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Original Article

The lncRNA-miRNA-integrin alpha V ceRNA network can affect the occurrence and prognosis of gastric cancer

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Abstract: Objectives: The aim of this study was to explore the role of integrin alpha V (ITGAV) and the related long noncoding RNA-microRNA-messenger RNA competing endogenous RNA (lncRNA-miRNA-mRNA ceRNA) network in the development and prognosis of cancers, especially gastric cancer (GC), through bioinformatic analysis. Methods: Pan-cancer and GC data were collected from the UCSC Xena website, and validation datasets were obtained from the Gene Expression Omnibus (GEO). R (version 3.6.3), GraphPad Prism 8, and SPSS 23.0 software were used to analyze data and prepare figures. Results: The expression of ITGAV in tumor tissues was higher than that of normal tissues in ten cancer types. A lower expression of ITGAV in five tumors (CESC, LGG, LIHC, MESO, and STAD) predicted better patient prognosis. In GC, the mRNA and protein expression of ITGAV in tumor tissues was higher than that of normal tissues. Patients with high ITGAV expression had poor prognosis and clinical characteristics, including worse grades and more advanced stages. Patients with higher ITGAV expression had higher immune and stromal scores and lower purity ($P<0.05$). In addition, seven miRNAs were found that were negatively correlated with ITGAV expression through the website; high expression of these miRNAs indicated a better prognosis. Using this correlation, the authors built the lncRNA-miRNA-ITGAV ceRNA network, to predict the prognosis of GC. Conclusions: This study showed that ITGAV could be considered a prognostic factor for GC, and an lncRNA-miRNA-ITGAV ceRNA network was built to promote the exploration of the mechanism and prognosis of GC.

Keywords: ITGAV, gastric cancer, prognosis, ceRNA

Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related morbidity and mortality worldwide. Although surgical treatment has advanced, the 5-year survival rate of postoperative mortality in patients with GC is still not ideal [1, 2]. In the past, research on GC mainly focused on the operative method and drug combination of macroeconomic research [3]. In recent years, researchers have gradually committed to the research of micromolecular structure [4], especially the extensive progress of promising targets such as tumor protein p53 (TP53) and Programmed cell death 1 ligand 1 (PD-L1) in cancer therapy [5-7]. The application of bioinformatic technology helps researchers better screen and study genes that potentially affect the prognosis of GC progression and molecules from microscopic aspects [8].

Integrins are combinations of extracellular matrix proteins or other adhesion receptors on neighboring cells of transmembrane receptors, and are composed of alpha and beta subunits [9]. Studies have shown that integrins play an important role in tumor invasion and metastasis, and different integrins can identify different ligands with regard to angiogenesis, validation, and the tumor microenvironment [10, 11]. For example, Alpha-v-beta-6 (αvβ6) and alpha-v-beta-8 (αvβ8) can regulate the expression of transforming growth factor β (TGF-β) signaling pathways [12-14], Alpha-v-beta-3 (αvβ3) and Alpha-v-beta-5 (αvβ5) can promote angiogenesis in tumor progression [15], and alpha-9-beta-1 (α9β1), alpha-3-beta-1 (α3β1), and αvβ3 cooperate with vascular endothelial growth factor (VEGF) in blood vessel formation [16-18]. These results suggest that integrin plays a significant role in tumor development.

Integrin alpha V (ITGAV), an av protein-encoding gene, plays an important role in cancer. The product of ITGAV belongs to the integrin alpha chain family. Integrins are heterodimer integration membrane proteins that are composed of one α subunit and one β subunit and play a role in cell surface adhesion and signaling. The coding proprotein is hydrolyzed to produce light and heavy chains containing the alpha V subunit. This subunit could combine with the beta 1, Beta 3, beta 5, Beta 6, and Beta 8 subunits, then regulate angiogenesis and cancer progression. Studies have shown that high expression of ITGAV can affect the targeted therapy of breast cancer and reflects a poor prognosis in esophageal cancer and bone tumors, but less research has been done on its role in GC [19-21]. This study aimed to explore the role of ITGAV in the progression and prognosis of gastric cancer. Based on data analysis of TCGA and GEO databases, we explored the potential role of ITGAV in the progression and prognosis of gastric cancer, and we first constructed the relevant ceRNA interaction network to reveal the potential targets correlated to ITGAV in GC.

Materials and methods

Data collection

Raw pan-cancer data and TCGA gastric cancer data (STAD) were downloaded from UCSC Xena (https://xena.ucsc.edu/) [22], and immunohistochemistry, single-cell, and immunofluorescence co-localization data were obtained from the Human Protein Atlas (https://www.proteinatlas.org/) [23]. The validation datasets GSE29272 (n=268), GSE122401 (n=160), and GSE15459 (n=200) were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). Targeted microRNAs (miRNAs) and related long noncoding RNAs (lncRNAs) were predicted using the starBase database (https://starbase.sysu.edu.cn/) [24]. Microarray data normalization was performed and gene expression levels were computed as the mean values of all annotated probe sets. EdgeR was used for the differentially expressed gene analysis of RNA sequencing data, including pan-cancer and STAD data.

Analysis of correlation between ITGAV expression and clinical characteristics

According to the cutoff expression of ITGAV, the patients with clinical information in each cohort were divided into two groups: ITGAV-High and ITGAV-Low. Differentially expressed genes ($P<0.05$, $|\log(FC)| \geq 2$) and highly correlated genes ($|R|>0.4$) were identified and analyzed through the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases using DAVID (https://david.ncifcrf.gov/) [25]. Information on basic clinical characteristics, including tumor stage, grade, and overall survival (OS), was collected for comparison. The tumor purity and immune and stromal scores were calculated using the Estimate package. Tumor mutational burden (TMB) was calculated based on the somatic mutation data.

Analysis of correlation between ITGAV expression and immune infiltration, TMB, and microsatellite instability (MSI)

Research hotspots, such as immune infiltration, tumor purity, TMB, and MSI, were calculated to identify a correlation between ITGAV expression and prognosis. Statistical significance was set at $P<0.05$. The TIMER website (http://timer.cistrome.org/) was used for primary analysis of the correlation between ITGAV and immune cells [26]. TMB of TCGA patients was obtained and calculated using the Genomic Data Common (GDC) data portal. The ESTIMATE package was used to calculate tumor purity and the stromal and immune scores [27].

Statistical analysis

Statistical analyses were conducted using R (3.6.3 version) and SPSS (version 23.0) software. Graphical representations were generated using R and GraphPad Prism 8 software. The chi-square and Wilcoxon rank-sum tests were used for categorical and continuous variables, respectively. The t-test was used for data with normal distribution and homogeneous variance. The Mann-Whitney U test was used for statistical inspection if the two sets of data were not normally distributed. Multiple sets of non-normal distribution data were compared using the Kruskal-Wallis method. $P<0.05$ was considered significant.

