



Long Non-coding RNA Small Nucleolar RNA Host Gene 14, a Promising Biomarker and Therapeutic Target in Malignancy

Shen Shen^{1,2*†}, Yanfang Wang^{3†}, Yize Zhang^{1,2}, Zihui Dong^{1,2} and Jiyuan Xing^{1,2}

¹ Precision Medicine Center, Gene Hospital of Henan Province, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, ² Department of Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, ³ Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

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*Correspondence:

Shen Shen
fccshenk@zzu.edu.cn

† These authors have contributed
equally to this work

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Small nucleolar RNA host gene 14 (SNHG14) is a long non-coding RNA found to be overexpressed in various types of cancers. Moreover, the expression level of SNHG14 was closely associated with multiple clinicopathological characteristics such as prognosis, tumor differentiation, TNM stage, and lymph node metastasis. Functionally, gain- and loss-of-function of SNHG14 revealed that overexpressed SNHG14 promoted cancer cell viability, invasion, and migration, whereas its down-regulation produced the opposite effect. Mechanistically, regulating its target gene expression by sponging distinct miRNAs might be the major mechanism underlying the oncogenic functions of SNHG14. Thus, SNHG14 might be a promising prognostic biomarker and therapeutic target for cancers. In this review, we discuss the expression profile, biological function, and molecular mechanisms of SNHG14 in cancers to provide a molecular basis for the clinical utility of SNHG14 in the future.

Keywords: malignancy, lncRNA, SNHG14, biomarker, prognosis

INTRODUCTION

Long non-coding RNAs (lncRNAs) are a group of non-protein-coding RNAs longer than 200 nucleotides in length (Chan and Tay, 2018). Growing evidence shows that lncRNAs play vital roles in normal cellular processes through complicated mechanisms (Ørom et al., 2010; Tian et al., 2010). Dysfunction of lncRNAs implicates pathological conditions, especially cancer (Huarte, 2015; Schmitz et al., 2016; Bhan et al., 2017; Yarani et al., 2018; Zhang and Tang, 2018; Simion et al., 2019). Previous studies have determined the biological function of lncRNAs in cellular development and metabolism, including genome rearrangement (Aznaourova et al., 2020), chromatin modification (Han and Chang, 2015), splicing (Romero-Barrios et al., 2018; Corona-Gomez et al., 2020), mRNA decay (Zhu et al., 2013), genetic imprinting (Barlow and Bartolomei, 2014), and translational regulation (Akhade et al., 2017). Emerging lncRNAs are understood to be involved in regulating gene expression at the transcriptional and post-transcriptional levels (Zhang et al., 2019a). Notably, several lncRNAs usually play an oncogenic role or tumor suppressor roles in carcinogenesis and cancer progression by affecting tumor cell differentiation, viability, invasion, migration, apoptosis, and drug resistance (Wang J. et al., 2018; Ghafouri-Fard et al., 2020a,b).

lncRNA small nucleolar RNA host gene 14 (SNHG14) is a new lncRNA located on chromosome 15q11.2 in humans. It has played an essential role in promoting inflammation microglia activation (Qi et al., 2017; Zhong et al., 2019; Jiang et al., 2021), sepsis-induced acute kidney injury (Shi et al., 2021), and LPS-induced acute kidney injury (Yang et al., 2021). In addition to its function in tumorigenesis and progression, SNHG14 was found to function as a competing endogenous RNA for microRNAs-382-5p (miR-382-5p) to regulate SPIN1 expression in non-small cell lung cancer (Chen et al., 2020). Tang and Yang (2020) reported that SNHG14 binds to miR-656-3p using dual-luciferase reporter assay in hepatocellular carcinoma (HCC). Xie et al. (2020) found that SNHG14 promoted pancreatic ductal adenocarcinoma progression by regulating E-cadherin expression by interacting with EZH2. Collectively, the regulatory mechanisms of SNHG14 are highly complicated and unclear.

In this study, we summarize the latest evidence of SNHG14 in human cancers, especially its abnormal expression, biological functions, and molecular mechanisms, and discuss the potential clinical value of SNHG14 as a novel method for cancer diagnosis, prognosis, and treatment.

CLINICAL RELEVANCE OF SMALL NUCLEOLAR RNA HOST GENE 14 IN CANCERS

Tissue-specific expression patterns indicate that lncRNAs might be served as potential biomarkers and provide a rationale to target them clinically (Statello et al., 2021; Winkle et al., 2021). To explore the role of SNHG14 in cancer, some research groups have studied the expression profile, roles, and clinical significance of SNHG14 in various types of cancers (Table 1). Feng et al. (2021) reported that 37 of 62 of SNHG14 expressions were significantly increased in bladder cancer tissues than in normal control tissues. Another study found this lncRNA was overexpressed in HCC tissues and cell lines (Lin et al., 2021). Up-regulation of SNHG14 in tumor tissues was also found in multiple cancer types, such as NSCLC (Zhang et al., 2019d), HCC (Pu et al., 2019), osteosarcoma (Hou and Mao, 2020), ovarian cancer (Zhao and Huang, 2019), glioma (Lu et al., 2020), prostate cancer (Luo et al., 2020), breast cancer (Dong et al., 2018a), clear cell renal cell carcinoma (Liu et al., 2017), retinoblastoma (Sun et al., 2020), acute myeloid leukemia (Wang et al., 2021a), pancreatic cancer (Zhang et al., 2019b), colorectal cancer (Han et al., 2020), cervical cancer (Ji et al., 2019), and endometrial cancer (Zhao et al., 2020). Notably, the expression of SNHG14 in glioma (Wang Q. et al., 2018), colorectal cancer (Zhang W. et al., 2020), and endometrial carcinoma (Zhang K. et al., 2020) was controversial. We suggest that large sample size and cross-regional or even cross-national multi-center large sample verification may provide better evidence for the conclusion. We believe that the existing studies are contradictory and may be affected by various factors such as detection methods, sensitivity and experimental conditions. These seemingly contradictory conclusions suggest that further research is needed to this regard.

