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ORIGINAL RESEARCH

Expression Analysis of VPS72 and Associated Biological Behaviors in Colon Cancer

Jun Cao[1,2], Hao Zhang[2], Xin Xie[3], Wei Wang[4]

[1]Department of Oncology, The Third Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi, 710061, People's Republic of China; [2]Department of Surgical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, People's Republic of China; [3]Department of Nuclear Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, People's Republic of China; [4]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, People's Republic of China

Correspondence: Wei Wang, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, People's Republic of China, Tel +8613891841656, Email wei.wang@xjtufh.edu.cn

Background: VPS72 is highly expressed in hepatocellular carcinoma and prostate cancer, participating in various cellular processes such as gene transcription, replication, DNA repair, maintenance of genome integrity, and cancer progression. However, its role in colorectal cancer remains unknown.

Methods: Bioinformatic methods were used to analyze gene expression, correlation and patient survival. Western blotting, colony formation assays and animal experiments were used to evaluate the function of VPS72 in colon cancer in vivo and in vitro.

Results: VPS72 was highly expressed in colon cancer tissues and correlated with poor overall survival ($P<0.05$) and relapse free survival ($P<0.01$). Furthermore, patients with III/IV clinical stage ($P<0.001$), N1 nodal metastasis ($P<0.001$) or N2 nodal metastasis ($P<0.05$) status had poor overall survival. Further analysis showed that VPS72 is correlated with proliferation and EMT biomarkers. Western blotting, colony formation assays and animal experiments showed that VPS72 overexpression promoted colon cancer proliferation and EMT progress.

Conclusion: Our study found that VPS72 was correlated with poor overall survival in colon cancer patients, and high expressed level of VPS72 promoted colon cancer progression, indicating its role as a potential prognosis biomarker.

Keywords: VPS72, colon cancer, biomarker, proliferation, epithelial–mesenchymal transformation

Introduction

Colorectal cancer poses a significant global public health challenge. According to 2020 estimates from the World Health Organization (WHO), colorectal cancer ranks as the third most prevalent cancer, accounting for approximately 1.9 million new cases (10.0% of total cases). It stands as the second leading cause of death among malignant tumors, resulting in around 900,000 deaths (9.4% of all cancer-related deaths) worldwide. Notably, Asia records the highest number of colorectal cancer cases, with almost 1 million new cases and 500,000 deaths, including nearly 300,000 cases in China alone.[1,2]

Colorectal cancer necessitates reliable biomarkers for early detection, prognosis, and treatment guidance, as traditional ones like CEA and CA 19–9 are limited in sensitivity and specificity. Recent studies have unveiled promising tissue polypeptide-specific antigen biomarkers such as, CYFRA 21–1, TK, IGF-1, and IGF-BP3, with CYFRA 21–1 showing strong potential as a prognostic marker.[3] The Glasgow Microenvironment Score evaluates peritumoural inflammation and tumor stromal content, proving valuable in prognosis and guiding chemotherapy, while the methylation status of SFRP2 gene and miRNAs like miR-17-92 provide insights into disease progression and treatment responses.[4]

Vacuolar Protein Sorting 72 (VPS72) gene, also known as YL-1 or YL1, is located on human chromosome 1q21. The protein encoded by this gene is a shared subunit of the histone acetyltransferase complex TRRAP/TIP60 and the chromatin remodeling complex SRCAP.[5] It plays a crucial role in the regulation of epigenetic modifications, participating in various cellular processes such as gene transcription, replication, DNA repair, maintenance of genome

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integrity, and ubiquitination.[6] In previous studies, VPS72 plays an important role in the development of multiple organs, and may also regulate tumor progression by mediating proliferation and migration in the occurrence and development of hepatocellular carcinoma and prostate cancer.[7,8] However, there is a lack of research on the role of VPS72 in colon cancer. Therefore, through the different expression levels of VPS72 in colon cancer, this paper attempts to explore its role in colon cancer.

Materials and Methods

Gene Screening

GEPIA (Interactive Analysis of Gene Expression Analysis, http://gepia.cancer-pku.cn/), UALCAN (http://ualcan.path.uab.edu/index.html), TNMplot (https://tnmplot.com/analysis/) and the Kaplan–Meier plotter (https://kmplot.com/analysis/), the web-based tools were used to analyze gene expression, correlation analysis, and patient survival analysis. We analyzed the expression level of VPS72 in colon adenocarcinoma accompanied with the expression level of VPS72 and relevant patient survival in different clinical characteristics including gender, cancer stages, nodal metastasis and TP53 mutation status. At the same time, we analyzed the expression level of VPS72 in normal tissues, tumor tissues, metastatic tissues and relevant patient survival. Further, the relationship between VPS72 and other correlated pathway factors was calculated.

