# Identification of Therapeutic Targets and Prognostic Biomarkers of IGF2BPs in the Lung Cancer Microenvironment

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# Abstract

**Background**: Lung cancer is one of the most common malignances with an ever-increasing incidence and high mortality. The insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) as RNA-binding proteins play an important role in messenger RNA (mRNA) regulation during tumor development. Even so, the expression and prognostic values of IGF2BPs in lung cancer have not been clarified.

**Main methods**: To address this issue, the study investigated the roles of IGF2BPs in the prognosis of lung cancer by using public databases and quantitative real-time PCR (Q-PCR).

**Results**: The transcriptional levels of IGF2BP1/2/3 in lung cancer tissues were significantly elevated, associating with pathological stages and poor prognosis of overall survival (OS) and progression-free survival (FP) in lung cancer patients. A high mutation rate of IGF2BPs (24%) was also observed of patients with lung cancer. The functions of differentially expressed IGF2BPs are primarily related to the spliceosome, hippo signaling pathway and transcriptional misregulation in cancer. Finally, we found significant correlations among the expression of IGF2BPs and the infiltration of six types of immune cells (B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells).

**Conclusions**: The results indicated that high mRNA expression of IGF2BP1/2/3 was found in lung cancer tissues, significantly associating with tumor grades and poor prognosis of OS and FP. Our results may provide insights for the selection of therapeutic targets and prognostic biomarkers for lung cancer patients.


# Introduction

Lung cancer is the second most common cancer and the major cause of cancer-related death all over the world. In 2018, 2.1 million new cases and 1.8 million deaths were reported worldwide, making lung cancer with high incidence and mortality [1, 2]. The histologic subtype of lung cancers has small cell lung cancer (SCLC) of 15% and non–small cell lung cancer (NSCLC) of 85%. Moreover, Lung adenocarcinoma and lung squamous cell carcinoma are the most common subtypes of NSCLC [3]. Recently, in spite of various efforts that have been made to facilitate the early diagnosis and treatment of lung cancer, this is far from sufficient, which urgently to identify novel therapeutic targets and prognostic biomarkers by understanding the underlying potential pathogenesis and etiology of lung cancer.

As we all know, RNA-binding proteins play an important role in mRNA regulation during tumor development. Relevantly, IGF2BPs are highly conserved RNA-binding oncofetal proteins that regulate RNA processing at various biological processes including cell migration, metabolism, proliferation and differentiation, etc.[4, 5]. IGF2BPs have been proven to be potential therapeutic targets and prognostic biomarkers for many types of tumors, including liver [6] and paralogue with liposarcoma [7], etc. However, the role of IGF2BP2s in lung cancer is worth studying.

The IGF2BPs is often linked to the regulation of gene expression in tumor development. In our study, we apply bioinformatics analysis to explore the difference of expression and mutation in IGF2BPs and their relationship with clinical parameters in lung cancer patients. At the same time, Q-PCR was used to verify the expressiong of IGF2BPs. Furthermore, we also assessed the predictive functions and pathways of IGF2BPs as well as 50 neighbor genes closely related to IGF2BPs. This analysis helps us find new tumor treatment targets and prognostic monitoring markers.

## Materials And Methods

# Study Population

Lung cancer and normal tissues specimens for Q-PCR analysis were obtained from patients undergoing surgery between 2018 and 2020 (N = 60). The current research work received approval from the Academic Committee of The Third Clinical Medical College of Xinjiang Medical University (affiliated Tumor Hospital) and was carried out in accordance with the rules put forward in the Declaration of Helsinki. Informed or alternative consent was obtained from all patients for the acquisition and use of tissue samples. As the public dataset, neither ethics committee approval nor patient informed consent was needed for analyzing data.

# Quantitative Real-time PCR

Total RNA was isolated from normal tissues and tumor tissues using Trizol according to the manufacturer's instructions. Extracted RNA was converted into cDNA using 5×primescript buffer, primescript RT enzyme mix I, oligo dT primer and random 6 mers. The quantitative real-time PCR was performed in a BioRad CFX96 Real-Time PCR Detection System machine in the presence of GAPDH, IGF2BP1, IGF2BP2 and IGF2BP3. Target gene transcription levels were measured and normalized to GAPDH expression. Statistical analysis was performed using Mann-Whitney *U* using Graphpad Prism 8 software (GraphPad Software). Differences with P values < 0.05 were considered statistically significant. The following primer sequences were used: GAPDH, 5'-GAAGGTGAAGGTCGGAGTC-3' and 5'-GAAGATGGTGATGGGATTTC-3'; IGF2BP1, 5'-ATCGGCAACCTCAACGAGAG-3' and 5'-GTTTCGATGGCCTTCATCGC-3'; IGF2BP2, 5'-TCGAGACCCTCTCGGGTAAA-3' and 5'-TGTTGACTTGTTCCACATTCTCC-3'; IGF2BP3, 5'-TAGAACTGCACGGGAAACCC-3' and 5'-TCCCACTGTAAATGAGGCGG-3'.

# Transcription-Related Databases of IGF2BPs in Patients of Lung Cancer

ONCOMINE database (www.oncomine.org) is an integrated cancer microarray database for DNA or RNA sequences analysis, which aims to provide powerful gene-wide expression analyses [8]. In this study, ONCOMINE database was used to evaluate the transcriptional expression of IGF2BPs between lung cancer and normal tissue and using a Student's *t* test to generate a *p* value. The cut-off of *p* value and fold change were as following: *p* value: 0.01, fold change: 2.0, gene rank: 5%.

UALCAN (http://ualcan.path.uab.edu), an interactive web resource, provides analyses based on level 3 RNA-seq and clinical data of 31 cancer types from TCGA database [9]. In this study, UALCAN was used to analyze the mRNA expressions of IGF2BPs in normal and primary tumor of lung cancer. Student's *t*-test was used to generate a *p*-value. The *p*-value cutoff was 0.05.

The Human Protein Atlas (https://www.proteinatlas.org) can provide immunohistochemistry-based expression data for near 20 highly common kinds of cancers [10]. We could identify tumor-specific protein expressions that are differentially expressed in a given tumor of type. In the study, a direct comparison of the protein expression of IGF2BPs between normal and lung tissues was investigated by immunohistochemistry images. We can get the immunohistochemistry results of different antibodies type under the tissue interface, and click the figure to see the detailed information.

# Lung Cancer Clinical Staging Analysis Database of IGF2BPs

GEPIA (http://gepia.cancer-pku.cn/index.html) is an analysis tool containing RNA sequence expression data of 9,736 tumors and 8,587 normal tissue samples from TCGA and the GTEx projects [11]. In our study, we performed pathological stages analysis of IGF2BPs in GEPIA using Student's *t*-test. The cut-off of *p* value was 0.05.

# Kaplan-Meier Plotter Database

The correlation between mRNA expression level of the IGF2BPs genes and the survival probability of lung cancer patients was analyzed using the Kaplan-Meier plot (http://kmplot.com/analysis/) database. In Kaplan-Meier plotter, cancer patients were divided into high and low expression groups based on median values of mRNA expression and validated by K-M survival curves. Survival type is OS and FP. The statistically significant of *p* is 0.05.