Results

Differential gene expression of ITGAV in pan-cancers

Figure 1A shows the differential mRNA expression of ITGAV in 14 types of cancers. The

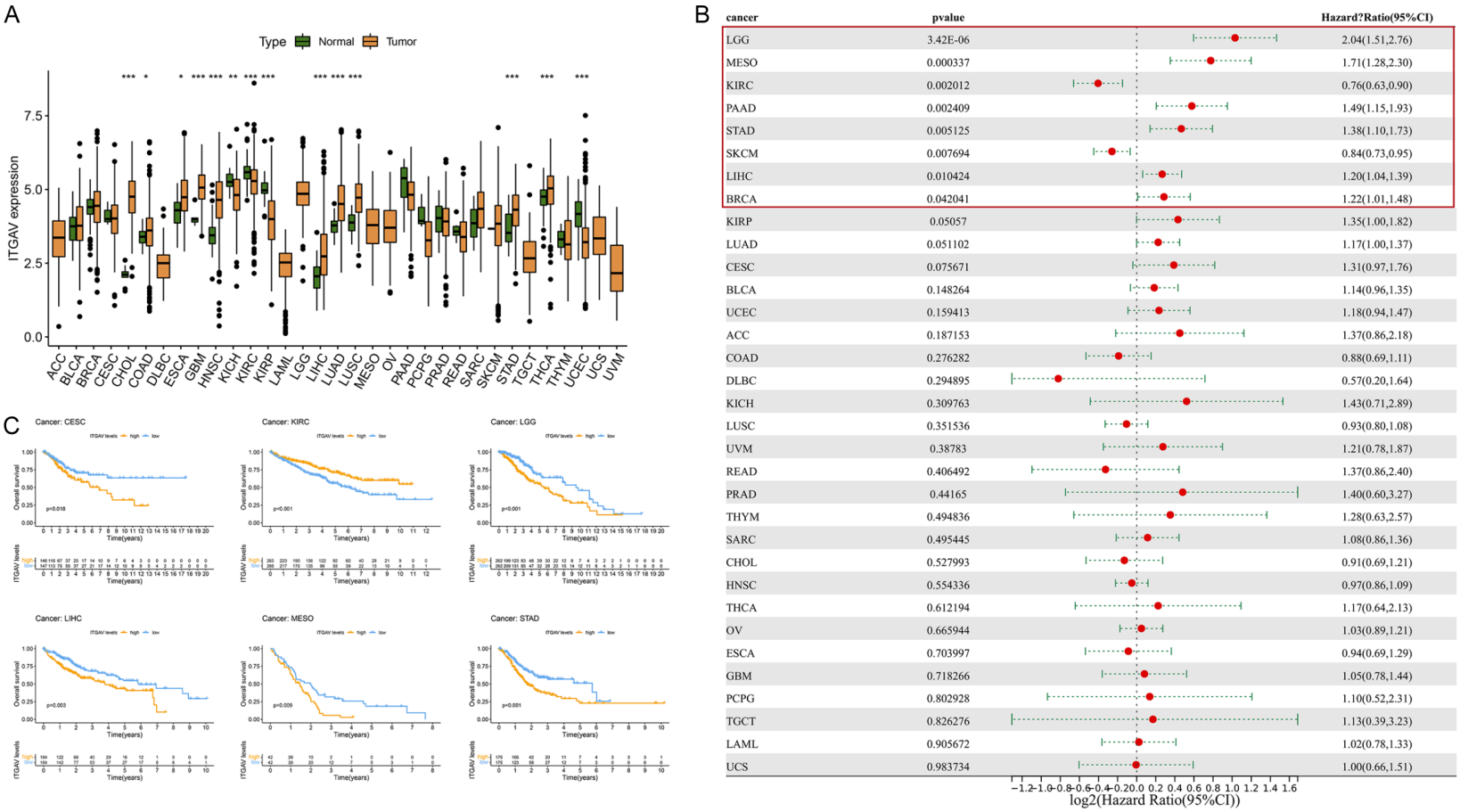

Figure 1. mRNA expression and survival KM plot of ITGAV in pan-cancer. A. mRNA expression of ITGAV in pan-cancer; B. Survival KM plot of ITGAV in pan-cancer (P<0.05); C. Univariate Cox regression analysis of ITGAV in pan-cancer. * means P<0.05, ** means P<0.01, *** means P<0.001; ACC: Adrenocortical carcinoma; BLCA: Bladder Urothelial Carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma.

