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RESEARCH PAPER

Investigating the role of LncRNA PSMG3-AS1 in gastric cancer: implications for prognosis and therapeutic intervention

Yi Wang[a,b*], Zhongshi Hong[a*], Shenghong Wei[b], Zaisheng Ye[b], Luchuan Chen[b], and Chengzhi Qiu[a]

[a]Department of General Surgery, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China; [b]Department of Gastrointestinal Surgical Oncology, Clinical Oncology School of Fujian Medical University, Fuzhou, Fujian, China

ABSTRACT

LncRNAs are widely linked to the complex development of gastric cancer, which is acknowledged worldwide as the third highest contributor to cancer-related deaths and the fifth most common form of cancer. The primary focus of this study is to examine the role of LncRNA PSMG3-AS1 in a group of individuals with gastric cancer. The results of our study indicate that PSMG3-AS1 is highly expressed in over 20 different types of cancer. Significantly, there was a clear association found between the expression of PSMG3-AS1 and a multitude of TMB and MSI tumors. PSMG3-AS1 exhibited significant upregulation in gastric cancer patients compared to healthy individuals within the gastric cancer cohort. The prognosis of gastric cancer patients is intrinsically associated with PSMG3-AS1, as confirmed by survival analysis and ROC curves. Furthermore, we created a disruption vector based on LncRNA PSMG3-AS1 and introduced it into AGS and MKN-45 cells, which are human gastric cancer cells. Significant decreases in the expression of the PSMG3-AS1 gene were noticed in both intervention groups compared to the NC group, reflecting the protein level expressions. Significantly, the proliferative and invasive capabilities of MKN-45 and AGS cells were notably reduced following transfection with PSMG3-AS1 siRNA. The results of our study indicate that disruption of the LncRNA PSMG3-AS1 gene may impact the CAV1/miR-451a signaling pathway, thereby leading to a reduction in the ability of gastric cancer cells to multiply and invade.

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Introduction

In 2015, approximately 1.3 million individuals were diagnosed with gastric cancer, positioning it as the fifth most prevalent form of malignancy and the third primary contributor to cancer-related fatalities globally [1]. The European Cancer Registry reported around 133,100 instances of gastric cancer diagnosis and approximately 102,200 fatalities caused by the disease [2].

In Western nations, despite a consistent decrease in overall GC occurrence in recent decades, there seems to be a rise in the number of instances in the upper part of the stomach [3]. Various factors contribute to the development of gastric cancer, such as infection with Helicobacter pylori, lifestyle choices like alcohol consumption and smoking, and genetic predisposition [4]. Before the era of genomics, Lauren proposed the most widely used classification scheme, dividing GC into "gut" and "diffuse" subtypes [5]. H. pylori infection is linked to intestinal-type gastric cancers, which exhibit glandular or papillary differentiated structures. On the other hand, diffuse-type gastric cancers are characterized by poorly cohesive, dedifferentiated tumor cells within a substantial cellular matrix. Nevertheless, the utilization of histopathological variations is not currently a standard practice for guiding the treatment and control of gastric cancer. Due to the elevated occurrence of genetic changes in individuals with gastric cancer, GCs could potentially serve as optimal candidates for immunotherapy [6].

Over the past few years, there has been a significant amount of research dedicated to precisely detecting gastric cancer and investigating the responsiveness of individuals with gastric cancer to immunotherapy [7]. The expression of markers for gastric cancer in primary tumors and patient-

CONTACT Chengzhi Qiu qchengzhi@fjmu.edu.cn Department of General Surgery, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian 362000, China
*These author contributed equally to this work.

derived xenografts was evaluated by Nguyen et al in immunodeficient mice, and the cells were examined for tumorigenic properties both in vitro and in vivo [8]. The findings indicated that CD44 and ALDH, in conjunction with CD133, EpCAM, and CD166, were determined to be the primary and distinctive indicators for chemoresistant gastric cancer [9]. Furthermore, dysplasia, lymph node metastasis, and cancer staging in gastric cancer were found to be linked with a particular isoform of ALDH, namely ALDH-3A1 [10].

Numerous recent studies have indicated that the majority of transcribed genomes in mammals are composed of noncoding RNAs [11]. According to a prior investigation, approximately 2% of the human genetic material is responsible for protein synthesis, whereas around 70–90% is transcribed into noncoding RNA [12]. Long noncoding RNAs, with over 200 nucleotides, not only play diverse roles in cell differentiation, metabolism, migration, and apoptosis [13]. Previous research has shown that long-nucleated RNAs (lncRNAs) have facilitated the growth of gastric cancer and functioned as oncogenic elements, negatively impacting the survival rate [14].

CAV1, also known as caveolin 1, is a transmembrane protein found in various cellular regions. Its expression is specific to different stages of tumorigenesis and is compartmentalized. CAV1 has been demonstrated to induce a range of cancerous conditions [15]. Earlier research has indicated that the protein CAV1 controls the process of epithelial-mesenchymal transition (EMT) and has a significant impact on the advancement of gastric cancer (GC) [16].

