Original Article

ITGAM sustains MAPK signaling and serves as an adverse prognostic factor and therapeutic target in acute myeloid leukemia

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Background: Acute myeloid leukemia (AML) is the second most frequently occurring type of leukemia in adults. Despite breakthroughs in genetics, the prognosis of AML patients remains dismal. The aim of this study is to find new therapeutic targets and diagnostic markers for AML and to explore their mechanisms of action.

Methods: The expression patterns of integrin subunit alpha M (ITGAM) were investigated across different cell types using the Human Protein Atlas (HPA) database. The ITGAM levels across cancer types were analyzed using the Gene Expression Profiling Interactive Analysis (GEPIA) database. Prognostic correlations in AML individuals were evaluated using The Cancer Genome Atlas (TGCA) database. ITGAM-associated functions were evaluated by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. The AML cells were transfected with short-hairpin RNA targeting ITGAM or a control, and subsequently subjected to analysis in order to ascertain the impact of ITGAM on proliferation and apoptosis.

Results: The expression of ITGAM was significantly higher in the AML patient samples compared to the control samples. High ITGAM expression was significantly associated with poor overall survival (OS). The knockdown of ITGAM in the AML cells resulted in a decrease in proliferation and an increase in apoptosis. This was accompanied by cell cycle arrest at the G1 phase and a downregulation of protein production for cyclin D1, cyclin E1, cyclin-dependent kinase 2 (CDK2), and cyclin-dependent kinase 4 (CDK4). A pathway analysis and a western blot analysis revealed that ITGAM positively regulated mitogen-activated protein kinase (MAPK) signaling by silencing attenuated p38 MAPK (P38), c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) phosphorylation, while the total protein levels remained unchanged.

Conclusions: ITGAM can serve as a potential prognostic biomarker and therapeutic target for AML. ITGAM production was elevated in AML and indicated poor survival. Silencing ITGAM suppressed AML cell viability and induced apoptosis by blocking cell cycle progression, likely by impeding the activation of the MAPK pathway. Further investigations that directly target the ITGAM-MAPK axis may offer novel strategies for mitigating AML pathogenesis and overcoming chemotherapy resistance.

Keywords: Acute myeloid leukemia (AML); integrin subunit alpha M (ITGAM); prognosis; proliferation; mitogen-activated protein kinase (MAPK)

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Introduction

Acute myeloid leukemia (AML) is a genetically heterogeneous hematologic malignancy that frequently occurs in adults, and comprises approximately 80% of acute leukemia cases in this patient population (1). The hallmark of AML is the uncontrolled proliferation and accumulation of myeloid progenitor cells in the bone marrow and peripheral blood, resulting in hematopoietic insufficiency (2). Advances in risk stratification, concurrent chemotherapy, innovative therapeutics, and hematopoietic stem cell transplantation have significantly improved patient outcomes; nevertheless, the overall prognosis of individuals with AML remains unfavorable (3). Research has shown that approximately 75% of AML patients relapse after an initial treatment response (4). Thus, there is a pressing need to discover innovative prognostic, diagnostic, and therapeutic targets for AML.

The mitogen-activated protein kinase (MAPK) pathway directs the reactions of cells to external stimuli and controls important functions, such as proliferation, differentiation, cell cycle progression, and apoptosis (5). The major MAPK branches comprise extracellular signal-regulated kinase (ERK), p38 MAPK (P38), and c-Jun N-terminal kinase (JNK) (6). Aberrant MAPK pathway activation has been implicated in the pathogenesis of AML. The genetic suppression of protein phosphatase Mg^{2+}/Mn^{2+} dependent 1D, a regulatory protein in the MAPK pathway, was discovered to inhibit AML cell viability and induce apoptosis by activating the P38/tumor suppressor protein (P53) system (7). The Fms-like tyrosine kinase-3 (FLT3) is an upregulated tyrosine kinase in AML cells, and its downregulated expression inhibits the ERK-MAPK pathway, thereby inducing apoptosis in AML cells (8). Curcumin causes apoptosis in THP1 cells by triggering the JNK/ERK/activator protein-1 (AP1) system (9). These findings suggest that differences in gene expression or drugs could influence AML cell progression by modulating the MAPK signaling pathway.

Integrin subunit alpha M (ITGAM), also known as complement component 3 receptor alpha chain (CD11b), or macrophage receptor 1 alpha subunit (Mac-1), is a cell-surface receptor that preferentially exists in myeloid leukemia cells (10). This protein not only mediates activation and effector responses, but also regulates leukemia cell-microenvironment interactions through ligand binding (11,12). Given these functions, it appears that ITGAM may be involved in the pathogenesis of AML. The present study aimed to analyze the expression patterns of ITGAM and its prognostic correlations in individuals with AML. Furthermore, the impact of suppressing ITGAM on AML cell growth, apoptosis, and MAPK signaling was also investigated. We present this article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-810/rc).

Highlight box

Key findings

- Integrin subunit alpha M (ITGAM), as a significantly overexpressed gene in acute myeloid leukemia (AML), is closely associated with poor prognosis in AML patients. Inhibiting the expression of ITGAM can inhibit the progression of AML cell cycle, leading to decreased cell proliferation and increased apoptosis. Inhibiting the expression of ITGAM can reduce the phosphorylation level of mitogen-activated protein kinase (MAPK) pathway-related proteins, thereby inhibiting the progression of AML.

What is known and what is new?

- The MAPK pathway plays a certain role in AML, regulating signal transduction and participating in processes such as cell proliferation, differentiation, cell cycle arrest, and apoptosis.
- ITGAM is a significantly overexpressed gene in AML. Its high expression is closely related to poor prognosis in AML patients. The regulatory effect of ITGAM on AML progression is closely related to the phosphorylation level of MAPK pathway-related proteins.

