Expression And Clinical Significance of Transcription Factor GRHL1 In Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia (AML) ranks sixth in the incidence of malignant tumors. It is the most common acute leukemia in adults with clinical and molecular heterogeneity of the bone marrow and lymphatic system.

Objective: In this study, we aimed to explore the expression and clinical significance of GRHL1 in acute myeloid leukemia.

Methods: RNA-seq data from The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx) and Gene Expression Omnibus (GEO) were analyzed combined with the related clinical data of patients with AML. Kaplan–Meier plot was constructed to assess survival differences. Log-rank test and correlation analysis were performed to evaluate the prognostic value and clinical significance of GRHL1 in patients with AML.

Results: In this study, we found that patients with AML showed significant differences in the GRHL1 gene expression compared to normal bone marrow controls. Kaplan-Meier survival analysis revealed that low expression of GRHL1 was significantly associated with worse prognosis in patients with AML. Multiple omics analysis and correlation analysis revealed that aberrant alterations of known factors were significantly associated with GRHL1 expression, which confirmed GRHL1 as a protective intervention factor in patients with AML.

Discussion: GRHL1 presented great potential in evaluating predicting prognostic values and clinical significance in patients with AML. GRHL1 might act as an important role in inhibiting the progression of tumors and serve as a protective factor for potential therapeutic strategies of AML. GRHL1 might provide a novel biomarker for precision oncology and benefit clinical cancer management.

Background

Acute myeloid leukemia (AML) is a hematopoietic cancer of the bone marrow and ranks sixth in the incidence of malignant tumors.[1] Acute myeloid leukemia represents a highly lethal form of acute leukemia with high molarity rate in adults.[2] Untreated acute myeloid leukemia naturally lives for less than six months. AML is characterized by its clinical and molecular heterogeneity and has an extremely poor prognosis with high mortality and recurrence rates.[3] Chemotherapy is almost the only available therapy for AML but the majority of patients with AML eventually die from chemoresistance and recurrence.[4] Although cytogenetic changes can provide potential therapeutic targets and prognostic prediction at the present day, this risk stratification model is merely suitable for AML patients with abnormal karyotypes.[5] It is difficult to predict the prognosis of patients with normal karyotypes, which account for more than 50% of all patients with AML.[6] Currently, lack of prognostic biomarkers is the major contributor to high cancer death.[7] Therefore, it is important to identify an effective biomarker to do help for prognosis prediction and precision treatment in clinical practice.

Recently, a great number of findings have indicated that inactivation or downregulation of genes played a key role in cancers. Transcription factor Grainyhead-Like Transcription Factor 1 (GRHL1) belongs to the Grainyhead-like (GRHL) family, which contains a DNA-binding human gamma globulin fold homologous to the core domain of key tumor suppressor p53.[8] It has an important role in the process of coding Drosophila embryo development, epidermal morphogenesis and central nervous system development.[9] In recent years, next-generation genome sequencing has significantly improved the molecular understanding and prognostic evaluation of patients with AML.[10] Increasing research have revealed that GRHL1 is involved in the occurrence and progression of different types of cancer including oesophageal squamous cell carcinoma, colon cancer, non-melanoma skin cancers, lung cancers and other tumors.[11–15]

Considering the different roles of GRHL1 in different tumors, GRHL1 has become a potential target for cancer treatment. The aim of our study was to investigate the expression of GRHL1 as well as its association with risk factors and prognosis in patients with AML. GRHL1 might act as an important role in inhibiting the progression of tumors and serve as a protective factor for potential therapeutic strategies of AML.

Materials & Methods

Patients and transcriptome data

150 patients with primary AML from TCGA-LAML project (https://portal.gdc.cancer.gov) and 70 normal healthy donors' samples from Genotype-Tissue Expression (GTEx) project (https://gtexportal.org) were included in this study. For further validation, several published datasets in Gene Expression Omnibus (GEO) were used for gene expression profiles including GSE30029[16] and GSE12417-GPL97[17]. The transcriptome data of the corresponding bone marrow (BM) tissues and related clinical characteristics were obtained by high throughput sequencing (RNA-Seq) or microarray from corresponding database. All design of experiments, quality control (QC) and data normalization were in accordance with the standard Affymetrix protocols. The patients were classified according to the French-American-British (FAB) classification. Detailed clinical characteristics of the patients have been shown in Table S1.

