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Original Article

The prognostic and immune infiltration role of ITGB superfamily members in non-small cell lung cancer

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Abstract: Purpose: We aimed to explore the prognostic value of integrin-β superfamily members (ITGBs) and their role in immune cell infiltration in non-small cell lung cancer (NSCLC). Materials and Methods: Study cases were acquired from The Cancer Genome Atlas database and The Human Protein Atlas. We then used R package and several online tools to analyze and visualize the roles of ITGBs in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Results: We found that ITGBs were differentially expressed in NSCLC. In LUAD, high expression of ITGB1 and ITGB4 was an independent risk factor for poor prognosis, and ITGB7 was an independent protective factor for overall survival; in LUSC, high expression of ITGB1, 3, 5, and 6 was associated with poor prognosis, and ITGB8 was an independent protective factor for disease-specific survival. Protein-protein interaction networks for the most associated co-expressed genes revealed the following target genes of ITGBs: PTPRC, ITGAM, and ITGB2 in LUAD and FN1, PTPRC, and ITGB2 in LUSC. Gene ontology analysis revealed that functions related to adhesion, junction, and binding were highly enriched in LUAD and LUSC. ITGBs were significantly associated with immune cell infiltration and the expression of immunomodulation-related genes in LUAD and LUSC. Conclusion: ITGBs were differentially expressed in NSCLC. ITGB1, 4, and 7 and ITGB1, 3, 5, 6, and 8 were found as prognostic markers in LUAD and LUSC, respectively. ITGBs were significantly associated with immune cell infiltration and the expression of immunomodulation-related genes.

Keywords: ITGBs, NSCLC, LUAD, LUSC, prognosis, immune infiltration

Introduction

Although great efforts have been made to study and control lung cancer, it remains the most common cause of cancer-related deaths [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases, with lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) as the most common subsets [2]; therefore, it is crucial to identify the genes involved in promoting the progression of LUAD and LUSC.

Integrins are composed of α and β subunits, and constitute a large family of cell surface receptors [3]. Through binding to the extracellular matrix (ECM), integrins participate in cell survival, proliferation, and migration [3, 4]. The deregulation of integrin signaling enables tumor cells to proliferate, invade, and survive [5]. Moreover, integrins can promote the expansion and self-renewal of cancer stem cells [6, 7], disrupt epithelial adhesion [8, 9], foster development of the tumor microenvironment (TME) [10], and encourage resistance to immune-targeted therapies [11-13]. Therefore, integrins play a vital role in tumor neogenesis, progression, colonization, recurrence, and resistance to therapy. The integrin-β (ITGB) superfamily comprises eight members, ITGB1-8 [4]. High expression of ITGB1, 4, and 8 is related to the progression and poor prognosis of lung cancer [14-16]. However, the roles of other ITGB superfamily members (ITGBs) in the prognosis and immune infiltration of NSCLC remain poorly understood. Furthermore, whether the role of ITGBs in prognosis and immune infiltration differ between LUAD and LUSC remains unclear.

Here, we conducted a systematic bioinformatics analysis to identify the gene expression levels, prognostic value, interactions, and related

infiltrated immune cells of ITGBs in LUAD and LUSC. We further clarify the pathogenesis and possible therapeutic targets of NSCLC.

Materials and methods

Data source

The case information of mRNA expression profiles and clinical features was acquired from The Cancer Genome Atlas (TCGA) and downloaded from the University of California Santa Cruz Xena (UCSC Xena; https://xena.ucsc.edu/) platform. Immunohistochemistry (IHC)-based protein expression patterns were acquired from The Human Protein Atlas (HPA; https://www.proteinatlas.org/). Genetic variation data were obtained from cBioPortal (http://www.cbioportal.org). Promoter methylation data were obtained from the University of Alabama at Birmingham Cancer data analysis Portal (UALCAN, http://ualcan.path.uab.edu/analysis-prot.html, TCGA dataset). Data regarding the relationship between ITGBs and immune cell infiltration as well as immunomodulation-related gene expression were obtained from the Tumor Immune Estimation Resource (TIMER, version 2, timer.cistrome.org).

ITGBs expression level in pan-cancer, LUAD, and LUSC

We downloaded RNA-seq data (normalized as transcripts per million reads, TPM) of ITGBs from pan-cancer, LUAD, and LUSC datasets on the UCSC Xena platform, and then analyzed and visualized the data using the "ggplot2" package in R. Unpaired samples t-test was used to compare the expression level of ITGBs between the normal and tumor groups; statistical significance was set at $P < 0.05$.

Validate the protein expression of ITGBs in LUAD and LUSC

To verify the expression of ITGBs at the histological level, IHC-based protein expression patterns in normal human lung, LUAD, and LUSC tissues were acquired from the HPA.

ITGBs and pathological stages

Gene expression profiling interactive analysis (GEPIA) is a web server that integrates TCGA and genotype-tissue expression (GTEx) (http://gepia.cancer-pku.cn/) data. We used GEPIA to assess the correlation between ITGBs and pathological stages; statistical significance was set at $P < 0.05$.

Survival and prognostic analysis

Clinical datasets from TCGA were used to analyze the survival outcomes of patients with LUAD and LUSC. With 50% as the cutoff value, samples were divided into low and high groups. Overall survival (OS) and disease-specific survival (DSS) were used to evaluate survival outcomes. We performed Kaplan-Meier analysis with Cox regression using the "survminer" and "survival" packages in R. Univariate analyses were conducted using the "survival" package in R. Significant variables in univariate Cox regression analysis ($P < 0.1$) were subjected to a multivariate Cox regression model; statistical significance was set at $P < 0.05$.

Genetic variation

We collected data of 586 LUAD and 511 LUSC samples from TCGA and analyzed and visualized their genetic variation as well as the impact of genetic variation on OS using cBioPortal (http://www.cbioportal.org).

Correlation analyses

For correlation analysis between every pair of ITGBs, expression data were tested using Pearson's correlation coefficient. The R package "ggplot2" was used to analyze and visualize the results; statistical significance was set at $P < 0.05$.

Co-expression heatmap and construction of protein-protein interaction (PPI) network

After being downloaded from TCGA, the co-expressed genes were ranked according to their co-expression correlation values with ITGBs. The top 20 genes that were significantly correlated with ITGBs were extracted to plot heatmaps in R using the "ggplot2" package. To explore the extent of interactions between the proteins expressed by these genes, the PPI network was constructed using STRING (https://cn.string-db.org, main parameters: network type: full STRING network, meaning of network edges: evidence, active interaction source: Textmining, Experiments, Databases, Co-ex-

pression, Neighborhood, Gene Fusion and Co-occurrence, minimum required interaction score: Medium confidence [0.400], max number of interactors to show: 1st shell [none/query proteins only]), and Cytoscape.

Functional annotation of ITGBs and the associated genes

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on ITGBs and the top five most relevant genes in R using the "ggplot2" and "clusterProfiler" packages, Fisher's exact *P*-value was corrected using the Benjamini-Hochberg (BH) method; statistical significance was set at *P* adj < 0.05 and q value < 0.2.

Relationship of ITGBs with immune cell infiltration and expression of immunomodulation-related genes

We evaluated the relationship of ITGBs with immune cell infiltration and expression of immunomodulation-related genes using TIMER2.

Results

ITGB expression levels in pan-cancer data

We evaluated the pan-cancer mRNA expression of ITGBs from TCGA and GTEx (**Figure 1**). The analysis indicated that ITGB1 expression was upregulated in 16 tumors and downregulated in six tumors. ITGB2 expression was upregulated in 22 tumors and downregulated in four tumors. ITGB3 expression was upregulated in eight tumors and downregulated in 18 tumors. ITGB4 expression was upregulated in 23 tumors and downregulated in six tumors. ITGB5 expression was upregulated in 17 tumors and downregulated in nine tumors. ITGB6 expression was upregulated in 20 tumors and downregulated in seven tumors. ITGB7 expression was upregulated in 18 tumors and downregulated in four tumors. ITGB8 expression was upregulated in 19 tumors and downregulated in nine tumors ($P < 0.05$).

Gene expression and validation of ITGBs in LUAD and LUSC

Owing to the scarcity of RNA-seq data from matched paracancerous tissues in TCGA-LUAD and TCGA-LUSC data, we acquired RNA-seq data from 288 normal lungs from the GTEx project. Finally, 515 LUAD cases matched with 347 controls (59 paracancerous tissues, 288 normal lung tissues), and 498 LUSC cases matched with 338 controls (50 paracancerous tissues and 288 normal lung tissues) were included in the analysis (**Figure 2**). In LUAD, high expression of ITGB4, 6, 7, and 8 and low expression of ITGB2, 3, and 5 were observed ($P < 0.05$). In LUSC, high expression of ITGB4, 5, and 8 and low expression of ITGB1, 2, 3, 6, and 7 were observed ($P < 0.05$).

To verify the expression of ITGBs at the histological level, IHC-based protein expression patterns in normal human lung (N), LUAD, and LUSC tissues were obtained from the HPA (**Figure 3**). These results validated the expression of ITGBs in LUAD and LUSC (except for ITGB7). IHC-based protein expression revealed that, ITGB4, 6, and 8 were upregulated, whereas ITGB2, 3, and 5 were downregulated in LUAD; ITGB4, 5, and 8 were up-regulated, whereas ITGB1, 2, 3, and 6 were downregulated in LUSC.

ITGB expression in different pathological stages

To identify whether ITGBs are differentially expressed among pathological stages, we analyzed the correlations between the expression of ITGBs and the pathological stages in LUAD and LUSC using GEPIA (**Figure 4**). The results revealed that ITGB4, 6, and 8 showed significantly differential expression among various pathological stages of LUSC ($P < 0.05$, **Figure 4B**). No significant differences were observed in the expression of other ITGBs in LUSC and in all the ITGBs in LUAD ($P > 0.05$, **Figure 4A**, **4B**).

The prognostic value of ITGBs in LUAD and LUSC

To thoroughly investigate the impact of ITGBs on the survival and prognosis of LUAD and LUSC, we chose OS and DSS as the prognostic indicators. In LUAD (**Figure 5A**), high expression of ITGB1 and 4 was related to decreased OS, whereas ITGB7 was related to increased OS ($P < 0.05$), and ITGB4 was related to decreased DSS ($P < 0.05$). In LUSC (**Figure 5B**), high expression of ITGB1, 3, 5, and 6 was associated with decreased OS ($P < 0.05$). ITGB1 was related to decreased DSS, whereas ITGB8 was

