Long non-coding RNA SNHG15 in various cancers: a meta and bioinformatic analysis

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Abstract

Background: The snoRNA host gene SNHG15 produces a long non-coding RNA (lncRNA) with a short half-life and has been reported to be dysregulated in multiple cancers and has recently been found to be correlated with tumour progression. Therefore, this meta-analysis was performed to evaluate the generalised prognostic role of small nucleolar RNA host gene 15 (SNHG15) in malignancies, based on variable data from different studies.

Methods: Four public databases were used to identify eligible studies. The association between prognostic indicators and clinical features was extracted and pooled to estimate the hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs). Publication bias was measured using Begg's test and Egger's test, and the stability of pooled results were measured using sensitivity analysis. Additionally, an online database based on The Cancer Genome Atlas (TCGA) was screened to further validate our results. Ultimately, we predicted the molecular regulation of SNHG15 based on the public databases.

Results: In total, 11 studies including 1,087 patients were ultimately enrolled in our meta-analysis. We found that SNHG15 overexpression was associated with worse overall survival (OS) and disease-free survival (DFS), and this was validated in the Gene Expression Profiling Interactive Analysis (GEPIA) cohort. Moreover, increased SNHG15 expression suggested advanced TNM stage and LNM, but was not associated with age, gender, or tumour size. No publication bias or instability of the results was observed. SNHG15 was significantly upregulated in seven cancers and elevated expression of SNHG15 indicated shorter OS and DFS in five malignancies based on the validation using the GEPIA cohort. Further functional prediction indicated that SNHG15 may participate in some cancer-related pathways.

Conclusions: Upregulation of IncRNA SNHG15 was notably associated with worse prognosis and clinical features, suggesting that SNHG15 might serve as a novel prognostic factor in various cancers.

Background

Cancer is a severe health problem and is the leading cause of death worldwide, with annually increasing incidence and mortality rates. According to the latest statistics reported in CA cancer journals, 1,806,590 new cancer cases and 606,520 cancer deaths are expected to occur in the United States in 2020 [1]. Although multidisciplinary treatments, such as surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, of malignancies have improved greatly in recent years, prognosis and early diagnosis remain extremely challenging [2]. As such, there is an urgent need to identify innovative and effective targets for investigating the signalling pathways in tumours, which may ultimately play an indispensable role in therapeutic decision-making for cancer patients.

Long non-coding RNAs (lncRNAs), which were initially speculated to be transcriptional noise with no specific biological function, have emerged as a novel category of non-coding RNAs (ncRNAs) exceeding 200 nucleotides in length that are transcribed by RNA polymerase II but do not encode proteins due to the lack of an open reading frame [3]. Nonetheless, a growing body of work has demonstrated that aberrant expression of lncRNAs is correlated with biological processes, including tumour progression, angiogenesis, metastasis, and invasion, indicating that lncRNAs can serve as tumour suppressors or oncogenes for cancer control [4, 5]. Recently, small nucleolar RNA host gene 6 (SNHG6), linc00152, and opa-interacting protein 5 antisense RNA 1 (OIP5-AS1) have been identified as potential prognostic biomarkers involved in the modulation of tumour-related genes and specific molecular mechanisms in human cancers [6-8].

Small nucleolar RNA host gene 15 (SNHG15), which is located at 7p13 and is 860 base pairs long, was initially reported as a lncRNA with a short half-life [9]. As a tumour oncogene, IncRNA SNHG15 functions as a competing endogenous RNA (ceRNA) to sponge miR-153, miR-38, miR-141, and miR-141-3p, which consequently promotes cell proliferation, migration, invasion, autophagy, and cisplatin resistance in glioma, breast cancer, osteosarcoma, and hepatocellular carcinoma [10-13]. Furthermore, SNHG15 enhances tumour development or drug resistance in glioblastoma multiforme, colorectal carcinoma, and prostate cancer through the SNHG15/CDK6/miR-627, SNHG15/miR-141/SIRT1/β-catenin, SNHG15/miR-338-3p/FKBP1A, and SNHG15/miR-338-3p/FOS-RAB14 axes [14-17]. Additionally, it was found that SNHG15 could facilitate cell proliferation, invasion, and drug resistance in colorectal cancer by acting as a bifunctional MYC-regulated noncoding locus encoding an lncRNA that interacts with AIF. Similarly, it was demonstrated that SNHG15 promoted tumour progression in colon cancer by stabilising the transcription factor Slug [18, 19]. However, only one report has found SNHG15 to be downregulated in thyroid cancer tissue samples and cells, suggesting its role as a tumor suppressor and the reduced expression of SNHG15 enhanced cell proliferation, migration, and invasion in vitro [20].