# Evaluation of Mutations of the IGF2BPs Genes in Lung Cancer

cBioPortal (www.cbioportal.org) is an online open-access website that involves in exploring, visualizing, and analyzing multidimensional cancer genomics data [12]. Genetic alterations of IGF2BPs were obtained from cBioPortal based on TCGA database. 1053 lung carcinoma samples (TCGA, PanCancer Atlas) were analyzed. mRNA expression z-scores (RNA Seq V2) were obtained using a z-score threshold of ± 2.0.

# Gene-Association Networks, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Analysis

GeneMANIA (http://www.genemania.org) is an open website that provides information for protein and genetic interactions, pathways, co-localization, co-expression, and protein domain similarity of submitted genes [13]. In our study, GeneMANIA is used to make gene-association networks of IGF2BPs. Then we performed protein-protein interaction (PPI) network analysis of the associated IGF2BPs gene to explore

interactions through the STRING database, with the goal of collecting, scoring and integrating all publicly available sources of PPI information [14].

DAVID 6.8 (https://david.ncifcrf.gov/home.jsp) is a comprehensive, functional annotation website that could clarify the biological function of submitted genes [15]. In this study, the GO enrichment analysis including biological processes (BP), cellular components (CC) and molecular function (MF), and KEGG pathway were analyzed. Then we visualized with R project using a “ggplot2” package and a *p*-value < 0.05. In addition, the “Express Analysis” module was used to further verify the enrichment of IGF2BPs and closely related neighbor genes in Metascape (http://metascape.org), which is a web-based portal designed to provide a comprehensive gene annotation and gene list enrichment analysis resource [16].

# TIMER Database Analysis

TIMER (https://cistrome.shinyapps.io/timer/) is an intuitive, reliable tool that provides systematic evaluations of the infiltration of different immune cells and their clinical impact [17]. In this study, "Gene module" was used to evaluate the correlation between IGF2BPs level and the infiltration of immune cells.

## Results

# Transcriptional Levels of IGF2BPs in Patients of Lung Cancer

To investigate the transcriptional and translational levels of IGF2BPs between tumor and normal tissues in lung cancer, we performed an analysis using the ONCOMINE database, UALCAN and the Human Protein Atlas. Based on the data from ONCOMINE, the transcriptional levels of IGF2BP1/2/3 were significantly elevated in lung cancer vs. normal lung tissue (Figure 1 and Table 1). In Garber’s dataset [18], IGF2BP1 was overexpressed in lung cancer tissues with a fold change of 2.281 (*P* = 4.73e-4). In Hou’s dataset [19], the fold change of IGF2BP2 was 3.066 (*P* = 1.77e-11), and the fold change of IGF2BP3 were 18.659 (*P* = 2.93e-14), 6.024 (*P* = 8.18e-12) and 9.679 (*P* = 3.08e-6), respectively. Moreover, in Okayama’s dataset [20], high expression of IGF2BP3 was found in lung cancer tissues with a fold change of 3.636 (*P* = 2.47e-18), while Su observed 3.073-fold (*p* = 2.07e-5) increase in IGF2BP3 [21] and Bhattacharjee found 3.496-fold (*p* = 1.40e-6), 18.143-fold (*P* = 2.47e-7) and 4.751-fold (*p* = 2.95e-4) increase in IGF2BP3, respectively [22]. In UALCAN, as expected, the transcriptional levels of IGF2BP1/2/3 in lung tissues were significantly elevated with all *p* value < 0.05 (Figure 2). Besides, the expression of IGF2BPs in lung cancer tissues and normal tissues was also examined by quantitative real-time PCR (Figure 3). IGF2BP1 (*p* = 0.035), IGF2BP2 (*p* = 0.002) and IGF2BP3 (*p* < 0.001) were significantly upregulated in lung cancer tissues compared with normal tissues (all *P* < 0.05). This was consistent with the findings in the database and further verified the transcriptional expression of IGF2BPs in lung cancer.

Table1

The significant changes of IGF2BPs expression in transcription level between different types of lung cancer (ONCOMINE).

| Gene | Type | Fold change | *P*-value | *t*-test | Reference |
|---|---|---|---|---|---|
| IGF2BP1 | Small Cell Lung Carcinoma vs. Normal | 2.281 | 4.73e-4 | 5.106 | Garber Lung Statistics [17] |
| IGF2BP2 | Squamous Cell Lung Carcinoma vs. Normal | 3.066 | 1.77e-11 | 9.492 | Hou Lung Statistics [18] |
| IGF2BP3 | Lung Adenocarcinoma vs. Normal | 3.496 | 1.40e-6 | 5.842 | Bhattacharjee Lung Statistics [21] |
| | Squamous Cell Lung Carcinoma vs. Normal | 18.143 | 2.47e-7 | 6.506 | Bhattacharjee Lung Statistics [21] |
| | Small Cell Lung Carcinoma vs. Normal | 4.751 | 2.95e-4 | 4.853 | Bhattacharjee Lung Statistics [21] |
| | Lung Adenocarcinoma vs. Normal | 3.636 | 2.47e-18 | 10.578 | Okayama Lung Statistics [19] |
| | Squamous Cell Lung Carcinoma vs. Normal | 18.659 | 2.93e-14 | 13.859 | Hou Lung Statistics [18] |
| | Lung Adenocarcinoma vs. Normal | 6.024 | 8.18e-12 | 8.810 | Hou Lung Statistics [18] |
| | Large Cell Lung Carcinoma vs. Normal | 9.679 | 3.08e-6 | 6.251 | Hou Lung Statistics [18] |
| | Lung Adenocarcinoma vs. Normal | 3.073 | 2.07e-5 | 4.718 | Su Lung Statistics [20] |

We also verified the protein expression of IGF2BPS in lung cancer. IGF2BP1/3 protein was not expressed in normal lung tissues, whereas medium and high expressions were observed in lung cancer tissues. Besides, low protein expression of IGF2BP2 was expressed in normal lung tissues, while high protein expression of IGF2BP2 was observed in lung cancer tissues (Figure 4). Taken together, the results showed that transcriptional and translational expressions of IGF2BPs were over-expressed in patients with lung cancer.

# The Pathological Stage and Prognostic Value of IGF2BPs in Patients with Lung Cancer

To evaluate the value of differentially expressed IGF2BPs in the tumorigenesis and progression of lung cancer, we assessed the correlation between differentially expressed IGF2BPs and clinical pathological stage in GEPIA. We found a significant correlation between the expression of IGF2BP1 ($p$ = 8.14e-03), IGF2BP2 ($p$ = 0.0369) and IGF2BP3 ($p$ = 3.18e-04) and pathological stages (Figure 5), and, as the tumor progressed, the expression of IG2BP1/2/3 increased.

Further, we used the Kaplan-Meier plotter to analyze the prognostic values of the expression of IGF2BPs in lung cancer patients. The patients with high transcriptional levels of IGF2BP1 ($p$ = 1.5e-07 and $p$ = 0.0014, respectively), IGF2BP2 ($P$ = 8e-09 and $p$ = 0.025, respectively) and IGF2BP3 ($p$ = 9.4e-06 and $p$ = 9.3e-09, respectively) were significantly associated with lower OS and FP (Figure 6). These data suggest that these IGF2BPs play an important role in the tumorigenesis and progression of lung cancer.