Statistical analysis

All statistical analysis were performed using GraphPad Prism 9.0 (La Jolla, CA, USA). Independent student's t test was processed to compare values of two different groups. One-way ANOVA test was used to the mean expression level among three and more subgroups. Spearman correlation test was assessed for the analysis of correlation between gene expression. Survival analysis were performed using log-rank test with Kaplan-Meier plots to compare the survival difference between different subgroups. The STRING database (https://www.string-db.org) was used to establish networks of protein–protein interaction (PPI) networks with GRHL1 target genes or other closely associated genes. High-frequency binding motifs of transcription factors GRHL1 were predicted in the JASPAR database (http://jaspar.genereg.net). Signaling pathway enrichment analysis were conducted using Metascape (https://metascape.org).[18] Gene set

enrichment analysis (GSEA) was performed using the Sangerbox tools, a free online platform for data analysis (http://www.sangerbox.com/tool). *P* values less than 0.05 were defined as with statistically significant.

Results

Decreased expression of GRHL1 in patients with acute myeloid leukemia

For the purpose of evaluating the expression level of GRHL1 gene in patients with AML, we analyzed the transcriptomic RNA-sequencing data from TCGA, GTEx and GEO database. The expression of GRHL1 was examined in bone marrow (BM) tissues between patients with AML and healthy donors. GRHL1 was lowly expressed in bone marrow tissues of patients with AML in TCGA-LAML project compared with counterparts of healthy donors in GTEx project (Fig. 1A). Additionally, bone marrow tissues derived from AML patients and healthy donors in GSE30019 dataset were used to further validate GRHL1's downregulation in patients with AML (Fig. 1B). Patients in TCGA dataset were classified according to the French-American-British (FAB) classification. GRHL1 was relatively highly expressed in patients who were in FAB classification of M6 and M7 (Fig. 1C)

The association between GRHL1 and clinical significance of patients with AML

To clarify the clinical significance of the expression level of the GRHL1 in AML, Sankey diagram was used to show the distribution trends between expression of GRHL1 and other clinical characteristics such as ages, gender and survival status in patients with AML (Fig. 2A). Different colors represent different types or status and lines represent the distribution of the same sample in different characteristics. We further analyzed potential prognosis significance of GRHL1 in TCGA and GEO database by Kaplan–Meier survival analysis. The patients were divided into high GRHL1 group and low GRHL1 group by the best cut-off point of GRHL1’s expression. Compared to high GRHL1 groups, patients in low GRHL1 group were significantly associated with shorter overall survival in TCGA cohort (Fig. 2B). Moreover, Kaplan–Meier survival analysis also indicated that the high GRHL1 group patients had longer overall survival than the low GRHL1 group in GSE12417-GPL97 dataset (Fig. 2C).

Genome-wide molecular landscape of patients with different GRHL1 expression

To further investigate the associations between transcriptome expression and GRHL1 expression, the gene expression profiles that closely related to GRHL1 were examined based on the median value of GRHL1 expression. 440 up-regulated and 58 down-regulated genes were found in high GRHL1 group (Fig. 3A). Hierarchical clustering analysis of differentially expressed genes between different GRHL1 subgroup were displayed in clustered heatmap (Fig. 3B). A protein–protein interaction (PPI) network of these differentially expressed genes were formed, in which tumorigenesis promoters HOX family genes were included (Fig. 3C). Signaling pathway enrichment analysis of the differentially genes also showed that some critical signaling pathways were significantly related to GRHL1 in AML, including those closely related to differentiation and development (Fig. 3D).

Transcription factor GRHL1 target genes and GSEA analysis

High-frequency binding motif of transcription factor GRHL1 was predicted in the JASPAR database (Fig. 4A). Considering the transcription factor role of GRHL1 and its function in regulating gene expression, a clustered PPI network of GRHL1 and the downstream target genes were formed by analyzing STRING database (Fig. 4B). We further performed gene set enrichment analysis (GSEA) to identify KEGG signaling pathways relevant to low GRHL1 expression in patients with AML. GSEA analysis results revealed enrichment for pathways associated with oxidative phosphorylation and ribosome (Fig. 4C).