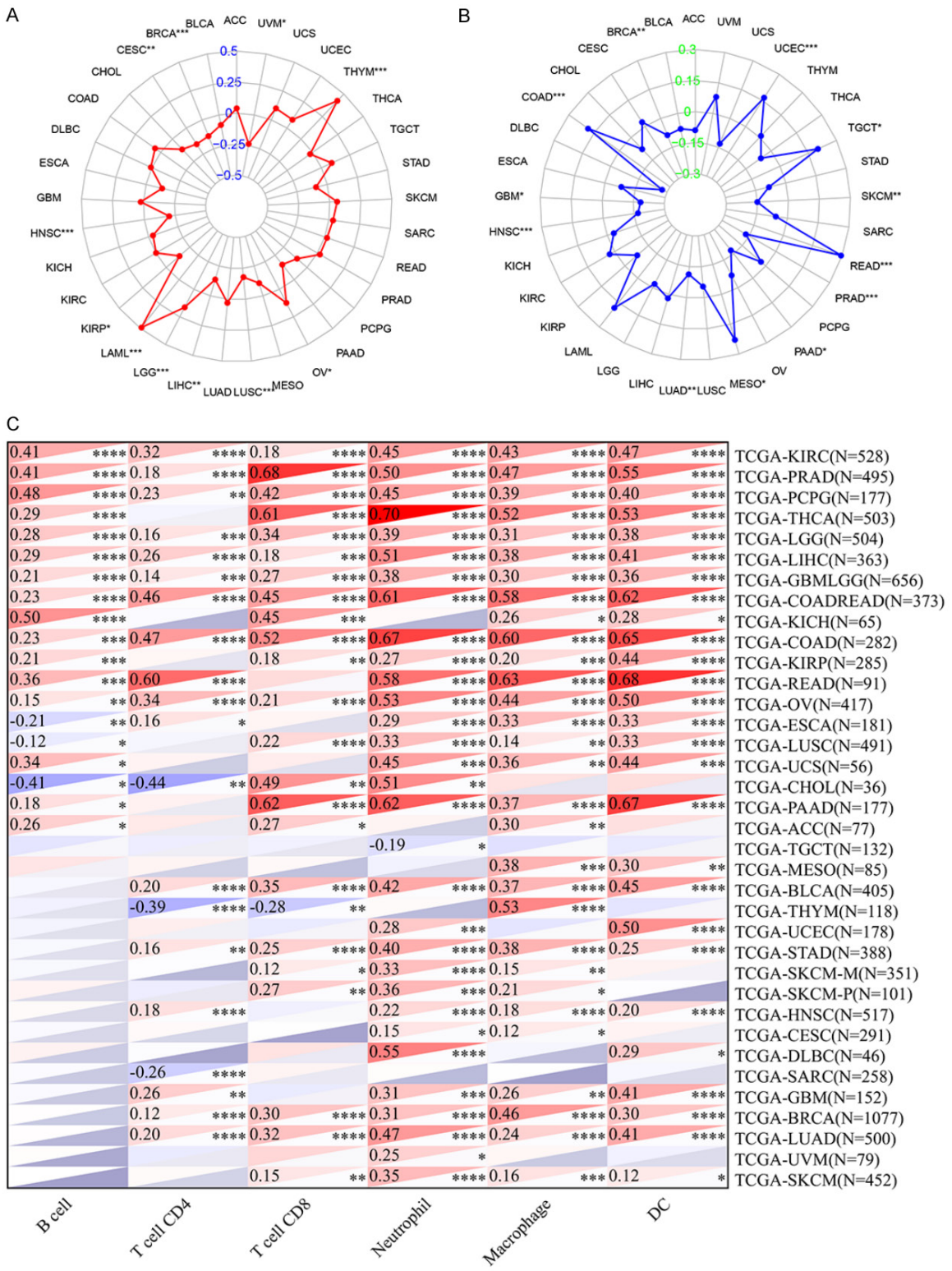

Figure 2. Correlation between ITGAV expression and MSI, TMB, and immune infiltration in six types of immune cells. A. The correlation between ITGAV expression and TMB; B. The correlation between ITGAV expression and MSI; C. The correlation between ITGAV expression an infiltration in six types of immune cells. * means P<0.05, ** means P<0.01, *** means P<0.001, **** means P<0.0001. COADREAD: Colon adenocarcinoma/Rectum adenocarcinoma Esophageal carcinoma; GBMLGG: Glioma; SKCM-M: Skin Cutaneous Melanoma Metastatic; SKCM-P: Skin Cutaneous Melanoma Primary; Other abbreviations were same as those in **Figure 1** legend.

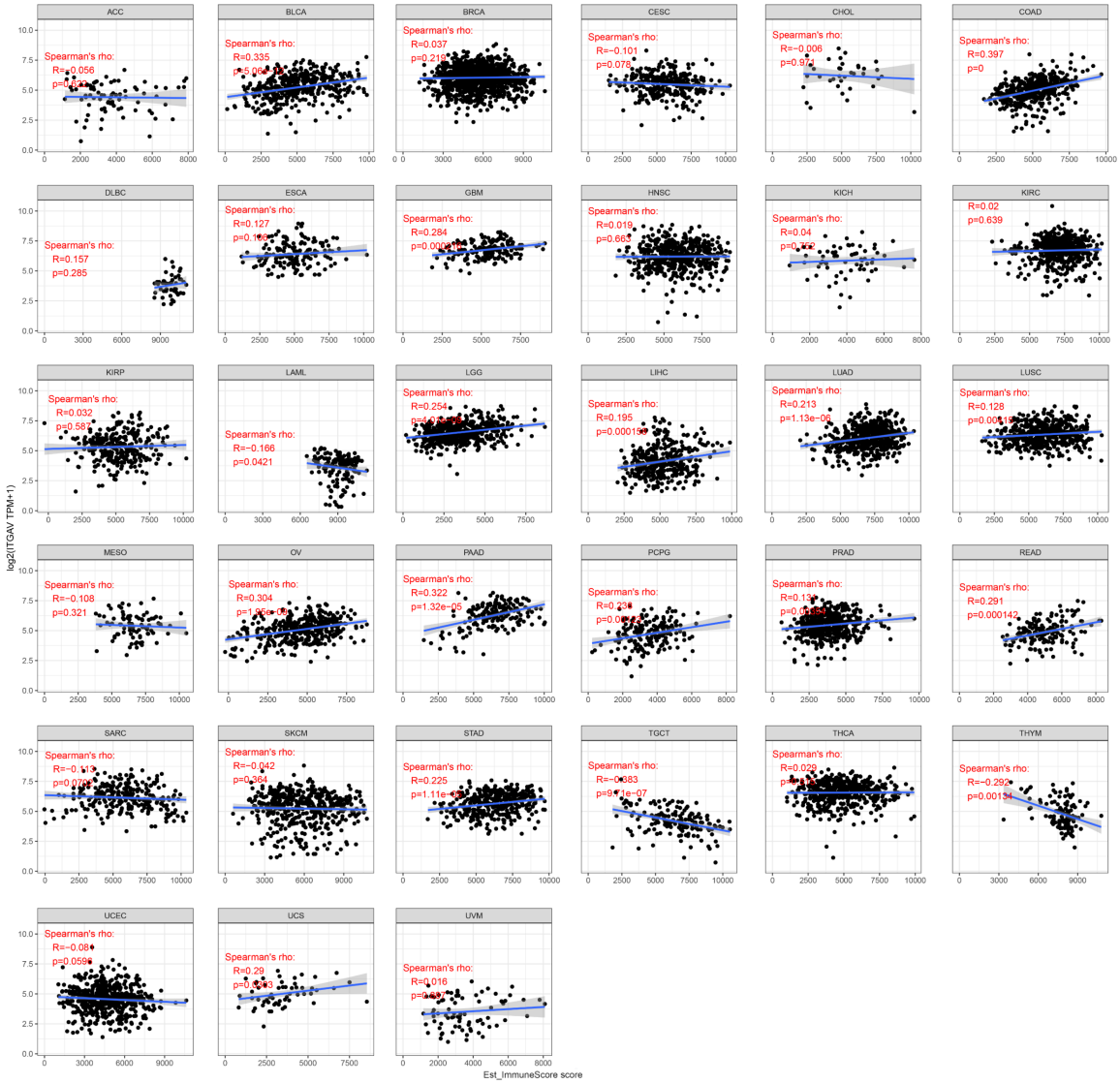

Figure 3. The correlation between ITGAV expression and immune scores in pan-cancers. DC means Dendritic cells; The abbreviations were same as those in **Figure 1** legend.

expression of ITGAV in tumor tissues was higher than that in normal tissues in ten cancers (CHOL, COAD, ESCA, GBM, HNSC, LIHC, LUAD, LUSC, STAD, and THCA). The expression of ITGAV was found to be the inverse in the other four cancers (KICH, KIRC, KIRP, and UCEC).

Relationship between ITGAV expression and OS time

Univariate Cox regression analysis of ITGAV showed that high ITGAV expression was associated with a high risk ratio in six cancers (LGG, MESO, STAD, PAAD, BRCA, and LIHC) (**Figure 1B**). It showed that lower expression of ITGAV reflected low risk in two cancers, KIRC and SKCM. The KM survival curve shows that the low expression of ITGAV in CESC, LGG, LIHC, MESO, and STAD 5 tumors predicted better patient prognosis. Contrastingly, high expression of ITGAV predicted a better prognosis in KIRC (**Figure 1C**).