# Genetic Alteration, Neighbor Gene Network, and Interaction Analyses of IGF2BPs in Patients with lung cancer

We performed a comprehensive analysis of the molecular characteristics of differentially expressed IGF2BPs. Provisional datasets of TCGA were utilized to analyze the genetic alterations of differentially expressed IGF2BPs. In the 1053 lung cancer patients, genetic alterations were found in 248 lung cancer patients and the alteration rate was 24%. Mutation and amplification are the main types of genetic alterations. As a result, IGF2BP1, IGF2BP2 and IGF2BP3 were altered in 2.9%, 18% and 4% of the lung cancer samples, respectively (Figure 7A-B). Moreover, we conducted a PPI network analysis of differentially expressed IGF2BPs with STRING to explore the potential interactions among them (Figure 7C). The function of these differentially expressed IGF2BPs was associated with the spliceosome, hippo signaling pathway and transcriptional misregulation in cancer (Figure 7D).

# Functional Enrichment Analysis of IGF2BP1s in Patients with lung cancer

DAVID and Metascape were utilized to analyze the functions of differentially expressed IGF2BPs and their neighboring genes. Figure 8A shows the top several most highly enriched GO items using DAVID. GO term analysis showed that differentially expressed in correlation with IGF2BPs were located mainly in the intracellular ribonucleoprotein complex, nucleoplasm, CRD-mediated mRNA stability complex, nucleus and membrane, where they participate gene expression, CRD-mediated mRNA stabilization, mRNA transport, negative regulation of translation and mRNA splicing, via spliceosome. They act as poly (A) RNA binding, nucleotide binding, RNA binding, protein binding and nucleic acid binding. KEGG pathway analysis showed enrichment in the spliceosome, epstein-barr virus infection, hippo signaling pathway, thyroid cancer and transcriptional misregulation in cancer (Figure 8B).

Supplementary Figure 1 shows the results of the functional enrichment analysis obtained from Metascape. As presented in Supplementary Figures 1A and 1B, the functions of differentially expressed IGF2BPs and their neighboring genes were mainly enriched in regulation of mRNA metabolic process and mRNA processing. To better understand the correlation between differentially expressed IGF2BPs and lung adenocarcinoma, the PPI network and mCODE components were analyzed. And a list of genes is identified in Supplementary Figure 1C and 1D. We extracted the three most significant mCODE components from the PPI network and found that biological function was mainly associated with regulation of mRNA metabolic process, mRNA processing, negative regulation of mRNA metabolic process, Insulin-like Growth Factor-2 mRNA Binding Proteins (IGF2BPs/IMPs/VICKZs) bing RNA, negative

regulation of translation and negative regulation of cellular amide metabolic process (Supplementary Figure 1E).

# Immune Cell Infiltration of IGF2BPs in Patients with Lung Cancer

We embarked on a comprehensive exploration of the correlation between differentially expressed IGF2BPs and immune cell infiltration using the TIMER database. In lung adenocarcinoma, there was a negative correlation between IGF2BP1 expression and the infiltration of B cells (Cor = -0.097, $p$ = 3.25e-02) (Figure 9A). IGF2BP2 expression was positively associated with $CD4^+$ T cells (Cor = 0.224, $p$ = 6.57e-07), macrophages (Cor = 0.138, $p$ = 2.40e-03), neutrophil (Cor = 0.276, $p$ = 7.12e-10) and dendritic cells (Cor = 0.171, $p$ = 1.41e-04) (Figure 9B). IGF2BP3 expression was negatively associated with the infiltration of B cells (Cor = -0.092, $p$ = 4.35e-02) and positively associated with the infiltration of $CD8^+$ T Cell (Cor = 0.098, $p$ = 3.11e-02), neutrophil (Cor = 0.157, $p$ = 5.17e-04) and dendritic Cell (Cor = 0.094, $p$ = 3.87e-02) (Figure 9C). In lung squamous cell carcinoma, the infiltration of CD8+T Cell (Cor = -0.222, $p$ = 1.01e-06 and Cor = -0.112, $p$ = 1.47e-02, respectively), neutrophil (Cor = -0.236, $p$ = 2.01e-07 and Cor = -0.137, $p$ = 2.79e-03, respectively) and dendritic Cell (Cor = -0.216, $p$ = 2.14e-06 and Cor = -0.094, $p$ = 4.07e-02, respectively) were negatively associated with IGF2BP2 and IGF2BP3 (Figures 9D-F). Therefore, IGF2BPs are involved in immune cell infiltration, thus affecting the clinical outcome of lung cancer patients.

# Discussion

Admittedly, lung cancer was related to genes' overexpression and mutations. It is highly significant to identify therapeutic targets and novel biomarkers for the development and prognosis of lung cancer. The present studies based on the public databases indicated that IGF2BPs expression was increased in lung cancer tissues compared to normal lung tissues, which was also confirmed by Q-PCR. Meanwhile, it was involved in pathological tumor stages. Moreover, high mRNA expressions of IGF2BP1/2/3 were found to be significantly associated with shorter OS and FP in lung cancer patients. Additionally, a high mutation rate of IGF2BPs (24%) was also found in patients with lung cancer. These results revealed that IGF2BPs played a role in lung cancer. Our findings may help to improve the accuracy of the prognosis and survival in lung cancer patients.

IGF2BP1 serves as a post-transcriptional fine-tuner that regulates the expression of some essential mRNA targets needed to control of tumor cell proliferation, growth, invasion, and chemo-resistance, connecting with a poor survival and metastasis in cancers [23]. For example, IGF2BP1 promotes G1/S cell cycle transition to result in cancer by relying on 3'UTR-, miRNA- and m6A-dependent regulation of the checkpoint like E2F1 [24]. Previous studies have shown that IGF2BP1 is highly expressed in lung cancer, predicting poor prognosis for lung cancer patients. Study carried out by Zhang et al. showed IGF2BP1 silencing inhibited cancer cell proliferation, migration and invasion, as well as induced cell cycle arrest and apoptosis through down-regulating Netrin-1 expression [25]. Similarly, Huang et al. indicated that low

IGF2BP1 expression was negatively correlated with pathological stage and lymph node metastasis, and its status is an independent prognostic factor for lung cancer after surgical resection [26]. Our results are consistent with the previous ones, showing the high mRNA expressions of IGF2BP1 was found in lung cancer tissues. Moreover, the high expression of IGF2BP1 was significantly related to tumor stages and the shorter OS and FP. All these results showed that IGF2BP1 contributed to the development and progression of lung cancer, and it might serve as potential therapeutic target and survival biomarker for patients with lung cancer.