Correlations of GRHL1 with leukemogenesis related markers

To further investigate the biological and functional role of GRHL1 in leukemogenesis, representative leukemogenesis related markers were examined in the gene expression profiles of TCGA project. Significant negative correlations (Spearman $R < -0.20$, $p < 0.05$) could be found between the expression of leukemogenesis related markers and GRHL1 (Fig. 5A, Table S2). The negative correlated genes included: 1) genes involving in leukemogenesis (HHEX[19]); 2) super-enhancer-associated genes (CDK7[20]); 3) independent prognostic factors in AML (WT1[21]) 4) tumorigenesis promoters (HOX family genes[22]). Signaling pathways play important roles in critical biological processes including carcinogenesis and cancer progression. Thus, we performed the signaling pathway enrichment analysis for GRHL1 negatively associated genes (Fig. 5B). These findings indicated that GRHL1 was strongly negatively relevant to leukemogenesis in patients with AML.

Discussion

Acute myeloid leukemia (AML) is a heterogeneous group of hematopoietic malignancies with high molarity rates worldwide. Although there have been a great amount of breakthroughs in the treatment of acute myeloid leukemia, AML patients with the exception of specific types of acute promyelocytic leukemia (APL) are prone to relapse after remission from chemotherapy, which induced poor quality of survival and poor prognosis.[23, 24] There are also extremely limited effective and suitable drugs precisely targeted in AML. Therefore, it is essential to explore new therapeutic strategies and find out suitable biomarkers involving in carcinogenesis and cancer development of leukemia.[25] In this study, we explored the expression and prognostic significance of GRHL1 in patients with AML in various clinical cohorts for the first time. In addition, we also assessed correlations between GRHL1 and other leukemogenesis related molecules or signaling pathways in order to preliminarily evaluate its clinical significance as an intervention molecule target for acute myeloid leukemia.

Grainyhead-like transcription factor (GRHL) family was first identified in the fruit fly Drosophila melanogaster, in which there are three family members in mammals.[26] GRHL family members are responsible for driving epithelial cell fate, which are known as Grainyhead-like 1 (GRHL1), Grainyhead-like 2 (GRHL2) and Grainyhead-like 3 (GRHL3).[27, 28] Increasing studies have indicated that GRHL family were mainly found in epithelial tissues, such as epidermis, oral and olfactory epithelium, kidney and urogenital tract and digestive tract.[29] As a member of the GRHL family, GRHL1 plays an important role

in regulating embryogenesis, embryonic development, formation of the epidermal barrier and repair of epidermal injury.[30–33] Furthermore, a great number of research have shown that the GRHL1 acted as a tumor suppressive factor in carcinogenesis, progression and prognosis of various cancer types including liver cancer, skin cancer, neuroblastoma and clear cell renal cell carcinoma.[34] GRHL1 plays a critical role in fate determination of pluripotent cells, which might be relevant to phenotypic plasticity in tumors.[35, 36] Moreover, GRHL1 is one of the major target genes upregulated in the inhibitor treatment of neuroblastoma.[37]

In the present study, the transcriptome expression in bone marrow samples of patients with AML from different cohorts were analyzed combining with the related clinical data. Patients with AML showed significant downregulation in the GRHL1 gene expression compared to normal bone marrow controls. Kaplan-Meier survival analysis were conducted to evaluate the prognostic value and clinical significance of GRHL1. Results showed that low expression of GRHL1 was significantly associated with worse prognosis in patients with AML, which indicated that GRHL1 expression might be an independent prognosis predictor of AML. Multiple omics analysis and correlation analysis revealed that aberrant alterations of known factors were significantly associated with GRHL1 expression, which confirmed GRHL1 as a protective factor in patients with AML. All in all, these results revealed that the decreased of GRHL1 expression level was strongly negatively relevant to leukemogenesis, progression and prognosis of AML.

In conclusion, our present study identified that GRHL1 presented great potential in evaluating predicting prognostic values and clinical significance in patients with AML. GRHL1 might act as an important role in inhibiting the progression of tumors and serve as a tumor suppressor gene involved in the occurrence and development of AML. GRHL1 might provide a novel biomarker for precision oncology and benefit clinical cancer management. What’s more, our research firstly revealed GRHL1 gene as a potential novel independent prognostic biomarker in AML. However, there are still a number of limitations of our present study. Therefore, more clinical cohorts and different subtypes of AML should be examined to further verify the relationship between GRHL1 and AML.

Conclusions

Our newly identified biomarker GRHL1 presented great potential in evaluating prognostic significance and clinical outcome in patients with AML. GRHL1 might play an important role in inhibiting the occurrence and progression of AML tumors and serve as a tumor suppressor for potential therapeutic strategies of AML. GRHL1 might provide a novel biomarker for precision oncology and benefit clinical cancer management.