Next-generation sequencing is an innovative method for categorizing patients with gastric cancer, enabling swift identification of cancer traits and providing valuable insights into optimal treatment strategies [17,18]. The use of HER2 as a predictive biomarker has been employed in drug therapy. Further validation is required for PD-L1 as an indicator for immunotherapy. Currently, there is an ongoing evaluation of additional biomarkers. Molecular subtypes are essential for guiding clinical practice, but the absence of subgroup classification hinders their use [19]. Hence, it is crucial to create a potent genetic marker that can predict the outlook and direct medical intervention, particularly in the context of targeted therapy and immunotherapy. The objective of this research was to develop a scoring system that categorizes individuals with gastric cancer using TCGA and GEO databases in order to forecast prognosis and provide guidance for clinical treatment. By conducting experiments to validate and offer guidance for the immunotherapy of gastric cancer.

Methods

Public database data acquisition

The Cancer Genome Atlas (TCGA), available at https//portal.gdc.cancer.gov/, encompasses various types of data such as tumor gene expression, miRNA expression, methylation, mutation, and copy number data. By utilizing this database, one can access additional experimental sequencing data that was utilized in prior research. Data on the expression of mRNA and miRNA, along with clinical information of patients with gastric cancer, were obtained from the TCGA database.

Determination of gene expression level in human cancer

Initially, information was obtained from The Cancer Genome Atlas (TCGA) and GTEx databases, which were subsequently merged to examine gene dysregulation across different cancerous and normal tissues. The datasets included RNA sequence data and clinical follow-up information for 32 different types of cancer.

Analysis of gene's prognostic value

By generating forest plots and Kaplan-Meier curves, we analyzed the correlation between gene and patients' survival outcomes, specifically overall survival (OS) and progression-free intervals (PFI). Afterwards, we computed hazard ratios (HRs) and 95% confidence intervals through univariate survival analysis.

Investigation into the correlation between gene expression and TMB or MSI

TMB stands for the overall count of somatic gene coding mistakes, including base substitutions,

insertions, or deletions, identified per million bases. The TMB in this research was determined by computing the frequency of mutations and the number of mutations per exon length for each tumor sample. Subsequently, the non-synonymous mutation sites were divided by the overall length of the protein coding region. TCGA provided all TMB and MSI scores, with MSI values for each patient obtained from a study that was published earlier.

Cell cultivation and gene transfer

MKN45 cells (CL-0292, Procell), AGS cells (CL-0022, Procell), and 293T cells (BNCC100530, BNCC) derived from human gastric cancer were cultured as required, with cell passage occurring at 80%-90% cell density.The cells were diluted based on the requirements of the experiment, and once the cell density reached 70%, it was prepared for transfection. The gene interference sequence was created based on the sequence of the human LncRNA PSMG3-AS1 (ENST00000532358.6) as given in the Ensembl gene bank. The sequence of the target that is causing interference is as follows: PSMG3-AS1-aso-511 TCATCGTAACACAAAAACC; PSMG3-AS1-aso-658 TTTAATTCAATCCAGTTCC; PSMG3-AS1-aso-842 TAAAATGTTAGCTATAGCC.

Real-time quantitative polymerase chain reaction

Trizon reagent was used to extract RNA from AGS and MKN-45 cells.RNA ultrapure extraction kit was used to extract total RNA, while miRNA ultrapure extraction kit was used to extract miRNA. The concentration and purity of both total RNA and miRNA were determined using a UV-Vis spectrophotometer, specifically by measuring the OD260/OD280 ratio. Reverse transcription kit was used to convert RNA and miRNA into cDNA, followed by real-time fluorescence PCR for fluorescence quantitative PCR. The reaction proceeded in the following manner: initial denaturation at a temperature of 95°C for a duration of 10 minutes, followed by denaturation at 95°C for 10 seconds, annealing at 58°C for 30 seconds, extension at 72°C for 30 seconds, and a total of 40 cycles. The $2^{-\Delta\Delta}$Ct method was used to calculate the relative expression of genes, with β-actin and U6 serving as internal controls. The table below displays the primer sequences for Hsa-miR-451a: forward primer – 5'-CGCGAAACCGTTACCATTAC-3', reverse primer – 5'-AGTGCAGGGTCCGAGGTATT-3'; U6: forward primer – 5'-CTCGCTTCGGCAGCACA-3', reverse primer – 5'-AACGCTTCACGAATTTG CGT-3'; Caveolin-1: forward primer – 5'-AACATCTACAAGCCCAACAACAAG-3', reverse primer – 5'-TTCCAAATGCCGTCAAAACTG-3'; PSMG3-AS1: forward primer – 5'-CACTTC ATCTCAGCCACCCG-3', reverse primer – 5'-GCAGAGGAAAACAGAAATCATCGT-3'.

CCK8 assay

The cells were cultured until they reached optimal condition. Then, the cells in the 96-well plate designated for testing were substituted with an equal amount of fresh medium, 100 μL per well. Additionally, 10 μl of CCK8 reagent was introduced to each well, followed by a 2-hour incubation in an incubator at a wavelength of 450 nm. The microplate reader (WD-2012B, Beijing Liuyi) was used to measure the absorbance value for each well.

Flow cytometry

To begin with, we gather one million cells, include one milliliter of PBS, spin at a speed of 1500 revolutions per minute for a duration of 3 minutes, and rinse two times. Afterwards, we mix 5×Binding Buffer with double distilled water to obtain 1×Binding Buffer. Next, we resuspend the cells by adding 300ul of 1×Binding Buffer that has been pre-cooled. Then, we add 5 ul of Annexin V-FITC and 10 ul of PI to each tube. Mix gently at ambient temperature for 10 minutes, then add 200ul of 1 X Binding Buffer, which has been pre-cooled, to each tube. Flow cytometry was performed after the mixture was combined.