Similarly, up-regulation of IGF2BP2 by multiple mechanisms promotes development and proliferation in multiple cancers. Mechanistically, IGF2BP2 activate the PI3K/Akt signaling pathway for cancer proliferation [27]. Study carried out by Png et al., found that IGF2BP2/IGF-1/IGF-1 receptor signaling pathways might involve in cancer mediated endothelial recruitment, which was a significant feature of metastatic cancer in the tumor microenvironment [28]. Equally, as for lung cancer, identified as a novel direct target of miR-485-5p, depletion of IGF2BP2 significantly inhibited cell proliferation and invasion [29]. In our study, we showed high mRNA expression of IGF2BP2 in lung cancer tissues, significantly associating with tumor stages and the shorter OS and FP. These results indicated that IGF2BP2 was involved in the development and progression of lung cancer, and it might serve as a prognostic biomarker and target for precision therapy of lung cancer patients.

IGF2BP3 sustains cancer cell growth and proliferation while putatively inhibiting apoptosis by a well-established mechanism of action of IGF2BP3 on account of its protection from Let-7 miRNA-mediated decay [30]. Further, Overexpression of IGF2BP3 in lung cancer cells promoted cell proliferation, tumor migration and invasion possibly via attenuating p53 stability [31]. In addition, IGF2BP3 has also been found to repress RNAs and miRNAs of lung cancer cells eiF4E-BP2 to promote the proliferation of cancer cells, and eIF4E encodes a negative regulator of eukaryotic translation initiation factor 4E [32]. Our results further confirm above results with high mRNA expression of IGF2BP3 in lung cancer tissues, significantly relevant with tumor grades and poor prognosis of OS and FP. These results suggest that IGF2BP3 may be a therapeutic target and prognostic biomarker by participating in the development and progression of lung cancer.

Collectively, this work was designed with bioinformatics analysis of multiple data sets directing against IGF2BPs expression level in clinical tissue and its clinical relevance. All data illustrated that IGF2BP1/2/3 hold potential promoting effects on lung cancer. Despite this, some limitations were still present in our study. First, analysis on the transcriptional level could reflect some aspects of tumor progression, but not global changes. We will try our best in the follow-up study to investigate the detailed mechanism between distinct IGF2BPs and lung cancer. Second, further studies consist of larger clinical sample sizes were required to explore and verify the clinical application of the IGF2BPs members in the treatment of lung cancer.

# Conclusion

In conclusion, the study systematically analyzed the expression as well as the prognostic value of IGF2BPs in lung cancer, and provided a comprehensive understanding of the heterogeneity and intricacy of the molecular biological properties of lung cancer. Our results indicated that high mRNA expression of IGF2BP1/2/3 was found in lung cancer tissues, significantly associating with tumor grades and poor prognosis of OS and FP. In addition, patients with a high mutation rate of IGF2BPs (24%) was also observed. All these results showed that IGF2BP1/2/3 contributed to the development and progression of lung cancer, and it might serve as potential targets of precision therapy and prognosis of biomarkers for patients with lung cancer.

## Abbreviations

IGF2BPs: insulin-like growth factor 2 mRNA-binding proteins; mRNA: messenger RNA; Q-PCR: Quantitative Real-time PCR; OS: overall survival; FP: progression-free survival; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; PPI: protein-protein interaction; BP: biological processes; CC: cellular components; MF: molecular function.

## Declarations

# Ethics approval and consent to participate

The current research work received approval from the Academic Committee of The Third Clinical Medical College of Xinjiang Medical University (affiliated Tumor Hospital) and was carried out in accordance with the rules put forward in the Declaration of Helsinki. Written informed or alternative consent was obtained from all patients for the acquisition and use of tissue samples.

# Consent for publication

Not applicable

# Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

# Competing Interest

We declare non competing interests.

# Funding

We declare non funding source.

# Author contribution

XW, WK and FG contributed equally to this work. XW and WK designed the study. FG, RS and GZ acquired the information. WQ and KX interpreted the data. XW and YF analyzed the data. WK and XM drafted and revised the manuscript. WS and XM supervised the manuscript. All authors read and approved the final manuscript.

