Expression and prognostic analyses of *ITGA11*, *ITGB4* and *ITGB8* in human non-small cell lung cancer

PanCheng Wu [Equal first author, 1], **Yanyu Wang** [Equal first author, 1], **Yijun Wu** [2], **Ziqi Jia** [2], **Yang Song** [3], **Naixin Liang** [Corresp. 3]

[1] Department of Thoracic Surgery, Peking Union Medical College Hospital,Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, CHINA

[2] Peking Union Medical College, Eight-Year MD Program, Chinese Academy of Medical Sciences, Beijing, CHINA

[3] Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, CHINA

Corresponding Author: Naixin Liang
Email address: pumchnelson@163.com

Background

Integrins play a crucial role in the regulation process of cell proliferation, migration, differentiation, tumor invasion and metastasis. *ITGA11*, *ITGB4* and *ITGB8* are three encoding genes of integrins family. Accumulative evidences have proved that abnormal expression of *ITGA11*, *ITGB4* and *ITGB8* are a common phenomenon in different malignances. However, their expression patterns and prognostic roles for patients with non-small cell lung cancer (NSCLC) have not been completely illustrated.

Methods

We investigated the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in patients with NSCLC through using a series of databases and various datasets, including ONCOMINE, GEPIA, HPA, TCGA and GEO datasets.

Results

We found that the expression levels of *ITGA11* and *ITGB4* were significantly upregulated in both LUAD and LUSC, while *ITGB8* was obviously upregulated in LUSC. Additionally, higher expression level of *ITGB4* revealed a worse OS in LUAD.

Conclusion

Our findings suggested that *ITGA11* and *ITGB4* might have the potential ability to act as diagnostic biomarkers for both LUAD and LUSC, while *ITGB8* might serve as diagnostic biomarker for LUSC. Furthermore, *ITGB4* could serve as a potential prognostic biomarker for LUAD.

Expression and prognostic analyses of *ITGA11*, *ITGB4* and *ITGB8* in human non-small cell lung cancer

Pancheng Wu[1*], Yanyu Wang[1*], Yijun Wu[3], Ziqi Jia[3], Yang Song[2], Naixin Liang[2†]

[1]Department of Thoracic Surgery, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

[2]Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, Beijing, China

[3]Peking Union Medical College, Eight-Year MD Program, Chinese Academy of Medical Sciences, Beijing 100730, China

Corresponding Author:

Naixin Liang, MD. Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China. Email address: pumchnelson@163.com.

Abstract

Background

Integrins play a crucial role in the regulation process of cell proliferation, migration, differentiation, tumor invasion and metastasis. *ITGA11*, *ITGB4* and *ITGB8* are three encoding genes of integrins family. Accumulative evidences have proved that abnormal expression of *ITGA11*, *ITGB4* and *ITGB8* are a common phenomenon in different malignances. However, their expression patterns and prognostic roles for patients with non-small cell lung cancer (NSCLC) have not been completely illustrated.

Methods

We investigated the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in patients with NSCLC through using a series of databases and various datasets, including ONCOMINE, GEPIA, HPA, TCGA and GEO datasets.

Results

We found that the expression levels of *ITGA11* and *ITGB4* were significantly upregulated in both LUAD and LUSC, while *ITGB8* was obviously upregulated in LUSC. Additionally, higher expression level of *ITGB4* revealed a worse OS in LUAD.

Conclusion

Our findings suggested that *ITGA11* and *ITGB4* might have the potential ability to act as diagnostic biomarkers for both LUAD and LUSC, while *ITGB8* might serve as diagnostic biomarker for LUSC. Furthermore, *ITGB4* could serve as a potential prognostic biomarker for LUAD.

Introduction

Lung cancer is the most frequent malignancy and the leading cause of cancer-related death all over the world. Five-year survival rate for lung cancer patients ranges from 4% to 17% depending on disease stage and regional differences (Hirsch et al. 2017). Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer and responsible for 85% to 90% of all lung cancer (Osmani et al. 2018). Owing to the problems in early diagnosis, patients with NSCLC are often diagnosed at advanced stage, which contributes a lot to the dismal prognosis (Ellis & Vandermeer 2011; Jan et al. 2019). Thus, there is an urgent need to discover new diagnostic and prognostic biomarkers for NSCLC.

Integrins function as bridges between the extracellular matrix (ECM) and the cytoskeleton and work as radars to detect changes in the cellular microenvironment, which enables cells to react according the external milieu (Bianconi et al. 2016; Ginsberg 2014). They play a crucial role in the regulation process of cell proliferation, migration, differentiation, tumor invasion and metastasis (Slack-Davis & Parsons 2004). Integrins family include 24 different transmembrane, multifunctional heterodimers and are composed of an α and a β subunit (Brakebusch et al. 2002). There are 18 different α subunits and 8 different β subunits in human body (Hynes 1992). Recently, the effects of integrins in tumor progression have been receiving a great deal of attention.

ITGA11 encodes integrin subunit α11, which dimerizes with β1 subunit and forms as a cell surface collagen receptor involved in the process of cell migration and collagen reorganization (Tiger et al. 2001). Integrin α11 was overexpressed in the stroma of most head and neck squamous cell carcinomas (HNSCC) and correlated positively with alpha smooth muscle actin expression (Parajuli et al. 2017). In addition, *ITGA11* was overexpressed by cancer-associated fibroblast (CAFs) in Pancreatic Ductal Adenocarcinoma (PDAC) stroma and may serve as an interesting stromal therapeutic target (Schnittert et al. 2019). Integrin subunit β4, also known as a laminin-5 receptor, is a protein encoded by *ITGB4* (Wang et al. 2012). Inhibition of *ITGB4* in glioma cells would decrease the self-renewal abilities of glioma stem cells and suppress the

malignant behaviors of glioma cells in vitro and in vivo (Ma et al. 2019). Moreover, higher *ITGB4* expression level was detected in tumor than adjacent non-tumor tissues in patients with hepatocellular carcinoma (HCC). Silencing of *ITGB4* could repress cell proliferation, colony forming ability and cell invasiveness (Li et al. 2017). Integrin β8, paired with αv subunit, is encoded by *ITGB8*. It has been reported that *ITGB8* is upregulated in laryngeal squamous cell carcinoma (Ni et al. 2012). Additionally, The expression level of *ITGB8* can be regulated by the tumor-promoting receptor tyrosine kinase-EphB4, while knockdown of *ITGB8* may suppress migration and invasion in prostate cancer cell lines (Mertens-Walker et al. 2015). These studies have shown that *ITGA11*, *ITGB4* and *ITGB8* might be candidate biomarkers and therapeutic targets with great potential.

Recent years, there have been developed multifarious platforms, databases as well as various datasets on the web that allow cancer researchers to make in-depth bioinformatic analysis in cancer with multi omics data. Several prognostic biomarkers with great potential for NSCLC have also been identified. For instance, It has been reported that STMN1 expression was correlated with poor OS in patients with Squamous Cell Lung Carcinoma (LUSC) and might serve as a prognostic biomarker (Bao et al. 2017). Using bioinformatics methods, Xie et al. have found that KRT8 expression might be an independent prognostic biomarker for poor OS and PFS in Lung Adenocarcinoma (LUAD) (Xie et al. 2019). Sun et al. have identified five genes that could predict metastasis in NSCLC and might serve as potential targets (Sun et al. 2019). As far as we know, bioinformatics analysis has not been applied to explore the roles of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC. Therefore, we conducted this study to analyze the expression patterns and prognostic values of these three genes in NSCLC based on online databases, platforms and various datasets.

Materials and Methods

ONCOMINE analysis

The expression levels of *ITGA11*, *ITGB4* and *ITGB8* and genes co-expressed with *ITGA11*, *ITGB4* and *ITGB8* were analyzed in ONCOMINE database (https://www.oncomine.org) (Rhodes et al. 2007; Rhodes et al. 2004). The cut-off of *p* value and fold change were defined as 0.01 and 2, respectively (Huang et al. 2019).