Transwell assay

The cells were grown under favorable conditions and subsequently suspended in a medium devoid of serum. The cells were placed in the upper

compartment of a Transwell chamber coated with Matrigel, while medium containing PBS was introduced into the lower compartment. Following incubation in a CO2 incubator at 37°C for 24 hours, the chamber was removed, the medium was discarded, and subsequently stained with 0.1% crystal violet for a duration of 1 hour. The chamber's cells were cleaned using a cotton swab and then examined under an Olympus microscope (model BX43). Following the photography process, the staining solution was eliminated, and then 33% acetic acid was introduced for treatment. Subsequently, the absorbance value of each well was assessed using a microplate reader (WD-2012B, Beijing Liuyi) at a wavelength of 562 nm.

Analysis and processing of data

Statistical analysis was conducted using SPSS 20.0 software. The experiments were conducted thrice, and the quantitative outcomes were presented as the average plus or minus the standard deviation (X ± S). The independent sample T test was used to perform a quantitative numerical comparison between two groups, while a one-way ANOVA was used to perform a quantitative numerical comparison among multiple groups. Pairwise comparison was conducted using the S-N-K method. Inspection level $\alpha = 0.05$.

Results

The expression profile of PSMG3-AS1 across multiple types of cancer

The examination of PSMG3-AS1 expression in 32 types of human cancers from TCGA and GTEx databases indicated that the gene was increased in 20 tumors, such as BLCA, BRCA, CESC, CHOL, COAD, ESCA, GBM, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, SARC, STAD, THCA, and UCEC (Figure 1).

Correlation between the expression of PSMG3-AS1 and TMB and MSI

Immunotherapy response is linked to the emergence of TMB and MSI as biomarkers. The correlation between the expression of PSMG3-AS1 and TMB was analyzed, showing a significant association with various tumor types such as STAD, PAAD, ACC, SARC, UCS, LGG, PRAD, MESO, and SKCM (Figure 2a). The examination of the correlation between PIMREG expression and MSI revealed that PSMG3-AS1 exhibited significant differential expression in DLBC, STAD, KIRC, UCS, KICH, and CHOL (Figure 2b).

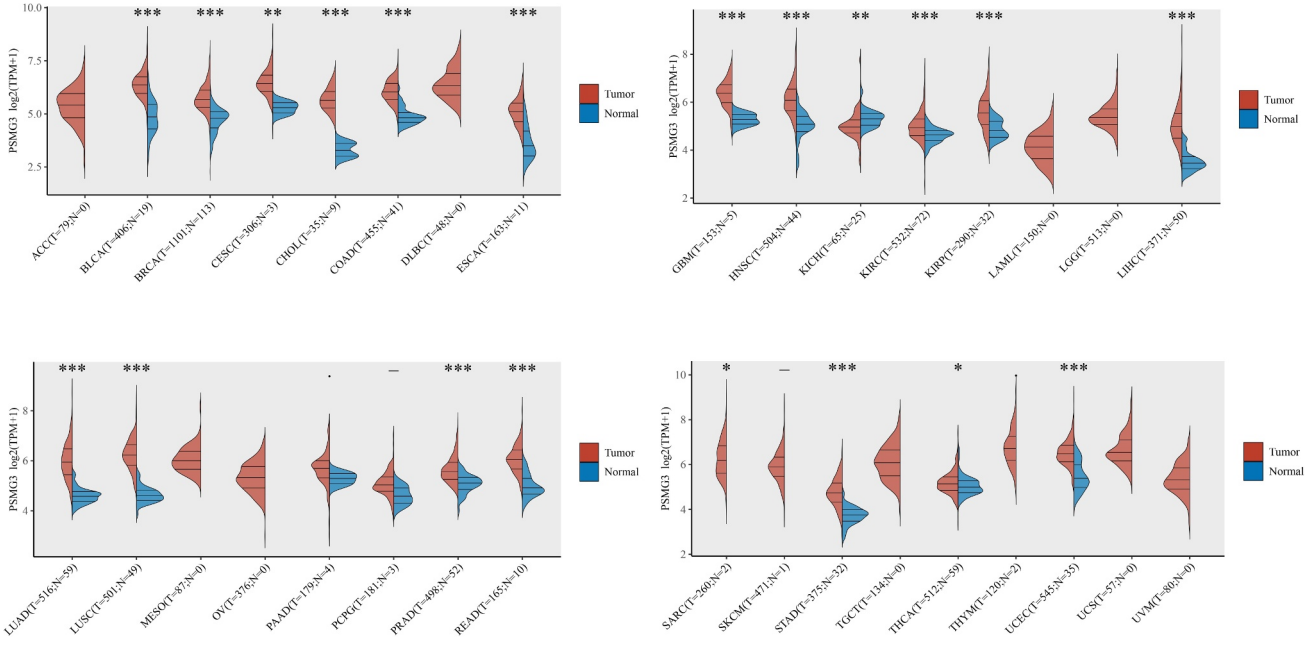

Figure 1. The pan-cancer analysis demonstrated the expression level of PSMG3-AS1 in variety of cancers.

