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KIAA1429 facilitates progression of hepatocellular carcinoma by modulating m6A levels in HPN

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ABSTRACT

Background: Most *N*6-methyladenosine (m6A)-associated modulatory proteins are involved in the pathogenesis of various cancers. The roles of m6A-related genes in liver hepatocellular carcinoma (LIHC) and the associated mechanisms remain unknown.
Methods: GEO and GEPIA2 databases were used to identify the m6A modification-related genes which were differentially expressed in LIHC and adjacent non-tumor tissues, and quantitative PCR was used to evaluate the expression of KIAA1429, a major m6A methyltransferase, in LIHC cells. The effect of KIAA1429 on the malignant phenotypes of LIHC cells was evaluated *in vitro*. The UALCAN, GEPIA, and GEO databases and western blotting assays were used to identify the target genes of KIAA1429.
Results: KIAA1429 expression was markedly elevated in LIHC tissues, and patients with LIHC who had high KIAA1429 expression had a worse prognosis than those who had low expression. KIAA1429 silencing attenuated LIHC metastasis and proliferation. KIAA142 regulates m6A levels in HPN to intensify LIHC progression.
Conclusion: Our study suggests a KIAA1429-HPN modulatory model based on m6A modifications, that offers insights into the occurrence and development of LIHC.

1. Introduction

In 2020, primary liver cancer, also known as hepatocellular carcinoma, was the third leading cause of cancer-related death and the sixth most commonly diagnosed tumor worldwide, with approximately 906,000 new cases and 830,000 deaths [1]. It was projected that in 2023, an estimated 41,210 adults (27,980 men and 13,230 women) in America will be diagnosed with primary liver cancer, which may cause death of 10,380 women and 19,000 men [2]. Liver hepatocellular carcinoma (LIHC) is the most common type of primary liver cancer, accounting for 75–85 % of all cases [1,3,4]. The pathogenesis of LIHC is complex and includes immune regulation disorders, cell cycle disorders, chromosome instability, microRNA (miRNA) disorders, increase in LIHC stem cells, epithelial-to-mesenchymal cell transformation, and DNA methylation changes [5]. Currently, treatment options for LIHC include liver transplantation, surgical resection, minimally invasive local treatment, monoclonal antibodies or immune checkpoint inhibitors, molecular-targeted agents, and transarterial chemoembolization [6,7]. However, the 5-year survival rate of patients with LIHC with advanced-stage remains low. A more in-depth understanding of the molecular biology of LIHC is required to improve treatment and patient survival.

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*N*6-methyladenosine (m6A) is the most prevalent post-transcriptional modification of eukaryotic mRNA which is involved in regulation and stability of various genes. RNA-binding proteins with YTH domain influence the fate of m6A RNA by binding m6A [8,9]. The mammalian mRNA m6A methylosome is a complex comprising several nuclear proteins (KIAA1429, Wilms tumor 1 associated protein, METTL14, and METTL3) [10]. m6A RNA methylation is involved in various biological processes, including stem cell formation and differentiation [11], transcription, translation, embryogenesis, nuclear export, alternative splicing, heat shock response control [12], circadian clock control [13], DNA damage response, and degradation of mRNAs [14–18]. Studies have suggested that abnormal m6A RNA methylation plays a vital role in the pathogenesis of diverse human diseases such as LIHC [19–24]. For example,

