognosis-related lncRNAs, including *SNHG16*, which may provide insights into the biological significance and clinical application of lncRNAs in breast cancer.³² The expression of *SNHG16* can be upregulated by c-Myc, which is a key determinant gene in the pathogenesis of human malignancies, in oral squamous cell carcinoma.³³ *SNHG16* overexpression and its known clinical significance in human cancers are summarized in [Tables 1 and 2](#).

More recently, *SNHG16* has been studied most frequently in HCC. Several studies have found that the expression of *SNHG16* is significantly increased in HCC tissues compared to adjacent noncancerous tissues. The expression of *SNHG16* is also remarkably upregulated in HCC cell lines.^{15,18–23} Further analysis showed that high expression of *SNHG16* is associated with high tumor grade, multiple tumors, macrovascular invasion, large tumor size, and lymph node status, as well as poor disease-free survival and shorter overall survival.^{15,19–21,23} In HCC patients, multivariate analysis identified *SNHG16* overexpression as a significant independent predictor of poor prognosis.^{20,23}

Moreover, there are other studies of *SNHG16* and related clinical effects in non-small cell lung cancer (NSCLC), osteosarcoma, glioma, bladder cancer (BC), ovarian cancer (OC), pancreatic cancer (PC), and papillary thyroid cancer (PTC). *SNHG16* expression is significantly upregulated in NSCLC tissues and cell lines.³⁰ Reduced *SNHG16* is correlated with poor prognosis and factors associated with tumor progression, including larger tumor size, advanced pathological stage, lymph node metastasis, and shorter OS, revealing that *SNHG16* may serve as an independent predictor of poor prognosis in NSCLC.³⁰ *SNHG16* was also overexpressed in human osteosarcoma tissues and cell lines when compared to matched normal tissues and cell lines, respectively.^{16,36–39} Osteosarcoma patients with high *SNHG16* expression are more likely to have shorter survival, larger tumors, more advanced TNM stage, metastasis, and poorer prognosis.^{37,39} Zhou et al revealed that high expression of *SNHG16* was associated with poor clinical pathological parameters and shorter OS and progression-free survival, which indicated that it can act as an independent prognostic factor of glioma.⁴⁰ Peng et al revealed that *SNHG16* was positively correlated with miR-17-5p. High expression of *SNHG16* and miR-17-5p was related to unfavorable clinicopathological factors, such as higher historical grade and more advanced tumor stage in bladder cancer. Yang et al reported that *SNHG16* expression was significantly increased in human ovarian

cancer (OC) as compared to normal ovarian tissue. In addition, higher *SNHG16* expression was significantly associated with higher clinical grade, tumor size, and lymph node and distant metastasis in OC patients. Liu et al revealed that *SNHG16* was upregulated in PC tissues and cell lines. Moreover, increased expression of *SNHG16* was correlated with poor differentiation, advanced TNM stage, lymph node metastasis, and shorter survival.⁴¹ *SNHG16* is upregulated in both papillary thyroid tissues and cell lines, which indicates advanced TNM stage and lymph node metastasis.⁴²

In addition to sequencing in tumor tissues, lncRNA levels can also be measured in exosomes. Exosomes, which are microvesicles (70–120 nm) derived from endosomes secreted by many cell types, can participate in intercellular communication by transferring intracellular substances (such as proteins, lipids, and nucleic acids, including lncRNA).⁴³ Certain lncRNAs within exosomes secreted by tumor cells have been described as candidate biomarkers to predict prognosis.²⁵ Zhang et al evaluated the serum exosomal expression of *SNHG16* in bladder cancer patients and found that *SNHG16* expression was correlated with TNM stage and invasion and predicted poor prognosis.⁴⁴ As a noninvasive marker of cancer prognosis, the measurement of lncRNA in exosomes is of great significance. Therefore, further studies are needed, including larger clinical samples, multicenter studies, and functional analysis.

These findings indicate that *SNHG16* may serve as a potential biomarker for human cancer diagnosis, prognosis, and effective treatment.

Implication of *SNHG16* in the Hallmarks of Cancer Promoting Proliferation

Proliferation is considered to be the most basic feature of cancer cells.⁴⁵ In normal cells, the regulation of proliferation is strictly controlled. The production and signal transmission of growth-promoting factors must be fully controlled, and checkpoints must be set up at each node of cell division to ensure tissue homeostasis (cell number, tissue structure, and function).⁴⁶ In cancer cells, this balance is disrupted. *SNHG16* has been shown to sustain proliferation of cancer cells in different types of cancers.

