IDH1-mutated B-cell acute lymphoblastic leukemia characterized by oncogenic reprogramming of lipid metabolism

B-cell acute lymphoblastic leukemia (B-ALL) is a highly aggressive hematologic malignancy with marked genetic heterogeneity, accounting for approximately 75% of adult ALL cases.[1] The ubiquitous application of high-throughput technologies has facilitated the discovery of novel B-ALL molecular subtypes, including *DUX4* and *MEF2D* rearrangements, which have refined risk stratification for affected individuals.[2,3] *Isocitrate dehydrogenase 1 (IDH1)* mutations, which occur in approximately 8% of acute myeloid leukemia (AML) patients, are comparatively infrequent in B-ALL.[4] *IDH1* mutations have been well-established as key drivers of leukemogenesis through the production of the oncometabolite (R)-2-hydroxyglutarate (R-2HG).[4,5] Although *IDH1*-mutated B-ALL had been documented to display distinct transcriptional signatures and prognostic features, this molecular subtype remains understudied due to its rarity.[6] Previously, we reported a case of *IDH1*-mutated B-ALL characterized by prominent cytoplasmic lipid droplet (LD) accumulation in leukemic blasts, a morphological phenotype typically associated with ALL-L3 in French-American-British (FAB) classification.[7] Inspired by this observation, we conducted a comprehensive analysis to characterize features of *IDH1*-mutated B-ALL in our cohort, which potentially provided novel insights into its biological properties and potential therapies.

In this study, a total of 30 patients with *IDH1*-mutated B-ALL were enrolled, and an additional 188 patients with *IDH1*-WT B-ALL were used as controls. All cases with the characteristic immunophenotype of B-ALL were newly-diagnosed and enrolled at the First Affiliated Hospital to Zhejiang University School of Medicine (IIT20240358B). All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants.

IDH1 mutation testing was performed for all patients, using a combination of next-generation sequencing (NGS) and polymerase chain reaction (PCR)-based methods. Among the *IDH1*-mutated patients, the mutation sites of the *IDH1* gene were heterogeneous. Specifically, 13 patients had the *R132C* mutation, 9 had the *R132S* mutation, and 3 had the *R132G* mutation; the mutation sites were unavailable for 5 patients (Figure 1A). Baseline characteristics analysis demonstrated that *IDH1*-mutated patients were significantly older at diagnosis than with *IDH1*-wild-type (WT) patients (56 [median, range 26-69] *vs*. 43 [median, range 14-85] years, respectively; $P<0.01$). Notably, *IDH1*-mutated patients showed significantly lower white blood cell (WBC) counts (2.6 [mean, interquartile range, IQR] 2.1-3.0] *vs*. 9.4 [mean, IQR 3.6-33.0] $\times 10^9$/L, respectively; $P=0.04$) and hemoglobin levels than IDH1-WT patients (70 [mean, IQR 57.5-84.5] *vs*. 89 [mean, IQR 67.0-114.3] g/L, respectively; $P<0.01$). For genetic alteration, a significantly lower frequency of *BCR*::*ABL1* fusion (0% *vs*. 34.6%; $P<0.01$) and a significantly higher frequency of BCOR (13.3% *vs*. 1.1%; $P<0.01$) mutation were found in *IDH1*-mutated patients compared with *IDH1*-WT patients. Regarding therapeutic outcomes, in comparison with the *IDH1*-WT group, the *IDH1*-mutated group exhibited lower complete remission (CR) rates (82% *vs*. 93%, respectively; $P=0.08$), higher relapse rates (53% *vs*. 30%, respectively; $P=0.07$), and higher mortality rates (32% *vs*. 16%, respectively; $P=0.09$) following standard chemotherapy protocols established by Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin[8] (Table 1). Consistently, *IDH1*-mutated patients had significantly worse event-free survival (EFS) compared to *IDH1*-WT patients (median 332 days *vs*. 446 days, respectively; $P=0.02$). Meanwhile, patients with *IDH1* mutation also tended to have worse overall survival (OS) and relapse-free survival (RFS) (Figure 1B). Through univariable and multivariable analysis, we found that *IDH1* mutation was an independent prognostic factor for poor EFS (univariable analysis: HR=1.882 [1.118-3.166]; $P=0.017$; multivariable analysis: HR=2.126 [1.168-3.867]; $P=0.014$) (*Online Supplementary Table S1*). These findings underscored the association between *IDH1* mutation and an aggressive clinical phenotype in the B-ALL cohort.