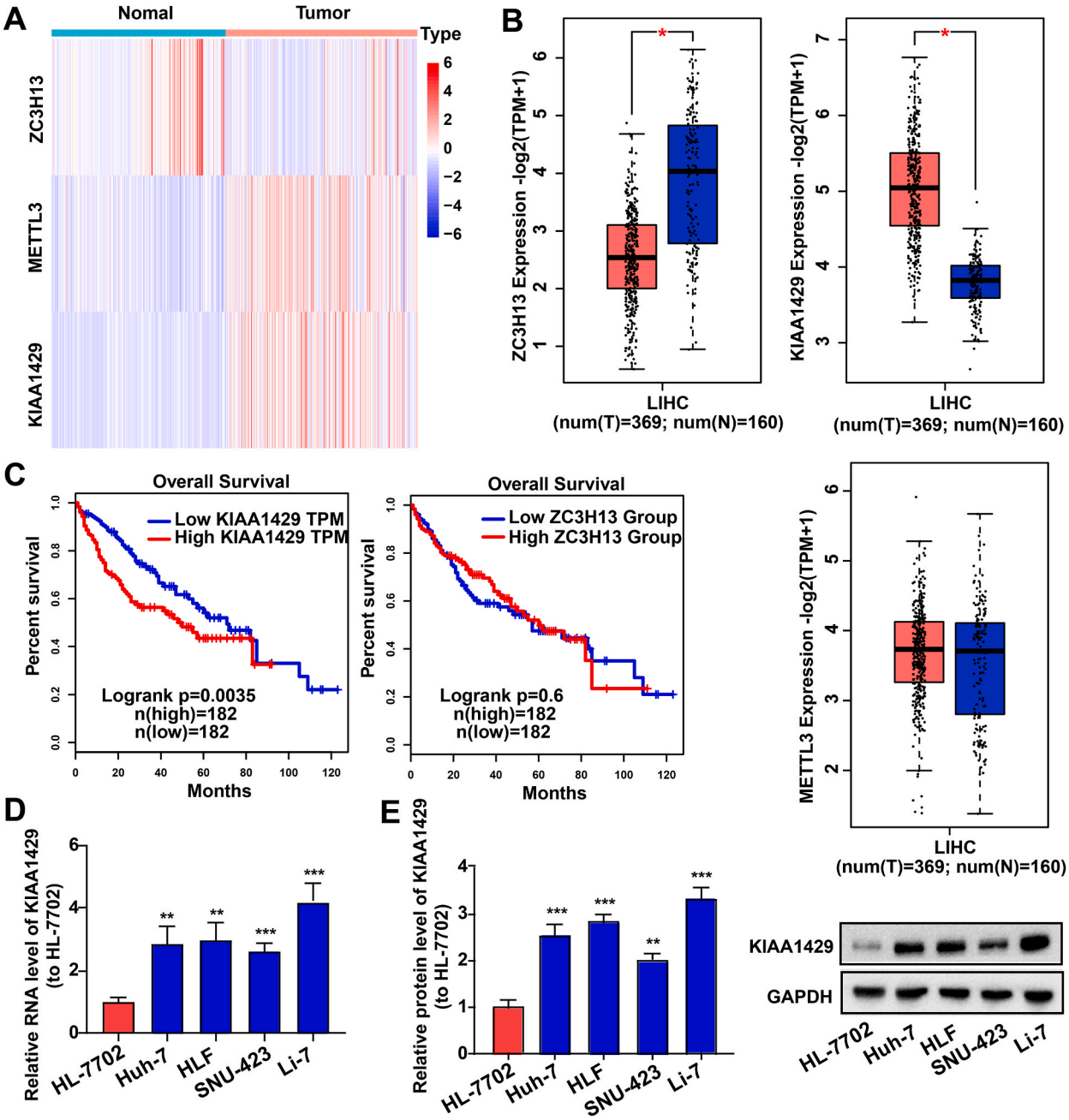

Fig. 1. KIAA1429 expression is increased in LIHC tissues and cells and is associated with poor prognosis (A) ZC3H13, METTL3, and KIAA1429 were differentially expressed in the GSE25097 database based on the comparison of tumor tissues (n = 268) to normal tissues (n = 243) with logFC >0.5 and p-value >0.05. (B) The expression of ZC3H13, METTL3, and KIAA1429 in LIHC as obtained from GEPIA2. (C) The effect of KIAA1429 and ZC3H13 levels on the survival of patients with LIHC. (D) The RNA expression of KIAA1429 in LIHC and the normal liver cell lines. (E) Western blotting was performed to detect protein levels of KIAA1429. *p < 0.05, **p < 0.01, ***p < 0.001.

WTAP methylation by PRMT1 promotes multiple myeloma tumorigenesis by activating oxidative phosphorylation via m6A modification of NADH:ubiquinone oxidoreductase subunit S6 (NDUFS6) [25]. METTL3 promotes stem cell properties of esophageal cancer by upregulating PTCH1 via m6A methylation [26]. By regulating glycolysis and ferroptosis, KIAA1429 accelerates oral squamous cell carcinoma [27]. METTL14 regulates myocardial I/R injury via the Akt/mTOR signaling pathway [28].

m6A methyltransferase KIAA1429 also known as VIRMA (vir-like m6A methyltransferase-associated protein) is a recently identified component of the RNA m6A methyltransferase complex that exerts substantial influence on guiding region-selective m6A deposition [29]. KIAA1429 regulates gastric cancer cell proliferation [30], promotes metastasis and growth of liver cancer [31], and acts as an oncogenic factor in breast cancer [32].

In current study, we observed that *KIAA1429* could serve as an oncogene in LIHC by regulating the m6A levels of HPN. This emphasizes the functional role of KIAA1429 as a promising therapeutic target and prognostic biomarker for LIHC.