GEPIA (Gene Expression Profiling Interactive Analysis) analysis

GEPIA (http://gepia.cancer-pku.cn/) is an interactive web application for gene expression analysis based on 9736 tumors and 8587 normal samples from the TCGA (The Cancer Genome Atlas) and the GTEx (Genotype-Tissue Expression) databases (Tang et al. 2017). The GEPIA database was used to compare mRNA levels of *ITGA11*, *ITGB4* and *ITGB8* between TCGA and GTEx databases. Meanwhile, the association among *ITGA11*, *ITGB4* and *ITGB8* in NSCLC were also analyzed in GEPIA.

Bioinformatics analysis of data using The Cancer Genome Atlas lung cancer datasets

The level 3 data of TCGA-LUAD and TCGA-LUSC were obtained from UCSC Xena platform (https://xenabrowser.net/datapages/) (Goldman et al. 2015) and RTCGA package (https://rtcga.github.io/RTCGA). The LUAD and LUSC gene expression RNAseq datasets included 524 tumor tissues and 499 tumor tissues, respectively. 502 of the LUAD patients and 492 of the 499 LUSC patients had complete survival data. The differences in overall survival (OS) of LUAD and LUSC patients with high and low expression of *ITGA11*, *ITGB4* and *ITGB8* were assessed by Kaplan-Meier curves. Meanwhile, the association between tumor stage and the expression levels of *ITGA11*, *ITGB4* and *ITGB8* were also analyzed. Clinicopathological parameters, including age at diagnosis, gender, vital status, tumor stage, smoking history and OS time, were extracted for univariate and multivariate cox regression analysis.

Gene Expression Omnibus (GEO) microarray datasets analysis

To validate the expression profiles of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC, we collected a total of 21 datasets including tumor and non-tumor tissues of NSCLC in GEO database (https://www.ncbi.nlm.nih.gov/geo/). We analyzed the mRNA levels of *ITGA11*, *ITGB4* and *ITGB8* between tumor and non-tumor controls for each GEO dataset. In addition, we performed a meta-analysis based on the enrolled GEO microarray datasets.

Immunohistochemistry analysis

The protein expression of *ITGA11*, *ITGB4* and *ITGB8* in normal lung and tumor tissues were examined using the Human Protein Atlas (HPA) (https://www.proteinatlas.org/) (Uhlen et al. 2015; Uhlen et al. 2017).

Statistical analysis

Statistical analysis was performed on R software (3.6.1) (https://www.r-project.org/) and an integrated development environment RStudio (1.2.1335) (https://rstudio.com/). The mRNA expression of *ITGA11*, *ITGB4* and *ITGB8* between NSCLC tissues and normal controls were

compared using Student's t-test. Data visualization was performed using an R package called "ggstatsplot" (https://CRAN.R-project.org/package=ggstatsplot). Kaplan-Meier curves of OS were performed in TCGA-LUAD and TCGA-LUSC raw data by setting median expression of *ITGA11*, *ITGB4* and *ITGB8* as cut-off. Statistical differences were assessed by the log-rank test. Univariate and multivariate survival analyses were performed using cox regression model, risk factors ($p < 0.2$) analyzed by univariate analysis were selected for multivariate analysis.

For GEO datasets analysis, mean (M) and standard deviation (SD) were calculated for each NSCLC tumor and normal control group. In addition, an R package called "meta" was used in R to perform a comprehensive meta-analysis (Schwarzer 2007). The Q test and I^2 statistic were calculated to assess the heterogeneity among the enrolled studies. If $p < 0.05$ or $I^2 > 50\%$, a random effects model would be selected. Sensitivity analysis was conducted to explore whether a specific study played a crucial influence in significant heterogeneity. Finally, the publication bias was examined through funnel plots and Egger's test (Egger et al. 1997). Once there was a publication bias, the "fill and trim" method would be selected to adjust for the bias (Duval & Tweedie 2000). $p < 0.05$ deemed statistically significant.

Results

The expression levels of *ITGA11*, *ITGB4* and *ITGB8* in patients with non-small cell lung cancer.

Using ONCOMINE database, we investigated the transcription levels of *ITGA11*, *ITGB4* and *ITGB8* in lung cancer vs. normal samples. ONCOMINE analysis revealed that the mRNA expression of *ITGA11*, *ITGB4* and *ITGB8* were obviously overexpressed in NSCLC tissues in ten datasets (Figure 1). These datasets were summarized in Table 1. The GEPIA analysis results also suggested that the expression levels of *ITGA11* and *ITGB4* were significantly higher in both LUAD and LUSC than that in normal tissues, while the expression level of *ITGB8* was only significantly upregulated in LUSC tissues (Figure 2). Furthermore, we analyzed *ITGA11*, *ITGB4* and *ITGB8* mRNA expression level in both lung cancer and normal tissues using the TCGA-LUAD and TCGA-LUSC original data. The results revealed that the expression levels of *ITGA11, ITGB4* and *ITGB8* were all significantly upregulated in tumor tissues compared with normal tissues (Figure S1).

To further explore the protein expression of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC, we analyzed the IHC images using the Human Protein Atlas (HPA) database. As shown in Figure 3,

the protein expression of *ITGA11* and *ITGB4* were upregulated in both LUAD and LUSC cancer tissues compared with normal lung tissues (Figure 3A-C and Figure 3D-F). In comparison, the protein expression of *ITGB8* was obviously upregulated in LUSC with medium staining, but not in LUAD (Figure 3G-I).

Confirmation of the expression profiles of *ITGA11*, *ITGB4* and *ITGB8* in non-small cell lung cancer using GEO datasets.

We also performed a data-mining analysis to investigate the differences in the expression levels of *ITGA11*, *ITGB4* and *ITGB8* between tumor and normal tissues in NSCLC using GEO datasets. The main characteristics of the enrolled GEO studies were described in Table S1. The results were shown in Figure 4 and Figure S2-S4. As illustrated in Figure 4A and Figure S2D, the expression level of *ITGB4* was significantly increased in tissues from patients with LUAD (SMD: 0.94; 95%CI: 0.65-1.24; $p < 0.01$) as well as LUSC (SMD:1.37; 95% CI: 0.71-2.04; $p < 0.01$) compared to the normal tissues. The heterogeneity was apparent for LUAD ($I^2 = 80\%$; $p < 0.01$) and LUSC ($I^2 = 89\%$; $p < 0.01$). The following sensitivity analysis demonstrated that no study was found to have a vital influence in the enrolled studies (Figure 4B and Figure S3D). In addition, we didn't find evidence of publication bias based on the funnel plot and the Egger's test (Figure 4C, $p = 0.7759$). However, the Figure S4D indicated publication bias (Egger's test, $p = 0.04729$). Therefore, we used the fill and trim method to adjust for the bias. The adjusted random effects model result showed that *ITGB4* was also significantly upregulated in LUSC tissues (SMD: 0.77; 95%CI: 0.03-1.52; $p = 0.04$).

The analysis results of *ITGA11* and *ITGB8* mRNA levels in LUAD and LUSC were the same as the above results (Figure S2-S4). The separate analyses of the expression levels of *ITGA11*, *ITGB4* and *ITGB8* in LUAD and LUSC tissues compared with normal tissues for each GEO dataset were presented in the Figure S5 and Figure S6.

The prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in non-small cell lung cancer.

By using GEPIA, we investigated the prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC. The survival curves revealed that high expression level of *ITGB4* could indicate a poor OS in LUAD ($p < 0.001$; Figure 5B), while *ITGA11* and *ITGB8* were not related with OS in LUAD ($p = 0.064$ and $p = 0.78$, respectively, Figure 5A and 5C). In comparison, there were no obvious associations between the expression levels of ITAG11, ITGB4 and ITGB8 and LUSC

(Figure 5D-5F). Moreover, using the TCGA original data, we performed survival analysis to validate these associations. The results were consistent with GEPIA analysis (Figure S7).

Next, we performed cox regression analysis to further assess and validate the prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC based on TCGA original data. The univariate cox analysis indicated that high *ITGB4* expression and advanced stages were significantly correlated with worse OS in LUAD (Table 2). Meanwhile, multivariate cox analysis confirmed that high *ITGB4* expression was an independent prognostic biomarker for patients with LUAD (HR: 1.417; 95%CI: 1.042-1.926; $p = 0.026$; Table 2). In addition, no significant results were found with other genes in the OS of LUAD and LUSC (Table 2). These results were consistent with that analyzed by GEPIA. Furthermore, we investigated the correlation between tumor stage and the expression levels of *ITGA11*, *ITGB4* and *ITGB8* (Figure S8). The results showed that there was a significant correlation between tumor stage and mRNA expression of *ITGB8* in LUSC (Figure S8F).