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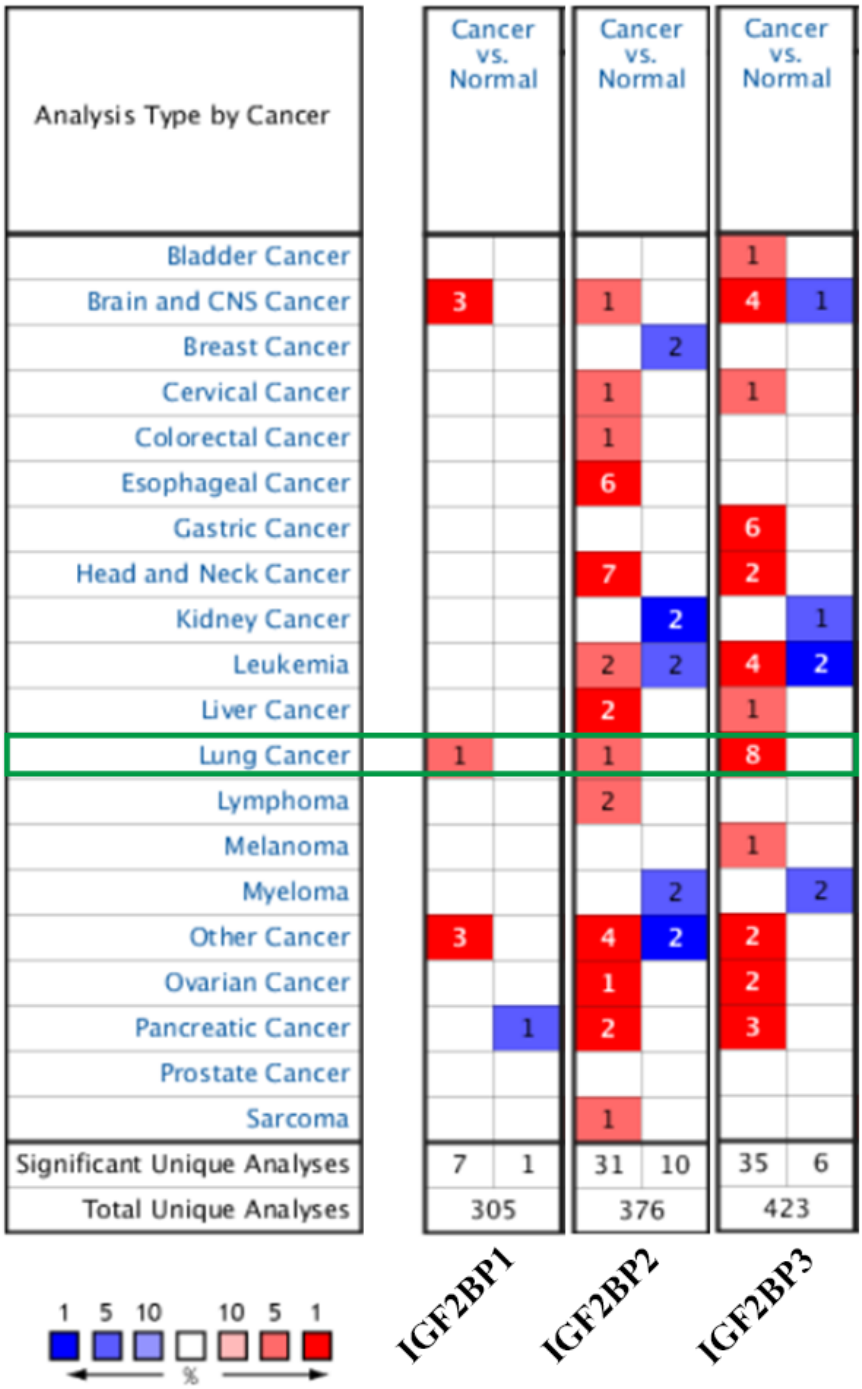
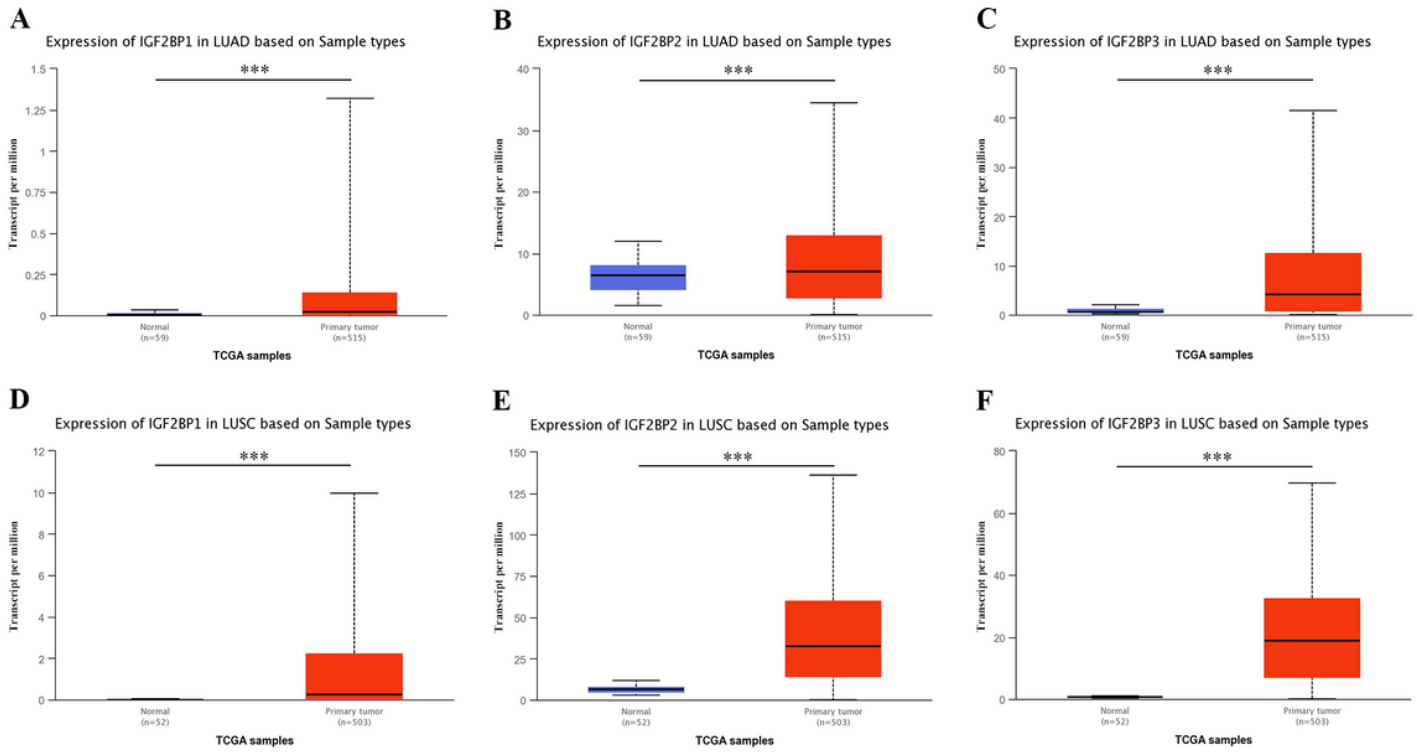
# Figures



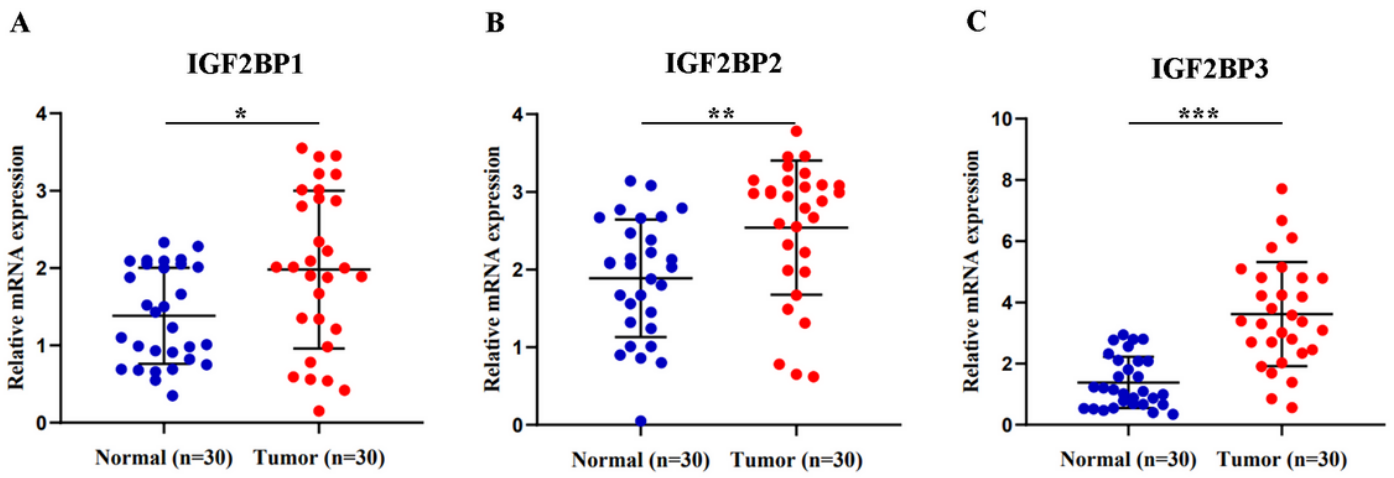

## Figure 1

mRNA levels of IGF2BPs in lung cancer (ONCOMINE). The figure shows the numbers of datasets with statistically significant mRNA over-expression (red) or down-regulated expression (blue) of IGF2BPs.