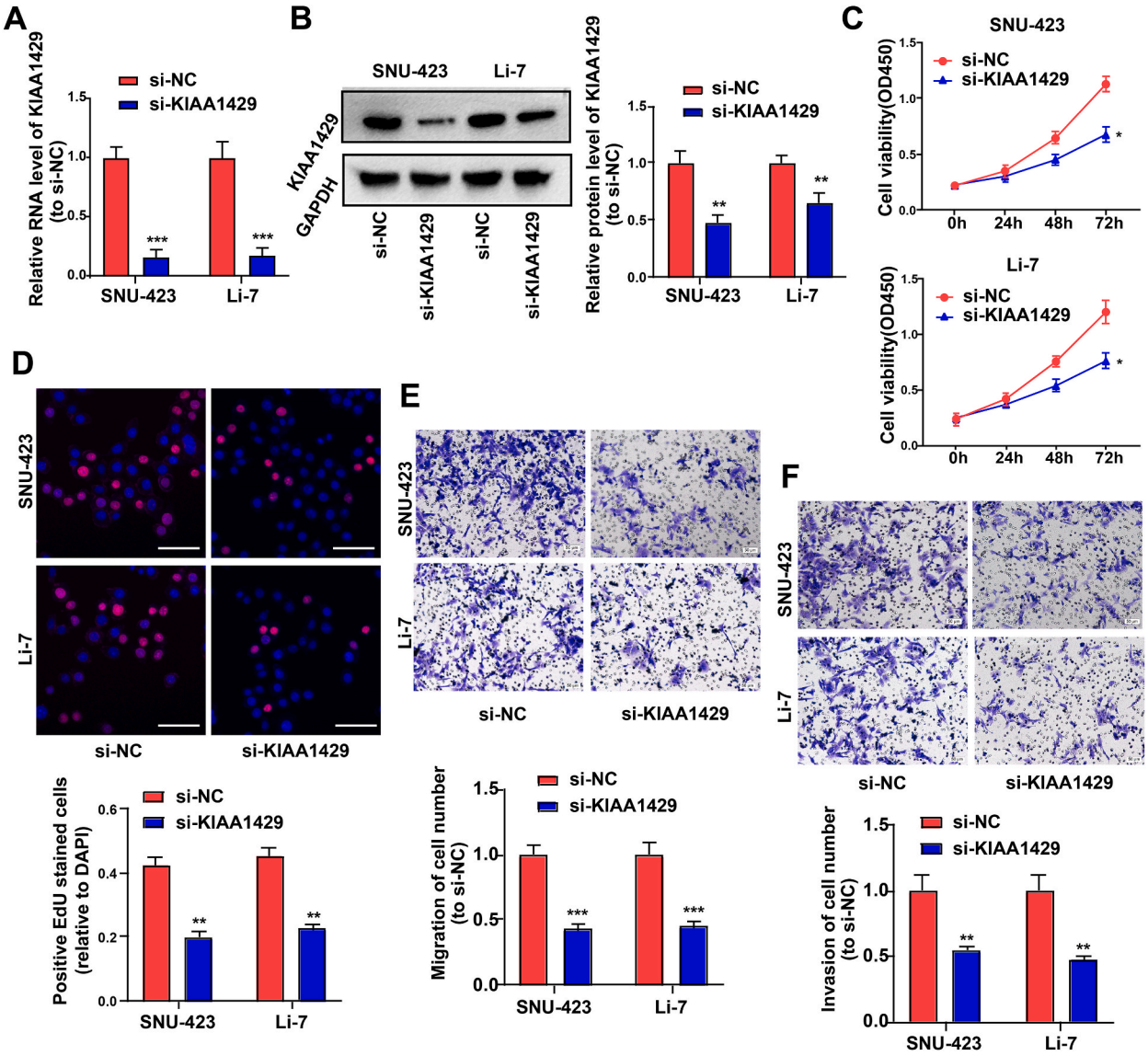

Fig. 2. KIAA1429 knockdown attenuates metastasis and proliferation of LIHC *in vitro* (A) KIAA1429 levels were decreased after transfection with si-KIAA1429. (B) Western blotting was performed to detect the protein levels of KIAA1429. (C, D) si-KIAA1429 inhibited LIHC proliferation. Scale bars: 100 μm (E, F). si-KIAA1429 inhibited the capacity of migration and invasion of LIHC cell. Scale bars: 50 μm. The data are presented as the means ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

2. Results

2.1. KIAA1429 was intensified in LIHC tissues and cells and was associated with poor prognosis

We selected 23 m6A-related genes to determine whether they were involved in the pathogenesis of LIHC. We downloaded the GSE25097 database from The Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/). The GSE25097 database was used to identify differentially expressed m6A-related genes by comparing their expression levels in tumor tissues to those in normal tissues (log FC > 0.5, $p > 0.05$; Fig. 1A). Among the 23 m6A-related genes identified, *METTL3* and *KIAA1429* were upregulated, and *ZC3H13* was downregulated in LIHC tissues. GEPIA2 analysis (http://gepia2.cancer-pku.cn/#index) revealed that *ZC3H13* was downregulated and *KIAA1429* was upregulated in LIHC tissues, and that *METTL3* expression was not significantly different between normal and tumor tissues (Fig. 1B). We observed that KIAA1429 was closely related to the prognosis of LIHC based on GEPIA2 database

