ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002

CEBPB Transcriptional Expression as a Potential Indicator of Survival Prognosis in Non-Small Cell Lung Cancer Patients

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Abstract: *CEBPB is an important transcription factor involved in the immune regulation of inflammatory diseases, and chronic inflammation is a key factor in cancer progression. CEBPB has been found to influence the occurrence and development of various malignancies in aspects such as cellular metabolism, drug resistance, migration, and invasion. However, its role in non-small cell lung cancer (NSCLC) remains unclear. To address this issue, this study analyzed the prognostic value of CEBPB in NSCLC and its relationship with clinical pathological parameters using the GEPIA 2, UALCAN, Human Protein Atlas, Kaplan-Meier Plotter, and c-BioPortal databases. It was found that CEBPB transcriptional expression is reduced in NSCLC patients and is significantly associated with cancer staging in LUAD patients and lymph node metastasis in LUSC patients. Additionally, higher CEBPB mRNA expression is significantly associated with shorter overall survival (OS) and disease-free survival (DFS) in NSCLC patients. Furthermore, the mutation rate of CEBPB in NSCLC patients is low at only 1%, but gene alterations of CEBPB are linked to shorter OS in NSCLC patients. In conclusion, these results suggest that CEBPB may serve as a biomarker for the survival prognosis of NSCLC patients.*

Keywords: *CEBPB, NSCLC, Prognosis, GEPIA 2, UALCAN*

1. Introduction

Lung cancer (LC) is highly invasive and deadly, with incidence and mortality rates increasing year by year, making it the leading cause of cancer-related deaths worldwide[1]. Approximately 85% of all lung cancer cases are non-small cell lung cancer (NSCLC), and more than half of these patients are diagnosed at an advanced stage or with distant metastasis. Although platinum-based chemotherapy regimens improve survival in advanced patients, the recurrence rate is high, and the toxicity is relatively high, making it difficult to achieve lasting clinical effects[2]. For early-stage NSCLC patients who are eligible, surgery combined with radiotherapy and chemotherapy is a common treatment strategy[3]. However, two-thirds of patients experience metastasis after surgery[4]. Furthermore, targeted therapies for oncogenic drivers such as epidermal growth factor receptor (EGFR)[5], ALK, or ROS1 mutations, as well as immunotherapies such as anti-PD-1/PD-L1 and anti-CTLA-4 antibody, have greatly changed the treatment landscape for NSCLC patients. However, these therapies come with unique challenges, including treatment resistance and immune dysfunction[6, 7]. Therefore, improving early diagnosis rates for NSCLC, identifying new prognostic markers, and discovering new therapeutic targets remain key areas of NSCLC research.

Among NSCLC subtypes, lung adenocarcinoma (LUAD) is the most common, accounting for approximately 50%[8]. LUAD is more prone to distant metastasis in the early stages, and its treatment and prognosis are poor compared to other types of lung cancer[9]. Lung squamous cell carcinoma (LUSC) is the second most common subtype, accounting for 30%-35% of NSCLC cases, and is closely associated with smoking[10, 11]. Unlike LUAD, patients with LUSC have limited treatment options due to a lack of effective targets for precision medicine[12].

CCAAT/enhancer-binding protein beta (CEBPB) is a transcription factor involved in various cellular processes, including cell proliferation, differentiation, metabolic regulation, and stress responses. One of

ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002

its well-known roles is its involvement in the immune regulation of various inflammatory diseases[13-15]. A series of studies have demonstrated that CEBPB plays a crucial role in tumor progression. For example, CEBPB promotes colorectal cancer growth and migration by enhancing STAT3 signaling through the transcriptional upregulation of SERPINA1[16]. In triple-negative breast cancer, specific isoforms of CEBPB participate in aerobic glycolysis to maintain immune suppression[17]. Furthermore, CEBPB has been reported to cooperate with NRF2 to regulate drug resistance in NSCLC with NRF2 activation[18]. However, the role of CEBPB in lung cancer remains controversial, possibly due to the presence of different co-transcription factors in each cellular environment. To understand the function and biological consequences of CEBPB in NSCLC, this study analyzed the expression and mutation status of CEBPB in LUAD and LUSC patients, and its relationship with clinical parameters.

2. Materials and methods

2.1. Ethical Statement

Since all the data were retrieved from the online databases, it is confirmed that all written informed consent has been obtained.

