Expression and gene regulatory network of SNHG1 in hepatocellular carcinoma

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Abstract

Background: Small nucleolar RNA host gene 1 (SNHG1), a long noncoding RNA (lncRNA), is a transcript that negatively regulates tumour suppressor genes, such as p53. Abnormal SNHG1 expression is associated with cell proliferation and cancer. We used sequencing data downloaded from Genomic Data Commons to analyse the expression and interaction networks of SNHG1 in hepatocellular carcinoma (HCC).

Methods: Expression was examined using the limma package of R and verified by Gene Expression Profiling Interactive Analysis. We also obtained miRNA expression data from StarBase to determine the IncRNA-miRNA-mRNA–related RNA regulatory network in HCC. Kaplan–Meier (KM) analysis was performed using the survival package of R. Gene Ontology annotation of genes was carried out using Metascape.

Results: We found that SNHG1 was overexpressed and often amplified in HCC patients. In addition, SNHG1 upregulation was associated with the promotion of several primary biological functions, including cell proliferation, transcription and protein binding. Moreover, we found similar trends of small nucleolar RNA host gene 1 (SNHG1), E2F8 (E2F transcription factor 8), FANCE (FA complementation group E) and LMNB2 (encodes lamin B2) expression. In the SNHG1-associated network, high expression levels of SNHG1 (log-rank P value = 0.0643), E2F8 (log-rank P value = 0.000048), FANCE (log-rank P value = 0.00125) and LMNB2 (log-rank P value = 0.0392) were significantly associated with poor survival. Single-cell analysis showed that E2F8 may play an important role in tumorigenesis or cancer development.

Conclusions: Our results highlight the benefit of utilizing multiple datasets to understand the functional potential regulatory networks of SNHG1 and the role of SNHG1 in tumours.

Keywords: LIHC, HCC, TCGA, ceRNA, SNHG1, Survival

Background

Liver cancer is the fourth leading cause of death from cancer in the world [1] and is one of the most fatal and algetic tumours. Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer, occurring in 75–85% of patients with primary liver cancer, and Africa and Asia have the highest incidences [1, 2]. Recent research shows that HCC patients tend to have a family history of HCC and that the pathological mechanisms are complex [3, 4]. Overall, medical practice has changed rapidly in the last few years with the aid of rapidly expanding genome sequencing techniques [5], and precision medicine is gradually becoming an emerging field in the treatment and prevention of diseases. Although medical researchers have overcome the challenges of assessing large amounts of data, the application of genetic testing in cancer treatment is progressing slowly. A primary reason for this slow progress is that large amounts of accumulated patient data are independent and discrete. Thus, researchers need to determine...
relationships between diverse data and their correlations with disease.

Noncoding RNAs (ncRNAs) are a class of RNA molecules that do not participate in protein coding but do regulate gene expression, contributing to many physiological and pathological processes, including tumours [6]. Long noncoding RNAs (lncRNAs) are an important subcategory of ncRNAs with lengths longer than 200 nucleotides [7, 8]. Recent studies show that lncRNAs participate in various biological processes, such as cell differentiation [9], signal transduction [10] and posttranscriptional regulation [11], that are conducive to the progression of tumours and many other diseases [12]. Increasing evidence suggests that lncRNAs can function alone or in cooperation with microRNAs (miRNAs). Typically, lncRNAs act as ceRNAs to regulate messenger RNAs (mRNAs). This mode is known as the “lncRNA-miRNA-mRNA network.” This regulation has been reported in some tumour-related studies, but traditional research methods are insufficient for analysing multi-omics data [13, 14]. Nevertheless, ceRNA network analysis can shed light on ncRNA expression alterations in cancers and uncover relationships between altered RNAs.

To reveal the roles of the lncRNA-miRNA-mRNA network in human HCC, we sought to identify ceRNA networks by identifying similar regulatory networks from an extensive collection of data from Genomic Data Commons (GDC) using a stringent bioinformatics pipeline. The identified ceRNA networks may help in identifying molecular subtypes or new biological markers to classify HCC patients. Moreover, by examining differences in patient survival based on the expression of each RNA subtype, our ceRNA networks offer potential clinical utility for personalized treatments and therapeutic targets.

