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Review

Long non-coding SNHG1 in cancer☆

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ABSTRACT

Objectives: Long non-coding RNAs (lncRNAs) consist of a cluster of RNAs having > 200 nucleotides lacking protein-coding function. Recent studies indicate that lncRNAs are involved in various cellular processes and their aberrant expression may lead to tumour development and progression. They may also serve as oncogenes or tumour suppressor genes in other diseases. In this review, we emphasize current investigations involving clinical management, tumour progression and the molecular mechanism of SNHG1 in human cancer.

Materials and methods: We investigate and summarize recent studies regarding the biologic functions and mechanisms of lncRNA SNHG1 in tumorigenesis. Related studies were obtained through a systematic search of google scholar, PubMed, Embase and Cochrane Library.

Results: SNHG1 is a novel oncogenic lncRNA aberrantly expressed in different diseases including colorectal, liver, lung, prostate, gastric and esophageal cancers as well as ischemic stroke, nasopharyngeal carcinoma, laryngeal squamous cell carcinoma, neuroblastoma, renal cell carcinoma and osteosarcoma. Upregulation of SNHG1 was significantly associated with advanced tumour stage, tumour size, TNM stage and decreased overall survival. Furthermore, aberrant expression of SNHG1 contributes to cell proliferation, metastasis, migration and invasion of cancer cells.

Conclusion: SNHG1 likely acts as a useful tumour biomarker for cancer diagnosis, prognosis and treatment.

1. Introduction

Cancer is a main cause of death worldwide [1]. Genetic and epigenetic modifications cause aberrant gene expression and uncontrolled cell division leading to carcinogenesis [2]. Methylation of DNA, chromatin remodelling and RNA interference are associated with carcinogenesis and are involved in genetic changes that contribute to tumorigenesis [3]. Eighty percent of human genome is transcribed into RNA, whereas only approximately 1.2–2% (~20,000) of the total human genome sequence encodes for protein-coding genes. The majority of the human genome is transcribed into non-protein-coding RNAs (ncRNAs) [4]. Most of non-coding RNAs (ncRNAs) such as rRNAs and tRNAs are involved in mRNA translation, whereas small nuclear RNAs (snRNAs) are elaborated in splicing. Small nucleolar RNAs (snoRNAs) are involved in the modification of rRNAs [5]. Noncoding RNAs (ncRNAs) comprise ribosomal RNA (rRNA) and other species that can be categorized into short and long ncRNAs. Long ncRNAs (lncRNAs) include antisense RNA (asRNA), pseudogenes, long intergenic ncRNA (lincRNA), and circular RNA (circRNA) [6,7]. LncRNAs contribute to important molecular and functional roles. Their dysregulation is important in the occurrence and development of diseases and numerous human cancers although they were once thought to be "junk RNAs" [7]. Their role has been widely reported in numerous human cancers (Fig. 1). They are transcribed by RNA polymerase II (PolI), but not translated into proteins [2]. Dysregulations of lncRNAs are associated with cell migration, invasion, metastasis, gene transcription, tumorigenesis in a large variety of cancer developments [8]. LncRNAs may be tumour suppressor genes and oncogenes that bind directly to RNA, DNA, or protein, and exert their biological functions, including cell proliferation, differentiation, apoptosis, immune response and migration. They are also involved in post-transcriptional gene regulation. They may be considerably beneficial as informative markers and

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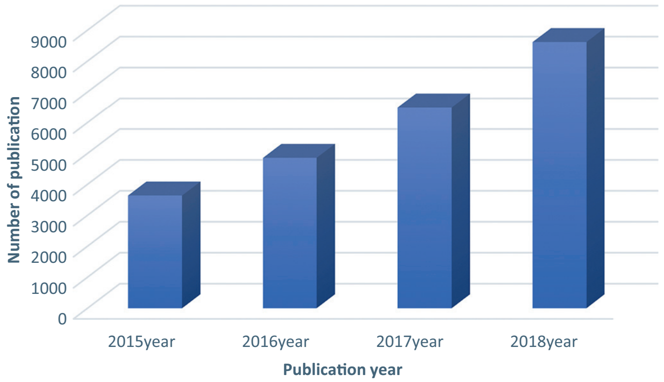

Fig. 1. PubMed showing the increasing number of articles, specialized on "lncRNA" or "long non-coding RNA" or "LncRNA" within recent four year.

therapeutic targets for cancer treatment because of their high tissue specificity, sensitivity and reliable stability [9]. They may also act as competing endogenous RNA (ceRNAs) or microRNA (miRNA) sponges by competitively binding to miRNAs and thereby indirectly influencing mRNA expression. Long non-coding RNA- differentiation antagonizing nonprotein coding RNA(DANCR) performs as ceRNA in various types of cancer [10]. Small nucleolar RNA host gene 1 (SNHG1) is a host to 8 snoRNAs and is localised at 11q12.3 region of the chromosome (SNHG1, GenBank accession ID: 23642) and has 11 exons [11]. It plays a crucial role in the development and prognosis of several cancers. This review briefly summarizes the aberrant expression of lncRNA-SNHG1 in numerous cancers and analyses its clinical importance and association in important process of carcinogenesis such as cell proliferation, invasion, metastasis and molecular pathways such as epithelial-mesenchymal pathway, wnt/β-catenin signalling pathway. Moreover, lncRNA-SNHG1 is one of the most significant regulatory RNAs in human cancers, and it has been highlighted as a great promise for diagnostic and therapeutic purposes in malignancies.