Many related mechanisms have been reported. *SNHG16* is negatively correlated with known miRNAs that act as tumor suppressors. In HCC, Xie et al revealed

Table 1 Functional Characterization of *SNHG16* in Various Cancers

Cancer Type	Expression	Numbers of Cases	Mainly Assessed Cell Lines	Related Genes	Phenotypes Affected	Role	References
Non-small cell cancer	Up	66	A549	miR-146a, MUC5AC, PCNA, MMP2, MMP9	Proliferation, migration, invasion, tumorigenesis	Oncogenic	[32]
Hepatocellular carcinoma	Up	40	HepG2, SMMC7721	miR-195	Proliferation, migration, invasion, tumorigenesis	Oncogenic	[29]
	Up	50	Hep-3B, Sk-hep-1	miR-186, ROCK1	Proliferation, migration, invasion	Oncogenic	[14]
	Up	30	HepG2	Has-miR-17-5p, p62, mTOR, NF- κ B	Proliferation, migration, invasion, cell cycle, apoptosis	Oncogenic	[26]
	Up	34	Huh7, HepG2	miR-302a-3p, FGF19	Proliferation	Oncogenic	[28]
	Up	88	SMMC7721	miR-4500, STAT3, E-cadherin, N-cadherin	Proliferation, migration, invasion, EMT	Oncogenic	[27]
	Up	103	HepG2/SOR	miR-140-5p	Sorafenib resistance	Oncogenic	[25,30]
Cervical cancer	Up	78	SiHa	miR-216-5p, ZEB1, E-cadherin, N-cadherin	Proliferation, migration, EMT	Oncogenic	[34,35]
Osteosarcoma	Up	30	SAOS2	miR-16, ATG4B	Proliferation, migration, invasion	Oncogenic	[41]
	Up	96	U2OS, SAOS2	miR-98-5p, ZEB1, E2F5, STAT3	Proliferation, migration, invasion, cell cycle, apoptosis	Oncogenic	[38]
	Up	38	U2OS, MG-63	miR-1301, BCL-9	Proliferation, migration, invasion	Oncogenic	[40]
	Up	25	U2OS, HFOB1.19, SaOS2	miR-340, Caspase 3, caspase 7	Viability, migration, invasion, apoptosis	Oncogenic	[15]
	Up	20	MG-63, U2OS	miR-205, ZEB1, caspase3, PARP	Proliferation	Oncogenic	[39]
Papillary thyroid cancer	Up	48	IHH-4, TPC-1	miR-497, BPNA, YAP1	Proliferation, migration, invasion, apoptosis	Oncogenic	[42]
Glioma	Up	40	U251, LN229	miR-373, PI3K, AKT, EGFR, MMP2, MMP9	Proliferation, migration, invasion, apoptosis	Oncogenic	[48]
	Up	40	LN229	P21, cyclinD1, cyclinB1	Proliferation, apoptosis, cell cycle	Oncogenic	[49]
	Up	48	U251, H4	miR-4518, PRMT5, Bcl, Bax, PI3K, AKT, caspase3	Proliferation, apoptosis	Oncogenic	[50]

(Continued)

Table 1 (Continued).

