AEBP1 as a potential immune-related prognostic biomarker in glioblastoma: a bioinformatic analyses

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Background: Adipocyte enhancer binding protein 1 (AEBP1) has been shown to be closely related to cancer progression; however research on its potential role in glioblastoma (GBM) remains limited.

Methods: Following an expression analysis of AEBP1 in GBM through the Oncomine database, other critical findings were accessed via The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression (GTEx) databases. Specifically, in addition to identifying differentially expressed genes, the Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) were further investigated. Additionally, a gene set enrichment analysis (GSEA) was performed to examine the enrichment pathways in the AEBP1 high-expression group. To examine the prognostic role of AEBP1 in GBM, survival information was obtained from the Chinese Glioma Genome Atlas (CGGA) database. Finally, the relationship between the expression of AEBP1 and immune infiltration in GBM was examined by using the “Gene Module”, “Survival Module”, and “SCNA Module” on the website “Tumor Immune Estimation Resource (TIMER)”.

Results: The Oncomine database revealed that AEBP1 was highly expressed in GBM. The prognostic analyses of 4 independent databases (i.e., TCGA, GTEx, Oncomine, and CGGA) revealed that AEBP1 was an independent predictable marker of GBM. The results of the GSEA showed that protein export, prion disease, cytokine receptor interaction, hematopoietic cell lineage, cell adhesion molecules, apoptosis, and the complement and coagulation cascades were differentially enriched in highly expressed AEBP1 phenotypes. Hence the conclusion is that the high expression of AEBP1 is closely correlated to poor prognosis of GBM. The immune analysis demonstrated that AEBP1 copy number alteration might affect immune infiltration in GBM tissues, and thus the survival outcomes of GBM patients.

Conclusions: High AEBP1 expression in GBM is closely correlated to patient prognosis. AEBP1 is a potential therapeutic target for the inhibition of cancerous progression and the development of new immunotherapies for GBM.

Keywords: Glioblastoma (GBM); adipocyte enhancer binding protein 1 (AEBP1); prognosis; The Cancer Genome Atlas (TCGA); the Chinese Glioma Genome Atlas (CGGA); immune infiltration
**Introduction**

Glioma is the most common primary tumor arising from the central nervous system (CNS) in adults, and glioblastoma (GBM) is one of the most aggressive types (1). Due to its high recurrence rate, the prognosis of GBM is rather poor (2,3). Further, despite decades of efforts by surgeons and researchers, there are still challenges in its treatment. More in-depth investigations on the mechanism of GBM initiation and progression are required for individualized treatment.

The identification of new effective biomarkers is a critical process, as such biomarkers not only predict patient prognosis, but could also potentially become new therapeutic targets for GBM (4-7). Adipocyte enhancer binding protein 1 (AEBP1) is a ubiquitously expressed protein, which was originally reported as a transcriptional repressor of the adipose P2 gene in preadipocytes (8). Additionally, AEBP1 is involved in the regulation of many tumors, such as ovarian and bladder malignancies (9,10). Similarly, AEBP1 also affects the occurrence and development of GBM (11). Relevant reports have shown that the high expression of AEBP1 has positive effects on the growth, survival, and apoptosis of GBM inhibition cells (12,13). We systematically studied the relationship between AEBP1 and GBM prognosis, and verified it with resources from different databases. And the unique and complex immune microenvironment of glioma is an important obstacle to immunotherapy (14). Therefore, we will study the potential mechanism and influence of AEBP1 and glioma immune microenvironment, which may help improve the efficacy of immunotherapy.

In the current study, we first examined the prognostic role of AEBP1 in GBM using multiple bioinformatic methods. A number of available databases, including Oncomine, Gene Expression Profiling Interactive Analysis (GEPIA), The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTeX), and Chinese Glioma Genome Atlas (CGGA), were integrated to investigate the comprehensive effects of AEBP1 on GBM. Figure 1 shows this study's workflow.

We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5183).