Correlation between ITGAV expression and TMB, MSI, and immune infiltration

Comparing the correlation between ITGAV expression and TMB (**Figure 2A**) showed a high correlation in LAML and THYM (|R|>0.4, P<0.05) and a low correlation in the other eight tumors (|R|<0.4, P<0.05). Similarly, the correlation between ITGAV expression and MSI was

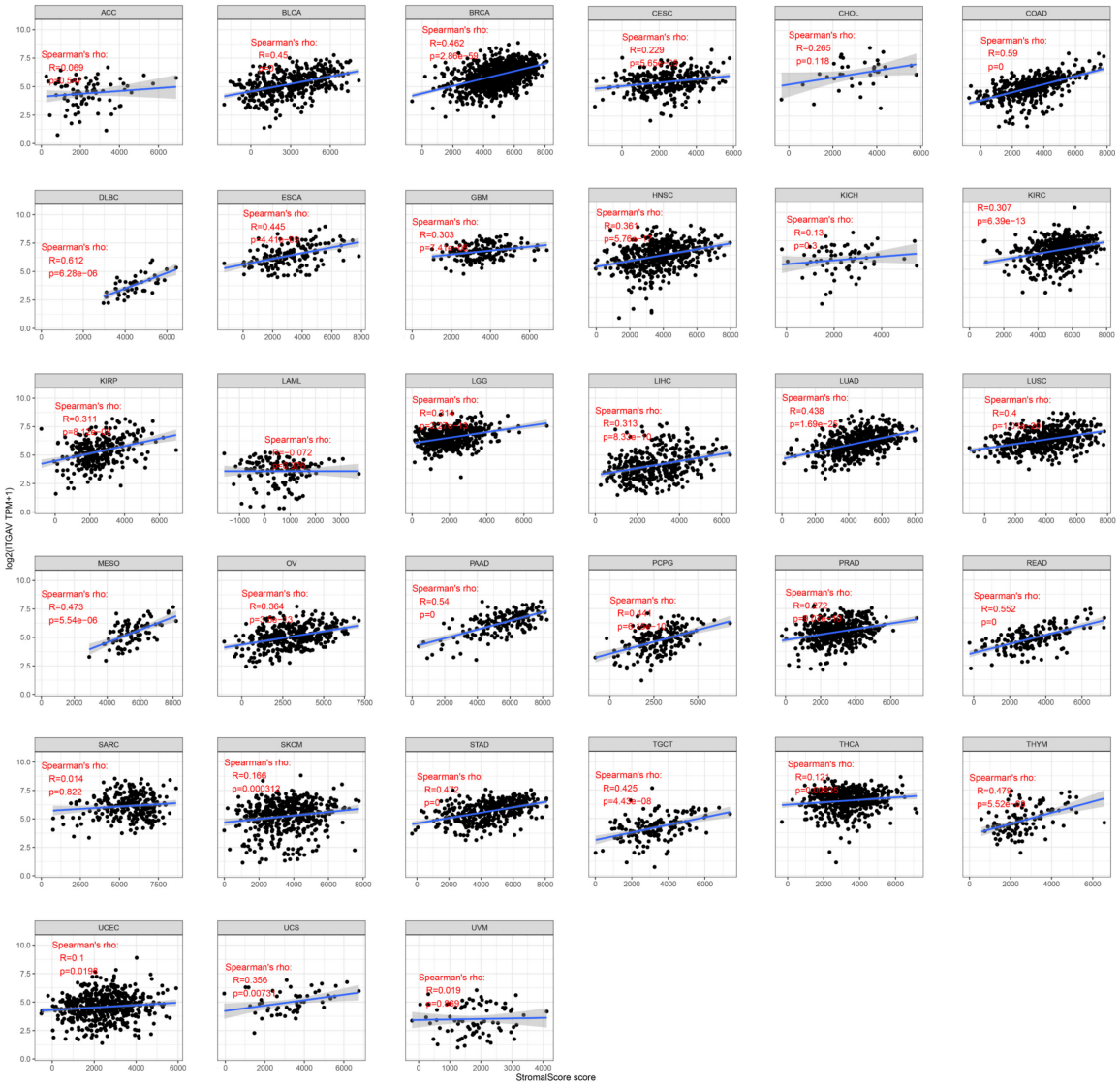

Figure 4. Correlation between ITGAV expression and stromal scores in pan-cancers. The abbreviations are the same as in **Figure 1** legend.

not high in all cancers (|R|<0.4), despite P<0.05 (**Figure 2B**).

Using TIMER, a strong correlation was observed between ITGAV expression and six types of immune cells, including B cells, CD8 T cells, CD4 T cells, macrophages, neutrophils, and dendritic cells (**Figure 2C**). In addition, the correlation between ITGAV expression and the immune score was not high in all tumor types (|R|<0.4) (**Figure 3**). However, ITGAV expression was highly correlated with the stromal score in 14 kinds of tumor (|R|≥0.4, P<0.05) (**Figure 4**).

As gastrointestinal surgeons, the authors focused on the expression set function of ITGAV in gastrointestinal cancer. Based on **Figure 1A-C**, the function of ITGAV in GC was further analyzed.

Expression of ITGAV in GC

First, the HPA website showed that ITGAV was mainly expressed in the cytoplasm (**Figure 5A**). Additionally, HPA single-cell sequencing results showed that in various GC cells, ITGAV expression was relatively high in gastric mucosal cells and macrophages, whereas that of other immune cells, such as T cells and B cells, was relatively low (**Figure 5D**).

The mRNA expression of ITGAV in GC was analyzed using the training (TCGA) and validation