List Of Abbreviations

AML, acute myeloid leukemia; BM, bone marrow; QC, quality control; RNA-seq, RNA sequencing; OS, overall survival; TCGA, The cancer genome atlas; GTEx, Genotype-Tissue Expression; GEO, Gene

Expression Omnibus; PPI, protein-protein interaction; GSEA, gene set enrichment analysis; APL, acute promyelocytic leukemia.

Declarations

Ethical approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication Not applicable.

Availability of data and material The datasets used and analyzed during the current study are available from TCGA database (https://portal.gdc.cancer.gov), GTEx project (https://gtexportal.org) and GEO database.

Competing interests The authors declare that they have no competing interests.

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Author's contributions Chuansheng Zhu and Jing Hua conducted the conceptualization and designed the study. Chuansheng Zhu, Jing Hua, Congcong Ma and Zhaoohui Wang were contributors in writing the manuscript. Congcong Ma and Xianliang Duan searched and integrated the related literature. Jing Hua, Xiaole Zhang, Yazhen Bi and Taiwu Xiao collected the case data and conducted data analysis and visualization. Yan Wang and Chuansheng Zhu revised the manuscript.

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Figures

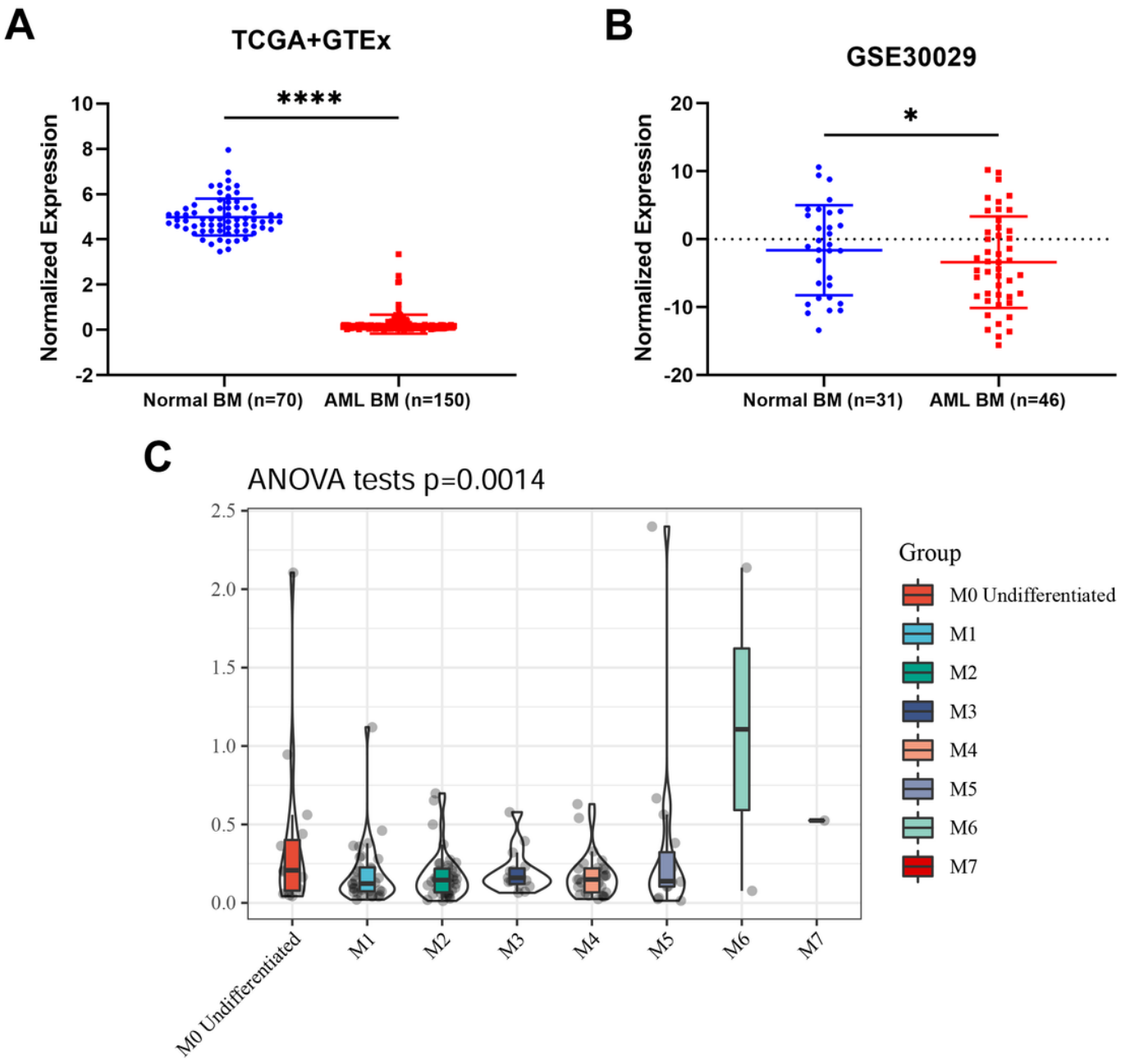

Figure 1

Differential expression of GRHL1 in patients with AML. (**A**) The normalized expression of GRHL1 between 150 AML BM tissues and 70 normal BM tissues from TCGA and GTEx database. Independent student's t test, ****, $p < 0.0001$. (**B**) The normalized expression of GRHL1 between 46 AML BM tissues and 31 normal BM tissues from GSE30029 dataset. Independent student's t test, *, $p < 0.05$. (**C**) The normalized expression of GRHL1 among subgroups of patients with different FAB classification.

