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Analysis

Prognostic and immunological role of RHEBL1 in pan-cancer: a target for survival and immunotherapy

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Abstract

RHEBL1 is the Rheb branch of the GTPase proteins that are members of the Ras superfamily. However, it remains unclear how it is relevant to the tumour immune microenvironment. This research evaluates the expression of RHEBL1 employing data from the Cancer Genome Atlas (TCGA) and Genotypic Tissue Expression (GTEx) databases. TCGA cohort was employed to identify the clinical characteristics and prognostic effect of RHEBL1. R Package clusterProfiler was employed to execute Gene Set enrichment analysis (GSEA) on RHEBL1. The association between RHEBL1 and immune cell infiltration (ICI) score was analyzed by employing TCGA samples copied from the public platform and TIMER2 database. Correlation analysis of IC50 values of 192 anti-cancer medicine copied from the Genomics of Drug Sensitivity in Cancer (GDSC) database. In the end, real-time fluorescence quantitative polymerase chain reaction (RT-qPCR) was employed to assessing RHEBL1 expression level in tumours and paracancerous tissues of colon cancer patients. It was found that the overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and progression free interval (PFI) progression of colon adenocarcinoma (COAD) are highly related with high expression of RHEBL1 ($p < 0.05$). In addition, pathways related to immune regulation were closely involved in RHEBL1 expression. Furthermore, the levels of tumour-associated macrophage (TAM) and CD8 + T-cell infiltration were positively correlated with the expression of RHEBL1 in TCGA Pan-cancer samples. Patients with high RHEBL1 expression may be more sensitive to treatment with 5-FU, ABT737, Afuresertib, AGI-5198, AGI-6780, and Alisertib ($p < 0.05$) and could benefit from these chemotherapeutic agents. In vitro experimental results showed that RHEBL1 was significantly increased in COAD ($p < 0.05$). These findings indicate that RHEBL1 is an oncogene for multiple tumours and an important factor affecting tumour prognosis. Pan-cancer samples suggested that high RHEBL1 expression facilitates TAM infiltration and is correlated with tumour immunosuppressive status (TCGA). High expression of RHEBL1 may benefit from the therapy of 5-FU, ABT737, Afuresertib, AGI-5198, AGI-6780, and Alisertib.

Keywords RHEBL1 · Immune cell infiltration · Tumour immune microenvironment · Drug sensitivity in cancer

Yue Chen and Xiao Feng contributed equally to this work and share the first authorship.

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1 Introduction

Cancer has become a significant cause of death and a primary impediment to improving human life expectancy [1]. As the population ages and grows, the incidence of cancer is escalating rapidly [2]. Nowadays, the primary therapies for cancer are surgery, radiotherapy and chemotherapy [3]. Nevertheless, the prognosis for cancer patients tends to remain poor in most cases. Novel therapeutic modalities such as targeted therapies and immunotherapies are expected to be the most important means of attacking cancer, these therapies with molecular precision are revolutionizing traditional treatment concepts, offering new options for cancer patients, and are starting to improve the prognosis for cancer patients [4]. RAS family genes were the first cancer-causing genes discovered [5]. It has been found that the RAS pathway is over-activated in several cancers, with about 30% of cancers having mutations in at least one of the RAS genes [6]. As a member of the Ras family, Rheb is a brain-rich RAS homologue and is part of the small GTPase protein [7]. It mainly regulates the upper reaches of mammalian target of rapamycin complex 1(mTORC1) [8]. In the human system Rheb is separated into Rheb1 and Rheb2, where Rheb2 is also known as RHEBL1 [9]. In tumour tissues, RHEBL1 shows high expression, which contributes to tumour progression [8]. It has been implicated in various cellular processes, including those relevant to cancer progression and immune responses. Studies have shown that RHEBL1 is involved in sphingosylphosphorylcholine-induced events in A549 lung cancer cells via binding to AKT1, leading to activation of it [10]. Additionally, RHEBL1 has been found to be highly expressed in certain breast cancer cells, suggesting a role in epithelial-mesenchymal transition and tumor progression [11]. Given the importance of the mTOR pathway in immune cell differentiation and function, RHEBL1's involvement in this pathway may have implications for cancer immunotherapy [12]. However, direct evidence linking RHEBL1 to cancer immunotherapy is currently limited, and further research is needed to elucidate its potential role in modulating immune responses within the tumor microenvironment (TME). However, studies addressing the TME, drug sensitivity (DS) and biological enrichment of RHEBL1 are not yet outlined.

In the paper, we explored the differential expression of RHEBL1 in 33 tumours, its impact on the TME and tumor prognosis. We underwent DS analysis of RHEBL1 to identify proper compounds to target this gene for tumor treatment. In terms of biological characterization, we conducted Kyoto Encyclopedia of Genes and Genomes (KEGG) and GO enrichment analyses of RHEBL1 to uncover the effects it has on biological functions and pathways. In summary, our Pan-cancer analysis supports that RHEBL1 is a predictive tumor biology marker that holds promise a new target for tumor treatment.

2 Materials and methods

2.1 Data collection and processing

The TCGA, GTEx, and CCLE transcriptome profiling and correlated clinical data were downloaded from UCSC XENA website (https://xenabrowser.net/datapages). The IC50 values of medicine and gene expression profiles in the relevant cell lines were obtained from the GDSC database (https://www.cancerrxgene.org/).

The expression level of RHEBL1 was evaluated by employing downloaded data in tumor samples, normal samples, and multiple tumor cell lines. In addition, due to defects in normal sample data in the TCGA cohort, normal samples data from the GTEx database and TCGA tumor tissue data were integrated to investigate differential expression of 33 types of cancers. We merged all tumor data from the TCGA database and performed a log2 transformation to normalize the data, from which we selected the transcriptome data. Among the transcriptome data, we selected RHEBL1 related data for subsequent analysis. Finally, violin and box plots were used to visualize the expression and paired differential expression of RHEBL1 at different pathological stages.

2.2 Data analysis software

We used the cBioPortal database to analyze the copy number change and alteration forms of RHEBL1 in TCGA pan-cancer samples. TIMER2 (http://timer.cistrome.org/) database was employed to identify the association between level

of ICI and RHEBL1 expression. Moreover, we employed R software packages gridExtra, ggpubr and ggplot2 to plot the expression profile of RHEBL1 (3.6.2). Kaplan Meier survival analysis, and univariate Cox regression analysis was performed using packages survival and survival analysis. GSEA was conducted using the clusterProfiler.

2.3 cBioPortal

cBioPortal was employed to elucidate mutation, copy number variation analysis and gene amplification in COAD (http://www.cbioportal.org/). It provides an overview of the genetic changes in each RHEBL1 and visualizes the full details of the mutation type in each sample.

2.4 TME analysis

Two methods were used to analyze the association between Immune Cell Infiltration (ICI) and RHEBL1: 1) The TIMER2 database was employed to analyze the association between ICI and RHEBL1 expression; 2) Analyze the ICI scores of TCGA pan-cancer samples taken from the ImmuCellAI database (http://bioinfo.life.hust.edu.cn/web/ImmuCellAI/). To compare the levels of ICI, tumor samples were separated into high and low RHEBL1 group according to the median value of RHEBL1 expression in each tumor type.

2.5 Evaluation of immune-related scores across 33 cancer types

We used the ESTIMATE R package to analyze gene expression data and assessed the presence of infiltrating stromal cells and immune cells in pernicious tumor. Three types of scores were generated according to the estimation algorithm analyzed through ssGSEA: (i) StromalScore (SS) is used to identify the level of stroma in tumor tissue, (ii) ImmuneScore (IS) to reflect the infiltration of immune cells in tumor tissue. (iii) ESTIMATEScore (ES) to calculate the sum of SS and IS. The higher score indicated the larger ratio of the corresponding component in tumor microenvironment (TME).

