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High expression of ARPC1B correlates with immune infiltration and poor outcomes in glioblastoma

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ABSTRACT

Objective: To investigate the role of ARPC1B in GBM and its prognostic value.
Methods: mRNA and protein expression of ARPC1B in GBM was analyzed using the TCGA; TIMER2 and the HPA databases, and protein expression differences were detected using immunohistochemistry. K-M analysis and Cox regression analysis were performed on high and low ARPC1B expression groups in the TCGA database. The relationship between immune cells and ARPC1B expression was explored using the TIMER2 database. GO and KEGG analyses were conducted to investigate the functions of ARPC1B-related genes in GBM.
Results: ARPC1B was highly expressed in both GBM tissues and cell lines, and it was demonstrated as a prognostic biomarker for GBM. ARPC1B expression levels showed associations with immune cell populations within the GBM microenvironment.
Conclusion: ARPC1B can regulating immune infiltration in the GBM microenvironment, indicating its potential as a novel therapeutic target for GBM.

1. Introduction

Glioblastoma is an extremely aggressive and malignant tumor that develops in the central nervous system. It is difficult to treat effectively. Despite the implementation of various therapeutic methods, the average overall survival (OS) for GBM remains bleak, with a prognosis of less than 2 years [1,2]. The tumor microenvironment (TME) is a crucial factor in the progression and recurrence of brain tumors [3–5]. It encompasses the surrounding cells, blood vessels, immune cells, and signaling molecules that interact with tumor cells. The poor prognosis of GBM is associated with TME-drive immune evasion [6]. The TME of GBM contains various immune cells, including macrophages, neutrophils, lymphocytes, etc., of which macrophages account for about 30 % [6]. Many genes have been confirmed to be closely related to TME. IGF2BP3 has been reported to significantly positively correlated with macrophages, B cells, and CD8 T cells in bladder urothelial carcinoma, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, and lower grade glioma [7]. YTHDF1is associated with tumor immune microenvironment in head and neck squamous cell carcinomas [8]. LncRNA MALAT1 regulates METTL3-mediated PD-L1 expression and immune infiltrates in pancreatic cancer [9]. Whether they affect tumor growth has become the focus of current research. The brain tumor cells secrete cytokines and chemo-attractants to recruit immune cells into the TME. Certain immune cells have been shown to facilitate the growth of tumors, whereas others exhibit tumor cytotoxicity, leading to the elimination of tumor cells [10]. The mechanisms underlying the interaction between immune cells and GBM cells remain unclear. Recent study has suggested that ARPC1B can recruit macrophages into the TME of GBM [11]. However, immune cell types that can be recruited by ARPC1B and the roles of these immune cells in GBM haven't been identified.

The human Arp2/3 protein complex has been implicated in promoting the growth and metastasis of various malignancies. Notably, the assembly of the complex is closely linked to the actin-related protein 2/3 complex subunit 1B (ARPC1B), which is a crucial subunit of the complex [12]. ARPC1B has been implicated in various types of tumors, including oral squamous cell carcinoma, prostate cancer, and melanoma [11,13,14]. ARPC1B has been implicated in predicting the efficacy of radiation therapy for choroidal malignant melanoma. And it is also associated with various immune disorders, such as immunodeficiency resulting

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from ARPC1B deficiency, which increases susceptibility to severe infections, inflammation, and allergic reactions in affected patients [15,16].

In this study, we investigated the prognostic implications of ARPC1B expression in GBM by comparing high and low expression groups using The Cancer Genome Atlas (TCGA; http://cancergenome.nih.gov), as well as the immune cells associated with GBM tissue prognosis using the Tumor Immune Estimation Resource 2.0 (TIMER2; http://timer.cistrome.org/). The findings provide valuable insights into the prognostic significance of ARPC1B in GBM and its potential impact on immune cells in the TME and contribute to the identification of novel targets for future GBM treatments, establishing a crucial foundation for further research in this field.

2. Materials and methods

The operational workflow of this study is Fig. 1.

2.1. Data collection

Transcriptomic and clinical data were got from TCGA database for 168 GBM patients and 5 healthy controls. Bulk RNA-sequencing data was downloaded in TPM format. We performed log2 transformation for expression comparisons between samples. Subsequently, we conducted prognostic and immune cell infiltration analyses using the downloaded data.

2.2. GBM samples collection

GBM tumor tissues were obtained from Department of Neurosurgery, East Hospital of the First Affiliated Hospital of Sun Yat-sen University from January–December 2022. The tissues were obtained from three pathologically sectioned GBM samples and three brain tissues that had been decompressed by brain tissue resection due to heavy traumatic brain injury in plain health. Exclusion criteria were as follows: 1) Combination of tumors in other organs of the body (including those who have already undergone tumor resection); 2) Combination of serious organic diseases, especially chronic inflammatory patients, such as chronic respiratory infections, tuberculosis, hepatitis, chronic colitis, etc. Informed consent was obtained from each patient or patient's immediate family member. The study obtained approval from the Ethics Committee of this hospital.