Importantly, the expression level of SNHG14 has been demonstrated correlated with prognosis in patients with NSCLC (Zhang et al., 2019d), HCC (Zhang H. et al., 2020), ovarian cancer (Zhao J. L. et al., 2019), retinoblastoma (Sun et al., 2020), pancreatic ductal adenocarcinoma (Xie et al., 2020), colorectal cancer (Pei et al., 2019), cervical cancer (Ji et al., 2019), and endometrial cancer (Zhao et al., 2020). Furthermore, some researchers discovered that highly expressed SNHG14 was positively correlated with large tumor size, advanced TNM stage, distant metastasis and poor tumor differentiation in bladder cancer (Feng et al., 2021), NSCLC (Zhang et al., 2019d), HCC (Liao et al., 2021), prostate cancer (Luo et al., 2020), retinoblastoma (Sun et al., 2020), pancreatic cancer (Deng et al., 2019), and cervical cancer (Ji et al., 2019). The results indicate that SNHG14 can become a prognostic indicator of cancers.

ROC curves analysis showed that the sensitivity of SNHG14 in HCC was 98.5% and the optimal cutoff value of SNHG14 was 1.22 (Tang and Yang, 2020). In bladder cancer, the survival curve analysis of SNHG14 showed that the area under the curve was 0.842 and the cutoff value was 2.714, indicating the diagnostic potential of SNHG14 (Li et al., 2019). Zhao et al. (2020) also confirmed the diagnosis efficiency of SNHG14 in ovarian cancer.

Generally, the aforementioned results suggest that SNHG14 plays an oncogenic role in various types of cancer, and it may serve as a new biomarker for cancer diagnosis and prognosis, although further investigation is required for clinical application.

BIOLOGY FUNCTION AND THE MOLECULAR MECHANISM OF SMALL NUCLEOLAR RNA HOST GENE 14 IN VARIOUS CANCERS

Emerging evidence revealed the expression of SNHG14 in tumor cell lines and the effect of knockdown or overexpression of this lncRNA on tumor cell malignant characteristics such as proliferation, invasion, migration, apoptosis, and drug resistance. The regulatory mechanisms of SNHG14 are complex in distinct types of cancers, even in one cancer. The major mechanism underlying the tumor-promoting function of SNHG14 is to regulate target genes via competing with miRNAs (Table 2). In the following sections, we focus on the function of SNHG14 in various cancers.

Bladder Cancer

Bladder cancer is one of the most common cancers and has high mortality worldwide (DeGeorge et al., 2017; Lenis et al., 2020). Recently, lncRNAs were found to be closely correlated with bladder occurrence and development (Martens-Uzunova et al., 2014; Cao et al., 2020; Li et al., 2020). However, the molecular mechanism of lncRNAs in the pathogenesis of bladder cancer is still unclear. The expression level of SNHG14 in bladder cancer cell lines (T24, 5637, UMUC-3, and EJ) was higher than in normal bladder epithelial cells SV-HCV-1 (Li et al., 2019; Feng et al., 2021). Feng et al. (2021) reported that knockdown of lncRNA in T24 cells suppressed cell proliferation, migration,

and invasion, while facilitating cell apoptosis, overexpression this lncRNA shows an opposite effect. The results of bioinformatic analysis and luciferase reporter assay demonstrated that SNHG14 functions as a cancer-promoting gene by targeting miR-211-3p to regulate ESM1 expression (Feng et al., 2021). In other studies, the overexpression of SNHG14 was found to accelerate the proliferative potential by sponging miR-150-5p to degrade VAMP2 expression (Li et al., 2019). The aforementioned results suggest that SNHG14 is a potential therapeutic target for bladder cancer.

Non-small Cell Lung Cancer

Lung cancer is the most commonly diagnosed cancer, with approximately 1.8 million cancer-related deaths worldwide in 2018 (Bray et al., 2018). NSCLC accounts for 85% of all lung cancer cases (Ginn et al., 2020). The 5-year survival rate for patients with advanced-stage NSCLC remains approximately 14% (Ko et al., 2018). This highlights a need to develop new ways to tackle the disease. Zhang et al. (2019d) reported

that SNHG14 expression was markedly higher in NSCLC cell lines (including A549, NCI-H1975, NCI-H1299, and SK-MES-1) than normal 16HBGE cells, and overexpression of SNHG14 promoted cell proliferation by targeting miR-340. A recent study found that overexpression of SNHG14 facilitates NSCLC cell proliferation, invasion, and migration by regulating G6PD expression by sponging miR-206 (Zhao et al., 2020). Similarly, Chen et al. (2020) demonstrated that SNHG14 accelerated NSCLC progression via the miR-382-5P/SPIN1 axis. Additionally, SNHG14 was reported to influence NSCLC cisplatin resistance by modulating the HMGB1 expression through targeting miR-34a (Jiao et al., 2019). Specifically, in this research, the expression of SNHG14 was remarkably high in cisplatin-resistant NSCLC cell lines (A549 and H1299) compared with that in the human bronchial epithelioid cell line (16HBE). SNHG14 silencing or overexpression miR-34a promoted cell sensitivity to cisplatin (Jiao et al., 2019). SNHG14 was also revealed to regulate the cisplatin resistance through the miR-133a/HOXB13 pathway (Xu L. et al., 2020). Wu et al. (2019)

TABLE 1 | Expression of SNHG14 in clinical samples.