2.6 Prediction of chemotherapeutic results

We used R package pRRophetic to assess the IC50 of COAD samples in multiple ICI score groups. The expression profiles of GDSC (www.cancerxgene.org/) cell lines and TCGA gene expression profiles were used to construct regression models [13].

2.7 The identification of immunotherapeutic effect

Due to the lack of immunotherapy information in the TCGA-COAD cohort, IMvigor210 (metastatic urothelial cancer) cohorts, NCT02684006 (KIRC), and the GSE135222 (NSCLC) were employed to estimate the predictive power of the risk scoring formula.

2.8 Source of organization

Tumors and paracancerous tissues were obtained from patients hospitalised in Jiangsu Provincial Hospital of Chinese Medicine and preserved at − 80 ℃. The protocol was approved by the Ethics Committee of Jiangsu Province Hospital of Chinese Medicine (approval number: 2021 NL-CAMT-010). Informed Consent was obtained from all the participants involved in the study.

2.9 Real-time quantitative PCR

Total RNA was collected with EASYspin Plus (PRN2802, proteinbio) according to protocol. Complementary DNA was reversed employing the HiScript II 1 st Strand cDNA Synthesis Kit (R323-01, Vazyme). Real-time PCR was employed using 10ul SYBR Premix Ex Taq (Q712-02, Vazyme) system with a 7500 Fast Real-time quantitative polymerase chain reaction. The messenger RNA (mRNA) levels of specific genes were normalized against GAPDH using the comparative Ct method (-ΔΔ2 Ct). Primer sequence: GAPDH: F: TGACTTCAACAGCGACACCCA; R: CACCCTGTTGCTGTAGCCAAA. RHEBL1: F: TGGGGAACAAGGCAGATCTCTCT; R: CATAAATGTCGCACCCCAGGACT.

2.10 Statistical analysis

Statistical analysis of the data was analyzed employing SPSS 25.0 software. T-tests were used to compare the differences between two groups. Spearman test was used for correlation analysis ($p < 0.05$).

3 Results

3.1 Expression of RHEBL1 in pan-cancer and normal tissues

As shown in Fig. 1B, we downloaded each tumor cell line from CCLE and analyzed the RHEBL1 expression levels in 30 tissues based on their tissue sources. Subsequently, RNA seq data from TCGA and GTEx databases were employed to explore the expression of RHEBL1 in pan-cancer cells. Except for cancers without normal tissue data, we found significant differences in RHEBL1 expression among 33 types of cancers. As shown in Fig. 1A, RHEBL1 is highly expressed in 18 types

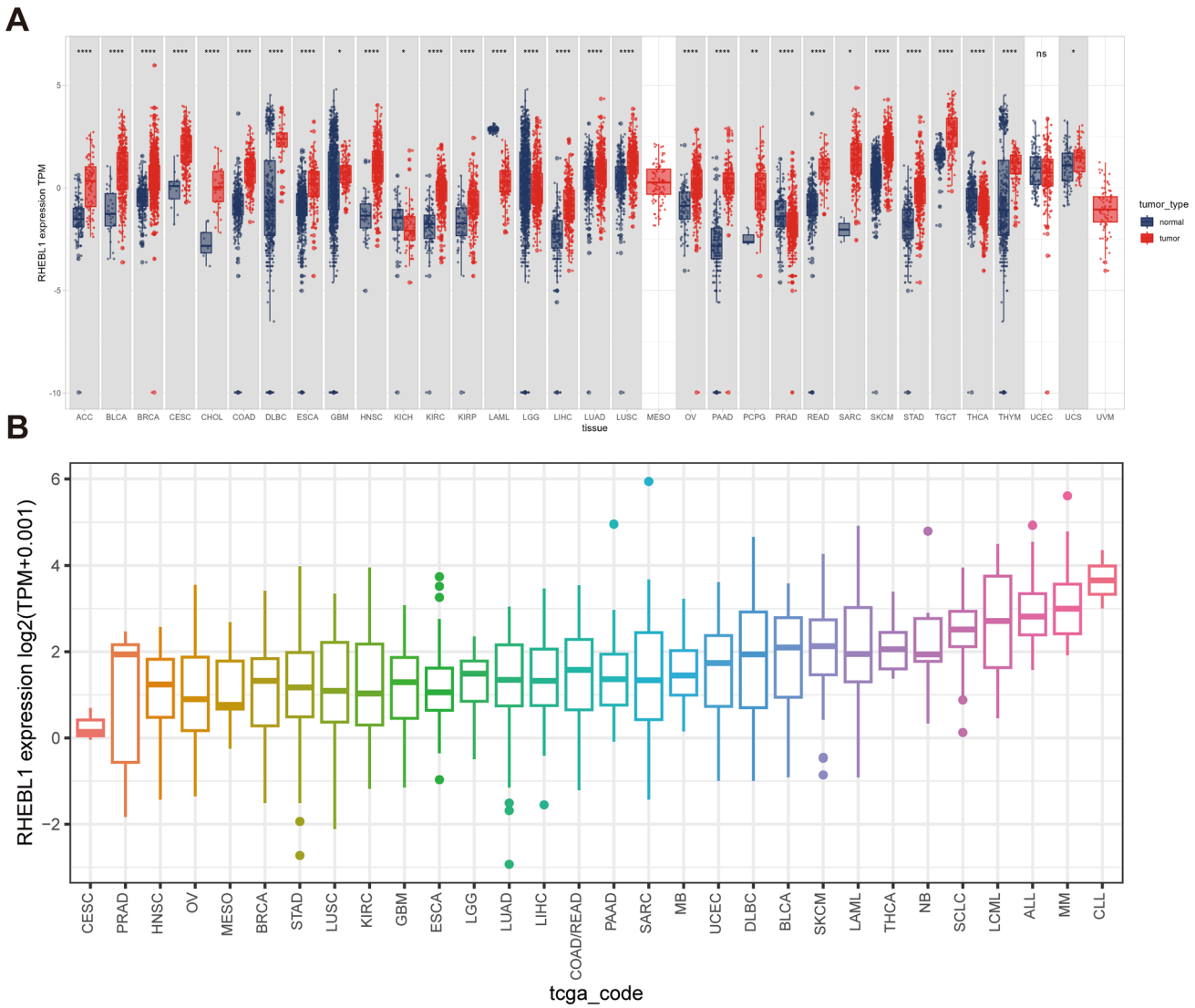

Fig. 1 Differential expression of RHEBL1. **A** Compare the differences in RHEBL1 mRNA expression between TCGA cancer and GTEX normal samples. Cancer samples are represented in red, normal samples are represented in blue. **B** Compare the expression degree of RHEBL1 gene in 30 tissues. Expressions gradually increase from left to right. (ns $p > 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)

of tumors compared to the control tissues. However, RHEBL1 was significantly reduced in THCA (thyroid cancer), LGG (low-grade glioblastoma), LAML (acute myeloid leukemia) and KICH (renal chromophobe cells).

3.2 Assessment of prognostic value of RHEBL1 in pan-cancer

The relationship between gene expression and prognosis in 33 tumors was analyzed using gene expression data. We investigated the association of RHEBL1 with overall patient survival using univariate analysis in 33 cancers (Fig. 2A). The prognostic K-M curve outcomes is displayed in Supplementary Figure S1.