Co-expression and correlation analyses of *ITGA11*, *ITGB4* and *ITGB8* in non-small cell lung cancer.

The co-expression analysis was conducted using ONCOMINE database. Based on Hou Lung dataset (Hou et al. 2010), we analyzed genes that were co-expressed with *ITGA11*, the result showed that *ITGA11* was co-expressed with COL10A1, THBS2, SULF1, CTRHC1, GREM1, C5orf46, COL11A1, NOX4 (Figure S9A). The Bild Lung dataset indicated that ITGB4 was co-expressed with LAD1, SFN, FXYD3, KRT19, DSG2, JUP, DSP, PERP (Bild et al. 2006) (Figure S9B). Based on Yamagata Lung dataset (Yamagata et al. 2003), we analyzed genes that were co-expressed with *ITGB8*, the result showed that *ITGB8* was co-expressed with ERC2, PDE6D, C17orf99, SNRNP27, C1orf61, GATA1, PPP2R2B, CCK, CRYBA1, APBA3, CYP3A4, UROS (Figure S9C).

By using GEPIA, we investigated the association among *ITGA11*, *ITGB4* and *ITGB8* in NSCLC based on Pearson correlation analysis. The results indicated that there was no correlation between *ITGA11* and *ITGB4* ($R = - 0.018$; $p > 0.05$) (Figure S10A). Also, there was scarcely any correlation between *ITGA11* and *ITGB8* ($R = 0.069$; $p < 0.05$) (Figure S10B). In addition, a weak positive correlation was found between *ITGB8* and *ITGB4* ($R = 0.32$; $p < 0.05$) (Figure S10C).

Discussion

Numerous studies have suggested that *ITGA11*, *ITGB4* and *ITGB8* are involved in

migration, epithelial-mesenchymal transition, invasion, and metastasis in different cancers (Gan et al. 2018; Huang et al. 2017; Kitajiri et al. 2002; Li et al. 2017). The aberrant expression of *ITGA11*, *ITGB4*, and *ITGB8* have been reported in many cancers (Grossman et al. 2000; Mertens-Walker et al. 2015; Parajuli et al. 2017; Tagliabue et al. 1998). Regrettably, the expression profiles and prognostic roles of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC are still not clear. Thus, we conducted this study to explore the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC.

It has been reported that *ITGA11* could serve as an important stromal factor in NSCLC, which can enhance tumorigenicity of human non-small cell lung cancer cells by regulating IGF2 expression in fibroblasts (Zhu et al. 2007). Moreover, in carcinoma-associated fibroblasts (CAFs), *ITGA11* signaling pathway may play an important role in carcinoma-associated fibroblasts (CAFs), which means Integrin α11β1 can promote tumor growth and metastatic potential of NSCLC cells by regulating cancer stromal stiffness (Navab et al. 2016). These results suggested that *ITGA11* might play an important role for NSCLC. In our study, ONCOMINE analysis showed that mRNA expression level of *ITGA11* was highly expressed in Lung Adenocarcinoma compared with that in normal controls. GEPIA revealed that the expression level of *ITGA11* was obviously higher in both LUAD and LUSC than that in normal tissues. In addition, we also downloaded TCGA original data, GEO datasets, and protein data from HPA to validate *ITGA11* expression profile, the results were consistent with the GEPIA analysis results. These results indicated that *ITGA11* might be a diagnostic biomarker for patients with LUAD and LUSC. Furthermore, we investigated the association between the expression level of *ITGA11* and OS in LUAD and LUSC using GEPIA and cox regression analysis. However, the results showed *ITGA11* expression had no prognostic role in terms of OS in LUAD and LUSC.

ITGB4 was found to have a strong positive correlation with tumor size ($p = 0.01$) and tumor nuclear grade ($p < 0.01$) in early breast cancer (Diaz et al. 2005). Furthermore, it is reported that *ITGB4* could promote the invasion and metastasis of tumor cells through a series of processes (Stewart & O'Connor 2015). These results imply us that *ITGB4* might also play a crucial role in NSCLC. In our report, ONCOMINE and GEPIA analysis revealed that the expression level of *ITGB4* was significantly upregulated in LUAD and LUSC. Additionally, we confirmed this expression feature by analysis TCGA original data and GEO datasets. The protein

level was also consistent with the mRNA expression level. Taken together, these results implied that *ITGB4* expression could act as a diagnostic biomarker for patients with LUAD and LUSC. Moreover, the survival curve showed that high *ITGB4* expression was strong correlated with inferior OS in LUAD. The following univariate cox and multivariate cox regression analysis confirmed that high *ITGB4* expression level was an independent prognostic biomarker for poor OS in LUAD.

It has been reported that *ITGB8* could mediate the activation of latent TGF-β, which subsequently derives the epithelial-to-mesenchymal (EMT) transition of some cancers and contributes to cancer cell migration and growth (Mu et al. 2002; Pozzi & Zent 2011). Furthermore, *ITGB8* was significantly upregulated in ovarian cancer tissues compared with that in normal ovary tissues (He et al. 2018). Moreover, It has been reported that *ITGB8* silencing could suppress the metastatic potential of human lung cancer cell lines A549 and PC (Xu & Wu 2012). These studies suggested that *ITGB8* might play an important role in NSCLC. In our study, we found that the mRNA expression level of *ITGB8* was highly overexpressed in LUSC both in ONCOMINE and GEPIA analysis. This expression feature was successfully validated by analyzing the TCGA original data and GEO datasets. These results suggested that *ITGB8* might act as a diagnostic biomarker in LUSC. It was worth mentioning that there was no significant correlation in *ITGB8* expression level between LUAD and normal tissues by GEPIA analysis. However, the expression feature was not showed when we analyzed the TCGA original data and GEO datasets. This may due to the lack of normal controls in TCGA datasets and the differences in enrolled participants in GEO datasets. Future large-scale studies are required to assess and validate this expression pattern. In addition, we explored the association between the expression level of *ITGB8* and OS in LUAD and LUSC using GEPIA and cox regression analysis. the results showed *ITGB8* expression had no prognostic role in terms of OS in LUAD and LUSC. Furthermore, we found that there was a strong correlation between *ITGB8* expression level and tumor stage in LUSC.

The potential limitations of our study need to be noted. First, the biological mechanisms of these three candidate markers in LUAD and LUSC are still unknown. Second, although this study had a comprehensive analysis based on several databases such as TCGA and GEO, traditional in-house experimental studies including enough specimens are required to further validate our findings.

Conclusions

In summary, we systematically analyzed the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in patients with LUAD and LUSC by conducting a bioinformatics analysis based on several web platforms and various datasets. Our results indicated that *ITGA11* and *ITGB4* might act as diagnostic biomarkers for both LUAD and LUSC, while *ITGB8* may serve as diagnostic biomarker for LUSC. Furthermore, *ITGB4* might serve as a potential prognostic biomarker for LUAD. We hope our findings will enrich the knowledge of diagnostic and therapy designs for patients with NSCLC.

Acknowledgements

We'd like to thank Dr. Yi Zheng for her kind encouragement during the study period.

References:

Bao P, Yokobori T, Altan B, Iijima M, Azuma Y, Onozato R, Yajima T, Watanabe A, Mogi A, Shimizu K, Nagashima T, Ohtaki Y, Obayashi K, Nakazawa S, Bai T, Kawabata-Iwakawa R, Asao T, Kaira K, Nishiyama M, and Kuwano H. 2017. High STMN1 Expression is Associated with Cancer Progression and Chemo-Resistance in Lung Squamous Cell Carcinoma. *Ann Surg Oncol* 24:4017-4024. 10.1245/s10434-017-6083-0

Bianconi D, Unseld M, and Prager GW. 2016. Integrins in the Spotlight of Cancer. *Int J Mol Sci* 17. 10.3390/ijms17122037

Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, Joshi MB, Harpole D, Lancaster JM, Berchuck A, Olson JA, Jr., Marks JR, Dressman HK, West M, and Nevins JR. 2006. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. *Nature* 439:353-357. 10.1038/nature04296

Brakebusch C, Bouvard D, Stanchi F, Sakai T, and Fassler R. 2002. Integrins in invasive growth. *J Clin Invest* 109:999-1006. 10.1172/JCI15468

Diaz LK, Cristofanilli M, Zhou X, Welch KL, Smith TL, Yang Y, Sneige N, Sahin AA, and Gilcrease MZ. 2005. Beta4 integrin subunit gene expression correlates with tumor size and nuclear grade in early breast cancer. *Mod Pathol* 18:1165-1175. 10.1038/modpathol.3800411

Duval S, and Tweedie R. 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56:455-463.