| Cancer types | Numbers of tissues | Expression | Clinicopathological characteristics | Prognosis | References |
|-------------------------------|--------------------------------|------------|---|-------------|-------------------------|
| Bladder cancer | 62 pairs | High | Advanced TNM stage, tumor invasion stage, and lymph node metastasis | Poor | Feng et al., 2021 |
| Non-small cell lung cancer | 24 pairs | High | Not studied | Poor | Li et al., 2019 |
| | 99 pairs | High | Larger tumor size and advanced TNM stage | Poor | Zhang et al., 2019d |
| | 74 pairs | High | Not studied | Not studied | Zhao et al., 2020 |
| Hepatocellular carcinoma | 50 pairs | High | Not studied | Not studied | Chen et al., 2020 |
| | 55 pairs | High | Later stage | Not studied | Xu X. et al., 2020 |
| | 40 pairs | High | Not studied | Poor | Zhang H. et al., 2020 |
| Osteosarcoma | 66 pairs | High | Advanced stage | Poor | Liao et al., 2021 |
| | 31 pairs | High | Not studied | Not studied | Hou and Mao, 2020 |
| Ovarian cancer | 24 pairs | High | Not studied | Poor | Zhao and Huang, 2019 |
| | 56 pairs | High | Not studied | Poor | Zhao J. L. et al., 2019 |
| Glioma | 8 pairs | High | Not studied | Not studied | Lu et al., 2020 |
| | 29 pairs | Low | Not studied | Not studied | Wang Q. et al., 2018 |
| Breast cancer | 36 pairs | High | Not studied | Not studied | Dong et al., 2018b |
| Retinoblastoma | 43 pairs | High | Advanced stage and differentiation grade | Poor | Sun et al., 2020 |
| Diffuse large B cell lymphoma | 3 pairs | High | Not studied | Not studied | Zhao L. et al., 2019 |
| | 21 pairs | High | Not studied | Not studied | Tian et al., 2021 |
| Acute myeloid leukemia | 57 pairs | High | Not studied | Not studied | Wang et al., 2021a |
| Pancreatic cancer | 65 tumor and 30 normal tissues | High | Not studied | Not studied | Zhang et al., 2019b |
| | 45 pairs | High | Poor tumor differentiation, advanced TNM stage, and nodal metastasis | Not studied | Deng et al., 2019 |
| | 58 pairs | High | Advanced TNM stage and positive lymph node metastasis | Poor | Xie et al., 2020 |
| Colorectal cancer | 92 pairs | Low | Not studied | Poor | Zhang W. et al., 2020 |
| | 50 pairs | High | Not studied | Not studied | Han et al., 2020 |
| | 32 pairs | High | Not studied | Poor | Pei et al., 2019 |
| Cervical cancer | 30 pairs | High | Tumor stage, tumor size, and distant metastasis | Not studied | Wang et al., 2021b |
| | 80 pairs | High | Advanced FIGO stage, differentiation, and lymph node metastasis | Poor | Ji et al., 2019 |
| Endometrial cancer | 30 pairs | High | Large tumor size, later stage and a higher incidence of lymph node metastasis | Poor | Zhang et al., 2019c |
| | 52 pairs | High | Larger tumor size and distance metastasis | Poor | Zhao et al., 2020 |
| | 53 pairs | Low | FIGO stage, histological grade, and lymphatic metastasis | Better | Zhang K. et al., 2020 |

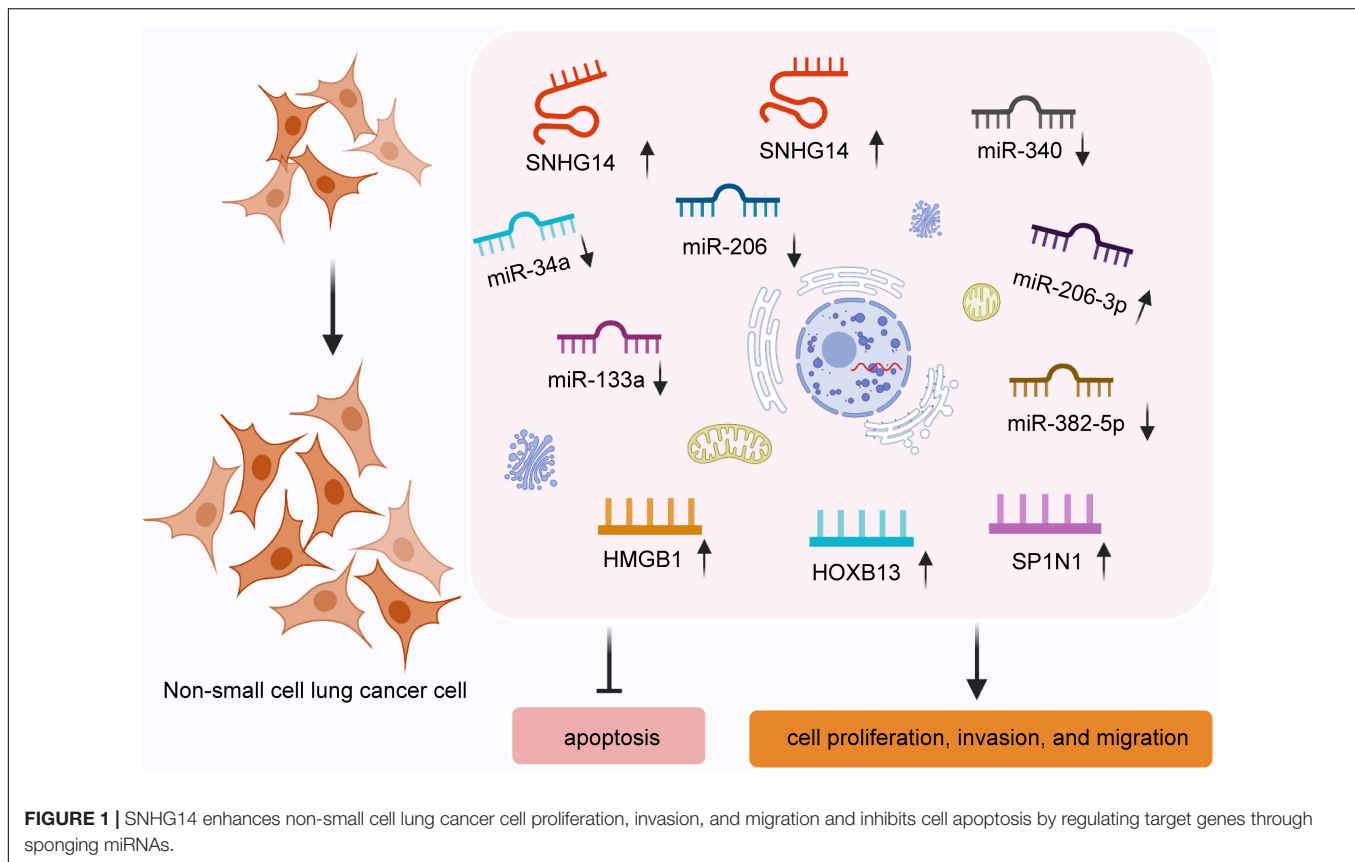
TABLE 2 | Mechanism underlying the function of SNHG14 in various cancers.