Collectively, most studies have demonstrated that SNHG15 is involved in gene regulation by acting as an oncogene in various malignancies, and its elevated expression might be associated with the prognosis and clinicopathological parameters of gastric cancer, hepatocellular carcinoma, lung cancer, non-small cell lung cancer, renal cell carcinoma, pancreatic ductal adenocarcinoma, breast cancer, papillary thyroid carcinoma, colorectal cancer, and epithelial ovarian cancer [21-31].

However, given the discrepancies between published studies, the small number of patient samples, and the different detection methods used, the prognostic value of SNHG15 remains unclear at this time. Therefore, we conducted this meta-analysis and bioinformatic validation to determine whether SNHG15 could be used as a non-invasive prognostic marker of tumours and attempted to reach a consensus regarding the prognostic value of this gene.

Methods

Search strategies for eligible literature
Relevant articles that investigated the association between SNHG15 expression and the clinical outcomes of cancer patients were searched using PubMed, Web of Science, Embase, and the Cochrane Library through February 26, 2020. Three domains of keywords in multiple combinations were utilised as search subjects as follows: (“long noncoding RNA” OR “lncRNA”) AND ("SNHG15" OR "small nucleolar RNA host gene 15") AND ("Cancer" OR "Cancers" OR "Tumors" OR "Tumor" OR "Malignancy" OR "Malignancies" OR "Neoplasia" OR "Neoplasias" OR "Neoplasm" OR "Malignant Neoplasms" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Neoplasms, Benign" OR "Benign Neoplasm" OR "Neoplasms, Malignant" OR "Benign Neoplasms" OR "Neoplasm, Benign"). Further, a manual search was conducted to avoid overlooking eligible papers by screening the title and abstracts of papers from the references lists of pertinent articles.

Inclusion and exclusion criteria

All enrolled studies were assessed by two independent investigators, and disagreements were resolved by reaching a consensus after discussion with the third author. Articles that met the following criteria were enrolled in our study: (1) original articles investigating the role of SNHG15 in cancers that were definitively diagnosed by histopathology; (2) samples were cancer tissue and adjacent normal tissue; (3) detection method was qRT-PCR; (4) clinical features, including age, gender, tumour size, TNM stage, lymph node metastasis or distant metastasis, and prognostic indicators, such as overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS), were reported in the paper; (5) patients were categorised into increased and decreased SNHG15 expression groups based on a cut-off value, and the number of patients in these two groups was explicitly stated; (6) hazard ratios (HRs) and 95% confidence intervals (CIs) were reported by multivariate analysis from the articles or were available to be indirectly calculated via Kaplan-Meier (K-M) curves; and (7) the language of the article was English.

Exclusion criteria: (1) studies exploring other IncRNAs or those that were not related to cancers; (2) duplicate articles; (3) other literature types, such as reviews, letters, conference abstracts, meta-analyses, case reports, retractions, etc.; (4) articles focussed on biological functions; and (5) lack of sufficient data for HR and 95% CI extraction.

Data extraction and quality evaluation

The main information from eligible studies was extracted as follows: first author, publication year, country, cancer type, sample type, sample size (high/low), cut-off value for SNHG15 expression, assay method, survival (OS/RFS/PFS), HR availability, HR (95% CI) with its P value, follow-up months, and Newcastle-Ottawa Scale (NOS) scores. If survival rates were not obtained from multivariate analysis, the survival HR (95% CI) was indirectly retrieved from K-M curves by using Engauge Digitiser software. The quality of the enrolled studies was assessed using the NOS score with a range from 0 to 9, and a score greater than 6 was considered as qualified literature.

Validation of bioinformatics database

Gene Expression Profiling Interactive Analysis (GEPIA), which is based on The Cancer Genome Atlas (TCGA), was performed to further verify the abnormal expression of SNHG15 among cancer tissues and to match TCGA normal and GTEx data among various neoplasms with P < 0.01 as the cut-off value. Survival plots of the correlation between SNHG15 expression and OS and DFS were retrieved as K–M curves based on different cancer datasets online.

Functional prediction of SNHG15

We identified SNHG15 relevant ceRNA regulations by starBase, LncBase Predicted v.2, miRDB, TargetScan, miRTarBase, mirDIP and used Cytoscape to construct visualized ceRNA network.

Statistical analysis

Stata (Version 12.0) was used to analyse all the data extracted from the articles included in this study, and a P value < 0.05 indicated a significant difference. The HR and odds ratio (OR), with their corresponding 95% CIs, were utilised to analyse the association between SNHG15 expression and prognostic indicators (OS/DFS) and clinical features, respectively. When HR/OR > 1 and a 95% CI not including 1 were observed in the results, this implied that patients with SNHG15 overexpression had a worse prognosis and advanced clinicopathological parameters. Cochran's Q and I² statistics were determined to measure the heterogeneity across all enrolled studies. A random-effect model was applied with the existence of marked heterogeneity as I² > 50% and P < 0.10, otherwise a fixed-effect model was used. Begg's and Egger's tests were quantitatively conducted to detect underlying publication bias. Accordingly, sensitivity analysis was used to evaluate the stability of the results.

