A Review on the Role of Small Nucleolar RNA Host Gene 6 Long Non-coding RNAs in the Carcinogenic Processes

Soudeh Ghafouri-Fard1, Tayyebeh Khoshbakht2, Mohammad Taheri3* and Seyedpouzhia Shojaei4*

1 Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 2 Men’s Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 3 Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 4 Department of Critical Care Medicine, Imam Hossein Medical and Educational Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Being located on 17q25.1, small nucleolar RNA host gene 6 (SNHG16) is a member of SNHG family of long non-coding RNAs (lncRNA) with 4 exons and 13 splice variants. This lncRNA serves as a sponge for a variety of miRNAs, namely miR-520a-3p, miR-4500, miR-146a miR-16–5p, miR-98, let-7a-5p, hsa-miR-93, miR-17-5p, miR-186, miR-302a-3p, miR-605-3p, miR-140-5p, miR-195, let-7b-5p, miR-16, miR-340, miR-1301, miR-205, miR-488, miR-1285-3p, miR-146a-5p, and miR-124-3p. This lncRNA can affect activity of TGF-β1/SMAD5, mTOR, NF-κB, Wnt, RAS/RAF/MEK/ERK and PI3K/AKT pathways. Almost all studies have reported oncogenic effect of SNHG16 in diverse cell types. Here, we explain the results of studies about the oncogenic role of SNHG16 according to three distinct sets of evidence, i.e., in vitro, animal, and clinical evidence.

Keywords: SNHG6, lncRNA, cancer, biomarker, expression

INTRODUCTION

Small nucleolar RNA host gene 6 (SNHG16) is a member of SNHG family of non-coding RNAs. Long non-coding RNAs (lncRNAs) are a class of transcripts that have sizes longer than 200 nt. These transcripts serve as scaffolds for establishment of different complexes of biomolecules. Moreover, the can serve as enhancers, modulators of chromatin structure and decoys for several molecules, particularly miRNAs [Zhang, 2019 #481]. Bioinformatics tools have facilitated identification of several classes of lncRNAs among them is SNHG group of lncRNAs [Li, 2020 #482].

Being annotated as NC_000017.11, SNHG16 gene is located on 17q25.1 and has 4 exons. Based on the Ensembl database1, 13 splice variants have been identified for this SNHG16 with one of them having a retained intron (ENST00000587743.1) and the rest being categorized as long non-coding RNAs (lncRNAs). These transcripts have sizes ranging from 556 nt (SNHG16-208) to 3607 nt (SNHG16-201). No protein has been recognized for any of these variants. It has been shown to be ubiquitously expressed in ovary, skin and several other tissues. This lncRNA has fundamental roles in the carcinogenesis in numerous types of tissues. Here, we summarize the results of these studies based on three distinct categories of evidence, i.e., in vitro, animal and clinical evidence.

1 http://asia.ensembl.org/
CELL LINE STUDIES

Small nucleolar RNA host gene 6 has been demonstrated to be up-regulated in lung cancer cell lines, where it acts as a sponge for miR-520a-3p. Through decreasing the availability of this miRNA, SNHG16 increases expression of EphA2. SNHG16 silencing has suppressed proliferation, migratory potential and invasiveness of these cells, while stimulating cell apoptosis. Further experiments have shown the prominence of SNHG16/miR-520a-3p/EphA2 axis in the regulation of oncogenicity in lung cancer (Yu et al., 2020). Being transcriptionally regulated by YY1, SNHG16 also sequesters miR-4500 to modulate expression of the deubiquitinase USP21. USP21 can further increase expression of SNHG16 (Xu P. et al., 2020). Another experiment in lung cancer cells has identified miR-146a as the target of SNHG16, through its sequestering SNHG16 enhances proliferation, migration and invasiveness of lung cancer cells. The sponging effect of SNHG16 on this miRNA leads to over-expression of MUC5AC, a protein which accelerates metastasis and recurrence of lung cancer cells (Han et al., 2019). Figure 1 depicts the roles of SNHG16 in lung cancer which are exerted via sponging miR-520a-3p, miR-4500 and miR-146a.