Egger M, Davey Smith G, Schneider M, and Minder C. 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629-634. 10.1136/bmj.315.7109.629

Ellis PM, and Vandermeer R. 2011. Delays in the diagnosis of lung cancer. *J Thorac Dis* 3:183-188. 10.3978/j.issn.2072-1439.2011.01.01

Gan L, Meng J, Xu M, Liu M, Qi Y, Tan C, Wang Y, Zhang P, Weng W, Sheng W, Huang M, and Wang Z. 2018. Extracellular matrix protein 1 promotes cell metastasis and glucose metabolism by inducing integrin beta4/FAK/SOX2/HIF-1alpha signaling pathway in gastric cancer. *Oncogene* 37:744-755. 10.1038/onc.2017.363

Ginsberg MH. 2014. Integrin activation. *BMB Rep* 47:655-659.
Goldman M, Craft B, Swatloski T, Cline M, Morozova O, Diekhans M, Haussler D, and Zhu J. 2015. The UCSC Cancer Genomics Browser: update 2015. *Nucleic Acids Res* 43:D812-817. 10.1093/nar/gku1073
Grossman HB, Lee C, Bromberg J, and Liebert M. 2000. Expression of the alpha6beta4 integrin provides prognostic information in bladder cancer. *Oncol Rep* 7:13-16.
He J, Liu Y, Zhang L, and Zhang H. 2018. Integrin Subunit beta 8 (ITGB8) Upregulation Is an Independent Predictor of Unfavorable Survival of High-Grade Serous Ovarian Carcinoma Patients. *Med Sci Monit* 24:8933-8940. 10.12659/MSM.911518
Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ, Jr., Wu YL, and Paz-Ares L. 2017. Lung cancer: current therapies and new targeted treatments. *Lancet* 389:299-311. 10.1016/S0140-6736(16)30958-8
Hou J, Aerts J, den Hamer B, van Ijcken W, den Bakker M, Riegman P, van der Leest C, van der Spek P, Foekens JA, Hoogsteden HC, Grosveld F, and Philipsen S. 2010. Gene expression-based classification of non-small cell lung carcinomas and survival prediction. *PLoS One* 5:e10312. 10.1371/journal.pone.0010312
Huang C, Liu J, Xiong B, Yonemura Y, and Yang X. 2019. Expression and prognosis analyses of forkhead box A (FOXA) family in human lung cancer. *Gene* 685:202-210. 10.1016/j.gene.2018.11.022
Huang L, Cai JL, Huang PZ, Kang L, Huang MJ, Wang L, and Wang JP. 2017. miR19b-3p promotes the growth and metastasis of colorectal cancer via directly targeting ITGB8. *Am J Cancer Res* 7:1996-2008.
Hynes RO. 1992. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 69:11-25.
Jan YH, Lai TC, Yang CJ, Huang MS, and Hsiao M. 2019. A co-expressed gene status of adenylate kinase 1/4 reveals prognostic gene signature associated with prognosis and sensitivity to EGFR targeted therapy in lung adenocarcinoma. *Sci Rep* 9:12329. 10.1038/s41598-019-48243-9
Kitajiri S, Hosaka N, Hiraumi H, Hirose T, and Ikehara S. 2002. Increased expression of integrin beta-4 in papillary thyroid carcinoma with gross lymph node metastasis. *Pathol Int* 52:438-441.
Li XL, Liu L, Li DD, He YP, Guo LH, Sun LP, Liu LN, Xu HX, and Zhang XP. 2017. Integrin beta4 promotes cell invasion and epithelial-mesenchymal transition through the modulation of Slug expression in hepatocellular carcinoma. *Sci Rep* 7:40464. 10.1038/srep40464
Ma B, Zhang L, Zou Y, He R, Wu Q, Han C, and Zhang B. 2019. Reciprocal regulation of integrin beta4 and KLF4 promotes gliomagenesis through maintaining cancer stem cell traits. *J Exp Clin Cancer Res* 38:23. 10.1186/s13046-019-1034-1
Mertens-Walker I, Fernandini BC, Maharaj MS, Rockstroh A, Nelson CC, Herington AC, and Stephenson SA. 2015. The tumour-promoting receptor tyrosine kinase, EphB4, regulates expression of integrin-beta8 in prostate cancer cells. *BMC Cancer* 15:164. 10.1186/s12885-015-1164-6
Mu D, Cambier S, Fjellbirkeland L, Baron JL, Munger JS, Kawakatsu H, Sheppard D, Broaddus VC, and Nishimura SL. 2002. The integrin alpha(v)beta8 mediates epithelial homeostasis through MT1-MMP-dependent activation of TGF-beta1. *J Cell Biol* 157:493-507. 10.1083/jcb.200109100
Navab R, Strumpf D, To C, Pasko E, Kim KS, Park CJ, Hai J, Liu J, Jonkman J, Barczyk M, Bandarchi B, Wang YH, Venkat K, Ibrahimov E, Pham NA, Ng C, Radulovich N, Zhu CQ, Pintilie M, Wang D, Lu A, Jurisica I, Walker GC, Gullberg D, and Tsao MS. 2016. Integrin alpha11beta1 regulates cancer stromal stiffness and promotes tumorigenicity and metastasis in non-small cell lung cancer. *Oncogene* 35:1899-1908. 10.1038/onc.2015.254
Ni RS, Shen X, Qian X, Yu C, Wu H, and Gao X. 2012. Detection of differentially expressed genes and association with clinicopathological features in laryngeal squamous cell carcinoma.

Oncol Lett 4:1354-1360. 10.3892/ol.2012.920

Osmani L, Askin F, Gabrielson E, and Li QK. 2018. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): Moving from targeted therapy to immunotherapy. *Semin Cancer Biol* 52:103-109. 10.1016/j.semcancer.2017.11.019

Parajuli H, Teh MT, Abrahamsen S, Christoffersen I, Neppelberg E, Lybak S, Osman T, Johannessen AC, Gullberg D, Skarstein K, and Costea DE. 2017. Integrin alpha11 is overexpressed by tumour stroma of head and neck squamous cell carcinoma and correlates positively with alpha smooth muscle actin expression. *J Oral Pathol Med* 46:267-275. 10.1111/jop.12493

Pozzi A, and Zent R. 2011. TGF-beta sequestration by mesangial cell integrin alphavbeta8: A novel mechanism of glomerular endothelial cell regulation. *Am J Pathol* 178:485-489. 10.1016/j.ajpath.2010.10.038

Rhodes DR, Kalyana-Sundaram S, Mahavisno V, Varambally R, Yu J, Briggs BB, Barrette TR, Anstet MJ, Kincead-Beal C, Kulkarni P, Varambally S, Ghosh D, and Chinnaiyan AM. 2007. Oncomine 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles. *Neoplasia* 9:166-180.

Rhodes DR, Yu J, Shanker K, Deshpande N, Varambally R, Ghosh D, Barrette T, Pandey A, and Chinnaiyan AM. 2004. ONCOMINE: a cancer microarray database and integrated data-mining platform. *Neoplasia* 6:1-6.

Schnittert J, Bansal R, Mardhian DF, van Baarlen J, Ostman A, and Prakash J. 2019. Integrin alpha11 in pancreatic stellate cells regulates tumor stroma interaction in pancreatic cancer. *FASEB J*:fj201802336R. 10.1096/fj.201802336R

Schwarzer G. 2007. meta: An R Package for Meta-Analysis. *R News* 7:40-45.