| Cancer types | Assessed cell lines | Function | Molecular mechanism | Target genes and related signal pathway | References |
|---|---|--|------------------------------|---|-------------------------|
| Bladder cancer (BCa) | BCa cell lines (T24, 5637, UMUC-3, and EJ) and normal bladder epithelial cells SV-HVC-1 | Invasion, migration, and proliferation | Sponging miR-211-3p | ESM1 | Feng et al., 2021 |
| | Normal bladder transitional epithelial cell line SV-HUC1 and BCa cell lines T24, UC9, PAL19, and UC19 | Proliferation | Sponging miR-150-5p | VAMP2 | Li et al., 2019 |
| Non-small cell lung cancer (NSCLC) | NSCLC cells A549, NCI-H1975, NCI-H1299, SK-MES-1, and normal human bronchial epithelial 16HBE cells | Proliferation | Sponging miR-340 | Not studied | Zhang et al., 2019d |
| | Bronchial epithelioid cell line 16HBE and two NSCLC cell lines A549 and H1299 | Cisplatin resistance | Sponging miR-34a | HMGB1 | Jiao et al., 2019 |
| | NSCLC cell line PC9, gefitinib-resistant PC9 cell line (PC9/GR) | Gefitinib resistance | Sponging miR-206-3p | Not studied | Wu et al., 2019 |
| | Normal bronchial epithelial 16HBE cells and two NSCLC cell lines (A549 and SK-MES-1) | Proliferation, invasion, and migration | Sponge for miR-206 | Not studied | Zhao et al., 2020 |
| | NSCLC cell (A549) and DDP-resistant NSCLC cell (A549/DDP) | Cisplatin resistance | Sponging miR-133a | HOXB13 | Xu L. et al., 2020 |
| | H1299 and A549 cells compared with that in normal lung cell BEAS-2B | Migration, invasion, and apoptosis | Sponging miR-382-5p | SPIN1 | Chen et al., 2020 |
| Hepatocellular carcinoma (HCC) | HCC cell lines (Hep3B and Huh-7) and normal liver cell line L02 | Proliferation and apoptosis | Sponging miR-4673 | SOCS1 | Pu et al., 2019 |
| | Liver epithelial cell line (THLE-2) and the HCC cell line (Huh-7, Hep3B) | Cell proliferation and apoptosis | Sponging miR-217-5p | MAPK/ERK signaling | Xu X. et al., 2020 |
| | HCC cells (HepG2, Hep3B, MHCC-97H, and Huh-7) and human hepatocyte cells (LO2) | Proliferation, invasion, and migration | Sponging miR-656-3p | SIRT5 | Tang and Yang, 2020 |
| | Human hepatic cell line L02 cells, human HCC cell lines Hep3B, SMMC7721, Huh7, HepG2, and MHCC-97H cells | Proliferation, migration, and angiogenesis | Regulating PABPC1 | PTEN signaling pathway | Zhang H. et al., 2020 |
| | Human hepatic cell line L02 cells and human HCC cell lines HepG2, Hep3B, HLF, MHCC-97H | Proliferation, migration, and invasion | Sponging miR-876-5p | SSR2 | Liao et al., 2021 |
| Osteosarcoma | 143B, MG-63, Saos-2, HOS, and U2OS cell lines and normal human osteoblastic cell line (HFOB1.19) | Proliferation, migration, and invasion | Sponging miR-433-3p | FBXO22 | Hou and Mao, 2020 |
| Ovarian cancer | Normal cell line HOSEpiC and ovarian cancer cell lines including C13K, SKOV3, 3AO, and OVCAR3 | Proliferation and cell cycle progression | Sponging miR-125a-5p | DHX33 | Zhao and Huang, 2019 |
| | A2780, TO-V112D, HO-8910, OVCAR-3, and SKOV3 and one normal ovarian cells (ISOE80) | Migration and invasion | Regulating DGCR8 | DGCR8 | Zhao J. L. et al., 2019 |
| Glioma | Glioma cell lines U251 and U87 and normal brain glial cell line HEB | Invasion, and apoptosis | Sponging miR-92a-3p | Not studied | Wang Q. et al., 2018 |
| Prostate cancer | Normal human myofibroblast stromal cell (WPMY1) and human prostate cancer cell lines, including LNCaP, 22RV1, PC-3, and DU145 | Not studied | Sponging miR-5590-3p | YY1 | Luo et al., 2020 |
| Breast cancer | Breast cancer cell lines SKBR-3 and BT474 | Trastuzumab resistance, proliferation, and invasion | Regulating expression PABPC1 | Not studied | Dong et al., 2018b |
| Clear cell renal cell carcinoma (ccRCC) | Human ccRCC cell lines A-498, 786-O, Caki-2, and Caki-1 and human normal renal epithelial cell line HK-2 | Migration and invasion | Regulating N-WASP | Not studied | Liu et al., 2017 |
| Retinoblastoma (RB) | Three RB cell lines Y79, SO-RB50, and Weri-RB-1 and normal retinal pigmented epithelial ARPE-19 cell line | Proliferation, migration and invasion, and apoptosis | Sponging miR-124 | STAT3 | Sun et al., 2020 |