Gene expression data was employed to identify the differences between expression and prognosis in 33 TCGA cancers. As shown in Fig. 2A, we used univariate survival analysis to study the forest plot of RHEBL1 gene in 33 cancers. We chose the best cut-off value, which could further classify the expression of RHEBL1 into high and low expression groups, so that the effect of RHEBL1 on cancer healing could be visually determined. The cut-off value with the smallest p-value was selected to be divided into the two groups using the survival R package. Possible non-tumor causes of death were considered during patient follow-up and differences between gene expression values and prognosis were elucidated for 33 TCGA cancers, and all of which are displayed in Fig. 2B. The differences between the genetic value and prognosis of 33 TCGA cancers were identified, as shown in Fig. 2C. Subsequently, as shown in Fig. 2D, the distinction between gene expression value and the prognosis-free interval of 33 TCGA cancers was also calculated.

3.3 Correlation between RHEBL1 expression and clinicopathological stage in pan-cancer

The relationship between RHEBL1 mRNA expression levels and clinicopathological staging in cancer patients has been extensively analyzed. The results demonstrate that RHEBL1 expression is significantly associated with the staging of 10 specific tumor types ($p < 0.05$) (Figs. 3A–J).

3.4 Genetic mutation demonstration of RHEBL1 in pan-cancer

Using the cBioPortal database, we found that RHEBL1 had the highest mutation frequency in patients with diffuse large B-cell lymphoma, followed by Adrenocortical carcinoma (Fig. 4A). In addition, the mutation of RHEBL1 expression in COAD was further analyzed and summarized in Figure S2. Finally, the relevance between RHEBL1 expression and copy number was revealed in 33 tumors, as shown in Fig. 4B. We found the expression of RHEBL1 in UCS, ESCA, SKCM, LUSC, HNSC, OV, CESC, LIHC, LIRP, LUAD and BRCA were positively correlated. In contrast, RHEBL1 expression was found to be negatively correlated in THCA.

Subsequently, a correlation analysis was conducted to investigate the relationship between the expression of the gene and its methylation status. The expression of RHEBL1 was negatively correlated with LGG, BLAC, KIRC, SKCM, UCS, MESO, CHOL, PRAD, and TGCT, which was shown in Fig. 4C.

3.5 Correlation between RHEBL1 expression and TME

The relationship between RHEBL1 expression and TME in TCGA tumors was demonstrated. In most of the tumors, RHEBL1 expression was found to have a positive correlation with several factors of the Tumor Microenvironment like DNA damage repair, immune checkpoint, antigen processing machinery, effector T cells, and EMT (Fig. 5A). Subsequently, we employed the ESTIMATE algorithm to reveal the association between RHEBL1 expression and the TME score. ISs, ES, SS and TumorPurity (TP) was evaluated separately (Fig. 5B). The correlation results were summarized using heat maps (Fig. 5C). According to SS, the expression of RHEBL1 is positively correlated with immune infiltration in 13 types of tumors. IS has demonstrated that the expression of RHEBL1 is positively associated with immune infiltration in 22 types of tumors. TP showed a negative relevance between the expression of RHEBL1 and immune infiltration in 21 types of tumors. The analysis revealed a positive correlation between RHEBL1 expression and immune infiltration levels in 20 distinct tumor types, with reduced RHEBL1 expression corresponding to decreased immune infiltration. Although there are numerical differences in these scores, overall, in most tumors, RHEBL1 is able to modulate the tumor immune microenvironment and thus alter tumor growth.

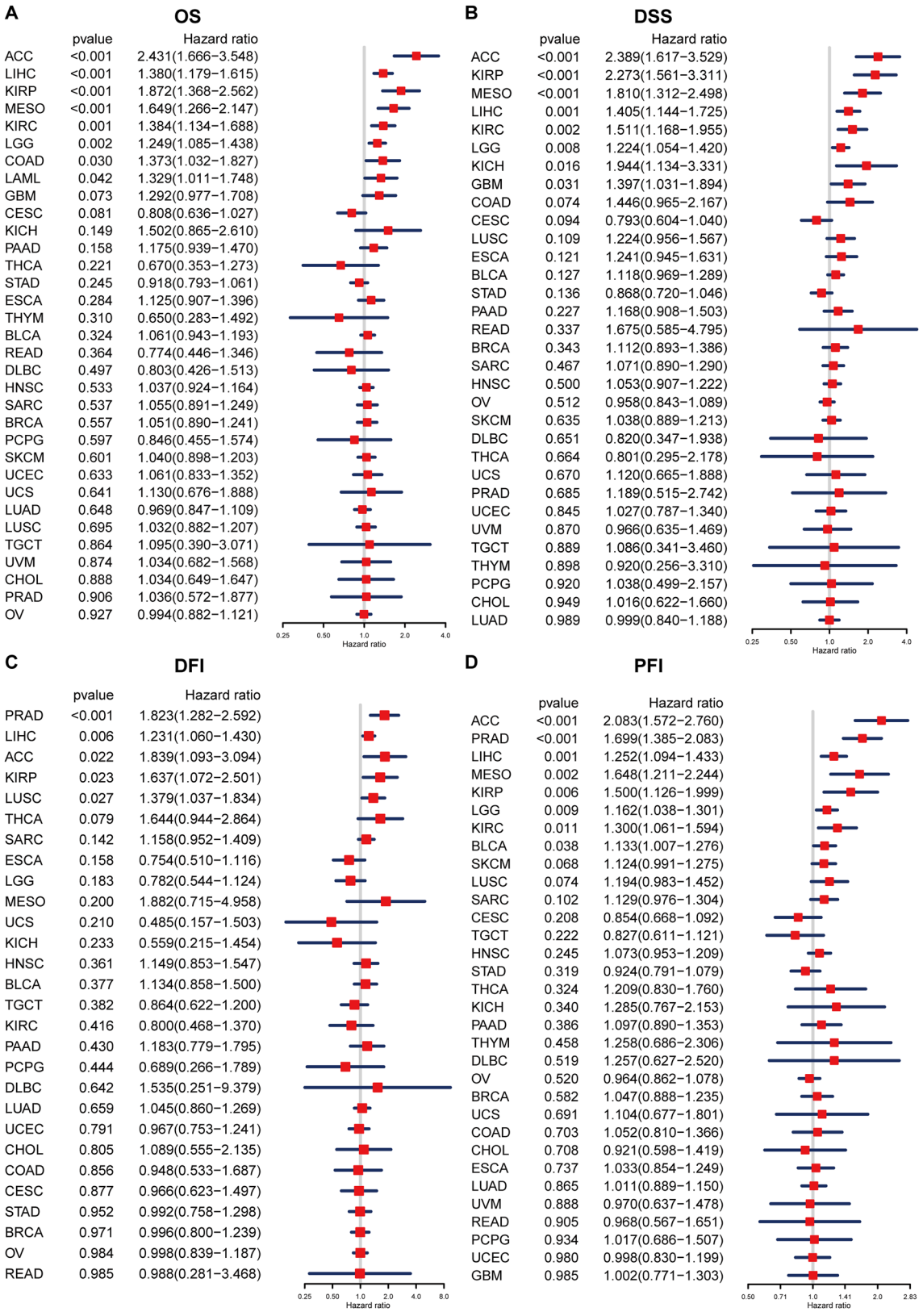

Fig. 2 Prognostic Assessment Value of RHEBL1 in TCGA PC. **A** The correlation between RHEBL1 gene overall survival time of tumor and non-tumor patients. **B** The correlation between RHEBL1 gene and tumor and non-tumor disease-specific survival rates. **C** The association between RHEBL1 gene and disease-free interval tumor and non-tumor. **D** The association between RHEBL1 gene and prognosis-free interval tumor and non-tumor