2.2. GEPIA 2

GEPIA 2 (http://gepia2.cancer-pku.cn/) is a web tool based on data from the TCGA and GTEx databases[19]. It allows for general gene analysis, differential expression analysis, survival analysis, and correlation analysis between genes or gene sets. In this study, GEPIA 2 was used to analyze the differential expression of CEBPB mRNA in LUAD, LUSC, and 31 other cancer types compared to their corresponding normal tissues, and to assess the prognostic value of CEBPB in these cancers. The impact of CEBPB mRNA expression on cancer staging in LUAD and LUSC patients was also evaluated. Correlation analysis was performed between CEBPB and inflammation-related factors, as well as immune checkpoint molecules. Differences in transcriptional expression was compared by Student's t-test, with statistical significance defined as $p < 0.05$.

2.3. UALCAN

UALCAN (http://ualcan.path.uab.edu) is an interactive web resource based on clinical data from 31 cancer types in the TCGA database and level 3 RNA-seq data. It provides graphical representations of the relative transcriptional expression of target genes between tumor and normal samples, as well as their association with clinicopathologic parameters, including patient survival information[20]. In this study, UALCAN was used to analyze the mRNA and protein expression of CEBPB in LUAD and LUSC patients and its association with clinical parameters. Differences in transcriptional expression were compared using Student's t-test, and the association between CEBPB expression and clinical pathological features was explored using chi-square tests, with $p < 0.05$ considered statistically significant.

2.4. Human Protein Atlas

The Human Protein Atlas (https://www.proteinatlas.org) is a database that integrates proteomics, transcriptomics, and systems biology data, covering protein expression in both normal and nearly 20 very common kinds of cancer[21]. Researchers can identify differences in the expression of tumor-specific proteins across a range of cancers. In this study, immunohistochemistry images were used to directly present the protein expression of CEBPB in human normal tissues and LUAD and LUSC tissues.

2.5. Kaplan-Meier Plotter

The Kaplan-Meier Plotter (http://kmplot.com/analysis/) is a web tool that provides survival analysis for patients with liver cancer[22], breast cancer[23], ovarian cancer[24], lung cancer[25], and gastric cancer[26], based on gene expression data. It categorizes cancer patients into high-expression and low-expression groups based on the median mRNA expression of target genes and verifies these groups using K-M survival curves. Information such as high-risk case numbers, median mRNA expression levels, 95% CIs, and p-values are provided. In this study, the prognostic value of CEBPB in lung cancer was analyzed. Log-rank tests were used to compare Kaplan-Meier survival curves. A p-value of < 0.05 was considered statistically significant.

ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002

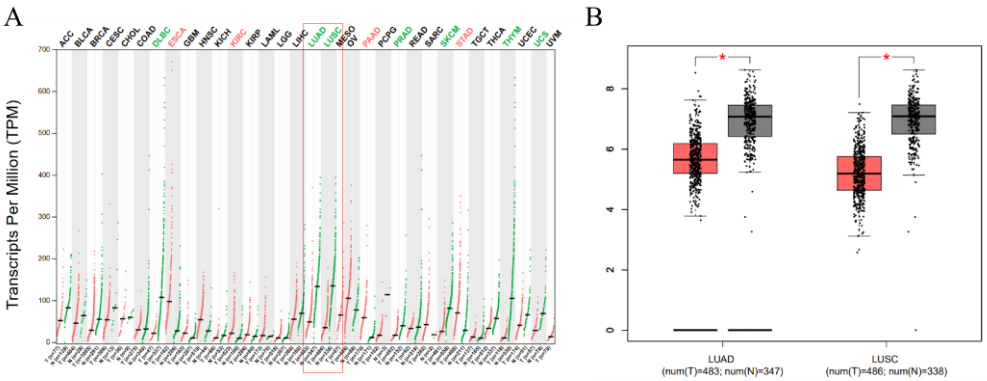
2.6. cBioPortal

cBioPortal (www.cbioportal.org) is an open-access resource that allows researchers to retrieve, analyze, and visualize genomic data from cancer samples. Data types include somatic mutations, DNA copy number alterations (CNAs), mRNA and microRNA (miRNA) expression, and DNA methylation. This platform enables the exploration of genetic alterations and links these alterations to clinical outcomes[27]. In this study, we analyzed the frequency of CEBPB mutations in LUAD and LUSC patients and examined their association with overall survival (OS) and disease-free survival (DFS). Kaplan-Meier plots were used, and log-rank test was performed to assess the significance of differences between survival curves, with a p-value of < 0.05 considered statistically significant.