GeneMANIA (http://www.genemania.org) is a web-based tool that was used to build protein–protein interaction (PPI) networks, generating hypotheses about gene function and analyzing gene lists. We visualized the physical interaction gene network and then highlighted the pathway using GeneMANIA.

Patients and Tissues

Sixty colon cancer tissues from colon cancer patients who received radical surgery were enrolled in the study at the First Affiliated Hospital of Xi'an Jiaotong University from July 2021 to April 2022. This study was complied with the Helsinki Declaration and approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. All patients provided their written informed consents. All patients did not receive any chemotherapy or radiotherapy before surgery.

Cell Culture

The cell lines HCT116 were purchased from Procell (China), which were periodically authenticated via STR profiling. HCT116 cells were cultured in DMEM (DMEM; Procell, China) supplemented with 10% fetal bovine serum (FBS; HyClone, USA) and 1% penicillin/streptomycin at 37 °C in a 5% CO2 incubator.

Western Blotting

For tissue samples, tissues were lysed on ice with RIPA buffer with 1% PMSF and 2% protease inhibitor cocktails (Beyotime, China). The concentration of protein was quantified by the bicinchoninic acid assay (Beyotime, China). Protein samples were separated on 10% sodium dodecyl sulfate-polyacrylamide gel, electrophoresed and then transferred to a polyvinylidene difluoride membrane. The membrane was blocked with 5% fat-free milk at room temperature for 2h and incubated overnight at 4°C with primary antibody targeting VPS72, Vimentin, Snai1, β-actin (Protein Tech, China), then followed by incubation with secondary antibody (Protein Tech, China) at room temperature for 1.5h. Immunoreactivity was detected by electrochemiluminescence system (Millipore, Germany). Expression of VPS72 in a total of 60 samples were analyzed, and the median was used as a cut-off for distinguishing high or low expression.

Generation of VPS72-Overexpressed HCT116 Cells

Human expression vectors for flag-VPS72 were purchased from Miaoling (Wuhan, China). Lipo8000™ Transfection Reagent (Beyotime, China) was added for transfection. Briefly, 5μg plasmid and 8μL Lipo8000 were added in HCT116 cells at an amount of 2*10^6. Transfection was validated via Western blotting.

Colony Formation Assay

HCT116 cells with or without VPS72 overexpression were seeded in a medium Petri dish (3000 cells per well) and were cultured for 14 days in a complete growth medium containing 10% FBS, which was replaced every two days. Two weeks later, colonies were fixed with methanol for 30 min and were stained with a phosphate-buffered saline (PBS) solution containing 0.1% crystal violet (Sigma) for 20 min. Colonies were photographed and counted.

Animal Experiments

The animal experimental procedures were approved by the Institutional Animal Care Committee of the Animal Experimental Center of Xi'an Jiaotong University, in compliance with the institutional guidelines for the care and use of animals. Athymic nod-SCID mice (6–8 weeks old, female) were purchased from Vitalriver (Beijing, China). 5×10^6 HCT116 cells with or without VPS72 overexpression were dispersed in 100 μL PBS and were subcutaneously injected. Tumor sizes were measured with a digital Vernier caliper every two days for a total of 36 days. Tumor volumes were calculated using the following formula: tumor volume (mm3) = (L × W2) ÷ 2. Mice were sacrificed on day 36 or when tumor volume reached 1000 mm3.

Bioluminescence imaging was performed with the ANIVIEW (BLT, China). Briefly, the mice were anaesthetized (using isoflurane inhalation) and intraperitoneally injected with 100 mg/kg D-luciferin potassium salt (Yeasen, China). After 10 min, the mice were imaged and assessed using ANIVIEW (BLT, China). The animal study was performed and assessed by two different investigators to minimise subjective bias.

Statistical Analysis

Continuous data were expressed as the mean ± standard deviation. Categorical variables were clustered and compared by the $\chi 2$ test or Fisher's exact test. A two-way ANOVA with Tukey's multiple comparison test was used for multiple group analysis. Continuous variables were compared by the Student's *t*-test. All statistical tests employed in this study were two-sided, and P values <0.05 were deemed statistically significant. Statistical analyses were conducted with R software version 3.6.2 (http://www.rproject.org).

Results

First, we tested the expression level of VPS72 in all types of cancer (Figure 1A), and found thatVPS72 was high expressed in bladder cancer, breast cancer, bile duct cancer, colon cancer, esophageal cancer, glioblastoma, head and neck cancer, kidney clear cell carcinoma, kidney papillary cell carcinoma, liver cancer, lung adenocarcinoma, lung squamous cell carcinoma, prostate cancer, rectal cancer, stomach cancer, thyroid cancer, and uterine carcinosarcoma. We chose colon adenocarcinoma for our next analysis, due to high mortality and diagnostic rates globally.[9]

We determined the expression level of VPS72 in colon adenocarcinoma and its correlation with patients' survival. We analyzed the TCGA datasets and found that the expression level of VPS72 in primary tumors was significantly higher than in normal tissues. The high expression level of VPS72 was correlated with poor overall survival and relapse-free survival (Figure 1B–D). Next, the differences in genders were analyzed. Results showed that the expression of VPS72 was higher in male patients and correlated with poor overall survival (Figure 1E–G).