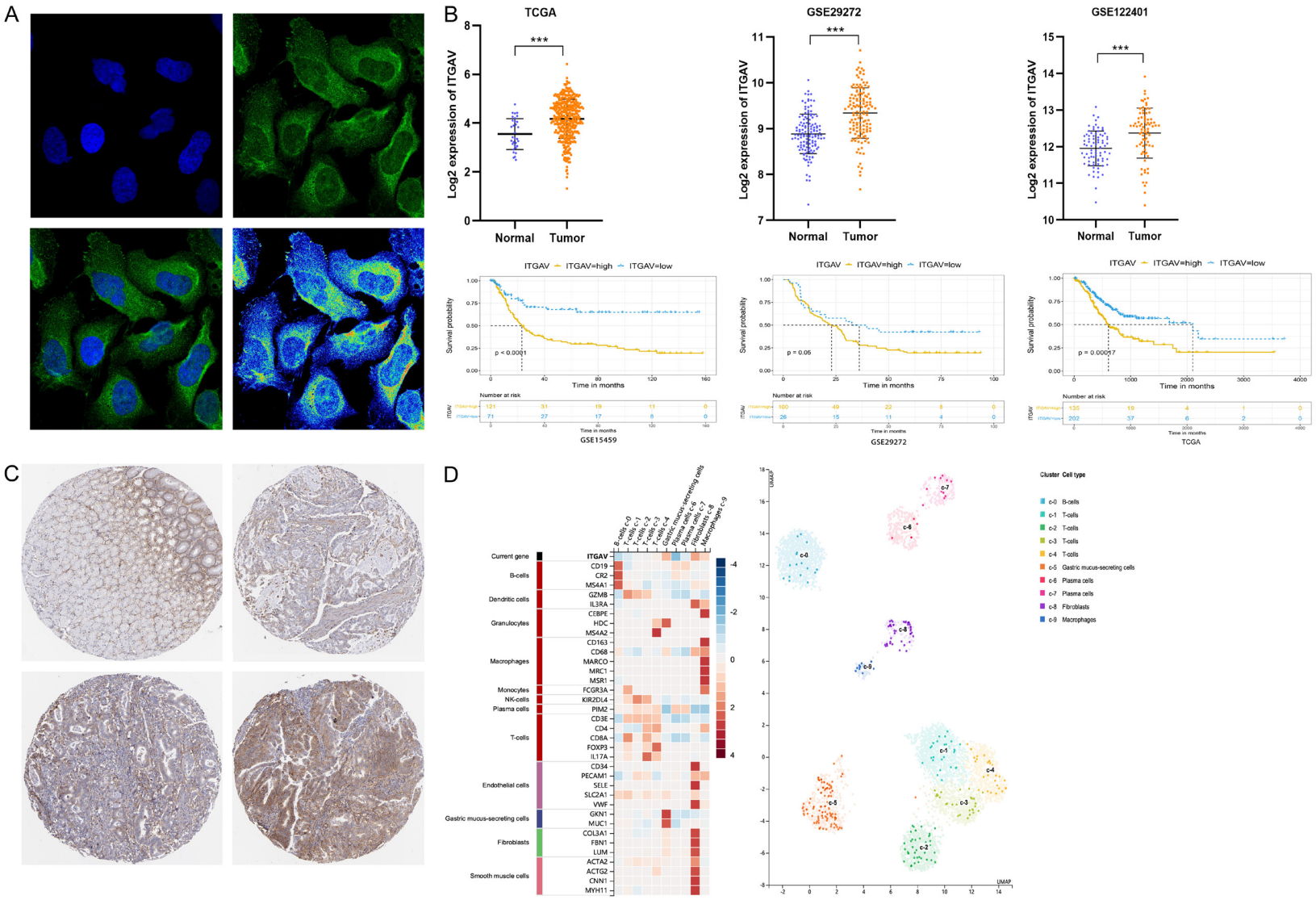

Figure 5. Validation of ITGAV expression in GC. A. The localization of ITGAV in cells: green represents ITGAV protein localization and blue represents nuclear localization; B. The expression validation of ITGAV in GC, including GSE29272, GSE122401, and TCGA data; The KM plot validation of ITGAV in GC, including GSE15459, GSE29272, and TCGA data; * means P<0.05, ** means P<0.01, *** means P<0.001; C. Immunohistochemistry showed different expression intensities of ITGAV proteins in GC, and the scale bar was 200 um; D. Single-cell data showed the expression of ITGAV in various cells, and the scale bar was 20 μm.

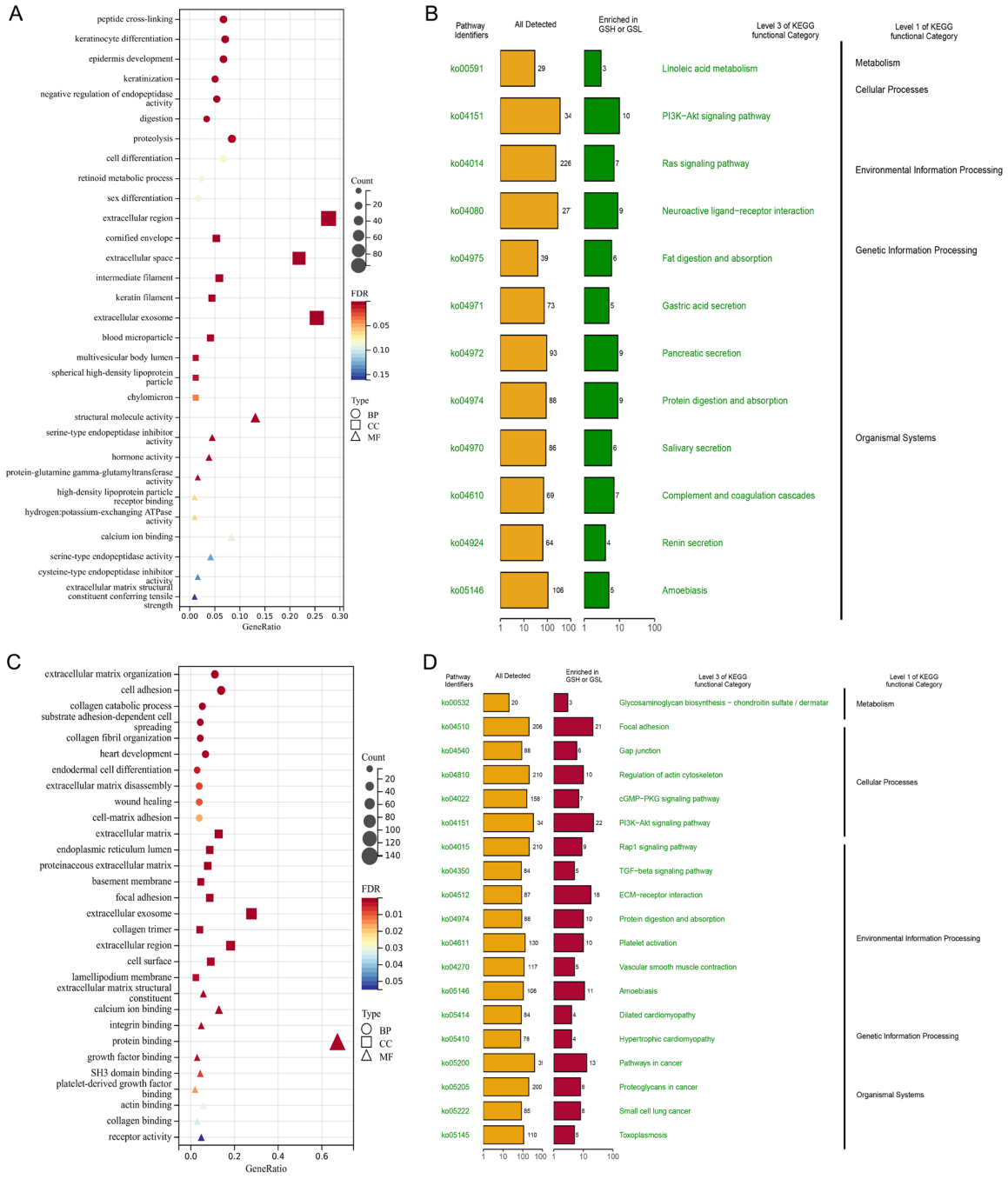

Figure 6. GO and KEGG enrichment analyses of differentially expressed and highly correlated genes. A. GO enrichment analysis of differentially expressed genes between ITGAV-high and ITGAV-low groups; B. The KEGG enrichment analysis of differentially expressed genes between ITGAV-high and ITGAV-low groups; C. The GO enrichment analysis of genes that were highly correlated with ITGAV; D. The KEGG enrichment analysis of genes that were high correlated with ITGAV.