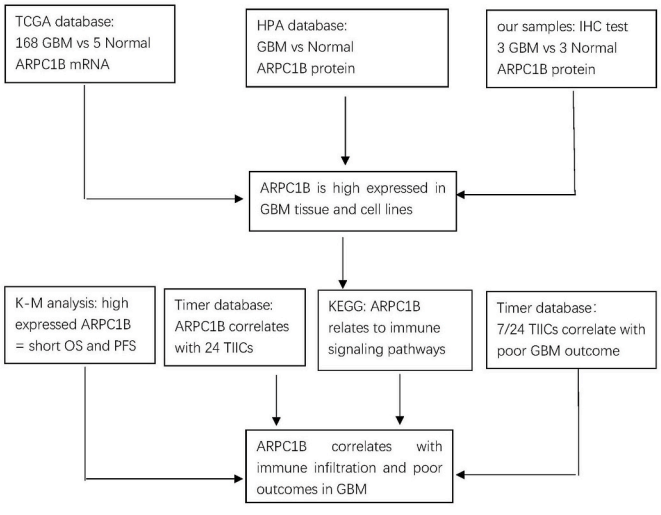

Fig. 1. The operational workflow of this study.

2.3. Immunohistochemistry

IHC staining was performed on paraffin sections of GBM and control group. They were incubated with anti-ARPC1B primary antibody (bs-10563R, Bioss Inc) and secondary antibody (GK500705, ChemMate TM DAKO). We utilized DAB solution and a hematoxylin re-staining agent to visualize the staining as the manufacturer's instructions. Images were captured at 100x magnification with an Olympus BX43 microscope.

2.4. Immune infiltration assessment

We download the immune datasets from TCGA database and used the R package GSVA and GGPLOT to assess the abundance of tumor-infiltrating immune cells (TIICs) in GBM and the variances in the infiltration levels of 24 TIICs between the high and low ARPC1B expression groups. Using the TIMER 2 database, we further investigated the correlation between ARPC1B and these different TIICs, the relationship between the TIICs and the prognosis of GBM.

2.5. Enrichment analysis

We downloaded RNA-sequencing data from TCGA database for TCGA-GBM and extracted data in TPM format as well as clinical data using R (version 4.2.1). We next removed data from 5 normal samples, extracted ARPC1B and total mRNA data. Pearson correlation analysis was performed between ARPC1B and all the remaining genes. 1647 genes exhibited a correlation greater than 0.3 and a p-value less than 0.05, and 1084 genes displayed a correlation coefficient less than −0.3 and a p-value less than 0.05, were identified. To explore the potential molecular mechanisms linking ARPC1B expression to GBM prognosis, we performed Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses for the two groups of genes.

2.6. Statistical analysis

We conducted data processing and statistical analyses using R software v 4.2.1 and SPSS v.25. To examine the correlation between ARPC1B expression and clinicopathological parameters of GBM, we employed the cardinality test. Survival analyses were conducted using the Kaplan-Meier (K-M) analysis, which is a non-parametric approach to estimate survival functions. The log-rank test was used to compare the survival curves between different groups. Both univariate and multivariate survival analyses were performed using Cox regression models. Statistical significance was defined as a p-value less than 0.05, indicating a level of significance.

3. Result

3.1. ARPC1B is highly expressed in GBM tissues and glioma cell lines

The TIMER 2 database provided mRNA expression data from TCGA database, consisting of 168 GBM and 5 normal samples. Analysis of this data revealed a significant increase in ARPC1B expression in GBM compared to control tissues (Fig. 2a). To further investigate ARPC1B expression, we conducted a search in the Human Protein Atlas database (HPA, https://www.proteinatlas.org/) databases, focusing on glioma cell lines. The results demonstrated significantly higher levels of ARPC1B expression in the glioma cell lines U-87MG, U-251MG, and U-138MG compared to the normal glial cell line AF22 (Fig. 2b). Immunohistochemical images of ARPC1B protein from the HPA database, showed a notable increase in ARPC1B expression in GBM compared to control tissues (Fig. 2c and d). To validate these findings, we performed immunohistochemistry analysis on six surgically resected specimens, evaluating ARPC1B protein expression pattern in both normal and GBM tumor samples. Our results demonstrated lower ARPC1B protein expression in normal cerebral cortex (Fig. 3a–c) and higher expression in