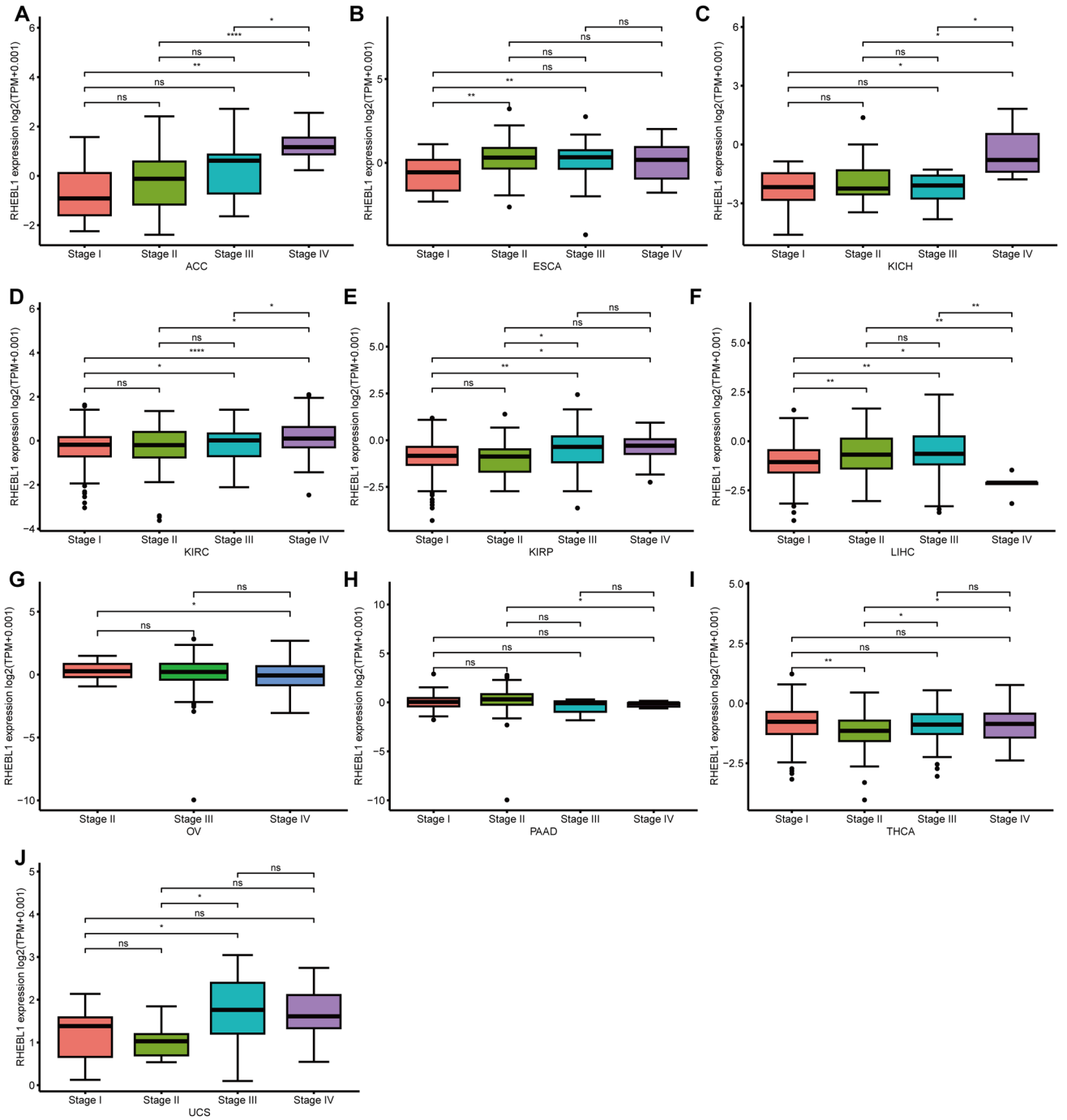

Fig. 3 Association Analysis Between the Expression of RHEBL1 in Pan-Cancer Tissues and Clinical pathological Staging. **A** ACC. **B** ESCA. **C** KICH. **D** KIRC. **E** KIRP. **F** LIHC. **G** OV. **H** PAAD. **I** THCA. **J** UCS

3.6 Analysis of immune cell infiltration

We employed TIMER2 to assess the relevance between RHEBL1 expression and ICI. Our data has shown that in some types cancers, the degree of tumor associated macrophages (TAMs) (BLCA, COAD, ESCA, HNSC, KIRC, LGG, LUAD, LUSC, PAAD, PRAD, ERAD, SARC, SKCM, STAD, THCA, THYM), Th1 cells (BLCA, BRAC, COAD, DLBC, ESCA, HNSC, KICH, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, MESO, OV, PAAD, PCPG, PRAD, READ, SARC, SKCM, STAD, TGCT, THCA, UVM), and CD8 + T (BLCA, BRCA, CESC, DLBC, KIRC, LGG, LUSC, TGCT,THCA, THYM) cell infiltration is clearly positively associated