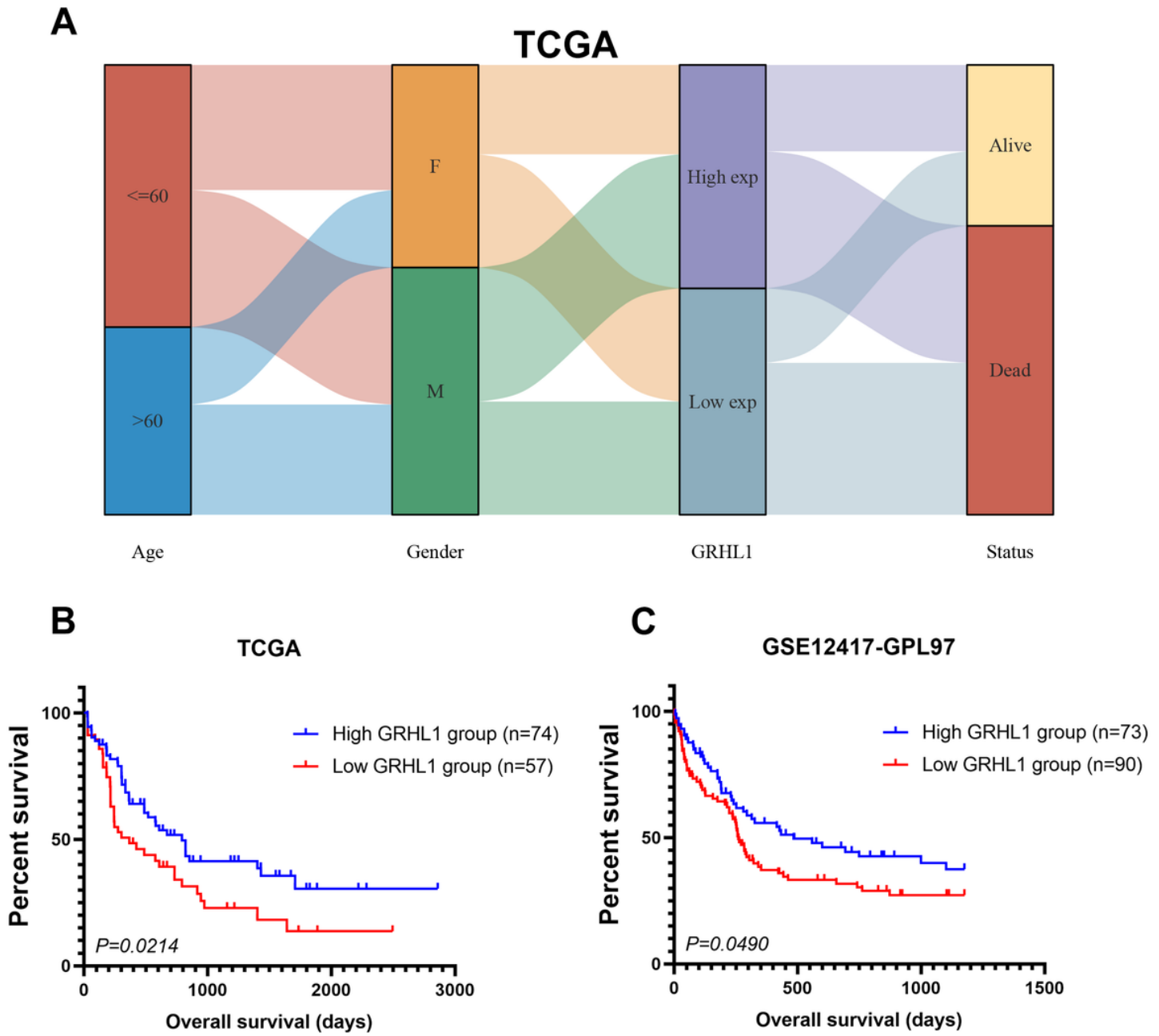

Figure 2

Clinical significance of GRHL1 in patients with AML. (**A**) Sankey diagram of expression of GRHL1 and other clinical characteristics in AML patients in TCGA. (**B**) Kaplan–Meier plot with log-rank *p* value for AML patients' overall survival (OS) of GRHL1 in TCGA cohort. (**C**) Kaplan–Meier plot with log-rank *p* value for AML patients' overall survival (OS) of GRHL1 in GSE12471-GPL97.