Investigating the involvement of PSMG3-AS1 in a cohort of gastric cancer

Afterwards, we assessed the association between PSMG3-AS1 and individuals diagnosed with gastric cancer. Based on the expression level of PSMG3-AS1 (Figure 2c), the patients with gastric cancer were categorized into groups with low and high expression. Figure 2d showed that gastric cancer patients with high levels of PSMG3-AS1 had a lower survival rate according to the survival analysis. Furthermore, in contrast to individuals without gastric cancer, patients with gastric cancer exhibit a heightened level of PSMG3-AS1 expression (Figure 2e). Moreover, the ROC graph demonstrates that PSMG3-AS1 exhibits favorable prognostic significance in individuals diagnosed with gastric cancer (Figure 2f).

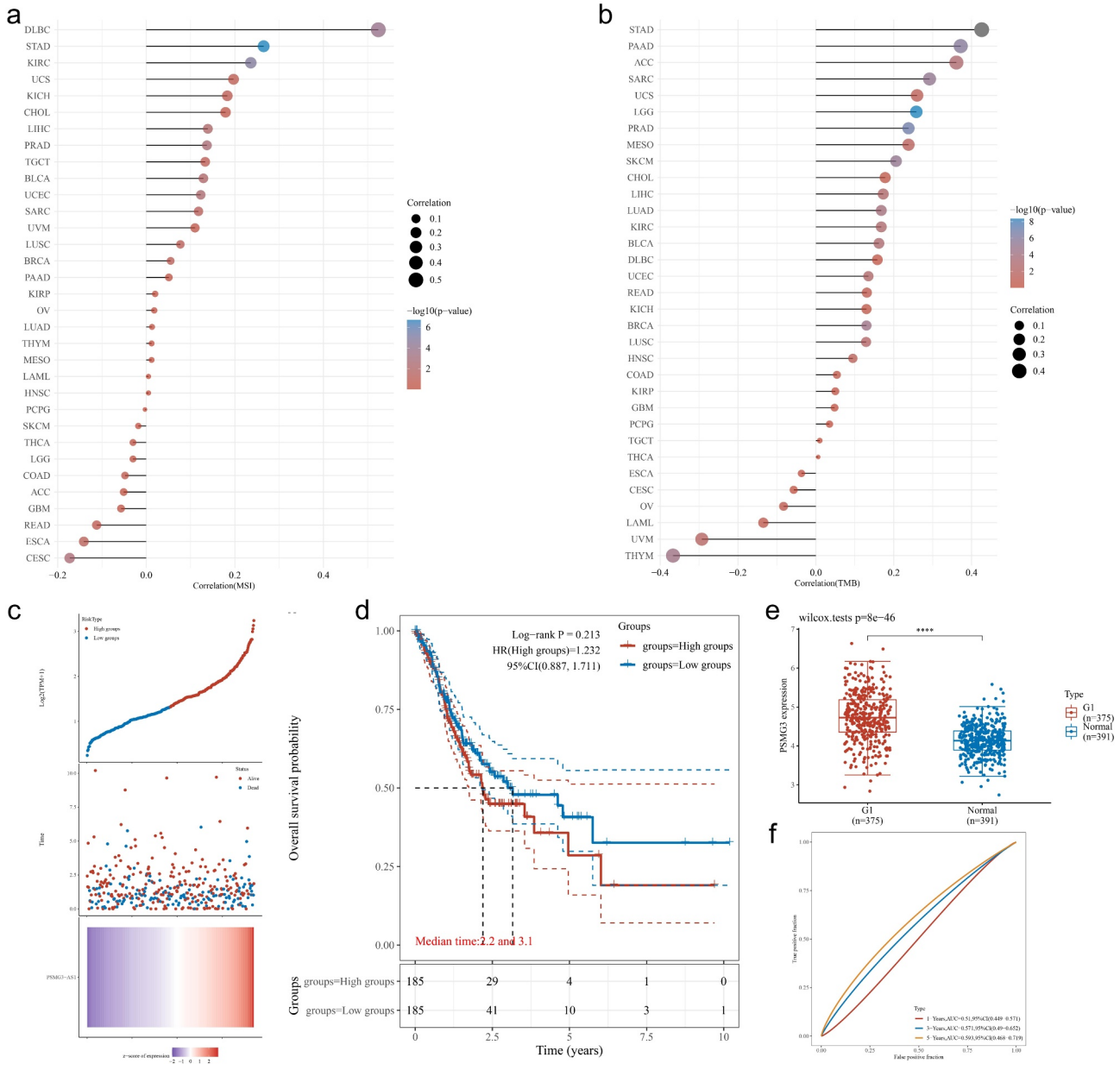

Figure 2. (a) the TMB analysis based on the expression level of PSMG3-AS1 in variety of cancers; (b) the MSI analysis based on the expression level of PSMG3-AS1 in variety of cancers; (c) the gastric cancer cohort was divided into low- and high-expression of PSMG3-AS1 group; (d) the survival analysis based on the different expression level of PSMG3-AS1; (e) the expression level of PSMG3-AS1 between gastric cancer cohort and normal group; (f) the ROC curve demonstrated the prognostic value for 1-year, 3-year and 5-year AUC score.