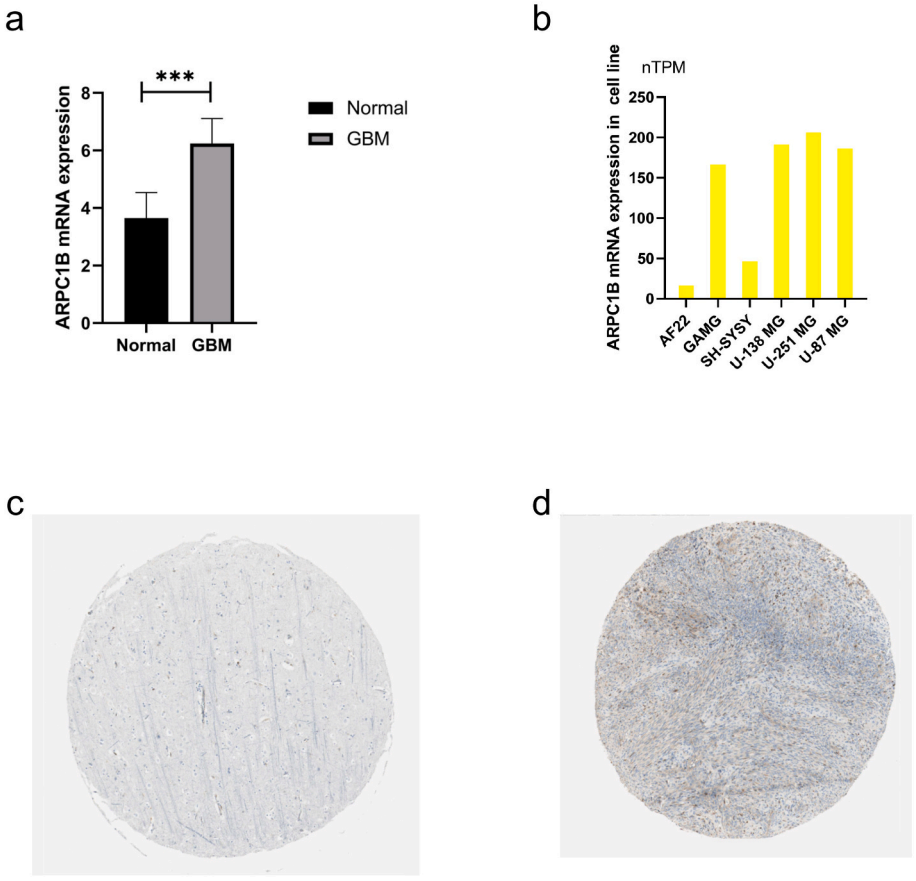

Fig. 2. ARPC1B expression in GBM tissues and cell lines.
(a) mRNA levels of ARPC1B in 168 tumor samples and 5 normal samples from TCGA database, ***: $p < 0.001$. (b) Glioma cell lines from the HPA database. (c) Immunohistochemical results of ARPC1B protein from the HPA database was barely expressed in normal cerebral cortex. (d) Immunohistochemical images of ARPC1B protein was increased in GBM tissues from HPA database.

GBM tumor samples (Fig. 3d–f). These findings collectively highlight the differential expression of ARPC1B between normal brain tissues and GBM, supporting its potential role as a biomarker in GBM.

3.2. Correlation of ARPC1B expression in GBM with clinicopathological features

To investigate the potential prognostic value of ARPC1B expression in GBM, we divided the 168 GBM patients into two groups based on the median expression value of ARPC1B. As shown in Table 1, the analysis of patient characteristics indicated that ARPC1B expression levels did not show a significant association with age, gender, ethnicity, or IDH1 mutation status among GBM patients. However, we observed a significant correlation between ARPC1B levels and several clinicopathological features, including OS and progression-free survival (PFS). To analyze the impact of ARPC1B expression on patient outcomes, K-M analysis displayed that high ARPC1B expression was significantly linked to improved OS ($p = 0.044$) and PFS ($p = 0.02$) (Fig. 4a and b).

3.3. Independent prognostic value of ARPC1B in GBM

Cox survival analysis was performed to assess the prognostic value of ARPC1B expression levels in GBM. In the univariate analysis, the hazard ratio (HR) for OS was 1.389 (95 % confidence interval [CI]: 1.113–1.733, $p = 0.004$), indicating that patients with high ARPC1B expression had a higher risk of poor survival compared to those with low expression (Table 2). Moreover, in the multivariate analysis, after adjusting for other prognostic factors, the HR for OS was 1.367 (95 % CI: 1.094–1.709, $p = 0.006$), further confirming that ARPC1B expression is an independent prognostic factor for GBM. The findings suggest that ARPC1B expression levels could have clinical utility in assessing prognosis and guiding treatment decisions in GBM patients.