What is the implication, and what should change now?

- ITGAM, as an independent prognostic marker for AML, may serve as a new target for the diagnosis and treatment of AML patients. The effect of ITGAM on AML needs further validation, and the detailed mechanism of action needs more in-depth studies.

Methods

HPA analysis

The Human Protein Atlas (HPA) (https://www.proteinatlas.org) database was used to analyze ITGAM expression across human cell types. ITGAM gene name queries in the HPA "Cell Types Category (RNA)" module were used to generate composite rankings of transcript abundance, which were reported as normalized transcripts per million (nTPM), for each profiled single-cell population. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Gene Expression Profiling Interactive Analysis (GEPIA)

The GEPIA database (https://www.gepia.cancer-pku.

cn) contains RNA-sequencing information for tumor and matched healthy specimens aggregated from The Cancer Genome Atlas (TCGA) and Genotypic Tissue Expression Project (GTEx) databases. A GEPIA of the ITGAM massager RNA (mRNA) levels was conducted using expression data from all the tumor samples and matched normal tissue controls; the sample size was plotted on the X-axis, and the TPM expression values were plotted on the Y-axis.

TCGA and Gene Expression Omnibus (GEO) analysis

The latest RNA-sequencing and medical information for AML were gathered from TCGA (https://portal.gdc.cancer.gov/) database. TCGA expression values were converted from HTSeq-fragments per kilobase per million (FPKM) to TPM. Differences in ITGAM expression between the AML and matched normal tissues were assessed using these expression data. An independent AML data set (GSE65409) was retrieved from the GEO (https://www.ncbi.nlm.nih.gov/gds/) repository for confirmation of our results. Based on the mean ITGAM expression, the AML patients were stratified into high and low ITGAM expression subgroups to evaluate correlations with overall survival (OS) employing a Kaplan-Meier (K-M) analysis. For the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses, individuals were classified into high and low ITGAM expression groups based on the median cut-off value.

Cell cultures

Human AML cell lines (THP1 and NB4) were acquired from the cell bank of the Typical Culture Preservation Centre of the Chinese Academy of Sciences (Shanghai, China). The cells were raised in Roswell Park Memorial Institute 1640 (RPMI-1640) medium with 1% penicillin-streptomycin and 10% fetal bovine serum at 37 ℃ in an atmosphere of 5% carbon dioxide (MeiLunBio, Dalian, China).

Lentiviral transfection

The THP1 and NB4 cells were transfected with lentivirus containing ITGAM short-hairpin RNA (sh-ITGAM) or a negative control (sh-NC). Green fluorescence was observed by fluorescence microscopy (magnification, 100×) after 48 hours. The lentiviral transfections were performed in the presence of a lentivirus. The cells were screened with puromycin 72 hours after transfection. The sh-RNA was synthesized by Genechem (Shanghai, China). The transfection efficiency was verified by quantitative polymerase chain reaction (qPCR) and western blot.

qPCR

The cell samples were collected and total RNA was extracted with TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and the complementary DNA (cDNA) templates were then synthesized using a cDNA reverse transcription kit (Thermo Fisher Scientific, Waltham, MA, USA). The quantitative real-time polymerase chain reaction (qRT-PCR) was performed by the ABI Prism 7500 system (Applied Biosystems, Foster City, CA, USA) using SYBR Green Supermix (Invitrogen, Carlsbad, CA, USA) kit. The assay data were analyzed using the $2^{-\Delta\Delta CT}$ method.

Western blot

The cells were collected and total protein was extracted with radioimmunoprecipitation assay lysis buffer (RIPA) lysate. Protein concentration was detected using a BCA kit (Beyotime Biotechnology, Shanghai, China). Proteins were separated by sodium dodecyl-sulfate polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride (PVDF) membranes. The PVDF membranes were closed in 5% skimmed milk for 2 hours at room temperature. They were then incubated with primary antibody at 4 ℃ overnight. The membranes were washed and then incubated with secondary antibody for 1 hour at room temperature. Details of the antibodies used in this study are shown in Table S1. The results were visualized using the ChemiDoc™ XRS development system (Bio-Rad Laboratories, Hercules, CA, USA), and quantified and analyzed by ImageJ software.

Cell proliferation assays

Cell proliferation was detected using the Cell Counting Kit-8 (CCK-8; MeiLunBio, Dalian, China). The cells were inoculated into 96-well plates and cultured for 0, 24, 48, 72, and 96 hours, and then treated with 10 μL of CCK-8 reagent. Next, 2 hours later, the absorbance value was detected at 450 nm using an enzyme marker.

Cell cycle and apoptosis assays

The cells were transfected in accordance with the

experimental group assignments and harvested after 48 hours. Cell cycle and apoptosis were evaluated by flow cytometry (CytoFLEX S, Beckman Coulter, Brea, CA, USA) using a cell cycle staining kit and an Annexin V-APC/7-AAD Apoptosis Kit (MultiSciences Biotech, Hangzhou, China), respectively.

Statistical analysis

The quantitative results were graphed and analyzed by the Student's *t*-test, and an analysis of variance using GraphPad Prism 8. A P value <0.05 was considered statistically significant. The data were expressed as the mean ± standard deviation (*, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001). All the experiments were replicated three times and the data were described as biological replicates (i.e., n=3).