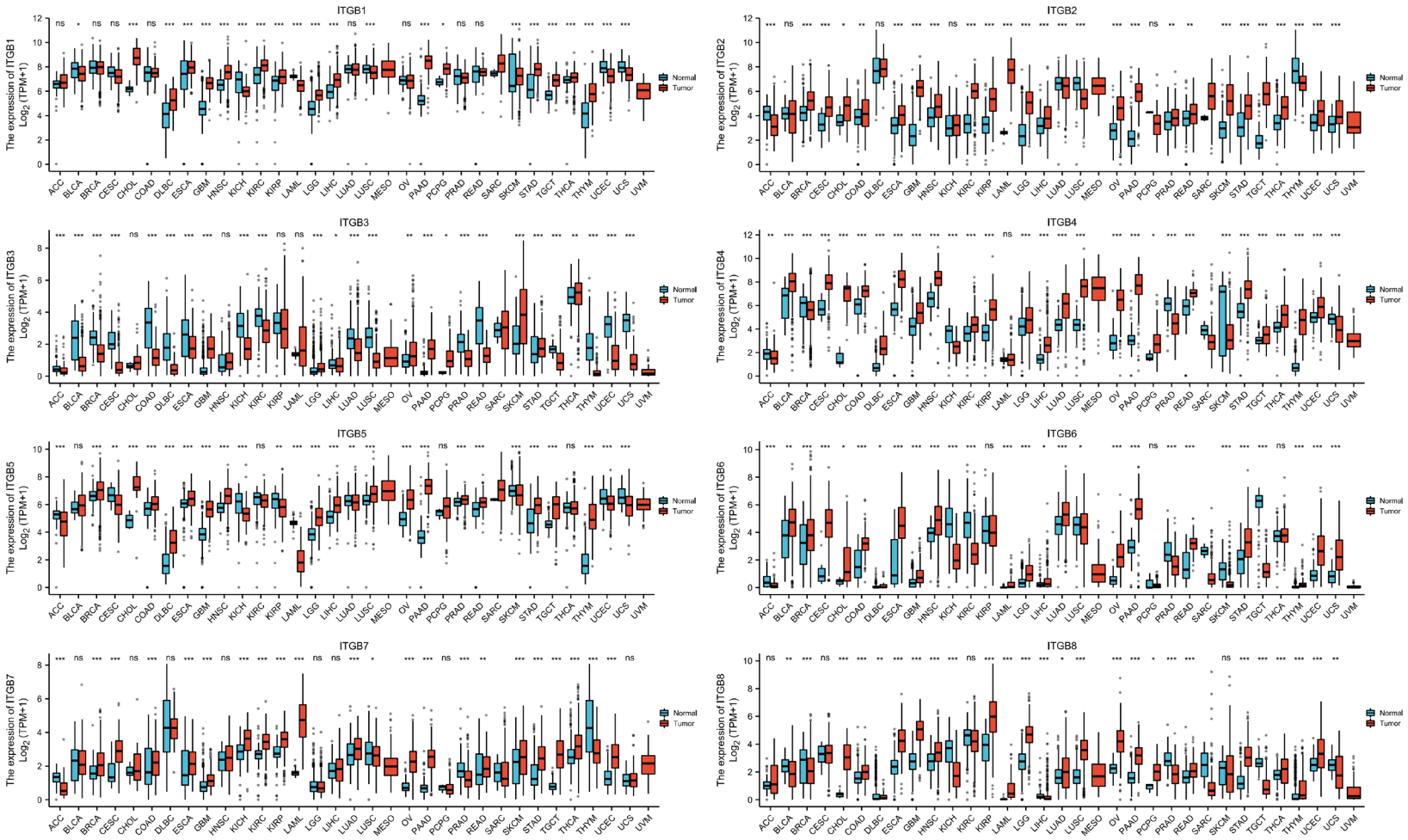


Figure 1. Expression level of ITGBs in pan-cancer data. ns, no statistical significance; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

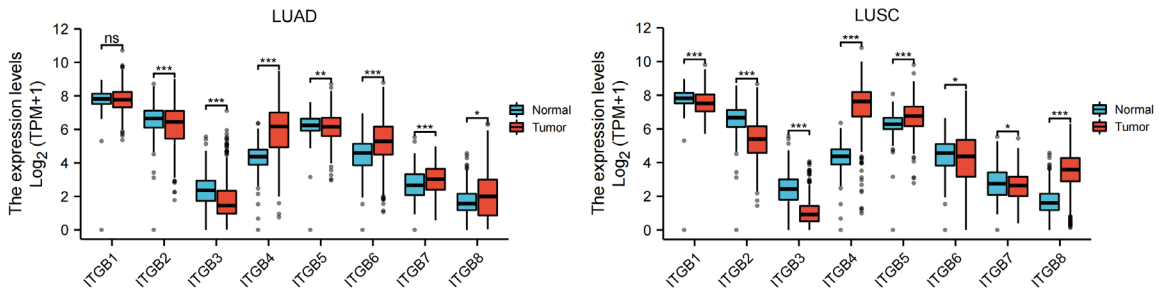


Figure 2. Expression level of ITGBs in LUAD and LUSC. ns, no statistical significance; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

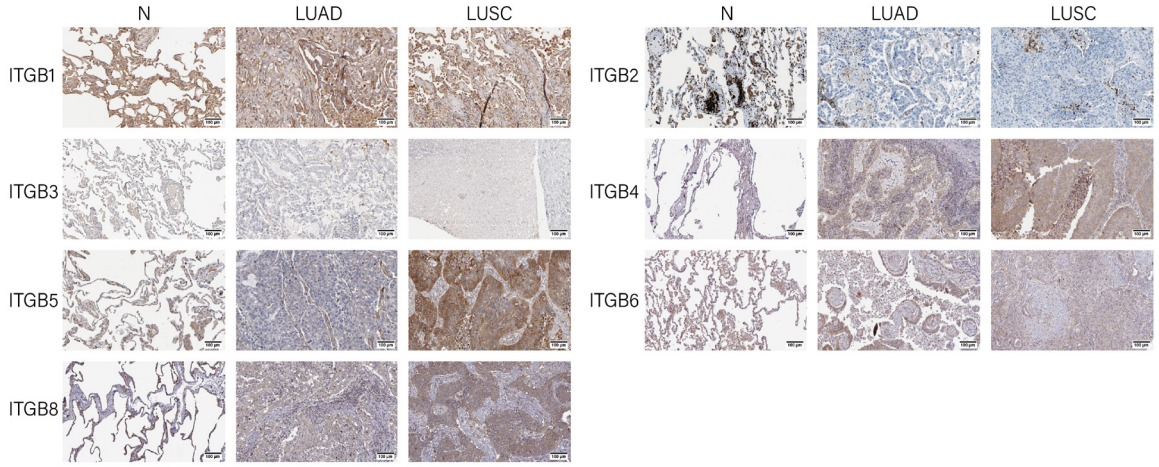


Figure 3. Validation of ITGB protein expression in LUAD and LUSC. N, normal human lung tissue; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

related to increased DSS ($P < 0.05$). The expression of other ITGBs had no significant effect on OS and DSS in either LUAD or LUSC ($P > 0.05$).

Univariate and multivariate COX regression analyses were conducted to explore whether ITGBs are independent risk factors for the prognosis of LUAD and LUSC. We found that, for LUAD (**Table 1**), ITGB1 and 4 were independent risk factors for decreased OS, whereas ITGB7 was an independent protective factor for OS ($P < 0.05$) and ITGB4 was an independent risk factor for decreased DSS ($P < 0.05$). For LUSC (**Table 2**), ITGB8 was an independent protective factor for DSS ($P < 0.05$), and none of the ITGBs were an independent risk factor for OS ($P > 0.05$).

Genetic variation of ITGBs in LUAD and LUSC

The genetic variation of ITGBs was explored using the cBioPortal database (**Figure 6**). The results showed that 23.11% (116/502) of the LUAD cases and 16.67% (86/516) of the LUSC cases harbored genetic variations. Amplification is the most frequent alteration in both LUAD and LUSC (**Figure 6A**). We then investigated the variation in ITGBs in LUAD and LUSC and found that ITGB8 (8%) and ITGB5 (11%) were the most frequently altered in LUAD and LUSC, respectively (**Figure 6B**, **6C**). However, no significant effect of genetic variation was observed on OS in LUAD and LUSC (**Figure 6D**, **6E**) ($P > 0.05$).

Promoter methylation level of ITGBs in LUAD and LUSC

Gene expression can be regulated at different levels [17], such as post-translational modifications [18] and chemical modifications of nucleobases [19]. Methylation is one of the ways in which nucleobases are chemically modified; genes can be silenced and reactivated by the methylation and demethylation of cytosines in

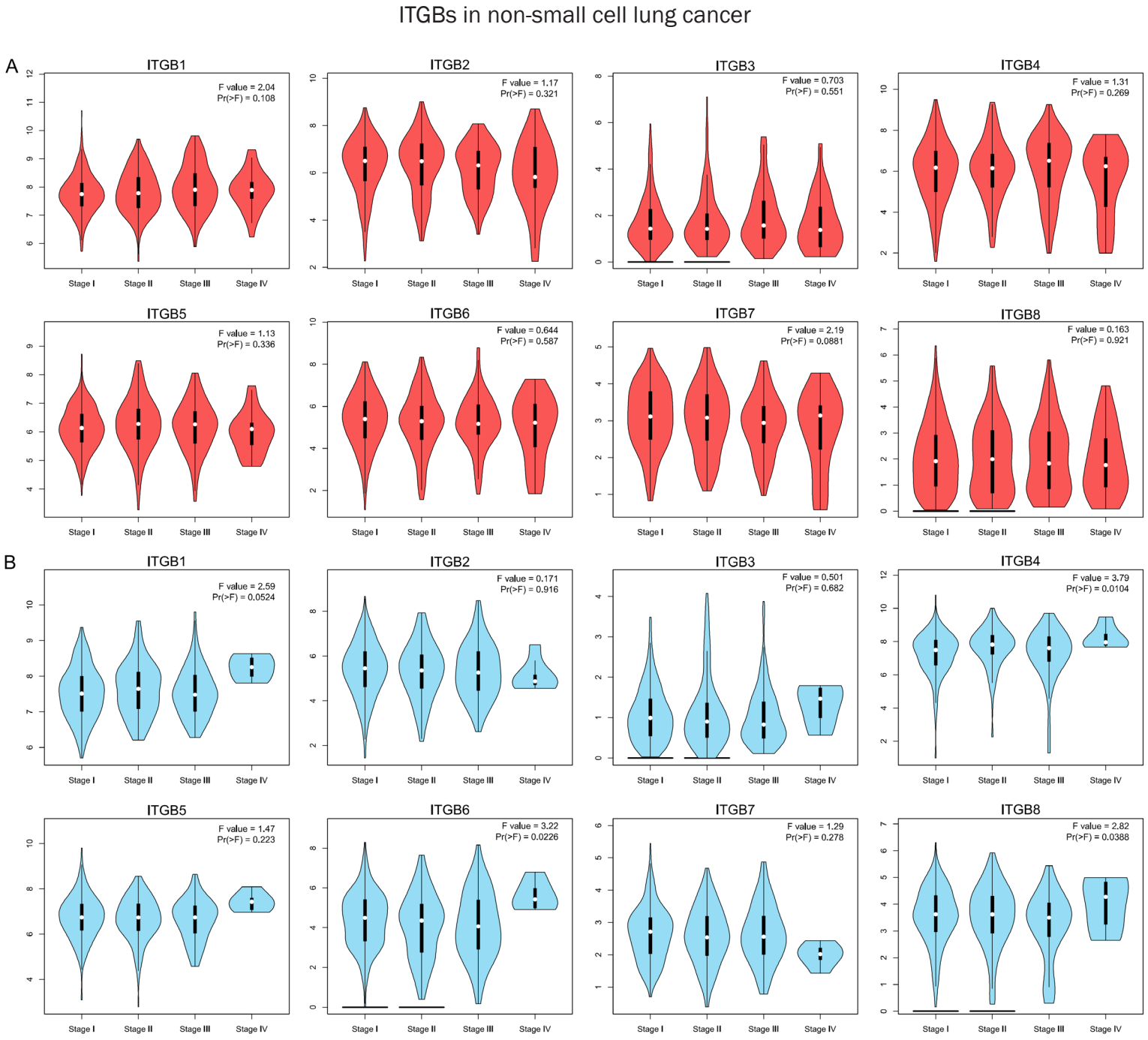
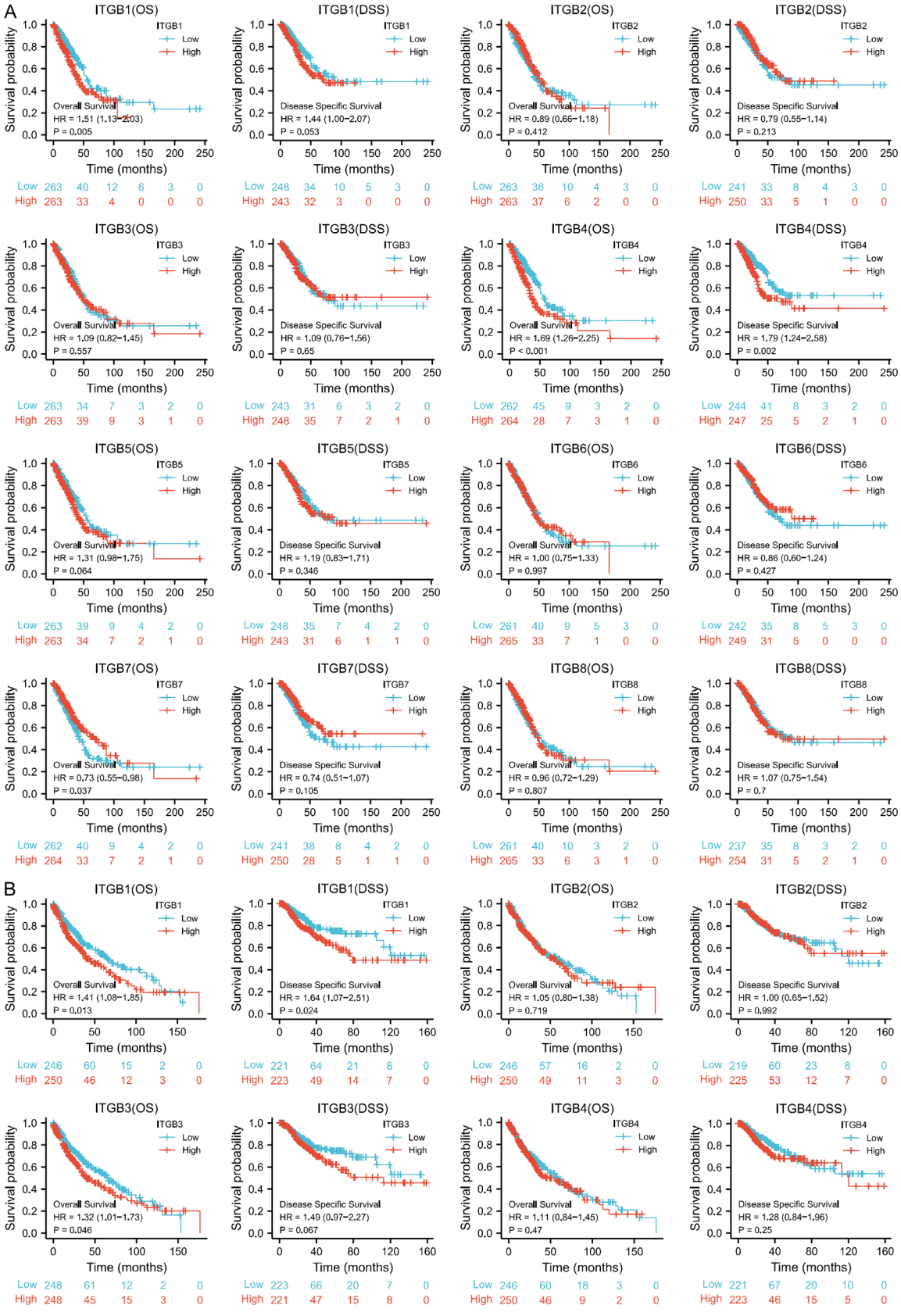