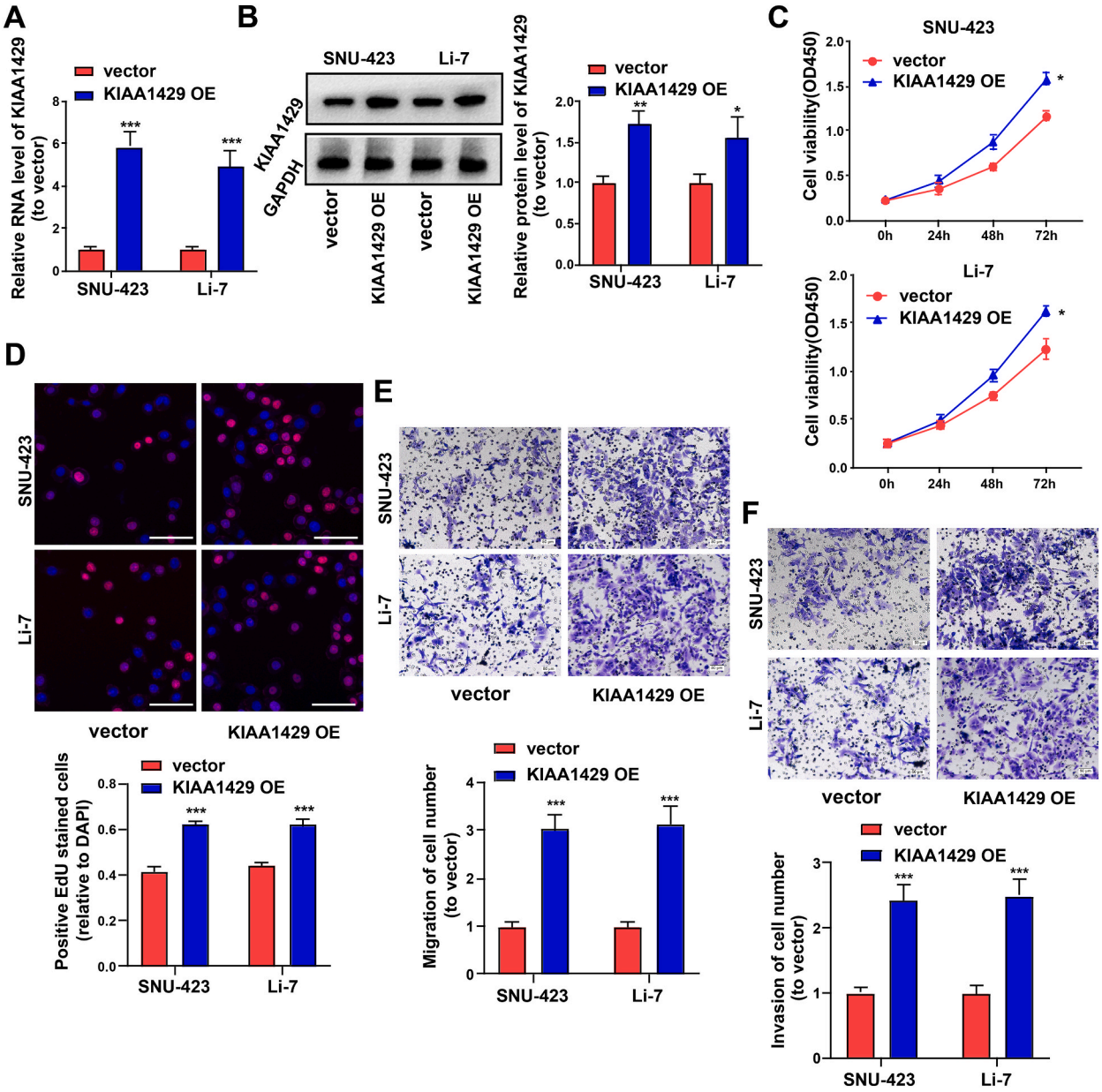

Fig. 3. KIAA1429 overexpression promotes proliferation and metastasis of LIHC *in vitro* (A) KIAA1429 levels increased after transfection with the KIAA1429 overexpression vector. (B) The protein level of KIAA1429 was detect by western blotting. (C, D) KIAA1429 overexpression promoted LIHC proliferation. Scale bars: 100 μm. (E, F) KIAA1429 overexpression promoted the migration and invasion of LIHC cells. Scale bars: 50 μm. The data are presented as the means ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001.

analysis (Fig. 1C). Patients with LIHC and high *KIAA1429* expression exhibited a shorter overall survival than those with low *KIAA1429* expression. The results of the qRT-PCR analysis also indicated that *KIAA1429* mRNA levels were higher in LIHC cells than in HL-7702 cells (Fig. 1D). Western blot analysis indicated that the KIAA1429 protein levels were higher in LIHC cells than in HL-7702 cells (Fig. 1E, Supplementary Figs. 1 and 2).

2.2. *KIAA1429 promoted proliferation and metastasis of LIHC in vitro*

The influence of KIAA1429 on the cell phenotype was evaluated to explore its oncogenic effects on metastasis and cell growth. We transfected SNU-423 and Li-7 cell lines with *KIAA1429* siRNA to knock down the expression level of KIAA1429 (Fig. 2A). The silenced cell line was labeled as si-KIAA1429 and the matched control cell line as si-NC. Western blotting was used to detect the protein levels in the si-NC and si-KIAA1429 cell lines. KIAA1429 protein expression was found to be reduced following KIAA1429 siRNA treatment (Fig. 2B, Supplementary Figs. 3 and 4). Cell Counting Kit-8 (CCK-8) and 5-Ethynyl-2′-deoxyuridine (EdU) assays showed that the proliferation of SNU-423 and Li-7 cells was remarkably inhibited in the si-KIAA1429 group compared to that in the si-NC group (Fig. 2C and D). Moreover, *KIAA1429* silencing markedly inhibited the migratory and invasive abilities of SNU-423 and Li-7 cells (Fig. 2E and F).

Next, SNU-423 and Li-7 cells were transfected with a KIAA1429 overexpression vector to upregulate the expression level of KIAA1429 (Fig. 3A). Cells transfected with the KIAA1429 overexpression vector were labeled as KIAA1429 OE and control cells were transfected with the corresponding negative control vector. KIAA1429 protein expression was elevated in KIAA1429 OE (Fig. 3B, Supplementary Figs. 5 and 6). The proliferation of SNU-423 and Li-7 cells was higher in the KIAA1429 OE group compared to the vector group (Fig. 3C and D). Moreover, overexpression of KIAA1429 substantially increased the migratory and invasive properties of the SNU-423 and Li-7 cells (Fig. 3E and F).