3. Results

3.1. Down regulation of CEBPB mRNA Expression in LUAD and LUSC Patients

To explore the prognostic and potential therapeutic value of CEBPB in LUAD and LUSC patients, we used GEPIA 2 (http://gepia2.cancer-pku.cn/) to analyze and compare CEBPB mRNA expression in 33 types of cancers and their normal tissues based on the TCGA and GTEx databases (Fig 1A). CEBPB transcriptional expression was significantly reduced in LUAD and LUSC patients compared to normal tissues (Fig 1B).



A: Dot plot of CEBPB mRNA levels from TCGA tumor samples and GTEx normal samples.B: Box plot of CEBPB mRNA levels in LUAD and LUSC tumor samples and normal tissues, with asterisks indicating significant differences.

Figure 1: CEBPB Transcriptional Expression in 33 Types of Cancers (GEPIA 2 Database).

3.2. CEBPB mRNA Expression Correlates with Clinical Pathological Parameters in LUAD and LUSC Patients

We further analyzed the relationship between CEBPB mRNA expression and clinical pathological parameters, including individual cancer stages and lymph node metastasis, using UALCAN (http://ualcan.path.uab.edu). The results indicated that the difference in CEBPB mRNA expression between tumor and normal tissues was not statistically significant in LUAD patients (Fig 2A), possibly due to the smaller sample size with only 59 normal tissue samples, despite a noticeable difference in expression. However, CEBPB mRNA expression was significantly downregulated in LUSC tissues ($p < 0.001$, Fig 2B). Further analysis of the relationship between CEBPB mRNA expression and individual cancer stages revealed that CEBPB mRNA expression was downregulated in stage I LUAD tumor samples compared to normal lung tissues. Conversely, stage III LUAD tissues exhibited a significant increase in CEBPB mRNA expression compared to stage I patients (Fig 2C), corroborated by GEPIA 2 analysis (Fig 2E, $p = 0.0418$). However, no notable differences across stages were observed in LUSC patients (Fig 2D), consistent with GEPIA 2 results (Fig 2F). Interestingly, there was no correlation between CEBPB mRNA expression and lymph node metastasis in LUAD tissues (Fig 2G). However, CEBPB mRNA levels were significantly correlated with lymph node metastasis in LUSC patients, with lower CEBPB mRNA levels observed in patients with more severe lymph node metastasis, and the expression tended to decrease as the degree of metastasis increased (Fig 2H). In summary, these results suggest that CEBPB mRNA expression is associated with individual cancer stages in LUAD patients and with lymph node metastasis in LUSC patients.