**Methods**

**AEBP1 analysis in the Oncomine database**

Oncomine (http://www.oncomine.org) integrates the transcriptomes of many major types of cancer and their respective normal tissues, and is a cancer microarray database and web-based data mining platform. It contains 715 gene expression data sets from 86,733 cancer and normal tissues (15). In this study, we used 5 glioma studies to examine the expression of AEBP1, including the Liang brain analysis, the Lee brain analysis, Bredel Brain 2 analysis, the Sun brain analysis, and the Rickman brain analysis from the Oncomine database (16-20). A P<0.01, FC of 2, and Gene Rank < top 10% were considered significant.

**AEBP1 analysis in the GEPIA database**

The GEPIA (http://gepia.cancer-pku.cn/) database was used to study the correlation between AEBP1 and GBM. GEPIA integrates 8,587 normal samples and 9,736 tumor samples from TCGA and GTEx projects to analyze ribonucleic acid (RNA) sequencing data, which were developed by Peking University (21). We performed a differential expression analysis of AEBP1 using a tumor and normal tissues, and conducted a survival analysis of patients in the GEPIA database.

**TCGA and GTEx data analysis**

To examine messenger RNA (mRNA) expression in normal brain tissues, we downloaded GTEx data (1,152 normal brain tissues) from (22) the UCSC Xena (http://xena.ucsc.edu/) and used a Perl (23) script to convert the Ensembl number of the gene to the Official Symbol of the gene for the subsequent analysis. Next, the R packages of gganatogram (24) and ggpubr on the GitHub (25) were used to examine the expression of AEBP1 in various organs of the human body. Combined with the GBM data downloaded from TCGA database (5 paracancer tissues and 160 GBM samples) (http://cancergenome.nih.gov/), we used (26) the limma package to screen DEGs (|logFC| >2, FDR <0.05) and used the (27) heatmap package to plot a heatmap. The clusterProfiler package was then used for the GO and KEGG pathway analyses (28), and the GOplot package was used for the cluster analysis (29). We used the GSEA program to investigate the functions correlated with high and low AEBP1 expression levels in the TCGA cohort (30).

**CGGA data analysis**

The data of 389 GBM patients were downloaded from the CGGA (www.cgga.org.cn) database. Due to incomplete information, 100 patients were excluded from the study,
and we only analyzed the data of the remaining 289 patients. Kaplan-Meier curves were plotted to show the relationship between the OS of patients and the expression level of AEBP1. We then used beeswarm plots to show the relationship between different clinical features and AEBP1 expression.

**AEBP1 analysis in the TIMER database**

TIMER (https://cistrome.shinyapps.io/timer/) is a website that comprehensively analyzes the immune invasion of different tumors (31). The website uses statistical methods to estimate the abundance of 6 immune cells (B cells, CD8+ T cells, macrophages, neutrophils, CD4+ T cells, and dendritic cells) in GBM. We then used the “Gene Module”, “Survival Module”, and “SCNA Module” on the website to examine the correlation between immune infiltration and the expression of AEBP1 in GBM patients.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

**Statistical analysis**

All data were shown as mean ± standard error of the mean (SEM). Multiple different groups were analyzed with a one-way analysis of variance (ANOVA) followed by Bonferroni test. A P value <0.05 was considered statistically significant.

**Results**

**AEBP1 expression in GBM tissues and normal human brain tissues**

First, we used the Oncomine database to detect the expression pattern of AEBP1 in GBM tissues. After screening, a total of 5 studies showed that AEBP1 was upregulated in CNS cancers, but its downregulation tendency was not reported (see Figure 2A,2B). In each study, the expression level of AEBP1 in glioma tissues was significantly higher than that in control peritumoral tissues (see Figure 3A-3E). Among the 950 different AEBP1 outlier analysis studies, 7 studies showed that the expression of AEBP1 was upregulated, and 6 studies showed that it was downregulated. To further determine whether AEBP1 was associated with glioma malignancies, a cancer versus cancer analysis (see Figure 4A) was conducted that showed that in 5 of the 6 studies, AEBP1 was significantly more highly expressed in GBM than in other glioma counterparts.
These results indicate that AEBP1 is differently expressed in glioma and may be a potential biomarker of GBM progression.