3.4. ARPC1B expression correlates with the proportion of TIICs in GBM

We utilized GSVA package in R to analyze the differences in the proportion of immune cell types between the high and low ARPC1B expression groups in 186 GBM patients. They focused on 24 TIICs for this analysis. The results revealed significant variations in the proportions of multiple immune cell types between the two groups. Specifically, 18 immune cell types such as Eosinophils, DC (dendritic cells), Cytotoxic cells, Macrophages, Neutrophils and NK cells, were found to be proportionally higher in the high ARPC1B expression group (Fig. 5a). Moreover, ARPC1B expression showed a significant positive correlation with 20 TIIC numbers, while exhibiting a negative correlation with TH2 cell numbers (Fig. 5b). These findings highlight the crucial role of ARPC1B in regulating immune cells within the TME of GBM.

3.5. Prognostic value of TIICs in GBM

Previous research has established the prognostic value of TIIC proportions in various cancers. We applied the Outcome prediction function of the Immune Association of the TIMER 2 database to further investigate the relationship between 24 TIIC subpopulations and the prognosis of GBM. Our findings revealed that several TIIC subpopulations, including $CD8^+$ T cell, Neutrophil, Macrophage M2, NK cell, and Mast

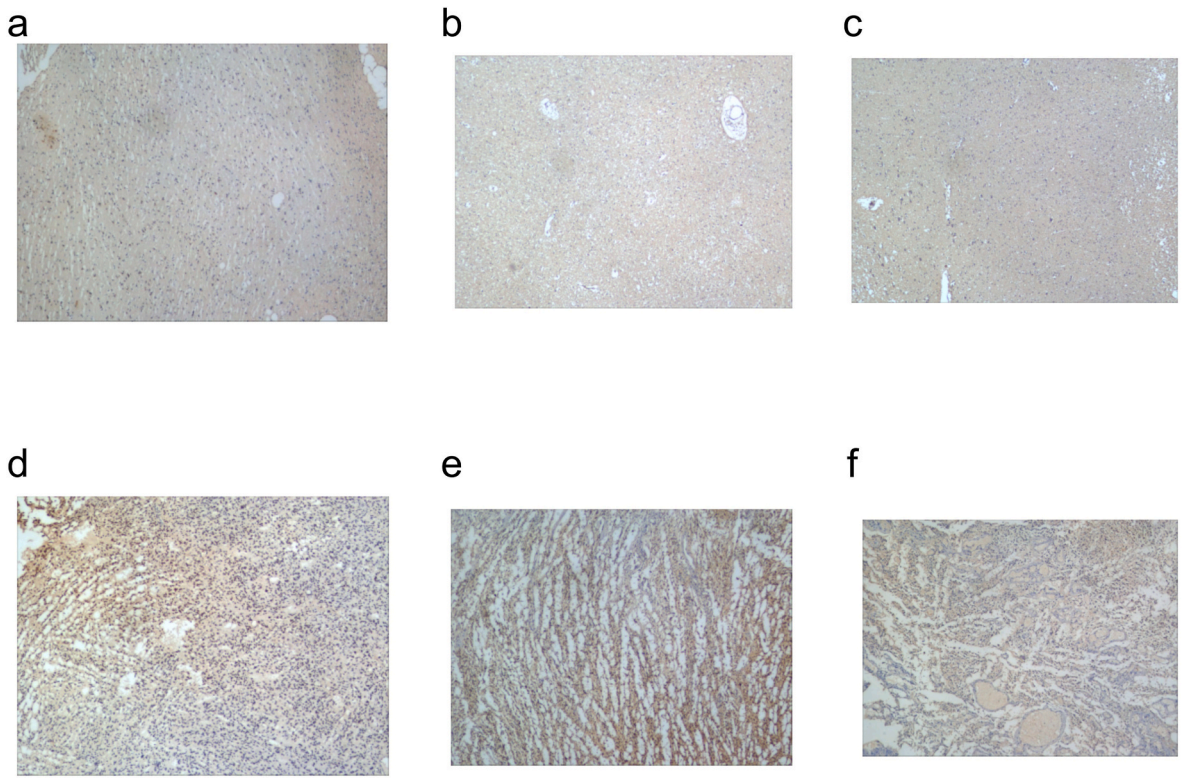

Fig. 3. ARPC1B protein expression was significantly increased in GBM tissues. Immunohistochemical results of ARPC1B protein in normal (a–c) and GBM (d–f) tissues. Microscope magnification is 10 × 10.

Table 1
Correlation between ARPC1B expression and clinicopathological features in GBM.