(GSE29272, GSE122401) sets. ITGAV was highly expressed in tumor tissues in both TCGA and GEO datasets, and this result was verified by immunohistochemical results from the HPA website (**Figure 5C**). Patients with high ITGAV expression had poor clinical outcome (**Figure 5B**).

GO and KEGG analysis of differentially expressed and highly correlated genes

The best cut-off value was calculated according to ITGAV expression and divided into ITGAV high-expression and low-expression groups. Calculations showed that there were 350 down-

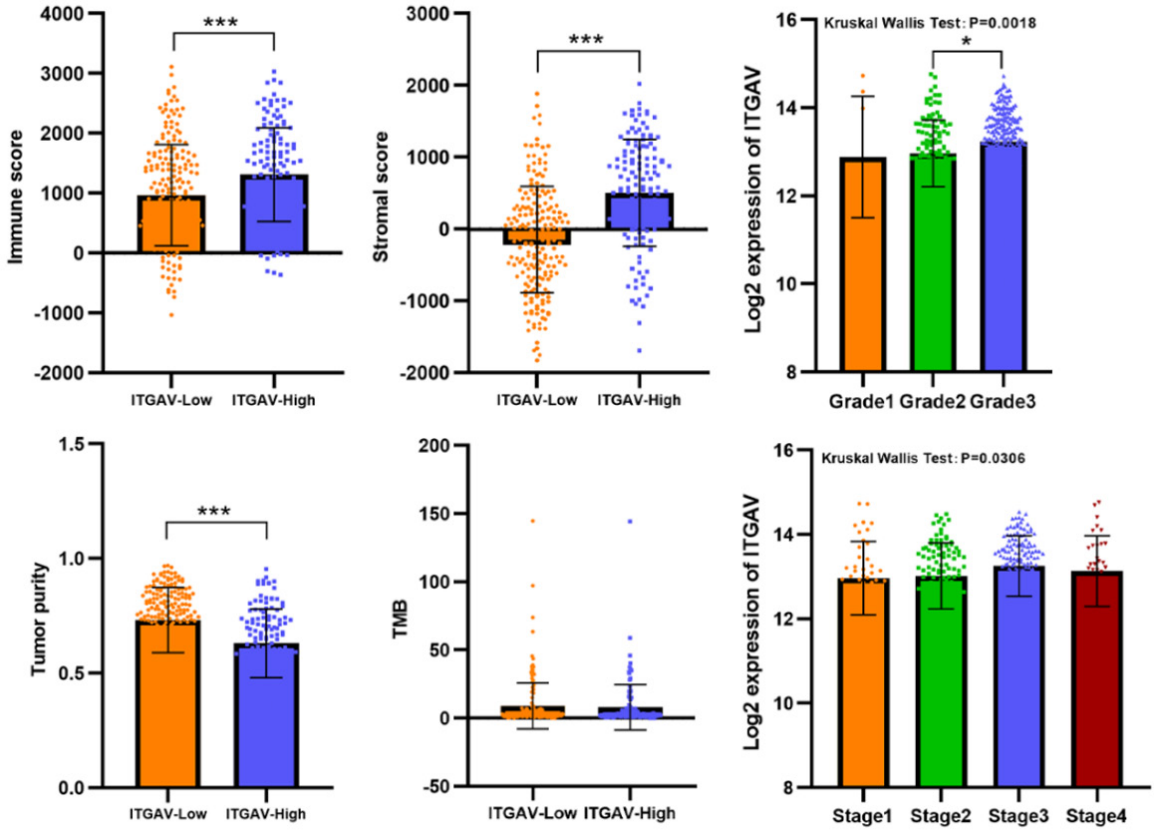

Figure 7. Correlation between ITGAV expression and immune score, stromal scores, tumor purity, TMB, stage and grade in TCGA-STAD. * means P<0.05, ** means P<0.01, *** means P<0.001.

regulated and 17 upregulated genes between the two groups. These differentially expressed genes were mainly enriched in the extracellular matrix and pathways closely related to tumor progression, such as the PI3K and RAS pathways (**Figure 6A**, **6B**).

In addition to the enrichment analysis of differentially expressed genes, the enrichment analysis of highly correlated genes (|R|>0.4, P<0.05) was also conducted. These genes were mainly positively correlated with ITGAV and closely related to cell adhesion connections as a function (**Figure 6C**, **6D**).

These results indicate that the function of genes, regardless of whether they are differentially expressed or closely related to ITGAV, plays an important role in tumor progression and prognosis.

Correlation between ITGAV and clinical characteristics in GC

In GC, high expression of ITGAV indicated that patients with higher ITGAV expression had higher immune and stromal scores but lower tumor purity (**Figure 7**). There was no obvious difference in the TMB between the groups. Regarding TNM classification, the more advanced stages seemed to have higher ITGAV expression (P=0.0306), but no significant difference was found between the two groups. Regarding grade classification, higher grades showed higher ITGAV expression, and significant differences were observed between grades 2 and 3. Therefore, in GC, ITGAV expression is closely related to clinical grade, stage, tumor purity, and prognosis. No significant differences were found in other clinical characteristics such as age and sex.

Correlation between ITGAV and miRNA

Using the starBase website, miRNAs that may regulate ITGAV expression were predicted (**Figure 8**). Through calculating the correlation between these miRNAs and ITGAV, the absolute correlation values of seven miRNAs were shown to be greater than 0.3 with P<0.05. All