(Continued)

TABLE 2 | (Continued)

| Cancer types | Assessed cell lines | Function | Molecular mechanism | Target genes and related signal pathway | References |
|----------------------------------|--|--|---------------------------|---|-----------------------|
| Diffuse large B cell lymphoma | Lymphoblastoid B cell (GM12878), human renal epithelial cell (293T), murine DLBCL cell (A20), and DLBCL cells (OCI-LY7, DB, U2932, and FARAGE) | Proliferation, migration and epithelial-mesenchymal transition | Sponging miR-5590-3p | ZEB1 | Zhao L. et al., 2019 |
| | Lymphoblastoid B cell (GM12878), germinal center B cell (GCB)-like cell line (OCI-LY-7), and activated B cell (ABC)-subtype cell line (OCI-LY-3 and RCK-8) | Proliferation, apoptosis, and migration | Sponging miR-152-3p | Not studied | Tian et al., 2021 |
| Acute myeloid leukemia (AML) | Human normal bone marrow CD34 ⁺ cells and AML cell lines (MV-4-11, AML-193, HL-60, and KG-1 cells) | Proliferation and apoptosis | Sponging miR-193b-3p/MCL1 | Not studied | Wang et al., 2021a |
| Pancreatic cancer | Pancreatic cancer cell line (SW1990), normal pancreatic cell line (HPDE6C7), and the human embryonic kidney 293T cell line | Proliferation, migration, and invasion | Sponging miR-101 | Not studied | Zhang et al., 2019b |
| | Normal immortalized human pancreatic epithelial cell line (HPDE6C7) and four human pancreatic cancer cell lines (CFPAC-1, BXP3, L3.6pl, and Panc-1) | Proliferative, invasive potentials, and apoptosis | Sponging miR-613 | Annexin A2 | Deng et al., 2019 |
| Pancreatic ductal adenocarcinoma | Panc1, Panc28, AsPC1, and BxPC3 and a human pancreatic ductal epithelial cell line HPDE | Proliferation and invasion ability | Interacting with EZH2 | Not studied | Xie et al., 2020 |
| Colorectal cancer (CRC) | Normal human colorectal cell line NCM460 and five CRC cell lines (LoVo, SW620, SW480, HCT116, and HT-29) | Proliferation, motility, and epithelial-mesenchymal transition | Interacting with EZH2 | EPHA7 | Di et al., 2019 |
| | Normal human colon epithelial cells (FHC) and other five human CRC cancer cells (Caco-2, HT-29, HCT-116, SW480, and SW620) | Cell growth, migration, invasion, and apoptosis | Sponging miR-92b-3p | Not studied | Zhang W. et al., 2020 |
| | CRC cell lines (SW620 and SW480), a normal human colon mucosal epithelial cell line (NCM460), and the human embryonic kidney (HEK) 293 T cell line | Cisplatin resistance, proliferation, migration, and invasion | Sponging miR-186 | ATG14 | Han et al., 2020 |
| | CRC cell lines SW620, HCT116 cells, and human normal epithelial colonic cells NCM460 | Proliferation, migration, invasion, and apoptosis | Sponging miR-944 | KRAS/PI3K/AKT pathway | Pei et al., 2019 |
| | CRC cell lines (LoVo, RKO, SW480, and HT-29) and normal colon epithelial cells (NCM460) | Proliferation, metastasis, and epithelial-mesenchymal transition process | Sponging miR-32-5p | SKIL | Ye et al., 2019 |
| | Human CRC cell lines (SW480, HT-29, HCT-8 and DLD-1) and human normal colon epithelial cells (NCM460) | Proliferation, migration, invasion, and apoptosis | Sponging miR-519b-3p | DDX5 | Wang et al., 2021b |
| Cervical cancer (CC) | CC cell lines (SiHa, HeLa, C33a, Me180, and Ms751) and human normal cervical cell lines (Ect1/E6E7) | Proliferation, migration, invasion, and apoptosis | Sponging miR-206 | YWHAZ | Ji et al., 2019 |
| | CC cell lines (SW756, SiHa, and HeLa) and normal endo-cervical epithelial cell line (End1/E6E7) | Proliferation and apoptosis | | JAK-STAT pathway | Zhang et al., 2019c |
| Endometrial cancer (EC) | Human EC cell lines (HEC-1A, HEC-1B, KLE, and Ishikawa) and human endometrial stromal cell line (T-HESC) | Cell proliferation and apoptosis | Sponging miR-655-3P | Not studied | Zhao et al., 2020 |
| | Human embryonic stem cell and EC cell lines (HEC1-A, HEC1-B, AN3CA, and Ishikawa) | Viability, migration, and invasion | Sponging miR-93-5p | Not studied | Zhang K. et al., 2020 |



found that SNHG14 expression was increased in gefitinib-resistant cells, and overexpression of SNHG14 promoted gefitinib resistance by facilitating cell growth and restraining cell apoptosis through interacting with miR-206-3P.