GTEx data were then used to compare the expression level of AEBP1 in GBM and normal human brain tissues. As Figure 5A,5B show, the lower expression of AEBP1 was only detected in seldom tissues, compared with brain tissue. No differences between males and females were observed (see Figure 5C), and subsequent analyses also indicated that the data of different sexes could be unbiasedly integrated.

**Relationship between the prognosis of GBM and AEBP1 expression and the prognostic role of AEBP1 in GBM**

To verify the analytic results from the Oncomine database and further explore correlations between AEBP1 expression and GBM, we analyzed relevant data from the GEPIA database, and confirmed that AEBP1 was significantly upregulated in GBM, acute myeloid leukemia, head and neck squamous cell carcinoma, thymoma, skin cutaneous melanoma, lymphoid neoplasm diffuse large b-cell lymphoma, and pancreatic adenocarcinoma (see Figure 6A). Conversely, endocervical adenocarcinoma and cervical squamous cell carcinoma, adrenocortical carcinoma, and kidney chromophore showed a decreased expression pattern of AEBP1. Interestingly, compared to normal brain tissue, the upregulation of AEBP1 was observed in highly aggressive GBM but not in low-grade glioma (see Figure 6B). A further prognostic analysis showed that the higher the expression of AEBP1, the shorter the overall survival (OS) of GBM patients (see Figure 6C). Thus, we found that AEBP1 was significantly upregulated in GBM and possessed a prognostic value for GBM. Together, these results suggest that AEBP1 plays a pro-cancerous role in GBM.

**Bioinformatic Analysis of TCGA and GTEx Database**

Through a differentially expressed gene (DEG) analysis, a total of 1,923 DEGs were identified from the GTEx and TCGA data [fold change (FC)] >2, false discovery rate (FDR) <0.05] (see https://cdn.amegroups.cn/static/public/atm-21-5183-1.xlsx and Figure 7). A further Gene Ontology (GO) analysis showed that these DEGs were
Figure 3 AEBP1 expression in cancer vs. normal tissues in 5 analyses. (A) Bredel brain, (B) Liang brain, (C) Lee brain, (D) Rickman brain, and (E) Sun brain. P<0.01. AEBP1, adipocyte enhancer binding protein 1.

significantly enriched in the regulation of vesicle-mediated transport, neutrophil degranulation, and the modulation of chemical synaptic transmission in the biological processes. The cellular components were mainly enriched in the presynapse, extracellular matrix, and neuronal cell body. The molecular functions were significantly enriched in phospholipid binding, substrate-specific channel activity, and ion channel activity (see Figure 8A). The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the DEG showed that it was mainly concentrated in cell adhesion molecules and immune-related signaling pathways (see Figure 8B). We then performed cluster analyses of the top pathways and GO terms. The top GO terms were enriched in neurotransmitter secretion, neurotransmitter transport, the regulation of vesicle-mediated transport, the signal release from synapse, and the modulation of chemical synaptic transmission (see Figure 8C). The pathways were enriched in the phagosome, type I diabetes mellitus, viral myocarditis, GABAergic synapse, and Epstein-Barr virus infection (see Figure 8D). Further, similar to the results of the GEPIA analysis, the survival curve of AEBP1 (see Figure 8E) showed that GBM patients with low AEBP1 expression lived longer than those with high AEBP1 expression (the P value was much less than 0.001).

Gene sets enriched in AEBP1 expression phenotype

To further examine the biological role of AEBP1 in GBM, a GSEA was performed (see Figure 9). The results showed that a series of functions, including apoptosis, antigen processing and presentation, the complement and the coagulation cascades, the B-cell receptor signaling pathway, lysosome, pathways in cancer, the toll-like receptor signaling pathway, and the T-cell receptor signaling pathway, were differentially enriched in the AEBP1 high-
Figure 4 AEBP1 expression in cancer vs. cancer tissues analysis. (A) Comparison of AEBP1 expression across 6 analyses. AEBP1 expression in (B) Liang brain, (C) Nutt brain, (D) Janoueix-Lerosey brain, (E) Bredel brain 2, (F) Sun brain and (G) Freije brain. P<0.01. AEBP1, adipocyte enhancer binding protein 1.
expression phenotype.