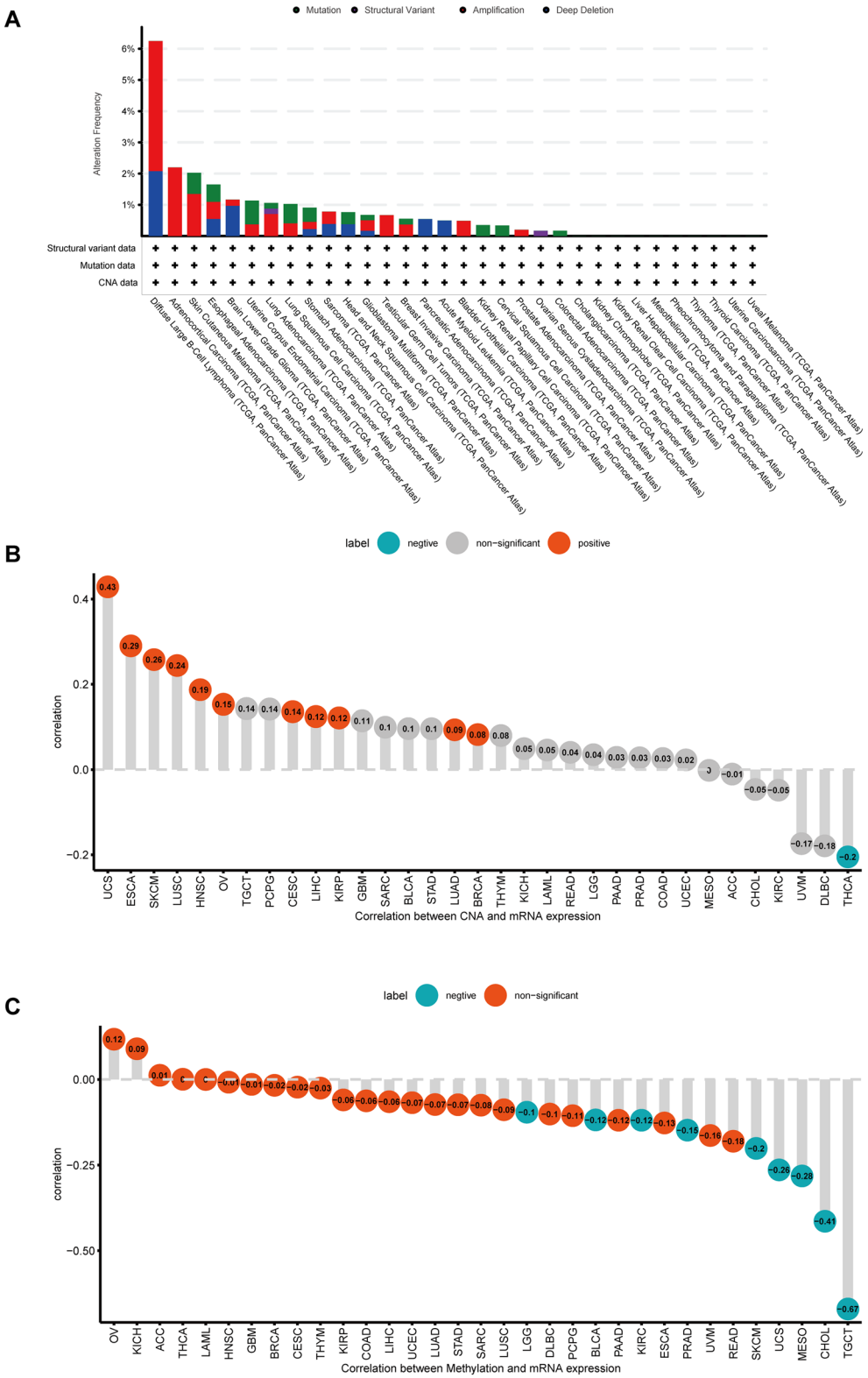

Fig. 4 The genetic mutation of RHEBL1 in TCGA PC datasets. **A** Alterations summary of RHEBL1. **B** Association between expression degrees of RHEBL1 mRNA and DNA copy number. Prominent outcomes are represented in red. **C** Association between mRNA levels of RHEBL1 and DNA methylation. Prominent outcomes are represented in blue

with the expression of RHEBL1 ($p < 0.05$) (Fig. 6A). Subsequently, we used the ImmuCellAI database to evaluate the association between ICI level and RHEBL1 expression in 33 types of cancer. Consistent with the TIMER2 outcomes, the clustering heatmap indicates there is a positive association between RHEBL1 expression and infiltration of TAMs and CD8 + T cells, which was shown in Fig. 6B ($p < 0.05$).

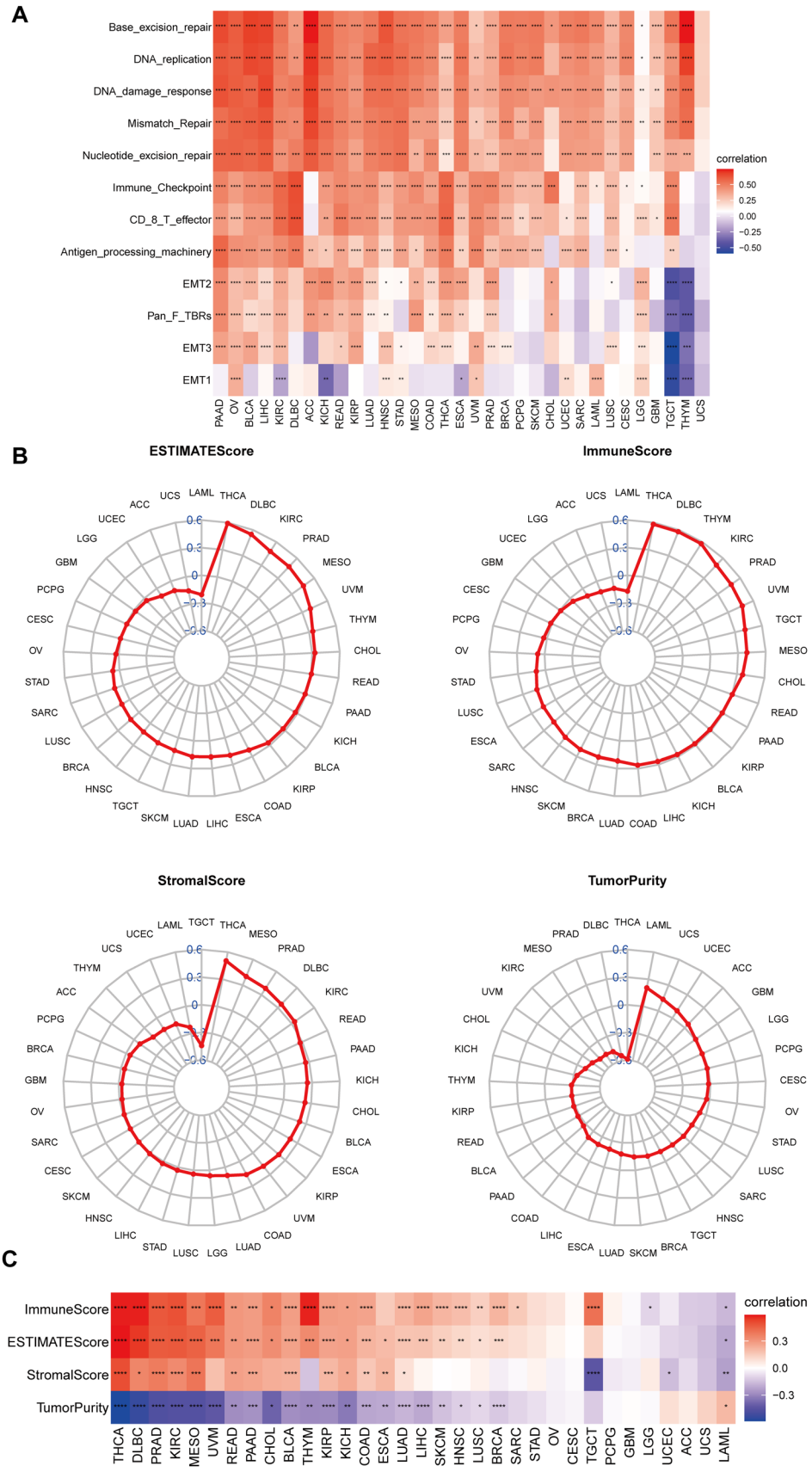

Fig. 5 Research on the association between RHEBL1 expression and TIM. **A** Relevance of RHEBL1 expression with tumor microenvironment; **B** Relevance of RHEBL1 expression with SS, IS, TP and ES; **C** The relevance between RHEBL1 expression and four kinds of scores. Red indicates positive relevance and blue indicates negative relationship