Briefly, SNHG14 plays a vital role in promoting NSCLC cell proliferation, migration, invasion, and chemoresistance and inhibiting cell apoptosis by regulating targets by sponging different miRNAs (Figure 1). SNHG14 is expected to provide a novel strategy for NSCLC treatment.

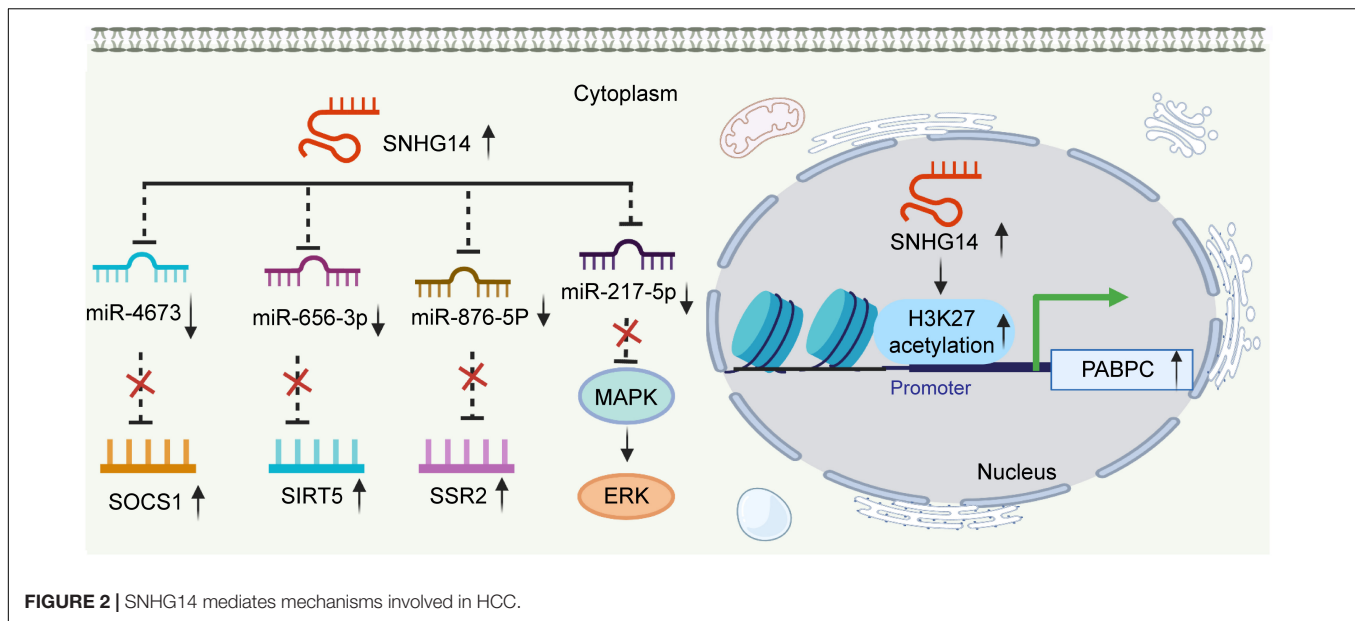
Hepatocellular Carcinoma

HCC is one of the most commonly diagnosed cancers and ranks the fourth leading cause of cancer-related deaths worldwide in 2018 (Bray et al., 2018). Dysregulated lncRNAs have been found closely related to tumorigenesis, prognosis, and diagnosis (Abbastabar et al., 2018; Wong et al., 2018; Pan et al., 2019). SNHG14 was found highly expressed in HCC cell lines compared with that in the normal cell line. As for biological function, the overexpression of this lncRNA accelerated cell proliferation, invasion, and migration and suppressed cell apoptosis. Conversely, knockdown of SNHG14 could cause the exact opposite effects on HCC cells (Pu et al., 2019; Tang and Yang, 2020; Xu X. et al., 2020; Zhang H. et al., 2020; Liao et al., 2021). Mechanistic investigations demonstrated that SNHG14 functions as a competing endogenous RNA and sponged miRNAs, such as miR-4673, miR-217-5p, miR-656-3p, and miR-876-5p (Pu et al., 2019;

Tang and Yang, 2020; Zhang H. et al., 2020; Liao et al., 2021). Thus, activating downstream gene expression, such as, SOCS1, SIRT5, and SSR2 (Figure 2; Pu et al., 2019; Tang and Yang, 2020; Liao et al., 2021). Another research group reported that SNHG14 contributed to tumor cell malignant cells by increasing poly(A) binding protein cytoplasmic 1 (PABPC1) expression through H3K27 acetylation. In this study, gain- and loss-of-function experiments also revealed that the phosphatase and tensin homolog (PTEN) signaling pathway was involved in SNHG14/PABPC1-mediated regulation of tumorigenesis *in vitro* and *in vivo* (Figure 2; Zhang H. et al., 2020). Accordingly, SNHG14 has an oncogenic role and might be a potential therapeutic target in HCC.

Ovarian Cancer

The SNHG14 expression level was enormously high in ovarian cancer cells compared with the control cell line (Zhao J. L. et al., 2019; Zhao and Huang, 2019). Zhao et al. discovered that overexpressed SNHG14 could accelerate cell proliferation and cell cycle. Dual-luciferase assay indicated that SNHG14 could directly bind to miR-125a-5p, and overexpression of miR-125a-5p reversed the effect of promoting tumor of SNHG14 on ovarian cancer cells (Zhao and Huang, 2019). SNHG14 was also found to promote ovarian cancer metastasis by regulating DGCR8 expression (Zhao J. L. et al., 2019). Although the underlying molecular mechanism and signaling pathway need to be further



studied, the aforementioned evidence proved novel clues for the treatment of ovarian cancer.