Validation of the clinical correlation from the CGGA

To further validate the prognostic value of AEBP1 for GBM, we downloaded the sequencing data and clinical information of 389 patients from the CGGA database. Using the Limma and beeswarm packages, we found that AEBP1 was markedly upregulated in GBM (see Figure 10A). Due to missing data, a total of 290 eligible patients were ultimately included in the prognostic analysis. Interestingly, consistent with the GEPIA and TCGA results, GBM patients with high AEBP1 expression had worse survival outcomes (see Figure 10B). Further, the differential expression of AEBP1 was noticeably associated with age, sample type, 1p19q codeletion status, and isocitrate dehydrogenase (IDH) mutation (see Figure 10C-10I).

In addition, we also examined the receiver operating characteristic (ROC) curves and undertook a logistic regression of the CGGA dataset. The ROC curves showed that risk score precisely predicted the 5-year survival rates of GBM patients [area under the curve (AUC) =70.7\%] (see Figure 10J). The univariate Cox analysis (see Figure 10K) revealed that AEBP1 [hazard ratio (HR) =1.12; 95\% confidence interval (CI): 1.04–1.19] and sample type (HR =1.47; 95\% CI: 1.23–1.75) were high-risk factors. Conversely, IDH mutation (HR =0.71; 95\% CI: 0.53–0.97), chemotherapy (HR =0.47; 95\% CI: 0.34–0.65), and radiation therapy (HR =0.58; 95\% CI: 0.41–0.82) were all low-risk factors. A further multivariate analysis
Figure 6 The relationship between the prognosis of GBM patients and AEBP1 expression. (A) AEBP1 expression was significantly upregulated in a variety of tumors. (B) The expression level of AEBP1 was significantly higher than that of normal controls in GBM. *, P<0.05. (C) OS curves of AEBP1 in the GEPIA. GBM, glioblastoma; AEBP1, adipocyte enhancer binding protein 1; OS, overall survival.

(see Figure 10L) confirmed that AEBP1 (HR =1.12; 95% CI: 1.04–1.21; P<0.01) was still independently related to the OS rate. The univariate and multivariate analyses showed that AEBP1 might be an independent prognostic marker in GBM patients. Consistent with the findings of the univariate Cox analysis, sample type (HR =1.89; 95% CI: 1.54–2.32; P<0.01) was a high-risk factor, and IDH mutation (HR =0.63; 95% CI: 0.44–0.90; P=0.01), and chemotherapy (HR =0.46; 95% CI: 0.33–0.64; P<0.01) were low-risk factors.

**AEBP1 expression is correlated with immune-infiltration level**

The GSEA analysis indicated that the genes in the AEBP1 high-expression group were enriched in immune-related pathways. Thus, the Tumor Immune Estimation Resource (TIMER) was employed to further investigate the immune infiltration of GBM. The results showed that AEBP1 was negatively correlated with cluster of differentiation 8 (CD8+) T cells and purity, but was positively correlated with CD4+...
T cells, B cells, and dendritic cells in GBM (see Figure 11A and Table 1). Next, the TIMER data were used for the univariate and multivariate Cox survival analyses. The results of the univariate analysis showed that dendritic cells and AEBP1 affected the survival outcome of GBM patients (see Figure 11B and Table 2). The results of the multivariate analysis showed that age, dendritic cell count, and AEBP1 were independent prognostic factors of GBM (see Table 3). In addition, the changes in the copy number of AEBP1 appeared to significantly affect the immune-infiltration level in GBM (see Figure 11C). Together, these results highlight that the alteration of AEBP1 copy number is closely related to the immune-infiltration level and predicts the prognosis of GBM patients. Thus, AEBP1 might be a potential reference value for determining the inhibition of GBM progression and the development of new immunotherapies.