2. SNHG1 in various cancers

2.1. Colorectal cancer (CRC)

Colorectal cancer (CRC), one of the most prevalent deadly cancers worldwide, is a very heterogeneous disease that is caused by the collaboration of genetic mutations and environmental factors. Epimutations in colonic mucosa cells eventually lead to cell proliferation, metastasis and the transformation of normal colonic mucosa into invasive cancer [12,13]. CRC includes chromosomal instability (CIN), K-ras, APC gene(adenomatous polyposis coli), P53 mutations, defective DNA mismatch repair genes, microsatellite instability (MSI) [14] and CpG island methylator phenotype (CIMP) [15]. The overall 5-year survival rate for initial stage I is > 90% in patients while that of stage IV patients is slightly higher than 10%. Therefore, new sensitive and specific markers for early diagnosis of CRC would be valuable to reduce the incidence and mortality of CRC [16].

Sun et al. showed that SNHG1 was highly expressed in CRC tissues compared with that in adjacent normal tissues. Increased expression of SNHG1 was associated with cancer stage and cellular metastasis demonstrating that it might act as an important biomarker in CRC. Downregulated SNHG1 inhibited tumorigenesis and closely related with occurrence and development of CRC [17]. Up-regulation of SNHG1 indicated poor prognosis and promoted cell proliferation and metastasis of CRC by activation of Wnt/β-catenin signalling pathway. Similarly, Zhu et al. [18] found that SNHG1 expression was aberrantly upregulated in CRC tissues, cell lines compared with that in adjacent normal tissues and tissues. Patients with high SNHG1 expression level had poorer overall survival (OS) and progression-free survival (PFS) than those with low SNHG1 expression. SNHG1 regulated β-catenin expression, transcription factor-4 (TCF-4), cyclin D1 and MMP-9 through activation of WNT/β-catenin pathway. Its knockdown may reduce proliferation, migration and invasion of CRC cells. Qi et al. also showed that SNHG1 promotes cell proliferation and tumorigenesis in CRC via Wnt/β-catenin signalling. It was high-expressed in CRC cells. SNHG1 knockdown hinders cell proliferation and encourages apoptosis in CRC [19]. Taken together, SNHG1-β-catenin-WNT signalling pathway regulatory network may play a role in CRC.

Zhao et al. [20] showed that SNHG1 had a tumour-promoting effect on CRC progression, viability, apoptosis and proliferation by partially suppressing p53 pathway.Tian et al. also found that SNHG1 was overexpressed in CRC, and its expression was correlated with advanced cancer stage and tumour recurrence. It indorsed cell proliferation by acting as a sponge of miR-145 which is a renowned tumour suppressor of CRC. CRC patients with higher SNHG1expression levels had a poorer prognosis [21]. Therefore, SNHG1 may serve as an innovative, prognostic and therapeutic target for the treatment of CRC and it may be related with the development of CRC. Yang et al. indicated that SNHG1 and its interconnected components might be future therapeutic goals of colon cancer and SNHG1 performed as an oncogene in colon cancer via the Wnt/β-catenin pathway to promote carcinogenesis [22].Taken together, SNHG1 may have a potential value in diagnosis, prognosis and therapeutic target of CRC (Fig. 2).

2.2. Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is one of the commonly found cancers worldwide with poor prognosis [23]. Alcohol consumption, tobacco use, chronic viral infection and cirrhosis by hepatitis B virus (HBV) or hepatitis C virus (HCV) are implicated in the development of HCC. Although advanced knowledge in the underlying molecular mechanisms of HCC and therapeutic methods such as liver transplantation, liver resection, ablation, chemoembolization depending on the tumour stage and liver function are available, OS time of HCC patients is still limited and treatment of HCC remains insufficient. The complexity of tumour progression still demands novel diagnostic or prognostic biomarkers and therapeutic targets for early diagnosis of HCC [24].LncRNAs have been identified as potential biomarkers in cancer development and they are aberrantly expressed in HCC tissue as compared to adjacent noncancerous tissue [25].

Zhang et al. showed that SNHG1 was upregulated in HCC tissues compared with that in adjacent noncancerous tissue and its high expression was associated with large tumour size, poor differentiation, poor prognosis and aggressive Barcelona clinic liver cancer (*BCLC*) *staging*. SNHG1 promoted HCC cells proliferation through inhibiting p53 and p53-target genes BAX, FAS, and CDKN1A expression. It endorsed cell cycle progression, and inhibited cells apoptosis [11]. LncRNA SNHG1 expression levels were remarkably upregulated in HCC tissues and cell lines compared with that in normal tissues and cell lines. It also contributed to the downregulation of miR-195 in HepG2 cells. Furthermore, SNHG1 impaired HCC cell proliferation, invasion, and migration in vitro through the inhibition of miR-195 indicating that it might play as a potential therapeutic candidate for HCC [26].

2.3. Lung cancer

2.3.1. Non-small cell lung cancer (NSCLC)

Lung cancer is one of the frequently occurred, cancer-related deaths among men and women worldwide [1]. Lung cancer includes two common types: small cell lung cancer (SCLC, 15% of cases), and (NSCLC, 85% of cases). NSCLC is the most prevalent histological type of lung cancer and can be further classified as adenocarcinoma (ADC,40%), squamous-cell carcinoma (SCC,30%), and large-cell carcinoma (LCC) [27]. According to the results from the National Lung Screening Trial (NLST), low-dose computed tomography (CT) can