ITGBs in non-small cell lung cancer
A
ITGB1
F value = 2.04
Pr(>F) = 0.108
ITGB2
F value = 1.17
Pr(>F) = 0.321
ITGB3
F value = 0.703
Pr(>F) = 0.551
ITGB4
F value = 1.31
Pr(>F) = 0.269
ITGB5
F value = 1.13
Pr(>F) = 0.336
ITGB6
F value = 0.644
Pr(>F) = 0.587
ITGB7
F value = 2.19
Pr(>F) = 0.0881
ITGB8
F value = 0.163
Pr(>F) = 0.921
B
ITGB1
F value = 2.59
Pr(>F) = 0.0524
ITGB2
F value = 0.171
Pr(>F) = 0.916
ITGB3
F value = 0.501
Pr(>F) = 0.682
ITGB4
F value = 3.79
Pr(>F) = 0.0104
ITGB5
F value = 1.47
Pr(>F) = 0.223
ITGB6
F value = 3.22
Pr(>F) = 0.0226
ITGB7
F value = 1.29
Pr(>F) = 0.278
ITGB8
F value = 2.82
Pr(>F) = 0.0388
Stage I
Stage II
Stage III
Stage IV

Figure 4. The expression level of ITGBs in different pathological stages. A. The expression level of ITGBs in different pathological stages of LUAD. B. The expression level of ITGBs in different pathological stages of LUSC.



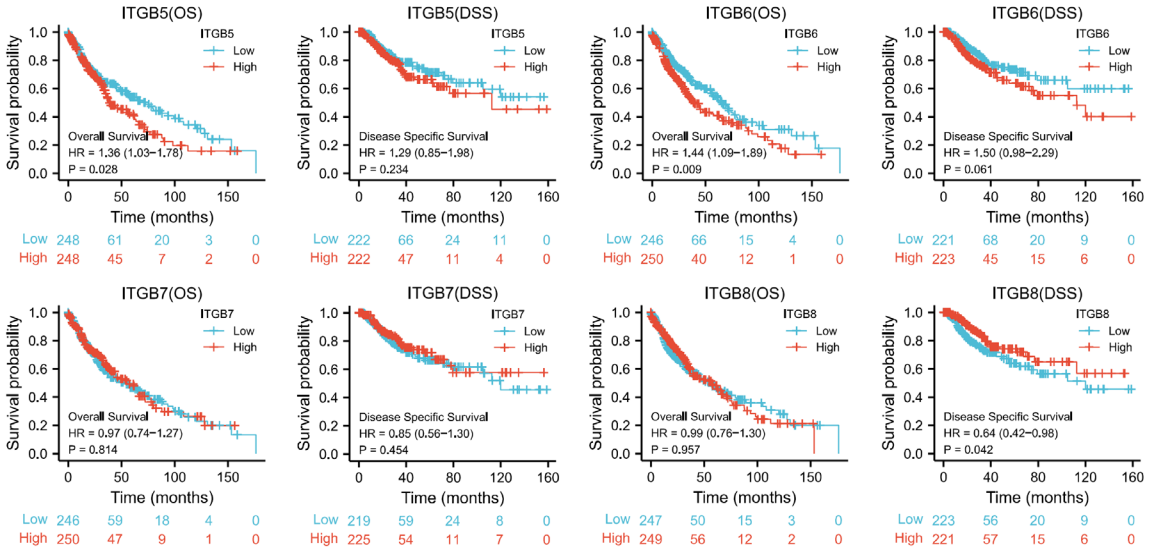


Figure 5. The prognostic value of ITGBs. A. The prognostic value of ITGBs in LUAD. B. The prognostic value of ITGBs in LUSC.

the promoter region [19]. To explore changes in the methylation level of promoters of ITGBs in NSCLC, we obtained the methylation data of ITGBs in LUAD and LUSC from TCGA database using UALCAN (**Figure 7**). In LUAD (**Figure 7A**), the promoters of ITGB2, 4, 5, 6, and 8 showed decreased methylation levels, whereas ITGB3 and 7 showed increased methylation levels; in LUSC (**Figure 7B**), the methylation levels of the promoters of ITGB2, 4, 6, and 7 were decreased, while those of ITGB1 and 8 were increased ($P < 0.05$).

These above results suggest that different gene variants and promoter methylation levels of ITGBs may contribute to their differential expression in LUAD and LUSC.

Correlation between ITGBs in LUAD and LUSC

Differential expression and prognostic effects of ITGBs in LUAD and LUSC suggest that ITGBs in these two NSCLC subtypes share different correlations. As shown in **Figure 8A**, ITGBs were positively correlated with each other in LUAD; in LUSC (**Figure 8B**), most ITGBs were positively correlated, and a few ITGBs were negatively correlated with each other. We further analyzed these results and found that in LUSC, the expression of most positively correlated ITGBs was upregulated or downregulated (except for ITGB5 and ITGB1), while the negatively correlated ITGBs showed the opposite expression trend. For example, ITGB4 and 8 were positively correlated, the expression of both ITGB4 and 8 was upregulated, while ITGB2 and 8 were negatively correlated, the expression of ITGB2 was downregulated, and ITGB8 was upregulated. However, this phenomenon was not observed in LUAD; for example, ITGB2 and 7 showed a significant positive correlation with a correlation coefficient of 0.65, while upregulation of ITGB2 and downregulation of ITGB7 were observed. Based on the above information, we speculate that in LUAD, the ITGBs mostly showed an indirect relation, whereas in LUSC, the ITGBs mostly showed a direct relation.

Co-expressed genes and PPI network construction

To investigate the function of ITGBs in LUAD and LUSC, we first identified the co-expressed genes of ITGBs and displayed the top 20 in a heatmap plot (**Figure 9A**, **9B**). Next, PPI networks of the top 20 correlated genes and ITGBs were constructed using STRING and Cytoscape. Our results showed the most closely interacting genes to be PTPRC, ITGAM, and ITGB2 in LUAD and FN1, PTPRC, and ITGB2 in LUSC, which may also act as target molecules of ITGBs in LUAD and LUSC, respectively (**Figure 9C**, **9D**).

GO and KEGG enrichment analysis

We performed GO and KEGG functional enrichment analyses on the top five correlated genes and ITGBs (in total 88 genes were included)

Table 1. Univariate and Multivariate analysis of OS and DSS in LUAD

Characteristics		Univariate analysis				Multivariate analysis			
		OS		DSS		OS		DSS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender	Female	Reference		Reference					
	Male	1.070 (0.803-1.426)	0.642	0.989 (0.687-1.424)	0.954				
Age	≤65	Reference		Reference					
	>65	1.223 (0.916-1.635)	0.172	1.013 (0.701-1.464)	0.944				
Smoker	No	Reference		Reference					
	Yes	0.894 (0.592-1.348)	0.591	1.040 (0.602-1.796)	0.889				
Pathological stage	I&II	Reference		Reference					
	III&IV	2.664 (1.960-3.621)	< 0.001	2.436 (1.645-3.605)	< 0.001	2.466 (1.809-3.363)	< 0.001	2.217 (1.490-3.298)	< 0.001
ITGB1	Low	Reference		Reference					
	High	1.514 (1.132-2.025)	0.005	1.435 (0.996-2.069)	0.053	1.438 (1.058-1.956)	0.020	1.258 (0.865-1.827)	0.229
ITGB2	Low	Reference		Reference					
	High	0.886 (0.665-1.182)	0.412	0.792 (0.549-1.143)	0.213				
ITGB3	Low	Reference		Reference					
	High	1.089 (0.818-1.451)	0.557	1.088 (0.757-1.563)	0.650				
ITGB4	Low	Reference		Reference					
	High	1.686 (1.262-2.251)	< 0.001	1.788 (1.238-2.584)	0.002	1.445 (1.047-1.995)	0.025	1.571 (1.075-2.296)	0.020
ITGB5	Low	Reference		Reference					
	High	1.311 (0.984-1.747)	0.064	1.190 (0.828-1.711)	0.346	1.024 (0.739-1.419)	0.886		
ITGB6	Low	Reference		Reference					
	High	0.999 (0.750-1.332)	0.997	0.863 (0.599-1.242)	0.427				
ITGB7	Low	Reference		Reference					
	High	0.734 (0.548-0.982)	0.037	0.737 (0.510-1.066)	0.105	0.699 (0.519-0.943)	0.019		
ITGB8	Low	Reference		Reference					
	High	0.965 (0.724-1.285)	0.807	1.074 (0.747-1.545)	0.700				

OS: Overall survival, DSS: Disease Specific survival, HR: Hazard Ratio, CI: Confidence interval.