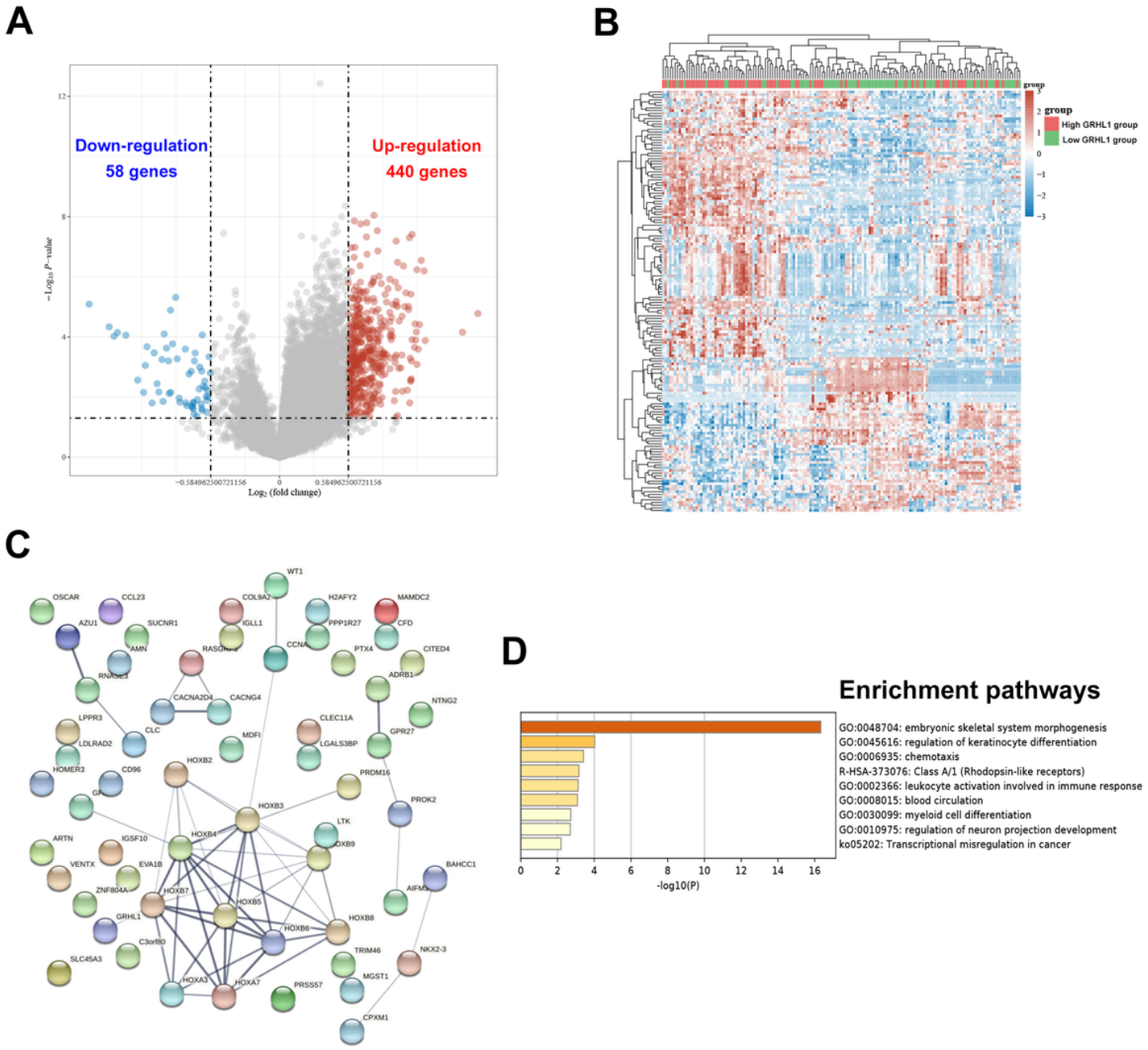

Figure 3

Differential genes and signaling pathways associated with GRHL1 expression. (**A**) Volcano plot of differential genes between high GRHL1 group and low GRHL1 group. (**B**) Expression heatmap of genes associated with GRHL1 expression. (**C**) PPI network of genes downregulated in high GRHL1 group. (**D**) Gene ontology