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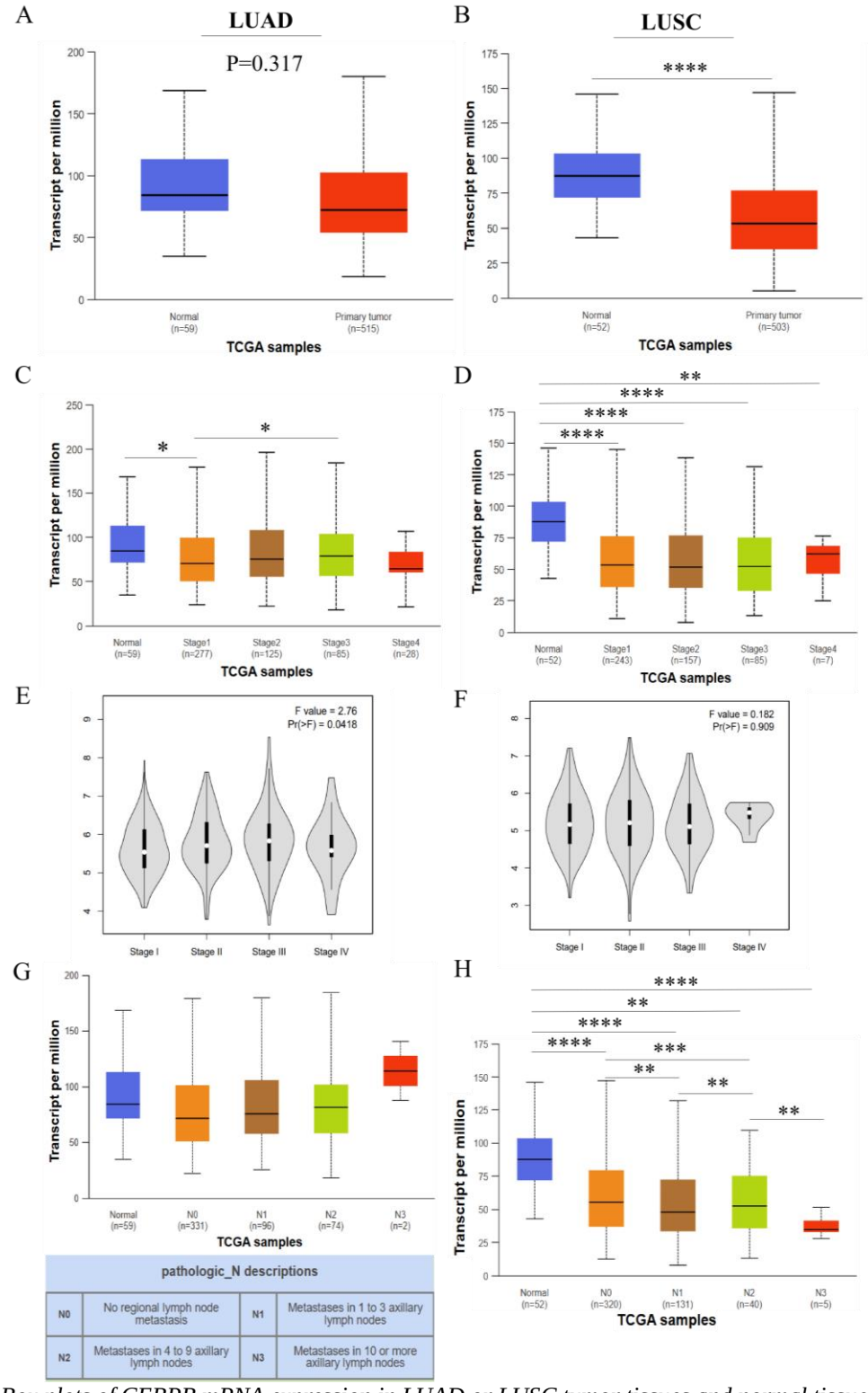


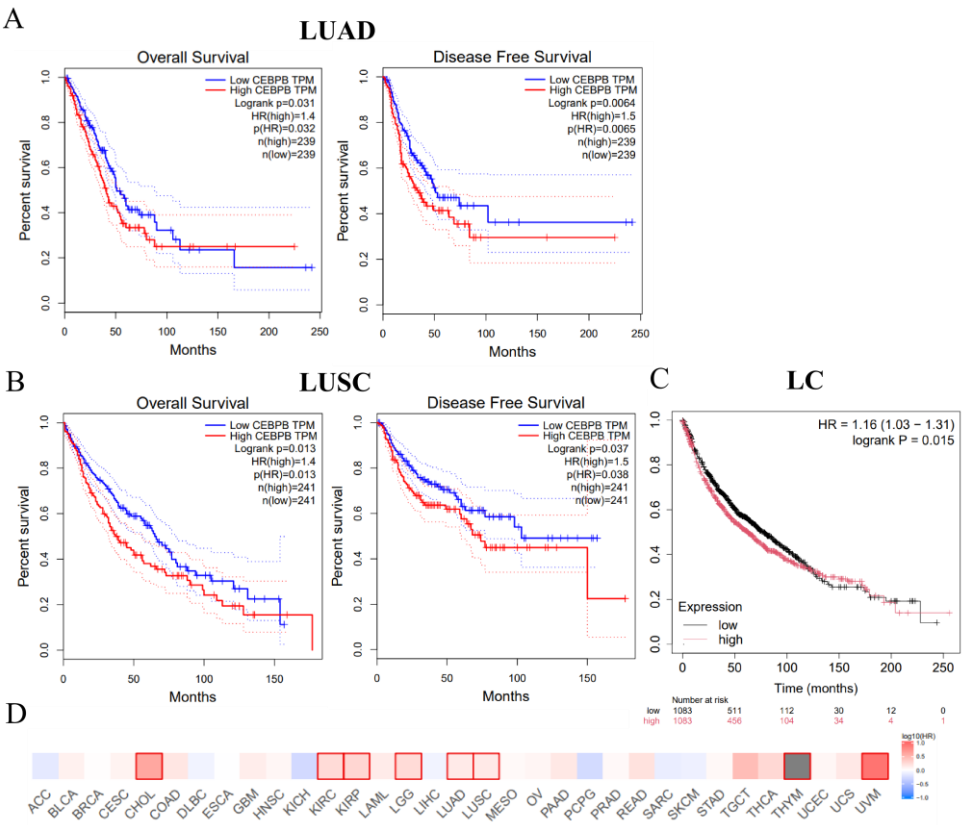
A-B: Box plots of CEBPB mRNA expression in LUAD or LUSC tumor tissues and normal tissues. C-D: Box plots showing the relationship between CEBPB mRNA expression and individual cancer staging in LUAD or LUSC patients. E-F: Violin plots showing the relationship between CEBPB mRNA expression and cancer staging in LUAD or LUSC patients (GEPIA 2 database).G-H: Box plots showing the relationship between CEBPB mRNA expression and lymph node metastasis in LUAD or LUSC patients. (p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001)*