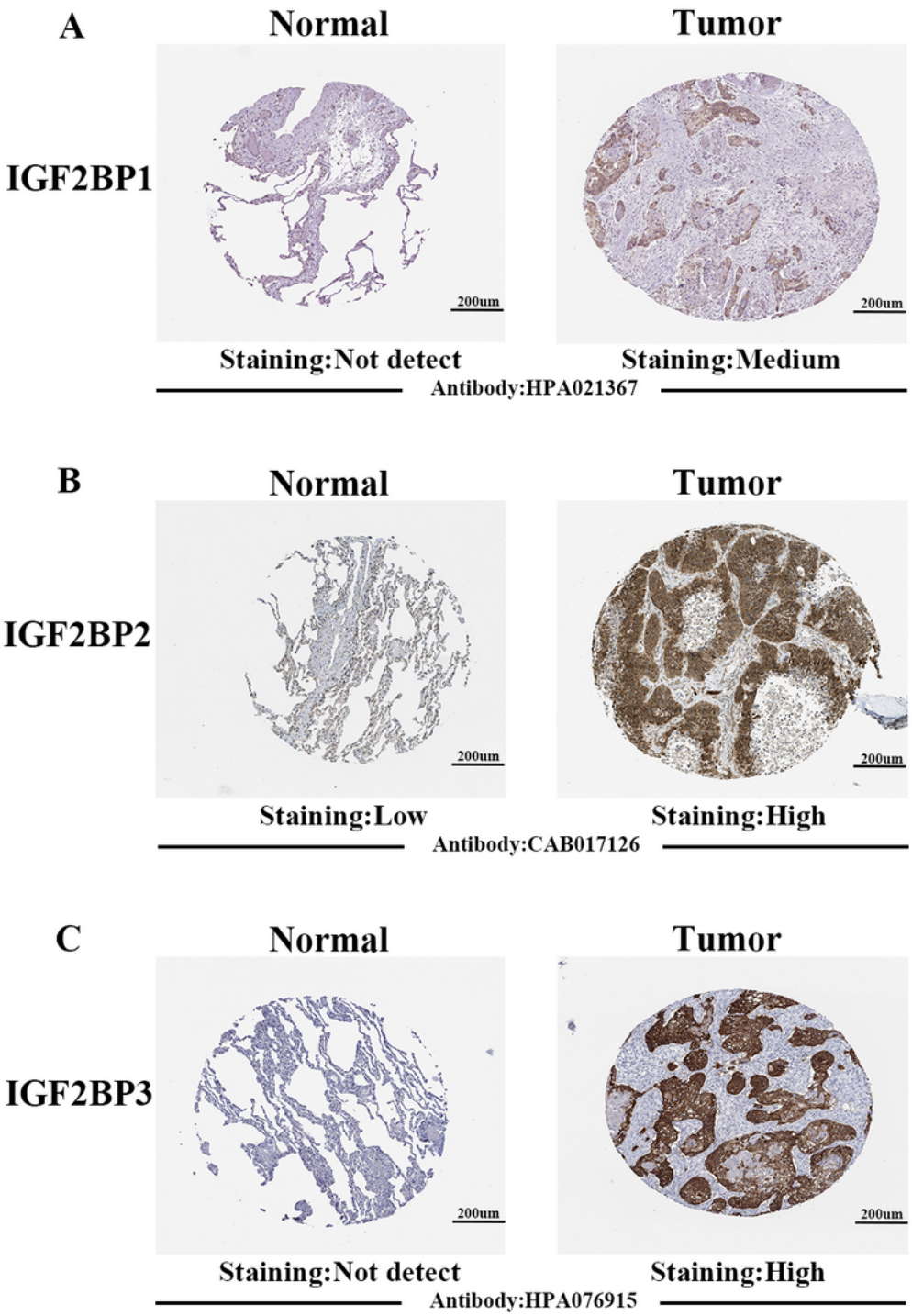

## Figure 2

The expression of distinct IGF2BPs in lung cancer tissues and adjacent normal tissues. The color of blue represented normal lung tissues, red color represented lung cancer tissues. ** p<0.001.



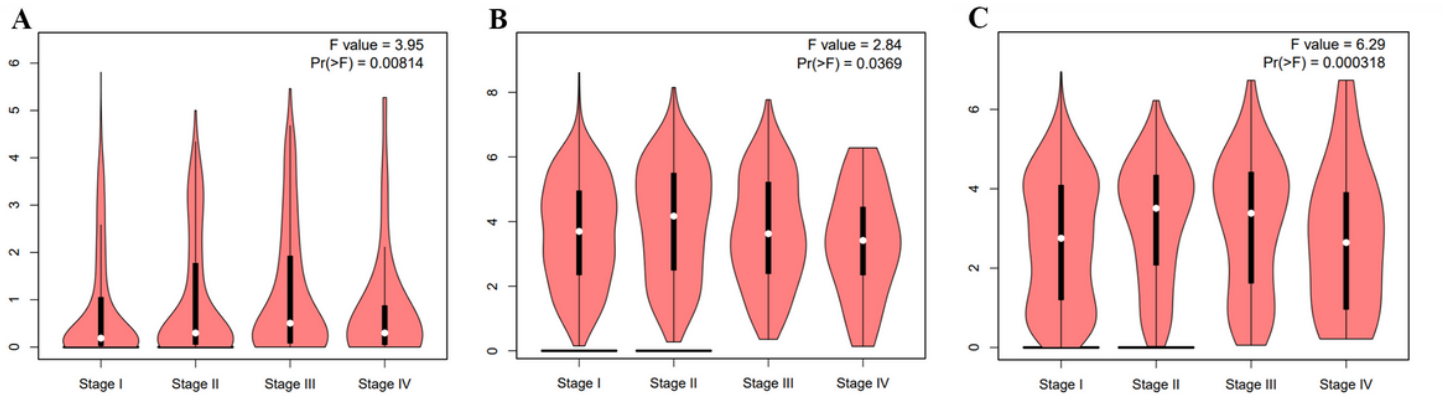

## Figure 3

Expression of IGF2BPs, mRNAs were significantly upregulated in lung cancer tissues compared to normal lung tissues using Q-PCR analysis. * p<0.05, ** P<0.01, *** P<0.001



