Original Article

Oncogenic role of SKA2 and its ceRNA network in hepatocellular carcinoma based on a comprehensive analysis

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Background: Genetic alterations have important roles in cancer development and progression. *SKA2* (spindle and kinetochore associated complex subunit 2) is a mitotic component that plays a critical role in maintaining the silence of the metaphase plate and spindle checkpoint. However, the exact role of *SKA2* in hepatocellular carcinoma (HCC) remains unclear. The current study aimed to comprehensively identify the function of *SKA2* in HCC.

Methods: We utilized various databases and bioinformatics tools, such as The Cancer Genome Atlas (TCGA), survminer package, Tumor Immune Estimation Resource (TIMER), cBioPortal website, clusterProfiler package, gene set enrichment analysis (GSEA), miRWalk, TargetScanHuman8.0, miRDB, DIANA and Cytoscape to identify the role of *SKA2* in HCC.

Results: Our results showed that patients with HCC exhibited a high *SKA2* expression. Further, the *SKA2* high expression group had a worse overall survival (OS). And *SKA2* was associated with tumor stage and the immune system. In addition, 188 co-expression genes of *SKA2* participated in some processes including cell cycle, DNA replication and so on. The tumor had a lower hsa-miR-19b-1-5p and hsa-miR-378a-5p expression, and these two microRNAs (miRNAs) were also correlated with OS. SNHG14, SNHG15, and SPCA6P-AS were significantly negatively correlated with hsa-378a-5p, and these three long non-coding RNAs (lncRNAs) showed a positive correlation with *SKA2* ($P<0.05$). *SKA2* is a member of competing endogenous RNA (ceRNA). Moreover, it is related to SPACA6P-AS/hsa-miR-378a-5p/*SKA2*, SNHG14/hsa-miR-378a-5p/*SKA2*, and SNHG15/hsa-miR-378a-5p/*SKA2*, which play significant roles in tumor progression.

Conclusions: *SKA2* is associated with OS, tumor stage, and immune infiltrating cells in HCC. Thus, we propose that *SKA2* functions as a ceRNA and influences tumorigenesis. These findings lay the foundation for future research in the field of HCC.

Keywords: Spindle and kinetochore associated complex subunit 2 (*SKA2*); bioinformatics analysis; competing endogenous RNA (ceRNA); hepatocellular carcinoma (HCC)

Submitted May 22, 2024. Accepted for publication Sep 06, 2024. Published online Oct 29, 2024.
doi: 10.21037/tcr-24-833
View this article at: https://dx.doi.org/10.21037/tcr-24-833

Introduction

According to the Global Cancer Statistics 2020 report, liver cancer is the sixth most common primary cancer worldwide and has the third highest mortality rate. In most countries, men have a higher incidence of liver cancer than women (1). In 2030, liver cancer is projected to cause over 1 million deaths globally (2). In China, hepatitis B virus (HBV) infection and aflatoxin exposure are the primary causes of liver cancer (3), HBV infection is a chronic condition that affects over 250 million people worldwide, and nearly 1 million deaths annually are caused by liver cirrhosis and liver cancer (4). Despite existing research on hepatocellular carcinoma (HCC), its therapeutic effect is not ideal. A previous study showed that the disease-free survival rates of patients who underwent resection was <70%, with a median over survival of 60.19 months. Moreover, the median time to recurrence was 20.2 months (5). Hence, its pathogenesis should be further explored. Another research has revealed that alterations or loss of function in certain genes can result in cancer development (6). Alpha-fetoprotein (AFP) is a biomarker currently used for the early diagnosis of HCC. However, the sensitivity of AFP in screening HCC ranges from 39% to 64%. Notably, in up to 20% of patients with HCC, AFP is not produced (7). Therefore, it is necessary to screen novel biomarkers for early diagnosis and to identify novel therapeutic targets for HCC by assessing changes in the gene function network related to the HCC development and progression.

The spindle and kinetochore-associated (SKA) complex is a mitotic component required for precise division of human cells and a key complex at the kinetochore microtubule interface, SKA complex and NdC80 complex participate in kinetochore-microtubule attachment during mitosis (8,9). The SKA complex is associated with the development and prognosis of many cancers, and its score may serve as a predictor of patients receiving anti-programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) therapy (10). The core structure of the SKA complex is the W-shaped coiled coil dimer, which is formed by the interaction between SKA1 (spindle and kinetochore associated complex subunit 1), SKA2 (spindle and kinetochore associated complex subunit 2), and SKA3 (spindle and kinetochore associated complex subunit 3). SKA2 and SKA3 form the skeleton of the dimerization interface and play a key role in maintaining the silence of the intermediate plate and spindle checkpoints, SKA3 affects the migration, proliferation, reproduction of HCC cells through the notch signaling pathway, *SKA2* is located in chromosome 17 (9,11-13), moreover, it plays essential roles in cell cycle progression, cell proliferation and tumorigenesis. Furthermore, the *SKA2* gene expression is regulated by micro-RNAs (14). It has been shown that there is a significant association between circ_0008039, miR-140-3p and *SKA2* in breast cancer (15). The competing endogenous RNA (ceRNA) axis is composed of mRNA, microRNA, and lncRNA, and it can significantly affect the development of some diseases. However, it may also provide novel avenues for disease therapies (16). Several studies have revealed that *SKA2* influences liver cancer proliferation and migration via the β-catenin signaling pathway (17,18). *SKA2* is related to tumor stage and tumor grade in HCC. The expression of *SKA2* in liver cancer is related to race. The expression level is higher in Asian HCC patients, and the expression level of *SKA2* is higher in HCC patients with TP53 mutations (19,20). However, knowledge regarding the regulatory network of *SKA2* in HCC is limited. Therefore, this study aimed to analyze *SKA2* using HCC data from The Cancer Genome Atlas (TCGA). Moreover, the ceRNA network was evaluated via bioinformatics analysis.