Figure 2: Relationship between CEBPB mRNA Expression and Cancer Staging and Lymph Node Metastasis in LUAD and LUSC Patients (UALCAN database).

ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002

3.3. Prognostic Value of CEBPB mRNA Expression in LUAD and LUSC Patients

Next, we used GEPIA 2 to predict the prognostic value of CEBPB mRNA expression in NSCLC patients. As shown in Figure 3A-B, CEBPB mRNA expression was significantly associated with prognosis in both LUAD and LUSC patients. High levels of CEBPB mRNA were correlated with poorer overall survival (OS) in LUAD patients (HR = 1.4, p = 0.032) and LUSC patients (HR = 1.4, p = 0.013), as well as with worse disease-free survival (DFS) in LUAD patients (HR = 1.5, p = 0.0065) and LUSC patients (HR = 1.5, p = 0.038). Additionally, Kaplan-Meier Plotter analysis and log-rank tests demonstrated that high CEBPB mRNA expression was associated with worse OS in all lung cancer patients (HR = 1.16, 95% CI = 1.03-1.31, p = 0.015, Fig 3C). GEPIA 2 analysis of the prognostic value of CEBPB mRNA expression across 33 types of cancers in the TCGA database revealed that high CEBPB mRNA expression was also significantly associated with worse OS in patients with CHOL, KIRC, KIRP, LGG, and UVM (Fig 3D).



A-B: The relationship between CEBPB mRNA expression and OS and DFS in LUAD or LUSC patients. C: The relationship between CEBPB mRNA expression and OS in lung cancer patients (Kaplan-Meier Plotter).D: The prognostic value of CEBPB mRNA expression in 33 types of cancers in the TCGA database.

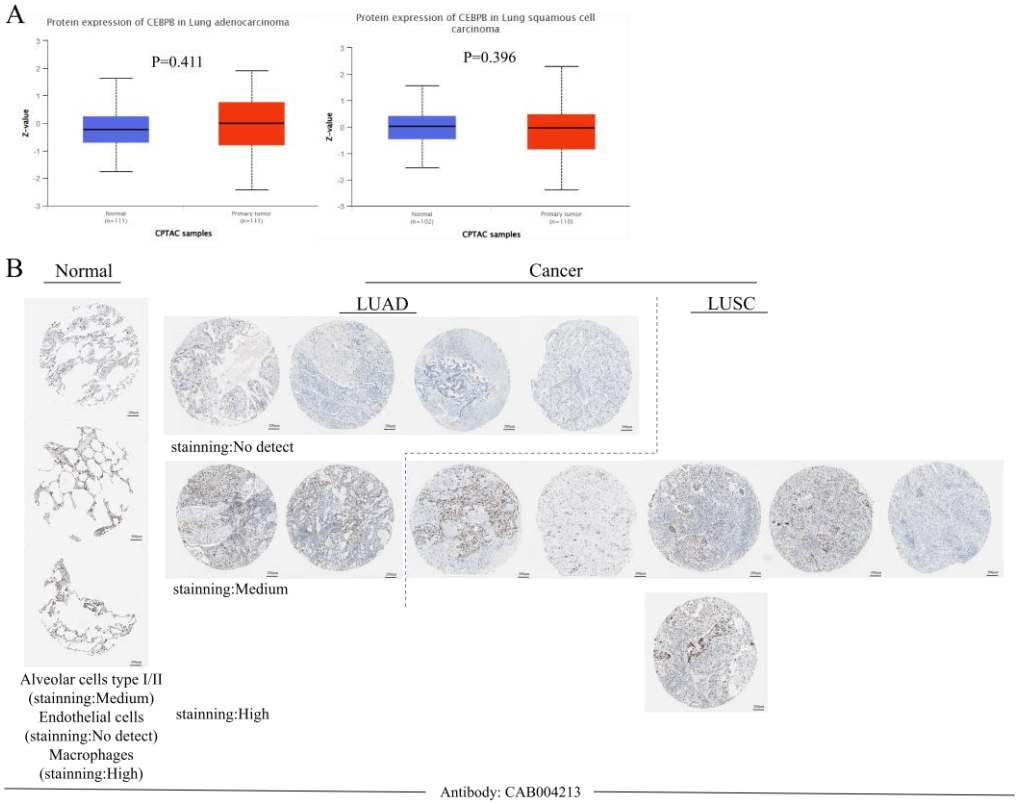
Figure 3: Prognostic Value of CEBPB mRNA Expression in Cancer (GEPIA 2 Database).