Our initially reported case with *IDH1*-mutated B-ALL presented with prominent cytoplasmic LD within leukemic blasts at diagnosis; that prompted us to conduct a systematic morphological analysis of B-ALL specimens in our centers. As revealed, cytoplasmic LD were obviously present in *IDH1*-mutated B-ALL blasts but were absent or minimal (<5%) in *IDH1*-WT cases in our cohort (Figure 1C). LD are specialized organelles primarily composed of neutral triglyceride (TG) and encased by a phospholipid monolayer,[9] and the accumulation of LD was reported to be caused by aberrant lipid metabolism, which promoted disease progression and predicted poor outcomes in a variety of cancers.[10] To explore the influence of *IDH1* mutation on lipid metabolism in B-ALL, RNA-sequencing (RNA-seq) was conducted to compare the transcriptomic profiles

of *IDH1*-mutated (N=7) with *IDH1*-WT (N=31) bone marrow blasts. The expression levels of mRNA in sequence data were calculated as RPKM (Reads Per Kilo-base per Million reads). The criteria of differential gene selection were $P<0.05$ and $|\log2(\text{fold change})|>2$. Gene Set Enrichment Analysis (GSEA) demonstrated significant enrichment of genes related to

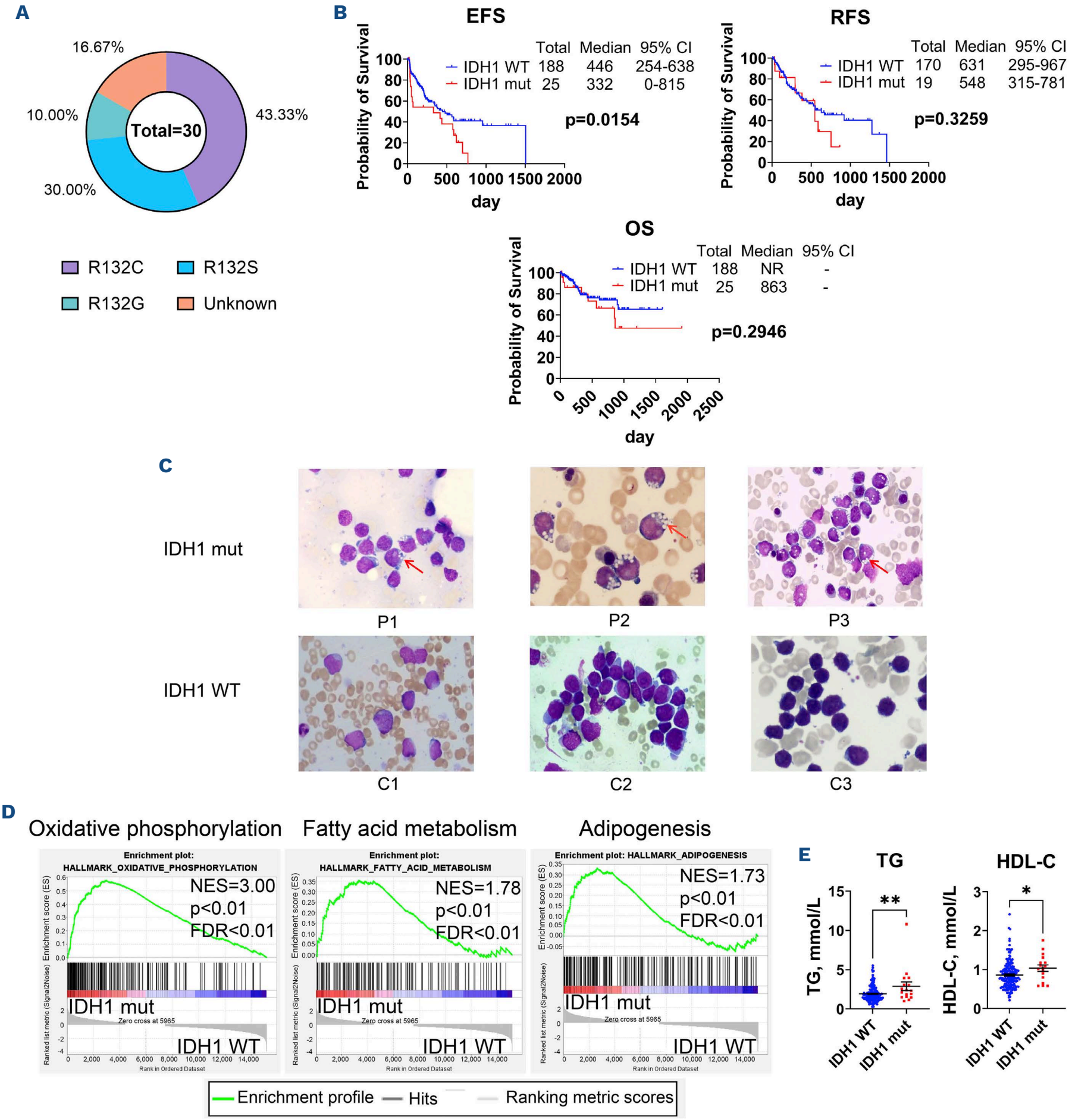

Figure 1. Characteristics of *IDH1*-mutated B-cell acute lymphoblastic leukemia patients. (A) Mutation types of *IDH1* gene in our B-cell acute lymphoblastic leukemia patients (B-ALL) patients. (B) Kaplan-Meier analysis of event-free survival (EFS), relapse-free survival (RFS), and overall survival (OS) for *IDH1*-mutated B-ALL patients. (C) Representative bone marrow morphology of *IDH1*-mutated (P1-P3) and *IDH1*-wild-type (WT) (C1-C3) B-ALL patients. Red arrows indicate the locations of prominent lipid droplets. (D) Gene Set Enrichment Analysis (GSEA)for the oxidative phosphorylation, fatty acid metabolism and adipogenesis pathways in IDH1-mutated *versus* *IDH1*-WT B-ALL samples. (E) Serum triglyceride (TG) and high-density lipoprotein-cholesterol (HDL-C) levels of *IDH1*-mutated *versus* *IDH1*-WT B-ALL patients at diagnosis. *$P<0.05$, **$P<0.01$.