Highlight box

Key findings

- Spindle and kinetochore associated complex subunit 2 (*SKA2*) is highly expressed in hepatocellular carcinoma (HCC) and is associated with tumor stage, immune infiltrating cells, and overall survival (OS) of HCC.
- *SKA2* is a member of competing endogenous RNA, it is related to SPACA6P-AS/hsa-miR-378a-5p/*SKA2*, SNHG14/hsa-miR-378a-5p/*SKA2*, and SNHG15/hsa-miR-378a-5p/*SKA2*, which play significant roles in tumor progression.

What is known and what is new?

- Relevant studies have shown that the expression of *SKA2* correlate with tumor staging, tumor grading, patient race, and TP53 mutation status in HCC.
- In this study, we constructed the competing endogenous RNA (ceRNA) network for *SKA2* and further elucidated its role in HCC.

What is the implication, and what should change now?

- *SKA2* plays an important role in HCC and affects tumorigenesis as a member ceRNA network. These findings might provide a theoretical foundation for further research in the field of HCC.

Methods

Collection of data on the SKA2 expression

This study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The Genomic Data Commons (GDC)-client tool was used to download HCC data on RNA-seq and miRNA-seq raw counts and clinical information from the TCGA database (http://cancergenome.nih.gov/). After removing repeated samples, 50 normal tissue samples and 373 tumor tissues samples were analyzed. Raw counts were converted to transcripts per kilobase of exon model per million mapped reads (TPM) and the expression of *SKA2* was compared between normal and tumor samples.

Associations between the SKA2 expression and prognostic, tumor stage, and immune infiltrating cells

To integrate RNA-seq data with clinical information (survive days >0), the surv_cutpoint function of the survminer package in R was utilized to determine the optimal cutoff of continuous independent variables based on survival data. In addition, the association between the *SKA2* expression and overall survival (OS) and tumor stage was analyzed using R software (version 4.2.0). In particular, TIMER is a database for comprehensive analysis of tumor-infiltrating immune cells, it was used to detect the association between the *SKA2* expression and six types of immune cells (21).

Functional enrichment analysis

The co-expression genes of *SKA2* were determined using cBioPortal v3.7.1 (https://www.cbioportal.org/), cBioPortal is an open-source software project that allows us to explore multidimensional cancer genomics data. The screening criteria with a |correlation coefficient| >0.4 and P value <0.05 were applied. The identified genes were used to perform Gene Ontology (GO) analysis to determine BP (biological process), CC (cellular component), and MF (molecular function) term enrichment and perform Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis using the R package clusterProfiler (22). In addition, the TCGA data of HCC were sorted based on the *SKA2* expression and divided into the *SKA2* high and low expression group according to the median. The data set was analyzed using gene set enrichment analysis (GSEA) 4.3.2 software, GSEA is used to evaluate the distribution trends of genes from a predefined gene set in the gene table sorted with phenotype correlation, and thereby determine their contribution to the phenotype (23).

Identification of miRNAs

MiRWalk3.0 (http://mirwalk.umm.uniheidelberg.de/), TargetScanHuman8.0 (https://www.targetscan.org/vert_80/), and miRDB (http://mirdb.org/) were utilized to predict the miRNAs of *SKA2* (24-26). The miRNAs predicted by these tools were then intersected, and the miRNAs negatively associated with the *SKA2* expression were further calculated. In addition, the expression of these miRNAs was determined using HCC miRNA-seq data from TCGA. To investigate the association between these miRNAs and OS, the surv_cutpoint function of the survminer package was used to determine the high and low expression groups.

Identification of lncRNAs

Based on the miRNAs predicted above, miRWalk2.0 (miRWalk, miRanda, RNAhybrid, Targetscan) and DIANA (LncBase v2) were further utilized to predict their lncRNAs (24,27). Meanwhile, the predicted results were intersected, and the expression of these lncRNAs in both tumor and normal tissues was calculated using HCC data from TCGA.

Associations between lncRNAs and prognostic, miRNA expression, and immunity

The RNA-seq and clinical data were downloaded and integrated, and the surv_cutpoint function was used to determine the optimal cutoff value. Then, the association between the identified lncRNAs and OS was examined. Furthermore, the association between the identified lncRNAs, miRNA and *SKA2* expression was evaluated.

Establishment of the ceRNA network

As mentioned above, The Cytoscape software (version 3.10.2) was used to draw the ceRNA network of the above-mentioned genes, Cytoscape is an open-source software project for the integration of biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework (28).

Statistical analysis

Data were analyzed using the R software (version 4.2.0) and the unpaired *t*-test was used to calculate the difference