Cancer Type	Expression	Numbers of Cases	Mainly Assessed Cell Lines	Related Genes	Phenotypes Affected	Role	References
Colorectal cancer	Up	56	SW480, LOV0	miR-200a-3p	Proliferation, migration, invasion, tumorigenesis	Oncogenic	[45]
	Up	281	HCT116, SW480	c-Myc	Viability, apoptosis, migration	Oncogenic	[13]
Ovarian cancer	Up	103	SKOV3, H08910	AKT, PAKT, MMP9	Proliferation, migration, invasion	Oncogenic	[53]
Bladder cancer	Up	275	J82	miR-17-5p, caspase3, E-cadherin, N-cadherin, TIMP3	Viability, apoptosis, EMT, proliferation	Oncogenic	[35]
	Up	19	T24	Bcl, Bax, caspase3, E-cadherin, N-cadherin, Wnt1, c-myc, P2Tkip1	Proliferation, viability, migration, invasion, apoptosis	Oncogenic	[34]
	Up	46	T24, BIU67	P21	Proliferation, migration, invasion, apoptosis, cell cycle	Oncogenic	[56]
Breast cancer	Up	30	MDA-MB-231, MCF-7	miR-98, E2F5	Migration	Oncogenic	[62]
Retinoblastoma	Up	30	SORB-50, Y-79	miR-140-5p	Proliferation, colony formation	Oncogenic	[48]
Gastric cancer	Up	54	BGC-823, SGC-7901	miR-628, NRPI	Apoptosis	Oncogenic	[68]
	Up	122	MGC-803	JAK2, p-STAT3, miR-135a	Proliferation, migration, invasion, apoptosis	Oncogenic	[66]
Pancreatic cancer	Up	46	ASPC-1	miR-218-5p, HMGB1	Migration, invasion	Oncogenic	[41]
Lymphoma	Up	48	OCL-LY7	miR-497-5p, PIMI	Proliferation, migration, invasion, apoptosis, cell cycle	Oncogenic	[50]

that knockdown of *SNHG16* inhibited cell proliferation of HCC cells by inhibiting the expression of proliferation protein Ki67 and miR195 acted as a direct target of *SNHG16*.²² Li et al found that the *SNHG16*/miR-302a-3p/fibroblast growth factor 19 (FGF19) axis was an important pathway in promoting proliferation of HCC cells.²¹ Lin et al found that *SNHG16* modulates signal transducer and activator of transcription 3 (STAT3) expression by competitively binding miR-4500.²⁰ In addition, Knockdown of *SNHG16* hinders osteosarcoma cell

proliferation. However, in osteosarcoma, mechanistic investigations revealed that *SNHG16* could act as a sponge for miR-98-5p, miR-1301, miR-16, miR-340, and miR-205.^{16,36–39} Inhibition of miR-98-5p and miR205 increases zinc finger E-box binding homeobox 1 (ZEB1), E2F transcription factor 5 (E2F5), and STAT3 expression to promote tumorigenesis.^{36,37} Li et al reported that *SNHG16* was revealed to bind with miR-200a-3p, leading to the proliferation of CRC cells.³¹ Zhou et al found that *SNHG16* regulated proliferation and invasion

Table 2 Clinical Significance of *SNHG16* in Diverse Cancers

Cancer Type	Overexpression of <i>SNHG16</i> and Clinical Features	References
Non-small cell cancer	Tumor size, TNM stage, lymph node metastasis, shorter DFS and OS	[32]
Hepatocellular carcinoma	TNM stage, metastasis	[29]
	Tumor size, TNM stage, ALT (U/L)	[14]
	Shorter DFS and OS, multiple tumors, macro vascular invasion	[26]
	Shorter DFS and OS	[28]
	Lymph node involvement, TNM stage	[27]
	Tumor size, TNM stage, vascular invasion	[25]
	Tumor size, TNM stage, metastasis, portal vein tumor thrombus (PVTT)	[30]
Cervical cancer	Tumor size, FIGO stage, lymph node metastasis, poor differentiation	[34,35]
Osteosarcoma	Tumor size, TNM stage, metastasis, shorter OS	[39]
	Tumor size, TNM stage, distance, metastasis, shorter OS	[41]
Papillary thyroid cancer	TNM stage, lymph nodes,	[42]
Glioma	Tumor size, WHO stage, shorter OS and PFS,	[51]
Colorectal cancer	Metastasis, lymph node metastasis	[13]
Ovarian cancer	Clinical stage, distance metastasis, shorter OS	[53]
Bladder cancer	Historical grade, tumor stage, lymph node metastasis	[35]
	Metastasis, lymph nodes, pathological stage	[34]
Gastric cancer	Lymph node metastasis, invasive depth, TNM stage	[67]
Pancreatic cancer	Tumor size, TNM stage, lymph node metastasis, differentiation	[41]

of glioma cells through the miR-373/epidermal growth factor receptor (EGFR) axis by the phosphatidylinositol 3-kinase (PI3K) -protein kinase B (AKT) pathway.⁴⁷ Xu et al explored the molecular mechanism and revealed that *SNHG16* acts as a miR-140-5p sponge in RB carcinogenesis. In addition, suppressing *SNHG16* can slow tumor growth in vivo.⁴⁸