Investigating the association among CAV1, PSMG3-AS1, and miR-451a

The ROC curve illustrated that both CAV1 and PSMG3-AS1 exhibit excellent prognostic significance among individuals with gastric cancer (Figure 3a,b). Afterwards, we assessed the association among CAV1, PSMG3-AS1, and miR-451a. The analysis of clinical correlation showed a strong connection between the level of CAV1 expression and TMN stage (Figure 3c). Furthermore, the expression level of CAV1 exhibits an inverse correlation with the expression level of miR-451a (Figure 3d). Furthermore, the miR-451a expression level exhibits a negative correlation with the expression level of PSMG3-AS1 (Figure 3e). The correlation analysis showed that the CAV1 expression level is positively linked to PSMG3-AS1 (Figure 3f,g). Figure 3h,i shows that CAV1, PSMG3-AS1, radiation therapy, age, and TMN stage are identified as independent prognostic factors for patients with gastric cancer, based on both univariate and multivariate independent prognostic analyses. Based on the expression profiles of CAV1 and PSMG3-AS1 and clinical symptoms, we developed an additional nomogram prediction model. The expression of CAV1 and PSMG3-AS1 in the model (Figure 3j) strongly predicted the value of patient prognosis.

Investigating the involvement of PSMG3-AS1 in a cohort of gastric cancer

Figure 4a demonstrates that the majority of LncRNA PSMG3-AS1 is found in the nucleus of MKN-45 cells, with a minor portion being present in the cytoplasm. Human gastric cancer AGS and MKN-45 cells were transfected with the interference vector of the synthesized LncRNA PSMG3-AS1.Real-time quantitative PCR detected the impact of the interfering carrier. In comparison to the NC group, the expression of LncRNA PSMG3-AS1 was notably reduced in both the siRNA 511 and siRNA 842 groups (Figure 4b). The CCK8 test was utilized to observe the alterations in cell growth within each category. Furthermore, the flow cytometry analysis revealed a notable enhancement in apoptotic potential following the introduction of PSMG3-AS1 siRNA (Figure 5). Moreover, the transwell test revealed a notable decrease in the invasive capacity of gastric tumor cells following the introduction of PSMG3-AS1 siRNA. To delve deeper, we overexpressed miR-451a and CAV1 in GC cells and assessed their impact on cellular functions using proliferation and transwell migration assays. The results demonstrate a significant decline in both proliferation and migratory abilities of GC cells post miR-451a overexpression, suggesting its tumor-suppressive role potentially through the inhibition of oncogenic factors (Figure 6a–). Conversely, upon CAV1 overexpression, an enhancement in these cellular capabilities was noted, supporting CAV1's possible oncogenic role in gastric cancer (Figure 6b,c). Upon knockdown of PSMG3-AS1, we observed a decrease in the mRNA levels of CAV1 alongside an increase in the expression of miR-451a. These findings align with our hypothesis that PSMG3-AS1 can regulate the miR-451a/CAV1 axis in gastric cancer (GC) cells (Figure 6d,e).

Discussion

Despite a continuous decline in the global occurrence and fatality of stomach cancer throughout the past century, the growing number of fresh instances annually can be attributed to the aging demographic [20]. Globally, gastric cancer ranks as the second most common cause of cancer-related mortality, following lung cancer [21]. Gastric cancer treatment options are limited, so new strategies are urgently needed to prolong lives. Complete removal of the tumor is guaranteed by performing a radical resection, which involves resecting the tumor both longitudinally and circumferentially, and is the sole remedy for resectable gastric cancer [22]. Surgical treatment is often ineffective due to the fact that a significant number of gastric cancer patients are diagnosed with advanced malignancies [23]. Hence, it is imperative to urgently discover pertinent tumor indicators in order to enhance the rate of early detection for gastric cancer and elevate its chances of being cured.

LncRNA PSMG3-AS1 has an impact on the signaling of miR-451a, as it exerts control over the pathway. As a result, the expression of the