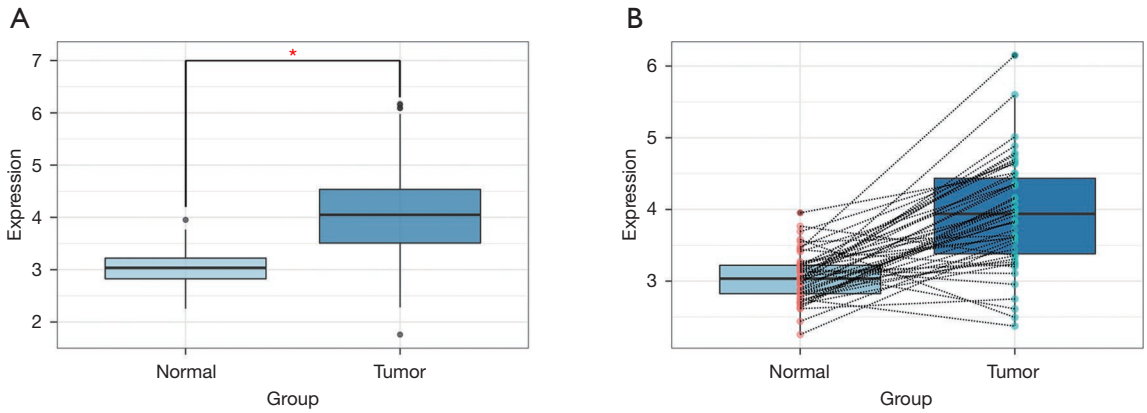

Figure 1 The expression of *SKA2* in HCC. (A) Expression between normal and tumor tissues; (B) expression in paired normal and tumor tissues. *, P<0.05. *SKA2*, spindle and kinetochore associated complex subunit 2; HCC, hepatocellular carcinoma.

between two groups of continuously distributed variables. P value <0.05 was considered statistically significant.

Results

High SKA2 expression in HCC

According to the HCC data from TCGA, the tumor tissues had a significantly higher *SKA2* expression than the normal tissues (P<0.05) (*Figure 1A*). As shown in *Figure 1B*, this was further confirmed by examining 50 paired normal and tumor tissues, which showed that *SKA2* was overexpressed in tumor tissues (P<0.05).

Association between SKA2 and OS, tumor stage and immunity

Data were divided into the two groups, *SKA2* high group and the *SKA2* low group based on the cutoff value of 26.01625 according to the surv_cutpoint function. As shown in *Figure 2A*, the *SKA2* high expression group had a worse OS than the *SKA2* low expression group (P<0.05). In addition, the *SKA2* expression was upregulated with increased tumor stage. However, it decreased in patients with stage IV disease (P<0.05), as shown in *Figure 2B*. Moreover, a significant association was observed between *SKA2* expression and tumor stage (P<0.05). According to the TIMER, there was an association between the *SKA2* expression and various immune cells. In particular, *SKA2* was found to be associated with B cell (correlation coefficient =0.255, P<0.05), CD8+ cell (correlation coefficient =0.203, P<0.05), CD4+ cell (correlation coefficient =0.329, P<0.05), macrophage (correlation coefficient =0.409, P<0.05), neutrophil (correlation coefficient =0.265, P<0.05), and dendritic cell (correlation coefficient =0.283, P<0.05). This information sheds light on the correlation between the *SKA2* expression and the immune system (*Figure 2C*).

Enrichment analysis of GO, KEGG, and GSEA

According to the screening criteria (Spearman's correlation >0.4, P<0.05), the study identified 188 co-expression genes of the *SKA2* in the cBioPortal website (https://www.cbioportal.org/). The enrichment pathways of these co-expression genes were analyzed. According to the analysis results using BP GO terms, these co-expression molecules were mainly enriched in mechanisms such as nuclear division, DNA replication, and regulation of cell cycle phase transition. The CC showed that these genes were related to chromosomal region, spindle, and condensed chromosome. Based on the MF, they were enriched in ATPase activity, DNA-dependent ATPase activity, and microtubule binding (*Figure 3A*). The KEGG results show that the co-expression molecules were mainly enriched in cell cycle, DNA replication, p53 signaling pathway, and so on (*Figure 3B*). As shown in *Figure 3C*, the GSEA results based on *SKA2* revealed that the group with high *SKA2* expression were mainly enriched in cell cycle, oocyte meiosis and DNA replication.