Table 2. Univariate and Multivariate analysis of OS and DSS in LUSC

Characteristics		Univariate analysis				Multivariate analysis			
		OS		DSS		OS		DSS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender	Female	Reference		Reference					
	Male	1.211 (0.879-1.669)	0.241	1.386 (0.833-2.307)	0.209				
Age	≤65	Reference		Reference					
	> 65	1.279 (0.960-1.704)	0.093	1.028 (0.668-1.582)	0.899	1.237 (0.921-1.661)	0.158		
Smoker	No	Reference		Reference					
	Yes	0.585 (0.259-1.325)	0.199	0.393 (0.123-1.251)	0.114				
Pathological stage	I&II	Reference		Reference					
	III&IV	1.570 (1.139-2.163)	0.006	2.600 (1.648-4.102)	< 0.001	1.601 (1.159-2.212)	0.004	2.626 (1.662-4.150)	< 0.001
ITGB1	Low	Reference		Reference					
	High	1.413 (1.076-1.854)	0.013	1.638 (1.068-2.510)	0.024	1.123 (0.814-1.549)	0.481	1.545 (0.931-2.564)	0.092
ITGB2	Low	Reference		Reference					
	High	1.051 (0.802-1.378)	0.719	0.998 (0.655-1.521)	0.992				
ITGB3	Low	Reference		Reference					
	High	1.319 (1.005-1.731)	0.046	1.487 (0.972-2.273)	0.067	1.140 (0.840-1.546)	0.401	1.227 (0.754-1.996)	0.409
ITGB4	Low	Reference		Reference					
	High	1.105 (0.843-1.450)	0.470	1.282 (0.840-1.958)	0.250				
ITGB5	Low	Reference		Reference					
	High	1.358 (1.034-1.785)	0.028	1.294 (0.847-1.975)	0.234	1.242 (0.921-1.674)	0.155		
ITGB6	Low	Reference		Reference					
	High	1.437 (1.095-1.886)	0.009	1.501 (0.981-2.294)	0.061	1.221 (0.902-1.653)	0.196	1.205 (0.741-1.960)	0.451
ITGB7	Low	Reference		Reference					
	High	0.968 (0.737-1.270)	0.814	0.851 (0.557-1.300)	0.454				
ITGB8	Low	Reference		Reference					
	High	0.993 (0.757-1.301)	0.957	0.641 (0.417-0.984)	0.042			0.594 (0.384-0.918)	0.019

OS: Overall survival, DSS: Disease Specific survival, HR: Hazard Ratio, CI: Confidence interval.

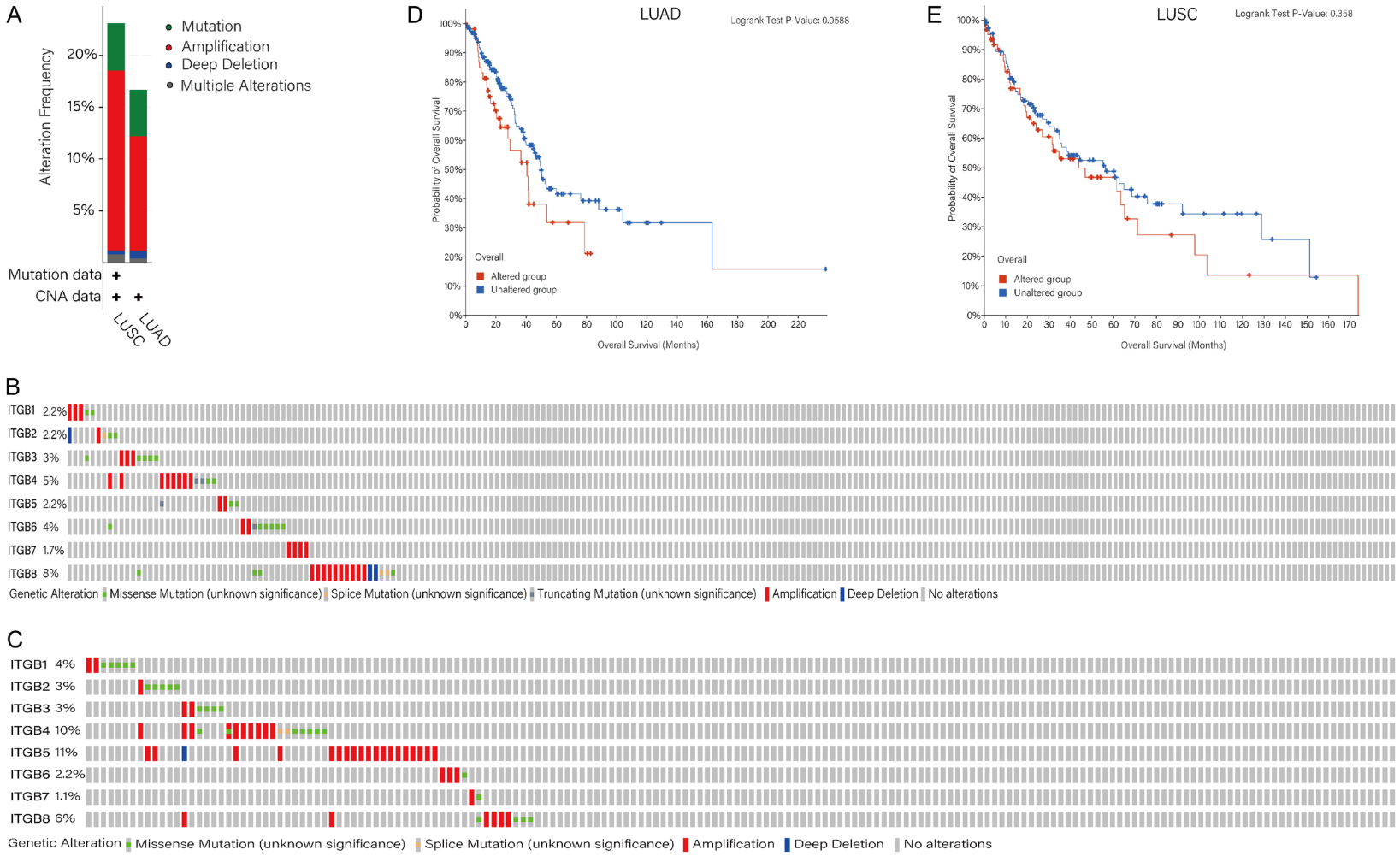


Figure 6. Genetic variation of ITGBs. A. Summary of genetic variation of ITGBs in LUAD and LUSC. B. Genetic variation of ITGBs in LUAD. C. Genetic variation of ITGBs in LUSC. D. The effect of genetic variation on OS in LUAD. E. The effect of genetic variation on OS in LUSC.

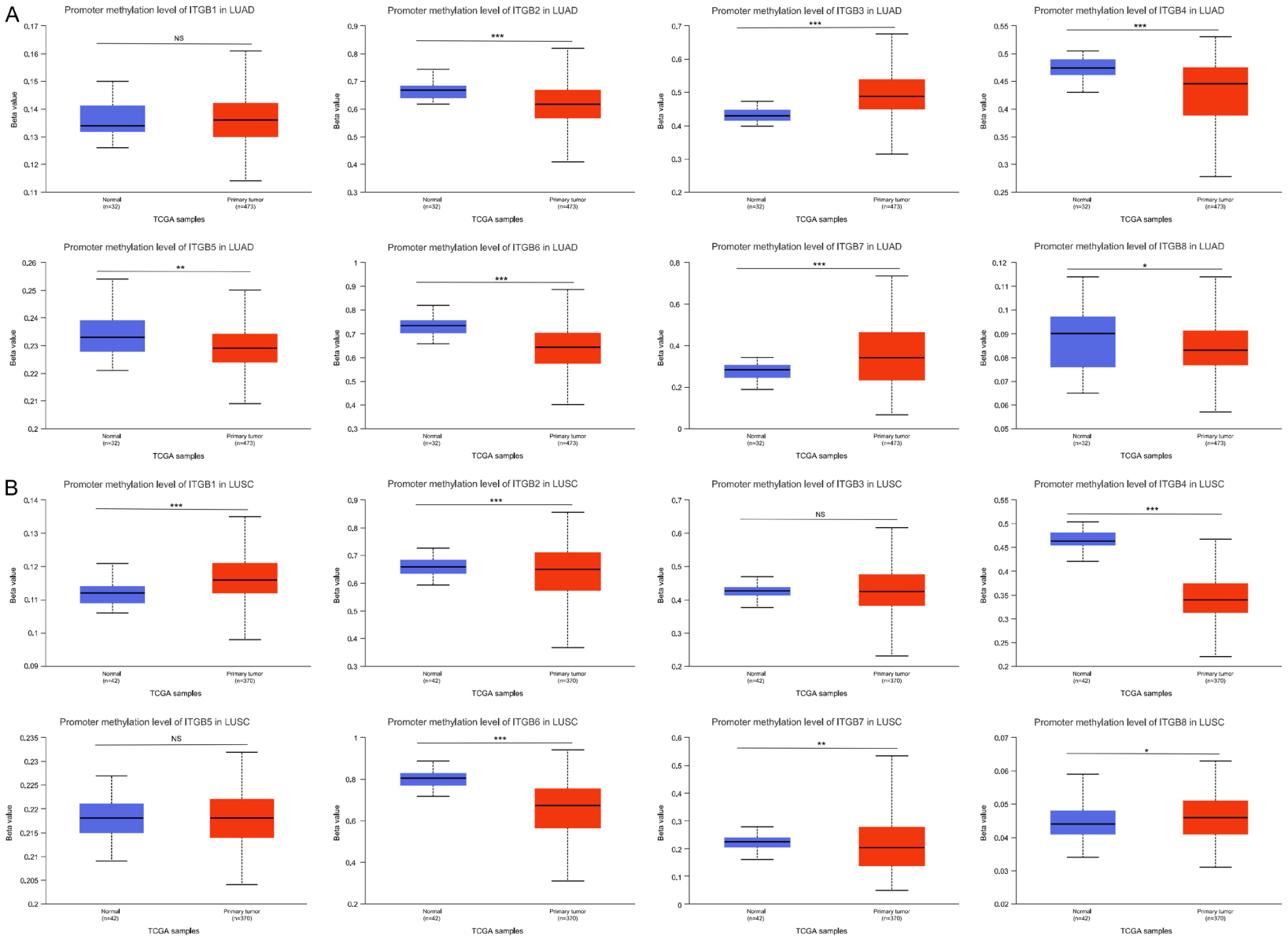


Figure 7. The promoter methylation level of ITGBs. A. The promoter methylation level of ITGBs in LUAD. B. The promoter methylation level of ITGBs in LUSC. NS, no statistical significance; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

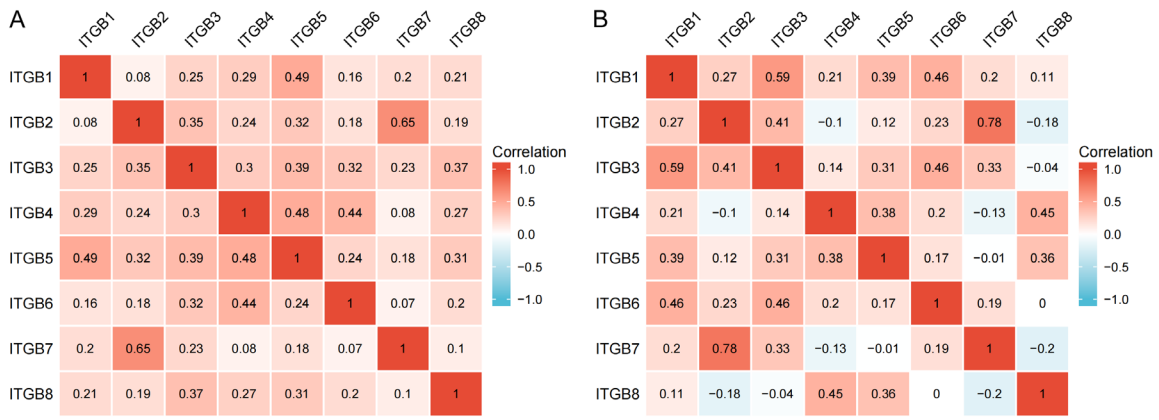


Figure 8. Correlation between ITGBs. A. Correlation between ITGBs in LUAD. B. Correlation between ITGBs in LUSC.

and presented the top five results. As shown in **Figure 10A**, GO analysis revealed that the above genes were highly enriched for functions related to adhesion, junction, and binding in both LUAD and LUSC. KEGG pathway enrichment analysis revealed that regulation of the actin cytoskeleton, ECM-receptor interaction, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy-related pathways were enriched in both LUAD and LUSC. The network plot shows that almost all ITGBs directly affected the clustering functions acquired by GO analysis in LUAD and LUSC. Target molecules other than ITGB2 obtained by PPI, namely PTPRC and ITGAM in LUAD, and FN1 and PTPRC in LUSC, indirectly affected the functions obtained in GO analysis (**Figure 10B**, **10C**).