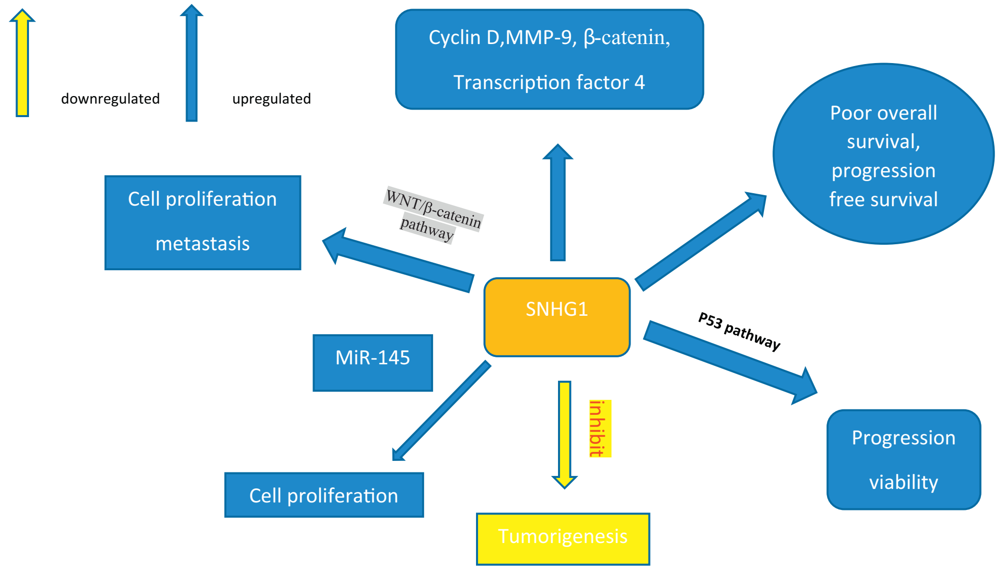

Fig. 2. Role of SNHG1 in colorectal cancer.

detect lung neoplasms in individuals at high risk [28]. But only 2–4% of individuals were screened by CT even in a top economic country like the United States of America [1]. Despite new diagnostic techniques, the overall 5-year survival rate of lung cancer remains at about 15% due to late-stage diagnosis and insensitivity to chemotherapy [2]. Better understanding and management of its development, progression and metastasis mechanisms can help identify new biomarkers for early diagnosis and more effective treatments. LncRNAs play critical molecular functions in tumorigenesis of lung cancer [29].

You et al. showed that SNHG1 expression was significantly upregulated in lung cancer cells compared with that in normal bronchial epithelial cells. Knockdown of SNHG1 inhibited cell proliferation suggesting that it might play as a potential therapeutic target for NSCLC [30]. Cui et al. also found that expression of SNHG1 was up-regulated in NSCLC tissues and cell lines compared with that in adjacent normal tissues and cell lines. Its high expression was also significantly associated with greater tumour size, advanced TNM stage, lymph node metastasis and poor overall survival (OS). SNHG1 promoted NSCLC tumorigenesis and progression via miR-101-3p/SOX9/Wnt/β-catenin axis [31]. Lu et al. also showed that SNHG1 supported NSCLC progression by up-regulating MTDH via sponging miR-145-5p. Its expression was markedly up-regulated in NSCLC tissues and cells compared with that in adjacent normal tissues and cell. SNHG1 silencing decreased tumour volumes. Down-regulation of SNHG1 suppressed NSCLC cell viability, proliferation, migration, and invasion in vitro. Additionally, epithelial-mesenchymal transition (EMT) was also inhibited. But its effect was rescued by miR-145-5p [32]. Taken together, SNHG1 could be a therapeutic target for treatment of NSCLC.

2.3.2. *Squamous cell carcinoma of the lung (SCC)*

Zhang et al. showed that SNHG1 regulated zinc finger *E*-box binding homeobox 1(ZEB1) expression by interacting with p63 TA isoform (TAp63). Knockdown of SNHG1 significantly inhibited the proliferation, metastasis, invasive ability and promoted apoptosis of SCC cells suggesting that SNHG1 might serve as a novel therapeutic target for SCC [33].

2.4. *Prostate cancer*

Prostate cancer is the commonest malignancy in males worldwide. In United States of America, it is the second leading cause of cancer-related death in men [34]. It is more common in men over the age of 65 years. Prostate cancer incidence is strongly associated with age and family history of prostate cancer. However, only 10% of men with prostate cancer die of this disease [35]. Survival of cancer patients tends to be poor in developing countries, due to diagnosis at a late stage and inadequate facilities of treatment. Prostate cancer patients have an excellent overall five years survival rate if the cancer is diagnosed at an early stage [34]. Therefore, new tumour markers are still needed for early diagnosis of prostate cancer.

Li et al. showed that SNHG1 was aberrantly up-regulated in prostate carcinoma tissues compared with that in adjacent normal tissues. SNHG1 negatively regulated miR-199a-3p to enhance CDK7 expression and promoted cell proliferation in prostate cancer. SNHG1 played as a competing RNA (ceRNA) for miR-199a-3p in prostate cancer cell proliferation. Furthermore, SNHG1 increased CDK7 expression by competitively binding miR-199a-3p, and then promoted cell proliferation and cell cycle progression in prostate cancer. Thus, SNHG1 might be useful for prostate cancer therapies [36]. Wan et al. also found that SNHG1 showed association with Gleason score and pT-stage. The expression levels of SNHG1 were correlated with a short biochemical recurrence-free survival time [37]. Taken togethr, SNHG1 might be important in clinical diagnosis, prognosis and disease progression of prostate cancer.

2.5. *Esophageal cancer*

Esophageal cancer is one of the deadliest cancers worldwide, mainly because of its extremely aggressive nature and poor survival rate [38]. The treatments for esophageal cancer depend on its etiology. Endoscopic mucosal resection, endoscopic submucosal dissection, esophagectomy, the Ivor Lewis esophagectomy (right thoracotomy and laparotomy), and neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy are particular methods for the treatment of oesophagal cancer [39]. The overall 5-year survival is around 15%–25%, and the best results of treatments are related to early diagnosis, which is critical to promote the overall survival [38]. Biomarkers for initial diagnosis are still needed for clinical usage.