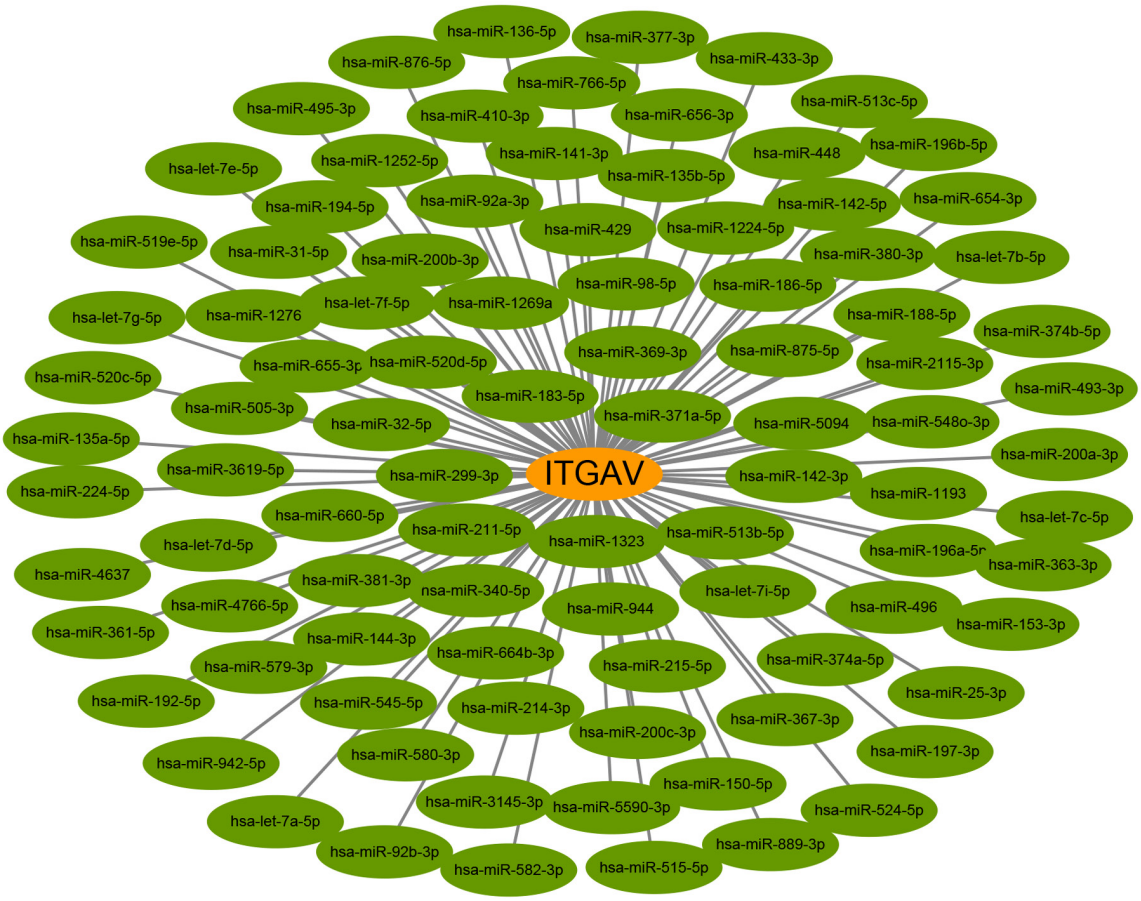

Figure 8. miRNA network correlated with ITGAV.

seven miRNAs were negatively correlated with ITGAV expression, and their expression was higher in tumor tissues than in normal tissues. High expression of the seven miRNAs showed better prognosis and survival in GC (**Figure 9**).

LncRNA-miR-92a-3p-ITGAV ceRNA network

The above results show that miR-92a-3p had the highest correlation with ITGAV; therefore, miR-92a-3p was selected for subsequent ceRNA network establishment (**Figure 10A**). A total of 94 lncRNAs associated with miR-92a-3p were identified using starBase. Using $P< 0.05$ and $|R|>0.3$ to filter these results, four lncRNAs were found that were closely negatively related to miR-92a-3p, and they showed a positive relationship with ITGAV expression (**Figure 10C**). The expression of the four lncRNAs in tumor tissues was significantly lower than that of normal tissues (**Figure 10D**). Except for LINC01550, high expression of the other three lncRNAs predicted better prognosis in GC (**Figure 10B**).

Thus, both the miRNA and lncRNA selected here significantly affected the prognosis of GC patients.

Discussion

Gastric cancer (GC) has high morbidity and mortality rates. Research on GC has been progressing continuously from macro to spectator [28]. The search for new therapeutic and prognostic targets is important in GC research.

Integrins are composed of a variety of α and β subunits, which can form different integrin proteins and serve as receptors for proteins such as cytokines and fibronectin [29, 30]. They can identify and bind to the RGD sequence in many ligands [31, 32]. Alpha-v-beta-3, 6, 8 (Avβ3, avβ6 and avβ8), formed by ITGAV and ITGB3, 6, 8-encoding products, can bind to CX3C, neuregulin 1 (NRG1), fibroblast growth factor 1 (FGF1), and other factors to activate kinds of signaling pathways, which play important roles in tumor progression and prognosis [33-37].

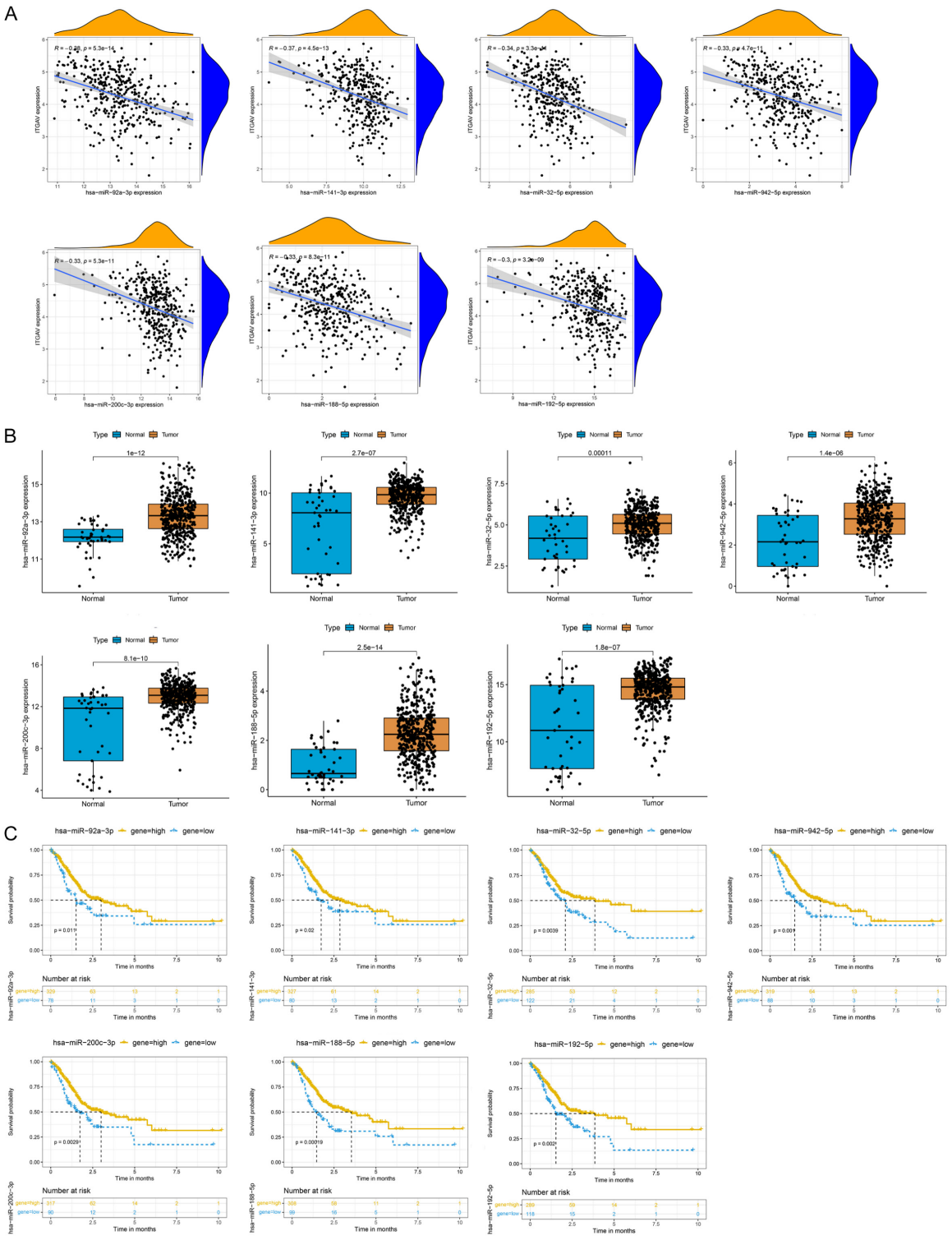

Figure 9. Correlation, expression, and KM plots of miRNA (|R|>0.3, P<0.05) in GC. A. The correlation of miRNA (|R|>0.3, P<0.05) in GC; B. The expression of miRNA (|R|>0.3, P<0.05) in GC; C. The KM plots of miRNA (|R|>0.3, P<0.05) in GC.