Small nucleolar RNA host gene 6 has also important impacts on the modulation of tumor microenvironment through influencing function of γδ immunosuppressive T cells. Mechanistically, SNHG16 works as a sponge for miR-16-5p, thus augmenting expression of SMAD5 and potentiating the TGF-β1/SMAD5 pathway to increase expression of CD73 in γδ T cells (Ni et al., 2020). In addition, SNHG16 can enhance migratory potential of breast cancer cells via sequestering miR-98 and releasing E2F5 from its inhibitory effects (Cai et al., 2017). In prostate cancer cells, siRNA-mediated silencing of SNHG16 results in down-regulation of GLUT-1, reduction of glucose uptake and inhibition of proliferation of cancerous cells without affecting normal prostate cells (Shao et al., 2020). Figure 2 shows the oncogenic roles of SNHG6 in breast and prostate cancers.

In hepatocellular carcinoma (HCC), SNHG16 has diverse oncogenic as well as tumor suppressor roles (Figures 3, 4). SNHG16 has been shown to accelerate proliferation, migratory aptitude and invasiveness of HCC cells through sequestering miR-186 and enhancing expression of ROCK1 (Chen et al., 2019). Moreover, miR-4500 is another sponged miRNA by SNHG16 through which this lncRNA promotes development of HCC (Lin et al., 2019). In this type of cancer, SNHG16 also interacts with miR-302a-3p to increase expression of FGF19 and enhance cell proliferation (Li W. et al., 2019). Metastatic ability of HCC cells can be regulated by SNHG16 through sequestering miR-605-3p. This miRNA can suppress epithelial-mesenchymal transition (EMT) and metastatic ability of HCC via directly suppressing TRAF6 expression and further modulating NF-κB signaling. Being up-regulated by SNHG16, TRAF6 can in turn increase activity of SNHG16 promoter through activation of NF-κB, thus constructing a positive feedback loop in favor of HCC progression (Hu et al., 2020).

Contrary to the mentioned studies which reported the oncogenic effects of SNHG16 in the development of HCC, a single study has revealed down-regulation of SNHG16 in HCC cell lines. Ectopic virus-mediated over-expression of SNHG16 has repressed proliferation of HCC cells and
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FIGURE 2 | Oncogenic roles of SNHG6 in breast and prostate cancers.

FIGURE 3 | Oncogenic roles of SNHG16 in hepatocellular carcinoma via sponging miR-17-5p, miR-186, miR-4500, miR-302a-3p, and miR-605-3p.

Attenuated their resistance to 5-FU through sponging hsa-miR-93 (Xu et al., 2018).

In osteosarcoma, sponging impact of SNHG16 on miR-98-5p has an essential impact on proliferation, migration and invasive aptitude of cancer cell. Simultaneously, it can enhance cell cycle progression and decrease cell apoptosis (Liao et al., 2019). Meanwhile, through sponging miR-16 and up-regulating ATG4B levels, SNHG16 can induce resistance to cisplatin in these cells (Liu Y. et al., 2019). SNHG16 can also promote proliferation of osteosarcoma cells through sponging miR-205 and enhancing expression of ZEB1 (Zhu C. et al., 2018). Finally, SNHG16 can facilitate EMT of osteosarcoma cells through miR-488/ITGA6.
In hepatocellular carcinoma, while SNHG16 exerts oncogenic effect via sponging miR-140-5p, miR-195, and let-7b-5p, it can have tumor suppressor effect via sponging has-miR-93.

Small nucleolar RNA host gene 6/miR-124-3p/MCP-1 has an important role in induction of cell proliferation and EMT in colorectal cancer (Chen et al., 2020). The sponging effect of SNHG16 on miR-200a-3p (Li Y. et al., 2019), miR-132-3p (He et al., 2020), and miR-302a-3p (Ke et al., 2019), also promotes tumorigenicity of colorectal cancer.

In cervical cancer cells, SNHG16 has been found to recruit transcriptional factor SPI1 to increase expression of PARP9,
thus promoting malignant behaviors of cells (Tao et al., 2020). Moreover, through sponging miR-216-5p, SNHG16 can increase expression of ZEB1, therefore increasing both cell proliferation and EMT process (Zhu H. et al., 2018). Finally, through sponging miR-128, it affects activity Wnt/β-catenin pathway (Wu et al., 2020). Figure 6 summarizes the role of SNHG16 in colorectal and cervical cancers.

In neuroblastoma cells, SNHG16 has been revealed to sequester miR-542-3p (Deng et al., 2020), miR-128-3p (Bao et al., 2020) and miR-338-3p (Xu Z. et al., 2020), thus increasing expressions of HNF4α, HOXA7, and PLK4, respectively (Figure 7).