We next investigated the expression of VPS72 in colon adenocarcinoma based on several clinical characteristics and related patient survival in TCGA datasets. The expression level of VPS72 was higher in patients with higher stages (Figure 2A), and survival analysis showed that VPS72 was correlated with poor overall survival in stage 3, 4, or stage 3/4, not in stage 1 or 2 (Figure 2E–J). Similarly, the expression level of VPS72 was higher in patients with nodal metastasis (Figure 2B) and correlated with poor overall survival in N1 or N2 (Figure 2K–M). However, despite the fact that the expression of VPS72 higher than both TP53-mutant and TP53-nonmutant patients (Figure 2C), the results of overall survival were not as consistent as before (Figure 2N–O). Notably, the expression of VPS72 was strongly higher in metastatic tissues than in primary tumor tissues (Figure 2D), indicating its role in cancer metastasis.

We then analyzed the correlation between these co-expressed genes with VPS72 in UALCAN. The heatmap is shown in Figure 3A. Due to that VPS72 had been proven to regulate nuclear reassembly during mitosis and targeted gene transcription,[10,11] we investigated other proteins interacting with VPS72 using GeneMAINA, and found that the five most

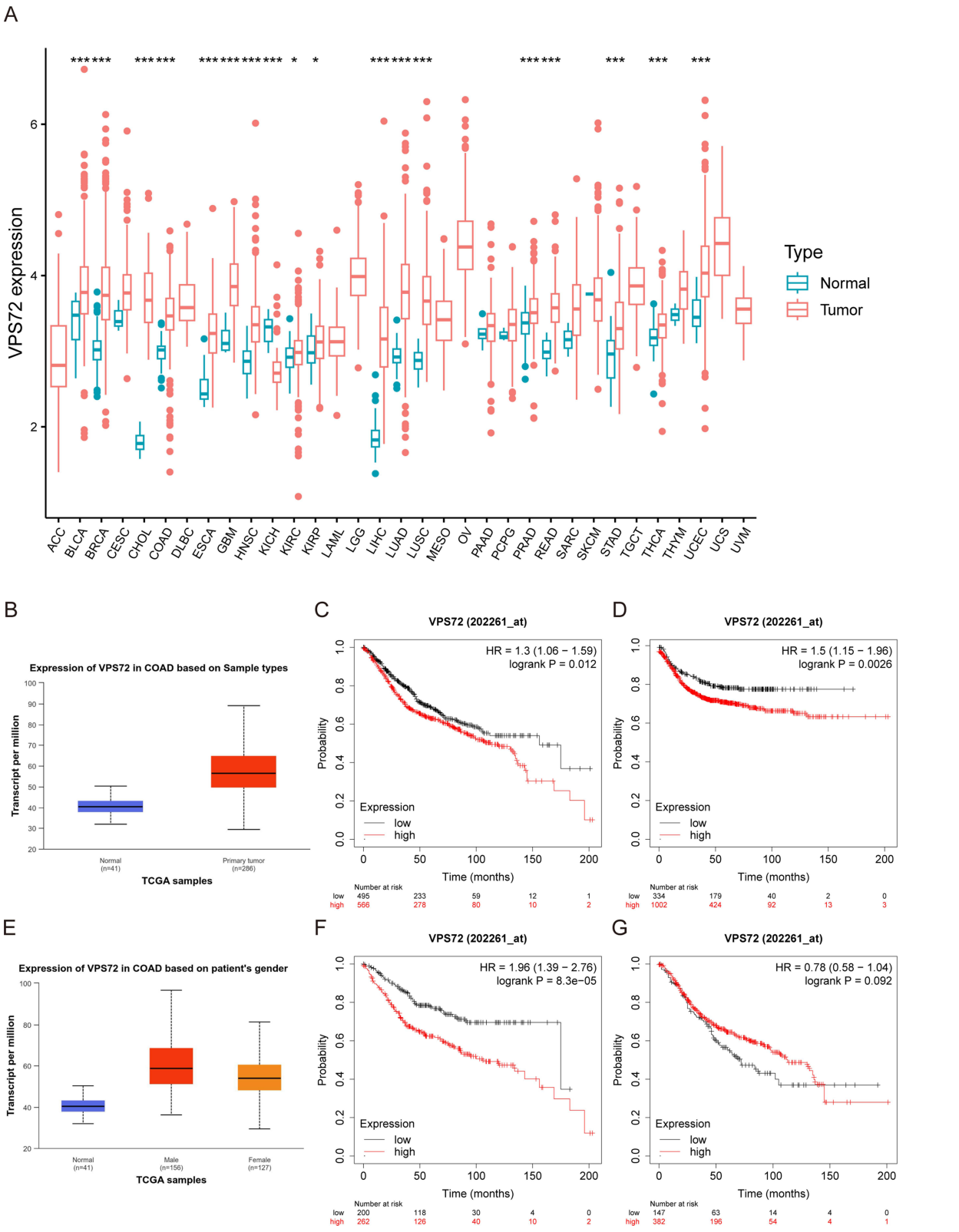

Figure 1 The expression level of VPS72 in colon adenocarcinoma. (**A**) pan-cancer expression of VPS72 using TCGA dataset. (**B**) the expression level of VPS72 in colon adenocarcinoma via UALCAN. (**C**) impact of VPS72 expression on overall survival. (**D**) impact of VPS72 expression on relapse free survival. (**E**) the expression level of VPS72 in colon adenocarcinoma based on patient's gender via UALCAN. (**F**) impact of VPS72 expression on overall survival in male patients. (**G**) impact of VPS72 expression on overall survival in female patients. (**A, B, F** and **G**) were analyzed via Kaplan-Meier plotter. **P* <0.05. ****P* <0.001.