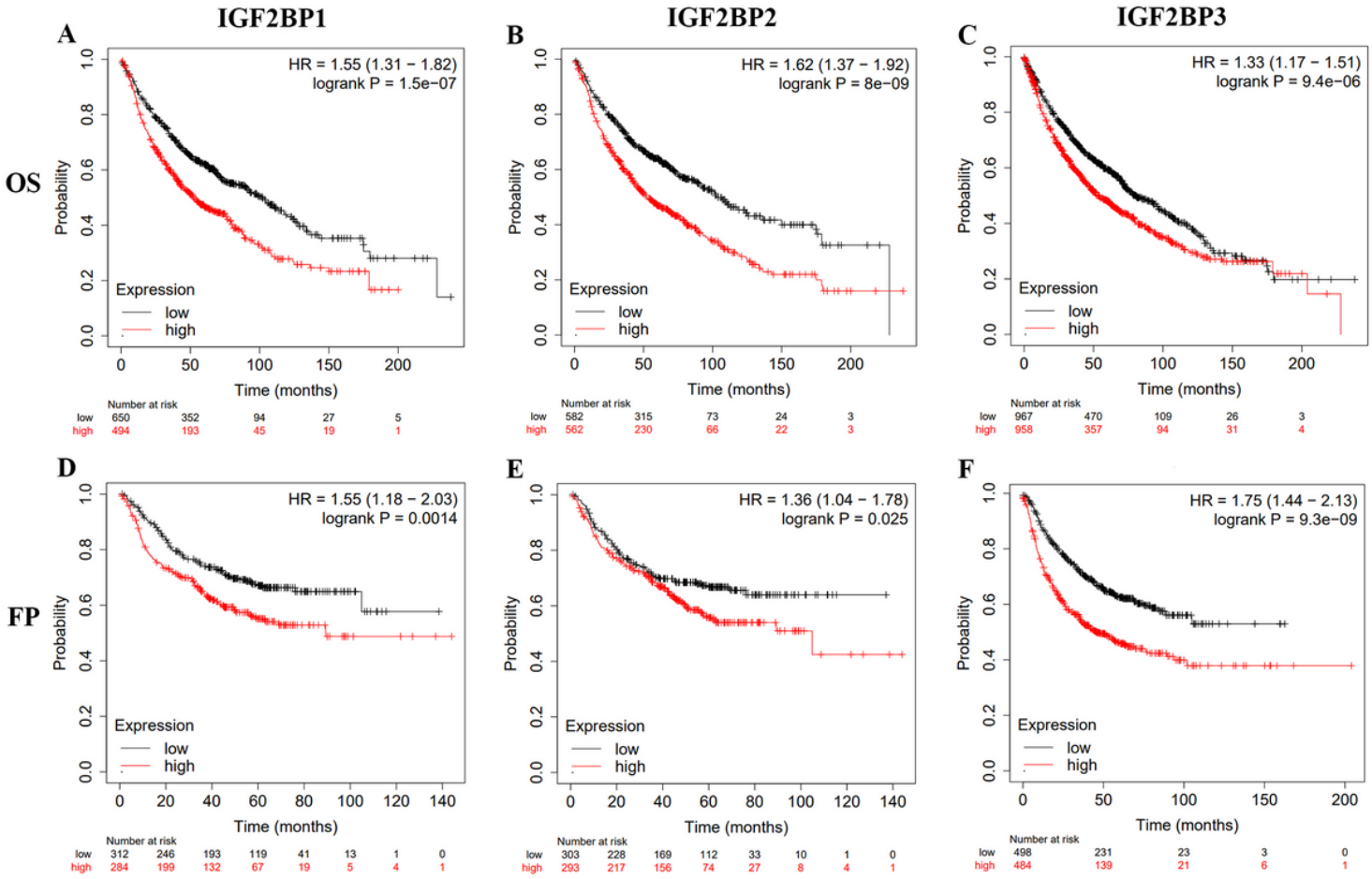

## Figure 4

Representative immunohistochemistry images of distinct IGF2BPs in lung cancer tissues and normal lung tissues (Human Protein Atlas). (A) IGF2BP1. (B) IGF2BP2. (C) IGF2BP3.



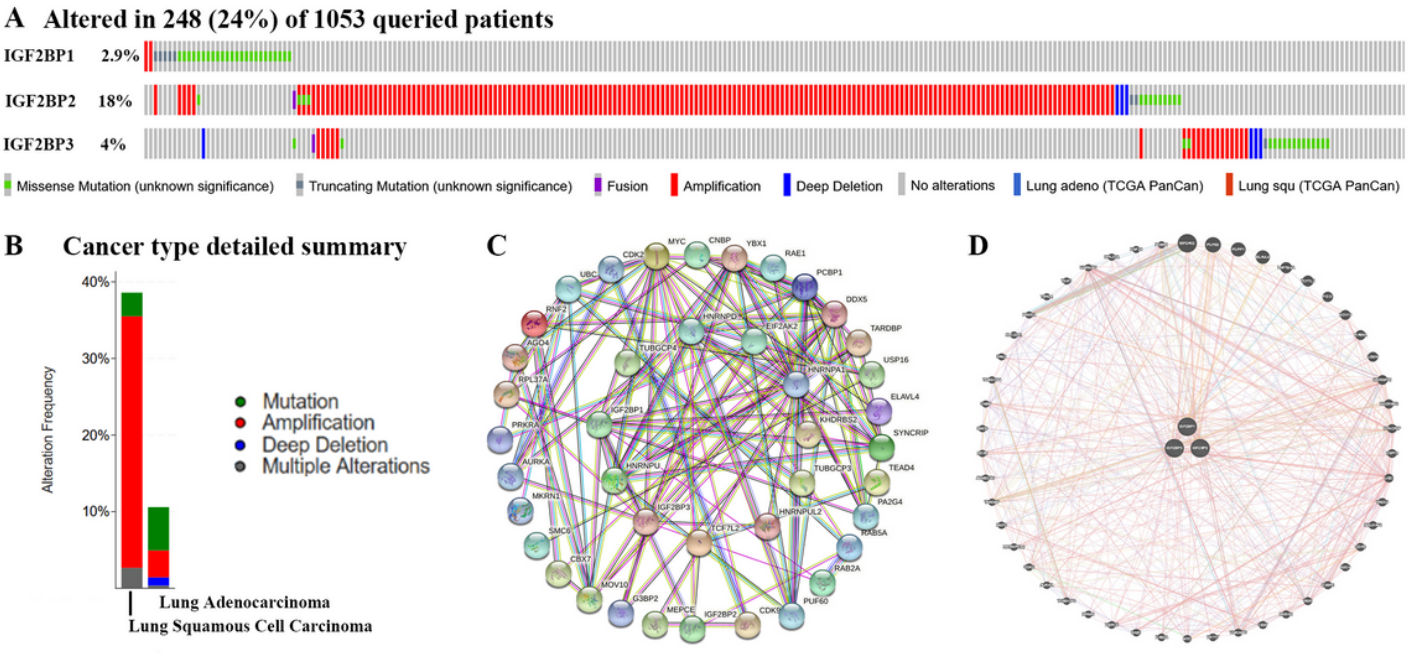

## Figure 5

Correlation between different expressed IGF2BPs and the pathological stage of lung cancer patients (GEPIA).