Results

Screening process of published literature

A systematic database search of the literature was conducted, including initially pertinent publications regarding the correlation between SNHG15 and cancers, in PubMed (n=36), Web of Science (n=35), Embase (n=75), and the Cochrane Library (n=0). After initially removing duplicates (n=49), the titles and abstracts of the remaining studies (n=97) were assessed. Seventy-two studies were removed due to being irrelevant topics, reviews, case reports, and conference abstracts. Next, 25 full-text articles were assessed for eligibility. Among them, nine were removed due to a focus on the functional exploration of SNHG15, two were excluded due to a lack of prognostic data, and three articles were excluded due to unclear group numbers. Ultimately, 11 articles containing sufficient data of both survival and clinical features were enrolled in our meta-analysis. Figure 1 presents the detailed selection process for qualified publications.
Characteristics of the enrolled studies

Eleven studies performed in China, including a total of 1,087 patients, that were published from 2016 to 2019 were included. Regarding cancer types, three studies explored lung carcinoma, including one lung cancer and two NSCLC, while the others investigated gastric cancer, hepatocellular carcinoma, renal cell carcinoma, pancreatic ductal adenocarcinoma, breast cancer, papillary thyroid cancer, colorectal cancer, and epithelial ovarian cancer. All samples were cancer tissues and adjacent normal tissues, and the detection assay was qRT-PCR in all cases. Patients were classified into high and low SNHG15 expression groups, and most studies used the median expression level as the cut-off value, except for one study which utilised the mean value and one which did not provide a cut-off value. All studies reported OS, while only two referred to DFS and one mentioned PFS. Regarding HR with 95% CI availability, there were five instances where this could be obtained directly from the papers, and for the remaining cohorts, this was retrieved from K-M curves using Engauge Digitiser software. The follow-up time ranged from 40 to 180 months. The quality of the enrolled studies was assessed by NOS, with scores ranging from 6 to 8. The main features of the enrolled studies are listed in Table 1.

Association between SNHG15 expression and clinical outcomes

The correlation between SNHG15 expression and clinical features was investigated by calculating the pooled OR and 95% CI of age, gender, tumour size, TNM stage and LNM. Results indicated that SNHG15 overexpression was not significantly associated with age (<60 vs. ≥60, OR = 0.98, 95% CI: 0.65-1.48, P = 0.912, Figure 2a), gender (male vs. female, OR = 0.95, 95% CI: 0.73-1.25, P = 0.728, Figure 2b), tumour size (large vs. small, OR = 1.88, 95% CI: 0.91-3.89, P = 0.087, Figure 2c). However, a significant association was observed between increased SNHG15 expression and advanced clinical features, including TNM stage (III-IV vs. I-II, OR = 3.01, 95% CI: 2.15-4.23, P < 0.001, Figure 2d) and LNM (positive vs. negative, OR = 3.20, 95% CI: 2.30-4.45, P < 0.001, Figure 2e). Four fixed-effect models and one random-effect model were adopted for the data with low heterogeneity (0%-35.7%) and significant heterogeneity (78.4%), respectively, and the details are shown in Table 2.

To further demonstrate whether SNHG15 could serve as a prognostic predictor in various cancers, we explored the association between elevated SNHG15 expression and survival indicators (OS/DFS). All enrolled studies reported the OS and a forest plot revealed that the pooled HR and 95% CI were 1.95 (1.53-2.49) by using the fixed-effect model (I² = 0%, P = 0.778), suggesting that SNHG15 overexpression indicated worse OS (P < 0.001, Figure 3a). Similarly, as shown in Figure 3b, no significant heterogeneity in DFS was observed in two studies (I² = 0%, P = 0.822); therefore, the fixed-effect model was employed. The pooled results revealed that increased SNHG15 expression was significantly associated with worse DFS (HR = 2.31, 95% CI: 1.48-3.61, P < 0.001, Figure 3b). Given that no obvious heterogeneity was observed in the results, we did not perform subgroup analysis. Additionally, we only analysed publication bias for OS given that only two studies reported DFS. More detailed information is provided in Table 2.

Publication bias and sensitivity analysis for prognosis

The pooled HR for OS and DFS was not influenced after removing any single study, one by one, in the sensitivity analysis, indicating the reliability and stability of our results (Figure 4a-b). Furthermore, Begg’s test and Egger’s test (P = 0.938 and P=0.970, respectively) both quantitatively revealed that there was no significant publication bias in OS (Figure 4c-d).