Results

ITGAM is upregulated in AML

To assess the cell type specificity of ITGAM expression, the transcript abundance rankings from the HPA single-cell RNA-sequencing database were analyzed. Among the top 40 cell populations exhibiting the highest ITGAM expression, myeloid cells demonstrated significantly elevated levels based on nTPM values (*Figure 1A*). We also investigated the expression of ITGAM across various tumor types by utilizing aggregated data from the TCGA and GTEx databases in the GEPIA platform (*Figure 1B*). A differential expression analysis of TCGA RNA-sequencing data revealed that ITGAM was more highly expressed in the AML samples (n=173) than the normal bone marrow samples (n=70) (P<0.001) (*Figure 1C*). The basic information of the 173 patients is detailed in Table S2. A receiver operating characteristic (ROC) curve analysis demonstrated that an area under the curve of 0.9686 for ITGAM could be used to distinguish between AML and normal bone marrow (P<0.001), which supports its potential utility as a diagnostic biomarker (*Figure 1D*). The upregulation of ITGAM was confirmed in an independent AML data set (GSE65409) obtained from the GEO repository, which also exhibited significantly elevated levels of ITGAM in AML samples compared to normal bone marrow samples (*Figure 1E*). The cohort of 151 AML patients was classified into high and low ITGAM expression subgroups based on the median expression level of ITGAM. The clinicopathological characteristics between the subgroups are summarized in *Table 1*. The K-M analysis revealed a correlation between low ITGAM expression and enhanced OS in AML (*Figure 1F*).

ITGAM silencing inhibits AML cell proliferation

To examine the metabolic function of ITGAM in the AML cells, THP1 and NB4 cell lines were transfected with lentivirus containing sh-ITGAM to stably knockdown ITGAM expression. Successful transfection was confirmed by green fluorescence in the AML cells at 48 hours post-infection (*Figure 2A*). ITGAM knockdown was validated at the mRNA and protein-production levels in the sh-ITGAM transfected cells compared to the controls transfected with sh-NC by RT-qPCR and a Western blot analysis, respectively. sh-ITGAM significant decreased ITGAM mRNA production in both the THP1 and NB4 (P<0.001) cell lines relative to the sh-NC controls (*Figure 2B*). The protein of ITGAM was significantly reduced in both the THP1 (P=0.004) and NB4 (P=0.003) cell lines compared to the sh-NC controls (*Figure 2C*,*2D*). The CCK-8 method was used to examine the effects of ITGAM silencing on AML cell growth in the NB4 and THP1 cell lines. Absorbance at 450 nm, which is indicative of a viable cell number, was lower in the sh-ITGAM transfected NB4 and THP1 cells than the sh-NC control cells at days 1–4 post-transfection. The differences in proliferation between the sh-ITGAM and sh-NC groups were statistically significant at day 3 in THP1 cell (P<0.001) and at day 2 in NB cell (P=0.01) (*Figure 2E*,*2F*). Taken together, these data indicated that ITGAM silencing had an inhibitory effect on AML cell growth.

ITGAM silencing induces cell cycle arrest and apoptosis in AML

To investigate whether the anti-proliferative effects of ITGAM knockdown were due to altered cell cycle progression, we conducted a flow cytometric assessment of cell cycle distribution. ITGAM silencing resulted in G1 phase arrest and a notable decrease in S phase cell populations in the THP1 and NB4 cells (P<0.001) (*Figure 3A*,*3B*). The amounts of important cell cycle control proteins engaged in the G1/S phase transition were also determined. The Western blot analysis revealed decreased protein production of cyclin D1, cyclin E1, cyclin-dependent kinase 2 (CDK2), and cyclin-dependent kinase 4 (CDK4) in the THP1 and NB4 cells (P<0.001) after ITGAM knockdown (*Figure 3C*,*3D*). These results