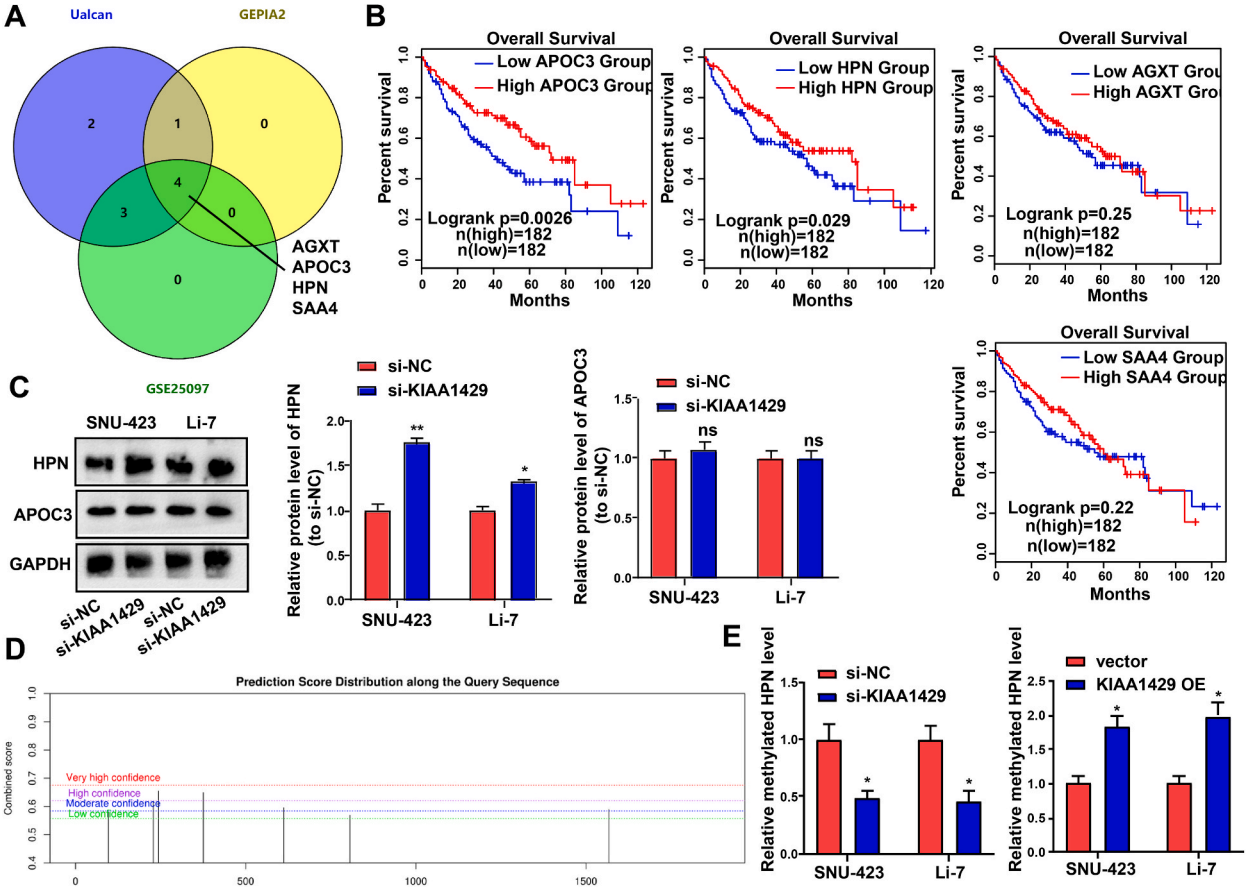

Fig. 4. KIAA1429 exhibits positive correlation with HPN expression level (A) We assessed intersection genes from the results of Ualcan, GEPIA2, and GSE25097 database analyses. (B) The effect of intersection genes level on the survival of patients with LIHC. (C) Protein levels of HPN and APOC3 in LIHC cells. (D) Bioinformatics prediction indicates that HPN can produce m6A methylation at multiple sites. (E) Identification of m6A-methylated levels of HPN in LIHC cells after transfection. *$p < 0.05$, **$p < 0.01$, ns: no significance.

2.3. HPN, modulated by KIAA1429, may be a promising target in LIHC

We selected genes that exhibited a negative correlation with *KIAA1429* expression using the Ualcan database (http://ualcan.path.uab.edu/analysis.html). In this study, *KIAA1429* was used as the gene input and the selected cancer type was LIHC and based on these

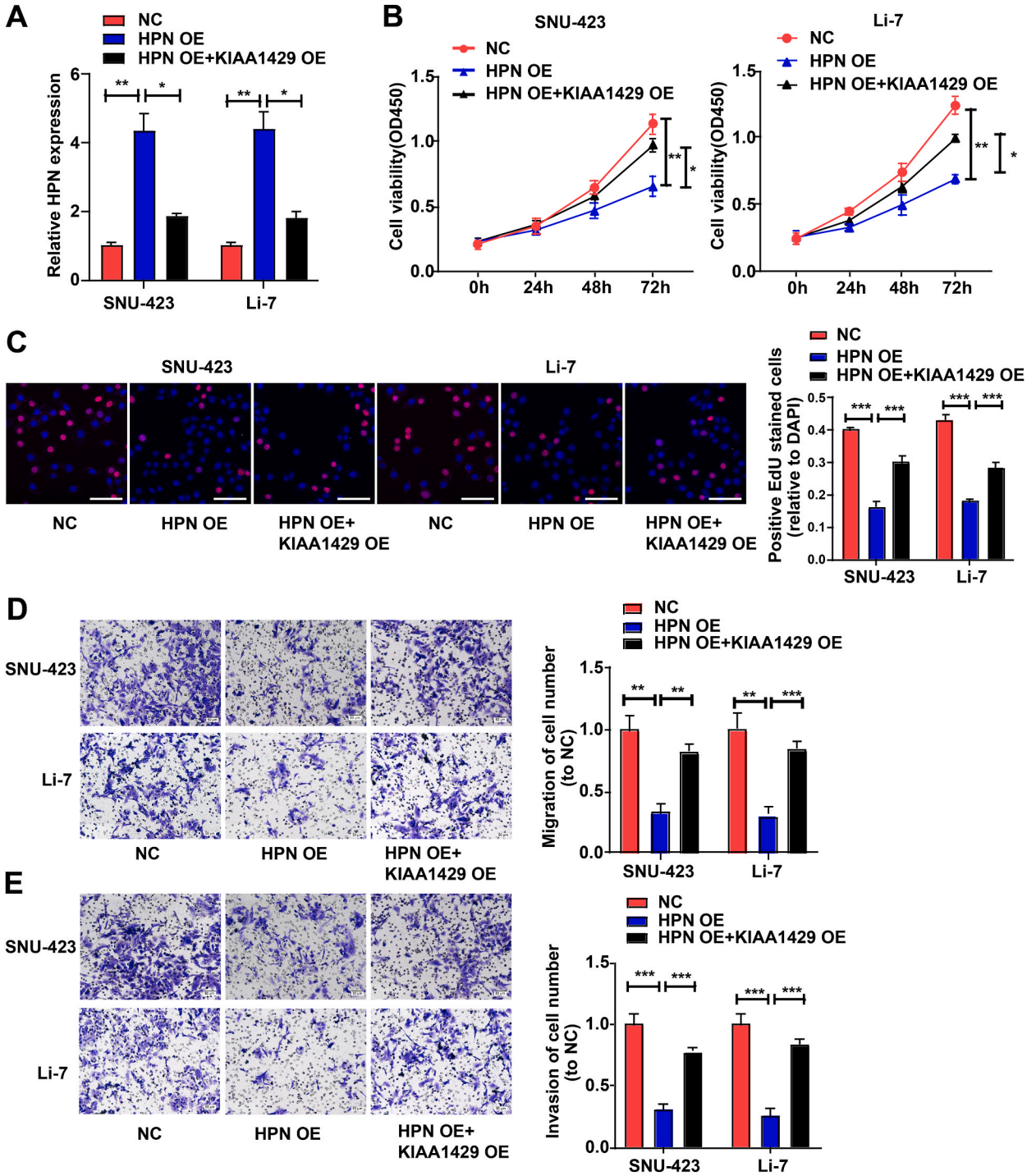

Fig. 5. KIAA1429 intensifies progression of LIHC through HPN (A) KIAA1429 level in SNU-423 and Li-7 cells after transfection with negative control, HPN overexpression, or HPN overexpression + KIAA1429 overexpression vectors. (B, C) KIAA1429 overexpression partially reversed the inhibitory effects of HPN overexpression on cell proliferation. Scale bars: 100 μm. (D, E) KIAA1429 overexpression partially reversed the inhibitory influences of HPN overexpression on cell invasion and migration. Scale bars: 50 μm *p < 0.05, **p < 0.01. ***p < 0.001.