Validation of the results in the GEPIA database

The GEPIA database was used to further validate our results. In terms of SNHG15 dysregulation, SNHG15 overexpression was identified in colon adenocarcinoma (COAD), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), kidney renal clear cell carcinoma (KIRC), pancreatic adenocarcinoma (PAAD), rectum adenocarcinoma (READ), testicular germ cell tumours (TGCT), and thymoma (THYM) (Figure 5). Regarding the association between SNHG15 expression and prognosis, survival plots assessing 9,502 patients with 33 types of malignancies in the GEPIA cohort divided into high and low expression groups based on median value revealed that SNHG15 upregulation was associated with worse OS and DFS (Figure 6), confirming the results of our meta-analysis. Furthermore, increased SNHG15 expression was correlated with worse OS in adenocortical carcinoma (ACC), KIRC, mesothelioma (MESO), uveal melanoma (UVM), and worse DFS in ACC, prostate adenocarcinoma (PRAD), UVM (log-rank P < 0.05) (Figures 7-8). These results support our conclusions and indicate that SNHG15 could be a novel prognostic biomarker for various cancers.

Prediction of SNHG15 function

To further understand the molecular mechanism of SNHG15 overexpression affecting the prognosis of various cancers, we predicted its possible biological function and involved signaling pathways of SNHG15 using six online databases. First, the ceRNA regulations for SNHG15 were identified through starBase, LncBase Predicted v.2, miRDB, TargetScan, miRTarBase, mirDIP online prediction, and then a SNHG15-miRNA-mRNA network was constructed by utilizing cytoscape software (Figure 9).

Discussion

LncRNAs were initially thought to be “transcriptional noise” or “junk DNA” and received little attention in the previous few decades [32]. However, as next-generation genome-wide sequencing and microarrays have been widely applied in clinical settings in recent years, new research has suggested that aberrant expression of IncRNAs may promote or suppress tumour growth, leading to carcinogenesis and cancer progression [33, 34]. For example, some IncRNAs, such as NOC2L-4.1, TUG1, and MALAT1, are well established to promote tumour growth, while other IncRNAs, such as ASMTL-AS1, LINC02381, and LINC02499 have been found to inhibit tumour progression [35-40].
SNHG15, a promising new cancer-related lncRNA, has been found to be upregulated in a diverse array of malignant tumours. It has been demonstrated that elevated expression of SNHG15 is significantly related to tumour size, TNM stage, and lymph node metastasis in pancreatic cancer patients [41]. However, the definitive prognostic role of this gene was previously unclear. In our meta-analysis, we investigated the potential association between SNHG15 expression and prognostic attributes and clinicopathological parameters by integrating data from 11 studies. We found that SNHG15 overexpression increased the risk of shorter OS and DFS with no conspicuous heterogeneity. Simultaneously, we demonstrated that patients with increased SNHG15 expression were more likely to develop advanced TNM stage and positive lymph node metastasis, while these effects were not associated with age, sex, or tumour size. Additionally, no evident publication bias in OS was identified throughout the study, and the robustness of the results was verified via sensitivity analysis. Furthermore, validating the TCGA datasets revealed that high SNHG15 expression levels were observed in COAD, DLBC, KIRC, PAAD, READ, TGCT, and THYM. We also evaluated the TCGA cohort to confirm the prognostic role of SNHG15 in various cancers, and the elevated expression of SNHG15 in 33 types of tumour tissues was associated with worse OS and DFS. In some cancers, including ACC, KIRC, MESO, and UVM, SNHG15 overexpression indicated shorter OS. Moreover, survival plots revealed that ACC, PRAD, and UVM patients with SNHG15 upregulation exhibited worse DFS. Taken together, these results indicate that SNHG15 could serve as a biological modulator and novel biomarker of poor prognosis in cancer patients.

LncRNAs can indirectly regulate the expression and function of target genes via ceRNA. Thus, we constructed a ceRNA network to assess the potential function and molecular mechanism of SNHG15 in cancers. The results of our functional analysis demonstrated that target genes indirectly affected by SNHG15 may be involved in some of these signaling pathways, and promoted the proliferation, invasion and metastasis of tumour cells. Accordingly, the potential molecular mechanism involved in tumour progression may be investigated in the future to better understand the association between altered SNHG15 expression and poor prognosis (Table 3). In gastric cancer, SNHG15 upregulation promotes cell proliferation and invasion by modulating the expression of MMP2/MMP9 [21]. In lung cancer, it has been reported that SNHG15 overexpression enhances tumour occurrence and development by targeting miRNA-211-3p to regulate cell proliferation and migration in vitro [23]. Similarly, in non-small cell lung cancer, two studies have demonstrated that SNHG15 knockdown suppresses tumorigenesis by inhibiting the expression of EMT, MMP2, and MMP9 and regulating the miR-486/CDK14 axis [24, 25]. Meanwhile, another study has identified that SNHG15 facilitates renal cell carcinoma invasion and migration through the NF-κB signalling pathway and by inducing the EMT process [26]. In breast cancer, it has been shown that SNHG15 functions as a ceRNA to sponge miR-211-3p, thereby promoting cell proliferation, migration, and invasion and inhibiting apoptosis [28]. Additionally, SNHG15 has been reported to act as a ceRNA to modulate the miR-200a-3p/YAP1-Hippo axis in papillary thyroid carcinoma [29]. Consistently, functional assays have revealed that upregulation of SNHG15 facilitates the migration, invasion, proliferation, and chemoresistance of epithelial ovarian cancer cells [31]. However, the signalling pathways involved in in HCC, PDAC, and colorectal cancer remain unclear; therefore, additional studies are needed to explore the potential mechanisms by which SNHG15 expression predicts survival across diverse malignancies [22, 27, 30].