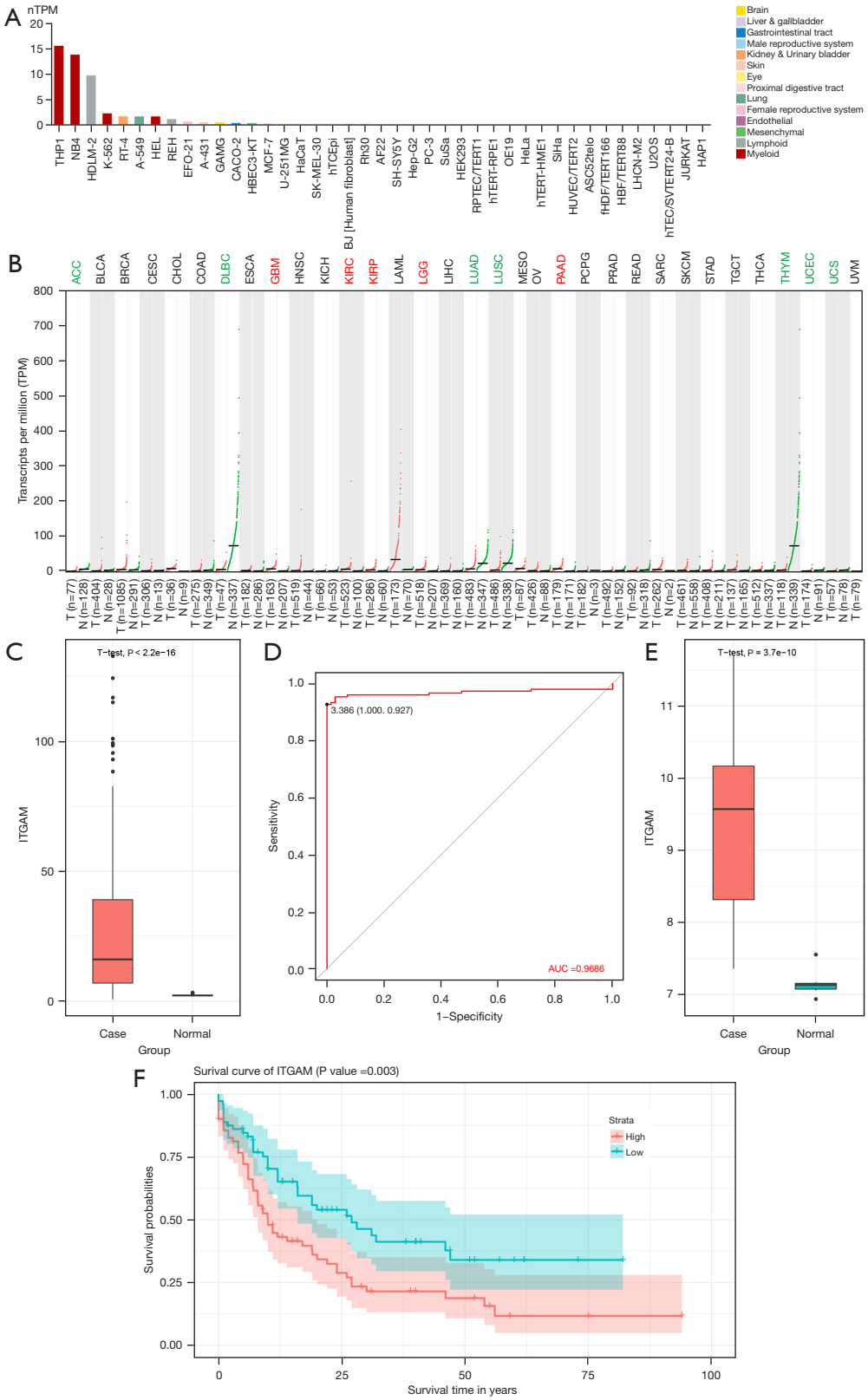


Figure 1 ITGAM expression in AML and normal tissues. (A) ITGAM expression in different cell types from the HPA single-cell RNA-

sequencing database. (B) The ITGAM expression in different cancers was analyzed by a GEPIA. The full name of the TCGA abbreviations sees the website: https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations. (C) The ITGAM expression in AML samples compared to normal bone marrow samples based on TCGA data. (D) ROC curves were used to analyze the ability of ITGAM to distinguish between AML and normal tissues. Data in the upper left corner is presented as expression intercept at the highest point (true positive rate, false positive rate). (E) ITGAM expression in an external data set (GSE65409) of AML patients and healthy controls. (F) K-M analysis of OS survival comparing AML patients with high and low ITGAM expression. nTPM, normalized transcripts per million; T, tumor tissue; N, normal tissue; ITGAM, integrin subunit alpha M; AUC, area under the curve; AML, acute myeloid leukemia; HPA, Human Protein Atlas; GEPIA, Gene Expression Profiling Interactive Analysis; TCGA, The Cancer Genome Atlas; ROC, receiver operating characteristic; K-M, Kaplan-Meier; OS, overall survival.

Table 1 Correlation between ITGAM levels and OS in AML

Variables	Overall (n=151), n (%)	ITGAM expression, n (%)		P value[†]
		High (n=75, 49.67%)	Low (n=76, 50.33%)	
Age group				0.002
≤60 years	88 (58.28)	34 (45.33)	54 (71.05)	
>60 years	63 (41.72)	41 (54.67)	22 (28.95)	
Sex				0.28
Female	68 (45.03)	30 (40.00)	38 (50.00)	
Male	83 (54.97)	45 (60.00)	38 (50.00)	
FAB				5e−05
M0 undifferentiated	15 (9.93)	5 (6.67)	10 (13.16)	
M1	35 (23.18)	16 (21.33)	19 (25.00)	
M2	38 (25.17)	13 (17.33)	25 (32.89)	
M3	15 (9.93)	1 (1.33)	14 (18.42)	
M4	29 (19.21)	25 (33.33)	4 (5.26)	
M5	15 (9.93)	12 (16.00)	3 (3.95)	
M6	2 (1.32)	2 (2.67)	0 (0.00)	
M7	1 (0.66)	0 (0.00)	1 (1.32)	
Not classified	1 (0.66)	1 (1.33)	0 (0.00)	

[†], Pearson's chi-squared test. ITGAM, integrin subunit alpha M; OS, overall survival; AML, acute myeloid leukemia; FAB, French, American and Britain.

indicated that ITGAM silencing inhibited G1/S phase transition, thereby suppressing AML cell proliferation.

To ascertain whether ITGAM silencing also affected AML cell viability, we examined the proportion of apoptotic cells by flow cytometry. The proportion of apoptotic cells was significantly increased in the sh-ITGAM transduced THP1 (15.67%) and NB4 (15.19%) cells (P<0.001) compared to the sh-NC (THP1: 5.19%; NB4: 6.08%) and untreated control cells (*Figure 3E,3F*). No difference in apoptosis was observed between the control and sh-NC groups. These results indicated that ITGAM silencing promoted apoptosis in AML cells.

ITGAM knockdown inhibits MAPK signaling in AML

There is increasing evidence that MAPK signaling is crucial in cancer growth and metastasis. Our data showed that ITGAM silencing inhibited AML cell proliferation and viability. Thus, we hypothesized that ITGAM would regulate MAPK pathway activity. First, using the median ITGAM value, TCGA AML individuals were stratified into high and low ITGAM expression groups.