Discussion
Glioma is a common malignancy originating from the glial cells in the brain and spine (32). Due to its high invasion and recurrence rate (33-35), surgical and other interventions cannot radically cure the tumor (36). Despite continuous advancements in treatments, the prognosis of GBM remains very poor, and on average, patients survive less than 2 years (37). Thus, identifying more effective biomarkers is critical to individualized therapy and prognostic prediction.

AEBP1 has been reported to be correlated with the initiation and progression of GBM (38,39); however, the mechanism underlying AEBP1 in GBM requires further study. In our study, using data from the Oncomine database, we found that AEBP1 was highly expressed in GBM tissues. Our results are consistent with previous reports and indicate
Figure 8 Bioinformatic analysis of TCGA and GTEx database. Bubble chart of GO (A) and KEGG (B) analysis of DEGs. (C) GO and (D) KEGG pathway cluster analyses. (E) Overall survival curves of AEBP1 for TCGA analysis. TCGA, The Cancer Genome Atlas; GTEx, Genotype Tissue Expression; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEG, differentially expressed gene; AEBP1, adipocyte enhancer binding protein 1.

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Figure 9 GSEA analysis. (A) The GSEA analysis showed that genes with high expression in the AEBP1 phenotype were differentially enriched in the complement and coagulation cascades, apoptosis, antigen processing and presentation, B-cell receptor signaling pathway, lysosome, toll-like receptor signaling pathway, and T-cell receptor signaling pathway pathways in cancer. (B) The integrated GSEA analysis. GSEA, gene set enrichment analysis; AEBP1, adipocyte enhancer binding protein 1.
Figure 10 Correlation analysis of AEBP1 expression and clinical features. (A) Analysis of the expression level of AEBP1 in glioblastoma. (B) The relationship between the expression level of AEBP1 and the survival rate. (C-I) Analysis of the correlation between AEBP1 expression and different clinical features. (J) ROC curve showing the predictive efficiency of AEBP1. (K) Univariate and (L) multivariate Cox regression analyses of the association between the overall survival of patients and clinical factors (including AEBP1 expression). AEBP1, adipocyte enhancer binding protein 1; ROC, receiver operating characteristic.
Figure 11 AEBP1-related immune infiltration analysis. (A) The correlation between AEBP1 and immune infiltration. (B) Immune-cell infiltration survival curve. (C) The relationship between AEBP1 copy number variation and the infiltration level of immune cell. **, P<0.01; ***, P<0.001. AEBP1, adipocyte enhancer binding protein 1.
Table 1 The relationship between AEBP1 expression and immune-infiltration levels in GBM

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Variable</th>
<th>Partial.cor</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>GBM</td>
<td>Dendritic cell</td>
<td>0.27</td>
<td>0.00</td>
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<tr>
<td>GBM</td>
<td>CD4+ T cell</td>
<td>0.20</td>
<td>0.00</td>
</tr>
<tr>
<td>GBM</td>
<td>Purity</td>
<td>0.13</td>
<td>0.01</td>
</tr>
<tr>
<td>GBM</td>
<td>CD8+ T cell</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>GBM</td>
<td>B cell</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>GBM</td>
<td>Neutrophil</td>
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<td>0.48</td>
</tr>
<tr>
<td>GBM</td>
<td>Macrophage</td>
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<td>0.58</td>
</tr>
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</table>

AEBP1, adipocyte enhancer binding protein 1; GBM, glioblastoma.

Table 2 Univariate analysis of the correlation between immune infiltration and AEBP1 expression with OS in GBM patients

<table>
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<tr>
<th>Cancer</th>
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</thead>
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<td>Dendritic cell</td>
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</tr>
<tr>
<td>GBM</td>
<td>AEBP1</td>
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</tr>
<tr>
<td>GBM</td>
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<tr>
<td>GBM</td>
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<tr>
<td>GBM</td>
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</table>

AEBP1, adipocyte enhancer binding protein 1; OS, overall survival; GBM, glioblastoma.