Breast Cancer

Breast cancer with overexpression of human epidermal growth factor receptor 2 (HER2) accounted for 20–30% of all breast cancers and had poorer prognosis (Vu and Claret, 2012; Robidoux et al., 2013). Trastuzumab is an HER2 inhibitor that is used for initial and advanced treatment. However, trastuzumab resistance has been a significant obstacle to improving the outcome of patients (Wolff et al., 2007; Narayan et al., 2009). To explore the contributions of lncRNAs in trastuzumab resistance and progression of breast cancer, Dong et al. (2018b) cultured human breast cancer cell lines SKBR-3 and BT474 and trastuzumab-resistant SKBR-3/Tr and BT474/Tr cells to identify the role of SNHG14 in breast cancer progression and drug resistance. Functional experimentation demonstrated that knockdown of SNHG14 restrain cell proliferation, invasion, trastuzumab resistance, and the overexpression of SNHG14 abolished this effect. Consistent with this effect, Dong et al. (2018a) also found SNHG14 promoted trastuzumab chemoresistance in breast cancer. Thus, SNHG14 may serve as a promising target for patients with HER2-positive breast cancer.

Colorectal Cancer

In colorectal cancer, Di et al. (2019) found that the level of SNHG14 was markedly upregulated in colorectal cancer cell lines compared with that in the control colonic cell line (Wang et al., 2021b). Overexpression of SNHG14 promoted colorectal cancer cell proliferation, invasion, and migration and epithelial-mesenchymal transition *in vitro* and enhanced tumor growth and distant metastasis *in vivo* (Di et al., 2019; Pei et al., 2019; Ye et al., 2019; Han et al., 2020). Furthermore, mechanistic investigations demonstrated that SNHG14 facilitates colorectal

cancer progression by targeting EZH2-regulated EPHA7 and absorbing miR-186-5p (Di et al., 2019). Pei et al. (2019) reported that SNHG14 could serve as an oncogene by regulating the miR-944/KRAS axis via the PI3K/AKT signaling pathway. SNHG14 was also found to regulate colorectal cancer progression via the miR-32-5p/SKIL and miR-186/ATG14 axes (Ye et al., 2019; Han et al., 2020). In contrast to the aforementioned study, a single study reported that SNHG14 was significantly down-regulated in colorectal cancer cell lines compared with that in a normal cell line and SNHG14 exerts an anti-tumor effect through sponging miR-92b-3p (Zhang W. et al., 2020). Thus, further studies are still needed before determining conclusions related to the function and regulatory mechanisms of SNHG14 in colorectal cancer.

Glioma

Lu et al. (2020) revealed that SNHG14 is involved in reprogramming glucose metabolism and tumorigenesis by interacting with RNA-binding protein Lin28A in glioma. Silencing SNHG14 inhibited glioma cell glycolysis and proliferation while enhancing apoptosis. In contrast to the aforementioned study, another study demonstrated the role of SNHG14 in the suppression of cell proliferation and invasion and promotion of apoptosis in glioma (Wang Q. et al., 2018).

Pancreatic Cancer

Pancreatic cancer a highly fatal gastrointestinal malignancy and ranks the seventh leading cause of cancer-related deaths (Luchini et al., 2016). Although the diagnosis and management of pancreatic cancer are improved, the 5-year survival rate is as low as 4% (Vincent et al., 2011; Gandhi et al., 2018). Pancreatic ductal adenocarcinoma is the most common pathological type of pancreatic cancer and lacks effective treatment (Luchini et al., 2016; Gallmeier and Gress, 2018). In recent years, growing amount of evidence shows that lncRNAs may play vital roles in the development and maintenance of pancreatic cancer