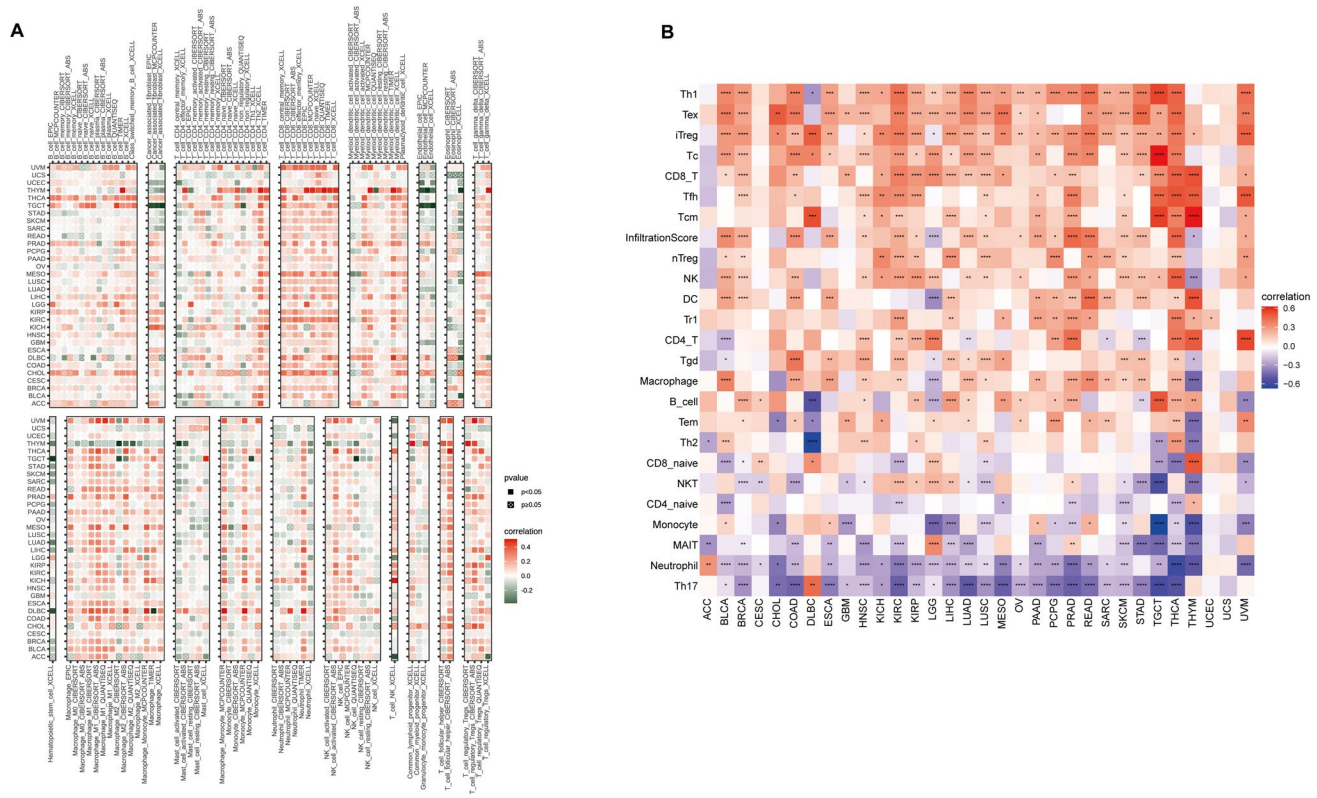

Fig. 6 Analysis of Immune Cell Infiltration. **A** Assessed the correlation between RHEBL1 expression and immune cells infiltration using TIMER2. **B** Assessed the correlations between immune cell infiltration and RHEBL1 expression in 33 cancers using the ImmuCellAI database

3.7 Drug resistance analysis

We predicted the IC50 values of each sample for multiple anti-cancer drugs and compared the differentiate in the values of the two groups of genes. A higher IC50 indicates less treatment sensitivity. As shown in Fig. 7A, B, drug sensitivity assessment demonstrates that high expression group of this gene were susceptible to six drugs, while the low expression group was only susceptible to one drug.

3.8 Analysis of anti-cancer treatment sensitivity

The public datasets GSE135222, NCT02684006 and IMvigor210 were employed to calculate the effect of immunotherapy. The results showed that high RHEBL1 expression had higher treatment responsiveness compared to the low expression group (Fig. 8A, C, E). Moreover, the ratio of immune weights was also significantly higher in the high-expression RHEBL1 group than in the low-expression group (Fig. 8B, D, F).

3.9 Functional enrichment assay of RHEBL1 in COAD

We performed a correlation analysis of RHEBL1 with all genes and used heatmaps to show the expression of the top 50 genes with positive (Figure S3 A) and negative (Figure S3 B) correlations. GSEA and KEGG were conducted on COAD. Tumor-associated signaling pathways activating RHEBL1 were performed and visualized by GSEA analysis. The GSEA outcomes showed GO affected by RHEBL1, including mitotic nuclear division, the regulation of cell cycle and chromatin remodeling (Fig. 9A).

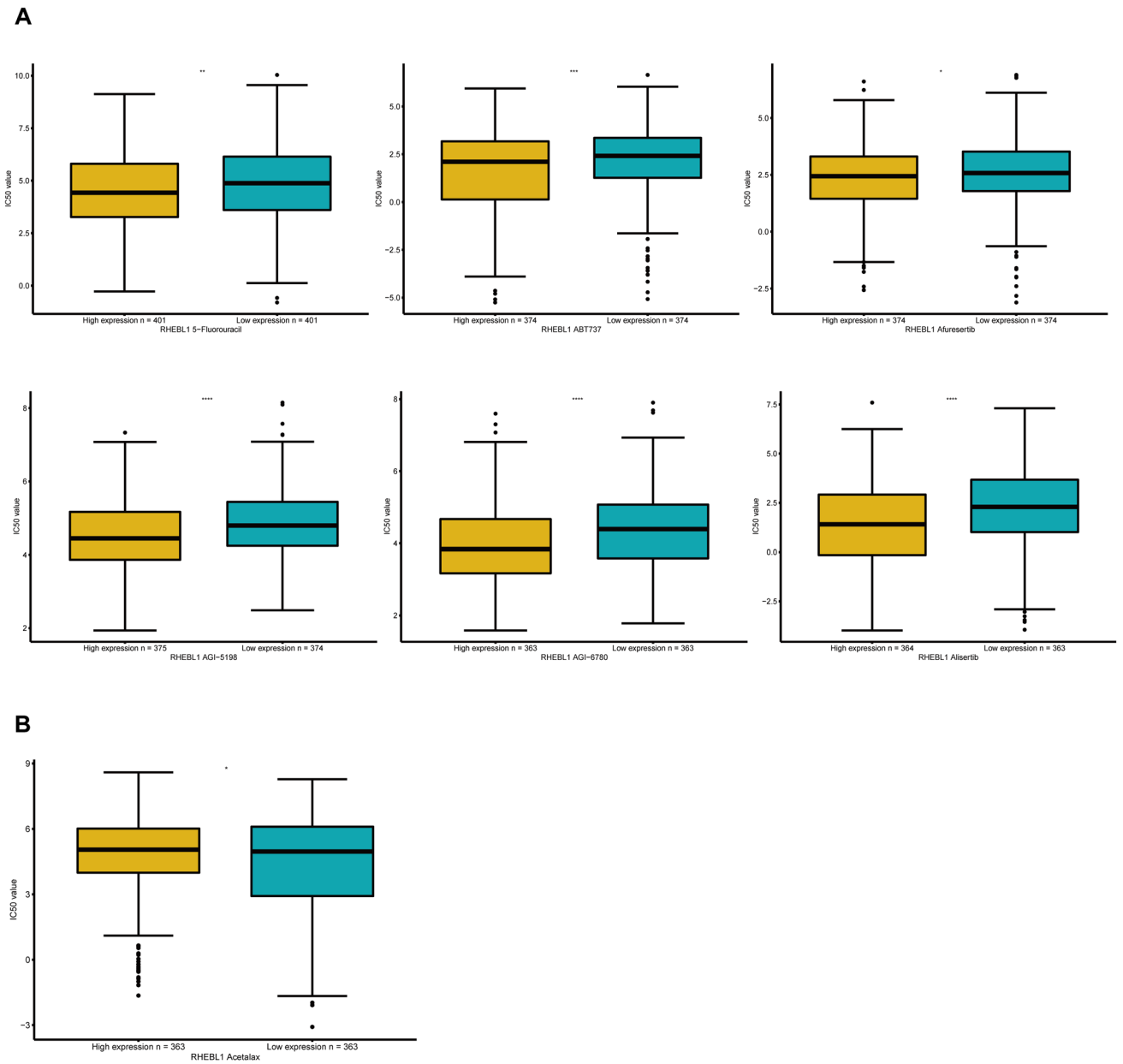

Fig. 7 Drug-fast assay. **A**, **B** Sensitivity of two groups to treatment

The GSEA results indicated that RHEBL1 is involved in multiple pathways, including the PD-1 checkpoint pathway and PD-L1 expression, the proteasome, the spliceosome, Epstein-Barr virus infection, DNA replication, ribosome biogenesis, Cell cycle and Viral carcinogenesis (Fig. 9B).