oxidative phosphorylation, fatty acid metabolism and adipogenesis in *IDH1*-mutated cells, indicating a transcriptional reprogramming toward lipid metabolic activation (Figure 1D). Moreover, serum TG and high-density lipoprotein-cholesterol (HDL-C) levels were significantly elevated in *IDH1*-mutated patients (N=17) compared to *IDH1*-WT patients (N=177) at diagnosis (Figure 1E). These results indicated an aberrant lipid metabolism in *IDH1*-mutated B-ALL cells.

To further explore the correlation between *IDH1* mutation and LD as well as TG accumulation, we utilized the LD Assay Kit-Blue from Dojindo Molecular Technologies (Kumamoto, Japan) and the enzymatic TG measurement assay from Applygen Technologies (Beijing, China). Following 24-hour oleic acid (OA, 100 μM) treatment,[11] as a positive control, both BALL-1 and RS4-11 cell lines displayed significant increases in LD numbers and TG content (*Online Supplementary Figure S1A-C*). R-2HG is the well-known oncometabolite produced by *IDH1* mutation.[4,5] Strikingly, both R-2HG and *IDH1*^{R132S} mutation could significantly augment LD formation and TG biosynthesis (Figure 2A, B and *Online Supplementary Figure S1D-G*). Moreover, AG120 (ivosidenib, a mutant IDH1 protein inhibitor) treatment significantly reversed the lipid droplet accumulation phenotype (*Online Supplementary Figure S1H*). R-2HG was reported to inhibit growth of IDH WT AML cells.[12] In contrast to its inhibitory effect in AML cells such as MV4-11, our results demonstrated that R-2HG treatment sustained the proliferation of B-ALL cell lines including BALL-1, REH, and RS4-11 (*Online Supplementary Figure S2A-C*). Furthermore, we ectopically expressed the *IDH1*^{R132S} mutant in B-ALL cells, using pCDH1-MSCV-MCS-EF1-GreenPuro plasmid vector for lentivirus-mediated stable transfection, and found that *IDH1*^{R132S} overexpression sustained B-ALL cell proliferation and conferred apoptotic resistance under serum-free culture conditions (Figure 2C and *Online Supplementary Figure S2D-F*). Thus, *IDH1* mutation and its oncometabolite R-2HG directly contributed to aberrant lipid metabolism and sustained B-ALL cell proliferation.