Yan et al. showed that SNHG1 acted as a sponge of miR-338-3p (miR-338) in the progression of oesophagal cancer and the ceRNA regulatory SNHG11/miR-338-3p/CST3 axis was explored. MiR-338 suppressed the expression of proto-oncogene CST3 protein (also Cystatin C, CysC) and promoted expression of apoptotic proteins caspase-8/3. It also decreased oesophagal carcinoma cell growth and induced its apoptosis [40]. Zhang et al. demonstrated that SNHG1 was highly expressed in oesophagal squamous cell cancer (ESCC) tissues compared with adjacent noncancerous tissues. Its increased expression was correlated with lymph node metastasis, depth of invasion, TNM stage, poor prognosis and reduced over survival time in ESCC patients. SNHG1 knockdown inhibited cell proliferation, cell invasion capacity and cell Epithelial-Mesenchymal Transition (EMT) phenomenon by upregulation E-cadherin and down-regulating Vimentin and N-cadherin in ESCC cells. Its knockdown also inactivated the Notch signalling pathway by reducing the Notch1 and Hes-1 expression levels in ESCC cells [41]. Therefore, these results indicated that lncRNA SNHG1 might be a potential predictor of prognosis in oesophagal cancer patients and a novel target for ESCC treatment.

2.6. Ischemic stroke (IS)

Ischemic stroke (IS) is a leading source of disease with high mortality and disability, as well as with limited therapeutic window. Biomarkers for earlier diagnosis of IS have long been explored. A large number of DNA and microRNA biomarkers using genome-wide associated study (GWAS) and microRNA expression profiling were discovered in polygenic IS (sporadic IS) [42]. The only treatment for acute IS was tissue-type plasminogen activator (tPA). First, only about 10% of patients with acute ischemic stroke possess a sizeable proximal artery occlusion in the anterior circulation and shows early enough to undergo mechanical thrombectomy within 6 h; an additional 9% to 10% of patients presenting within the 6 to 24-hour time gap may also qualify for the procedure. However, widespread use of mechanical thrombectomy is limited and more powerful diagnostic marker for ischemic stroke is still needed [43].

Zhang et al. [44] found that SNHG1 expression was upregulated in oxygen-glucose deprivation (OGD)-cultured mice brain microvascular endothelial cells (BMECs), and isolated cerebral microvessels of a middle cerebral artery occlusion (MCAO) mice model. SNHG1 inhibition presented larger brain infarct size and worsened neurological scores in MCAO mice. Its inhibition also significantly increased caspase-3 activity and cell apoptosis in OGD-cultured BMECs. Furthermore, SNHG1 regulated cerebrovascular pathologies as a competing endogenous RNA for miR-18a through HIF-1α/VEGF signalling in ischemic stroke.

Wang et al. clarified the function and mechanism of SNHG1 in brain microvascular endothelial cells (BMECs) angiogenesis after OGD insult. Upregulated SNHG1 promoted the angiogenesis of brain microvascular endothelial cells after oxygen-glucose deprivation treatment by targeting miR-199a. SNHG1 overexpression and the loss of miR-199a after stroke might promote angiogenesis and functional recovery. Functional effects of SNHG1 on BMEC survival and angiogenesis depended on miR-199a, which elaborated in the regulation of hypoxia-inducible factor (HIF-1a) and vascular endothelial cell growth factor (VEGF) expression. Understanding the involvement of SNHG1 in the pathogenesis of ischemic stroke may provide an advanced therapeutic method for this disease.

2.7. Nasopharyngeal carcinoma (NPC)

Nasopharyngeal carcinoma (NPC) is a squamous epithelial cancer arising from the mucosa of the nasopharynx. The superior respiratory tract is the initial site of contact with environmental carcinogens including certain chemicals (in cigarette smoke or alcohol), air pollutants, oncogenic viruses. Therefore, the incidence of head and neck cancer (epithelial malignancies of the oral cavity, tongue, floor of the mouth, pharynx, larynx, oropharynx, nasopharynx, paranasal sinuses, and the salivary glands) will probably continue to rise in the next decade [45]. Epidemiological studies show that NPC is multiple genes inherited tumours. First-line treatment for early-stage NPC is radiotherapy, and radiotherapy combined with chemoradiotherapy is the standard treatment for advanced NPC. Despite the improvement in the survival rate of NPC, local recurrence and distant metastases after radiotherapy hinder NPC treatment [46]. Further useful biomarkers are still needed in urgency. Lan et al. showed that down-regulation of SNHG1 facilitated the expression of miR-145-5p and further suppressed the level of NAUK1. SNHG1 promoted the expression of NUAK1 by down-regulating miR-145-5p and thus improved the aggressiveness of nasopharyngeal carcinoma cells through AKT signalling pathway. It also induced epithelial-mesenchymal transition (EMT) indicating its potential in the development of NPC [47].

2.8. Neuroblastoma

Neuroblastoma is a heterogeneous, malignant pediatric disease derived from neural crest cells. It is characterized by a generalized reduction of mitochondrial oxidative phosphorylation. Tumours can spontaneously regress or mature and display an aggressive, therapy-resistant phenotype. Patients with low-risk disease are treated by surgery alone with excellent outcome, whereas patients at high risk for disease relapse are treated with intensive multimodality therapy with low survival rates of $< 50\%$ [48,49]. LncRNAs brings a new sight to the prognosis and treatment of high-risk neuroblastoma patients [50].

Sahu et al. identified SNHG1 as a novel predictor for event-free survival (EFS) in neuroblastoma. N-MYC and MYCN amplification regulated SNHG1. Its expression was positively associated with MYCN expression in both MYCN amplified and MYCN non-amplified NB tumours [51]. This study elucidated the functional characterization of SNHG1 and its functional role as a therapeutic target for NB.