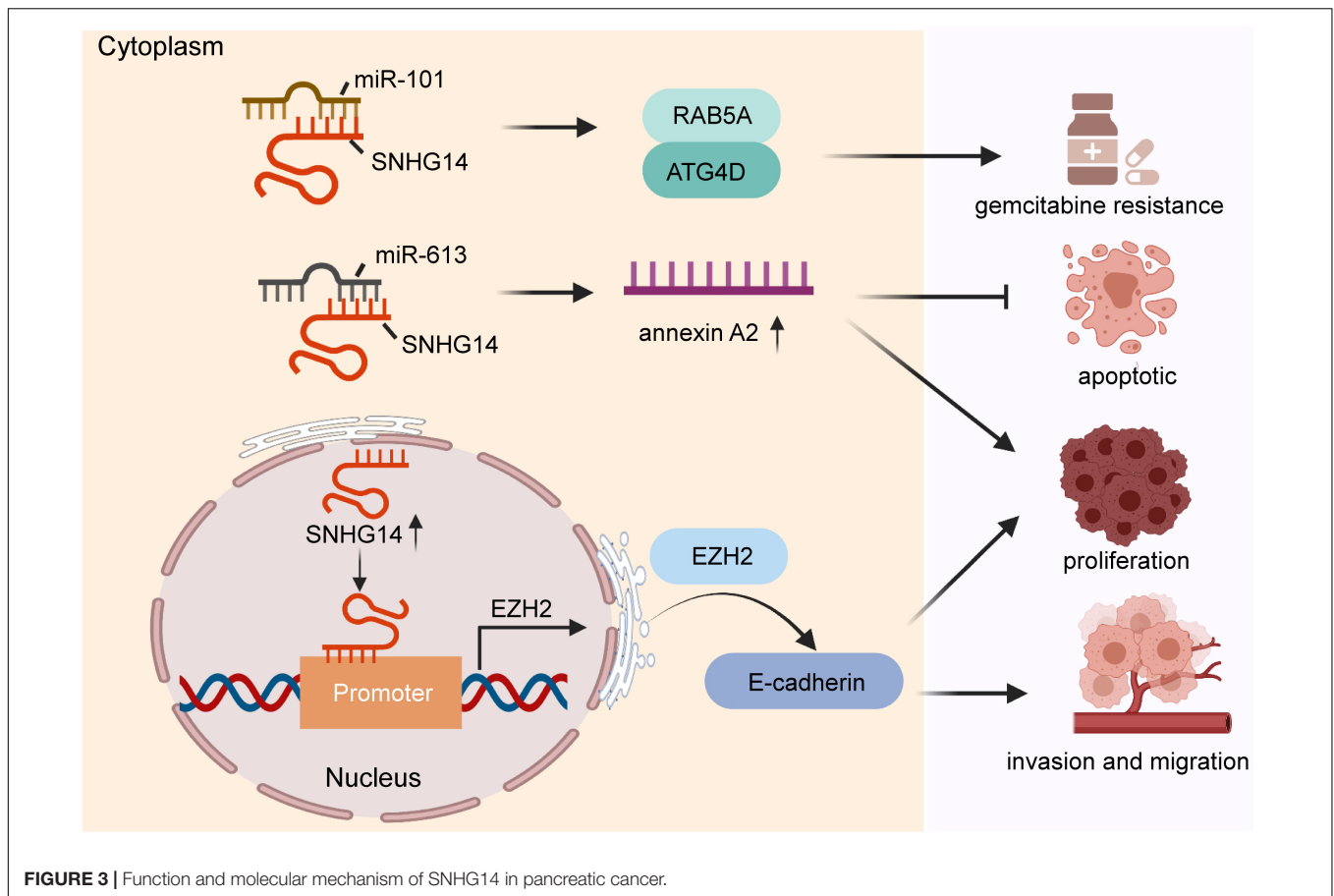


FIGURE 3 | Function and molecular mechanism of SNHG14 in pancreatic cancer.

(Taucher et al., 2016; Moschovis et al., 2017; Wang J. et al., 2020). Some studies have reported that SNHG14 expression was significantly higher in pancreatic cancer cells compared with that in normal cell lines, and upregulated this lncRNA enhanced cell proliferation and invasion through regulating E-cadherin expression via binding on promoters of EZH2 (Xie et al., 2020). Mechanistically, this lncRNA was also found to potentiate tumor progression through modulation of target gene annexin A2 via sponging miR-613 (Deng et al., 2019). Alternatively, Zhang et al. (2019b) reported that SNHG14 increased gemcitabine resistance to pancreatic cancer cells by increasing autophagy-related proteins (such as RAB5A and ATG4D) through interacting with miR-101. The function and molecular mechanism of SNHG14 are shown in **Figure 3**. Collectively, SNHG14 shows its role in the initiation, progression, and drug resistance, suggesting its potential role in tumor treatment of pancreatic cancer.

Others

Other studies on cervical cancer (Ji et al., 2019; Zhang et al., 2019c), prostate cancer (Luo et al., 2020), osteosarcoma (Hou and Mao, 2020), endometrial cancer (Zhao et al., 2020), retinoblastoma (Sun et al., 2020), clear cell renal cell carcinoma (Liu et al., 2017), diffuse large B cell lymphoma (Zhao L. et al., 2019; Tian et al., 2021), and acute myeloid leukemia (Wang et al., 2021a) indicated a tumor promoter role

for SNHG14 through complex molecular mechanisms. **Table 2** summarizes the current results of the function, target genes, and signaling pathways in various malignancies.

CONCLUSION AND PERSPECTIVES

With the development of RNA-seq technologies, bulk lncRNAs are being identified and characterized (Jathar et al., 2017; Wang J. et al., 2018; Qian et al., 2019; Gu et al., 2021). Dysregulation in the expression of lncRNAs has been demonstrated to participate in diverse diseases, especially cancer (Poliseno et al., 2015; Peng and Croce, 2016; Kristensen et al., 2018). lncRNA SNHG14 has been found to be overexpressed in various cancer tissues and is closely associated with multiple clinicopathological characteristics such as prognosis, tumor differentiation, TNM stage, and lymph node metastasis. As a tumor promotion gene, the results of functional experiments have demonstrated that overexpression of this lncRNA could promote tumor cell proliferation, migration, invasion, and chemoresistance and inhibit cell apoptosis. The regulatory mechanism of SNHG14 is complex in distinct types of cancers. To regulate target genes via competing with miRNAs is the major mechanism underlying the tumor-promoting function of SNHG14 by regulating target genes via sponging different miRNAs, such as miR-5590-3p, miR-152-3p, miR-193b-3p, miR-92b-3p, miR-186, miR-32, and miR-93-5p (**Table 2**).

As for clinical application, high expression of SNHG14 was closely correlated with poorer clinicopathological characteristics; thus, it may be served as a potential biomarker for diagnosis and prognosis. However, most of the studies lack a sufficiently large sample and might have artificial errors. The expression of SNHG14 was tested only in tissues. The expression level of SNHG14 in serum or other biological samples remains unclear and is worth investigating. Therefore, exploring the expression of SNHG14 in blood and other fluids would be beneficial to its clinical application as a diagnostic marker in the future. Additionally, although several studies have addressed the promising role of SNHG14 as a target for cancer treatment, research on SNHG14 is still in its early stages. When could targeting SNHG14 be used in clinical treatment? The main determinant is the availability of drugs (whether oligonucleotide or small molecule drugs) that manipulate SNHG14 activity and deliver them effectively to tumor cells with lasting effects. Furthermore, clarification of the functions and mechanisms

of SNHG14 under physiological and pathological conditions is also necessary.

AUTHOR CONTRIBUTIONS

SS and YW wrote and reviewed the manuscript. YZ collected the references. ZD and JX reviewed the manuscript. All authors contributed to the writing and revision of the manuscript, knew the content of it, and approved its submission.

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