parameters, we explored the genes that correlated with *KIAA1429* expression in LIHC. Pearson correlation coefficient indicated that the top 10 genes that were negatively correlated with *KIAA1429* in LIHC were *APOC3*, *MRPL54*, *SAA4*, *APOC1*, *ENDOG*, *HP*, *AGXT*, *HPN*, *ATP5D*, and *APOC2* (Pearson CC = −0.34 to −0.44; Supplementary Table 1). In the GEPIA2 database, we observed that *AGXT*,

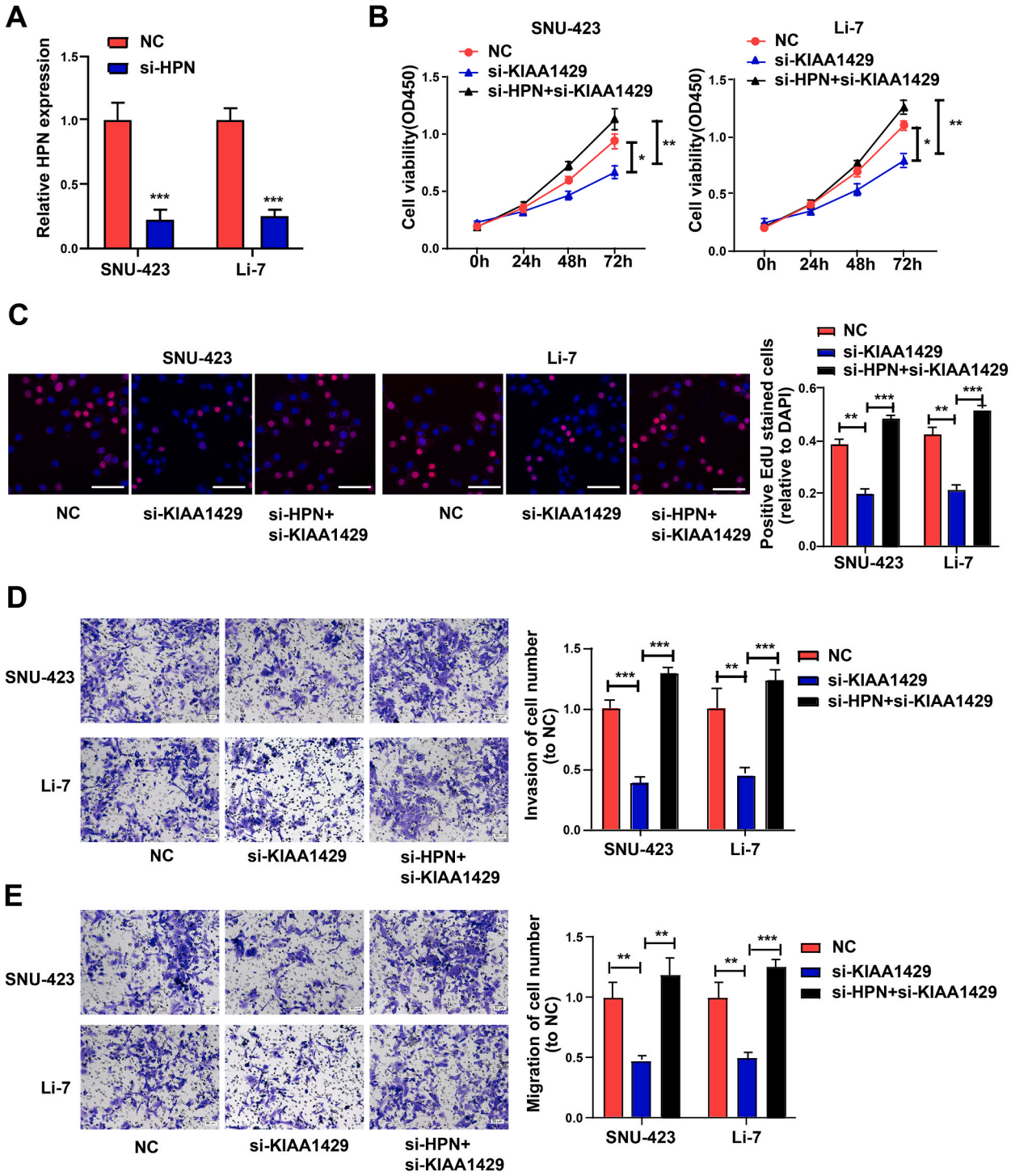

Fig. 6. si-HPN attenuates the inhibitory effects of si-KIAA1429 on cell proliferation, invasion, and migration
(A) KIAA1429 level in SNU-423 and Li-7 cells after transfection with negative control, KIAA1429 siRNA, or HPN siRNA + KIAA1429 siRNA. (B, C) si-HPN rescued the inhibitory effects of si-KIAA1429 on cell proliferation. Scale bars: 100 μm. (D, E) si-HPN rescued the inhibitory effects of si-KIAA1429 on cell migration and invasion. Scale bars: 50 μm *p < 0.05, **p < 0.01. ***p < 0.001.