2.9. Parkinson's disease (PD)

Parkinson's disease (PD) is a high prevalence, neurodegenerative disorder with evolving layers of complexity that affects dopaminergic neurons in the substantia nigra of the brain. PD seems to result from a complicated relationship of genetic and environmental factors, distressing numerous critical cellular processes. Ultimate diagnosis at the earliest stages of the disease and complications in the managing of signs at later stages are the significant clinical challenges and the complexity of PD. Furthermore, no treatments can slow the neurodegenerative process in PD [52–54]. Among numerous advanced studies, researches explored the impacts of non-coding RNAs (ncRNAs) including microRNAs (miRNAs) and lncRNAs on the pathogenesis of PD [55].

Chen et al. [56] also suggested that SNHG1 promoted α-synuclein aggregation and toxicity by targeting miR-15b-5p to activate SIAH1 in SH-SY5Y cells. These facts light on the mechanisms of Lewy body formation and loss of dopaminergic neurons (novel molecularly targeted therapies) for PD. Theo et al. [57] found that SNHG1 showed a significant twofold increase in PD compared with controls. Their studies indicated the potential of SNHG1 as a diagnostic and prognostic marker for PD.

2.10. Osteosarcoma (OS)

Osteosarcoma is an aggressive malignant tumour that primarily affects the long bones but can also involve other bones in skeletal system of the body [58]. The molecular and mechanistic deviations might be new targets for the treatment strategies of osteosarcoma. miRNAs, lncRNAs played as oncogenes or tumour suppressor genes in osteosarcoma cell migration, invasion, angiogenesis, apoptosis and proliferation in osteoclast function and multidrug resistance [59].

Jiang et al. found that SNHG1 was up-regulated in osteosarcoma (OS) tissues and cell lines compared with that in adjacent normal tissues and cell lines. Increased expression of SNHG1 was correlated with larger tumour size, advanced TNM stage and lymph node metastasis of OS patients. Overexpression of SNHG1 indorsed OS progression, cell proliferation, cell migration, EMT process in U2OS and MG63 cells and tumour growth in vivo. SNHG1 reserved cell migration by hindering

EMT process in OS cells. WNT2B acted as a target of miR-577 and played an oncogenic role in OS cells by triggering Wnt/b-catenin pathway. Moreover, SNHG1 worked as an oncogenic lncRNA that promoted OS tumorigenesis and development via the miR-577/WNT2B/Wnt/b-catenin axis [60].

Wang et al. also demonstrated that SNHG1 was upregulated in OS tissues and cell lines compared with that in adjacent normal tissues and cell lines. Knockdown of SNHG1 repressed OS cell growth and metastasis in vitro and in vivo. A reciprocal relationship between SNHG1 and miR-326 expression was also discovered in OS tissues.Their study demonstrated the critical aspect of a SNHG1/miR-326/NOB1 signalling pathway in OS pathogenesis, clinical diagnosis and treatment [61].Therefore, these findings suggested that SNHG1 could perform as a possible therapeutic goal for the treatment of OS.

2.11. Ovarian carcinoma

Ovarian cancer is one of the most cancer-associated mortality in the world [1]. It is the fatal malignancy of the female genital tract, mostly due to the failure of initial diagnosis, diverse histology subtypes and the restrictions for the conventional chemotherapies. The significant prognostic factors include tumour stage, age at initial diagnosis, tumour morphological subtypes and grade, optimal resection for advanced ovarian cancer, as well as the effect of chemotherapy following primary surgery. Molecular markers are still needed as potential therapeutic targets for the treatent of ovarian carcinoma [62].

Ge et al. found that SNHG1 was upregulated in ovarian carcinoma and endorsed proliferation, growth, invasion and metastasis of ovarian carcinoma cells through the regulation of EMT and MMPs. The underlying mechanism was related to the activation of mitochondrial apoptotic pathway after inhibition of SNHG1. Moreover, down-regulation of SNHG1 could inhibit the proliferation, invasion and metastasis of SKOV-3 cells [63].

Wang et al. showed that SNHG1 was an unfavourable prognostic factor in epithelial ovarian cancer (EOC). Dysregulation of SNHG1 promoted tumorigenesis, progression, cell proliferation and migration by Wnt/β-catenin pathway. Moreover, the downregulation of SNHG1 remarkably inhibited the EOC cells proliferation, migration and invasion. Its downregulation also suppressed S-phase entry in vitro, and repressed tumour growth in vivo. SNHG1 was markedly increased in human EOC tissues and cell lines compared with that in adjacent normal tissues and cell lines. High expression of SNHG1 was associated with aggressive clinical features and poor prognosis of EOC patients. SNHG1 improved the expression of numerous downstream genes in Wnt/β-catenin pathway [64]. These studies provided a novel perspective that SNHG1 functioned as a non-coding oncogene in ovarian carcinoma tumorigenesis and a diagnostic marker for early diagnosis and treatment of ovarian carcinoma.

2.12. Glioma

Glioma, the most lethal adult brain tumours with 12 to 15 months median survival, is highly invasive and angiogenic. The treatment of GBM is multimodal and includes surgical resection, followed by adjuvant radio-and chemotherapy [65]. Extracellular vesicles mediate cell to cell communication by transporting cell-derived proteins,nucleic acids and miRNAs [66]. LncRNAs may act as oncogenes or tumour suppressors in a wide range of biological processes in glioma and may also have significant clinical implications in glioma subclassification [67]. Wang et al. [68] found that SNHG1 was upregulated in glioma tissues compared with that in normal adjacent tissues and predicted a poor prognosis. It also promoted cell proliferation and invasion, and reduced apoptosis in glioma. Its upregulation was closely associated with old age and poor overall survival. Taken together, SNHG1 performed as an oncogene in glioma and it might serve as a novel prognostic marker and therapeutic target in glioma treatments.