Methods

Data downloading and organization

The gdc-client method was used to download RNA-seq, miRNA and clinical data from the GDC database via TCGA-Assembler (http://www.compgenome.org/TCGA-Assembler/) of R (3.6.2) [15]. A total of 424 RNA-seq, 425 miRNA and 377 clinical data points were included in the study. Duplicates were filtered out before analysis of the metadata download from the GDC database. We also removed samples that were not from primary tumours or normal solid tissues. The TMM method implemented in edgeR of R (3.6.2) [16] was used to normalize RNA-seq and miRNA raw count data, after which we removed genes with a logcpm of expression below 1 in more than half of the samples. We used the limma [17] package in R (3.6.2) (https://www.r-project.org/) to screen genes and miRNAs showing significant differential expression between tumour and normal tissues. Significant differently expressed genes (DEGs) (based on P < 0.01 and fold change (FC) > 2) were identified in the RNA-seq and miRNA expression profiles, and volcano plots and bar plots were constructed in R to visualize these DEGs. Expression analysis of different sample types (tumour vs. normal tissues) was performed with GEPIA (http://gepia.cancer-pku.cn/) [18]. Next, we assessed the levels of protein expression for these genes based on immunohistochemistry data obtained from the Human Protein Atlas database (https://www.proteinatlas.org/) [19–21].

cerNA network analysis

Competing lncRNA-mRNA pairs were identified using the gdcCEAnalysis function of GDCRNATools [15]. The precise identification of lncRNA-miRNA-mRNA interactions was based on three lines of evidence. First, the hypergeometry of shared miRNAs was evaluated to reduce the number of lncRNA-mRNA pairs; hypergeometric analysis was performed to determine whether a lncRNA-mRNA pair shares many miRNAs. Second, we excluded all lncRNA and mRNA pairs that exhibited variable correlations in expression. Finally, the lncRNA-mRNA pairs retained were required to have regulation similar to that of all shared miRNAs. After these steps, several lncRNA-miRNA-mRNA interactions were identified, and functional analysis was then carried out. To identify the number of miRNAs related to lncRNAs and mRNAs, miRNA-mRNA and miRNA-lncRNA interactions were obtained from StarBase v2.0 [22]. The network was visualized using Cytoscape (3.4.0) (https://cytoscape.org) [23, 24].

Univariate survival analysis

GdcSurvival Analysis in GDCRNATools was employed to analyse the association with overall survival for each gene [15]. First, we divided the patients into high- and low-expression groups based on the median expression level. Then, Kaplan–Meier (KM) analysis was performed using the survival package, and the results were examined in univariate survival analysis. The final results are presented as the hazard ratio (HR) and significance (log-rank P value).

Functional analysis

Gene Ontology (GO) annotation for the genes was carried out using the Metascape database (http://metascape.org/gp/index.html#/main/​step1) [25]. Then, Online Mendelian Inheritance in Man (OMIM) (https://www.omim.org/) was applied to analyse associations between diseases and the genes in the lncRNA-miRNA-mRNA network.
Single-cell analysis
To assess gene expression in different cell types, we obtained single-cell sequencing data from a previous report [26]. Gene expression was normalized by log2 (filteredexpr + 1) as mentioned in [26]. Cell clusters were generated with seurat software [27], and the cell clustering information was retrieved from the same report [26]. The expression of these genes in endothelial cells and macrophages was evaluated, and the results of gene expression in different cell clusters are illustrated in a violin plot.

Results

RNA expression in HCC
Using the limma package, we identified 807 upregulated DEGs, 1590 downregulated DEGs, 59 upregulated differentially expressed miRNAs (DEM), and 71 downregulated DEMs (Fig. 1). In total, we identified 2397 DEGs and 130 DEMs.

Biological interaction networks in HCC
We next sought to determine the biological interaction networks in HCC by using internally incorporated miRNA-mRNA and miRNA-lncRNA interactions, and we identified seven mRNA-miRNA-lncRNA networks (Fig. 2). All the ceRNA networks share similar regulation of all miRNAs interacting with the lncRNA-mRNA pairs. For example, the neighbouring genes of MAGI2-AS3, namely, ADAMTSL3, AUTS2, BHLHE40, DUSP6, ERRFI1, GADD45A, GNPNAT1, HIVEPI, MYLK, MYO10, PNRC1, RIPOR2, SMAD6, SPRY2, and SYBU, share the same miRNAs. Additionally, two miRNAs (hsa-miR-374a-5p and hsa-miR-374b-5p) mediated the MAGI2-AS3-mRNA network.