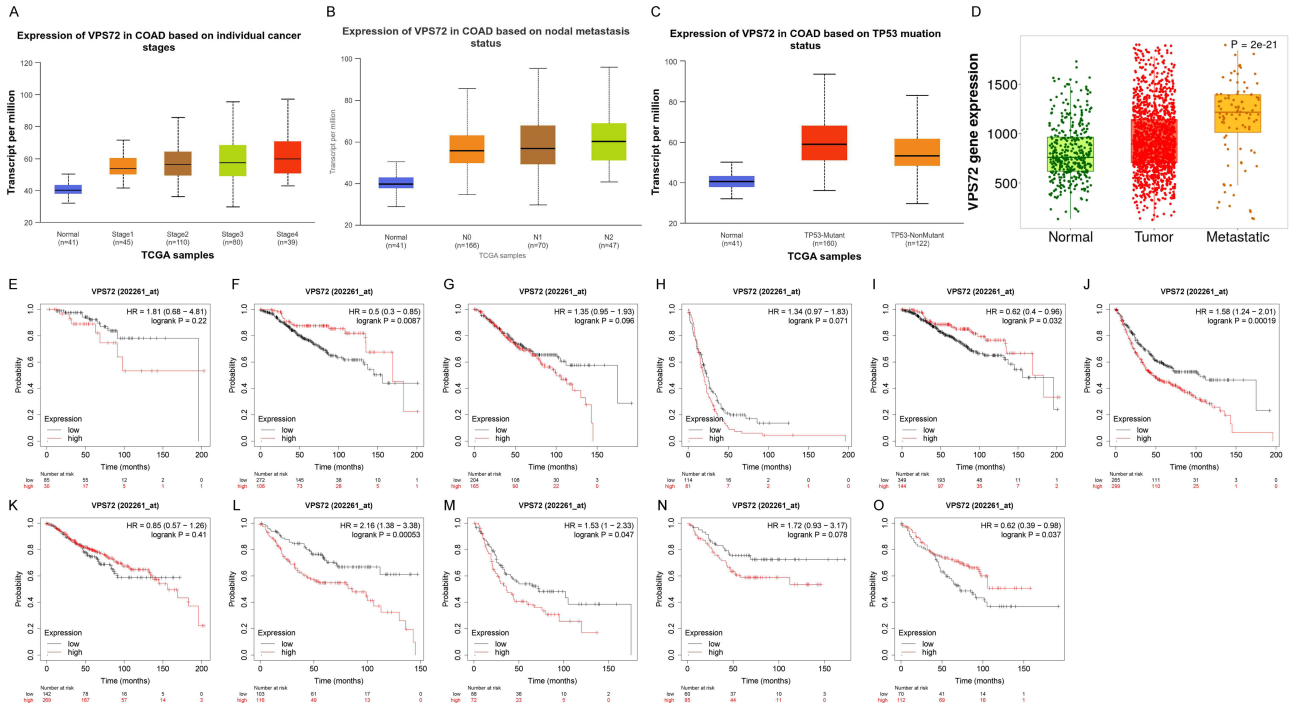

Figure 2 The expression level of VPS72 in colon adenocarcinoma in different clinical characteristics and relevant overall survival. (**A**) the expression level of VPS72 based on individual cancer stages (normal, stage 1, stage 2, stage 3 and stage 4) via UALCAN; (**B**) the expression level of VPS72 based on nodal metastasis (normal, N0, N1 and N2) via UALCAN; (**C**) the expression level based on TP53 mutation status (normal, TP53-mutant and TP53-NonMutant) via UALCAN; (**D**) the expression level of VPS72 in normal, tumor and metastatic tissues via TNMplot; (**E**–**H**) impact of VPS72 expression on overall survival from stage 1 to stage 4; (**I** and **J**) impact of VPS72 expression on overall survival in stage 1–2 and 3–4; (**K**–**M**) impact of VPS72 expression on overall survival from N0 to N2; (**N** and **O**) impact of VPS72 expression on overall survival in TP53 nonmutant and TP53 mutant. (**E**–**O**) were analyzed via Kaplan-Meier plotter.

reliable proteins were INO80C, DAMP1, RUVBL2, ZFC3H1, KAT5 (Figure 3B). It is reported that VPS72 and these five most reliable proteins have function to regulate either chromatin remodeling and DNA damage signaling repair or transcriptional activities of proto-oncogenes such as c-Myc. These results revealed the potential ability of VPS72 to regulate biological behaviors in tumorigenesis and tumor development.

To determine the function of VPS72 in cancer progression, we used TNMplot to investigate the relationship between the expression of VPS72 and expression of several proliferation and EMT biomarkers (Figure 3C). We found that expression of VPS72 positively correlated to proliferation molecules, such as cyclin D1, CDK4, CDK6 and Ki67. Due to EMT is an essential part of tumor metastasis, we also found that expression of VPS72 positively correlated to snai1, vimentin and N-cadherin. Furthermore, its expression is also positively correlated to the expression of oncogene Bcl2. These results suggested the function of VPS72 to promote tumor progression.

Based on these results, we further explored the relationship between the expression level of VPS72 and clinical characteristics. As is shown in Table 1, the high expression of VPS72 correlated with poor T (T3/4), N (N1/2/3) stage, and low degree of differentiation (P=0.033 for T stage, P<0.001 for N stage, and P=0.039 for differentiation).

To explore the role of VPS72 in contributing to tumor growth in colon cancer, we performed in vivo and in vitro studies using HCT116 cells overexpressed VPS72. Results showed that overexpression of VPS72 could promote colon cancer cell proliferation via colony formation assays (Figure 4A and B). We next evaluated the effect of VPS72 in colon cancer in vivo. HCT116-cell-derived xenograft tumors grew progressively in the control mice, whereas the respective tumors grew in a larger size in HCT116-cell-derived xenograft tumors overexpressed VPS72 (Figure 4C–G). Western blotting showed that overexpression of VPS72 enhanced the protein level of cell-cycle markers, cyclin D1, CDK6 and CDK4, and anti-apoptosis marker Bcl-2 (Figure 4H and I). We next explored whether overexpression of VPS72 influenced metastasis markers such as EMT markers. Results showed that overexpression of VPS72 promoted EMT by downregulating E-cadherin, upregulating N-cadherin, β-catenin, vimentin, snail (Figure 4H–K). We next examined the potential role of VPS72 in tumor metastasis by distinguishing colon tumor tissues into high expression and low