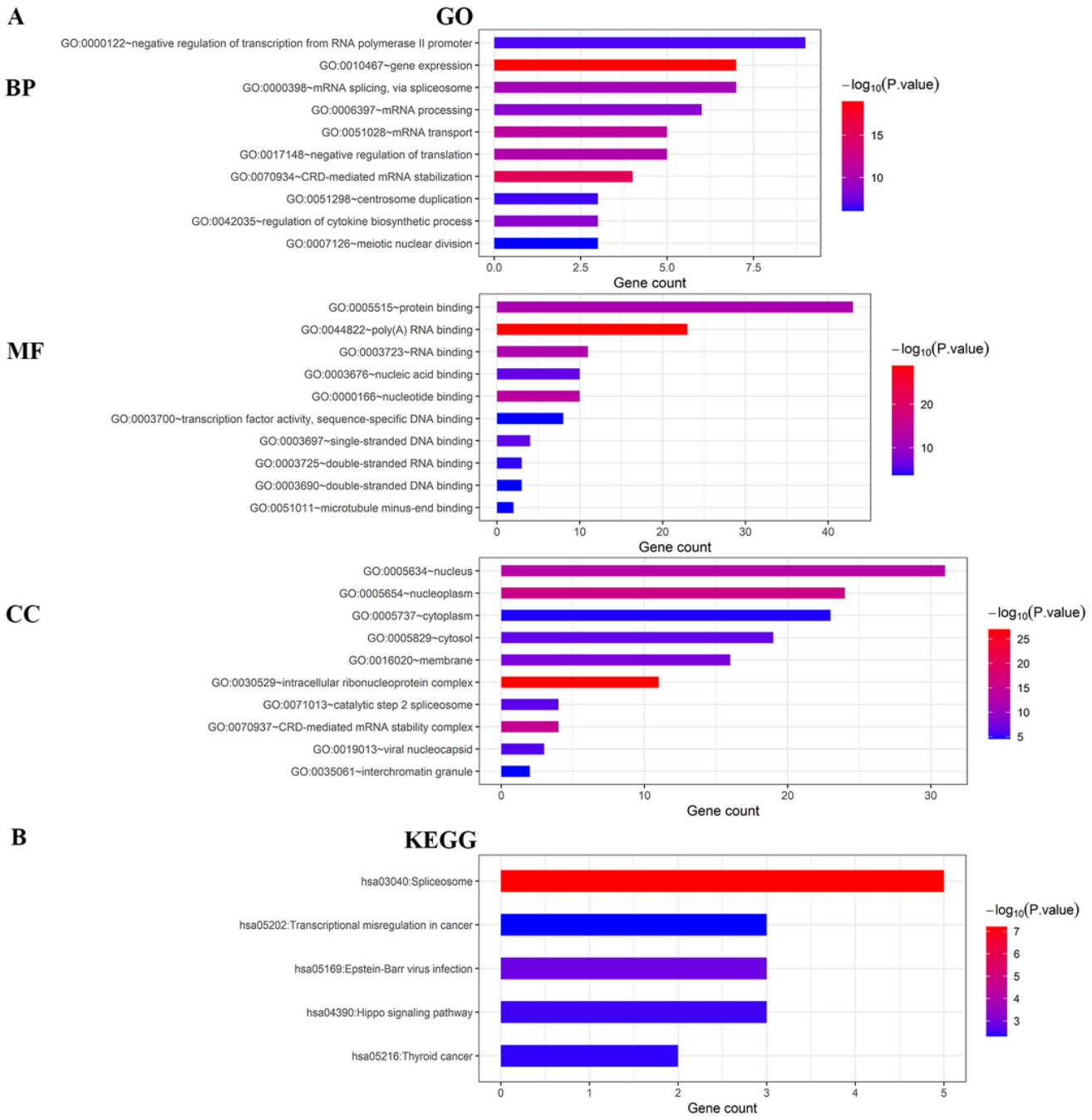

## Figure 6

The prognostic value of different expressed IGF2BPs in lung cancer patients in the overall survival and disease free survival curve (Kaplan-Meier Plotter).




## Figure 7

Genetic alteration, neighbor gene network and interaction analyses of different expressed IGF2BPs in lung cancer patients. (A-B) Summary of alterations in different expressed IGF2BPs in lung cancer. (C-D) Protein-protein interaction network of different expressed IGF2BPs.




## Figure 8

The functions of IGF2BPs and 50 neighbor genes were predicted by the analysis of GO and KEGG (DAVID). (A) bar-plot of GO enrichment in biological process terms, molecular function terms and cellular component terms. (B) bar-plot of KEGG enriched terms.

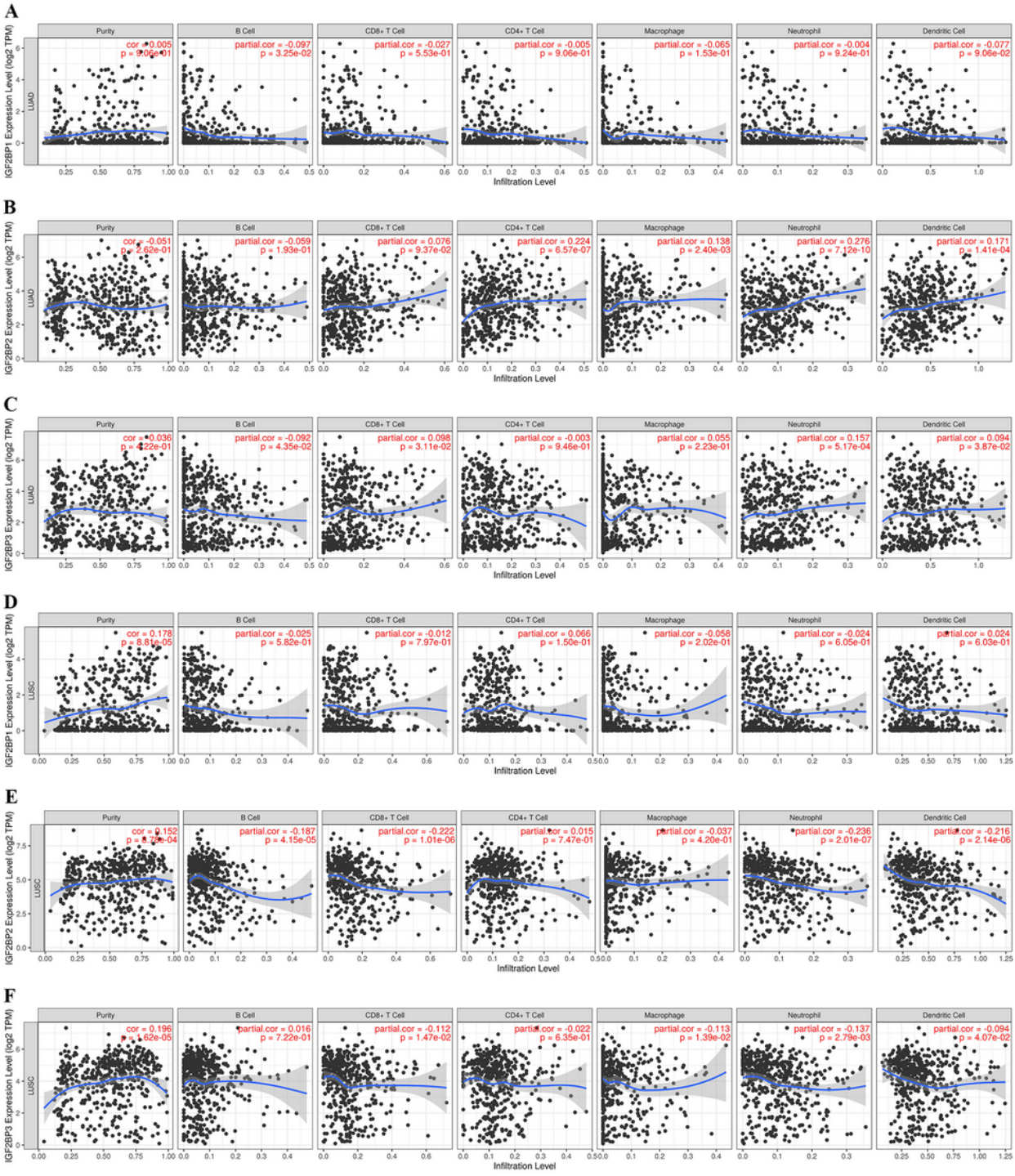



**Figure 9**

The correlation between different expressed IGF2BPs and immune cell infiltration (TIMER).

# Supplementary Files

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