Univariate survival analysis of coexpressed genes in HCC
Abnormal expression of many genes affects the duration of human survival. By constructing a ceRNA network, we identified hub genes with which miRNAs might interact. In addition, we established survival-related networks. Then, we focused on SNHG1 and related genes that predict the same direction of correlation with prognosis.

We evaluated SNHG1 transcription levels in HCC studies from GDC. Data in the GDC database revealed significantly higher mRNA expression of SNHG1 in HCC samples than in normal solid tissue samples (log-rank P value = 6.43E-18) (Table 1), with a fold difference above 2. The results of the expression analysis for SNHG1, LMNB2, FANCE, and E2F8 were verified by GEPIA (Fig. 3). We also verified the low protein levels of these four genes in normal samples using the Human Protein Atlas database (Fig. 4). Four miRNAs (hsa-miR-421, hsa-miR-377-3p, hsa-miR-330-5p, and hsa-miR-326) mediated the SNHG1 network. Thus, SNHG1 expression may serve as a prognostic indicator in HCC.

To better understand the functions of the coexpressed genes (E2F8, FANCE, and LMNB2) correlated with SNHG1, we compared survival time among patients with different levels of gene expression and found that high expression of SNHG1 was associated with decreased
Fig. 2 Visualization of the ceRNA network. The ceRNA network containing 101 nodes and 209 edges in HCC demonstrated paired bonds among IncRNA-miRNA-mRNA interactions. Red, yellow, and blue represent lncRNAs, miRNAs, and mRNAs, respectively. Circle size represents the number of edges connected to the node.

Table 1 Biological functions of the genes in the SNHG1-related network

| Gene symbol | Description          | OMIM   | Type          | LogFC          | P value       |
|-------------|----------------------|--------|---------------|----------------|---------------|
| SNHG1       | Small nucleolar RNA host gene 1 | 603222 | Long non coding | 1.495397836    | 6.43E−18     |
| LMNB2       | E2F transcription factor 8 | 612047 | Protein coding | 1.115366226    | 5.95E−13     |
| FANCE       | FA complementation group E | 613976 | Protein coding | 1.459672439    | 9.12E−14     |
| E2F8        | Lamin B2             | 150341 | Protein coding | 3.729047657    | 8.89E−27     |

The table lists 5 genes in the SNHG1-related network and the following information: Gene symbol, Description, OMIM, Type, LogFC (trimmed binary logarithm of average expression level fold change), and P value.
survival (log-rank P value = 0.0643) (Fig. 5). Additionally, in the SNHG1-associated network, high expression levels of E2F8 (log-rank P value = 0.000048), FANCE (log-rank P value = 0.00125) and LMNB2 (log-rank P value = 0.0392) correlated significantly with poor survival (Fig. 5); these genes affect transcription activity, DNA repair, and protein binding, respectively. Overall, we detected interaction effects of SNHG1 and the other three genes on survival.

Functional analysis of the coexpressed genes correlated with SNHG1 in HCC
To examine the roles that the 3 coexpressed genes we identified play in the cell, we annotated all three genes and SNHG1 using the Custom Analysis function of Metascape (http://metascape.org/) (Table 1). All of these genes are involved in primary life processes, such as transcription activity, DNA repair, and protein binding. Two of these genes encode plasma proteins, and E2F8 encodes a transcription factor with a winged helix-turn-helix DNA-binding domain.

SNHG1-related mRNA expression in endothelial and macrophage populations
We analysed the expression of the three coexpressed genes described above in endothelial cells (ECs) and macrophages, which were significantly different based on single-cell data [26] (Figs. 6 and 7). LMNB2 was found to be uniformly expressed in the 11 EC clusters. Specifically, E2F8 was expressed at low levels in clusters 0, 1, 4, and 8, corresponding to normal cells [26]. At the same time, FANCE was expressed at low levels in clusters 8 (adjacent normal), 9 (core tumour), and 10 (peripheral tumour), indicating no difference between tumour and normal cells. Mononuclear phagocyte-based subclustering analysis also suggested low levels of E2F8 expression in peripheral tumours and adjacent normal tissues. However, LMNB2 and FANCE were uniformly expressed in the 9 macrophage clusters. These results suggest that several clusters of E2F8-deficient endothelial cells and macrophages may be tuned to regulate cancer processes in HCC.