In other types of cancers, including retinoblastoma, oral squamous cell carcinoma, nasopharyngeal carcinoma, SNHG16...
sequesters a number of miRNAs, namely miR-140-5p, miR-182-5p, miR-128-3p, miR-183-5p, miR-17-5p, and miR-520a-3p (Figure 8). In pancreatic cancer, SNHG16 acts in favor of tumor progression through sponging miR-302b-3p and subsequently increasing expression of SLC2A4 (Xu et al., 2021). Moreover, it can contribute in this process through sponging miR-218-5p (Liu S. et al., 2019). Finally, SNHG16-mediated enhancement of lipogenesis through affecting expression of SREBP2 facilitates progression of pancreatic cancer (Yu et al., 2019b).
| Tumor type | Interactions | Cell line | Function | References |
|------------|--------------|-----------|----------|------------|
| **Non–small cell lung cancer (NSCLC)** | mir-520a-3p, EphA2 | 16HBE, A549, NCI-H292, NCI-H460, NCI-H1703 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion, ↑ apoptosis | Yu et al., 2020 |
| | mir-4500, USP21, YY1 | A549, H1299, NCI-H460, and NCI-H520 | \( \Delta \) USP21: ↓ proliferation, ↓ migration, ↓ invasion | Xu P. et al., 2020 |
| | mir-146a, MUC5AC | A549, NCI-H292, NCI-H460, NCI-H1703, 16HBE | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion ↑ SNHG16: ↑ proliferation, ↑ migration | Han et al., 2019 |
| **Breast cancer** | mir-16–5p, SMAD5, TGF-β1/SMAD5 pathway, CD73 | MCF-10A, MCF-7, T-47D, MDA-MB-231, HEK293T | \( \Delta \) SNHG16: ↓ migration, did not affect proliferation ↑ SNHG16: ↑ migration, did not affect proliferation | Cai et al., 2017 |
| | mir-98, E2F5 | MDA-MB-231, MCF-7, MDA-MB468 and HEK293T | \( \Delta \) SNHG16: ↓ proliferation | Zhong et al., 2019 |
| | let-7a-5p, RRM2 | MCF-7 | \( \Delta \) SNHG16: ↓ proliferation | Shao et al., 2020 |
| **Prostate carcinoma** | GLUT1 | 22Rv1, HPrEC | \( \Delta \) SNHG16: ↓ proliferation, ↓ glucose uptake ↑ SNHG16: ↓ proliferation, ↓ 5-FU chemoresistance | Xu et al., 2018 |
| **Hepatocellular carcinoma (HCC)** | hsa-miR-93 | Hep3B, HuH7, SNU398, SNU423, SNU429, Hep3B, HepG2, p53, PK-1, and PLC/PRF/5 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion ↑ SNHG16: ↑ proliferation, ↑ migration, ↑ invasion, ↑ cell cycle progression, ↓ apoptosis | Zhong et al., 2020 |
| | mir-17-5p, p62, mTOR pathway, NF-κB pathway | Huh-7 and HepG2 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion ↑ SNHG16: ↑ proliferation, ↑ migration, ↑ invasion, ↓ cell cycle progression, ↓ apoptosis | Li W. et al., 2019 |
| | mir-186 | Hep-3B, HuH7, Ske-hep-1, SMMC-7721, PLCL, HL-7702 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion | Chen et al., 2019 |
| | mir-4500, STAT3 | SMMC-7721, L02, MHCC-97H, HepG2 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion, ↑ apoptosis | Lin et al., 2019 |
| | mir-302a-3p, FGFl9 | Huh7, HepG2, SMMC7721, SK-Hep1 and Hep 3B, L02 | \( \Delta \) SNHG16: ↓ proliferation | Li W. et al., 2019 |
| | mir-605-3p, NF-κB pathway | HCCM3, MHCC97L, MHCC-97H, L02, Hep3B and HepG2 | \( \Delta \) SNHG16: ↓ metastasis, ↓ EMT process | Hu et al., 2020 |
| | mir-140-5p | HepG2, SK-hep1, HuH7, and HCCM3, L02, HepG2/SOR | \( \Delta \) SNHG16: ↓ sorafenib resistance | Ye et al., 2019 |
| | mir-195 | HepG2, SMMC7721, Hep3B, Bel7402, HuH7, L02 | \( \Delta \) SNHG16: ↓ proliferation, ↓ invasion | Xie et al., 2019 |
| | let-7b-5p, CDC25B, HMG2 | HL-7702, SK-Hep-1, Huh7, Hep3B, HepG2 | \( \Delta \) SNHG16: ↓ G2/M cell cycle arrest, ↓ cisplatin resistance, ↓ apoptosis ↑ SNHG16: ↑ cell cycle progression, ↓ EMT process | Li S. et al., 2020 |
| **Osteosarcoma** | mir-98-5p | U2OS, Saos-2, HOS, MG-63, hFOB 1.19 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion ↑ cell cycle arrest, ↑ apoptosis | Liao et al., 2019 |
| | mir-16, ATG4B | SAOS2, U2OS, OB3, 293T | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion ↑ autophagy, ↓ chemoresistance | Liu Y. et al., 2019 |
| | mir-340 | hFOB1.19, U2OS, SaOS2 | \( \Delta \) SNHG16: ↓ viability, ↓ apoptosis, ↑ caspase 3/7 activity | Su et al., 2019 |
| | mir-1301, BCL9 | U2OS, MG-63 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion | Wang et al., 2019a |
| | mir-205, ZEB1 | MG-63, U2OS, SAOS2, HOS, OB3 | \( \Delta \) SNHG16: ↓ proliferation | Zhu C. et al., 2018 |
| | mir-488, ITGA6 | U2OS, HOS | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ EMT process | Bu et al., 2021 |
| | mir-1285-3p, cleaved-caspase-3, Bax, pro-caspase-3, Bcl-2 | U2OS, MNNG/HOS, 143b, SJSA, MG63, 293, hFOB 1.19 | \( \Delta \) SNHG16: ↓ proliferation, ↓ migration, ↓ invasion, ↑ cell cycle arrest, ↑ apoptosis | Xiao et al., 2021 |
| | mir-146a-5p, NOVA1 | hFOB1.19, MG63, U2OS, 143B, MNNG/HOS | ↑ SNHG16: ↑ proliferation, ↑ migration | Zheng et al., 2019 |
| **Colorectal cancer (CRC)** | mir-124-3p, MCP-1 | HEK293T, FHC, SW480, HCT116, DLD-1, LOVO | \( \Delta \) SNHG16: ↓ proliferation, ↓ invasion, ↓ EMT process | Chen et al., 2020 |
TABLE 1 | (Continued)