The present study showed, first, from the work on pan-cancer, that overexpression of ITGAV occurred in various types of tumors, and high expression of ITGAV reflected poor prognosis in

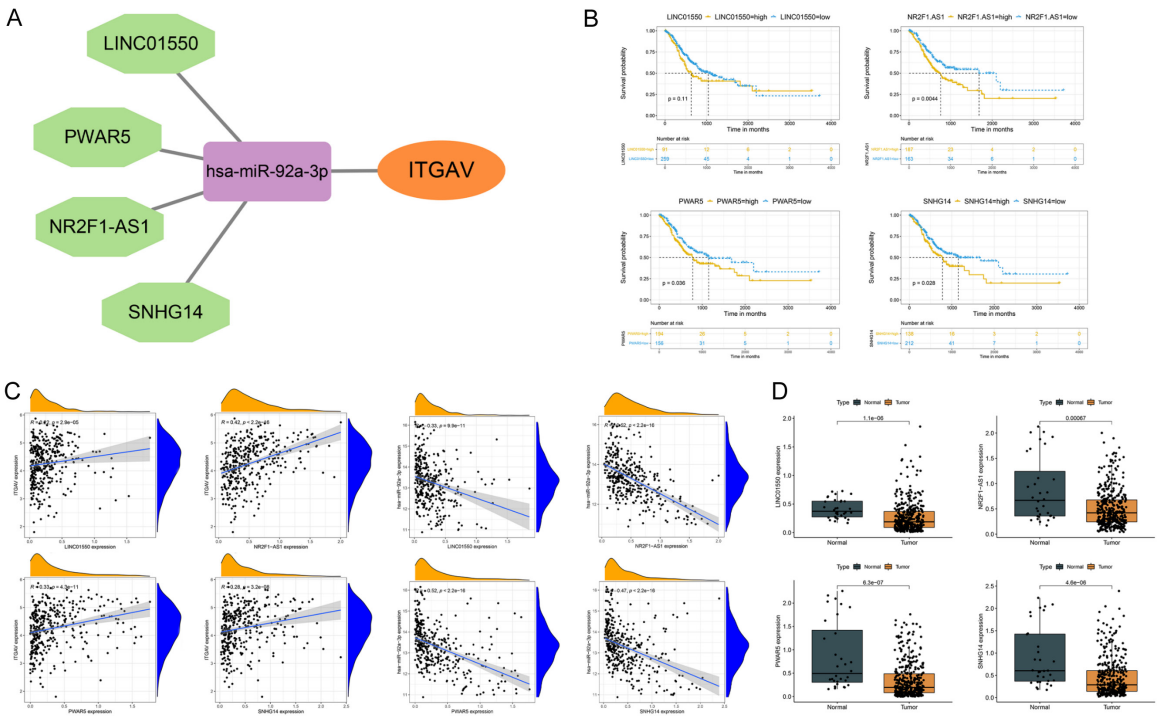

Figure 10. Correlation, expression, and KM plots of LncRNA. A. lncRNA-miR-92a-3P-ITGAV ceRNA network; B. The KM plots of lncRNA in GC; C. The correlation between lncRNA and miR-92a-3p, lncRNA, and ITGAV in GC; D. Expression of lncRNA in GC.

six cancers. Both mRNA and protein expression levels were higher in GC tissues than in normal tissues. These results were consistent with those of previous pan-cancer studies. In the clinic, GC patients with high ITGAV expression had relatively advanced clinical stages and high grades, with poor prognosis and survival. In addition, patients with high ITGAV expression had lower tumor purity. Tumor purity is an important factor that affects tumor progression and prognosis [38]. Studies have shown that the higher the tumor purity, the lower the impurity components of the tumor, such as mesenchymal and immune cells, and the better the prognosis of patients [39]. In addition, the higher the purity of the tumor, the more likely the targeted drugs are to act on the tumor cells and the better the therapeutic effect. Patients with high ITGAV expression showed lower purity, which could result in a worse prognosis for survival to some extent.

The ceRNA network is an effective means of studying the mechanisms of tumor progression and prognosis [40]. miRNAs and lncRNAs are factors that regulate the expression of related target genes. In the present study study, ITGAV-related miRNAs were predicted through a starBase online website and seven miRNAs with a high correlation between hormone ITGAV and miRNA ($|R|>0.4$, $P<0.05$) were found. Through expression and prognosis analyses, all seven miRNAs were found to be negatively correlated with ITGAV, and their expression in GC tissues was lower than that in normal tissues. In addition, high expression of the seven miRNAs predicted better survival prognosis in patients with GC. The miRNA with the highest correlation, miR-92a-3p, was selected to predict the lncRNAs that modulate miRNAs. Four significantly correlated lncRNAs were screened using the same criteria. The expression of these four lncRNAs was positively correlated with ITGAV, and their expression in tumor tissues was significantly higher than that in the adjacent normal tissues. Except for LINC01550, the high expression of the other three lncRNAs was associated with poor prognosis in GC. Therefore, an lncRNA-miRNA-ITGAV ceRNA network was constructed.

Studies have shown that the lncRNA SNHG14 can promote the occurrence and development of GC by targeting the miR-145/SOX9 axis [41].

Similarly, studies have also shown that NR2F1-AS1 can promote the progression of GC through the miR-92a-3p/VAMP7, miR-493-5p/MAP3K2, or the miR-190a/PHLDB2 axes [42-44]. Thus, the lncRNAs in the ceRNA network predicted by this study play a role in the progression and prognosis of GC, and their correlation with ITGAV shows that ITGAV may play an important role in the study of GC. Intervention in the function of ITGAV in tumor progression and prognosis through regulating the expression of related lncRNAs or miRNAs could be considered.

Of course, there are some shortcomings in our article. Although TCGA and GEO data were used for verification, it is still lacking of our own sample data for verification. In addition, the mechanism for the function of ITGAV on GC is still vague, which would be explored by vitro experiments later. In summary, ITGAV is an important prognostic factor for patients with GC. According to the ceRNA network, the expression of the ITGAV gene and protein can be regulated by intervening with miRNAs and lncRNAs upstream of ITGAV to regulate GC progression and prognosis.

Acknowledgements

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Disclosure of conflict of interest

None.

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