Several key points from our paper should be noted. First, our meta-analysis was the first study to exhaustively investigate the association between SNHG15 expression and clinical outcomes in cancer patients. In addition, only one random-effect model was employed in the analysis, indicating that the results are credible and accurate. Furthermore, we determined rigorous inclusion and exclusion criteria to enrol only high-quality studies.

Nonetheless, several limitations in our study should be considered. First, all the included subjects were from China, with small case numbers of certain cancer types and a small sample size, which led to our results being only applicable to Asia. To address this, we further validated these results using the GEPIA database to support our conclusion as broadly as possible. Further, HRs with 95% CIs were retrieved from K-M curves in six studies, which may inevitably exaggerate the prognostic value of SNHG15 and introduce bias. Moreover, the lack of articles with negative results may have caused an overestimation of the clinical value of this gene. Additionally, the inconsistent cut-off values may introduce heterogeneity among the studies.

Conclusions

Taken together, despite the above limitations, our study revealed that SNHG15 overexpression is significantly associated with unfavourable prognosis and advanced clinical features. However, high-quality studies with standardised methods and larger sample sizes from different countries are still needed to confirm our results.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data used in this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions
WZ conceptualized the study. YL collected and analysed the data. CZC wrote the manuscript and arranged the tables and figures. JJW and YQF revised the paper. All authors have reviewed and approved the final manuscript.

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Not applicable.

Abbreviations
ACC: adrenocortical carcinoma; ceRNA: competing endogenous RNA; CI: confidence interval; COAD: colon adenocarcinoma; DFS: disease-free survival; DLBC: lymphoid neoplasm diffuse large B-cell lymphoma; EMT: Epithelial-Mesenchymal Transition; GEPIA: Gene Expression Profiling Interactive Analysis; GTeX: Genotype-Tissue Expression; HCC: hepatocellular carcinoma; HR: hazard ratio; K-M: Kaplan-Meier; KIRC: kidney renal clear cell carcinoma; lncRNA: long non-coding RNA; LNM: lymph node metastasis; MESO: mesothelioma; ncRNA: non-coding RNA; NOS: Newcastle-Ottawa Scale; NSCLC: non-small cell lung cancer; OIP5-AS1: opa-interacting protein 5 antisense RNA 1; OR: odds ratio; OS: overall survival; PAAD: pancreatic adenocarcinoma; PDAC: pancreatic ductal adenocarcinoma; PFS: progression-free survival; PRAD: prostate adenocarcinoma; qRT-PCR: Real-time quantitative-Polymerase Chain Reaction; READ: rectum adenocarcinoma; RFS: relapse free survival; s.e.: standard error; SNHG15: small nucleolar RNA host gene 15; SNHG6: small nucleolar RNA host gene 6; snoRNA: small nucleolar RNA; TCGA: The Cancer Genome Atlas; TGCT: testicular germ cell tumours; THYM: thymoma; TNMUV: uveal melanoma