3.4. No Difference in CEBPB Protein Expression between LUAD and LUSC Patients Compared to Normal Tissues

The transcriptional expression of CEBPB was downregulated in LUAD and LUSC patients compared to normal tissues (Figures 1-2). However, survival analysis showed that higher CEBPB mRNA expression was associated with worse overall survival (OS) (Fig 3). Therefore, we sought to explore the protein expression patterns of CEBPB in LUAD and LUSC patients to better understand its role in NSCLC. Analysis of the UALCAN database showed no significant difference in CEBPB protein expression between tumor tissues and normal lung tissues in either LUAD (p = 0.411) or LUSC (p = 0.396) (Fig 4A). The Human Protein Atlas data indicated moderate expression of CEBPB in type I/II alveolar cells, no detectable expression in endothelial cells, and high expression in lung macrophages. In a sample of 12 NSCLC patients, 8 cases (66.67%) were detected with CEBPB protein expression, all of undetected cases belonged to LUAD patients. Only 1 case of high expression was seen in LUSC patients,

ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002

and of the 7 cases with moderate expression, 5 were LUSC patients (Fig 4B). This suggests that at the protein level, CEBPB expression in LUAD and LUSC patients is not downregulated as it is at the mRNA level, and LUSC patients seem more likely to exhibit detectable CEBPB protein expression. This may relate to the pathophysiological role of CEBPB.



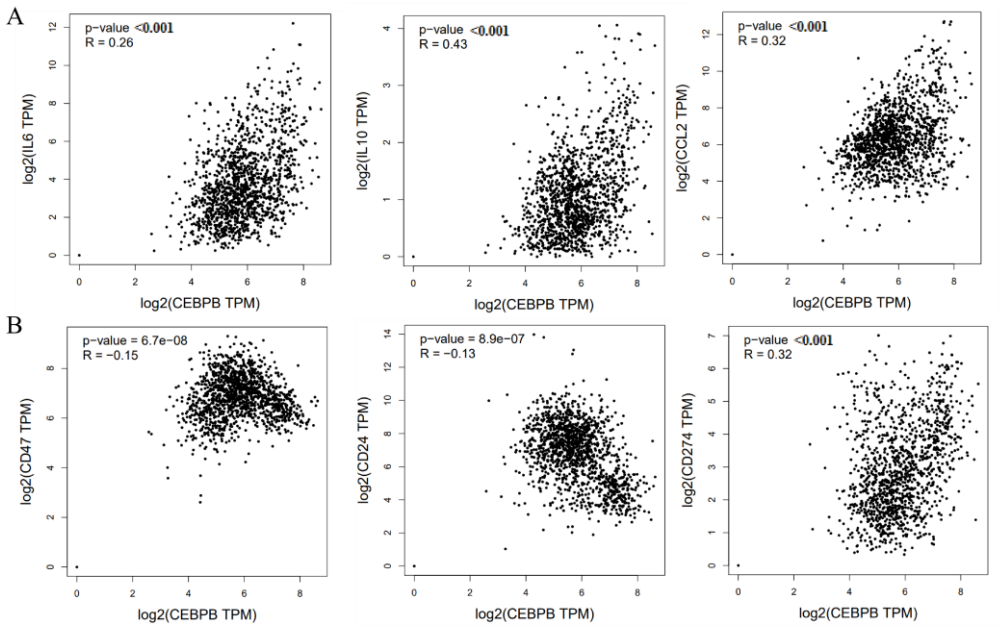
A: UALCAN database analysis of CEBPB protein expression levels in LUAD or LUSC tumor tissues compared to normal samples. B: Human Protein Atlas analysis of CEBPB protein expression in normal lung tissues and tumor tissues from LUAD and LUSC patients.