Discussion
Using RNA-seq, miRNA and clinical data downloaded from the GDC database, we identified 807 and 1590 upregulated and downregulated DEGs and 59 and 71 upregulated and downregulated DEMs, respectively. A total of 2397 DEGs and 130 DEMs were found, and by constructing a ceRNA network, we detected hub genes with which miRNAs may interact. We observed 7 lncRNA-miRNA-mRNA interactions and performed survival analysis on all genes in the networks.

We analysed data for 377 patients from the GDC database and found that high SNHG1 expression indicated poor survival; high E2F8, FANCE and LMNB2 levels were also associated with poor patient survival. A previous study revealed a strong negative correlation between SNHG1 expression and survival time in patients with high-risk neuroblastoma (NB) [28]. In addition, downregulation of E2F8 resulted in a series of embryonic defects affecting vasculature and cell survival [29]. FANCE is reported to be a vital factor influencing the poor survival of FANCE-deficient cells among breast cancer cell lines [30], and upregulation of LMNB2 is associated with significantly poorer prognosis in lung
adenocarcinoma patients [31]. Therefore, SNHG1 may affect survival through E2F8, FANCE and LMNB2. Further experiments are needed to examine interactions in this SNHG1-related network.

CeRNAs are RNA molecules that affect mRNA expression by competing for miRNAs in the same interaction network. Disruption of interactive networks can cause disease, including various cancers [32]. It is widely recognized that SNHG1 plays roles in cell proliferation and tumours. The patients showed poor prognosis when SNHG1 was upregulated, which indicated the prognostic value of SNHG1 [33, 34]. They also identified several miRNA-SNHG1 subnetworks (such as hsa-miR-195-5p-SNHG1, hsa-miR-497-5p-SNHG1, and hsa-miR-101-3p-SNHG1) and several mRNA-SNHG1 pairs (such as MYLK-AS1-SNHG1, CHEK1-SNHG1, and KIF2C-SNHG1) in the ceRNA regulatory network of HCC [33, 34]. Through ceRNA network studies, SNHG1 was found to be important in HCC (SNHG1-hsa-miR-101-3p-KIF2C) [33], colorectal cancer (SNHG1-hsa-miR-484-ORC6, SNHG1-hsa-miR-423-5p-EZH2, and SNHG1-let-7b-5p-ATP6V1F) [35], lung adenocarcinoma

Fig. 4 Translational levels of SNHG1, LMNB2, FANCE, and E2F8 in Normal tissue. The immunohistochemistry result was obtained from Human Protein Atlas database. Number of tumour is 369; and number of normal is 50.
SNHG1 was found to be highly expressed in posterior longitudinal ligament patients, cholangiocarcinoma, and osteosarcoma. In the ceRNA network established in this study, we found SNHG1-hsa-miR-421-3p-E2F8, SNHG1-hsa-miR-377-3p-E2F8, SNHG1-hsa-miR-330-5p-LMNB2, and SNHG1-hsa-miR-326-FANCE axes in HCC. E2F8 was found to be required for cell cycle progression and proliferation [43], FANCE to be essential for protection against chromosome breakage [44], and LMNB2 to be required for early replication and transcription [45]. These genes mediate links between miRNAs, which affect the development of HCC as a network. However, studies with large samples are needed to confirm how these miRNAs are connected.