Characteristic	Low expression of ARPC1B	High expression of ARPC1B	p
N	84	84	
Gender, n (%)			1.000
Female	29 (17.3 %)	30 (17.9 %)	
Male	55 (32.7 %)	54 (32.1 %)	
Race, n (%)			0.705
Asian	3 (1.8 %)	2 (1.2 %)	
Black or African American	4 (2.4 %)	7 (4.2 %)	
White	76 (45.8 %)	74 (44.6 %)	
Age, n (%)			1.000
≤60	43 (25.6 %)	44 (26.2 %)	
>60	41 (24.4 %)	40 (23.8 %)	
Age, mean ± SD	59.62 ± 13.95	58.82 ± 13.15	0.703
IDH status, n (%)			0.563
WT	74 (46 %)	75 (46.6 %)	
Mut	7 (4.3 %)	5 (3.1 %)	

ARPC1B expression levels did not show a significant association with age, gender, ethnicity, or IDH1 mutation status among GBM patients.

cell, were associated with a poorer prognosis for GBM patients (Table 3). Interestingly, all of these immune cell types exhibited a higher proportion in the ARPC1B high expression group. K-M analysis demonstrated that a higher proportion of Macrophage, Macrophage M1, Macrophage M2, and NK cells corresponded to lower survival rates in GBM patients (Fig. 6). These results suggest that TIICs was able to affect the GBM prognosis.

3.6. GO and KEGG analyses of ARPC1B related genes

To explore the potential molecular mechanisms linking ARPC1B expression to GBM prognosis, we employed Pearson correlation analysis to examine the correlation between ARPC1B and all other genes in the TCGA-GBM dataset. The analysis identified 1647 genes that exhibited a correlation coefficient greater than 0.3 and a corresponding p-value less than 0.05, indicating a positive association with ARPC1B expression. On the other hand, 1084 genes displayed a correlation coefficient less than −0.3 and a corresponding p-value less than 0.05, indicating a negative association with ARPC1B expression. These genes were analyzed by GO and KEGG analyses to identify differentially activated signaling pathways.

Genes positively related to ARPC1B involved in some immune and inflammatory responses related biologic processes (BPs), such as positive regulation of cytokine production, monocyte differentiation, leukocyte-mediated immunity, etc. The KEGG analyses showed that some immune and inflammatory responses related signaling pathways, such as cytokine -cytokine receptor interaction and chemokine signaling pathway, are involved in (Fig. 7a).

Genes negatively related to ARPC1B involved in BPs are mainly proteasomal proteolytic processes, mRNA processing, RNA splicing, ribonucleoprotein complex biogenesis, and establishment of protein localization to organelles. The signaling pathways involved are herpes simplex virus 1 infection and some inflammatory diseases, such as Huntington's disease, Alzheimer's disease. (Fig. 7b).

4. Discussion

Despite the development of new treatments such as electric field therapy, the prognosis of GBM remains disheartening, with an average survival time of around 14 months. This highlights the urgent need for the discovery of new therapeutic targets that can improve the outcomes of GBM treatment [1,2].

Our study, utilizing data from the TCGA and Timer2 databases, unveiled that ARPC1B mRNA expression was notably elevated in GBM tumor tissues and cell lines. Furthermore, utilizing the HPA database, we

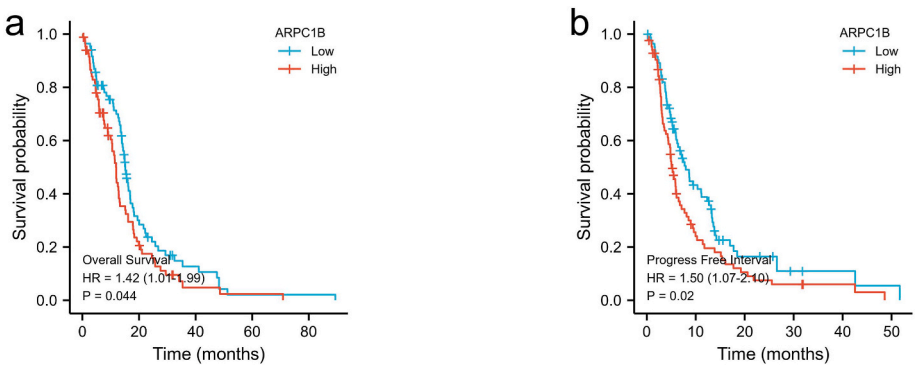

Fig. 4. Association between ARPC1B expression levels and OS and PFS.
168 GBM patients were equally divided into two groups, High ARPC1B expression was significantly associated with poorer OS (a) and poor PFS (b) in the TCGA database.

Table 2
Univariate and multivariate Cox regression analyses.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95 % CI)	P value	Hazard ratio (95 % CI)	P value
Gender	168				
Female	59				
Male	109	1.026 (0.719–1.466)	0.887		
Race	166				
Asian & Black or African American	16				
White	150	0.864 (0.451–1.653)	0.658		
Age	168				
≤60	87				
>60	81	1.365 (0.973–1.915)	0.072	1.305 (0.929–1.834)	0.125
ARPC1B	168				
low	84				
high	84	1.389 (1.113–1.733)	0.004	1.367 (1.094–1.709)	0.006

High expressed ARPC1B group has a worse prognosis.

observed a higher expression of ARPC1B protein in GBM tumor tissues. Immunohistochemistry analysis exhibited that ARPC1B protein expression was higher in GBM compared to normal cortical samples from our hospital. To further investigate the prognostic value of ARPC1B, Cox regression analyses were performed. These analyses confirmed that ARPC1B expression served as an independent prognostic factor for both OS and PFS in GBM patients. These findings suggest that ARPC1B may hold potential as a valuable prognostic biomarker and therapeutic target in the context of GBM.