and signaling pathway enrichment analysis of genes downregulated in high GRHL1 group.

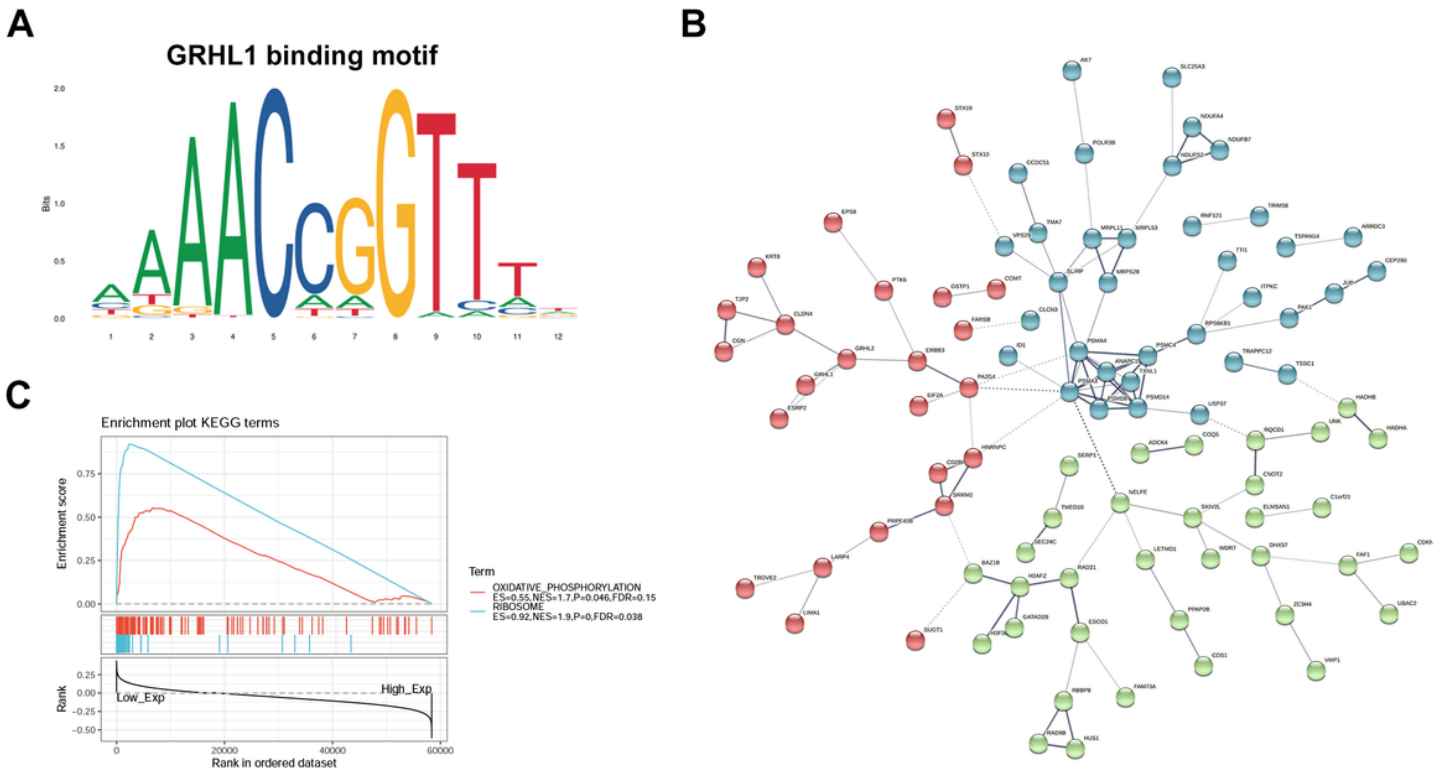

Figure 4

Transcription factor GRHL1 targets and GSEA analysis (**A**) Binding motif of GRHL1. (**B**) Clustered PPI network of GRHL1 and its downstream targets. (**C**) GSEA analysis for KEGG signaling pathways enriched in low GRHL1 group.