References
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020, 70(1):7-30.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017, 67(1):7-30.
3. Zhang Y, Tao Y, Liao Q. Long noncoding RNA: a crosslink in biological regulatory network. Brief Bioinform 2018, 19(5):930-945.
4. Geisler S, Coller J. RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. Nat Rev Mol Cell Biol 2013, 14(11):699-712.
5. Chen X, Yan CC, Zhang X, You ZH. Long non-coding RNAs and complex diseases: from experimental results to computational models. Brief Bioinform 2017, 18(4):558-576.
6. Zhao S, Zhu H, Jiao R, Wu X, Ji G, Zhang X. Prognostic and clinicopathological significance of SNHG6 in human cancers: a meta-analysis. BMC Cancer 2020, 20(1):77.
7. Wang H, Liu Y, Tang A. Prognostic Values of Long Noncoding RNA linc00152 in Various Carcinomas: An Updated Systematic Review and Meta-Analysis. Oncologist 2020, 25(1):e31-e38.
8. Ren X, He J, Qi L, Li S, Zhang C, Duan Z, Wang W, Tu C, Li Z. Prognostic and clinicopathologic significance of long non-coding RNA OIP5-AS1 in multiple human cancers. Artificial cells, nanomedicine, and biotechnology 2020, 48(1):353-361.
9. Tani H, Toramura M. Identification of short-lived long non-coding RNAs as surrogate indicators for chemical stress response. Biochemical and biophysical research communications 2013, 439(4):547-551.
10. Ma Y, Xue Y, Liu X, Qu C, Cai H, Wang P, Li Z, Li Z, Liu Y. SNHG15 affects the growth of glioma microvascular endothelial cells by negatively regulating miR-153. Oncology reports 2017, 38(5):3265-3277.
11. Mi H, Wang X, Wang F, Li L, Zhu M, Wang N, Xiong Y, Gu Y. SNHG15 Contributes To Cisplatin Resistance In Breast Cancer Through Sponging mir-381. OncoTargets and therapy 2020, 13:657-666.
12. Liu K, Hou Y, Liu Y, Zheng J. LncRNA SNHG15 contributes to proliferation, invasion and autophagy in osteosarcoma cells by sponging miR-141. Journal of biomedical science 2017, 24(1):46.
13. Ye J, Tan L, Fu Y, Xu H, Wen L, Deng Y, Liu K. LncRNA SNHG15 promotes hepatocellular carcinoma progression by sponging miR-141-3p. Journal of cellular biochemistry 2019, 120(2):19775-19783.
14. Li Z, Zhang J, Zheng H, Li C, Xiong J, Wang W, Bao H, Jin H, Liang P. Modulating LncRNA SNHG15/CDK6/miR-627 circuit by palbociclib, overcomes temozolomide resistance and reduces M2-polarization of glioma associated microglia in glioblastoma multiforme. Journal of experimental & clinical cancer research : CR 2019, 38(1):380.
15. Sun X, Bai Y, Yang C, Hu S, Hou Z, Wang G. Long noncoding RNA SNHG15 enhances the development of colorectal carcinoma via functioning as a ceRNA through miR-141/SIRT1/Wnt/beta-catenin axis. Artificial cells, nanomedicine, and biotechnology 2019, 47(1):2536-2544.
16. Zhang Y, Zhang D, Lv J, Wang S, Zhang Q. LncRNA SNHG15 acts as an oncogene in prostate cancer by regulating miR-338-3p/FKBPA1A axis. Gene 2019, 705:44-50.
17. Li M, Bian Z, Jin G, Zhang J, Yao S, Feng Y, Wang X, Yin Y, Fei B, You Q et al. LncRNA-SNHG15 enhances cell proliferation in colorectal cancer by inhibiting miR-338-3p. Cancer medicine 2019, 8(5):2404-2413.
18. Saeinasab M, Bahrami AR, Gonzalez J, Marchese FP, Martinez D, Mowla SJ, Matin MM, Huarte M. SNHG15 is a bifunctional MYC-regulated noncoding locus encoding a lncRNA that promotes cell proliferation, invasion and drug resistance in colorectal cancer by interacting with AIF. Journal of...
Long non-coding RNA SNHG15 functions as a tumor suppressor in thyroid cancer. *Journal of cellular biochemistry* 2019, **120**(4):6120-6126.

Chen SX, Yin JF, Lin BC, Su HF, Zheng Z, Xie CY, Fei ZH: Uregulated expression of long noncoding RNA SNHG15 promotes cell proliferation and invasion through regulates MMP2/MMP9 in patients with GC. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* 2016, **37**(5):6801-6812.

Zhang JH WH, Yang HG: *Long Non-Coding RNA SNHG15, a Potential Prognostic Biomarker for Hepatocellular Carcinoma*. *Eur Rev Med Pharmacol Sci* 2016, **20**(9):1720-1724.

Cui HX ZM, Liu K, Liu J, Zhang ZL, Fu L.: *LncRNA SNHG15 Promotes Proliferation and Migration of Lung Cancer via Targeting microRNA-211-3p*. *Eur Rev Med Pharmacol Sci* 2018, **22**(20):6838-6844.

Dong YZ MX, Li GS.: *Long non-coding RNA SNHG15 indicates poor prognosis of non-small cell lung cancer and promotes cell proliferation and invasion*. *Eur Rev Med Pharmacol Sci* 2018, **22**(9):2671-2679.

Jafarzadeh M, Soltani BM, Soleimani M, Hosseinkhani S: *Epigenetically silenced LINC02381 functions as a tumor suppressor by regulating PI3K-Akt signaling pathway*. *International journal of oncology* 2018, **53**(1):384-394.

Guo XB YH, Wang JY.: *Evaluating the diagnostic and prognostic value of long non-coding RNA SNHG15 in pancreatic ductal adenocarcinoma*. *Eur Rev Med Pharmacol Sci* 2018, **22**(18):5892-5898.

Muller S, Raulefs S, Bruns P, Afonso-Grunz F, Plotner A, Thermann R, Jager C, Schlitter AM, Kong B, Regel I: *Knockdown of SNHG15 suppresses renal cell carcinoma proliferation and EMT by regulating the NF-kappaB signaling pathway*. *Biochemical and biophysical research communications* 2018, **495**(2):1594-1600.