Slack-Davis JK, and Parsons JT. 2004. Emerging views of integrin signaling: implications for prostate cancer. *J Cell Biochem* 91:41-46. 10.1002/jcb.10665

Stewart RL, and O'Connor KL. 2015. Clinical significance of the integrin alpha6beta4 in human malignancies. *Lab Invest* 95:976-986. 10.1038/labinvest.2015.82

Sun R, Meng X, Wang W, Liu B, Lv X, Yuan J, Zeng L, Chen Y, Yuan B, and Yang S. 2019. Five genes may predict metastasis in non-small cell lung cancer using bioinformatics analysis. *Oncol Lett* 18:1723-1732. 10.3892/ol.2019.10498

Tagliabue E, Ghirelli C, Squicciarini P, Aiello P, Colnaghi MI, and Menard S. 1998. Prognostic value of alpha 6 beta 4 integrin expression in breast carcinomas is affected by laminin production from tumor cells. *Clin Cancer Res* 4:407-410.

Tang Z, Li C, Kang B, Gao G, Li C, and Zhang Z. 2017. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res* 45:W98-W102. 10.1093/nar/gkx247

Tiger CF, Fougerousse F, Grundstrom G, Velling T, and Gullberg D. 2001. alpha11beta1 integrin is a receptor for interstitial collagens involved in cell migration and collagen reorganization on mesenchymal nonmuscle cells. *Dev Biol* 237:116-129. 10.1006/dbio.2001.0363

Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson A, Kampf C, Sjostedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J, and Ponten F. 2015. Proteomics. Tissue-based map of the human proteome. *Science* 347:1260419. 10.1126/science.1260419

Uhlen M, Zhang C, Lee S, Sjostedt E, Fagerberg L, Bidkhori G, Benfeitas R, Arif M, Liu Z, Edfors F, Sanli K, von Feilitzen K, Oksvold P, Lundberg E, Hober S, Nilsson P, Mattsson J, Schwenk JM, Brunnstrom H, Glimelius B, Sjoblom T, Edqvist PH, Djureinovic D, Micke P, Lindskog C, Mardinoglu A, and Ponten F. 2017. A pathology atlas of the human cancer

transcriptome. *Science* 357. 10.1126/science.aan2507

Wang L, Dong Z, Zhang Y, and Miao J. 2012. The roles of integrin beta4 in vascular endothelial cells. *J Cell Physiol* 227:474-478. 10.1002/jcp.22769

Xie L, Dang Y, Guo J, Sun X, Xie T, Zhang L, Yan Z, Amin H, and Guo X. 2019. High KRT8 Expression Independently Predicts Poor Prognosis for Lung Adenocarcinoma Patients. *Genes (Basel)* 10. 10.3390/genes10010036

Xu Z, and Wu R. 2012. Alteration in metastasis potential and gene expression in human lung cancer cell lines by ITGB8 silencing. *Anat Rec (Hoboken)* 295:1446-1454. 10.1002/ar.22521

Yamagata N, Shyr Y, Yanagisawa K, Edgerton M, Dang TP, Gonzalez A, Nadaf S, Larsen P, Roberts JR, Nesbitt JC, Jensen R, Levy S, Moore JH, Minna JD, and Carbone DP. 2003. A training-testing approach to the molecular classification of resected non-small cell lung cancer. *Clin Cancer Res* 9:4695-4704.

Zhu CQ, Popova SN, Brown ER, Barsyte-Lovejoy D, Navab R, Shih W, Li M, Lu M, Jurisica I, Penn LZ, Gullberg D, and Tsao MS. 2007. Integrin alpha 11 regulates IGF2 expression in fibroblasts to enhance tumorigenicity of human non-small-cell lung cancer cells. *Proc Natl Acad Sci U S A* 104:11754-11759. 10.1073/pnas.0703040104

Table 1(on next page)

The transcription levels of ITGA11, ITGB4 and ITGB8 between lung cancer and normal samples in ONCOMINE database.

Gene ID	Types of lung cancer vs. normal	Fold change	P value	t-Test	References
ITGA11	Lung Adenocarcinoma vs. Normal	2.047	6.79E-16	10.685	(Selamat et al. 2012)
	Lung Adenocarcinoma vs. Normal	2.968	7.47E-09	7.945	(Okayama et al. 2012)
ITGB4	Squamous Cell Lung Carcinoma vs. Normal	2.867	1.32E-05	8.706	(Wachi et al. 2005)
	Squamous Cell Lung Carcinoma vs. Normal	3.505	5.33E-06	6.406	(Garber et al. 2001)
	Squamous Cell Lung Carcinoma vs. Normal	2.637	4.64E-10	7.458	(Talbot et al. 2005)
	Squamous Cell Lung Carcinoma vs. Normal	6.818	5.21E-04	3.57	(Bhattacharjee et al. 2001)
	Lung Adenocarcinoma vs. Normal	2.99	1.17E-14	9.575	(Selamat et al. 2012)
	Squamous Cell Lung Carcinoma vs. Normal	3.591	8.92E-10	8.599	(Hou et al. 2010)
ITGB8	Squamous Cell Lung Carcinoma vs. Normal	2.455	1.95E-05	5.627	(Garber et al. 2001)
	Squamous Cell Lung Carcinoma vs. Normal	2.876	1.26E-07	6.484	(Hou et al. 2010)

References:

Bhattacharjee A, Richards WG, Staunton J, Li C, Monti S, Vasa P, Ladd C, Beheshti J, Bueno R, Gillette M, Loda M, Weber G, Mark EJ, Lander ES, Wong W, Johnson BE, Golub TR, Sugarbaker DJ, and Meyerson M. 2001. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. *Proc Natl Acad Sci U S A* 98:13790-13795. 10.1073/pnas.191502998

Garber ME, Troyanskaya OG, Schluens K, Petersen S, Thaesler Z, Pacyna-Gengelbach M, van de Rijn M, Rosen GD, Perou CM, Whyte RI, Altman RB, Brown PO, Botstein D, and Petersen I. 2001. Diversity of gene expression in adenocarcinoma of the lung. *Proc Natl Acad Sci U S A* 98:13784-13789. 10.1073/pnas.241500798

Hou J, Aerts J, den Hamer B, van Ijcken W, den Bakker M, Riegman P, van der Leest C, van der Spek P, Foekens JA, Hoogsteden HC, Grosveld F, and Philipsen S. 2010. Gene expression-based classification of non-small cell lung carcinomas and survival prediction. *PLoS One* 5:e10312. 10.1371/journal.pone.0010312

Okayama H, Kohno T, Ishii Y, Shimada Y, Shiraishi K, Iwakawa R, Furuta K, Tsuta K, Shibata T, Yamamoto S, Watanabe S, Sakamoto H, Kumamoto K, Takenoshita S, Gotoh N, Mizuno H, Sarai A, Kawano S, Yamaguchi R, Miyano S, and Yokota J. 2012. Identification of genes upregulated in ALK-positive and EGFR/KRAS/ALK-negative lung adenocarcinomas. *Cancer Res* 72:100-111. 10.1158/0008-5472.CAN-11-1403

Selamat SA, Chung BS, Girard L, Zhang W, Zhang Y, Campan M, Siegmund KD, Koss MN, Hagen JA, Lam WL, Lam S, Gazdar AF, and Laird-Offringa IA. 2012. Genome-scale analysis of DNA methylation in lung adenocarcinoma and integration with mRNA expression. *Genome Res* 22:1197-1211. 10.1101/gr.132662.111