Table 3 Multivariate analysis of the correlation between immune infiltration and AEBP1 expression with OS in GBM patients

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<th>Coef</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>Sig</th>
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<td>Age</td>
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<td>1.02–1.04</td>
<td>0.00</td>
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<tr>
<td>Dendritic</td>
<td>0.47</td>
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<td>1.15–2.23</td>
<td>0.01</td>
<td>**</td>
</tr>
<tr>
<td>AEBP1</td>
<td>0.10</td>
<td>1.11</td>
<td>1.02–1.20</td>
<td>0.02</td>
<td>*</td>
</tr>
<tr>
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<td>0.27–1.04</td>
<td>0.06</td>
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</tr>
<tr>
<td>CD8_T cell</td>
<td>0.38</td>
<td>1.47</td>
<td>0.94–2.30</td>
<td>0.10</td>
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<tr>
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<td>1.78</td>
<td>0.72–4.40</td>
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<td>0.72–3.35</td>
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<tr>
<td>Gender: male</td>
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<td>1.08</td>
<td>0.86–1.36</td>
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<tr>
<td>Race: Black</td>
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<td>1.38</td>
<td>0.50–3.84</td>
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<td>1.20</td>
<td>0.38–2.99</td>
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<td>Purity</td>
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<td>1.10</td>
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<td>CD4_T cell</td>
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<td>1.02</td>
<td>0.46–2.27</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

*, P<0.05; **, P<0.01; ***, P<0.001. AEBP1, adipocyte enhancer binding protein 1; OS, overall survival; GBM, glioblastoma.
that AEBP1 appears to play a crucial regulatory role in the initiation and progression of GBM (40). We also found that the AEBP1 expression pattern was positively related with survival outcomes, which indicates that AEBP1 might be an effective marker in predicting the prognosis of GBM patients. In a further analysis, using data from the CGGA database, we once again confirmed the predictive role of AEBP1 in GBM.

Chemotherapy and radiotherapy are classic treatments for GBM. However, in our clinical investigation, we demonstrated the therapeutic superiority of chemotherapy to radiotherapy. Consistent with the conclusions of previous research, we also found that IDH mutation is a key factor affecting prognosis, and the expression of AEBP1 in IDH wild-type GBM is also significantly different from that in IDH mutant GBM cases. Thus, AEBP1 might be a key driver oncogene that promotes the tumorigenesis of GBM.

In relation to our immune analyses, the KEGG and GSEA results showed that immunity-related signaling pathways were significantly involved in the regulation network of AEBP1 (41). Molecularly, the TIMER analysis highlighted the inducible role of copy number alteration in the process of AEBP1 increasing immune infiltration. Specifically, dendritic cell infiltration might increase the negative risk of GBM (42). It has been reported that AEBP1 may promote the proliferation and progression of glioma cells in GBM through the NF-κB pathway and its downstream targets, such as MMP-2 and Bcl-2 (43). NF-κB is associated with immunity in tumors (44,45), and NF-κB activity promotes tumor growth by inhibiting the infiltration, proliferation and immune response of effector T cells (45). we may begin to study the NF-κB pathway and immune infiltration in GBM in future studies. This novel finding might be used to develop more promising immunotherapies for GBM (46).

In conclusion, the survival rate of GBM patients decreased as AEBP1 expression levels increased. Further, Chemotherapy had an encouraging therapeutic effect on GBM. Additionally, the infiltration of immune cells might be regulated by the expression pattern of AEBP1. The immune-related pathways were also abundantly enriched in AEBP1. These novel findings are expected to lead to the development of novel solutions for GBM treatment. However, it should be noted that only public databases (i.e., TCGA and the CGGA) were employed to analyze and confirm the relationship between AEBP1 expression and prognosis using bioinformatic methods, and our study lacks more in vivo and in vitro evidence. After we establish an appropriate design and make the appropriate preparations, we will conduct further research on the molecular functions and mechanisms of AEBP1 in GBM through a series of cell-line, tissue, and animal experiments.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5183). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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