To characterize global alterations in lipid-related metabolic profiles, we performed untargeted metabolomic profiling via mass spectrometry in *IDH1*^{R132S}-overexpressed and R-2HG-treated RS4-11 cells. Differentially abundant metabolites were identified using a combination of VIP (variable importance in projection) >1 and P<0.05 as being statistically significant (Figure 2D): 60 upregulated and 29 downregulated metabolites were identified in *IDH1*^{R132S}-overexpressed cells relative to control cells; 35 upregulated and 108 downregulated metabolites were identified in R-2HG treated cells relative to DMSO-treated ones. KEGG pathway enrichment analysis revealed significant upregulation of glycerophospholipid metabolism in both *IDH1*^{R132S}-overexpressed and R-2HG-treated RS4-11 cells (Figure 2E). Glycerophospholipids as well as sphingomyelins are the main components of biological membranes, including LD. As indicated, enhanced glycerophospholipid metabolism was a key metabolic signature of *IDH1*^{R132S}-mutated B-ALL, which potentially promoted LD formation.

Collectively, this study provides evidence that *IDH1* mutation is a prognostic biomarker predicting poor therapeutic response and adverse clinical outcomes in B-ALL, supporting its role in clinical risk stratification. Previous study by Yasuda *et al*. identified 7 *IDH1/IDH2*-mutated patients,[6] but only 4 of them were included in the subsequent survival analysis. As a result, *IDH1/IDH2* mutation as a predictor for poor prognosis was not conclusive enough in their study. By including a larger number of patients, our analysis has

Table 1. Baseline characteristics of IDH1-mutated and wild-type B-cell acute lymphoblastic leukemia patients.

Characteristics	B-ALL categories, N=218		
	***IDH1*-mutated**	***IDH1*-WT**	***P***
N	30	188	
Median age, years (range)	56 (26-69)	43 (14-85)	<0.01
Age, N (%) <35 ≥35	 2 (7) 28 (93)	 80 (43) 108 (57)	
Gender, N (%) Female Male	 17 (57) 13 (43)	 87 (46) 101 (54)	0.33
WBC count, x10^9/L, mean (IQR)	2.6 (2.1-3.0)	9.4 (3.6-33.0)	0.04
PLT count, x10^9/L, mean (IQR)	100 (79.5-129.5)	59 (30.5-131.0)	0.75
Hb, g/L, mean (IQR)	70 (57.5-84.5)	89 (67.0-114.3)	<0.01
BM blast, %, mean (IQR)	74 (61.0-88.8)	82 (66.0-90.0)	0.42
Cytogenetic features, N (%) Diploid Hyperdiploid Hypodiploid	 20 (91) 2 (9) 0	 126 (78) 24 (15) 11 (7)	0.31
Molecular features, N (%) *BCR*::*ABL1* *KMT2A*::*AFF1* *TCF3*::*PBX1* *TP53* mutation *BCOR* mutation *KMT2A* mutation *DNMT3A* mutation *NRAS* mutation *KRAS* mutation	 0 0 0 3 (10) 4 (13.3) 2 (6.7) 2 (6.7) 0 0	 65 (34.6) 4 (2.1) 7 (3.7) 16 (8.5) 2 (1.1) 2 (1.1) 3 (1.6) 21 (11.2) 16 (8.5)	 <0.01 >0.99 0.60 0.73 <0.01 0.09 0.14 0.09 0.14
Therapeutic outcomes, N (%) CR rate MRD negative rate Relapse rate Mortality rate	 18 (82) 15 (79) 10 (53) 8 (32)	 169 (93) 141 (81) 54 (30) 31 (16)	 0.08 0.76 0.07 0.09
BM transplantation, N (%)	7 (23)	79 (42)	0.07

B-ALL: B-cell acute lymphoblastic leukemia; BM: bone marrow; CR: complete remission; Hb: hemoglobin; IQR: interquartile range; MRD: minimal residual disease; N: number; PLT: platelets; WBC: white blood cell; WT: wild-type.