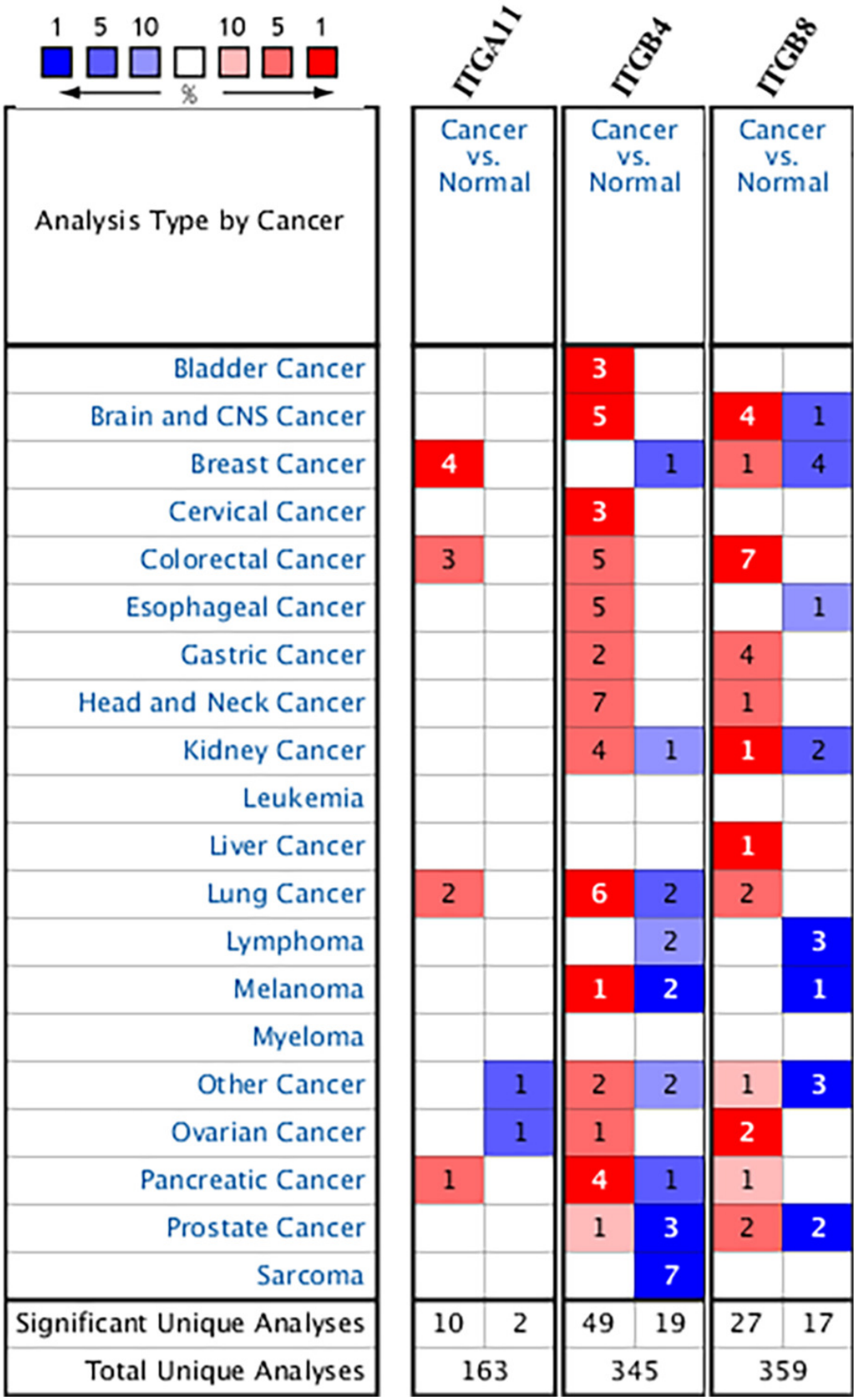
Talbot SG, Estilo C, Maghami E, Sarkaria IS, Pham DK, P Oc, Socci ND, Ngai I, Carlson D, Ghossein R, Viale A, Park BJ, Rusch VW, and Singh B. 2005. Gene expression profiling allows distinction between primary and metastatic squamous cell carcinomas in the lung. *Cancer Res* 65:3063-3071. 10.1158/0008-5472.CAN-04-1985

Wachi S, Yoneda K, and Wu R. 2005. Interactome-transcriptome analysis reveals the high centrality of genes differentially expressed in lung cancer tissues. *Bioinformatics* 21:4205-4208. 10.1093/bioinformatics/bti688

Figure 1

The transcription levels of ITGA11, ITGB4 and ITGB8 in different cancers compared with normal tissues in the ONCOMINE dabase.

Cell color is determined by the best gene rank percentile for the analysis within the cell



Analysis Type by Cancer	ITGA11 Cancer vs. Normal		ITGB4 Cancer vs. Normal		ITGB8 Cancer vs. Normal	
Bladder Cancer			3			
Brain and CNS Cancer			5		4	1
Breast Cancer	4			1	1	4
Cervical Cancer			3			
Colorectal Cancer	3		5		7	
Esophageal Cancer			5			1
Gastric Cancer			2		4	
Head and Neck Cancer			7		1	
Kidney Cancer			4	1	1	2
Leukemia						
Liver Cancer					1	
Lung Cancer	2		6	2	2	
Lymphoma				2		3
Melanoma			1	2		1
Myeloma						
Other Cancer		1	2	2	1	3
Ovarian Cancer		1	1		2	
Pancreatic Cancer	1		4	1	1	
Prostate Cancer			1	3	2	2
Sarcoma				7		
Significant Unique Analyses	10	2	49	19	27	17
Total Unique Analyses	163		345		359	

Figure 2

The expression levels of ITGA11 (A), ITGB4 (B) and ITGB8 (C) between NSCLC tissues and normal tissues in GEPIA

*Indicate that the results are statistically significant.

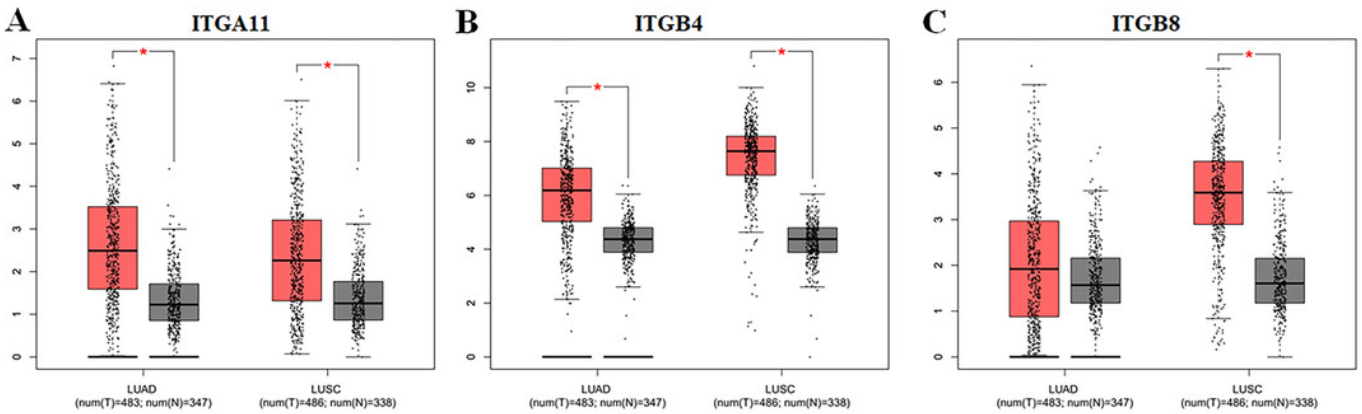


Figure 3

Immunohistochemistry analysis for ITGA11, ITGB4 and ITGB8 in NSCLC (HPA database).

(A-F) The protein expression of ITGA11 and ITGB4 were significantly higher in both LUAD and LUSC tissues compared with the normal lung, respectively. (G-I) The protein expression level of ITGB8 was significantly higher in LUSC tissues compared with the normal lung.