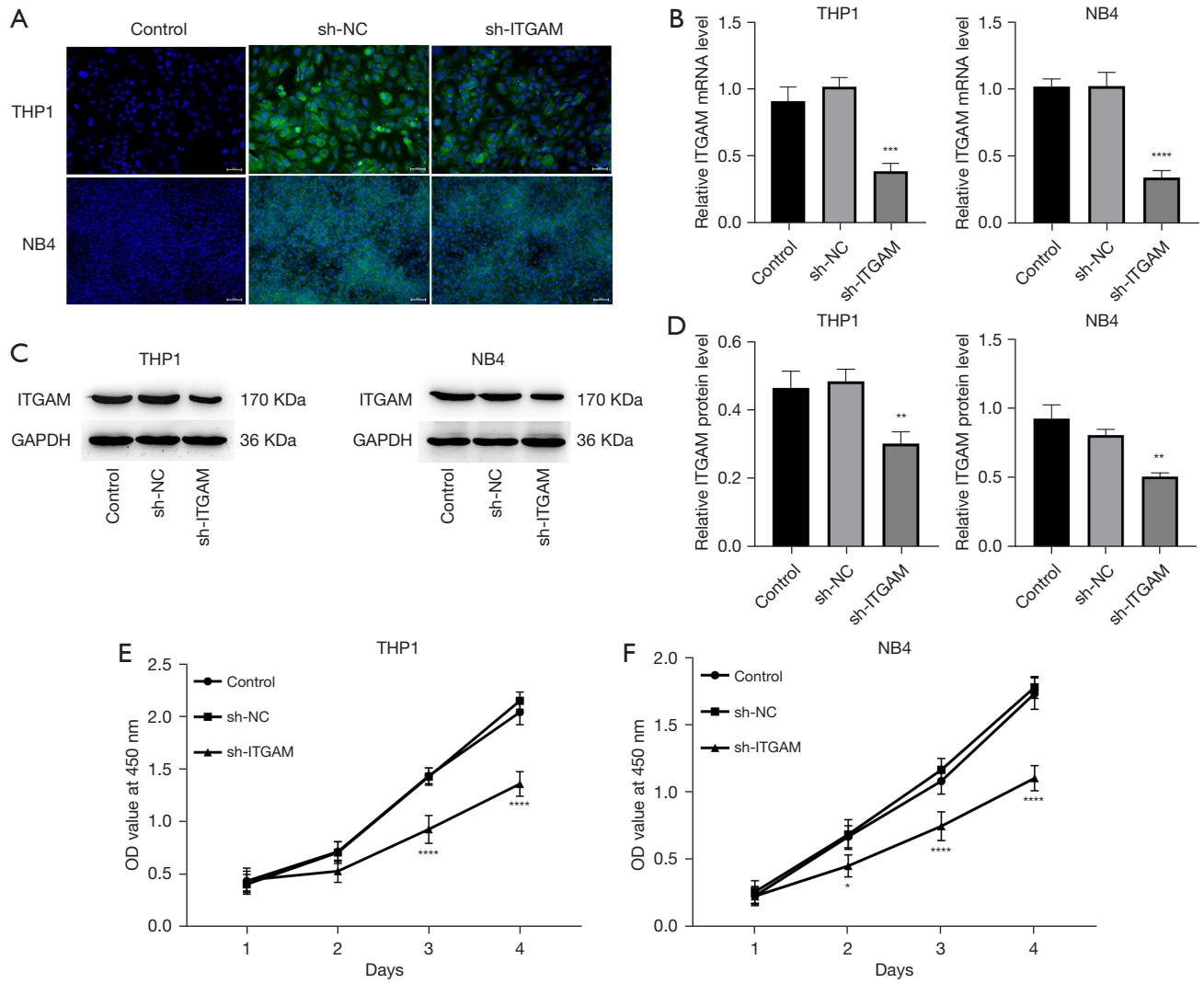
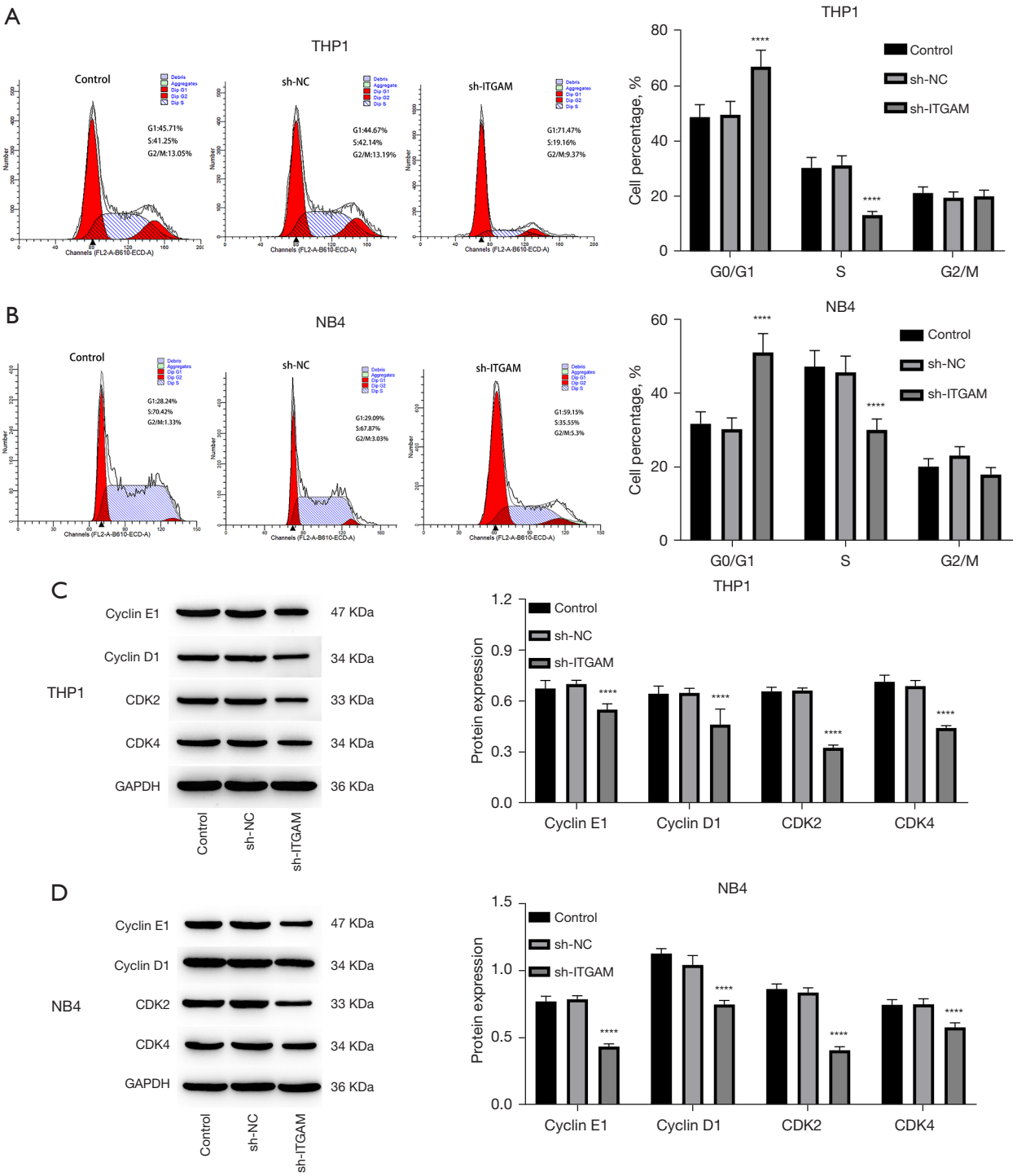