The association between ARPC1B expression and prognosis has been investigated in many tumors. In oral cell carcinoma, high expression of ARPC1B linked to poor prognosis and an increased risk of lymph node metastasis [13]. Similarly, in prostate cancer, high ARPC1B expression has been associated with poorer OS and PFS [11]. In the present study, although no significant associations were found between high ARPC1B expression and clinical characteristics such as age and sex, the K-M analysis demonstrated that high ARPC1B expression group had shorter OS and PFS. These findings emphasize the potential of ARPC1B as a valuable prognostic biomarker for GBM, capable of providing independent prognostic information regarding patient outcomes in terms of OS and PFS.

ARPC1B is associated with many immune diseases in humans, such as immunodeficiency caused by ARPC1B deficiency, and patients are susceptible to severe infections, inflammation and allergic reactions [15,

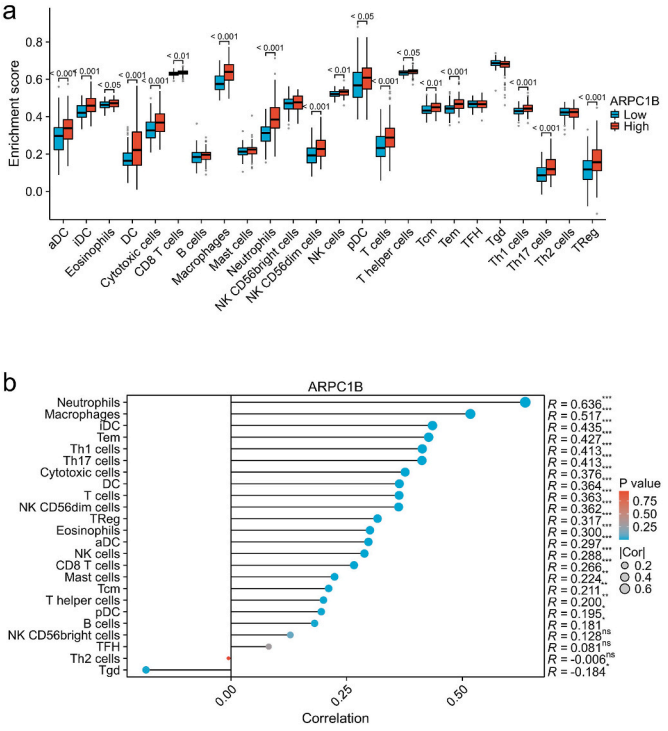

Fig. 5. Correlation between ARPC1B expression and the proportion of TIICs in GBM.
168 GBM patients were equally divided into two groups, (a) The graph illustrates a significant difference in the proportion of various TIICs between the high and low ARPC1B expression groups. (b) The association between ARPC1B expression and TIICs.

Table 3
Multiple immune cells are associated with the survival of GBM patients.

TIICs	HR	95%CI	Z	P
T cell CD8$^+$	13.975	1.955–99.894	2.628	0.009
Neutrophil_	10.479	1.893–58.011	2.691	0.007
Macrophage	280.076	1.054–74423.791	1.978	0.048
Macrophage M1	2468.862	1.100–5543220.315	1.984	0.047
Macrophage M2	108198.198	7.520–1.556751e+09	2.373	0.018
NK cell	129.978	3.755e+51–7.062e+272	2.874	0.04
Mast cell	104.804	4.429–2479.861	2.728	0.004