Moreover, *SNHG16* can also promote cancer cell proliferation by activating cell cycle progression through G1/S transition. Knockdown of *SNHG16* in osteosarcoma results in the inhibition of cell proliferation in vitro by the induction of a G0/G1 arrest.⁴⁹ Zhu et al revealed that silencing of *SNHG16* inhibited proliferation, migration, and invasion, in addition to causing cell cycle arrest. *SNHG16* acts by repressing miR-497-5p, blocking its repression of interacting with Moloney murine leukaemia virus 1 in diffuse large B-cell lymphoma (DLBCL).⁵⁰ *SNHG16* can also stimulate cell cycle progression through repressing p21 by recruiting

enhancer of zeste homolog 2 (EZH2) to its promoter region. p21 belongs to a family of cyclin-dependent kinases (CDK) inhibitors and has been reported to be able to block cell cycle progression at the G0/G1 checkpoint.⁵¹ p21 can therefore act as a tumor suppressor in bladder cancer.²⁹

These results show the significance of *SNHG16* in the molecular etiology of proliferation of cancer cells and suggest the potential application of *SNHG16* as an essential diagnostic marker.

Activating Migration and Invasion

Metastasis is the main cause of cancer treatment failure and death. Its molecular mechanism is complex, involving multistep, multistage, multigene changes.² At the initial stage of cancer formation, epithelial cells are transformed into cells with a mesenchymal phenotype through specific signaling pathways.⁵² The main characteristics of this transformation are decreased expression of cell adhesion

molecules (such as E-cadherin), vimentin, rather than cytokeratin, as the main cytoskeletal protein, and the cells taking on the morphological characteristics of mesenchymal cells.⁵³ This phenotypic plasticity, named epithelial-to-mesenchymal transition (EMT), causes epithelial cells to lose cell polarity, lose the connection with basement membrane and other epithelial phenotypes, and gain higher migration and invasion ability.⁵²

Several studies have shown that the overexpression of *SNHG16* can promote EMT and migration, thus promoting the invasion of cancer cells. Lin et al showed that inhibition of *SNHG16* in HCC reverses EMT and represses cell migration and invasion in vitro.²⁰ Peng et al reported metalloproteinases 3 (TIMP3) can be down-regulated by elevated *SNHG16* and miR-17-5p, promoting proliferation, migration, invasion, and EMT in bladder cancer cells.⁵⁴ Previous studies have shown that activating the Wnt/ β -catenin pathway affected cell metastasis and induced EMT in cancers. Feng et al found that suppressing *SNHG16* can inhibit proliferation, migration, invasion, and EMT and promote apoptosis in bladder cancer cells. They further stated that *SNHG16* could sponge miR-98 and target STAT3 through the Wnt/ β -catenin pathway to act as an oncogene in bladder cancer.⁵⁵ And *SNHG16* acts as a ceRNA in colorectal cancer cells to suppress miR-200a-3p and increase the expression of ZEB1 and, thereby, promote the expression of EMT-related genes, such as cadherins and vimentin, and promote cell migration and invasion. Similarly, Zhu et al revealed that silencing *SNHG16* inhibits cell migration and invasion, and EMT in vitro, indicating that *SNHG16* is involved in the tumorigenesis of cervical cancer (CC). Although the oncogenic function of *SNHG16* in CC is not completely known, it is known to act in a miR-216-5p-dependent manner and positively regulate the miR-216-5p target ZEB1 in CC cells.^{34,35}

In addition, *SNHG16* can also regulate migration and invasion by sponging miRNA through transcriptional activation of mRNA. Chen et al reported *SNHG16* might function as a ceRNA for miR-186 to regulate rho-associated coiled-coil-containing protein kinase 1 (ROCK1) expression, which plays important roles in regulating cell polarity and migration in HCC.¹⁵ Su et al have found that *SNHG16* directly bind to miR-340 to promote OS cells migration and invasion.¹⁶ Additionally, Wang et al found that *SNHG16* promotes B Cell Lymphoma 9 (BCL9) expression by sponging miR-1301 to facilitate the migration and invasion of osteosarcoma cells.³⁸ Cai et al revealed that *SNHG16* competitively