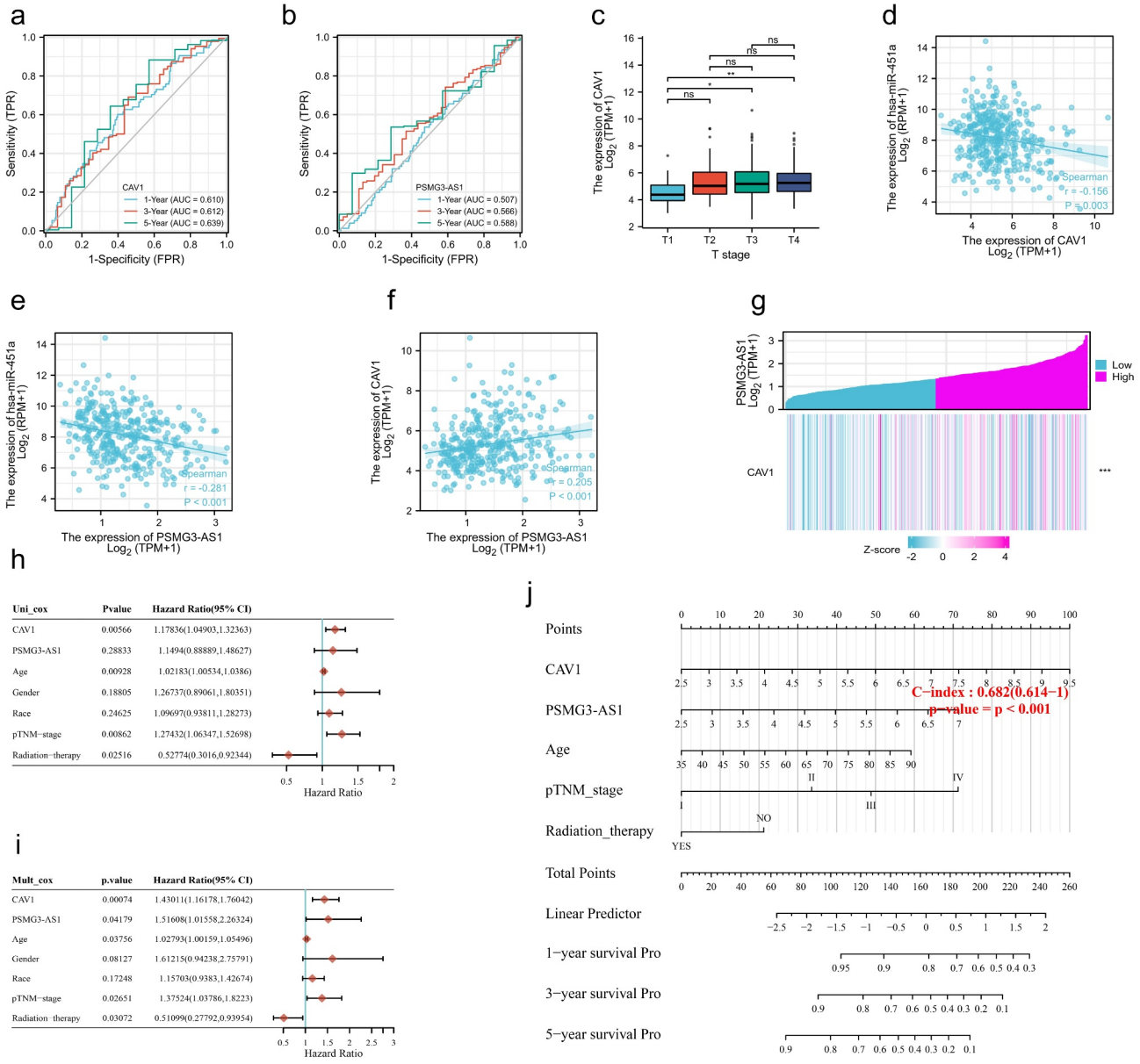

Figure 3. (a) the time-dependent ROC curve demonstrated the prognostic value of CAV1; (b) the time-dependent ROC curve demonstrated the prognostic value of PSMG3-AS1; (c) the correlation analysis based on the expression level of CAV1 and T stage; (d) the correlation analysis between the expression level of miR-451a and CAV1; (e) the correlation analysis between the expression level of miR-451a and PSMG3-AS1; (f) the correlation analysis between the expression level of CAV1 and PSMG3-AS1; (g) the heatmap demonstrated the potential relationship between CAV1 and PSMG3-AS1; (h) the univariate independent prognostic analysis based on the CAV1, PSMG3-AS1 and clinical characteristics; (i) the multivariate independent prognostic analysis based on the CAV1, PSMG3-AS1 and clinical characteristics; (J) the nomogram was applied to construct the prognosis-prediction model in gastric cancer cohort.

Caveolin-1 gene and protein will eventually decrease, thereby inhibiting the proliferation of gastric cancer cells to some degree. Research has shown that long non-coding RNAs (LncRNAs) are essential in the development of gastric cancer. Various elements play a role in controlling cellular behavior mediated by LncRNA. Furthermore, an increasing amount of research indicates that lncRNAs function as miRNA decoys, controlling various cellular mechanisms [24]. Pan et al. found that lnc-CTSLP4 has the potential to function as both a predictive indicator and a target for treatment in advanced gastric cancer [25]. A second study reveals that increased expression of