Relationship between ITGBs and immune cell infiltration in LUAD and LUSC

To further clarify the role of ITGBs in LUAD and LUSC, we assessed the relationship between ITGBs and tumor-infiltrating immune cells using TIMER2 (**Figure 11**, purity adjustment).

In LUAD (**Figure 11A**, representative images are shown in **Figure 11B**), nearly all ITGBs were positively associated with the infiltration of CD8+ T cells, CD4+ T cells, dendritic cells (DCs), macrophages, and neutrophils ($P < 0.05$). Except ITGB7, which was positively correlated with B cell infiltration, ITGB1, 3, 4, and 5 were all negatively correlated with B cell infiltration ($P < 0.05$).

In LUSC (**Figure 11A**, representative images are shown in **Figure 11B**), ITGB1, 2, 3, 5, 6, and 7 were almost all positively correlated with CD8+ T cells, CD4+ T cells, DCs, macrophages, and neutrophils (except ITGB5, which was negatively correlated with neutrophils infiltration) ($P < 0.05$). ITGB4 and 8 were not associated with almost all infiltrating immune cells (except ITGB4, which was negatively correlated with B cell infiltration) ($P > 0.05$).

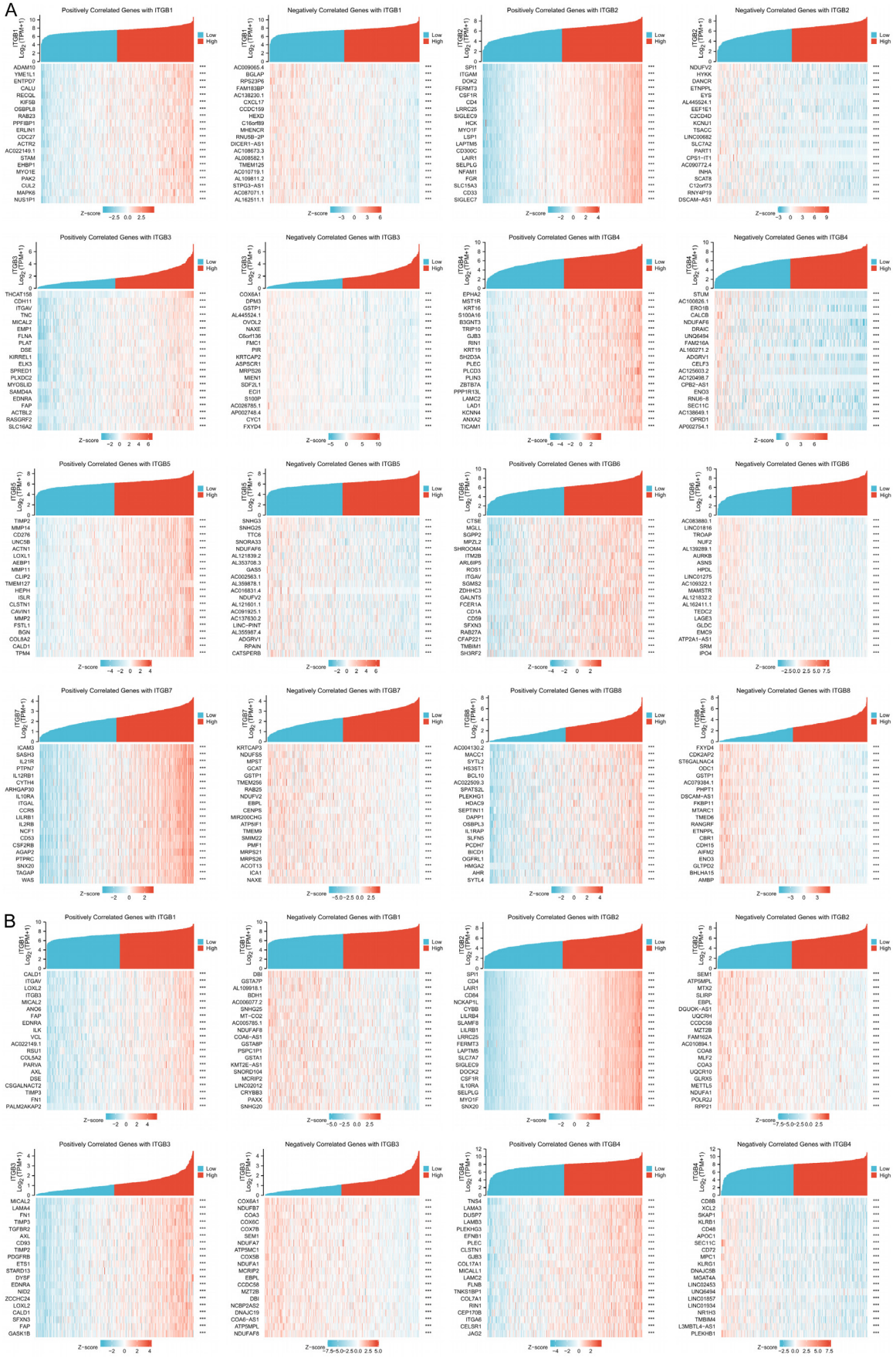
Relationship of ITGBs with the expression of immunomodulation-related genes in LUAD and LUSC

To explore the mechanism by which ITGBs affect immune cell infiltration, we downloaded data from TIMER2 on the relationship between ITGBs and the expression of immune activation-related (**Figure 12A**), immunosuppression-related (**Figure 12B**), chemokine (**Figure 12C**), and chemokine receptor genes (**Figure 12D**) in LUAD and LUSC (purity adjustment). The results showed that in LUAD, ITGBs showed a generally positive correlation with the expression of these immunomodulation-related genes; in LUSC, ITGB1, 2, 3, 5, 6, 7 showed a generally positive correlation with the expression of these immunomodulation-related genes, whereas ITGB4 and 8 showed a generally negative correlation with these genes.

Based on the above information, we speculated that ITGBs may affect immune cell infiltration in LUAD and LUSC through the expression of immunomodulation-related genes.

Discussion

In the present study, for the first time, we used multiple public database platforms to conduct an in-depth exploration of the role of ITGBs in


A
Positively Correlated Genes with ITGB1
Negatively Correlated Genes with ITGB1
Positively Correlated Genes with ITGB2
Negatively Correlated Genes with ITGB2
Positively Correlated Genes with ITGB3
Negatively Correlated Genes with ITGB3
Positively Correlated Genes with ITGB4
Negatively Correlated Genes with ITGB4
Positively Correlated Genes with ITGB5
Negatively Correlated Genes with ITGB5
Positively Correlated Genes with ITGB6
Negatively Correlated Genes with ITGB6
Positively Correlated Genes with ITGB7
Negatively Correlated Genes with ITGB7
Positively Correlated Genes with ITGB8
Negatively Correlated Genes with ITGB8
B
Positively Correlated Genes with ITGB1
Negatively Correlated Genes with ITGB1
Positively Correlated Genes with ITGB2
Negatively Correlated Genes with ITGB2
Positively Correlated Genes with ITGB3
Negatively Correlated Genes with ITGB3
Positively Correlated Genes with ITGB4
Negatively Correlated Genes with ITGB4
Low
High
Z-score

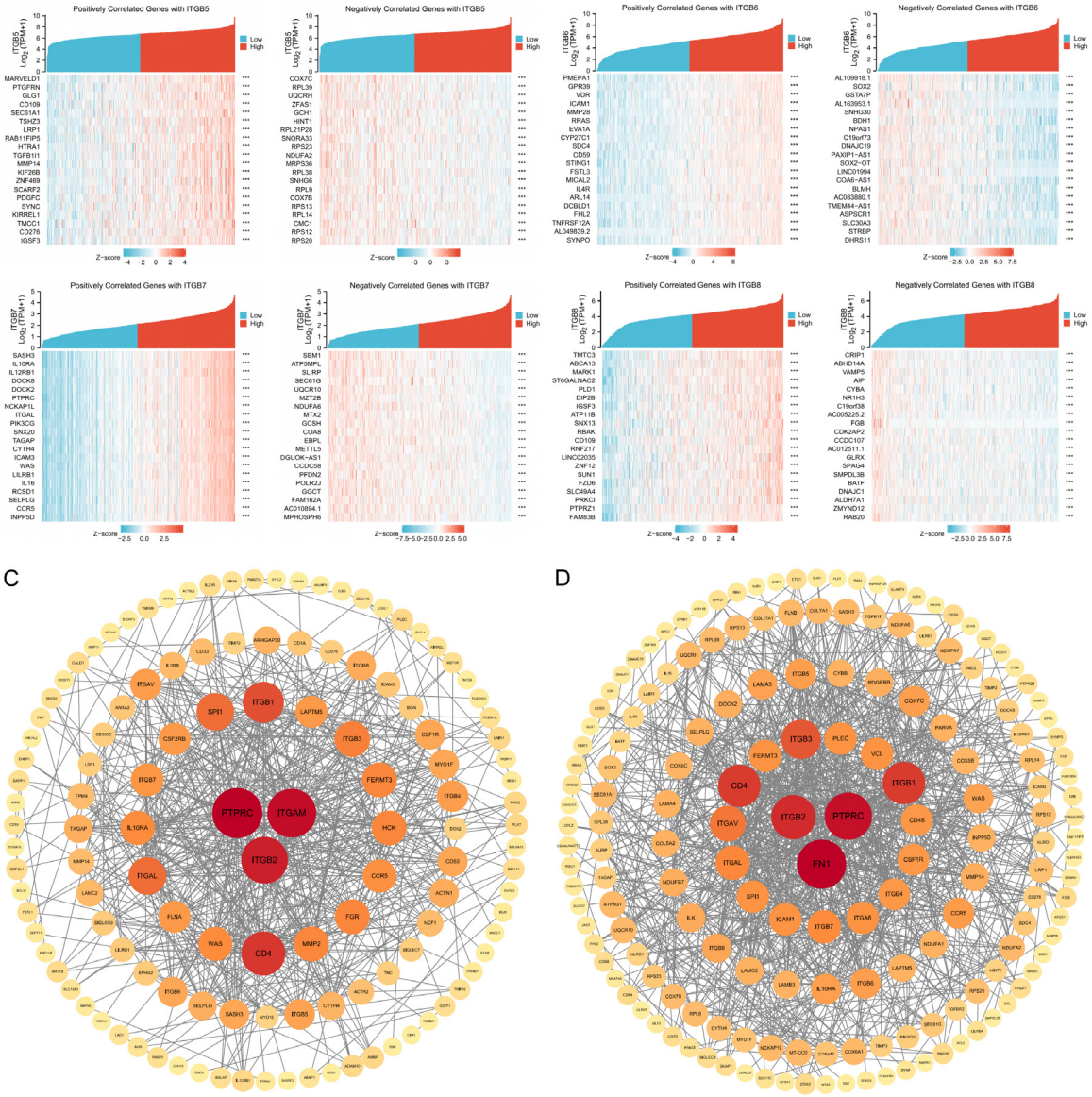


Figure 9. Top 20 co-expressed genes of ITGBs. A. Top 20 co-expressed genes of ITGBs in LUAD. B. Top 20 co-expressed genes of ITGBs in LUSC. C. PPI network of ITGBs and related top 20 co-expressed genes in LUAD. D. PPI network of ITGBs and related top 20 co-expressed genes in LUSC.

NSCLC with respect to mRNA and protein expression, clinical outcome, and tumor-infiltrating immune cells. Our results indicate that ITGBs are differentially expressed in LUAD and LUSC, possibly because of different mutation degrees/types and promoter methylation levels of ITGBs in LUAD and LUSC. Prognostic analysis revealed that in LUAD, ITGB1, 4, and 7 could be prognostic markers, while in LUSC, ITGB1, 3, 5, 6, and 8 could be prognostic markers. Analysis of the most associated co-expressed genes and their PPI network revealed that the most closely interacting genes in LUAD were PTPRC, ITGAM, and ITGB2 whereas those in LUSC were FN1, PTPRC, and ITGB2, which may be the target molecules of ITGBs in these cancers. GO analysis showed that the most related genes were highly enriched for functions related to adhesion, junction, and binding in both LUAD and LUSC, whereas the target molecules of PTPRC and ITGAM in LUAD, and those of FN1 and PTPRC in LUSC, indirectly affected the functions obtained by GO analysis. Immune cell infiltration analysis indicated that ITGBs were significantly related to immune cell infiltration in NSCLC, which may be affected by the expression of immunomodulation-related genes.