SNHG1 is a IncRNA that is generally thought to be produced by a small nuclear RNA host gene. Cell proliferation and changes in the tumour protein p53 occur when SNHG1 is abnormally expressed [46]. Considering the very important functions of SNHG1, its 3 coexpressed genes can be expected to be related to disease, with altered expression in many human diseases. Of these genes, $E2F8$ is usually accompanied by overexpression of genes during progression of the cell cycle and cell proliferation [47]. Expression of $E2F$ target genes is required in the S phase of the cell cycle. As a part of this nuclear complex, FANCE interacts with BRCA1 at sites of DNA damage by activating the downstream protein FANCD2 [44]. LMNB2, replicated in the first minute of S phase in humans, is essential for early replication and transcription [48]. In addition, LMNB2, which is located on the inner side of the nuclear envelope, is required for nuclear stability, chromatin structure, and gene expression [48].
Fig. 6  Tumor-Associated Endothelial Cells. a UMAP analysis and graph-based clustering results were obtained from [26]. Identifies 11 endothelial cell clusters from 14 HCC patients and one healthy donor in liver. b–d Violin graph represent gene expression in endothelial cell population. ECs: endothelial cells

Fig. 7  Tumor-Associated Myeloid Cells. a UMAP analysis and graph-based clustering results were obtained from [26]. Identifies 9 Myeloid cell clusters from 14 HCC patients and one healthy donor in liver. b–d Violin graph represent gene expression in Myeloid cell population. DC1, DC2, pDC: dendritic cells; TAMs: tumor-associated macrophages
To explore the cell type specifically of these genes in tumour and normal samples, we analysed their expression in endothelial cells and macrophages and found low expression of E2F8 in normal epithelial cells, which may indicate that its presence promotes cancer. This is also consistent with the conclusion drawn from TCGA data, whereby no difference between LMNB2 and FANCE was detected in these two cell types from normal and tumour samples.

Conclusions
In this work, we identified 7 IncRNA-miRNA-mRNA interactions. Furthermore, we demonstrated that ADAMTSL3, AUTS2, BHLHE40, DUSP6, ERFF1, GADD45A, GNPAT1, HIVEP1, MYLK, MY010, PNRC1, R IPO R2, SMAD6, SPRY2, and SYBUI show the same expression trends as SNHG1 in HCC. By generating IncRNA-miRNA-mRNA interaction networks and performing univariate survival analysis of the genes co-expressed with IncRNAs in HCC, we demonstrated that SNHG1 has the same effect on patient survival as E2F8, FANCE and LMNB2. Single-cell analysis also demonstrated that E2F8 may play an important role in tumorigenesis or cancer development. Therefore, SNHG1, E2F8, FANCE and LMNB2 may represent therapeutic targets for HCC with complex regulation. Taken together, our research provides genetic resources for capturing the majority of essential genes involved, which will yield a global view of the minimum set of genes and pathways. The biological interaction network of SNHG1-related IncRNA-miRNA-mRNA interactions provides insight into the function of SNHG1 and its molecular regulation in HCC.

Abbreviations
HCC: Hepatocellular carcinoma; GEPIA: Gene Expression Profiling Interactive Analysis; LIHC: Liver hepatocellular carcinoma; SNHG1: Small nuclear RNA host gene 1; MiRNA: MicroRNA; LncRNA: Long noncoding RNA; ceRNAs: Competing endogenous RNAs; DEGs: Differentially expressed genes; DEMs: Differentially expressed miRNAs; GO: Gene Ontology; PPI: Protein–protein interaction; TCGA: The Cancer Genome Atlas; E2F8: E2F transcription factor 8; FANCE: FA complementation group E; LMNB2: Lamin B2.

Acknowledgements
We thank the editor and reviewers for taking the time and effort to provide insightful and critical discussion.

Authors’ contributions
CZ and SY conceived the study. SY collected raw data and analysed the GDC data. CZ performed the Cytoscape analysis. SY performed the gene function and analysis. CZ and SY wrote the manuscript. All authors read and approved the final manuscript.

Funding
This study was supported by an unrestricted grant from the Guangdong Postdoctoral Research Foundation (CNI (0)39030Q2). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and material
The RNA-seq, miRNA and clinical data of LIHC (Liver hepatocellular carcinoma) were downloaded from the DATA PORTAL of GDC (Genomic Data Commons) https://portal.gdc.cancer.gov/projects/TCGA-LIHC. Immunohistochemistry data were downloaded from the Human Protein Atlas database (https://www.proteinatlas.org/) under gene symbols described in Table 1. Single-cell sequencing data is available from NCBI Gene Expression Omnibus (GEO: GSE156337).

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
We declare that we have no conflict of interest.

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Received: 10 October 2020 Accepted: 17 January 2021

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