Determination of miRNAs of SKA2

In total, 749 miRNAs of *SKA2* were obtained from

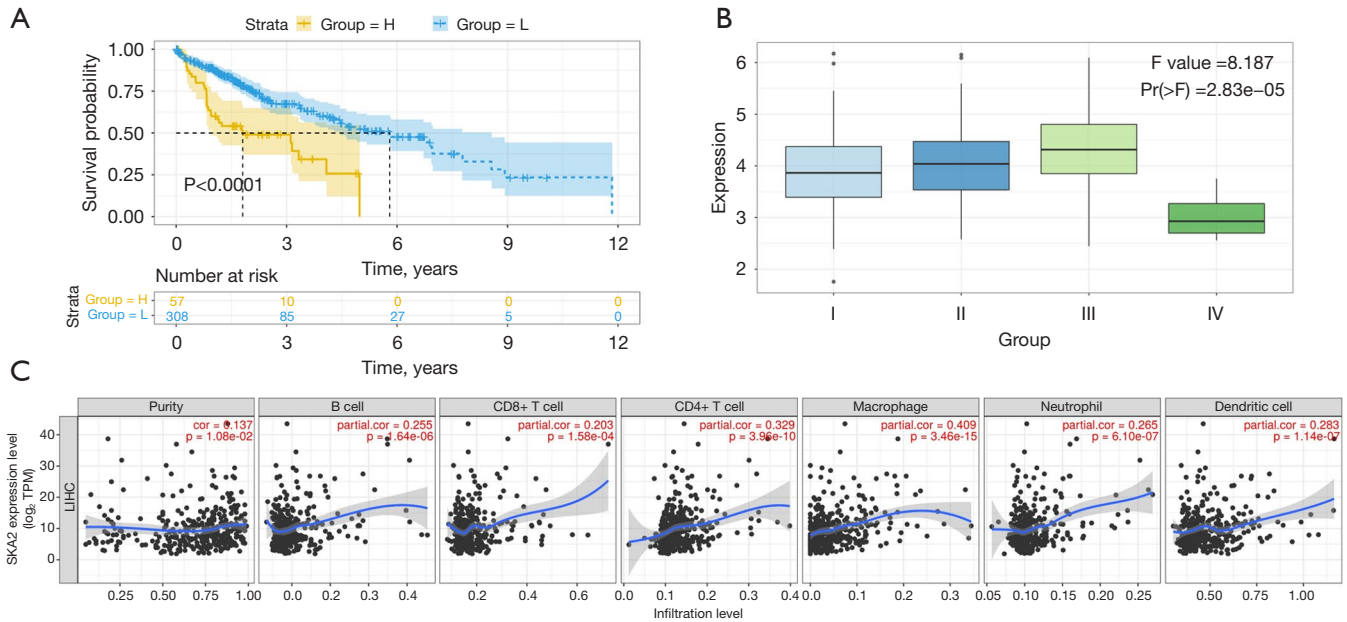

Figure 2 The association between the *SKA2* and OS (A), tumor stage (B), immunity (C). H, high expression group; L, low expression group. *SKA2*, spindle and kinetochore associated complex subunit 2; TPM, transcripts per kilobase of exon model per million mapped reads; LIHC, liver cancer; OS, overall survival.

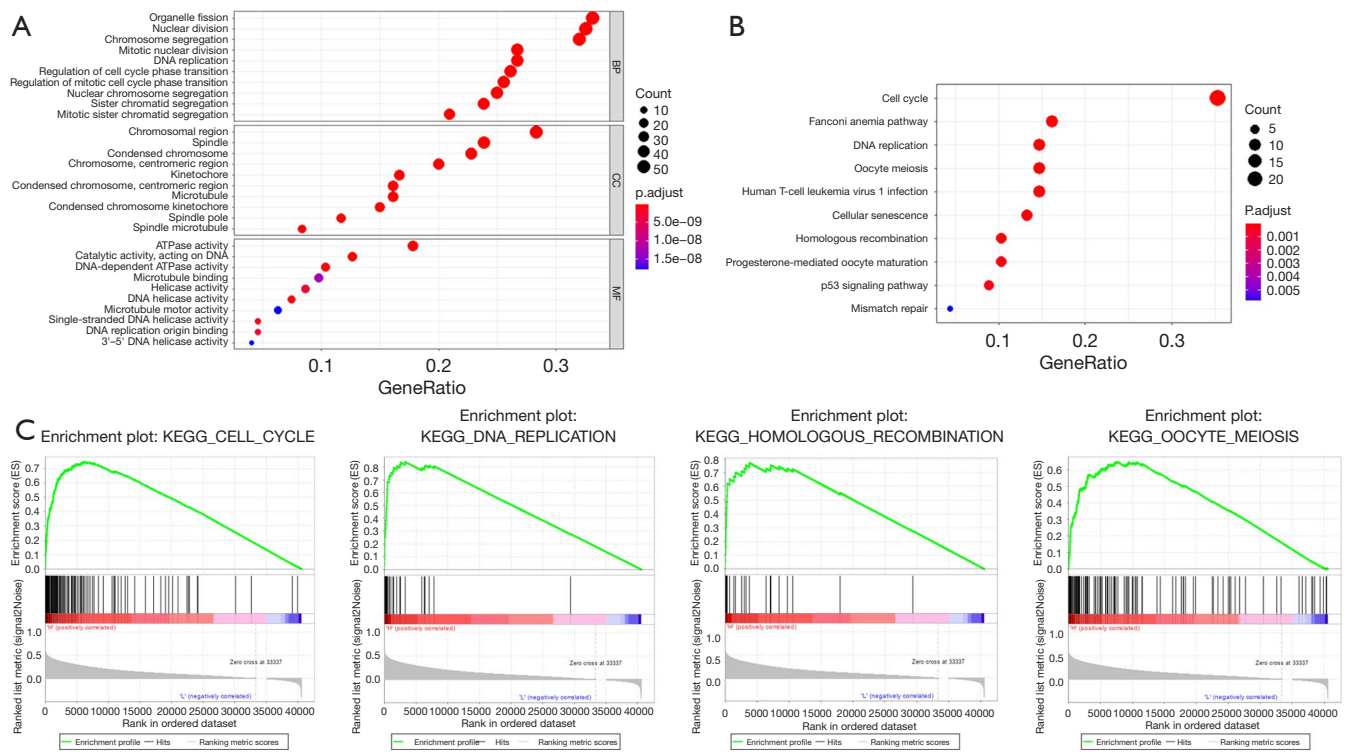

Figure 3 Results of GO, KEGG enrichment analysis and GSEA. (A) GO terms for *SKA2* co-expression genes; (B) KEGG terms for *SKA2* co-expression genes; (C) GSEA terms for *SKA2* co-expression genes. BP, biological process; CC, cellular component; MF, molecular function; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, gene set enrichment analysis; *SKA2*, spindle and kinetochore associated complex subunit 2.