| Tumor type | Interactions | Cell line | Function | References |
|------------|--------------|-----------|----------|------------|
| Cervical cancer | PARP9, SP1 | SiHa, CaSiK, C33A, ME180, HeLa, HcErEpic | ↑ SNHG16: proliferation, ↑ migration, ↓ invasion | Tao et al., 2020 |
| Neuroblastoma (NB) | – | SH-SY5Y | ↑ SNHG16: proliferation, ↑ migration, ↓ invasion, ↓ EMT process | Yu et al., 2019a |
| Retinoblastoma (RB) | miR-140-5p | ARPE-19, WERI-Rb1, SO-RB-50, Y79, SO-Rb50 | ↑ SNHG16: proliferation, ↓ colony formation, ↑ apoptosis | Xu et al., 2019 |
| Oral squamous cell carcinoma (OSCC) | c-Myc, E-cadherin, N-cadherin, Snail, MMP-2, MMP-9, PCNA | ARPE-19 and human RB cell lines Y-79, WERI-Rb1, 67BR and SO-Rb50 | ↑ SNHG16: proliferation, ↓ migration, ↓ invasion, ↑ apoptosis | Li S. et al., 2019 |
| Nasopharyngeal carcinoma (NPC) | | NOK, CAL27, TCA8113, OEC-M1, TW2.6 | ↑ SNHG16: proliferation, ↑ apoptosis | Wang et al., 2021 |
| Pancreatic cancer (PC) | | HPY-5, BxPC3, Panc-1, MIA Paca-2, SW1990 | ↑ SNHG16: proliferation, ↓ migration, ↓ invasion, ↑ apoptosis | Xu et al., 2021 |
| Papillary thyroid cancer (PTC) | | | ↑ SNHG16: proliferation, ↓ colonization formation, ↓ migration, ↓ invasion | Liu S. et al., 2019 |
| | | | ↑ SNHG16: proliferation, ↓ migration, ↓ invasion, ↓ lipogenesis | Wu et al., 2019 |
| | | | ↑ SNHG16: proliferation, ↓ metastasis | Wang et al., 2021 |
| | | | ↑ SNHG16: proliferation, ↓ invasion | Pang et al., 2019 |
| | | | ↑ SNHG16: proliferation, ↓ invasion | Wang et al., 2019b |
| | | | ↑ SNHG16: proliferation, ↓ apoptosis | Wen et al., 2019 |
| | | | ↑ SNHG16: proliferation, ↓ apoptosis | Cao et al., 2018 |
| | | | ↑ SNHG16: proliferation, ↓ viability, ↓ EMT process, ↑ apoptosis | Peng and Li, 2019 |
| Ovarian cancer | P-AKT, MMP9 | SKOV-3, ES2, HO8910, OMC685, OSE-29 | ↑ SNHG16: proliferation, ↓ migration, ↓ invasion | Yang et al., 2018 |