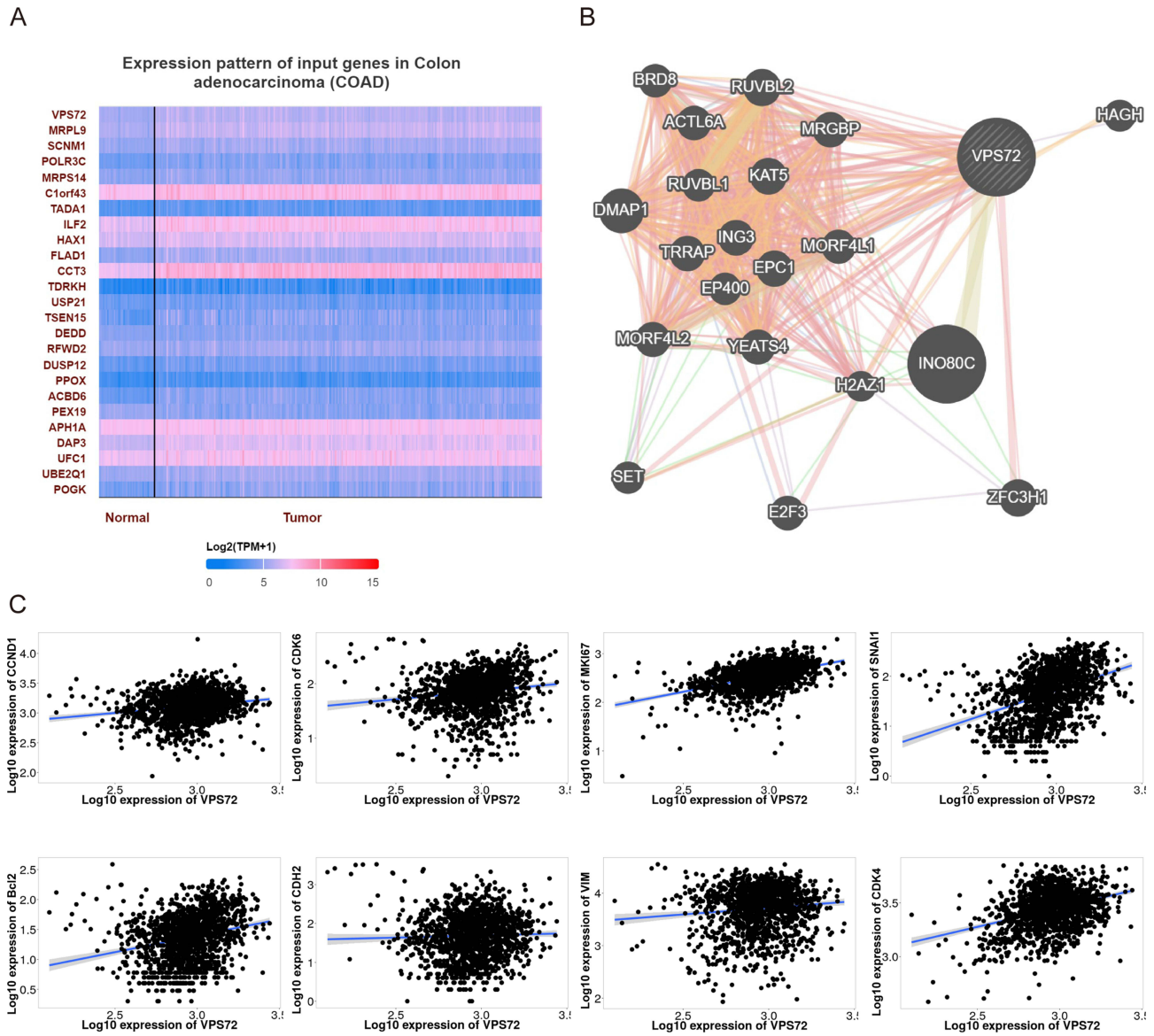

Figure 3 Functional annotations of VPS72 co-expressed genes and interaction proteins in TCGA-CESC. (**A**) Heat maps showing genes positively correlated with VPS72 in TCGA-CESC. (**B**) Protein–protein interaction network of VPS72 (GeneMANIA). (**C**) The scatter plot shows Spearman correlation of VPS72 expression with expression cyclin D1, CDK 6, Ki67, Bcl2, Cdx2, N-cadherin, Snail and Vimentin via TNMplot.

expression of VPS72 (Supplementary Figure 1). We found that the mesenchymal markers vimentin and snai1 were upregulated in tumor tissues with highly expressed VPS72 (Figure 4L and M).

Discussion

The recurrence and metastasis of colorectal cancer is critical in predicting poor prognosis and is contributing to a high fatality rate. Presently, the pathogenesis of colon cancer remains inadequately understood, including a combination of environmental and genetic factors.[12] The primary reason for the elevated mortality rate among colon cancer patients is the absence of early symptoms, compounded by the limited efficacy of commonly used tumor biomarkers in early colorectal cancer diagnosis and prognosis prediction. Furthermore, the expression levels of certain molecules varied among individuals, making early screening and diagnosis of colon cancer complicated. Given that identifying biomarkers associated with tumor progression could enhance treatment effectiveness and benefit patient prognosis, it becomes imperative to explore novel biomarkers for colorectal cancer.[13,14]

Table 1 Analysis of Correlation Between VPS72 Protein Levels and Clinicopathological Parameters of Colon Cancer Patients

Variable	*n* (n=60)	VPS72 Expression		*p*-value
		Low (n=24)	High (n=36)	
Age				0.662
≤50 years	21	8	14	
>50 years	39	16	22	
Sex				0.750
Male	34	13	21	
Female	26	11	15	
T stage				0.033
T1/2	25	14	11	
T3/4	35	10	25	
N stage				0.000
N0	22	17	5	
N1/2/3	38	7	31	
Differentiation				0.039
Low	37	11	26	
Moderate/well	23	13	10	