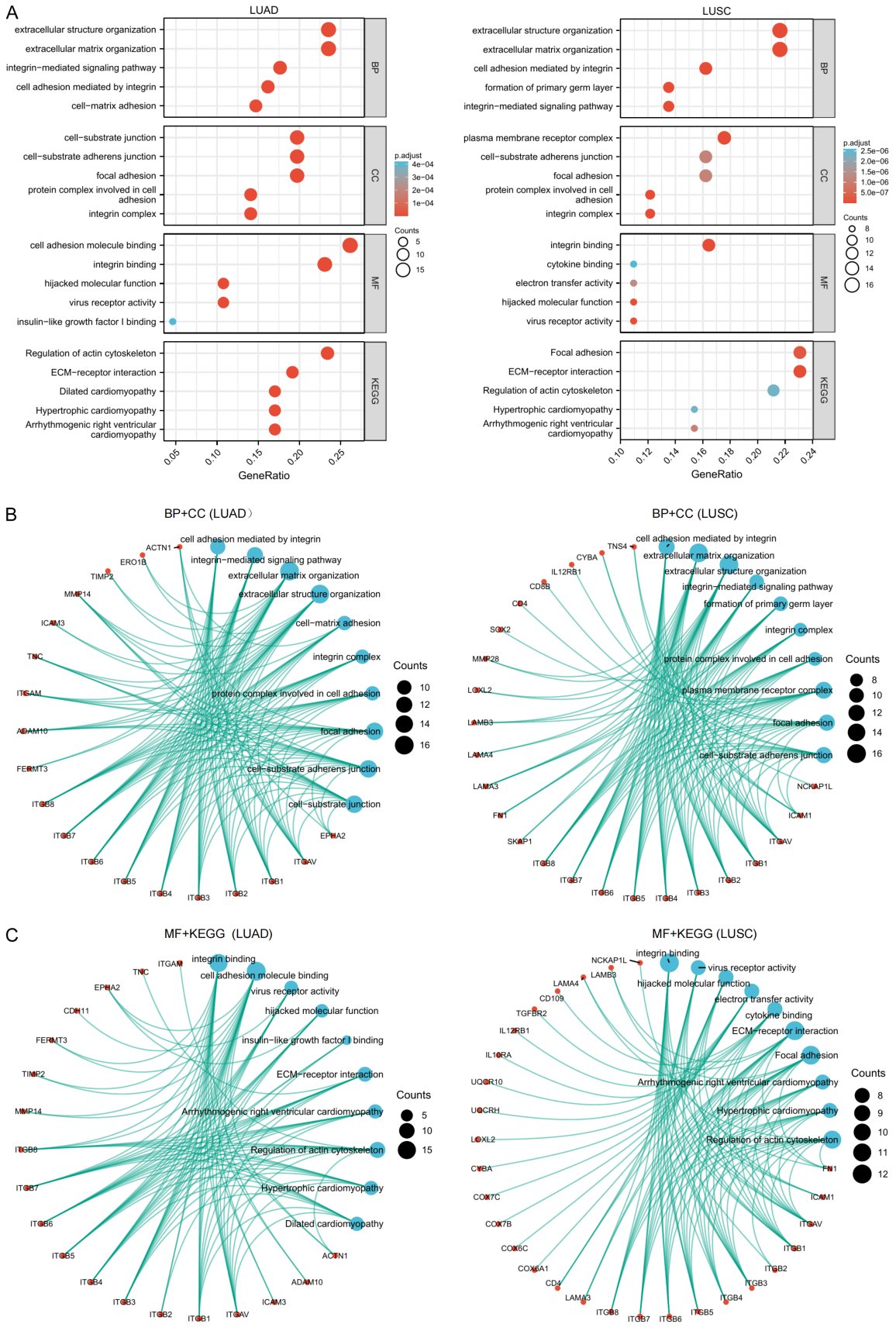

A
LUAD
extracellular structure organization
extracellular matrix organization
integrin−mediated signaling pathway
cell adhesion mediated by integrin
cell−matrix adhesion
cell−substrate junction
cell−substrate adherens junction
focal adhesion
protein complex involved in cell adhesion
integrin complex
cell adhesion molecule binding
integrin binding
hijacked molecular function
virus receptor activity
insulin−like growth factor I binding
Regulation of actin cytoskeleton
ECM−receptor interaction
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
BP
CC
MF
KEGG
p.adjust
4e−04
3e−04
2e−04
1e−04
Counts
5
10
15
0.05
0.10
0.15
0.20
0.25
GeneRatio
LUSC
cell adhesion mediated by integrin
formation of primary germ layer
plasma membrane receptor complex
Focal adhesion
p.adjust
2.5e−06
2.0e−06
1.5e−06
1.0e−06
5.0e−07
8
10
12
14
16
0.10
0.12
0.14
0.16
0.18
0.20
0.22
0.24
B
BP+CC (LUAD)
BP+CC (LUSC)
Counts
C
MF+KEGG (LUAD)
MF+KEGG (LUSC)

Figure 10. GO and KEGG enrichment analysis. A. GO [in biological process (BP), cellular component (CC), molecular function (MF)] and KEGG enrichment analysis in LUAD and LUSC. B. Crosstalk between enriched functions (BP+CC) and genes in LUAD and LUSC. C. Crosstalk between enriched functions (MF+KEGG) and gene s in LUAD and LUSC.

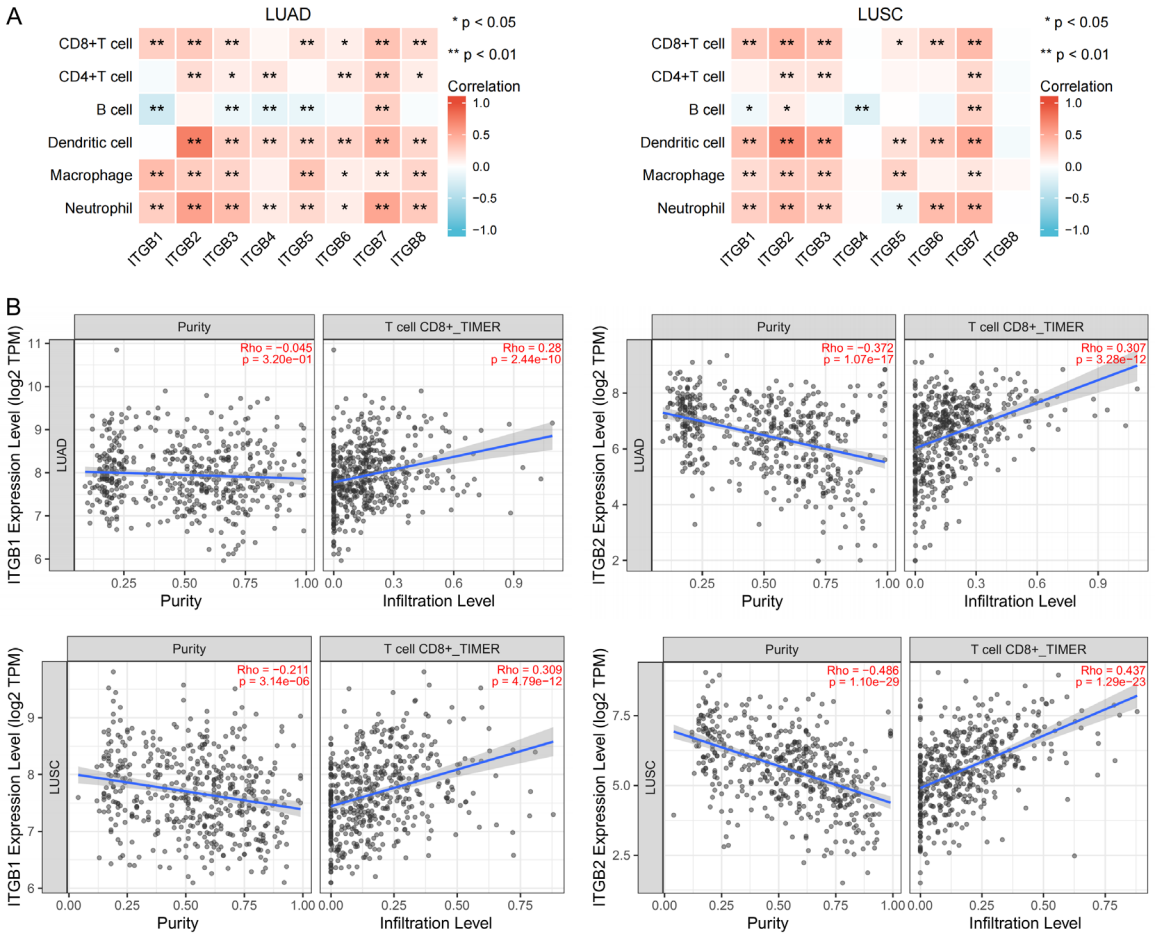


Figure 11. Relationship between ITGBs and immune cell infiltration. A. Relationship between ITGBs and immune cell infiltration in LUAD and LUSC. B. Representative images of the relationship between ITGBs and immune cell infiltration in LUAD and LUSC.

ITGB1 associates with at least ten α-subunits, forming the largest integrin subfamily [20]. Overexpression of ITGB1 has been observed in several solid tumors [21, 22]. Consistent with our results, Deng et al. found that upregulation of ITGB1 indicated poor prognosis in patients with LUAD [23]. In addition, ITGB1 is also involved in the initiation, metastasis, stemness, and radioresistance of lung cancer [24-27]. Thus, ITGB1 may be a potential therapeutic target for lung cancer.

Similar to ITGB1, ITGB3 downregulation could restrain the migration and invasion of NSCLC [28, 29], and inhibition of ITGB3 could promote the antitumor activity of ALK inhibitors in NSCLC [30]. Another study revealed that ITGB3 is overexpressed in both drug resistance and mesenchymal status, indicating its potential as a target to overcome chemoresistance in lung cancer [31].

Through the intracytoplasmic region, ITGB4 can activate intracellular signaling and maintain epithelial cell integrity [32]. Huang et al. performed bioinformatics analysis and found that ITGB4 is a pan-cancer oncogene across 33 different human tumors [33]. ITGB4 overexpression is associated with venous invasion and decreased OS in NSCLC [34]. Furthermore, ITGB4 is also closely related to other diseases of the respiratory system, such as airway