(Continued)
Small nucleolar RNA host gene 6 participates in the progression of gastric cancer via sequestering miR-628-3p and consequently decreasing expression of NRP1 (Pang et al., 2019). Animal studies have consistently shown that SNHG16 silencing decreases malignant feature of the grafted cancer cells (Fig. 9).

Table 1 summarizes the results of in vitro studies regarding the role of SNHG16 in carcinogenesis.

### ANIMAL STUDIES

Animal studies have consistently shown that SNHG16 silencing decreases malignant feature of the grafted cancer cells (Table 2). The only exception has been reported in HCC where SNHG16 over-expression has significantly suppressed the in vivo expansion of grafted HuH7 cells (Xu et al., 2018). Another study in HCC xenograft model has shown that SNHG16 silencing enhances response of HepG2/SOR cells to cytotoxic effect of sorafenib and attenuates tumor growth (Ye et al., 2019). In xenograft models of retinoblastoma, up-regulation SNHG16 (Xu et al., 2019) or its downstream target NRAS (Sun et al., 2019) can increase tumor growth. Finally, in gastric cancer where SNHG16 sponges miR-628, in vivo studies have shown that up-regulation of miR-628 can decrease tumor expansion (Pang et al., 2019).

### CLINICAL STUDIES

Except for a single study which demonstrated down-regulation of SNHG16 in HCC samples versus nearby non-malignant hepatic tissues (Xu et al., 2018), other studies have indicated up-regulation of SNHG16 in malignant tissues of different origins compared with non-neoplastic samples (Supplementary Table 1). Consistent with these findings, up-regulation of SNHG16 has been revealed to predict poor survival of patients. Moreover, its expression has been related with greater chance of
distant metastasis, lymph node involvement and low
differentiation of tumor cells.

**DISCUSSION**

Small nucleolar RNA host gene 6 has been regarded as an oncogenic lncRNA in almost all tissues. This lncRNA affect carcinogenesis through multifaceted mechanisms including mechanisms related to both tumor cells and their niche. In fact, it can both affect cellular functions and processes, particularly those related with proliferation, survival and apoptosis as well as microenvironmental aspects of cancer progression.

More than 20 miRNAs have been found to interact with SNHG16. The sponging effects of SNHG16 on miRNAs have been well studied. miR-520a-3p, miR-4500, miR-146a miR-16–5p, miR-98, let-7a-5p, hsa-miR-93, miR-17-5p, miR-186, miR-302a-3p, miR-605-3p, miR-1301, miR-140-5p, miR-195, let-7b-5p, miR-16, miR-340, miR-1301, miR-205, miR-488, miR-1285-3p, miR-302a-3p, miR-605-3p, miR-140-5p, miR-195, let-7b-5p, miR-16, miR-340, miR-1301, miR-205, miR-488, miR-1285-3p, miR-146a-5p, and miR-124-3p are examples of miRNAs sponged by this lncRNA in different types of cancers. Verification of interaction between this lncRNA and a number of miRNAs such as miR-98 in different tissues raises the possibility of independence of such interactions from the tissue type. TGF-β1/SMAD5, mTOR, NF-κB, RAS/RAF/MEK/ERK, PI3K/AKT, and Wnt/β-catenin pathways are among cancer-related pathways.