The biological behaviors of cancer, such as apoptosis, proliferation, differentiation, angiogenesis, and invasion, are controlled by the accumulation of mutations in specific genes, leading to the deregulation of signaling pathways. Three decades ago, Vogelstein et al introduced a multistep model outlining pivotal mutated genes contributing to colorectal cancer development.[15] The current comprehension of colorectal cancer tumorigenesis molecular etiology stems from diverse pathways and mechanisms, driven by advancements in technology. The extensively studied pathways disrupted in colorectal cancer are broadly categorized into tumor suppressor pathways (like APC/β-catenin/Wnt pathway, TGF-β pathway and TP53 pathway) and oncogenic pathways (like EGFR pathway, RAS/RAF/MAPK pathway and PI3K/Akt/mTOR pathway), marked by loss-of-function and gain-of-function mutations in specific genes, respectively. Numerous tumor suppressor genes and oncogenes within these pathways play a crucial role in promoting colorectal cancer.[16]

The VPS72 gene is located on human chromosome 1q21, and its encoded protein is a shared subunit of the histone acetyltransferase complexes TRRAP/TIP60 and the chromatin remodeling complex SRCAP. It also serves as a chaperone protein for the histone variant H2A.Z. The TRRAP/TIP60 complex induces acetylation of core histones in nucleosomes, impacting gene expression regulation, DNA double-strand break repair, chromatin stability, and apoptosis.[10] This study utilized bioinformatics methods to analyze the TCGA dataset and discovered that VPS72 exhibits a high expression state in colon cancer, holding certain diagnostic value for colon cancer. Survival analysis revealed a significant reduction in overall survival in cases where VPS72 is highly expressed, demonstrating a close correlation between VPS72 expression levels and prognosis in colon cancer. These results suggest that VPS72 holds reference significance in the early diagnosis of colon cancer. Regarding prognostic relevance, the study found a notable association between the expression levels of VPS72 and the prognosis of colon cancer patients. With variations in clinical pathological staging, the expression of VP72 in stage III/IV colon cancer was significantly higher compared to other pathological stages, indicating that VPS72 holds crucial clinical significance in assessing the prognosis of colon cancer patients.

It is reported that VPS72 and the related five most reliable proteins (such as INO80C, DAMP1, RUVBL2, ZFC3H1, KAT5) had ability to regulate either chromatin remodeling and DNA damage signaling repair or transcriptional activities of proto-oncogenes.[17–20] DNA damage signaling and repair play crucial roles in maintaining genomic stability, and their dysregulation is often associated with the development of various cancers, including colon cancer. It also plays a crucial role in the treatment of colon cancer, especially in immunotherapy and efficacy assessment.[21]

Our research found that VPS72 overexpression promoted proliferation of colon cancer in vivo and in vitro. We also found that VPS72 is involved in the Epithelial–Mesenchymal Transition (EMT) progress, which influences distant