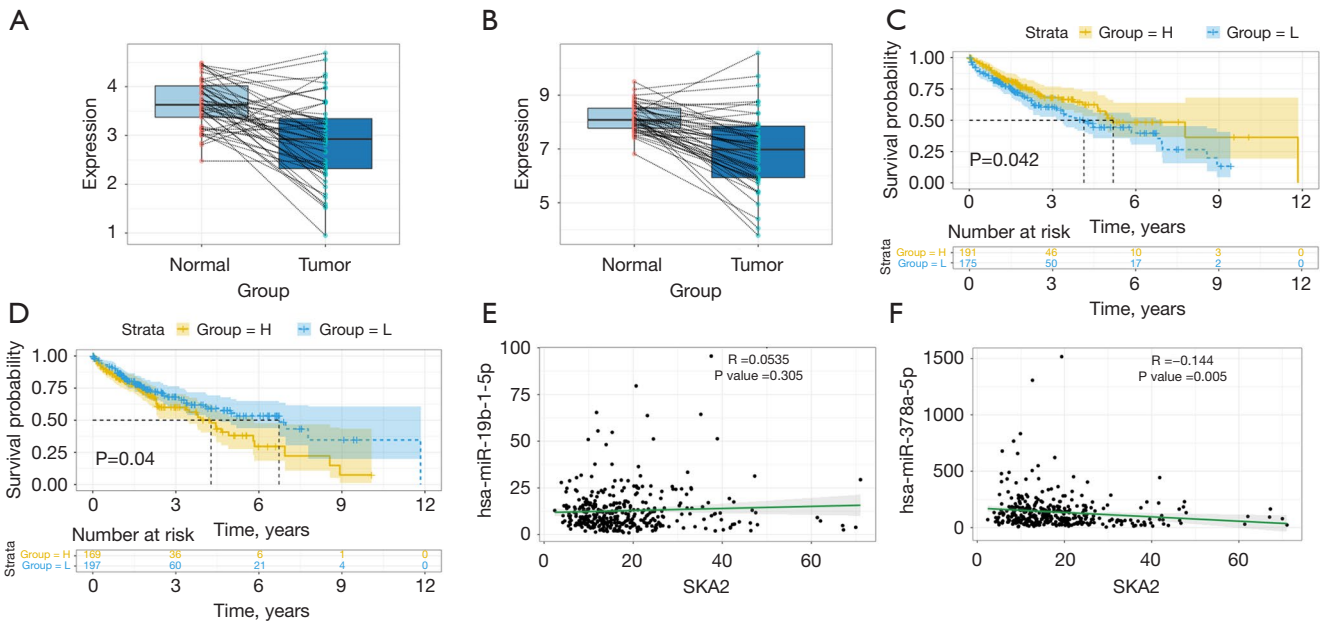

Figure 4 Relationship between miRNAs and *SKA2* in HCC. (A,B) The hsa-miR-19b-1-5p and hsa-miR-378a-5p expression; (C,D) the association between survival and hsa-miR-19b-1-5p and hsa-miR-378a-5p expression; (E,F) the Pearson correlation coefficient of *SKA2* and hsa-miR-19b-1-5p and hsa-miR-378a-5p. H, high expression group; L, low expression group. *SKA2*, spindle and kinetochore associated complex subunit 2; HCC, hepatocellular carcinoma.

miRWalk 3.0 using a screening standard score >0.95. Meanwhile, 695 miRNAs were screened using TargetScan, and 78 miRNAs were obtained using miRDB. Then, 23 miRNAs were obtained from the intersection of three databases [namely, miRWalk 3.0 (http://mirwalk.umm.uni-heidelberg.de/), TargetScan (https://www.targetscan.org/vert_80/), and miRDB (https://mirdb.org/)]. The 23 miRNAs identified were hsa-miR-135a-3p, hsa-miR-19b-1-5p, hsa-miR-3160-5p, hsa-miR-3176, hsa-miR-3177-5p, hsa-miR-378a-5p, hsa-miR-3916, hsa-miR-3925-5p, hsa-miR-4330, hsa-miR-4433a-3p, hsa-miR-4524b-3p, hsa-miR-4690-5p, hsa-miR-5584-5p, hsa-miR-5588-5p, hsa-miR-595, hsa-miR-642a-3p, hsa-miR-6785-5p, Hsa-miR-6799-5p, hsa-miR-6859-5p, hsa-miR-6867-3p, hsa-miR-6867-5p, hsa-miR-6886-3p, and hsa-miR-877-5p. Furthermore, based on the downloaded data on miRNA in HCC, as shown in *Figure 4A*,*4B*, the cancer tissues had a lower hsa-miR-19b-1-5p and hsa-miR-378a-5p expression than the normal tissues. hsa-miR-19b-1-5p and hsa-miR-378a-5p were significantly associated with OS (*Figure 4C*,*4D*). Furthermore, the association between *SKA2* and these two miRNAs was evaluated. As shown in *Figure 4*, the expression of *SKA2* was negatively correlated with hsa-miR-378a-5p (P<0.05) (*Figure 4F*), but not with hsa-miR-19b-1-5p (*Figure 4E*).

Determination of lncRNAs of miRNAs

DIANA (LncBase v2) was used to obtain 2317 lncRNAs related to hsa-miR-378a-5p, with a threshold >0.9. At least three algorithms from miRWalk, miRanda, RNAhybrid, and Targetscan were taken as the standard, and data from miRWalk2.0 were used to predicted 57 lncRNAs. Meanwhile, 26 lncRNAs were obtained from the intersection of the two databases. As shown in *Figure 5*, 12 lncRNAs were significantly highly expressed in the tumor tissues (P<0.05). These lncRNAs were AC005154.6, EXTL3-AS1, GABPB1-AS1, KCNQ1OT1, MALAT1, MUC19, NEAT1, RAMP2-AS1, SNHG14, SNHG15, SPACA6P-AS, TPTEP1.