APOC3, *HP*, *HPN*, and *SAA4* exhibited low expression levels, which were negatively correlated with *KIAA1429* expression. However, *APOC1*, *APOC2*, *ATP5D*, and *MRPL54* were highly expressed, and their expression positively correlated with *KIAA1429* expression in LIHC (Supplementary Fig. 7). Furthermore, according to the GSE25097 database, among the 10 genes that were negatively correlated with *KIAA1429*, seven (*APOC3*, *MRPL54*, *SAA4*, *AGXT*, *HPN*, *ATP5D*, and *APOC2*) were expressed at lower levels in LIHC tumors than in adjacent non-tumor samples (Supplementary Table 2). Based on this information, we determined that *AGXT*, *APOC3*, HPN, and *SAA4* were weakly expressed and were negatively correlated with *KIAA1429* expression (Fig. 4A). We also observed that among these four genes, low expression levels of *APOC3* and HPN were related to poor overall survival as indicated in the GEPIA2 database; and there was not correlation with survival for expression of *AGXT* and *SAA4* (Fig. 4B). Therefore, we selected *APOC3* and HPN for further analysis and excluded *AGXT* and *SAA4*. Western blotting also revealed that *KIAA1429* silencing significantly increased HPN protein levels (Fig. 4C, Supplementary Figs. 8–10). Importantly, using the SRAMP database (http://www.cuilab.cn/sramp), we determined that HPN possessed multiple m6A methylation sites (Fig. 4D). Using methylation tests, we determined that in LIHC cells transfected with si-KIAA1429, the m6A level of HPN was significantly lower than that in the control cells (Fig. 4E). KIAA1429 OE increased m6A levels of HPN (Fig. 4E). Based on this evidence, we deduced that HPN may act as a downstream target of KIAA1429-mediated m6A methylation.

2.4. KIAA1429 accelerated the progression of LIHC via HPN

To determine the influence of KIAA1429 expression on the function of HPN, we co-transfected LIHC cells with HPN OE vectors and/or KIAA1429 OE vectors (Fig. 5A). CCK-8, EdU, and transwell assays demonstrated that HPN overexpression inhibited the invasion, migration, and proliferation of LIHC cells (Fig. 5B–E). Overexpression of KIAA1429 partially reversed the inhibitory effects of HPN overexpression (Fig. 5B–E). Thus, HPN serves as a tumor suppressor.

We also assessed whether HPN inhibition could rescue the effects of the KIAA1429 knockdown on the physiological behavior of LIHC cells. HPN-specific siRNAs were used to downregulate HPN levels (Fig. 6A). LIHC cells were then co-transfected with negative control, KIAA1429 siRNA, or HPN siRNA + KIAA1429 siRNA. CCK-8, EdU, and transwell assays demonstrated that si-HPN rescued the inhibitory effects of si-KIAA1429 on cell proliferation, migration, and invasion (Fig. 6B–E). These results suggest that KIAA1429 intensifies LIHC progression by regulating HPN expression.

3. Discussion

Current therapeutic interventions for LIHC are unsatisfactory, and there is need for more precise prognostic indicators as well as novel promising treatment strategies. Bioinformatics analysis suggested that high KIAA1429 expression was closely related to the poor overall survival rate of patients with LIHC. This suggests that KIAA1429 may have a significant impact on LIHC. Furthermore, we detected abnormally high expression of KIAA1429 in LIHC cells using qRT-PCR and western blotting, suggesting that KIAA1429 may serve as an oncogene in LIHC.

Subsequently, we observed that KIAA1429 knockdown inhibited the progression of tumorigenesis in LIHC and that KIAA1429 OE promoted LIHC progression, further indicating that KIAA1429 has a crucial biological function in LIHC development. The molecular mechanisms underlying the influence of KIAA1429 on LIHC was explored using multiple databases. These analyses, suggested a strong negative correlation between HPN and KIAA1429 expression. Moreover, HPN expression in LIHC tissues was not only decreased but was also related to the prognosis of patients with LIHC. HPN is a transmembrane serine protease implicated in numerous biological processes including auditory nerve development, hepatocyte growth, adipocyte differentiation, urinary protein secretion, and cancer metastasis [33,34]. According to the relevant literature, HPN is expressed at low levels in LIHC and is a potential independent prognostic biomarker for LIHC [35,36]. Low hepsin expression is associated with poor survival [37]. HPN is a potential thrombotic and metastatic biomarker [38]. Our experiments confirmed that the overexpression of HPN inhibited the proliferation, invasion, and migration of LIHC cells.

KIAA1429 is the largest known component of the m6A methyltransferase complex [10,39,40], and mediates RNA methylation. m6A is the most prevalent post-transcriptional base modification of mRNA, which is involved in modulating RNA splicing, stability, and translation [41]. Methylation in the 5′UTR region of mRNA plays an important role in mRNA editing, stability, degradation, polyadenylation, splicing, and other processes. Methylation in the 3′UTR region helps in the initiation of translation, exonuclear transport of mRNA, and structural stability of mRNA with polyA binding proteins [41]. We speculate that KIAA1429 mediates the methylation of HPN mRNA and participates in LIHC pathogenesis. Using the SRAMP database, we confirmed that *HPN* can undergo m6A methylation at multiple sites and speculated that KIAA1429 could regulate HPN expression through methylation. Subsequently, methylation analysis indicated that KIAA1429 down-regulation reduced the m6A level of *HPN* and increased its expression. Additionally, using a torsion test, we observed that the upregulation of KIAA1429 reversed HPN-mediated changes in LIHC. This suggests that KIAA1429 and HPN can be potential novel targets for improving prognosis and treatment of patients with LIHC.

However, there are some limitations to this study, including the retrospective nature of the data analysis, reliance on public databases for gene expression information, and the lack of *in vivo* experiments. In the future studies, we plan to evaluate the KIAA1429 and HPN RNA and protein levels in clinical samples using next-generation sequencing and immunohistochemistry. *In vivo* studies (using mice animal model) will be conducted to confirm the roles of KIAA1429 and HPN in LIHC.