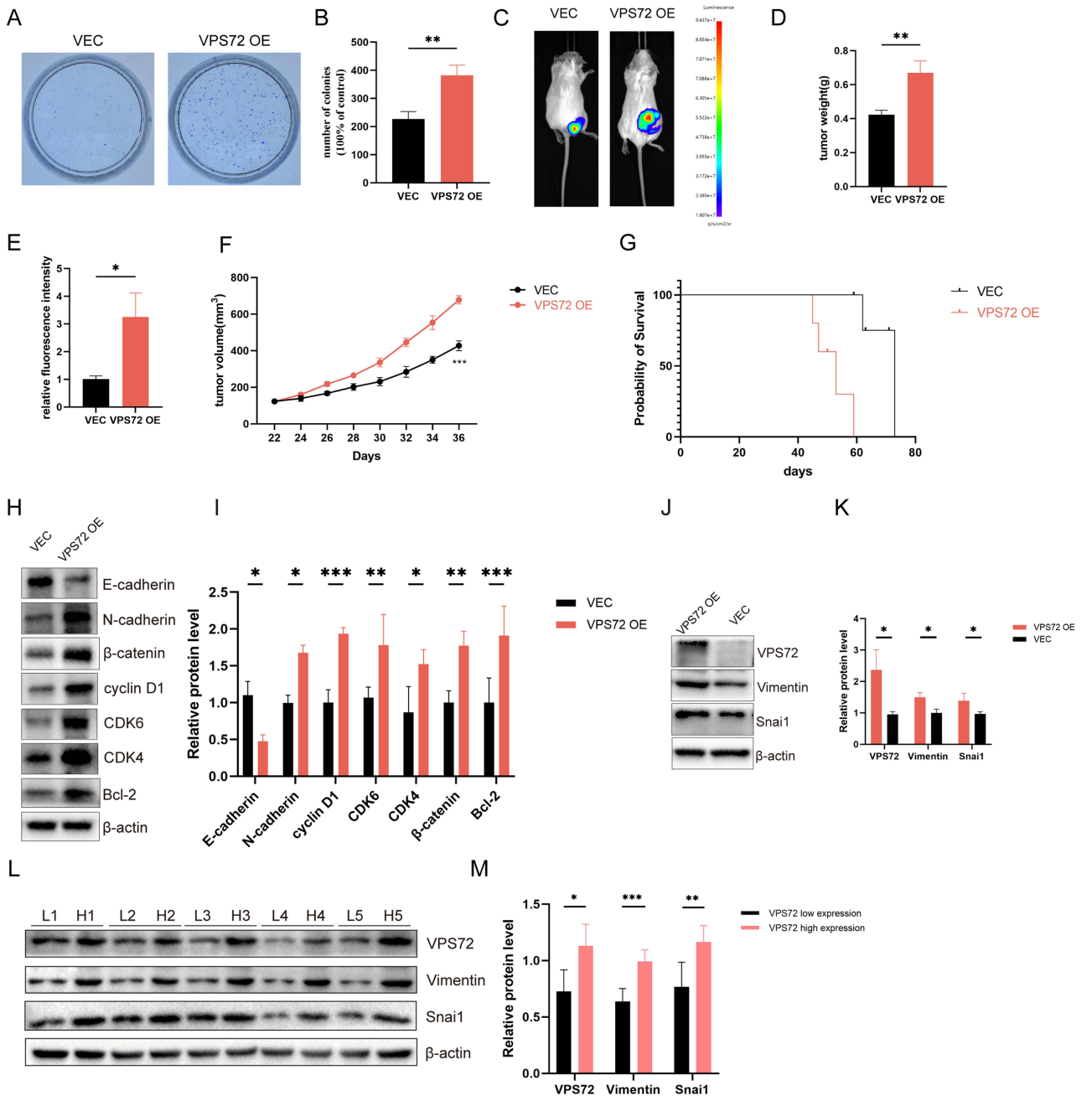

Figure 4 Function of VPS72in cancer progression. (**A**) colony formation assays of HCT116 cells with or without overexpression of VPS72. (**B**) Quantification analysis of colony formation assays. (**C**–**G**) xenograft animal models and quantification analysis. (**C**) Representative bioluminescent image HCT116 inoculation of nod-SCID mice with or without overexpression of VPS72 (n=5). (**D**) change of tumor weight. (**E**) quantification analysis of bioluminescent signal present in tumors. (**F**) change of tumor volume. (**G**) survival curve of xenograft animal models. (**H**) expression level of E-cadherin, N-cadherin, β-catenin, cyclin D1, CDK6, CDK4, and Bcl-2 in HCT116 cells with or without overexpression of VPS72. β-actin was used as control. (**I**) Quantification analysis of protein levels. (**J**) expression level of VPS72, vimentin, and snai1 in HCT116 cells with or without overexpression of VPS72. β-actin was used as control. (**K**) Quantification analysis of protein levels. (**L**) expression level of VPS72, vimentin and snai1 in colon cancer tissues lowly and highly expressed VPS72. β-actin was used as control. (**M**) Quantification analysis of protein levels. **P* <0.05, ***P*<0.01, ****P* <0.001.

metastasis in colon cancer. It is worth noting that the EMT progress plays a pivotal role in fostering tumor metastasis, stemness, and resistance to chemotherapy.[22] This meticulously orchestrated process is regulated at the epigenetic level, under the influence of various cell signaling pathways. The EMT status typically exhibits heterogeneity within individual tumors. In the context of colon cancer, the overactivation of Wnt/β-catenin signaling not only initiates tumorigenesis but also facilitates advanced metastasis by inducing EMT progress.[23] Understanding the role of EMT in metastatic colon cancer is crucial for developing targeted therapeutic strategies. Researchers are exploring ways to intervene in the EMT

process to limit the invasive and metastatic potential of cancer cells, ultimately improving the prognosis for individuals with metastatic colon cancer.[23]

Our research still exhibits certain limitations. Firstly, we failed to stratify colorectal cancer patients based on distinct microsatellite statuses, despite the potential close association between VPS72 and microsatellite status, as well as mismatch repair. Secondly, a more in-depth investigation into the specific mechanisms through which VPS72 participates in colon cancer is lacking in our study.

Conclusions

In conclusion, our study revealed that high expression of VPS72 correlated with poor prognosis in colon cancer patients. VPS72 overexpression promoted colon cancer proliferation. Our study revealed that VPS72 appears to function as an oncogene in colorectal cancer, potentially serving as a valuable biomarker. However, its role in tumorigenesis remains to be further studied.

Data Sharing Statement

All the data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approvement

All animal maintenance and treatment protocols were in accordance with the Institutional Animal Care Committee of the Animal Experimental Center of Xi'an Jiaotong University and followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978). All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China) and with the Helsinki Declaration of 1975, as revised in 2008.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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