**TABLE 2** | Outline of studies which judged function of SNHG16 in animal models (Δ, knock-down or deletion; VM, vasculogenic mimicry).

| Tumor Type | Animal models | Results | References |
|------------|---------------|---------|------------|
| Non–small cell lung cancer (NSCLC) | male Athymic BALB/c mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth | Yu et al., 2020 |
| | female BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Han et al., 2019 |
| Hepatocellular carcinoma (HCC) | athymic nude mice | ↑ SNHG16: ↑ tumor size, ↑ tumor growth | Xu et al., 2018 |
| | female BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight, ↑ SNHG16: ↑ tumor size, ↑ tumor weight | Zhong et al., 2020 |
| | nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth | Chen et al., 2019 |
| | Male Athymic nu/nu nude mice | Δ SNHG16: ↓ tumor size, ↓ tumor weight, ↓ tumor growth, ↓ sorafenib resistance | Ye et al., 2019 |
| Osteosarcoma | male BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor growth | Xie et al., 2019 |
| | BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight, ↓ metastatic | Li S. et al., 2020 |
| Colorectal cancer (CRC) | male BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor growth, ↓ metastatic | Bu et al., 2021 |
| | nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Xiao et al., 2021 |
| | male BALB/c nude mice | Δ SNHG16: ↓ tumor size, ↓ tumor weight, ↓ metastasis | Chen et al., 2020 |
| | male BALB/c nude mice | ↑ SNHG16: ↑ tumor size | Li Y. et al., 2019 |
| Cervical cancer | specific-pathogen-free | Δ SNHG16: ↓ tumor growth | He et al., 2020 |
| Neuroblastoma (NB) | BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Tao et al., 2020 |
| Retinoblastoma (RB) | athymic BALB/c mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Deng et al., 2020; Bao et al., 2020; Wen et al., 2020 |
| | male BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Xu Z. et al., 2020 |
| | female BALB/c nude mice | Δ NRAS: ↓ tumor volume, ↓ tumor weight | Sun et al., 2019 |
| | BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Li S. et al., 2019 |
| Oral squamous cell carcinoma | male athymic BALB/c nude mice | Δ SNHG16: ↓ tumor growth ↑ SNHG16: ↑ tumor growth | Wang et al., 2021 |
| Pancreatic cancer | male BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor growth | Sun et al., 2019 |
| Nasopharyngeal carcinoma (NPC) | male BALB/C nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Liu S. et al., 2019 |
| Gastric cancer | female BALB/c nude mice | ↑ mir-628: ↓ tumor volume, ↓ tumor weight | Wu et al., 2021 |
| Acute lymphoblastic leukemia (ALL) | null mice | Δ SNHG16: ↓ tumor volume, ↓ ALL tumor transplants | Pang et al., 2019 |
| Large B–cell lymphoma (DLBCL) | male NOD/SCID mice | Δ SNHG16: ↓ tumor growth | Yang T. et al., 2019 |
| Glioma | athymic BALB/c nude mice | Δ SNHG16: ↓ tumor volume, ↓ number of VMs, ↑ survival period | Zhu et al., 2019 |
| Endometrial carcinoma | male nude BALB/c mice | Δ SNHG16: ↓ tumor volume, ↓ tumor growth | Wang et al., 2019 |
| Laryngeal squamous cell carcinoma (LSCC) | female nude mice | Δ SNHG16: ↓ tumor volume, ↓ tumor weight | Zhang G. et al., 2019 |
| Esophageal cancer | female BALB/c athymic nude mice | Δ SNHG16: ↓ tumor growth | Han et al., 2018 |
being affected by this lncRNA. Moreover, SNHG16 has been shown to affect expression of a number of EMT-associated transcription factors and enhance this process. SNHG16 has also been found to affect response of cancer cells to 5-FU and sorafenib.

Based on the results of functional studies that confirmed the ability of siRNA-mediated SNHG16 silencing in reduction of cancer cell proliferation and invasiveness, this strategy can be proposed as a therapeutic strategy for cancer. In vivo studies have also confirmed applicability of these methods; however no clinical study has applied these methods yet. Antisense oligonucleotides as a promising strategy for suppression of expression of SNHG16 should be appraised in clinical settings considering the bioavailability and safety issues.

Although over-expression of SNHG16 has been verified in tissue samples of different types of tumors, application of this lncRNA as a circulatory marker for early detection of cancer has not been assessed. Since clinical studies have revealed correlation between expression amounts of SNHG16 and malignant features, one can suppose that SNHG16 can be used as both diagnostic and prognostic marker. However, this speculation should be verified in future.

**AUTHOR CONTRIBUTIONS**

MT and SG-F wrote the draft and revised it. TK and SS collected the data and designed the tables and figures. All authors read and approved submitted version.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcell.2021.741684/full#supplementary-material
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