binding miR-98 with E2F5 may promote breast cancer metastasis in an miR-98-dependent manner.⁵⁶ Interestingly, in this model, *SNHG16* transcript levels were significantly positively associated with E2F5 mRNA levels, indicating an activation loop of that metastasis process.⁵⁶ A similar situation was posited in another study. Wang et al found that knockdown of *SNHG16* suppressed gastric cancer cell migration and invasion in vitro. Further, mechanistic investigation revealed that *SNHG16* could mediate Janus kinase 2 (JAK2) and STAT3 expression as a ceRNA of miR-135a. Additionally, STAT3 can affect the expression of *SNHG16*.⁵⁷ Another study found that miR-628 is regulated by *SNHG16* and its target Neuropilin-1 (NRP1) can promote tumor metastasis.⁵⁸ *SNHG16* was shown to promote cell invasion and migration in pancreatic cancer cells via mediating high mobility group box 1 (HMGB1) (a known oncogene in PC) expression through sponging miR-218-5p.⁴¹ Wen et al found that knockdown of *SNHG16* inhibits migration and invasion of TPC-1 cells via regulating miR-497.⁴² Interestingly, Vahid found a correlation between *SNHG16* expression and the vitamin D receptor (VDR), which supports the hypothesis of an interactive network between *SNHG16*, VDR, and miR-98 in the context of cancer.⁵⁹ *SNHG16* is expected to become a novel molecular marker for diagnosis, prognosis, and treatment of BC.

Moreover, matrix metalloproteinases (MMPs) are highly expressed in tumor tissues. MMPs cause degradation of protein components in the extracellular matrix and increased tumor invasion and metastatic risk. Xie et al found *SNHG16* significant increase in expression of MMP-2 and MMP-9 through a novel *SNHG16*-miR-195 axis in HCC cells. *SNHG16* was shown to induce OC cell migration and invasion through the upregulation of P-AKT and MMP-9, indicating its potential in promoting tumor progression by regulating the PI3K/AKT pathway and MMPs.⁶⁰

Inhibiting Apoptosis

Apoptosis is a natural, multistep process that plays an important role in development and homeostasis.⁶¹ Cancer cells exhibit enhanced tolerance to both environmental and genomic stresses, resulting in resistance to apoptosis and tumor progression.⁶² The B-cell lymphoma protein 2 (Bcl-2) family proteins, PI3K-AKT pathway, and nuclear factor κ B (NF- κ B) signaling are vital regulators of apoptosis.^{63,64} It has been shown that overexpressed *SNHG16* directly interacted with miR-4518 and promoted protein arginine methyltransferase 5 to inhibit apoptosis in glioma cells. Furthermore,

downregulation of *SNHG16* could lead to the repression of anti-apoptotic Bcl-2 family members and PI3K/Akt signaling.⁴⁰ Additionally, Zhou et al revealed that *SNHG16* suppressed the expression of p21, caspase 3, and caspase 9, while promoting cyclin D1 and cyclin B1 expression, to inhibit apoptosis in glioma cells.⁶⁵ Silencing *SNHG16* increases caspase 3/7 to promote apoptosis in osteosarcoma cells.¹⁶ NF- κ B is a eukaryotic transcription factor that can cause abnormal expression of tumor necrosis factors and promote carcinogenesis and apoptosis. Zhang et al found that *SNHG16* may act as an endogenous sponge of miR-17-5p to upregulate its target p62 and activate the mammalian target of rapamycin (mTOR) pathway to promote metabolism and proliferation in HCC cells, as well as activating PI3K/Akt and NF- κ B signaling to resist apoptosis.¹⁹ Christensen et al reported *SNHG16* overexpression is an early event in CRC, which is regulated by the Wnt pathway and c-Myc. They also found that knockdown of *SNHG16* can reduce cell viability and induce apoptotic death.¹⁴ Another study found that miR-628 is regulated by *SNHG16* and the expression of miR-628-3p is down in GC tissues and GC cell lines, and its target NRP1 can inhibit cell apoptosis.⁵⁸

Affecting Lipid Metabolism

Lipid biosynthesis has been frequently observed in tumor tissues.⁶⁶ Enhanced lipid synthesis is required for the metabolic reprogramming of cancer cells and tumor development.⁶⁶ Christensen et al found that *SNHG16* is enriched in the cytoplasm of CRC cell lines and associated with ribosomes, which may lend a better understanding of its function and means of action.¹⁴ Overexpression of *SNHG16* is positively correlated to the expression of Wnt-regulated transcription factors, including achaete-scute complex homolog 2 (ASCL2) and c-Myc. Moreover, knockdown of *SNHG16* predominantly affects genes involved in lipid metabolism. Interestingly, these genes contain a common sequence motif, suggesting that a broad spectrum of lncRNA-miRNA targets may converge on a few co-target genes.¹⁴