Survival assessment of lncRNAs

The association between prognosis and 12 lncRNAs was analyzed. *Figure 6* shows that 9 of the 12 genes were associated with OS (P<0.05). These genes were

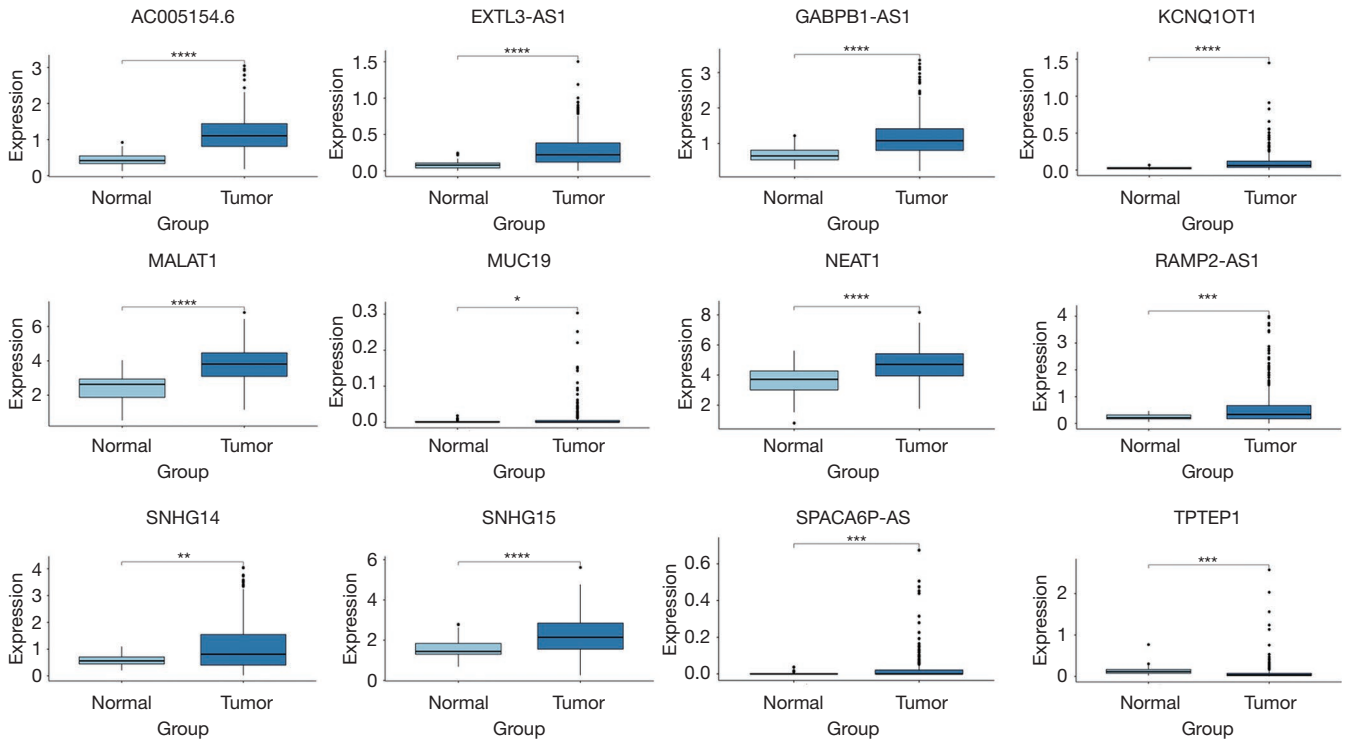

Figure 5 The lncRNAs expression. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.

EXTL3-AS1, GABPB1-AS1, NEAT1, RAMP2-AS1, SNHG14, SNHG15, SPACA6P-AS, TPTEP1, and AC005154.6.

Analysis of the association between SKA2, miRNAs and lncRNAs

The association between *SKA2* and miRNA as well as lncRNAs was analyzed. As shown in *Figure 7A*, SNHG14, SNHG15, and SPCA6P-AS were significantly negatively associated with hsa-378a-5p (P<0.05). In addition, these three lncRNAs were positively associated with *SKA2* (P<0.05), as depicted in *Figure 7B*.

Establishment of ceRNA network

As shown in *Figure 8*, the SPACA6P-AS/hsa-miR-378a-5p/*SKA2*, SNHG14/hsa-miR-378a-5p/*SKA2*, and SNHG15/hsa-miR-378a-5p/*SKA2* regulatory axes were identified.

Discussion

SKA2 is a protein-coding gene that plays a crucial role in the normal metabolism of the human body. Moreover, it is associated with various cellular processes such as cell cycle, tumorigenesis, and mental illnesses (14). For example, overexpression of *SKA2* promotes the invasion and metastasis of breast cancer cells (15,29,30). *SKA2* is highly expressed in gastric cancer and influences the tumor growth (31). In addition, it is associated with psychiatric disorders (32-35). However, its role in HCC is not completely elucidated. The current study aims to comprehensively investigate the role of *SKA2* in HCC.

In this study, using the TCGA datasets, *SKA2* was found to be overexpressed in the HCC tissues. This result is consistent with that of previous studies (17,18). Based on our findings, a high *SKA2* expression could be a predictor of worse prognosis. This finding is supported by the study of Wang *et al.*, which showed that a high *SKA2* expression is associated with negative prognostic outcomes in breast cancer (29). In addition, Yu *et al.* found that the SKA family is associated with immune infiltrating cells (19). Our study revealed that the *SKA2* expression was related to tumor stage and immune infiltrating cells.