GSEA outcomes indicated that Dectin-1 mediated noncanonical NF-kB signaling, Control of Apoptosis and Regulation of mitotic cell cycle, Ubiquitin-dependent degradation of Cyclin D were concentrated in COAD (Fig. 9C). These outcomes supported that RHEBL1 is involved in the inflammatory response and plays an important role in TME. Finally, vitro experiments by qPCR confirmed that RHEBL1 mRNA was remarkable upregulated in colon cancer tissues, which is unanimous with our bioinformatics findings (Fig. 9D).

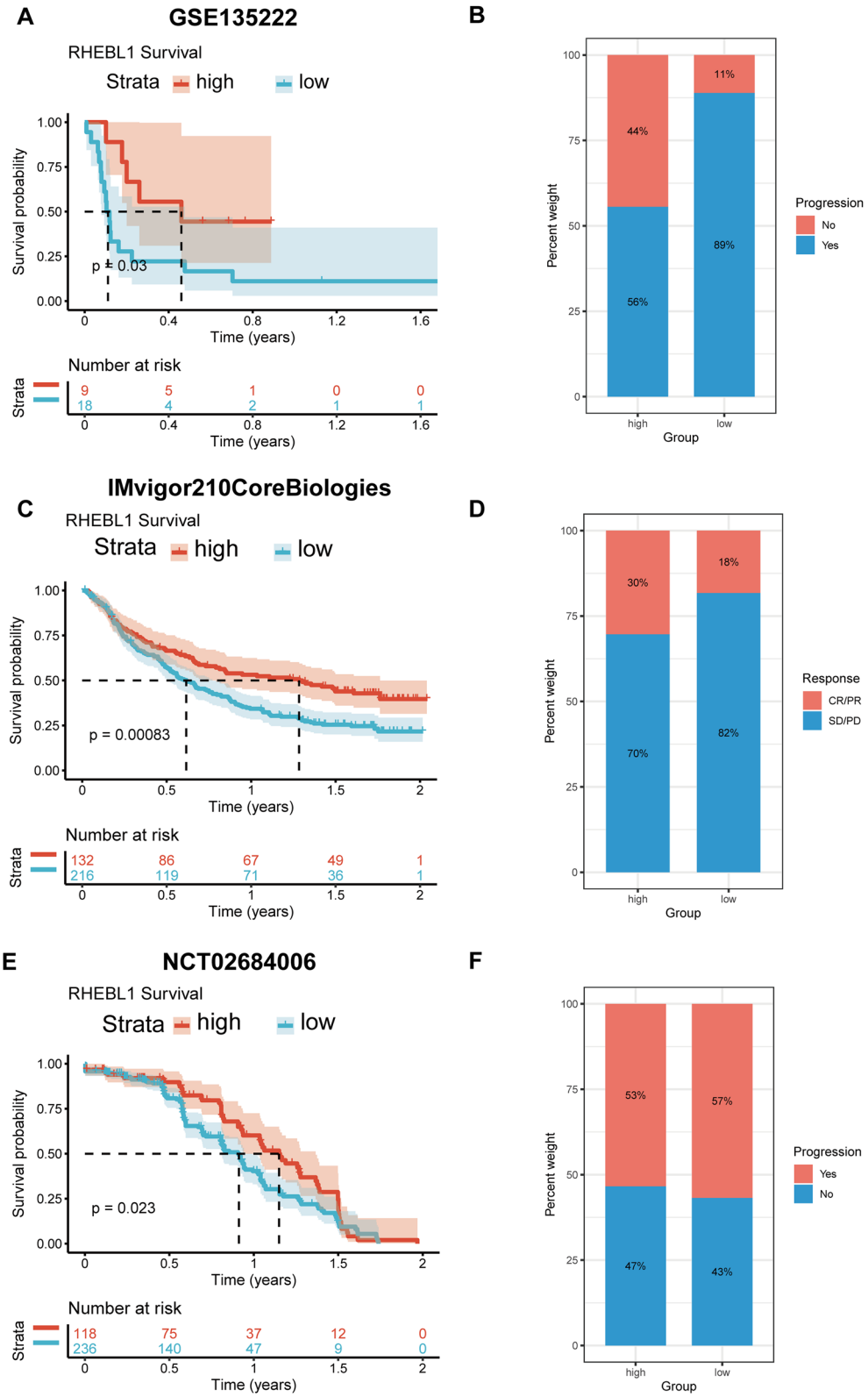

Fig. 8 The mRNA expression of immune checkpoint genes and immunotherapeutic advantage. **A**, **B** Different immunotherapy responses between the RHEBL1 mRNA expression of two groups in GSE135222. **C**, **D** Different immunotherapy responses between the RHEBL1 mRNA expression of two groups in IMvigor210 datasets. **E**, **F** Different immunotherapy responses between the RHEBL1 mRNA expression of two groups in NCT02684006