Wu DM, Wang S, Wen X, Han XR, Wang YJ, Shen M, Fan SH, Zhang ZF, Shan Q, Li MQ et al: *Long non-coding RNA SNHG15 acts as a ceRNA to regulate YAP1-Hippo signaling pathway by sponging miR-200a-3p in papillary thyroid carcinoma*. *Cell death & disease* 2018, **9**(10):947.

Huang L, Lin H, Kang L, Huang P, Huang J, Cai J, Xian Z, Zhu P, Huang M, Wang L et al: *Aberrant expression of long noncoding RNA SNHG15 correlates with liver metastasis and poor survival in colorectal cancer*. *Journal of cellular physiology* 2019, **234**(5):7032-7039.

Chen SX, Yin JF, Lin BC, Su HF, Zheng Z, Xie CY, Fei ZH.: *Epigenetically silenced LINC02381 functions as a tumor suppressor by regulating PI3K-Akt signaling pathway*. *Biochimie* 2020, **171**:63-71.

Ma X, Mo M, Tan HJJ, Tan C, Zeng X, Zhang G, Huang D, Liang J, Liu S, Qiu X: *LINC02499, a novel liver-specific long non-coding RNA with potential diagnostic and prognostic value, inhibits hepatocellular carcinoma cell proliferation, migration, and invasion*. *Hepatol Res* 2020.

Zhang JH WH, Yang HG: *Long Non-Coding RNA SNHG15 Inhibits P15 and KLF2 Expression to Promote Pancreatic Cancer Proliferation Through EZH2-mediated H3K27me3*. *OncoTarget* 2017, **8**(48):84153-84167.

### Tables

Table 1 Characteristics of the included studies
| First author | Year | Country | Cancer type | Sample | Sample size (high/low) | Cut-off value | Method | Survival | HR availability | HR (95% CI) | P value | Follow-up months | NOS |
|--------------|------|---------|-------------|--------|------------------------|--------------|--------|----------|-----------------|------------|---------|----------------|-----|
| Chen        | 2016 | China   | gastric cancer | tissue | 106(53/53) | Median | qRT-PCR | OS/DFS | reported | 2.928(1.304–6.575) | 0.009 | 40 | 8 |
| Zhang       | 2016 | China   | HCC       | tissue | 152(77/75) | Median | qRT-PCR | OS | reported | 2.247(1.331–6.255) | 0.001 | 70 | 7 |
| Cui         | 2018 | China   | lung cancer | tissue | 55(27/28) | NM | qRT-PCR | OS | reported | 2.234(1.033–4.829) | 0.041 | 80 | 7 |
| Dong        | 2018 | China   | NSCLC       | tissue | 49(23/26) | Mean | qRT-PCR | OS/DFS | K-M curve | 1.879(0.840–4.200) | 0.125 | 120 | 7 |
| Du          | 2018 | China   | RCC       | tissue | 96(48/48) | Median | qRT-PCR | OS | K-M curve | 1.022(0.480–2.180) | 0.953 | 160 | 6 |
| Guo         | 2018 | China   | PDAC       | tissue | 171(82/89) | Median | qRT-PCR | OS | reported | 3.251(1.177–6.362) | 0.004 | 60 | 7 |
| Jin         | 2018 | China   | NSCLC       | tissue | 35(20/15) | Median | qRT-PCR | OS | K-M curve | 1.414(0.380–5.260) | 0.606 | 60 | 6 |
| Kong        | 2018 | China   | breast cancer | tissue | 58(29/29) | Median | qRT-PCR | OS | K-M curve | 2.126(0.900–5.020) | 0.086 | 60 | 6 |
| Wu          | 2018 | China   | PTC       | tissue | 92(50/42) | Median | qRT-PCR | OS | K-M curve | 1.081(0.350–3.340) | 0.892 | 60 | 6 |
| Huang       | 2019 | China   | colorectal cancer | tissue | 91(46/45) | Median | qRT-PCR | OS | reported | 2.731(1.005–7.424) | 0.049 | 84 | 7 |
| Qu          | 2019 | China   | EOC       | tissue | 182(73/109) | Mean | qRT-PCR | OS/PFS | K-M curve | 1.918(1.210–3.040) | 0.009 | 60 | 8 |

HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; PDAC: pancreatic ductal adenocarcinoma; PTC: papillary thyroid cancer; EOC: epithelial ovarian cancer; NM: not mention; OS: overall survival; DFS: disease-free survival; PFS: progression-free survival; K-M curve: Kaplan–Meier curve; qRT-PCR: quantitative real time polymerase chain reaction; NOS: Newcastle-Ottawa Scale.
Table 2: Results of the association between SNHG15 and clinicopathological outcomes

| Outcome                          | Studies(n) | OR  | 95%CI       | P value | Model | Chi2 | I2   | P Value |
|---------------------------------|------------|-----|-------------|---------|-------|------|------|---------|
| age(<60 vs ≥60)                 | 4          | 0.98| 0.65-1.48   | 0.912   | Fixed | 1.84 | 0%   | 0.607   |
| gender male vs female           | 9          | 0.95| 0.73-1.25   | 0.728   | Fixed | 12.44| 35.7%| 0.133   |
| TNM stage III-IV vs I-II        | 6          | 3.01| 2.15-4.23   | 0.000   | Fixed | 2.76 | 0%   | 0.737   |
| lymph node metastasis (positive vs negative) | 8          | 3.20| 2.30-4.45   | 0.000   | Fixed | 3.20 | 0%   | 0.866   |
| tumor size (large vs small)     | 7          | 1.88| 0.91-3.89   | 0.087   | Random| 27.76| 78.4%| 0.000   |
| overall survival                | 11         | 1.95| 1.53-2.49   | 0.000   | Fixed | 6.43 | 0%   | 0.778   |
| disease-free survival           | 2          | 2.31| 1.48-3.61   | 0.000   | Fixed | 0.05 | 0%   | 0.822   |

Table 3: Summary of SNHG15 with their aberrant expression, biological functions, and related signaling pathways.

| Study       | Cancer                  | Expression | biological functions                                                                 | related signaling pathways |
|-------------|-------------------------|------------|-------------------------------------------------------------------------------------|-----------------------------|
| Chen2016    | gastric cancer          | upregulation| promote cell proliferation and invasion, inhibit apoptosis                           | MMP2/MMP9                   |
| Cui2018     | lung cancer             | upregulation| promote cell proliferation, invasion                                                | microRNA-211-3p             |
| Dong2018    | non-small cell lung cancer| upregulation| promote cell proliferation, invasion and metastasis, inhibit apoptosis.             | EMT/MMP2/MMP9               |
| Du2018      | renal cell carcinoma    | upregulation| promote cell proliferation, invasion and migration                                  | EMT/NF-κB                   |
| Jin2018     | non-small cell lung cancer| upregulation| promote cell proliferation, induce apoptosis and cycle arrest at G0/G1 phase       | miR-486/CDK14               |
| Kong2018    | breast cancer           | upregulation| promote cell proliferation, migration, invasion and induce apoptosis                | miR-211-3p/EMT              |
| Wu2018      | papillary thyroid cancer| upregulation| promote cell growth and migration                                                    | miR-200a-3p/YAP1-Hippo      |
| Qu2019      | epithelial ovarian cancer| upregulation| promote cell migration, invasion, proliferation and induce chemoresistance          | ---                         |
Figures

**Figure 1**
Flow diagram of the meta-analysis.
Figure 2

Forest plots evaluating the association between SNHG15 expression and clinical features. (a) Age, (b) Gender, (c) Tumour size, (d) TNM stage, (e) Lymph node metastasis.

Figure 3
Forest plots assessing the association between SNHG15 expression and prognosis. (a) OS. (b) DFS.

Figure 4
Forest plots of sensitivity analysis and publication bias. (a) Sensitivity analysis of the relationship between SNHG15 expression and OS. (b) Sensitivity analysis of the relationship between SNHG15 expression and DFS, the solid line represents the meta-analysis fixed-effect estimates, in which the 95% CI is represented by the width of the dotted horizontal line. The circle represents each study. (c) Begg's forest plot of publication bias for OS. (d) Egger's forest plot of publication bias for OS, HR, s.e.; standard error. Each point represents a separate study.

Figure 5
SNHG15 expression in seven types of cancer vs. normal tissue. **Log2Fold Change>1 and P < 0.01. The red box plots represent SNHG15 expression in cancer tissues and the grey box plots represent SNHG15 expression in normal tissues.
The relationship between SNHG15 expression and cancer patient prognosis in the GEPIA cohort. (a) OS plots based on SNHG15 expression in 33 types of cancer (n (low) = 4,751 vs n (high) = 4,751). (b) DFS plots based on SNHG15 expression in 33 types of cancer (n (low) = 4,751 vs n (high) = 4,751).
Validation of the prognostic value of SNHG15 based on the TCGA database. (a) OS plots of SNHG15 in ACC. (b) OS plots of SNHG15 in KIRC. (c) OS plots of SNHG15 in MESO. (d) OS plots of SNHG15 in UVM.
Figure 8

Validation of the prognostic value of SNHG15 based on the TCGA database. (a) DFS plots of SNHG15 in ACC. (b) DFS plots of SNHG15 in PRAD. (c) DFS plots of SNHG15 in UVM.
Figure 9

Construction of SNHG15-mediated ceRNA network. SNHG15-mediated ceRNA network is comprised of 2 miRNAs and 45 mRNAs. Blue rectangle represents mRNA, green oval stands for miRNA, red polygon is SNHG15.