4. Conclusion

KIAA1429 is overexpressed in LIHC and is associated with a poor prognosis. KIAA1429 regulates HPN expression via m6A methylation to regulate the LIHC invasion, migration, and proliferation. These data suggest that the prognosis in patients with LIHC can be predicted by detecting the RNA level of *KIAA1429*. Development of drugs similar to the HPN vector or KIAA1429 siRNA may be of great significance for LIHC treatment.

5. Methods

5.1. Cell culture

Human LIHC cell lines (Huh-7, HLF, SNU-423, and Li-7) and normal liver cell line (HL-7702) were purchased from the Cell Bank of the Chinese Academy of Sciences (shanghai, china). The cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM; HyClone, Logan, UT, USA) at 37 °C and 5 % CO_2 supplemented with 10 % fetal bovine serum (HyClone).

5.2. Cell transfection

Negative control against KIAA1429, overexpression vectors for KIAA1429 (KIAA1429 OE), and small interfering RNAs (si-KIAA1429) were purchased from RiboBio (Guangzhou, Guangdong, China). Overexpression vector for HPN (HPN-OE) and siRNAs (si-HPN) were purchased from GenePharma (Shanghai, China). At greater than 60 % cell adherence, the cells were transfected with lipofectamine 3000 reagent (Invitrogen, Shanghai, China) according to the manufacturer's specification, and cultured at 37 °C under 5 % CO_2 in an incubator.

5.3. Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted using TRIzol reagent (Life Technologies, Shanghai, China) following the manufacturer's instructions and a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Shanghai, China) was used to measure the RNA concentration. PrimeScript RT kit (Takara, Dalian, China) was used for reverse transcription. qRT-PCR was performed using SYBR Premix Dimer Eraser (Takara) and a StepOnePlus Real-Time PCR System (Applied Biosystems, Shanghai, China) using the following primers:

KIAA1429: F: 5′-GCTGTGCAACTGCACGTTTA-3′ and R: 5′-AAATCCTGCCAGCTCAGCAT-3′,

HPN: F 5′-AGGAAACCTACGCTCAGGC-3′, and R: 5′-GAGTGAGTCTGGGGAAAGACA-3′.

5.4. m6A RNA methylation

Total RNA was extracted as described in the previous (*Quantitative real-time polymerase chain reaction [qRT-PCR]*) section. The m6A quantification in the total RNA was determined using an EpiQuik m6A RNA Methylation Quantification Kit (colorimetric; P-9005, Epigentek, USA) according to the manufacturer's instructions and the m6A level was colorimetrically quantified according to the optical density (OD) of each well at 450.

5.5. Cell Counting Kit-8 (CCK-8) experiment

Cell proliferation was detected by CCK-8 (Dojindo, Tokyo, Japan) according to the manufacturer's protocol. LIHC cells were seeded into 96-well plates (approximately 2×10^3 cells/well) and cultured for the indicated time periods.

5.6. 5-Ethynyl-2′-deoxyuridine (EdU) experiment

Using Click-iT® EdU Imaging Kits obtained from Invitrogen, we evaluated the effect of KIAA1429 and HPN on LIHC cell proliferation according to the product specification. We cultured the cells in 96-well plates (8×10^3 cells/well), incubated them using 10 μL of EdU reagent for 3 h at 37 °C, and fixed them with 4 % formaldehyde for 20 min at room temperature. After washing off the formaldehyde with PBS, the cells were incubated with 0.5 % Triton X-100 (Sigma-Aldrich, Shanghai, China). Subsequently, the cells were incubated with 1 mL of Hoechst 33,342 nuclear staining solution (Sigma) and washed three times with PBS. Stained cells were photographed using an Olympus fluorescence microscope (CKX41-F32FL, Beijing, China).

5.7. Cell migration and invasion assay

Transwell inserts (Costar, Cambridge, MA, USA) were used to evaluate the cell invasion and migration potential. Approximately 2×10^4 cancer cells were seeded into the coated (for the invasion assay) or uncoated (for the migration assay) upper chambers of Matrigel assays (BD Biosciences, San Jose, CA, USA). In the bottom chamber, 750 μL of complete DMEM was added. After culturing for 24 h, the cells were removed from the upper chamber, fixed in the bottom chamber with 4 % paraformaldehyde, and stained with 0.1 % crystal violet (Beyotime Institute of Biotechnology). The numbers of invading and migrating cells were counted under a light microscope.

5.8. Western blot experiment

The cells were inoculated into six-well plates (1×10^6 cells/well) for 4 h and then examined for protein expression levels. Next, total protein from the cells was isolated using RIPA lysis buffer and the total protein content was determined. After separation of proteins (100 μg of protein from each group) using gel electrophoresis, the separated proteins were transferred onto PVDF membranes (Beyotime Institute of Biotechnology). The primary antibody was used for overnight hypothermal incubation after 1 h of incubation at room temperature. On the following day, using the coloring reagent and photography, we performed color development, added the secondary antibodies labeled with horseradish peroxidase, and incubated the membranes for 1 h. The primary antibodies used in this study were: GAPDH (1/10,000; ab181602; Abcam), KIAA1429, and HPN (1/1000; ab189246; Abcam); (1/1000; ab108205; Abcam).

5.9. Data analyses

All assays were performed in triplicate, and GraphPad Prism 8 software (GraphPad Software Inc., San Diego, CA, USA) was used for analysis. Differentially expressed m6A-related genes in GSE25097 database were calculated using the "limma" package. Statistical analyses were performed using the *t*-test or ANOVA. Data are presented as mean ± SD. Statistical significance was set at $P < 0.05$.

Data availability statement

The GSE25097 database is openly available from the GEO database. The datasets used in this study are included in supplementary material or available from the corresponding author upon request.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Yu Meng: Writing – review & editing, Writing – original draft, Methodology, Data curation. **Wenwen Yang:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Jinchao Li:** Writing – review & editing, Resources. **Wei Cai:** Writing – review & editing, Visualization, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22084.

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