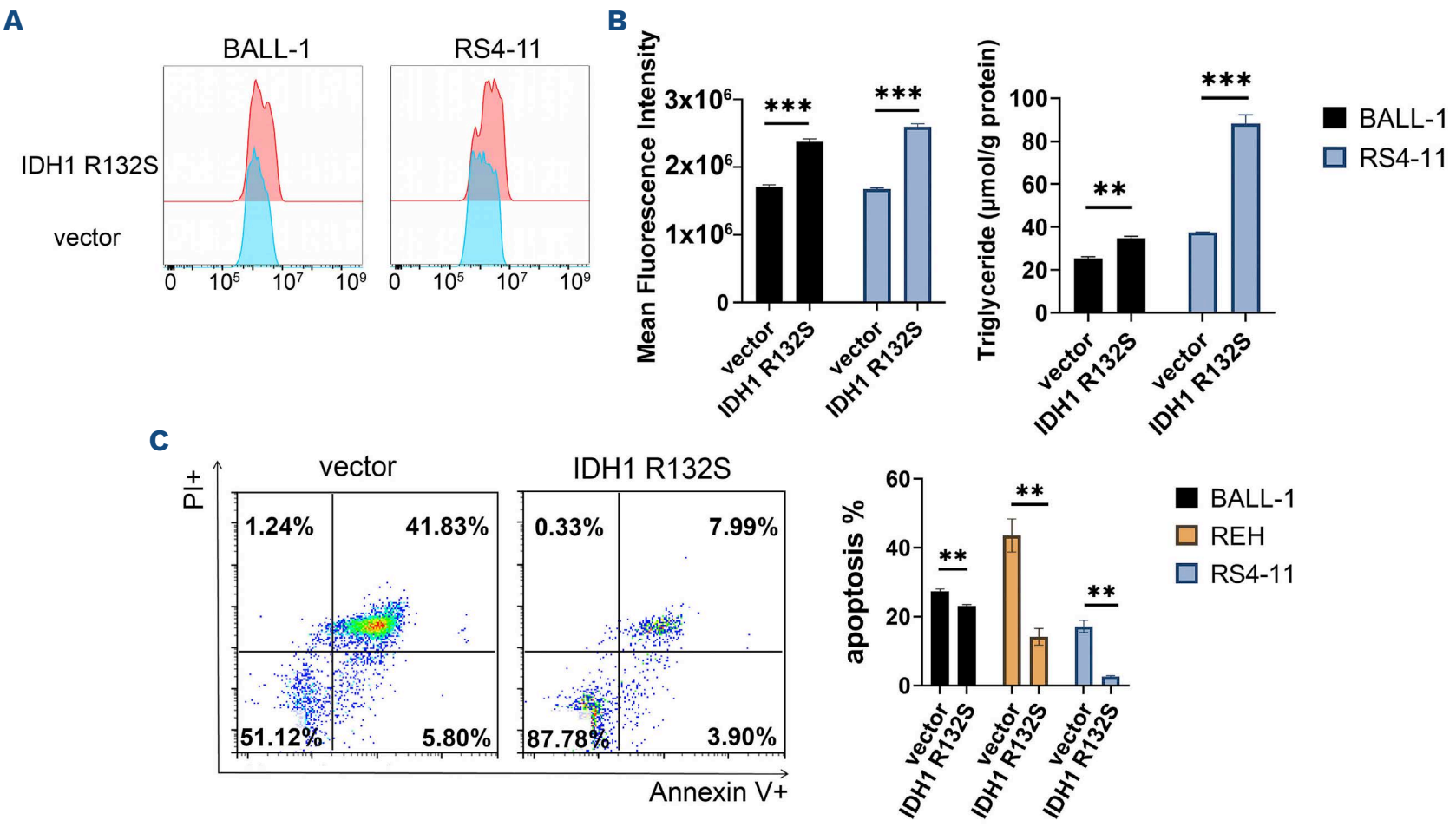

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Figure 2. *IDH1*^{R132S} conferred an oncogenic reprogramming of lipid metabolism in B-cell acute lymphoblastic leukemia patients. (A) Lipid droplets (LD) were stained with Lipi-Blue dye and measured by flow cytometry (FCM). The bar graph represented the mean fluorescence intensity of cells stained with Lipi-Blue dye. (B) Triglyceride (TG) levels were detected in B-cell acute lymphoblastic leukemia (B-ALL) cells with *IDH1*^{R132S} mutation. (C) Starvation (remove FBS for 72 hours)-induced apoptosis was detected in *IDH1*^{R132S}-overexpressed B-ALL cell lines. The representative FCM analysis of REH cells is shown: gating with the equivalent GFP positivity, cells for the vector control group (N=8,000) and IDH1-mutant group (N=5,000) were analyzed for apoptosis. (D) Dysregulated cell metabolites were analyzed by LC-MS/MS and GC-MS/MS in *IDH1*^{R132S}-mutated *versus* vector cells or R-2HG-treated *versus* DMSO-treated cells. (E) KEGG pathway analysis was conducted for upregulated cell metabolites in *IDH1*^{R132S}-mutated or R-2HG-treated groups were presented. Data are presented as mean ± Standard Error of Mean from three independent experiments (N=3). ***P*<0.01, ****P*<0.001.