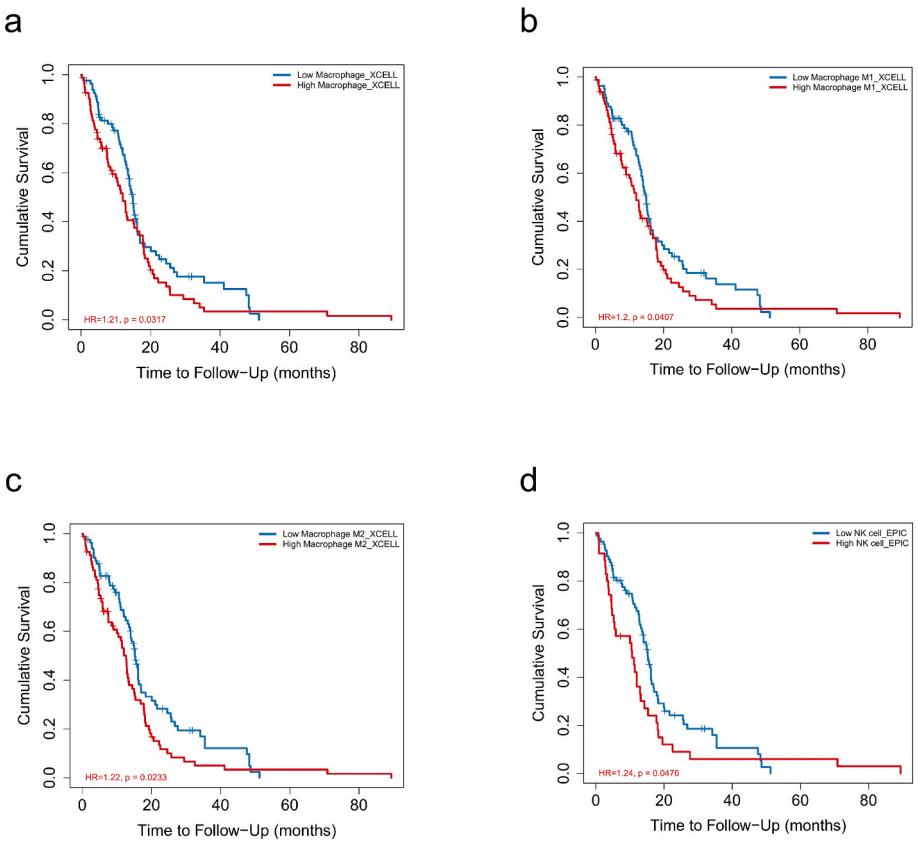

Fig. 6. Association between the proportion of immune cells and the survival of GBM patients.
168 GBM patients were equally divided into two groups, (a–d) A higher proportion of Macrophages (a), M1 Macrophages (b), M2 Macrophages (c), and NK cells (d) were significantly associated with short survival time in GBM patients.

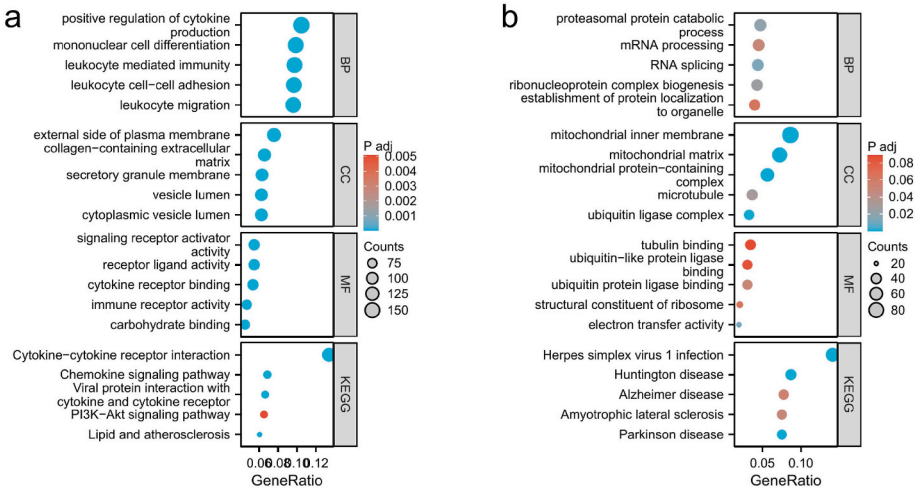

Fig. 7. GO and KEGG enrichment analyses.
GO and KEGG analyses of positively associated genes (a) positively associated genes, (b) negatively associated genes.

16]. Lyra O. Randzavola et al. has found that mutations in the ARPC1B gene can lead to various immune disorders, including immunodeficiency, which is characterized by susceptibility to infections, inflammation, and allergic reactions [17]. It has been reported that Patients with double allele mutations in ARPC1B have been reported to have reduced T-cell lymphocytes and low numbers of naive T cells [17].

The growth and progression of malignant tumors are not solely determined by the intrinsic characteristics of tumor cells but are also influenced by TME [5]. It is a complex ecosystem consisting of diverse cell types, including fibroblasts, blood vessels, and some immune inflammatory cells. Among these, immune cells encompass granulocytes and lymphocytes [18,19].TME plays a crucial role in cancer development. Specifically, the proportion and composition of TIICs have been demonstrated to have prognostic value in various cancers. Sui S et al. have demonstrated that immune cell infiltration accurately predicts the prognosis and chemotherapeutic efficacy of patients with breast cancer [20]. Similarly, the presence of specific immune cell types, such as Tregs and tumor-associated macrophages (TAMs), were significantly

associated with the prognosis of colon cancer and serves as independent prognostic factors [21]. Evaluating the composition and activity of immune cells within the TME can provide valuable insights into the prognosis and potential treatment strategies for cancer patients. Gao Z et al. have demonstrated that endogenous ARPC1B in glioma plays a role in promoting macrophage recruitment to the TME [22], which is consistent with our findings. In our present study, we observed that the high ARPC1B expression group has significantly higher proportions of various immune cells. These findings further support the role of ARPC1B in modulating immune cell infiltration within the TME of GBM.