2.13. Gastric cancer (GC)

Although gastric cancer is no longer the most common cancer worldwide, it remains as the second major killer of cancer-related mortality worldwide. GC is the most prevalent disease in Eastern Asia and China [69]. Circulating miRNAs and lncRNAs were dysregulated in GC patients compared with healthy individuals and their high expression were significantly related to tumour stage, size, differentiation and metastasis [7,70].

A recent study by Hu et al. showed that the expression of SNHG1 was significantly increased in gastric cancer tissues compared with that in adjacent normal tissues and was correlated with TNM stage, T stage, lymph node metastasis and the survival time of patients. SNHG1 accelerated the proliferation of gastric cancer cells obviously and increased the expression of DNMT1.Therefore, SNHG1 might serve as a novel predictor of gastric cancer prognosis and potential therapeutic target for gastric cancer treatment [71].

2.14. Laryngeal squamous cell carcinoma

Laryngeal squamous cell carcinoma (LSCC) is one of the commonest types of the head and neck cancer. The majority of laryngeal cancers are located in the glottic area [72]. Emerging evidence shows that coding RNAs and non-coding RNAs play critical roles in the formation and progression of LC. LncRNAs appears to be involved in laryngeal cancer growth, invasion, metastasis and the establishment of the laryngeal tumour microenvironment through various mechanisms [73].

Lin et al. suggested that SNHG1 acted as an oncogene in the occurrence and development of laryngeal carcinoma. The expression of SNHG1 in laryngeal carcinoma tissues was significantly higher than that in para-carcinoma tissue and it was associated with a poor prognosis, proliferation and metastasis in laryngeal squamous cell carcinoma. SNHG1 knockdown in HEp-2 cells could inhibit cell proliferation, invasion, and metastasis. Its knockdown also promoted apoptosis [74]. This study suggested that SNHG1 might serve as a biomarker for the diagnosis, prognosis, and clinical significance of laryngeal cancer.

2.15. Cervical cancer

Despite a key role of genetic mutation and epigenetic alteration, human papillomavirus (HPV) infection is the commonest cause of cervical cancer cases. Cervical cancer is one of the best preventable malignancies in women as primary prevention with HPV-vaccination and secondary prevention by detecting and treating true precursor lesions can be received. A combination of HPV vaccination and screening with annual cytology smears could almost eradicate cervical cancer and reduce the burden of other tumours and diseases related to HPV [75]. Recent research strategies keep insight into the role of noncoding RNAs in cervical cancer development, especially miRNA and lncRNA. Moreover,numerous studies are increasing to access the use of their changes as biomarkers to determine disease development and as the therapeutic targets [76].

Liu et al. showed that SNHG1 was highly expressed in cervical cancer tissues compared with that in adjacent normal tissue and it promoted the development of cervical cancer cells. Knock-down of SNHG1 decreased cell proliferation, migration and invasiveness in HeLa and C-33A cells. Taken together, SNHG1 might be useful in cervical cancer therapy [77].

2.16. Breast cancer (BC)

Breast cancer (BC) is the second commonest cause of cancer-related deaths in the United States of America according to cancer statistics. And it stands at the first place with 266,120 new estimated cases (30% of all cancer) [1]. Breast cancer screening can reduce mortality as it is helpful not only in finding cancers early but also in decreasing the

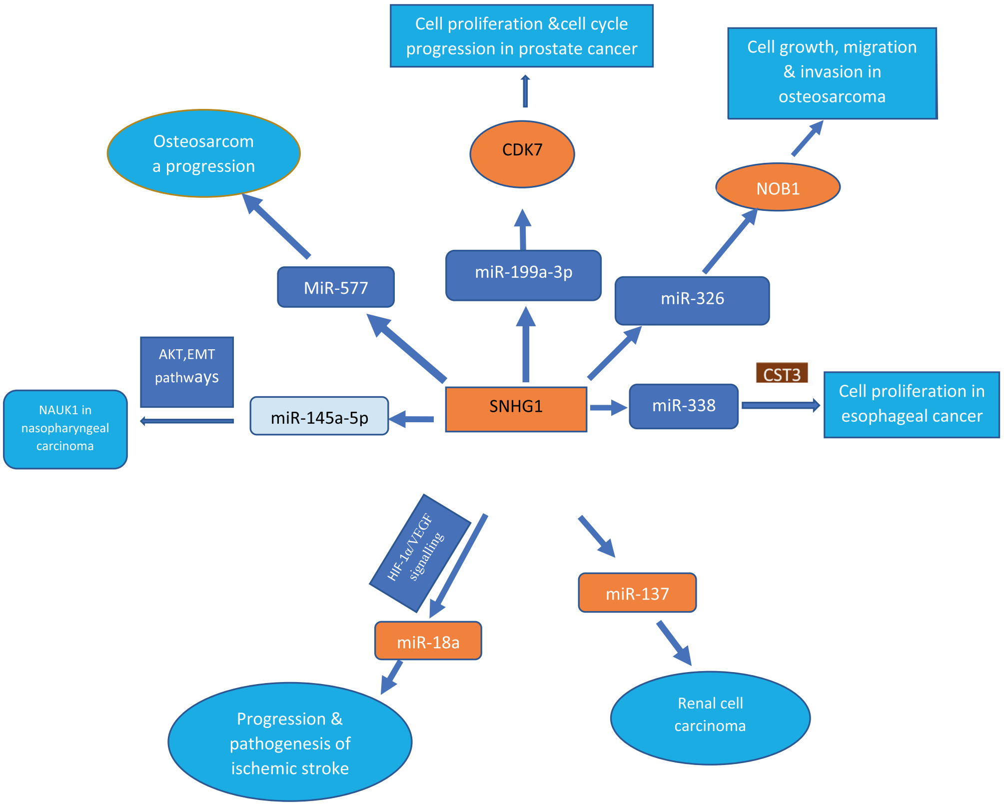

Fig. 3. SNHG1 as a competing endogenous RNA (ceRNA) in a variety of cancers.

chance of dying from these cancers [78]. Biomarkers play an essential role in the detection and management of patients with breast cancer [79].mRNA-miRNA-lncRNA relations have been shown to play a critical governing role in cancer biology [80]. Pei et al. demonstrated that interference SNHG1 could inhibit the differentiation of Treg cells through promoting miR-448 expression and reducing IDO level, subsequently alleviating the immune escape in BC [11]. Their experiments showed that SNHG1 might play a role in breast cancer management.