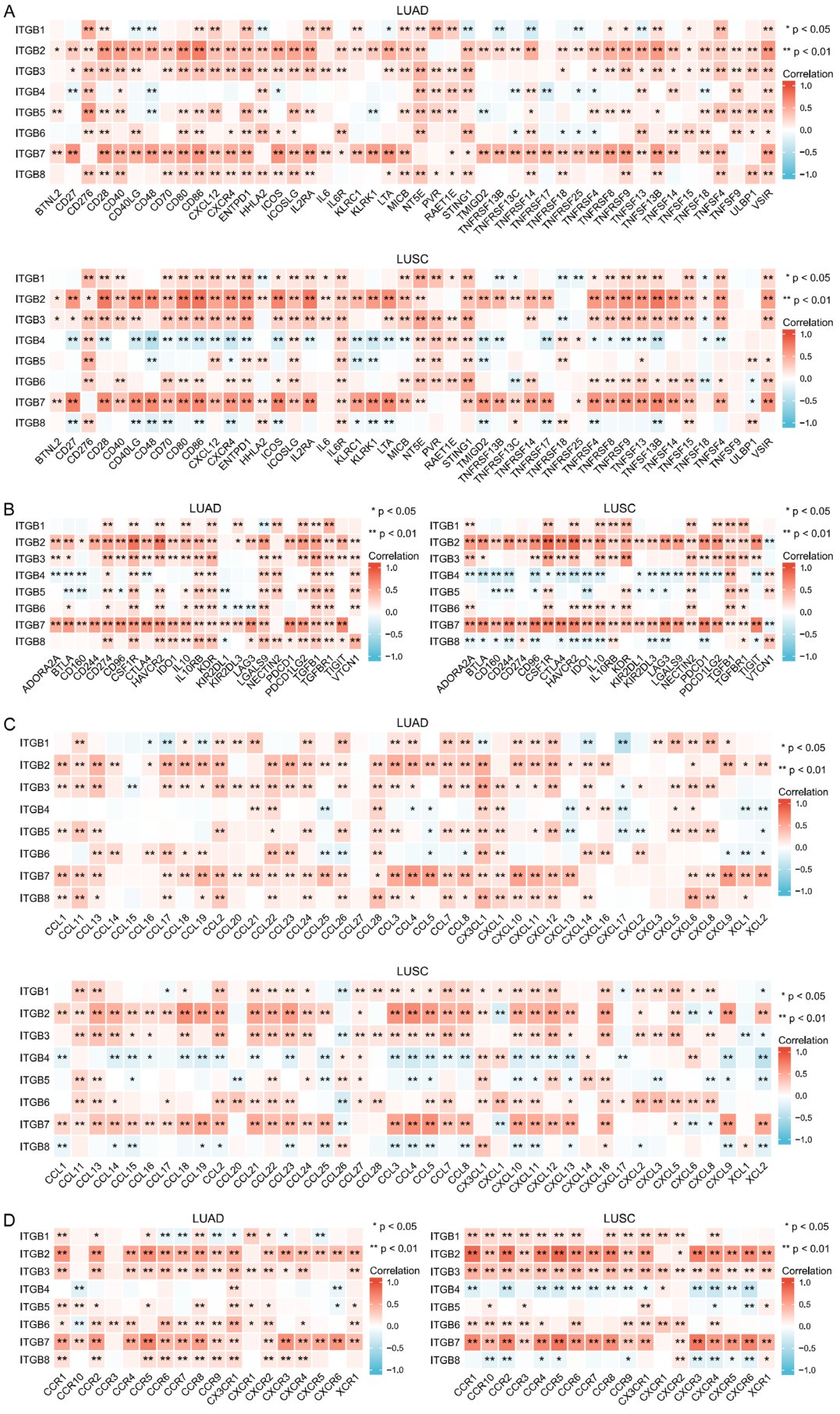

A
LUAD
LUSC
ITGB1
ITGB2
ITGB3
ITGB4
ITGB5
ITGB6
ITGB7
ITGB8
BTNL2 CD27 CD276 CD28 CD40 CD40LG CD48 CD70 CD80 CD86 CXCL12 CXCR4 ENTPD1 HHLA2 ICOS ICOSLG IL2RA IL6 IL6R KLRC1 KLRK1 LTA MICB NT5E PVR RAET1E STING1 TMIGD2 TNFRSF13B TNFRSF13C TNFRSF14 TNFRSF17 TNFRSF18 TNFRSF25 TNFRSF4 TNFRSF8 TNFRSF9 TNFSF13 TNFSF13B TNFSF14 TNFSF15 TNFSF18 TNFSF4 TNFSF9 ULBP1 VSIR
B
LUAD
LUSC
ADORA2A BTLA CD160 CD244 CD274 CD96 CSF1R CTLA4 HAVCR2 IDO1 IL10 IL10RB KDR KIR2DL1 KIR2DL3 LAG3 LGALS9 NECTIN2 PDCD1 PDCD1LG2 TGFB1 TGFBR1 TIGIT VTCN1
C
LUAD
LUSC
CCL1 CCL11 CCL13 CCL14 CCL15 CCL16 CCL17 CCL18 CCL19 CCL2 CCL20 CCL21 CCL22 CCL23 CCL24 CCL25 CCL26 CCL27 CCL28 CCL3 CCL4 CCL5 CCL7 CCL8 CX3CL1 CXCL1 CXCL10 CXCL11 CXCL12 CXCL13 CXCL14 CXCL16 CXCL17 CXCL2 CXCL3 CXCL5 CXCL6 CXCL8 CXCL9 XCL1 XCL2
D
LUAD
LUSC
CCR1 CCR10 CCR2 CCR3 CCR4 CCR5 CCR6 CCR7 CCR8 CCR9 CX3CR1 CXCR1 CXCR2 CXCR3 CXCR4 CXCR5 CXCR6 XCR1
* p < 0.05
** p < 0.01
Correlation
1.0
0.5
0.0
−0.5
−1.0

Figure 12. Relationship of ITGBs with the expression of immunomodulation-related genes. A. The relationship of ITGBs and the expression of immune activation-related genes in LUAD and LUSC. B. The relationship of ITGBs and the expression of immunosuppression-related genes in LUAD and LUSC. C. The relationship of ITGBs and the expression of chemokine genes in LUAD and LUSC. D. The relationship of ITGBs and the expression of chemokine receptor genes in LUAD and LUSC.

inflammation and hyperresponsiveness, acute lung injury, and spontaneous pulmonary inflammation [35-37].

The oncogenic effects of ITGB5 have previously been observed in prostate, colorectal, and hepatocellular carcinoma [38-40]. Currently, research on the role of ITGB5 in lung cancer is limited. Our study indicates that ITGB5 is a risk factor for OS in patients with LUSC. Hu et al. reported that ITGB5 is involved in regulating lung cancer cell motility [41]. Moreover, several studies have reported the impact of ITGB5 on the lungs [42, 43].

SMYD3, together with ITGB6 and TGFβ1-Smad3, can facilitate the adhesion and invasion of ovarian cancer cells [44]. ITGB6 is a pro-tumorigenic gene that has also been identified in gastric and pancreatic cancers [45, 46]. Few studies have evaluated the effects of ITGB6 on lung cancer. Most studies on the relationship between ITGB6 and lung disease have focused on pulmonary fibrosis and emphysema. Both ELK1 and TGF-β can aggravate pulmonary fibrosis by increasing the expression of ITGB6 [47, 48]. Congenital deletion of ITGB6 can cause severe emphysema [49]. Overall, these studies demonstrate that ITGB6 plays a complex role in lung diseases.

However, no study has investigated the influence of ITGB7 on lung cancer. Our results indicate that ITGB7 is a protective factor against OS in LUAD, and the same protective effect has been observed in colorectal cancer [50]. Zhang et al. demonstrated that ITGB7 limits colorectal cancer progression by maintaining antitumor immunity [50].

In our study, ITGB8 was found to act as a protective factor for DSS in LUSC; however, upregulation of ITGB8 has been previously reported to indicate poor prognosis in lung cancer [51-53]. The different prognostic indicators might be responsible for the discrepancy between our results and those of previous studies, as our prognostic indicator was DSS, whereas that used in the previous studies was OS.

The TME is an integral part of cancer that significantly affects treatment response and clinical outcomes. As part of the TME, immune cells have an important impact on tumor progression and prognosis [54]. Our results demonstrated the most closely interacting genes to be PTPRC, ITGAM, and ITGB2 in LUAD and FN1, PTPRC, and ITGB2 in LUSC. PTPRC, also known as CD45, is important for regulating B- and T-cell antigen receptor-mediated activation [55]. Wei et al. showed that PTPRC may be involved in regulating the TME immune status, affecting the function of immune cells in LUAD [56]. The ITGB2 subfamily is often referred to as leukocyte integrins [57]. Altered ITGB2 expression causes adhesion defects in circulation and weakens the ability of the immune system to combat foreign antigens [58]. ITGAM combines with ITGB2 to form a leucocyte-specific integrin, which exerts an important influence on the adhesion and migration of leukocytes [57]. A predictive marker has been previously reported for ITGB2 immunotherapy in gliomas [59]. FN1 is widely expressed in multiple cells and is involved in cell adhesion and migration [60]. FN1 is associated with the function of infiltrating macrophages and T cells in the TME of lung cancer [61, 62]. Based on the above information and our findings, we speculate that ITGBs may influence tumor cells and infiltrating immune cells by affecting their adhesion, junction, and binding, thereby affecting the prognosis of NSCLC.

However, our study has some limitations. First, our research was based on data obtained from TCGA, without further validation of the results using cellular, animal, and human specimens. Further, we failed to systematically explore the pathophysiological mechanisms underlying our findings. Thus, further studies are required to understand the mechanisms underlying our findings.

Conclusion

ITGBs were differentially expressed in NSCLC. ITGB1, 4, and 7 and ITGB1, 3, 5, 6, and 8 were found as prognostic markers in LUAD and LUSC,

respectively. ITGBs were significantly associated with immune cell infiltration and the expression of immunomodulation-related genes.

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Disclosure of conflict of interest

None.

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References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[2] Herbst RS, Morgensztern D and Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018; 553: 446-454.

[3] Giancotti FG and Ruoslahti E. Integrin signaling. Science 1999; 285: 1028-1032.

[4] Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. Cell 1992; 69: 11-25.

[5] Cooper J and Giancotti FG. Integrin signaling in cancer: mechanotransduction, stemness, epithelial plasticity, and therapeutic resistance. Cancer Cell 2019; 35: 347-367.

[6] Kowalski-Chauvel A, Gouaze-Andersson V, Baricault L, Martin E, Delmas C, Toulas C, Cohen-Jonathan-Moyal E and Seva C. Alpha6-Integrin regulates FGFR1 expression through the ZEB1/YAP1 transcription complex in glioblastoma stem cells resulting in enhanced proliferation and stemness. Cancers (Basel) 2019; 11: 406.

[7] Lathia JD, Gallagher J, Heddleston JM, Wang J, Eyler CE, Macswords J, Wu Q, Vasanji A, Mclendon RE, Hjelmeland AB and Rich JN. Integrin alpha 6 regulates glioblastoma stem cells. Cell Stem Cell 2010; 6: 421-432.

[8] Guo W and Giancotti FG. Integrin signalling during tumour progression. Nat Rev Mol Cell Biol 2004; 5: 816-826.

[9] Christofori G. Changing neighbours, changing behaviour: cell adhesion molecule-mediated signalling during tumour progression. EMBO J 2003; 22: 2318-2323.

[10] Robinson SD and Hodivala-Dilke KM. The role of beta3-integrins in tumor angiogenesis: context is everything. Curr Opin Cell Biol 2011; 23: 630-637.

[11] Dickreuter E, Eke I, Krause M, Borgmann K, van Vugt MA and Cordes N. Targeting of beta1 integrins impairs DNA repair for radiosensitization of head and neck cancer cells. Oncogene 2016; 35: 1353-1362.

[12] Vehlow A and Cordes N. Growth factor receptor and beta1 integrin signaling differentially regulate basal clonogenicity and radiation survival of fibroblasts via a modulation of cell cycling. In Vitro Cell Dev Biol Anim 2022; 58: 169-178.

[13] Jiang H, Hegde S, Knolhoff BL, Zhu Y, Herndon JM, Meyer MA, Nywening TM, Hawkins WG, Shapiro IM, Weaver DT, Pachter JA, Wang-Gillam A and Denardo DG. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nat Med 2016; 22: 851-860.

[14] Zhang C, Wu S, Song R and Liu C. Long noncoding RNA NR2F1-AS1 promotes the malignancy of non-small cell lung cancer via sponging microRNA-493-5p and thereby increasing ITGB1 expression. Aging (Albany NY) 2020; 13: 7660-7675.

[15] Stewart RL, West D, Wang C, Weiss HL, Gal T, Durbin EB, O'Connor W, Chen M and O'Connor KL. Elevated integrin alpha6beta4 expression is associated with venous invasion and decreased overall survival in non-small cell lung cancer. Hum Pathol 2016; 54: 174-183.

[16] Zheng C, Li X, Ren Y, Yin Z and Zhou B. Coexisting EGFR and TP53 mutations in lung adenocarcinoma patients are associated with COMP and ITGB8 upregulation and poor prognosis. Front Mol Biosci 2020; 7: 30.

[17] Wang Z, Sun X, Zhao Y, Guo X, Jiang H, Li H and Gu Z. Evolution of gene regulation during transcription and translation. Genome Biol Evol 2015; 7: 1155-1167.