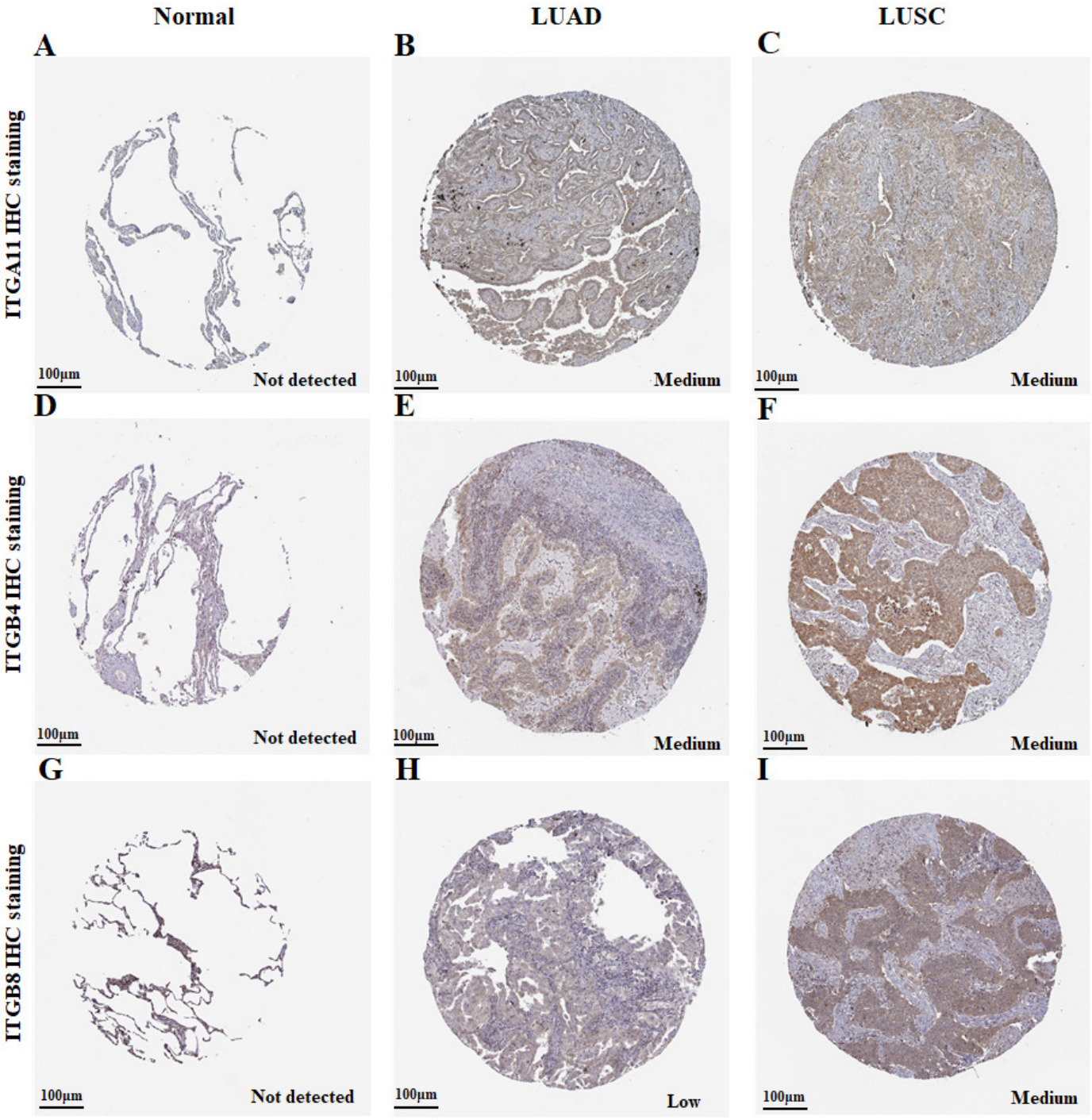

Normal
LUAD
LUSC
A
B
C
D
E
F
G
H
I
ITGA11 IHC staining
ITGB4 IHC staining
ITGB8 IHC staining
100μm
Not detected
Medium
Low

Figure 4

Meta-analysis of ITGB4 expression in LUAD tissues compared with normal controls based on GEO datasets

(A) Forest plot of SMD comparing ITGB4 expression in LUAD tissues with normal controls from the enrolled GEO datasets. (B) Sensitivity analysis of the enrolled GEO datasets. (C) The evaluation of the publication bias of the enrolled GEO datasets (Egger's test, $p = 0.7759$).