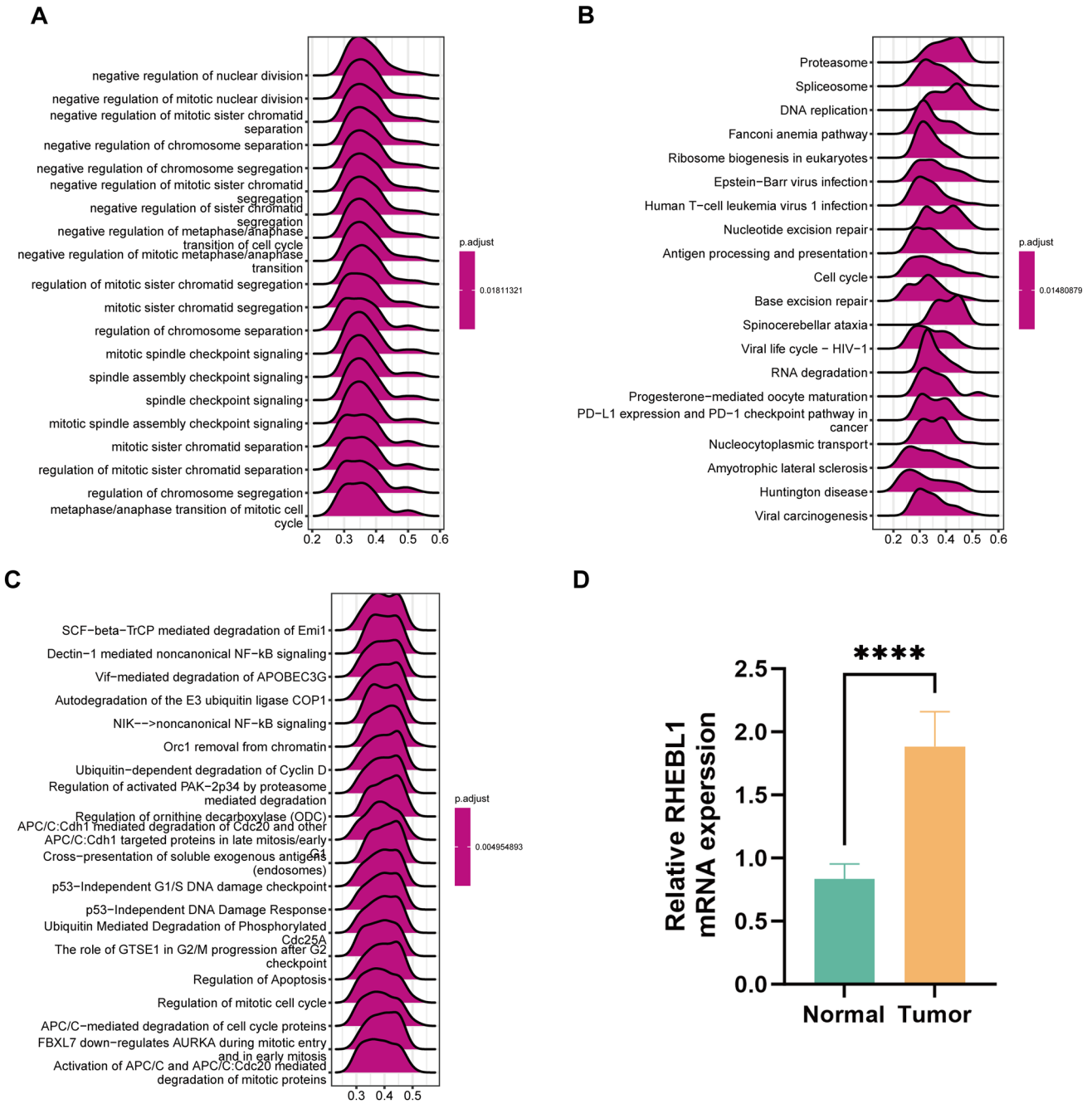

Fig. 9 The conflated enrichment map of HSF1 was acquired from GSEA, and the RHEBL1 mRNA expression in COAD. **A**–**C** In COAD, the merged graph of GSEA demonstrated signaling pathways correlated with RHEBL1 expression. **D** The RHEBL1 mRNA expression in colon cancer tissues

4 Discussion

Research has shown that RHEBL1 is highly expressed in the human heart, spleen, bladder and uterus [14]. It has been reported that RHEBL1 promotes keratin phosphorylation and recombination induced by sphingosine phosphatidylcholine by binding to activated AKT1, which enhances the viscosity of some metastatic cancer cells [14]. Wang et al. showed that saponins and polyphenols VI can upgrade the prognosis of lung cancer patients by reducing the expression of RHEBL1 [15]. Several reports have indicated that RHEB-mTORC1 signaling may be involved in tumor formation and high expression of RHEBL1 increases the proliferation of malignant mesothelioma cells [16]. However,

research on RHEBL1 in other cancers is still limited. In this study the expression of RHEBL1 in human Pan-cancer tissue was performed to explore its effect in clinical, prognostic, and therapeutic aspects of different cancers. We integrated gene expression data of 33 tumors from several public databases.

Our research demonstrated that RHEBL1 is highly expressed in tumor tissues, including ACC, BLCA, ARCA, CESC, CHOL. RHEBL1 was found to show low expression in KICH, LAML, LGG, THCA. Survival analysis was employed to assess whether the expression of RHEBL1 is correlated with the prognosis of 33 tumors, and we found a correlation between RHEBL1 expression and the prognosis of 17 tumors. We found that high expressed RHEBL1 exhibited a correlation with poor prognosis in all 16 tumors other than CESC. The box plot identified that the gene expression of RHEBL1 was associated with the clinical staging of 10 tumors, such as ACC and ESCA. Genetic mutations are significant factors in tumour development [17]. Using the CbioPortal database, we comprehensively analyzed the types of RHEBL1 mutations in various cancers. The outcomes showed that amplification is the most common form of mutation, and this is particularly evident in diffuse large B-cell lymphoma as well as adrenocortical carcinoma. In addition, by analyzing the expression level of RHEBL1 in relation to copy number and methylation, we found that genetic variation and methylation may be one of the reasons for the aberrant expression of RHEBL1 in tumor cells. TME is the growth environment of tumors, which have an important impact in the process of tumor development [18–21]. Increasing number of reports point to ICI as a critical reason in tumor march and immunotherapy response [22, 23]. In this research, a forward association between RHEBL1 and immune scores of 22 types of tumors was identified, including THCA, PRAD, UVM, THYM and DLBC, with stromal scores in 13 tumors, and with composite scores in 21 tumors. These outcomes indicated that RHEBL1 is correlated with immune infiltration within TME. Moreover, in most tumors, the positive associated between immune RHEBL1 and the abundance of infiltrated immune cells has been identified, which provides a brand-new direction for immunotherapy. Results from analyses in the public datasets GSE135222, IMvigor210 and NCT02684006 demonstrate that patients with high RHEBL1 expression have a more positive response to immunotherapy. In terms of chemotherapy, we analyzed the sensitivity between RHEBL1 expression and some anticancer drugs. Research identified that Acetalax was more exquisited to patients with low RHEBL1 expression, while 5-fluorouracil, ABT737, Afuresertib, AGI-5198, AGI-6780, and Alisertib showed better sensitivity to patients with high RHEBL1 expression. These data may help with the selection of clinical therapeutic options, however further experimental validation is still needed to test whether RHEBL1 can be an immunotherapeutic target for tumors. In an effort to explore the mechanism of RHEBL1 action in tumors in more depth, we characterized the biology of RHEBL1 in colon cancer. The analysis demonstrated that RHEBL1 has an effect on the regulation of cell cycle, mitotic nuclear division, and is involved in PD-L1 expression and PD-1 checkpoint in tumor, the proteasome, DNA replication, the spliceosome, ribosome, biogenesis, among other pathways.

In conclusion, we found that RHEBL1 may be a potential biomarker for a multiple of tumours and is highly correlated with tumour prognosis, mutation and immunity. RHEBL1 is supposed to be a new biomarker for various cancers.

5 Conclusion

In this research, RHEBL1 was thoroughly identified and demonstrated its pro-cancer affect and potential role as a prognostic factor for patients. Critically, high expression of RHEBL1 suggests tumor immune suppression, which may suggest that immune checkpoint paralyst are not appropriate for therapy. In addition, the high expression of RHEBL1 indicated that patients have higher sensitive to 5-FU, ABT737, Afuresertib, AGI-5198, AGI-6780, and Alisertib. In summary, the impact of RHEBL1 on multiple cancers needs to be further elucidated based on its broad impact on the efficacy of anti-cancer medicine, in order to thoroughly acquire its role as a prognostic biomarker for patients.

5.1 Limitations

Our study only comprehensively analyzed RHEBL1 in a database and did not have comprehensive experiments to corroborate the role of RHEBL1 in all cancers. We hope that this study will provide new ideas and a bioinformatics basis for follow-up studies.

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Author contributions Yue Chen: Writing-review and editing, Resources, Investigation, Formal analysis, Data curation, Conceptualization, Data analysis. Xiao Feng: Writing original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Performed material preparation and data analysis. Xindong Yin: Writing-review and editing, Investigation, Formal analysis,

Data curation. Nan Yi: Writing-review and editing, Methodology, Investigation. Ya Zhao: Writing-review and editing, Software, Investigation. Qian Wang: Writing-review and editing, Software. Wenya Xing: Writing-review and editing, Methodology. Chaoqun Ma: Funding acquisition, Supervision, Project administration. Dexuan Chen: Writing-review and editing, Supervision, Project administration.

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Data availability The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Jiangsu Province Hospital of Chinese Medicine (protocol code 2021 NL-CAMT-010). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Competing interests The authors declare no competing interests.

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