[18] Martinez-Ferriz A, Ferrando A, Fathinajafabadi A and Farras R. Ubiquitin-mediated mechanisms of translational control. Semin Cell Dev Biol 2021: [Epub ahead of print].

[19] Traube FR and Carell T. The chemistries and consequences of DNA and RNA methylation and demethylation. Rna Biol 2017; 14: 1099-1107.

[20] Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell 2002; 110: 673-687.

[21] Schaffner F, Ray AM and Dontenwill M. Integrin alpha5beta1, the fibronectin receptor, as a pertinent therapeutic target in solid tumors. Cancers (Basel) 2013; 5: 27-47.

[22] Blandin AF, Renner G, Lehmann M, Lelong-Rebel I, Martin S and Dontenwill M. Beta1 integrins as therapeutic targets to disrupt hallmarks of cancer. Front Pharmacol 2015; 6: 279.
[23] Deng H, Huang Y, Wang L and Chen M. High expression of UBB, RAC1, and ITGB1 predicts worse prognosis among nonsmoking patients with lung adenocarcinoma through bioinformatics analysis. Biomed Res Int 2020; 2020: 2071593.
[24] Zhao M, Tong C, Hao Z, Zhao R and Wang L. MicroRNA-374b mediates the initiation of non-small cell lung cancer by regulating ITGB1 and p53 expressions. Thorac Cancer 2020; 11: 1670-1678.
[25] Wang XM, Li J, Yan MX, Liu L, Jia DS, Geng Q, Lin HC, He XH, Li JJ and Yao M. Integrative analyses identify osteopontin, LAMB3 and ITGB1 as critical pro-metastatic genes for lung cancer. PLoS One 2013; 8: e55714.
[26] Guo L, Sun C, Xu S, Xu Y, Dong Q, Zhang L, Li W, Wang X, Ying G and Guo F. Knockdown of long non-coding RNA linc-ITGB1 inhibits cancer stemness and epithelial-mesenchymal transition by reducing the expression of Snail in non-small cell lung cancer. Thorac Cancer 2019; 10: 128-136.
[27] Li Y, Sun C, Tan Y, Zhang H, Li Y and Zou H. ITGB1 enhances the radioresistance of human non-small cell lung cancer cells by modulating the DNA damage response and YAP1-induced epithelial-mesenchymal transition. Int J Biol Sci 2021; 17: 635-650.
[28] Ni R, Huang Y and Wang J. MiR-98 targets ITGB3 to inhibit proliferation, migration, and invasion of non-small-cell lung cancer. Onco Targets Ther 2015; 8: 2689-2697.
[29] Zhao B, Han H, Chen J, Zhang Z, Li S, Fang F, Zheng Q, Ma Y, Zhang J, Wu N and Yang Y. MicroRNA let-7c inhibits migration and invasion of human non-small cell lung cancer by targeting ITGB3 and MAP4K3. Cancer Lett 2014; 342: 43-51.
[30] Noh KW, Sohn I, Song JY, Shin HT, Kim YJ, Jung K, Sung M, Kim M, An S, Han J, Lee SH, Lee MS and Choi YL. Integrin beta3 inhibition enhances the antitumor activity of ALK inhibitor in ALK-Rearranged NSCLC. Clin Cancer Res 2018; 24: 4162-4174.
[31] Hong SK, Lee H, Kwon OS, Song NY, Lee HJ, Kang S, Kim JH, Kim M, Kim W and Cha HJ. Large-scale pharmacogenomics based drug discovery for ITGB3 dependent chemoresistance in mesenchymal lung cancer. Mol Cancer 2018; 17: 175.
[32] Yang H, Xu Z, Peng Y, Wang J and Xiang Y. Integrin beta4 as a potential diagnostic and therapeutic tumor marker. Biomolecules 2021; 11: 1197.
[33] Huang W, Fan L, Tang Y, Chi Y and Li J. A pan-cancer analysis of the oncogenic role of integrin beta4 (ITGB4) in human tumors. Int J Gen Med 2021; 14: 9629-9645.
[34] Stewart RL, West D, Wang C, Weiss HL, Gal T, Durbin EB, O'Connor W, Chen M and O'Connor KL. Elevated integrin alpha6beta4 expression is associated with venous invasion and decreased overall survival in non-small cell lung cancer. Hum Pathol 2016; 54: 174-183.
[35] Liu C, Yuan L, Zou Y, Yang M, Chen Y, Qu X, Liu H, Jiang J, Xiang Y and Qin X. ITGB4 is essential for containing HDM-induced airway inflammation and airway hyperresponsiveness. J Leukoc Biol 2018; 103: 897-908.
[36] Jiang W, Wang JM, Luo JH, Chen Y, Pi J, Ma XD, Liu CX, Zhou Y, Qu XP, Liu C, Liu HJ, Qin XQ and Xiang Y. Airway epithelial integrin beta4-deficiency exacerbates lipopolysaccharide-induced acute lung injury. J Cell Physiol 2021; 236: 7711-7724.
[37] Tang S, Du X, Yuan L, Xiao G, Wu M, Wang L, Wu S, Duan Z, Xiang Y, Qu X, Liu H, Zou Y, Qin X, Qin L and Liu C. Airway epithelial ITGB4 deficiency in early life mediates pulmonary spontaneous inflammation and enhanced allergic immune response. J Cell Mol Med 2020; 24: 2761-2771.
[38] Yang Y, Feng Q, Hu K and Cheng F. Using CRISPRa and CRISPRi technologies to study the biological functions of ITGB5, TIMP1, and TMEM176B in prostate cancer cells. Front Mol Biosci 2021; 8: 676021.
[39] Shi W, He J, Huang Y, Zeng Z, Feng Z, Xu H and Nie Y. Integrin beta5 enhances the malignancy of human colorectal cancer by increasing the TGF-beta signaling. Anticancer Drugs 2021; 32: 717-726.
[40] Xiong C, Wang G and Bai D. A novel prognostic models for identifying the risk of hepatocellular carcinoma based on epithelial-mesenchymal transition-associated genes. Bioengineered 2020; 11: 1034-1046.
[41] Hu J, Niu M, Li X, Lu D, Cui J, Xu W, Li G, Zhan J and Zhang H. FERM domain-containing protein FRMD5 regulates cell motility via binding to integrin beta5 subunit and ROCK1. Febs Lett 2014; 588: 4348-4356.
[42] Tong Y, Bao C, Xu YQ, Tao L, Zhou Y, Zhuang L, Meng Y, Zhang H, Xue J, Wang W, Zhang L, Pan Q, Shao Z, Hu T, Guo Q, Xue Q, Lu H and Luo Y. The beta3/5 Integrin-MMP9 axis regulates pulmonary inflammatory response and endothelial leakage in acute lung injury. J Inflamm Res 2021; 14: 5079-5094.
[43] Ding X, Tong Y, Jin S, Chen Z, Li T, Billiar TR, Pitt BR, Li Q and Zhang LM. Mechanical ventila-

tion enhances extrapulmonary sepsis-induced lung injury: role of WISP1-alphavbeta5 integrin pathway in TLR4-mediated inflammation and injury. Crit Care 2018; 22: 302.
[44] Jiang Y, Zhou T, Shi Y, Feng W and Lyu T. A SMYD3/ITGB6/TGFbeta1 positive feedback loop promotes the invasion and adhesion of ovarian cancer spheroids. Front Oncol 2021; 11: 690618.
[45] Wu M, Li X, Zhang T, Liu Z and Zhao Y. Identification of a Nine-Gene signature and establishment of a prognostic nomogram predicting overall survival of pancreatic cancer. Front Oncol 2019; 9: 996.
[46] Li Z, Sun Y, Xu J, Yang H, Liu X, Tian Y, Cao S and Zhou Y. Integrin-beta6 serves as a potential prognostic serum biomarker for gastric cancer. Front Oncol 2021; 11: 770997.
[47] Tatler AL, Goodwin AT, Gbolahan O, Saini G, Porte J, John AE, Clifford RL, Violette SM, Weinreb PH, Parfrey H, Wolters PJ, Gauldie J, Kolb M and Jenkins G. Amplification of TGFbeta induced ITGB6 gene transcription may promote pulmonary fibrosis. PLoS One 2016; 11: e158047.
[48] Cairns JT, Habgood A, Edwards-Pritchard RC, Joseph C, John AE, Wilkinson C, Stewart ID, Leslie J, Blaxall BC, Susztak K, Alberti S, Nordheim A, Oakley F, Jenkins G and Tatler AL. Loss of ELK1 has differential effects on age-dependent organ fibrosis. Int J Biochem Cell Biol 2020; 120: 105668.
[49] Takatsuki S, Nakamura R, Haga Y, Mitsui K, Hashimoto T, Shimojima K, Saji T and Yamamoto T. Severe pulmonary emphysema in a girl with interstitial deletion of 2q24.2q24.3 including ITGB6. Am J Med Genet a 2010; 152A: 1020-1025.
[50] Zhang Y, Xie R, Zhang H, Zheng Y, Lin C, Yang L , Huang M, Li M, Song F, Lu L, Yang M, Liu Y, Wei Q, Li J and Chen J. Integrin beta7 inhibits colorectal cancer pathogenesis via maintaining antitumor immunity. Cancer Immunol Res 2021; 9: 967-980.
[51] Wu P, Wang Y, Wu Y, Jia Z, Song Y and Liang N. Expression and prognostic analyses of ITGA11, ITGB4 and ITGB8 in human non-small cell lung cancer. PeerJ 2019; 7: e8299.
[52] Li N and Zhu D. Circ_0017956 promotes the proliferation and metastasis of non-small cell lung cancer through regulating miR-515-5p/ITGB8 axis. Cell Cycle 2021: 1-13.
[53] Zheng C, Li X, Ren Y, Yin Z and Zhou B. Coexisting EGFR and TP53 mutations in lung adenocarcinoma patients are associated with COMP and ITGB8 upregulation and poor prognosis. Front Mol Biosci 2020; 7: 30.
[54] Pitt JM, Marabelle A, Eggermont A, Soria JC, Kroemer G and Zitvogel L. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. Ann Oncol 2016; 27: 1482-1492.
[55] Al BM, Ali A, Mcmullin MF and Mills K. Protein tyrosine phosphatase receptor type C (PTPRC or CD45). J Clin Pathol 2021; 74: 548-552.
[56] Wei J, Fang D and Zhou W. CCR2 and PTPRC are regulators of tumor microenvironment and potential prognostic biomarkers of lung adenocarcinoma. Ann Transl Med 2021; 9: 1419.
[57] Solovjov DA, Pluskota E and Plow EF. Distinct roles for the alpha and beta subunits in the functions of integrin alphaMbeta2. J Biol Chem 2005; 280: 1336-1345.
[58] Nawaz TH, Raza R, Jaffar S, Khan A, Anwar MZ, Ahmad W and Raza SI. Beta2 Integrin Gene (ITGB2) mutation spectra in Pakistani families with leukocyte adhesion deficiency type 1 (LAD1). Immunobiology 2020; 225: 151938.
[59] Xu H, Zhang A, Han X, Li Y, Zhang Z, Song L, Wang W and Lou M. ITGB2 as a prognostic indicator and a predictive marker for immunotherapy in gliomas. Cancer Immunol Immunother 2022; 71: 645-660.
[60] Gao W, Liu Y, Qin R, Liu D and Feng Q. Silence of fibronectin 1 increases cisplatin sensitivity of non-small cell lung cancer cell line. Biochem Biophys Res Commun 2016; 476: 35-41.
[61] Yang Q, Zhang H, Wei T, Lin A, Sun Y, Luo P and Zhang J. Single-Cell RNA sequencing reveals the heterogeneity of tumor-associated macrophage in non-small cell lung cancer and differences between sexes. Front Immunol 2021; 12: 756722.
[62] Luo L, Lv M, Zhuang X, Zhang Q and Qiao T. Irradiation increases the immunogenicity of lung cancer cells and irradiation-based tumor cell vaccine elicits tumor-specific T cell responses in vivo. Onco Targets Ther 2019; 12: 3805-3815.