Figure 2 ITGAM silencing inhibited AML cell proliferation. (A) Fluorescence imaging displaying transfection efficiency in the THP1 and NB4 cells at 48 hours. Scale bar (magnification): 50 μm (200×). (B) ITGAM mRNA expression in the THP1 and NB4 cells after sh-ITGAM transfection. (C) A Western blot analysis of ITGAM protein production in the THP1 and NB4 sh-ITGAM and sh-NC cells. (D) Quantitative analysis of ITGAM protein expression in (C). (E,F) Proliferative ability of the THP1 and NB4 cells after ITGAM silencing. **, P<0.01; ***, P<0.001; ****, P<0.0001. sh-NC, short-hairpin negative control; sh-ITGAM, ITGAM short-hairpin RNA; ITGAM, integrin subunit alpha M; mRNA, massager RNA; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OD, optical density; AML, acute myeloid leukemia.

A Bayesian differential analysis revealed that the MAPK signaling pathway was enriched between the subgroups (*Figure 4A-4D*). Thus, we assessed the effect of the ITGAM knockdown on MAPK protein activation in the THP1 and NB4 cells. The Western blot analysis showed decreased phosphorylation of the MAPK proteins P38, JNK, and ERK (P<0.001) after ITGAM silencing (*Figure 4E,4F*). These results demonstrated that ITGAM knockdown inhibited phosphorylation and the activation of key MAPK signaling proteins in the AML cells.

Discussion

The field of AML, a heterogeneous hematologic malignancy, has witnessed significant advancements in treatment over the past three decades. However, despite



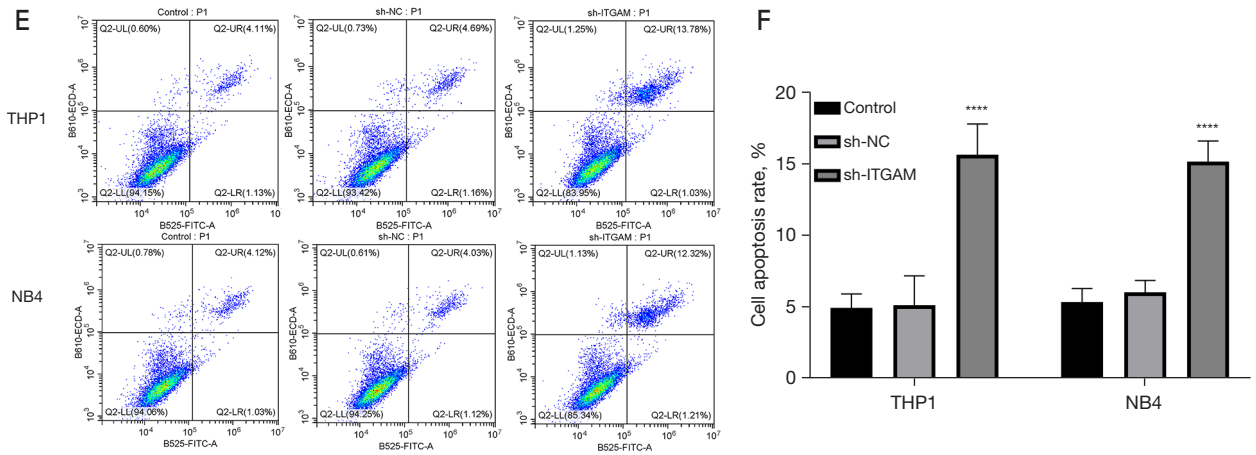
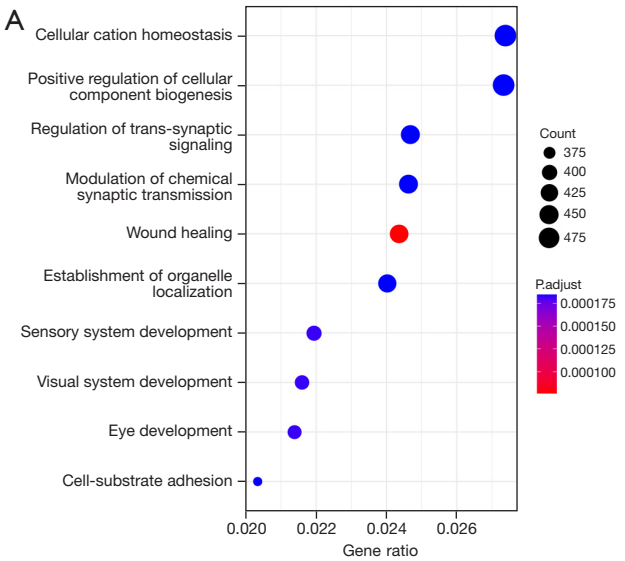