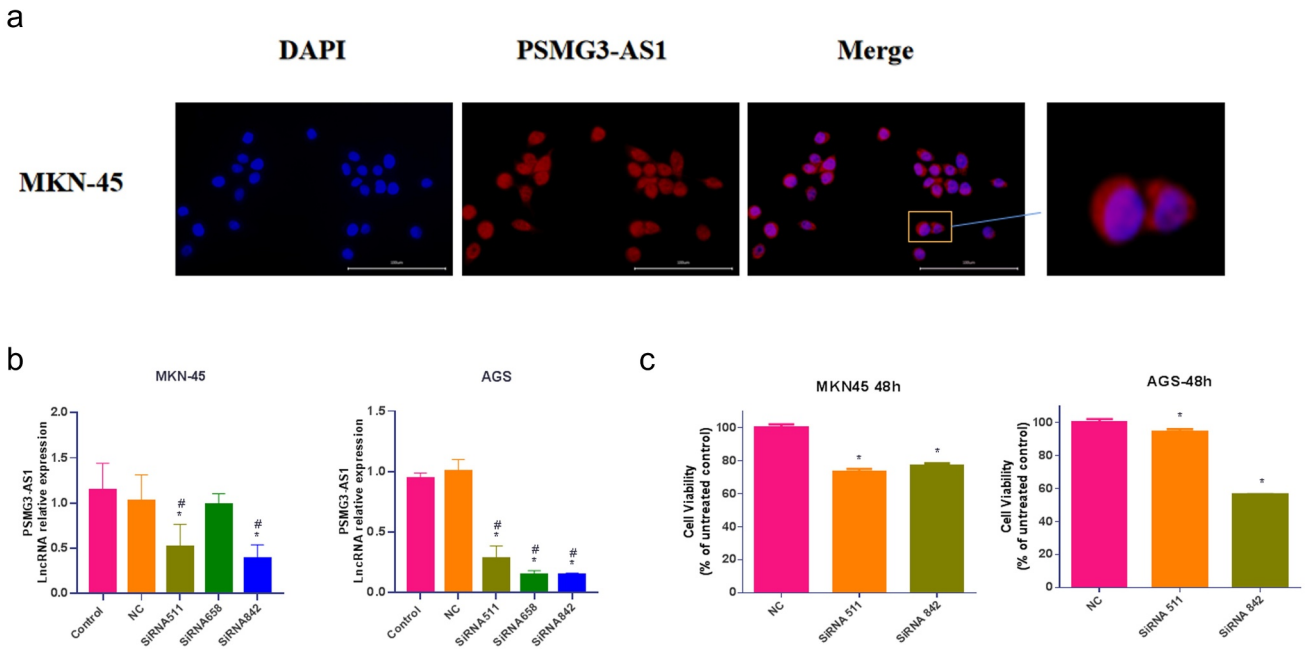

Figure 4. (a) the localization of LncRNA PSMG3-AS1 in cells by in situ hybridization; (b) the efficiency of siRNA in gastric cancer cells; (c) the results of CCK8 assay.

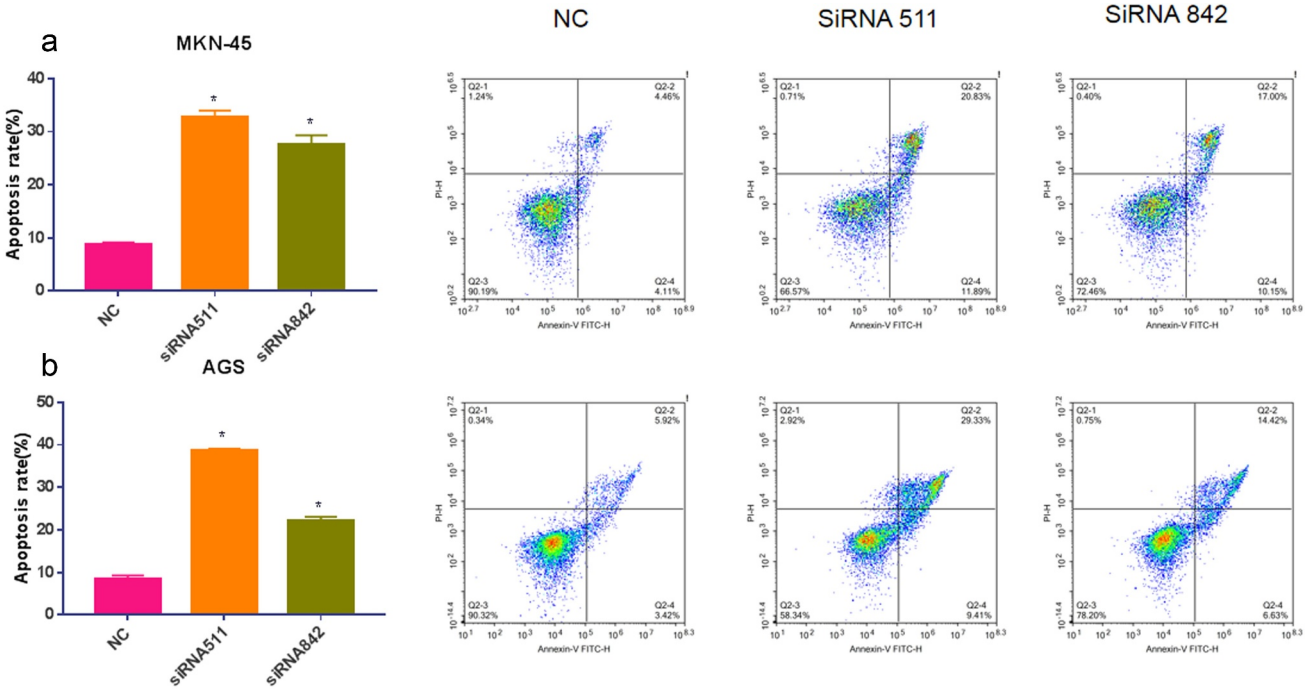

Figure 5. Flow cytometry for detection of cell apoptosis.

HOTAIR is linked to bigger tumor size, advanced pathological stage, widespread metastasis, and reduced overall survival rate [26]. Moreover, excessive expression of HOTAIR stimulates the proliferation, migration, and invasion of gastric cancer cells [27-28]. Our research unveiled that PSMG3-AS1 exhibits increased expression in over 20 different cancer types, thus providing a comprehensive pan-cancer expression profile of PSMG3-AS1.Furthermore, the expression of PSMG3-AS1 exhibited a significant correlation with numerous tumors characterized by high