Figure 4: CEBPB Protein Expression in LUAD and LUSC Patients.

3.5. CEBPB Expression is Correlated with Immune-Related Cytokines and Immune Checkpoint Molecules

It is well known that CEBPB is a critical transcription factor regulating the expression of genes involved in immune and inflammatory responses[28]. Cancer progression is accompanied by a dynamic imbalance of inflammatory factors. Additionally, CEBPB is a major regulator of macrophage differentiation[29], and macrophages exhibit distinct roles in different tumor microenvironments, promoting either tumor regression or progression, metastasis, and drug resistance[30]. Some studies have shown that high CEBPB expression is significantly associated with active inflammation and immune response pathways in macrophages and skin cutaneous melanoma (SKCM) tissues[31]. Through GEPIA 2, we analyzed the correlation between CEBPB mRNA expression and immune-related cytokines such as IL-6, IL-10, and CCL2 in LUAD and LUSC, finding that CEBPB was positively correlated with these cytokines (correlation coefficients: 0.26, 0.43, 0.32)(Fig 5A). Other studies have reported that CEBPB enhances IL-6 expression in renal cell carcinoma, promoting the phosphorylation of STAT3 and expression of its downstream target genes, which contributes to tumor progression[32]. This may also explain the association between high CEBPB mRNA levels and worse OS in lung cancer patients. Additionally, we explored the relationship between CEBPB and immune checkpoints such as CD47, CD24, and PD-L1. There was little correlation between CEBPB and CD47 or CD24 (R = -0.15, -0.13), but a positive correlation with PD-L1 (R = 0.32, Fig 5B). It is hypothesized that high CEBPB expression leads to poor OS in LUAD and LUSC patients due to the immune escape caused by PD-L1 upregulation. Some research suggests that CEBPB regulates PD-L1 expression in NSCLC[33]. Overall, CEBPB mRNA expression is lower in LUAD and LUSC compared to normal tissues (Figures 1-2), but its role in immune regulation during cancer progression may results in a poorer prognosis for patients (Figures 3-5).

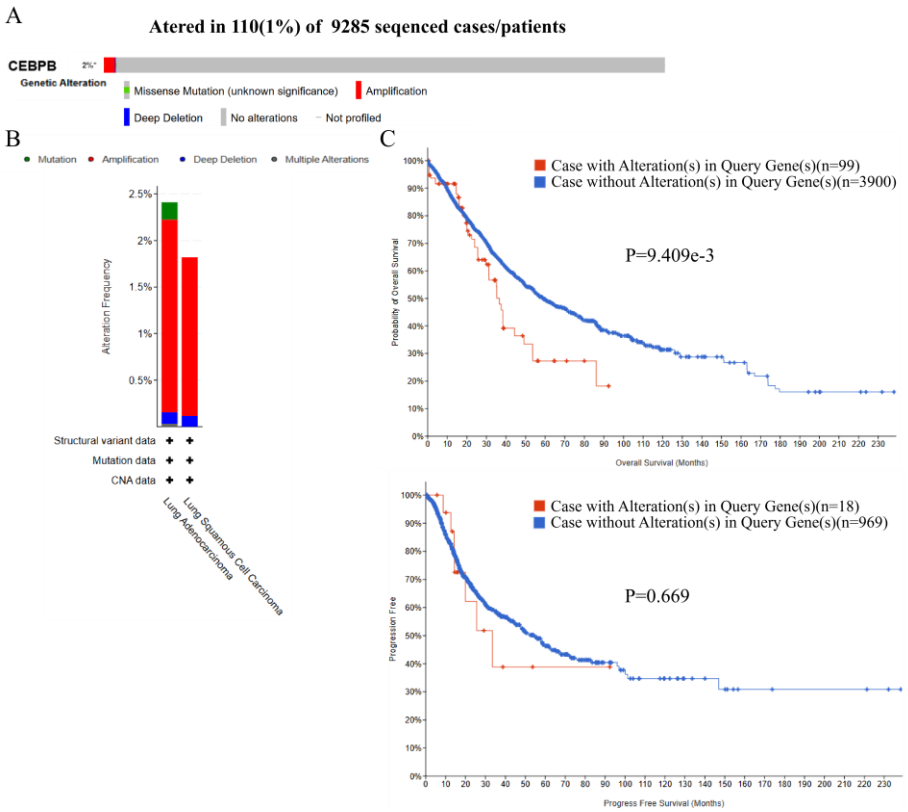
ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002



A-B: The correlation between CEBPB mRNA expression and immune-related cytokines (IL-6, IL-10, CCL2) and immune checkpoints (CD47, CD24, CD274) in LUAD and LUSC tumor samples from the TCGA database.