Inhibiting Inflammation

There are few data available about the link between *SNHG16* and cancer inflammation. NF- κ B is a eukaryotic transcription factor that helps regulate the immune and inflammatory response, cell proliferation, apoptosis, tumor growth, and differentiation. NF- κ B signal transduction can cause the abnormal expression of tumor necrosis factors (TNF) and promote tumorigenesis and apoptosis. Zhang et al found that *SNHG16* may act as an endogenous sponge of miR-17-5p to

upregulate its target p62 and activate the mTOR pathway to promote metabolism and proliferation in HCC cells, as well as activating the NF- κ B pathway to aggravate inflammation.¹⁹

Chemoresistance and Vasculogenic Mimicry

There are evidences that *SNHG16* is involved in drug resistance. Ye et al and Guo et al both found that knocking down *SNHG16* increased sensitivity to sorafenib in HCC cells via acting as an endogenous sponge for miR-140-5p, which indicates that *SNHG16* might be a promising therapeutic target to boost the effectiveness of chemotherapy for HCC patients.^{18,23} Osteosarcoma is a rare cancerous bone tumor characterized by high metastasis, rapid progression, and poor prognosis.⁶⁷ In the past few decades, there has been great progress in the diagnosis and treatment of osteosarcoma, but the OS is still unsatisfactory.⁶⁸ The molecular mechanisms underlying the development and progression of osteosarcoma remain unclear, and multidrug resistance severely limits the development and use of neoadjuvant chemotherapy.⁶⁹ Therefore, it is particularly urgent to find feasible molecular therapeutic targets for osteosarcoma. Interestingly, increases in autophagy-related genes (such as ATG4B) via downregulation of miR-16 can reduce cell apoptosis by inducing cell autophagy, which leads to chemoresistance.³⁹ This finding may signify novel therapeutic directions in osteosarcoma.

In addition, glioma is one of the most common and aggressive malignant primary brain tumors, with a 5-year survival rate of less than 10% and a median survival period of only 14 months.⁷⁰ Glioma is poorly understood, and the dismal clinical outcome makes the study of molecular mechanisms in glioma urgent.⁷¹ The anti-angiogenic treatment of malignant glioma cells is an effective method to treat high-grade gliomas. However, the effect is limited in glioma due to the presence of vasculogenic mimicry (VM).⁷² Wang reported that knockdown of *SNHG16* can promote the expression of miR-212-3p and inhibit VM to sensitize glioma to anti-angiogenic treatment, which provides deeper comprehension and a novel direction for the treatment of glioma.⁷² The results indicate that *SNHG16* plays a key role in glioma and it can be a novel therapeutic target.

Conclusion and Future Perspectives

A growing number of studies have shown that dysregulated lncRNAs are potential oncogenes or tumor