2.17. Renal cell carcinoma (RCC)

Renal cell cancer (also called kidney cancer) is a disease in which malignant cells form in the lining of tubules in the kidney. Renal cell cancer (RCC) is the most common type of renal carcinoma. RCC is classically regarded as extremely resistant to standard fractionated radiation therapy (RT) [81]. A total of 25–30% of patients with RCC have overt metastases at early symptoms, and a substantial fraction of patients have subclinical metastases at that time explaining the hitherto poor outcome of treatment [82]. Zhao et al. demonstrated that SNHG1 promoted RCC progression and metastasis by negatively regulating miR-137. SNHG1 was overexpressed in RCC tissues and RCC cell lines. High levels of SNHG1 were correlated with poor prognosis of RCC patients. Knockdown of SNHG1 suppressed renal cell proliferation, invasion, and EMT capacity indicating its potential role in RCC development [83].

2.17.1. SNHG1 acts as a competing endogenous RNA (ceRNA) in a variety of cancers

Competing endogenous RNA (ceRNA) is a newly emerged mechanism that describes a crosstalk among lncRNAs, mRNAs and their shared miRNAs [40]. ceRNAs compete common miRNAs and share microRNA (miRNA) response elements (MREs) which can regulate mRNA expression, thereby regulating each other's expression. Compelling evidence suggests that lncRNAs can interact with miRNAs and regulate the expression of mRNAs as ceRNAs [84]. Therefore, mRNAs, miRNAs, long non-coding RNAs and circular RNAs create ceRNA regulatory networks and play critical roles in tumorigenesis. Accumulating evidences showed that the disorders of ceRNA networks might contribute to the pathogenesis of various cancer [85,86].

In a study by Li et al., SNHG1 acted as a ceRNA for miR-199a-3p and suppressed miR-199a-3p activities. It increased the expression of CDK7 which was a target of miR-199a-3p, and finally promoted cell proliferation and progression in prostate cancer. Their findings suggested that the SNHG1/miR-199a-3p/CDK7 axis played a vital role in prostate cancer and could serve as a critical target for therapy [36].

Yan et al. showed that SNHG1 served as a non-degradable sponge for miR-338 and it promoted cell proliferation and expression of proto-oncogene CST3 in primary oesophagal cancer cells [40]. Similarly, Zhang et al. [44] found that SNHG1 mediated by HIF-1α/VEGF signalling provided novel therapeutic options for ischemic stroke. SNHG1 played a role in the progression and pathogenesis of ischemic stroke through acting as a ceRNA for miR-18a. Lan et al. showed that SNHG1 performed as a ceRNA to provoke the effect of miR-145a-5p on the down-regulation of NUAK1 in nasopharyngeal carcinoma cell. It also promoted the aggressiveness of NPC cells through AKT signalling pathway. Furthermore, it induced EMT suggesting that the SNHG1/miR- 145-5p/NUAK1 axis played a crucial role in NPC and could serve as a critical target for therapy [47]. A study by Jiang et al. showed that miR-577 could act as a ceRNA of SNHG1 in osteosarcoma (OS) cells. Promotion of OS progression induced by SNHG1 overexpression required the inactivity of miR-577. The SNHG1/miR-577/WNT2B/Wnt/b-catenin axis regulatory network might provide a potential new therapeutic strategy for OS treatment [60].In the same way, Wang et al. demonstrated that SNHG1 regulated the expression of human nin one binding protein (NOB1) by sponging miR-326 as ceRNA. Finally it prompted cell growth, migration and invasion in OS [61].Similarly, Zhao et al. also demonstrated that SNHG1 performed as an oncogene by sponging miR-137 or served as its ceRNA. Furthermore, overexpression

Table 1
Functional characterization of lncRNA-SNHG1 in various cancers.