Using TIMER2 database, we found a significant correlation between the proportion of immune cells in TME and GBM prognosis. Among these immune cell subpopulations, T cell $CD8^+$, neutrophils, macrophage M2, NK cells, and mast cells stood out as particularly noteworthy. Interestingly, higher proportions of these immune cells were associated with increased mortality rates in GBM patients. Additionally, we observed that the high expression group of ARPC1B had significantly higher infiltration proportions of immune cells, including T cell $CD8^+$, neutrophils, macrophage M2, and NK cells. These findings highlight the association between ARPC1B expression, immune cell infiltration, and the prognosis of GBM, suggesting a potential role for ARPC1B in shaping the tumor immune microenvironment and influencing patient outcomes.

Neutrophils can promote tumor growth and metastasis through various mechanisms such as cytokine production, regulation of angiogenesis, and promotion of pro-metastatic niche formation and progression. Neutrophils have been shown to induce S100A4 expression in glioma cells, which further promotes tumor growth, and deficiency of S100A4 can increase the efficacy of anti-VEGFA treatment in mouse models of glioma [23].

The immune-associated cells, including TAMs, in the TME of GBM primarily consist of microglia and macrophages, with macrophages comprising approximately 30 % of the TAM population, Macrophages are commonly classified into two subpopulations: classical M1 and alternative M2 macrophages. In TME, TAMs promote tumor growth, metastasis, and angiogenesis [6]. Furthermore, some immune cells within the TME of GBM have been shown to inhibit tumor growth. For instance, NK cells present in the TME have potent cytotoxic effects on tumor cells [24]. CD8 cytotoxic T lymphocytes (CTLs) are an essential component of tumor-specific adaptive immunity that play a crucial role in attacking and killing tumor cells [25]. The disruption of mast cell mediated STAT3 signaling has been shown to have inhibitory effects on glioma cell proliferation and migration by suppression of stemness characteristics. This disruption leads to the promotion of differentiation in glioma cells by down-regulating glycogen synthase kinase 3 beta (GSK3β) [26]. These immune cells were found to be increased in the TME of GBM, which suggests that the mechanisms of immune cell recruitment into the tumor are complex and require further investigation.

The GO and KEGG analyses showed that the genes positively related to ARPC1B are mainly involved in some immune and inflammatory responses related BPs, such as positive regulation of cytokine production, monocyte differentiation, leukocyte-mediated immunity and leukocyte cell adhesion leukocyte migration etc. The KEGG analyses showed that some immune and inflammatory responses related signaling pathways, such as cytokine-cytokine receptor interaction, chemokine signaling pathway, and viral protein interaction with cytokines and cytokine receptors, are involved in. These findings suggest that ARPC1B and its positively related genes may contribute to poor survival of GBM patients by promoting the aggregation of leukocytes such as macrophages and monocytes in GBM tissues through mechanisms such as immune evasion. Therefore, ARPC1B may affect the prognosis of GBM patients by regulating immune cell infiltration in the TME.

The GO and KEGG analyses also revealed that the genes negatively related to ARPC1B are mainly involved in BPs such as proteasomal proteolytic processes, mRNA processing, RNA splicing, ribonucleoprotein complex biogenesis, and establishment of protein localization to organelles. The KEGG signaling pathways associated with these genes include Herpes simplex virus 1 infection, Huntington's disease, etc., which are associated with many immune diseases. These findings also suggest that ARPC1B may affect immune function through various signal pathways.

This study provides important insights into the potential role of ARPC1B in GBM prognosis and immune infiltration, laying the groundwork for future research in this area. However, it still has some limitations. Firstly, our findings are predominantly based on data from databases such as TCGA, which primarily include patients of Asian or white ethnicity. Therefore, it is important to validate our results using data from patients of diverse races and ethnicities to ensure the generalizability of our findings across different populations. Secondly, the estimation of TIIC rates using TIMER2 might have inherent biases, which should be considered while interpreting the results. Lastly, although our study provides correlative evidence suggesting the involvement of ARPC1B in GBM and its potential mechanisms, further experimental validation is necessary to confirm the functional role of ARPC1B in GBM and elucidate the underlying molecular mechanisms.

CRediT authorship contribution statement

Chuangxin Liao: Conceptualization, Methodology, Writing – review & editing. **Wenli Chen:** Writing – original draft. **Guixin Xu:** Investigation, Visualization. **Jingshan Wang:** Software. **Weijie Dong:** Resources.

Declaration of competing interest

Declarations of interest: none'.

Data availability

Data will be made available on request.

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