Figure 5: Correlation between CEBPB Transcriptional Expression and Inflammatory Cytokines and Immune Checkpoint Molecules (GEPIA 2 Database).

3.6. CEBPB Gene Mutations are Associated with Poor OS in LUAD and LUSC Patients



A: CEBPB gene alterations in LUAD and LUSC patients.B: Specific alterations in LUAD or LUSC patients.C: Prognostic value of CEBPB genetic alterations in LUAD and LUSC.

Figure 6: CEBPB Gene Mutations and Their Association with OS and DFS in patients with LUAD and LUSC (cBioPortal database).

ISSN 2618-1584 Vol. 6, Issue 10: 8-17, DOI: 10.25236/FMSR.2024.061002

Next, we analyzed the genetic alterations of CEBPB and their prognostic significance in LUAD and LUSC patients using the cBioPortal database (www.cbioportal.org). The mutation rate of CEBPB was found to be low in both LUAD and LUSC patients. Among 9,285 sequenced LUAD and LUSC patients, 110 cases of genetic alterations were detected, representing a mutation rate of 1% (Fig 6A). Specifically, amplifications were the most common form of alteration, with LUAD patients showing a higher frequency of CEBPB gene alterations compared to LUSC patients (Fig 6B). Kaplan-Meier plots and log-rank test results showed that CEBPB gene alterations were significantly associated with shorter OS ($p = 9.409E-4$), but not with DFS ($p = 0.669$), possibly due to the small sample size of the gene alteration group in DFS analysis ($n = 18$) (Fig 6C). These findings suggest that CEBPB genetic alterations significantly affect the prognosis of LUAD and LUSC patients.

4. Discussion

Lung cancer (LC) is one of the most common malignancies worldwide, with the highest cancer-related mortality rate[34, 35]. Non-small cell lung cancer (NSCLC) accounts for the majority of these cases, and most patients are diagnosed at an advanced stage or with distant metastasis[36], significantly limiting treatment options and leading to poor prognosis. Therefore, there is an urgent need for biomarkers or characteristics that can help predict NSCLC patient prognosis or serve as therapeutic targets for immunotherapy.

CEBPB plays an important role in tumor progression. However, different cancers exhibit varying roles due to different stimulatory signals. CEBPB expression is downregulated in squamous cell carcinoma[37], but it is upregulated in gastric cancer[38], colorectal cancer[16, 39], renal cell carcinoma[40], glioma[41], and breast cancer[42, 43], where it promotes cancer stemness, proliferation, migration, and regulation of oxidative stress. However, there has been no systematic study on the prognostic impact of CEBPB in NSCLC. Our study demonstrated that CEBPB transcriptional expression was significantly downregulated in LUAD and LUSC tissues and was associated with cancer staging in LUAD patients and lymph node metastasis in LUSC patients. However, due to its role in immune regulation in inflammatory diseases, high CEBPB expression is often associated with poor OS and DFS in NSCLC patients. Furthermore, genetic alterations in CEBPB were linked to poor prognosis in LUAD and LUSC patients.

Although this study provided some insights, it has limitations. First, the effects of different CEBPB isoforms on NSCLC were not analyzed in detail. Second, the specific regulatory mechanisms of CEBPB in inflammation modulation and macrophage differentiation within the NSCLC tumor microenvironment require further investigation. Future research will focus on these aspects and validate the potential of CEBPB as a tumor biomarker through in vitro and in vivo experiments.

5. Conclusions

CEBPB is a key transcription factor involved in the progression of NSCLC. Our results highlight the biological impact of CEBPB transcriptional expression on the prognosis of NSCLC patients, especially those with LUAD and LUSC, and its relationship with clinicopathological parameters. Therefore, CEBPB transcriptional expression levels hold promise as a potential biomarker for predicting the survival prognosis of non-small cell lung cancer patients.

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