Next, GO and KEGG enrichment analysis of the co-expression genes were performed. Results showed that

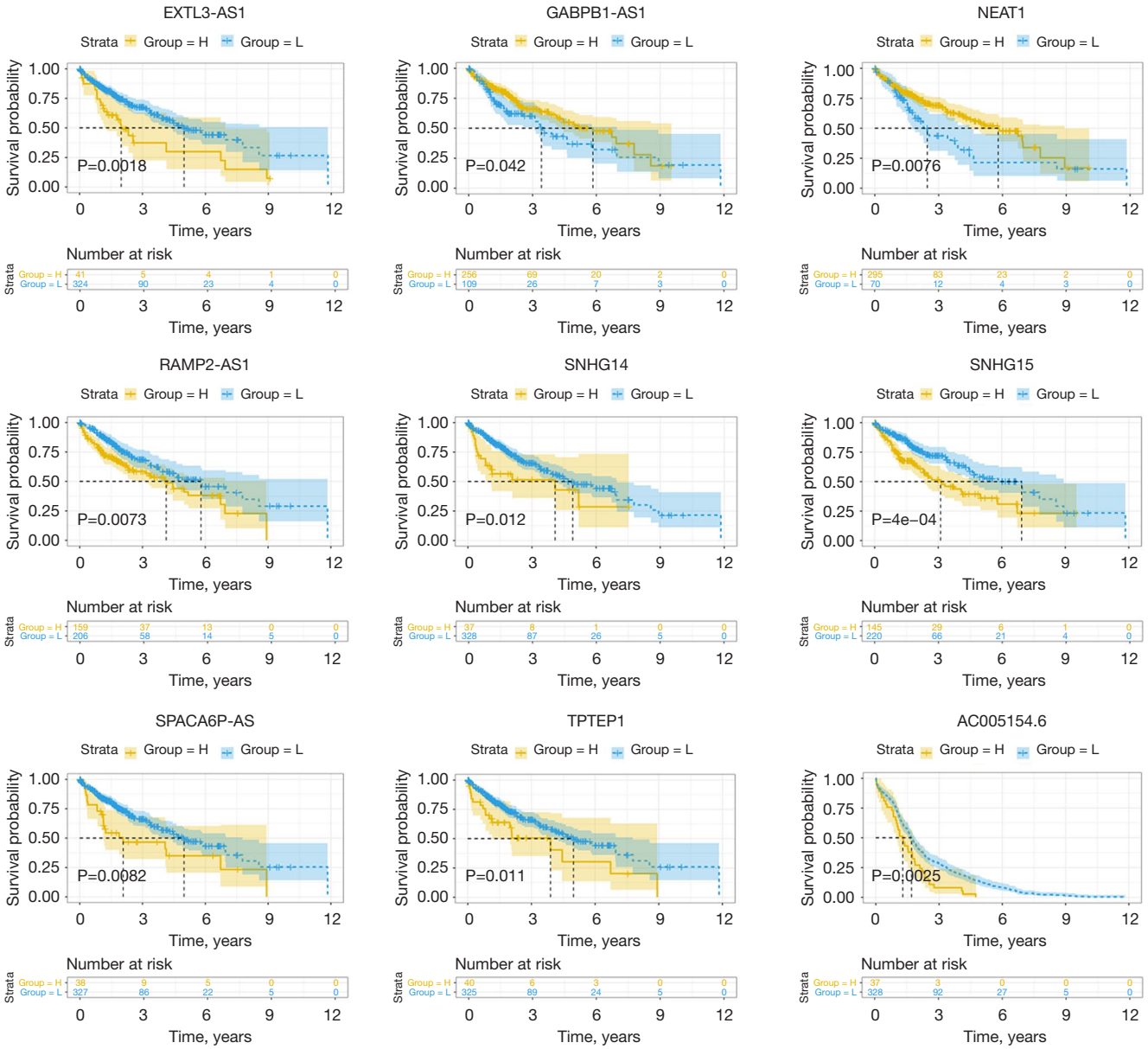

Figure 6 Association between overall survival and lncRNAs. H, high expression group; L, low expression group.

several genes were mainly enriched in several processes including DNA replication, chromosomal region, ATPase activity, and cell cycle. The GSEA analysis revealed that a high *SKA2* expression was involved in cell cycle and DNA replication, which is consistent with the results of GO and KEGG enrichment analysis. Ding *et al.* have reported that the SKA family is associated with prognostic value and immune infiltration in breast cancer (36). Yu found that SKA complex is related to prognosis in gliomas (37).

MicroRNA is a single-stranded non-coding small RNAs, which mainly acts in post-transcriptional regulation and plays different roles in various pathological processes. It can be oncogenes or tumor suppressor factors (38). Recent literature has shown that miR-29a-3p affects the metastasis of HCC by targeting LOX, LOXL2, and VEGFA (39), Moreover, miR-125b expression is downregulated in HCC, and miR-125b has anti-metastatic properties (40), Zou *et al.*'s emphasized that LIX1L drives hepatocarcinogenesis and tumor progression via miR-21-3p (41). Our study performed a comprehensive screening and analysis, results