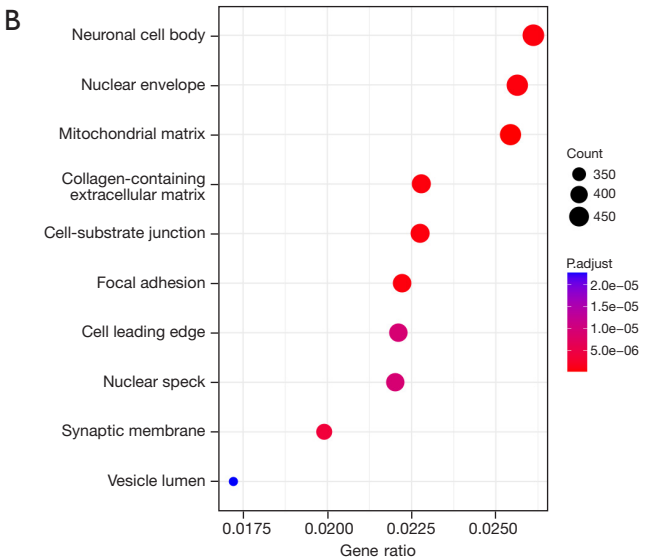
Figure 3 ITGAM silencing induced cell cycle arrest and apoptosis in AML. (A) ITGAM silencing inhibited cell cycle progression in the THP1 cells. (B) ITGAM silencing suppressed the advancement of the cell cycle in the NB4 cells. (C,D) ITGAM silencing inhibited the amounts of cell cycle-related proteins in the THP1 and NB4 cells. (E,F) ITGAM silencing promoted apoptosis in the THP1 and NB4 cells. ****, P<0.0001. sh-NC, short-hairpin negative control; sh-ITGAM, ITGAM short-hairpin RNA; ITGAM, integrin subunit alpha M; CDK2, cyclin-dependent kinase 2; CDK4, cyclin-dependent kinase 4; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; UL, upper left; UR, upper right; LL, lower left; LR, lower right; ECD, electron coupled dye; FITC, fluorescein isothiocyanate; AML, acute myeloid leukemia.

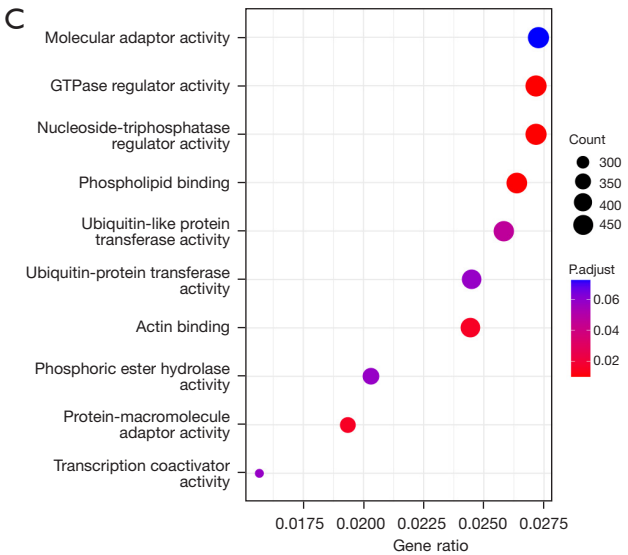
these improvements, patient survival rates remain unsatisfactory when utilizing current standard therapies involving induction chemotherapy and post-remission regimens (13,14). High-throughput gene expression profiling has shed light on the genetic basis of AML and identified potential prognostic biomarkers and therapeutic targets (15). The aberrant expression of multiple genes is now recognized as a major factor in AML pathogenesis (16,17). For instance, serine/threonine kinase 10 (STK10) is upregulated in AML and is linked to poor prognosis, while ITGAM and integrin beta 2 (ITGB2) expression are positively correlated with STK10 levels and reduced OS in AML (18).

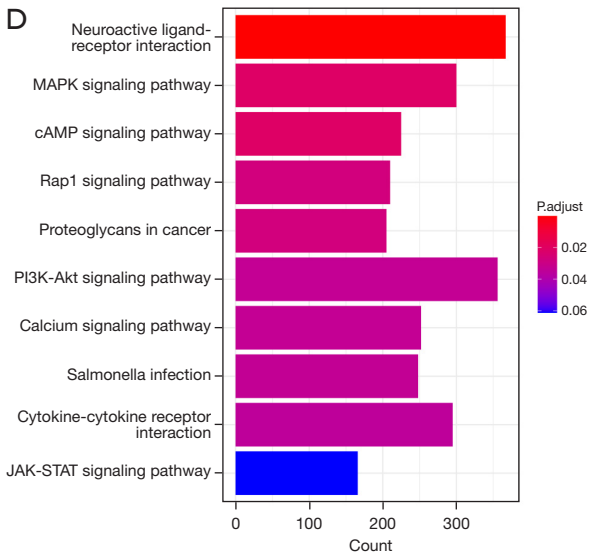
ITGAM (CD11b) is highly expressed in leukocytes, including neutrophils, monocytes, and natural killer cells, in which it regulates migration and adhesion (19). The results of this study confirmed that ITGAM was overexpressed across immune cell populations. A previous study identified ITGAM as part of a prognostic gene signature for osteosarcoma (20). High CD11b levels have also been associated with postoperative infections, cancer recurrence, and sleep deprivation-induced hepatocellular carcinoma (21,22). However, the role of ITGAM in AML remains controversial. Some studies have found that ITGAM is hypermethylated and downregulated in AML, while Hu *et al.* and Chen *et al.* showed that ITGAM was hypomethylated and upregulated (23,24). These discrepancies might be related to the differences in the sample sizes analyzed. More recently, Huang *et al.* conducted a protein-protein interaction network analysis and identified ITGAM as a core gene linked to poor OS in AML (25). This aligns with our results that ITGAM was overexpressed in AML samples compared to normal bone marrow samples. The ROC curve analysis supported the utility of ITGAM as a diagnostic AML marker. Furthermore, high ITGAM expression was associated with inferior patient survival in our cohort.