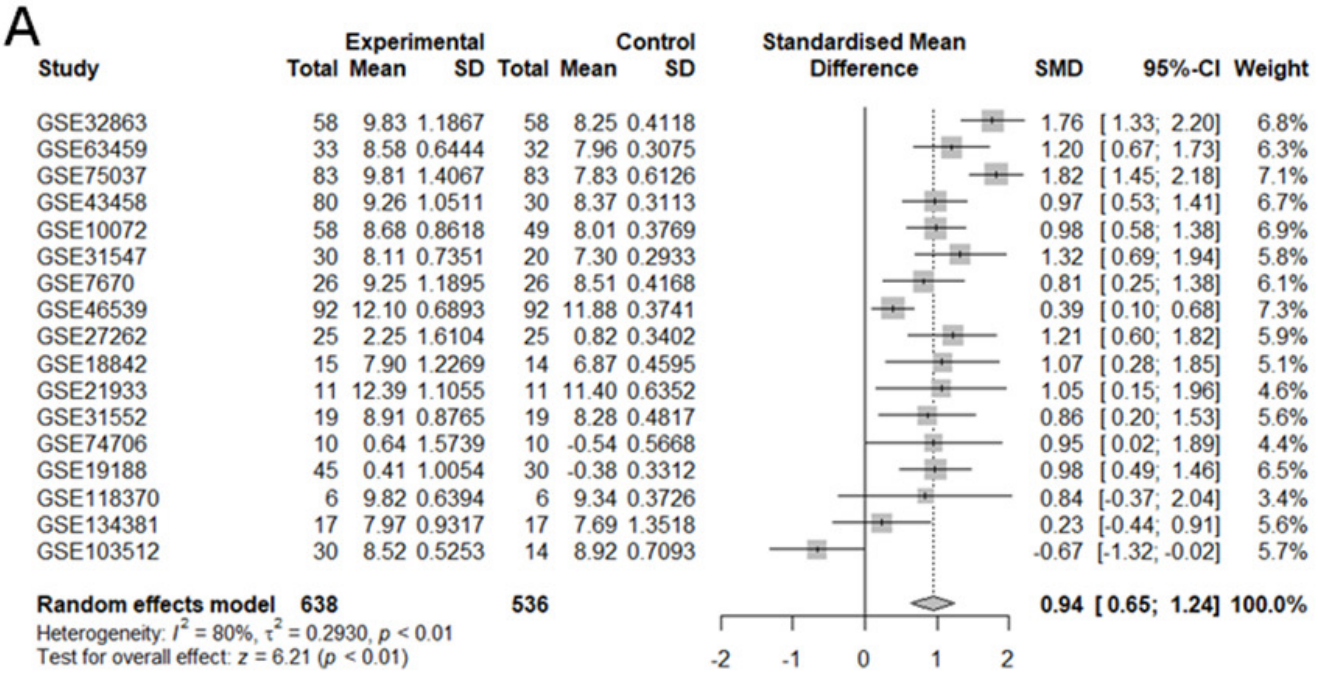

A
Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI Weight
GSE32863 58 9.83 1.1867 58 8.25 0.4118 1.76 [1.33; 2.20] 6.8%
GSE63459 33 8.58 0.6444 32 7.96 0.3075 1.20 [0.67; 1.73] 6.3%
GSE75037 83 9.81 1.4067 83 7.83 0.6126 1.82 [1.45; 2.18] 7.1%
GSE43458 80 9.26 1.0511 30 8.37 0.3113 0.97 [0.53; 1.41] 6.7%
GSE10072 58 8.68 0.8618 49 8.01 0.3769 0.98 [0.58; 1.38] 6.9%
GSE31547 30 8.11 0.7351 20 7.30 0.2933 1.32 [0.69; 1.94] 5.8%
GSE7670 26 9.25 1.1895 26 8.51 0.4168 0.81 [0.25; 1.38] 6.1%
GSE46539 92 12.10 0.6893 92 11.88 0.3741 0.39 [0.10; 0.68] 7.3%
GSE27262 25 2.25 1.6104 25 0.82 0.3402 1.21 [0.60; 1.82] 5.9%
GSE18842 15 7.90 1.2269 14 6.87 0.4595 1.07 [0.28; 1.85] 5.1%
GSE21933 11 12.39 1.1055 11 11.40 0.6352 1.05 [0.15; 1.96] 4.6%
GSE31552 19 8.91 0.8765 19 8.28 0.4817 0.86 [0.20; 1.53] 5.6%
GSE74706 10 0.64 1.5739 10 -0.54 0.5668 0.95 [0.02; 1.89] 4.4%
GSE19188 45 0.41 1.0054 30 -0.38 0.3312 0.98 [0.49; 1.46] 6.5%
GSE118370 6 9.82 0.6394 6 9.34 0.3726 0.84 [-0.37; 2.04] 3.4%
GSE134381 17 7.97 0.9317 17 7.69 1.3518 0.23 [-0.44; 0.91] 5.6%
GSE103512 30 8.52 0.5253 14 8.92 0.7093 -0.67 [-1.32; -0.02] 5.7%
Random effects model 638 536 0.94 [0.65; 1.24] 100.0%
Heterogeneity: I^2 = 80%, τ^2 = 0.2930, p < 0.01
Test for overall effect: z = 6.21 (p < 0.01)
-2 -1 0 1 2
B
Study
Standardised Mean Difference
SMD 95%-CI
Omitting GSE32863 0.88 [0.59; 1.18]
Omitting GSE63459 0.93 [0.61; 1.24]
Omitting GSE75037 0.88 [0.60; 1.16]
Omitting GSE43458 0.94 [0.62; 1.26]
Omitting GSE10072 0.94 [0.62; 1.26]
Omitting GSE31547 0.92 [0.61; 1.23]
Omitting GSE7670 0.95 [0.64; 1.27]
Omitting GSE46539 0.99 [0.69; 1.29]
Omitting GSE27262 0.93 [0.61; 1.24]
Omitting GSE18842 0.94 [0.63; 1.25]
Omitting GSE21933 0.94 [0.63; 1.25]
Omitting GSE31552 0.95 [0.63; 1.26]
Omitting GSE74706 0.94 [0.63; 1.25]
Omitting GSE19188 0.94 [0.62; 1.26]
Omitting GSE118370 0.95 [0.64; 1.25]
Omitting GSE134381 0.99 [0.68; 1.29]
Omitting GSE103512 1.05 [0.78; 1.31]
Random effects model 0.94 [0.65; 1.24]
-1 -0.5 0 0.5 1
C
P = 0.7759
Standard Error
0.0 0.1 0.2 0.3 0.4 0.5 0.6
-0.5 0.0 0.5 1.0 1.5 2.0
Standardised Mean Difference

Figure 5

Kaplan-Meier survival curves of overall survival (OS) in LUAD and LUSC (GEPIA database).

Survival curves of OS based on the high and low expression of ITGA11, ITGB4 and ITGB8 in LUAD (A-C) and LUSC (D-F), respectively.

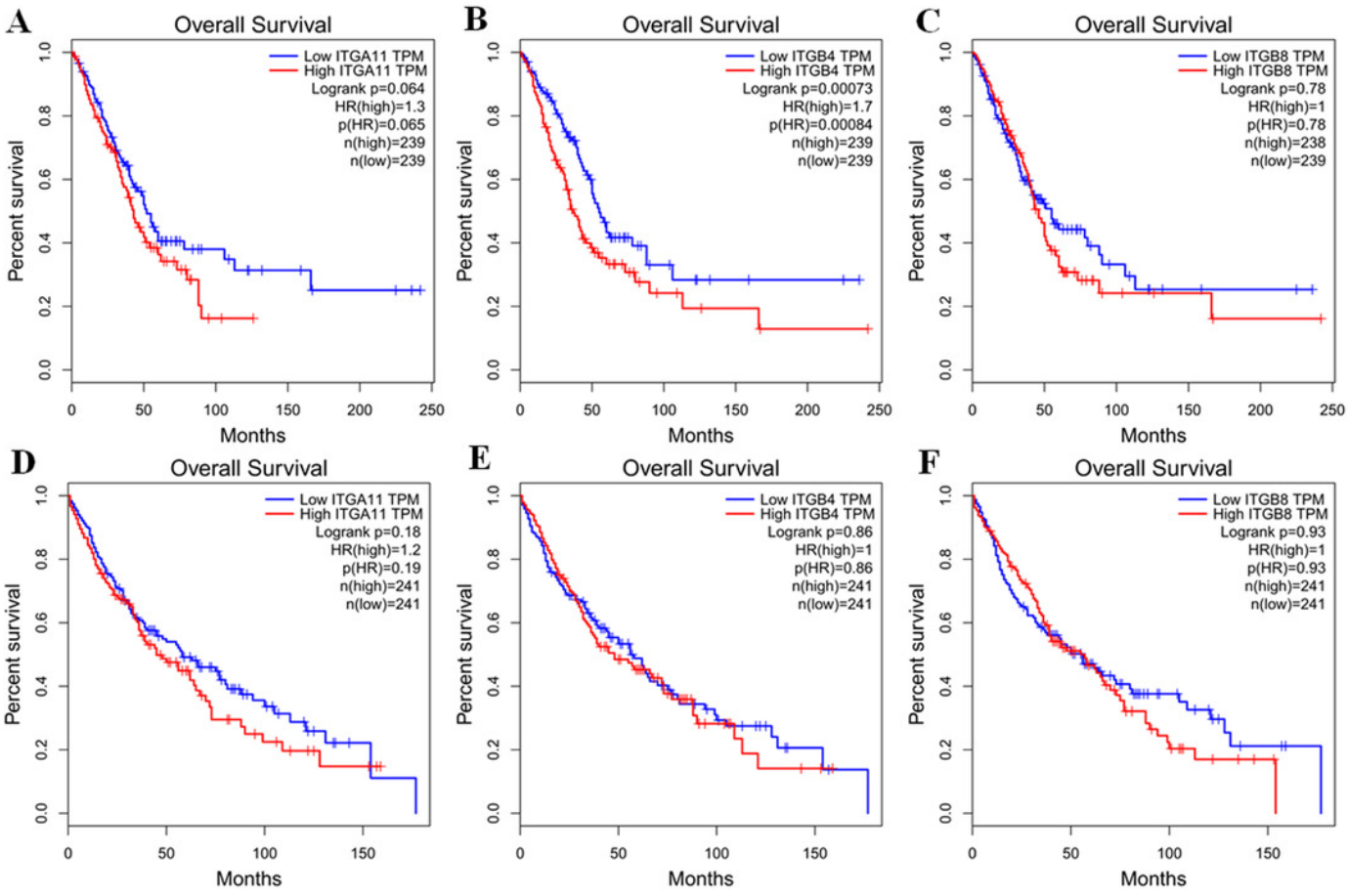


Table 2(on next page)

Univariate and multivariate cox analysis of OS in LUAD and LUSC

Characteristics	Univariate analysis			Multivariate analysis		
	p value	HR	95%CI	*p* value	HR	95%CI
LUAD-OS						
Gender Male vs. Female	0.745	1.050	0.784-1.405			
Age >65 vs. ≤65	0.229	1.198	0.892-1.610			
Smoking history 2/3/4/5 vs. 1	0.530	0.875	0.578-1.325			
Clinical stage III/IV vs. I/II	0	2.466	1.786-3.404	0	2.329	1.682-3.226
ITGA11 expression High vs. Low	0.076	1.306	0.973-1.753	0.361	1.153	0.849-1.566
ITGB4 expression High vs. Low	0.002	1.575	1.175-2.112	0.026	1.417	1.042-1.926
ITGB8 expression High vs. Low	0.925	0.986	0.737-1.320			
LUSC-OS						
Gender Male vs. Female	0.179	1.251	0.902-1.736	0.177	1.253	0.903-1.739
Age >65 vs. ≤65	0.124	1.253	0.940-1.670	0.049	1.343	1.001-1.803
Smoking history 2/3/4/5 vs. 1	0.430	0.698	0.286-1.704			
Clinical stage III/IV vs. I/II	0.002	1.655	1.199-2.284	0.002	1.665	1.204-2.301
ITGA11 expression High vs. Low	0.385	1.128	0.860-1.479			
ITGB4 expression High vs. Low	0.388	1.127	0.859-1.479			
ITGB8 expression High vs. Low	0.875	0.978	0.746-1.283			

1 Smoking history: 1. lifelong non-smoker; 2. current smoker; 3. current reformed smoker (for >15 years); 4. Current
2 reformed smoker (for ≤ 15 years); 5. current reformed smoker (duration not specified).