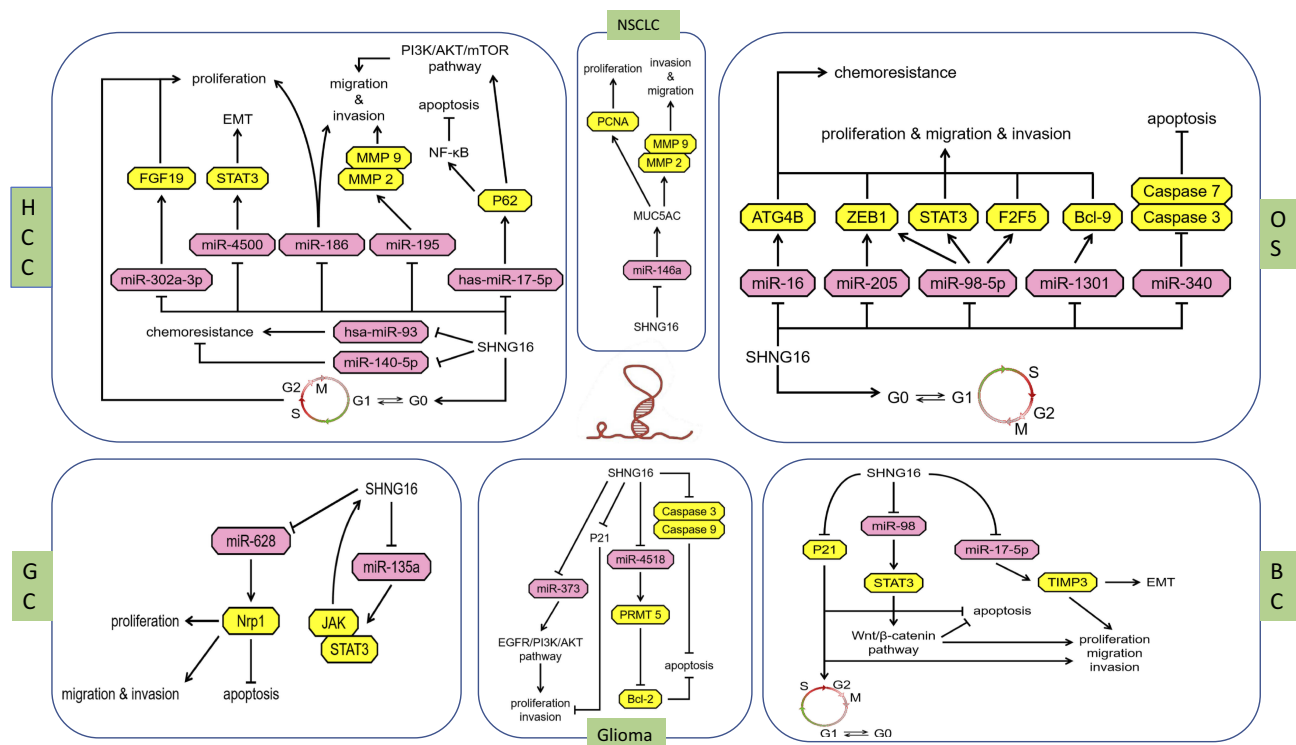


Figure 1 The different regulatory mechanisms of SNHG16 in different human cancers.

Abbreviations: HCC, Hepatocellular carcinoma; NSCLC, non-small cell lung cancer; OS, Osteosarcoma; GC, gastric cancer; BC, bladder cancer.

suppressors that play important roles in tumorigenesis and tumor progression. LncRNAs can be used as biological markers and therapeutic targets for tumors and have broad applications in the diagnosis and treatment of tumors. *SNHG16* is a newly discovered lncRNA, and it has been shown to be upregulated in many tumor types and associated with tumor stage, lymph node metastasis, and tumor size, indicators of poor prognosis. *SNHG16* binds to endogenous miRNAs, resulting in abnormal expression of downstream target genes or dysregulation of classical signaling pathways (Table 1, Figure 1). The studies discussed here highlight that the study of *SNHG16* is of great significance for further study of the mechanism of tumor development and progression, and *SNHG16* may be considered as a new diagnostic/prognostic biomarker and a therapeutic target for cancer. Although the role of *SNHG16* in cancer has been studied, there are still many areas that need further research. For example, there are few studies on thyroid cancer, breast cancer and retinoblastoma, and the understanding of the molecular mechanisms by which it drive carcinogenesis is not deep enough, instead focusing on in vitro experiments. Further research should be focused on investigating the precise molecular

regulatory mechanisms of *SNHG16*, and a larger cohort of tumor samples should also be included to facilitate the clinical application of *SNHG16* as early as possible.

Abbreviations

BC, breast cancer; CC, cervical cancer; ceRNA, competitive endogenous RNA; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; EMT, epithelial-mesenchymal transition; GC, gastric cancer; HCC, hepatocellular carcinoma; lncRNA, long noncoding RNA; MMP, matrix metalloproteinase; ncRNA, noncoding RNA; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; PC, pancreatic cancer; PI3K, phosphatidylinositol 3-kinase; PTC, papillary thyroid carcinoma; RB, retinoblastoma; SNHG16, small nucleolar RNA host gene 16; STAT3, Signal Transducers and Activators of Transcription 3; TNM, tumor, node, metastasis; VDR, vitamin D receptor; VM, vasculogenic mimicry; ZEB1, zinc finger E-box binding protein 1.

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