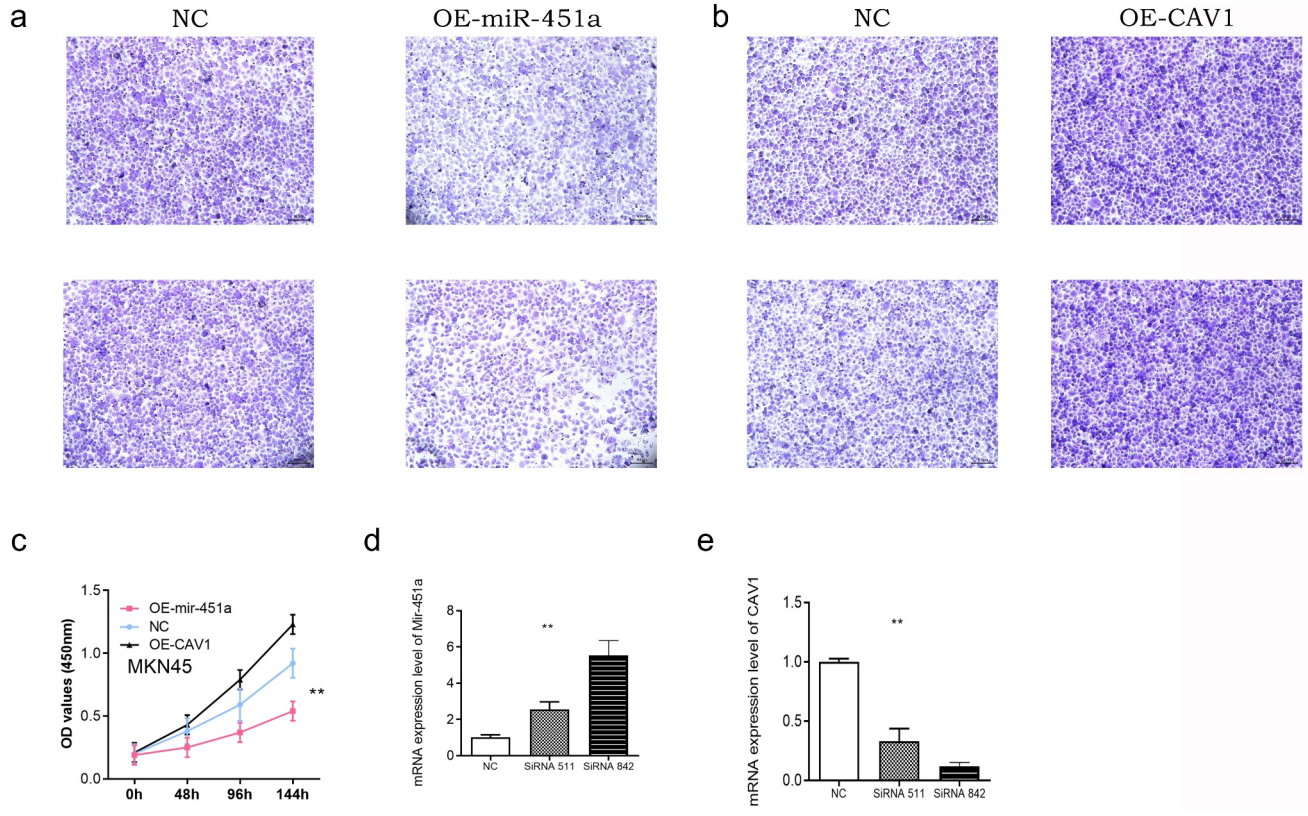

Figure 6. (a-b) the transwell assay showed the invasive ability in AGS cells; (c) the cck8 assay showed the proliferation ability in AGS cells; (d-e) the QPCR assay showed the mRNA expression level of CAV1 and mir-451a after the knockdown of LncRNA PSMG3-AS1.

TMB and MSI. In the cohort of individuals with gastric cancer, PSMG3-AS1 exhibits a notable increase in expression levels among gastric cancer patients when compared to individuals without the condition. Moreover, the analysis of patient survival and the ROC curve revealed a strong correlation between PSMG3-AS1 and the prognosis of individuals with gastric cancer. For this research, we developed a disruption vector using LncRNA PSMG3-AS1 and introduced it into AGS and MKN-45 human gastric cancer cells. PSMG3-AS1 gene expression was markedly reduced in both interference groups when compared to the NC group, and protein levels corresponded with gene expression. Furthermore, the transfection of PSMG3-AS1 siRNA notably decreased the proliferation capacity of MKN-45 and AGS cells.

Afterwards, we assessed the correlation among CAV1, PSMG3-AS1, and miR-451a. There is an inverse relationship between the expression level of CAV1 and the expression level of miR-451a. Furthermore, the miR-451a expression level exhibits a negative correlation with the expression level of PSMG3-AS1.The correlation analysis indicated that there is a positive association between the expression level of CAV1 and PSMG3-AS1.

To investigate the enrichment pathways associated with CAV1 and PSMG3-AS1, we conducted both GSEA and GSVA enrichment analyses. The findings indicated that CAV1 has a strong correlation with the reaction to oxidative stress and programmed cell demise. Under conditions of oxidative stress and injury, the CAV1 membrane protein has been demonstrated to function as a crucial integral membrane protein that controls autophagy. Gastric cancer cohort includes PSMG3-AS1, ribosome, oxidative phosphorylation, neuroactive ligand receptor interaction, arrhythmogenic right ventricular cardiomyopathy (ARVC), and calcium signaling.

While bioinformatics analyses offer powerful insights into biological and medical research, they are not without limitations. The quality of the initial data can greatly influence the outcome, as analyses are highly sensitive to biases, noise, or other issues in the raw data [16]. Furthermore,

the inherent complexity and heterogeneity of biological systems pose challenges in data interpretation and model construction [29]. No single algorithm excels in all scenarios, with some performing well on specific datasets but poorly on others. When conducting large-scale gene or protein analyses, the issue of multiple comparisons arises, leading to potential false positives [30]. Although methods like Bonferroni or FDR corrections exist to address this, they might also increase the risk of false negatives [31]. Thus, caution and thoroughness are paramount when utilizing and interpreting bioinformatics findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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