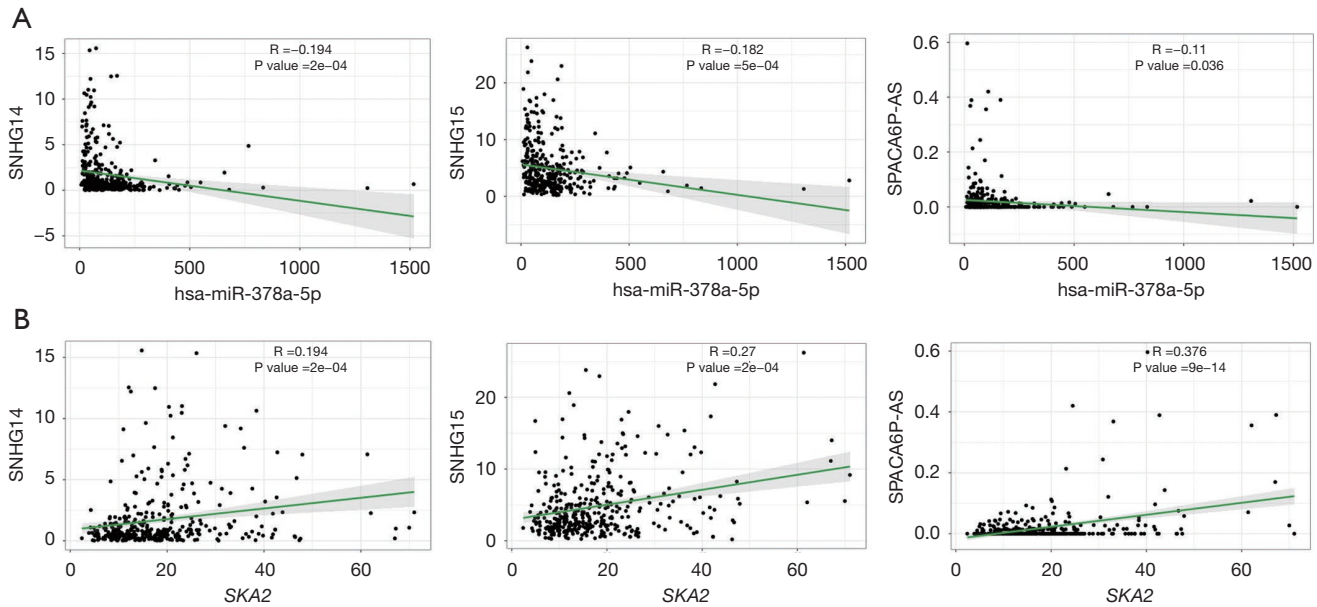

Figure 7 Correlation analysis. (A) The association between hsa-miR-378a-5p and lncRNAs; (B) the association between *SKA2* and lncRNAs. *SKA2*, spindle and kinetochore associated complex subunit 2.

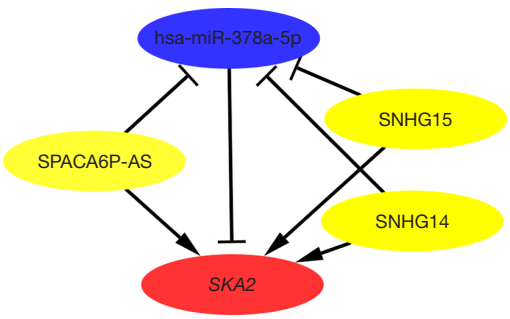

Figure 8 ceRNA network. *SKA2*, spindle and kinetochore associated complex subunit 2; ceRNA, competing endogenous RNA.

showed that hsa-miR-378a-5p was related to *SKA2*. Furthermore, the hsa-miR-378a-5p expression is low in tumors and is associated with prognosis. Previous studies have revealed that hsa-miR-378a-5p is significantly associated with the prognostic outcome of digestive system cancer (42) and sarcoma (43).

LncRNA is a type of RNA molecule that is >200 nucleotides long. They play an essential role in various biological processes, including tumor metastasis, cancer development, DNA damage, tumor immune microenvironment, and metabolic reprogramming (44-49). It has been shown that lncRNA HERH-1 and HERH-4 are involved in regulating cell cycle progression in advanced HCC (50). We predicted lncRNAs (SNHG14, SNHG15 and SPACA6P-AS) about hsa-miR-378a-5p, and they are overexpressed in HCC and associated with OS. According to RNALocate (51), SNHG14 is located in the insoluble cytoplasm, nuclear, cytosol, and membrane in HCC cell lines. A high SNHG14 expression promotes cell proliferation and colony formation and inhibits cell apoptosis in the HCC cells (52). In addition, SNHG14 is negatively associated with hsa-miR-378a-5p. SNHG14 is overexpressed in colorectal cancer, leading to enhanced cell proliferation and invasion (53). Furthermore, SNHG14 promotes cell proliferation and angiogenesis via PTEN signaling in HCC (54). According to Du *et al.* research, SNHG15 is associated with breast cancer (55), and lncRNA SNHG15 contributes to oncogenesis by targeting miR-506-5p (56). Finally, SPACA6P-AS act as a ceRNA, which promotes HCC oncogenicity (57).

Previous studies have revealed that ceRNA plays a significant role in various types of tumors. For instance, GAS6-AS1/miR-24-3p/GIMAP6 regulatory axes affect the progression of lung adenocarcinoma (58). Cao *et al.* has revealed that TMEM220-AS1 affects the proliferation and metastasis of liver cancer via the miR-484/MAG1 axis (59). In addition, lncRNA SNHG14 enhances HCC

growth by acting as a molecular sponge of miR-876-5p to regulate SSR2 expression (60). Our study investigated the SPACA6P-AS/hsa-miR-378a-5p/*SKA2*, SNHG14/hsa-miR-378a-5p/*SKA2*, and SNHG15/hsa-miR-378a-5p/*SKA2* regulatory axes HCC. Results showed that they may influence tumor growth, metastasis, and OS.

Conclusions

SKA2 is significantly overexpressed in HCC and is associated with OS, tumor stage, and immune infiltrating cells. Furthermore, *SKA2* is a member of ceRNA that affects tumorigenesis. These findings might provide a theoretical foundation for further research in the field of HCC.

Acknowledgments

Funding: This work was supported by Key R&D and Promotion Projects in Henan Province (grant No. 242102310126) and the Joint Special Funds for the Department of Science and Technology of Yunnan Province-Kunming Medical University (grant No. 202101AY070001-075).

Footnote

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-833/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-833/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Hu W, Hu X, Zhu Y, Li M, Meng H, Zhao H. Oncogenic role of SKA2 and its ceRNA network in hepatocellular carcinoma based on a comprehensive analysis. Transl Cancer Res 2024;13(10):5190-5201. doi: 10.21037/tcr-24-833