provided robust evidence for the role of *IDH1* mutation in B-ALL. Therapeutically, small-molecule inhibitors targeting mutant IDH1 (e.g., ivosidenib) have demonstrated efficacy in newly diagnosed *IDH1*-mutated AML.[13] In contrast, clinical data on IDH1 inhibitors in B-ALL remain extremely scarce. Our findings position *IDH1* mutations and their associated lipid metabolic aberrations as potentially tractable therapeutic targets. It will be critical for future research to evaluate whether integrating *IDH1*-directed therapy with conventional chemotherapy can improve treatment responses and long-term survival in this patient subset.

A cornerstone of our work is the discovery of pervasive cytoplasmic LD accumulation in *IDH1*-mutated B-ALL blasts, a previously unrecognized morphological hallmark. We propose a lineage-specific model wherein the oncometabolite R-2HG promotes a net gain in lipid storage by driving lipogenesis that surpasses oxidative consumption. This metabolic reprogramming likely stems from the unique B-cell context, where transcription factors such as PAX5 or constitutive kinase signaling may synergistically amplify lipogenic signals.[14] This stands in contrast to *IDH1*-mutated AML, where R-2HG often co-operates with mutations that favor oxidative metabolism, accounting for the distinct metabolic phenotypes between these malignancies.[15] Notably, *IDH1*-mutated B-ALL may converge with ALL-L3 through shared MYC activation, providing a parallel route to LD accumulation.[7] Functionally, we posit that these LD are not passive reservoirs but active organelles integral to leukemic pathobiology. They may serve as a readily available energy source, modulate membrane fluidity and signaling, and critically, buffer against oxidative stress and ferroptosis, a multifaceted role that represents a compelling avenue for future investigation.

While our findings establish a strong association between *IDH1* mutation and LD accumulation, they do not elucidate the underlying causal relationship. Therefore, it remains to be determined whether the aberrant lipid metabolism actively drives LD biogenesis or merely occurs in parallel. Directly testing these competing hypotheses through isotopic tracing and genetic rescue experiments will be an important objective for future work.

Authors

Yu Qian,[1-4*] Dan Shen,[1-4*] Qing Ling,[1-4*] Shuqi Zhao,[1-4] Yutong Zhou,[1-4] Yanchun Zhao,[1-4] Xia Li,[1-4] Yungui Wang,[1-4] Jiansong Huang,[1-4] Jinghan Wang,[1-4] Wenjuan Yu,[1-4] Hongyan Tong,[1-4] Jie Sun,[1-4] Xiang Zhang[1-4] and Jie Jin[1-5]

[1]Department of Hematology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang; [2]Zhejiang Key Laboratory for Precision Diagnosis and Treatment of Hematological Malignancies, Hangzhou, Zhejiang; [3]Zhejiang Provincial Clinical Research Center for Hematological disorders, Hangzhou, Zhejiang; [4]Zhejiang University Cancer Center, Hangzhou, Zhejiang and [5]Jinan Microecological Biomedicine Shandong Laboratory, Jinan, People's Republic of China

**YQ, DS and QL contributed equally as first authors.*

Correspondence:
J. SUN - sunjiehm@zju.edu.cn
X. ZHANG - hillhardaway@zju.edu.cn
J. JIN - jiej0503@zju.edu.cn

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Disclosures

No conflicts of interest to disclose.

Contributions

JJ, XZ and JS designed the research study and supervised the experiments; YQ, DS and QL performed the research; YW and JH contributed essential reagents and tools; SZ, YZho, YZha and XL collected clinical samples and analyzed the data; HT and WY contributed their expertise in an advisory capacity to this study; YQ and XZ wrote the paper; JJ reviewed the paper. All authors read and approved the final version of the manuscript for publication.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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