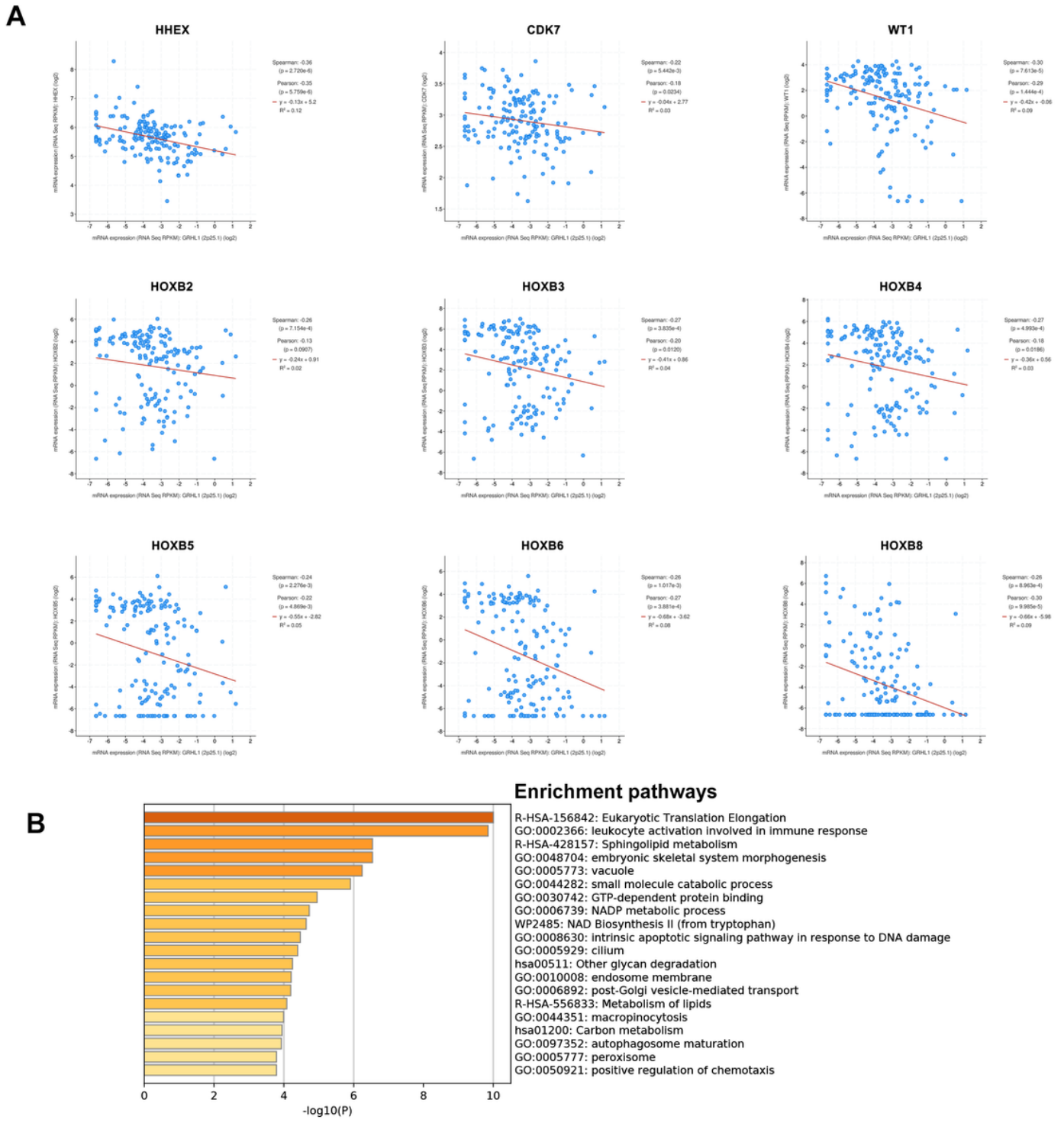

Figure 5

Correlations of GRHL1 with leukemogenesis related markers. (**A**) Correlations of GRHL1 expression and leukemogenesis related markers. (**B**) Gene ontology and signaling pathway enrichment analysis of genes negatively related with GRHL1 in patients with AML.

Supplementary Files

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