Cancer	Expression	Functional role	Related gene	Sample	Role	Pathway, axis	Reference
CRC	Up-regulated [17–22]	Tumour genesis [17,19,22], cell proliferation [18–22], metastasis [18], cell invasion, migration, apoptosis [22]	p53 [20], miR-145 [21]	Tissue [17,18,20,22]	Oncogene [17–19,22]	p53 pathway [20], WNT/β-catenin pathway [18,19,22]	[17–22]
HCC	Up-regulated [11,26]	Tumorigenesis [11], cell proliferation [11,26], invasion, and migration [26]	p53 [11], miR-195 [26]	Tissue [11,26]	Oncogene [11,26]		[11,26]
NSCLC	Up-regulated [31,32]	Cell proliferation [30–32], migration, invasion, Inhibition of EMT, cancer progression [32],NSCLC progression [31]	miR-145-5p, MTDH [32], miR-101-3p [31]	Tissue [31,32]	Oncogene [31,32]	SNHG1/miR-145-5p/MTDH axis [32], Wnt/β-catenin signalling pathway [31]	[31,32]
Lung squamous cell carcinoma	Up-regulated [33]	Cell proliferation, metastasis, invasion, apoptosis [33]	(ZEB1) [33]	Tissue [33]	Oncogene [33]	TAp63/ZEB1 pathway [33].	[33]
Prostate cancer	Up-regulated [36]	Cell proliferation [36]	miR-199a-3p, CDK7 [36],	Tissue [36]	Oncogene [36]	SNHG1/miR-199a-3p/CDK7 [36]	[36]
Esophageal cancer	Up-regulated [40,41]	Cell proliferation [40,41],invasion [41]	miR-338, CST3 [40]	Tissue [40,41]	Oncogene [40,41]	Notch signalling pathway, EMT [41]	[40,41]
Nasopharyngeal carcinoma	Up-regulated [47], [88]	Cell invasion and migration [47], [88]	miR-145a-5p, NUAK1 [47]	Tissue [47], [88]	Oncogene [47], [88]	AKT signalling Pathway, (EMT) [47], [88], SNHG1/miR-145-5p/*NUAK1* axis [88]	[47], [88]
Osteosarcoma	Up-regulated [60,61]	Cell proliferation, cell migration [60,61],invasion [61]	miR-577 [60], miR-326, NOB1 [61]	Tissue [60,61]	Oncogene [60,61]	SNHG1/miR-577/WNT2B/Wnt/b-catenin axis [60], SNHG1/miR-326/NOB1 signalling axis [61]	[60,61]
Ovarian carcinoma	Up-regulated [63,64]	The growth, invasion and metastasis [63], cell proliferation and migration [64]		Tissue [63,64]	Oncogene [63,64]	Wnt/β-catenin pathway [64]	[63,64]
Neuroblastoma	Up-regulated [51]			Tissue [51]	Oncogene [51]		[51]
Glioma	Up-regulated [68]	Cell proliferation and invasion, apoptosis [68]		Tissue [68]			[68]
Gastric cancer	Up-regulated [71]	Cell proliferation [71]	DNMT1 [71]	Tissue [71]	Oncogene [71]		[71]
Laryngeal squamous cell carcinoma	Up-regulated [74]	Proliferation, invasion and metastasis [74]		Tissue [74]	Oncogene [74]		[74]
Cervical cancer	Up-regulated [77]	Cell proliferation, migration, and invasion [77]		Tissue [77]	Oncogene [77]		[77]
Breast cancer	Up-regulated [89]		miR-448/IDO [89]		Oncogene [89]		[89]
Renal cell Carcinoma	Up-regulated [83]	Progression and Metastasis proliferation, invasion, tumorigenesis and EMT capacity [83]	miR-137(83)	Tissue [83]	Oncogene [83]		[83]

Epithelial-mesenchymal transition (EMT), zinc finger *E*-box binding homeobox 1(ZEB1), p63 TA isoform (TAp63), of SNHG1 participated in RCC tumorigenesis by regulating miR-137 [83].

ceRNA is associated with some diseases and involved in the pathogenesis of numerous cancers such as prostate cancer, lung cancer, gastric cancer, endometrial cancer, and so on [86]. Numerous studies are focusing on them as they can provide new insight into cancer pathogenesis and opportunities for therapy exploration [87]. The above studies showed that SNHG1 could function as ceRNA, playing a role in cancer development and therapy (Fig. 3).

3. Conclusion

LncRNAs have been implicated as important regulators in the process of tumour formation and cancer development. With the development of lncRNAs mechanism in the tumour, its role in the cancer development is worthy of exploring and summarizing. Previous studies have demonstrated that SNHG1 was a well-characterized oncogenic lncRNA. SNHG1 is upregulated in several types of cancer, including ovarian cancer, neuroblastoma, glioma, gastric cancer, laryngeal squamous cell carcinoma, cervical cancer, renal cell carcinoma, colorectal cancer, hepatocellular cancer, lung cancer, prostate cancer, oesophagal cancer, nasopharyngeal cancer, osteosarcoma and so on (Table 1). Aberrant expression of SNHG1 was significantly associated with important clinical characteristics such as vascular invasion, advanced tumour size, stage, TNM stage and overall survival in various kinds of human cancer (Table 2). Furthermore, SNHG1 was included in cellular function such as cell proliferation, migration, invasion and cell apoptosis. The molecular functions and cellular mechanisms by which SNHG1 mediates its actions is complicated and associated with multiple factors. SNHG1 is interacted with miRNAs and proteins and showed its role in critical signalling pathways like WNT/β-catenin pathway, p53 pathway, Notch signalling pathway and EMT. Nevertheless, the complex mechanisms of SNHG1 involved in cancer development are only tested in tissue. Therefore, multiple effects between SNHG1 and molecular target markers should be explored in most available diagnostic samples like blood and other body fluids to apply it in clinical use. Further studies on the clinical application of SNHG1 and the related pathways are still needed. In conclusion, the current studies indicate that SNHG1 may act as a tumour biomarker for cancer diagnosis and treatment.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Khaing Zar Thin wrote the manuscript. Sudheesh Raveendran edited and Tu Jian Cheng finalized the manuscript. All authors have read and approved the final manuscript.

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Table 2
The clinical significance of lncRNA-SNHG1 in various tumours.

Type of cancer	Vascular invasion	Shorter survival rate	Lymph node metastasis	Poorer histological grade	Advanced tumour stage	Tumour size	Poorer prognosis	Tumour recurrence	TMN stage	Poor differentiation	Gleason score
CRC	[18]	[18,21]	[18]		Ca [21]	[18]	[17,18,21,22]	[21]	[18]		
HCC		[11]				[11,26]	[11]		[26]	[11]	
NSCLC		[31]	[31]			[31]			[31]		
SCC			[33]			[33]			[33]		
PC		[37]									[37]
ESCC	[41]	[41]	[41]						[41]		
Osteosarcoma		[61]	[60]			[60]			[60]		
Ovarian carcinoma		[64]		[64]	[64]						
NB		[51]									
Glioma		[68]									
GC		[71]	[71]						[71]		
Laryngeal squamous cell carcinoma		[74]	[74]						[74]		
Cervical cancer		[77]									
(RCC)		[83]									

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