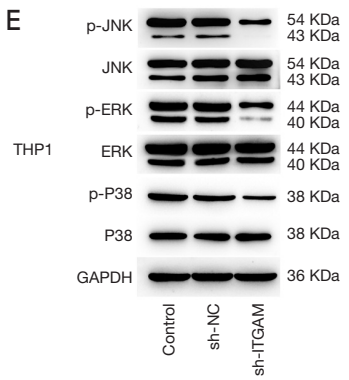
In the vitro experiment of this study, the ability of AML cells to promote growth was suppressed, and the proportion of apoptosis increased following the knockdown of ITGAM. This was accompanied by a G1 phase cell cycle arrest and a reduction in the production of cyclin D1, cyclin E1, CDK2, and CDK4 proteins. In addition, KEGG pathway analysis revealed a close relationship between ITGAM expression and the MAPK pathway, which is essential for G1/S phase progression (26). The knockdown of ITGAM suppressed the P38, JNK, and ERK phosphorylation levels in the MAPK pathway. Given the widely recognized role of MAPK pathway activation in AML cell growth and disease progression, these findings support the notion

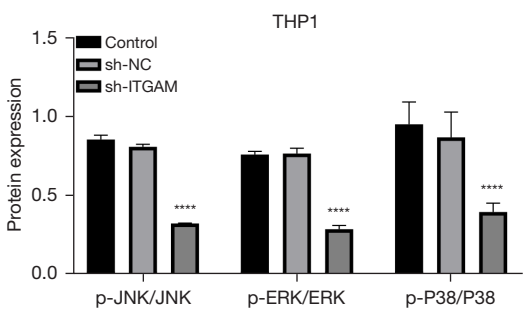












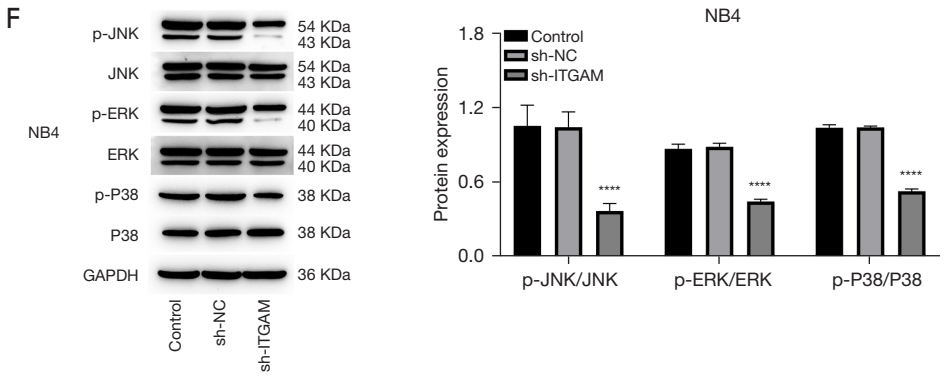


Figure 4 ITGAM knockdown inhibited MAPK signaling in AML. (A-C) GO analysis comparing TCGA AML patients with high versus low ITGAM expression. (D) KEGG pathway analysis displaying the enrichment of MAPK signaling associated with ITGAM expression. (E) ITGAM silencing inhibited MAPK protein phosphorylation in THP1 cell. (F) ITGAM silencing inhibited MAPK protein phosphorylation in NB4 cell. ****, P<0.0001. MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinas; P38, p38 MAPK; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; sh-NC, short-hairpin negative control; sh-ITGAM, ITGAM short-hairpin RNA; ITGAM, integrin subunit alpha M; AML, acute myeloid leukemia; GO, Gene Ontology; TCGA, The Cancer Genome Atlas; KEGG, Kyoto Encyclopedia of Genes and Genomes.

that disturbances in gene expression can influence MAPK pathway activation, thereby affecting AML progression (27). Additionally, our results align with those of a previous study that demonstrated that chromobox homolog 2 (CBX2) silencing led to decreased p-P38 and p-ERK expression, ultimately inhibiting AML cell proliferation (28). These results suggest that the dysregulation of gene expression disrupts the activation of the MAPK pathway, subsequently impacting the progression of AML.

Conclusions

Overall, this study performed a systematic analysis of ITGAM expression in AML. ITGAM was highly upregulated in the AML samples compared to the normal bone marrow samples from multiple data sets. Increased ITGAM expression was linked to poor OS in the AML population, thus ITGAM can serve as a prognostic biomarker for AML. Functional investigations revealed that the knockdown of ITGAM in AML cell lines suppressed MAPK pathway activation, cell cycle progression, and cell growth, and promoted apoptosis. These results revealed the mechanistic role of ITGAM in promoting AML pathogenesis through the regulation of oncogenic signaling and cell survival. This study also clarified the molecular underpinnings of AML progression. Our findings suggest that ITGAM may serve as a novel diagnostic marker and therapeutic target for AML. More investigations are required to validate the medicinal utility of ITGAM as a biomarker and explore strategies for the therapeutic targeting of ITGAM in AML.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-810/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-810/dss

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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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