Supplemental Information

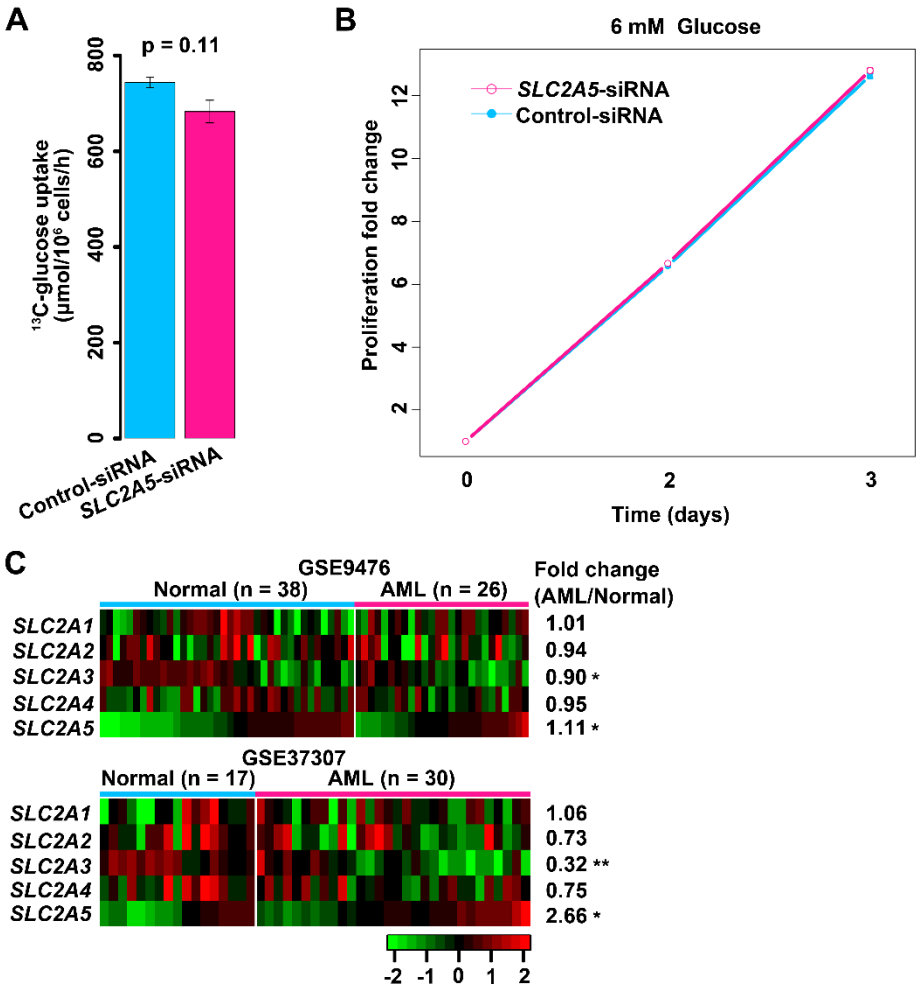

Figure S1. Related to Figure 1. (A,B) The influence of *SLC2A5* deletion on glucose uptake and glucose-induced proliferation in K562 cells; (C) The sugar transporter gene expression between normal hematopoietic cells and primary AML blast cells.

(A) Uptake of ^{13}C-glucose by K562 cells with or without *SLC2A5* deletion.

(B) Proliferation of K562 cells with or without *SLC2A5* deletion in complete medium containing 6 mM glucose.

(C) The expression of sugar transporter genes including *SLC2A1*, *SLC2A2*, *SLC2A3*, *SLC2A4* and *SLC2A5* between normal hematopoietic cells of healthy controls and AML blast cells of patients. The data were taken from public microarray database.

Error bars represent mean ± SEM. * $p < 0.05$, ** $p < 0.01$ (Student's t test).

Table S1. Related to Figure 1. Characteristics of AML cell lines included in the study.

Cell line	FAB	Cytogenetics	Genetic aberrance	Incidence	Prognosis
U937	M5	t(10;11)(p13;q14)	*CALM*/*AF10*	5% (Lillington et al., 1998)	High relapse risk
OCI-AML3	M4	Normal karyotype	Mutated *NPM1* and *DNMT3A*	30% (Lowenberg, 2008)	Poor survival; High relapse risk
HL-60	M2	Hypotetraploid	Amplified *c-Myc*	4% (Bruckert et al., 2000)	Intermediate risk
K562	M6	t(9;22)(q34;q11)	*BCR*/*ABL*	1-3% (Keung et al., 2004)	Poor risk; High relapse risk

Table S2. Related to Figure 1. Spearman correlation analysis between *SLC2A5* expression and fusion genes/gene mutations.

Fusion gene/gene mutation	GSE1159 (n = 260)		GSE425 (n = 111)		TCGA data (n = 173)	
	Correlation r	p	Correlation r	p	Correlation r	p
PML-RARA	-0.32	< 0.001	-0.33	< 0.001	/	/
AML1-ETO	0.26	< 0.001	0.28	0.003	/	/
CBFβ-MYH11	-0.18	0.004	-0.13	0.16	/	/
FLT3-ITD	0.20	0.001	0.03	0.80	/	/
CEBPA[ζ]	-0.26	< 0.001	/	/	/	/
NPM1	0.20	0.001	/	/	/	/
RUNX1	/	/	/	/	0.21	0.01

[ζ]Biallelic CEBPA mutations.

"/" indicates not available.

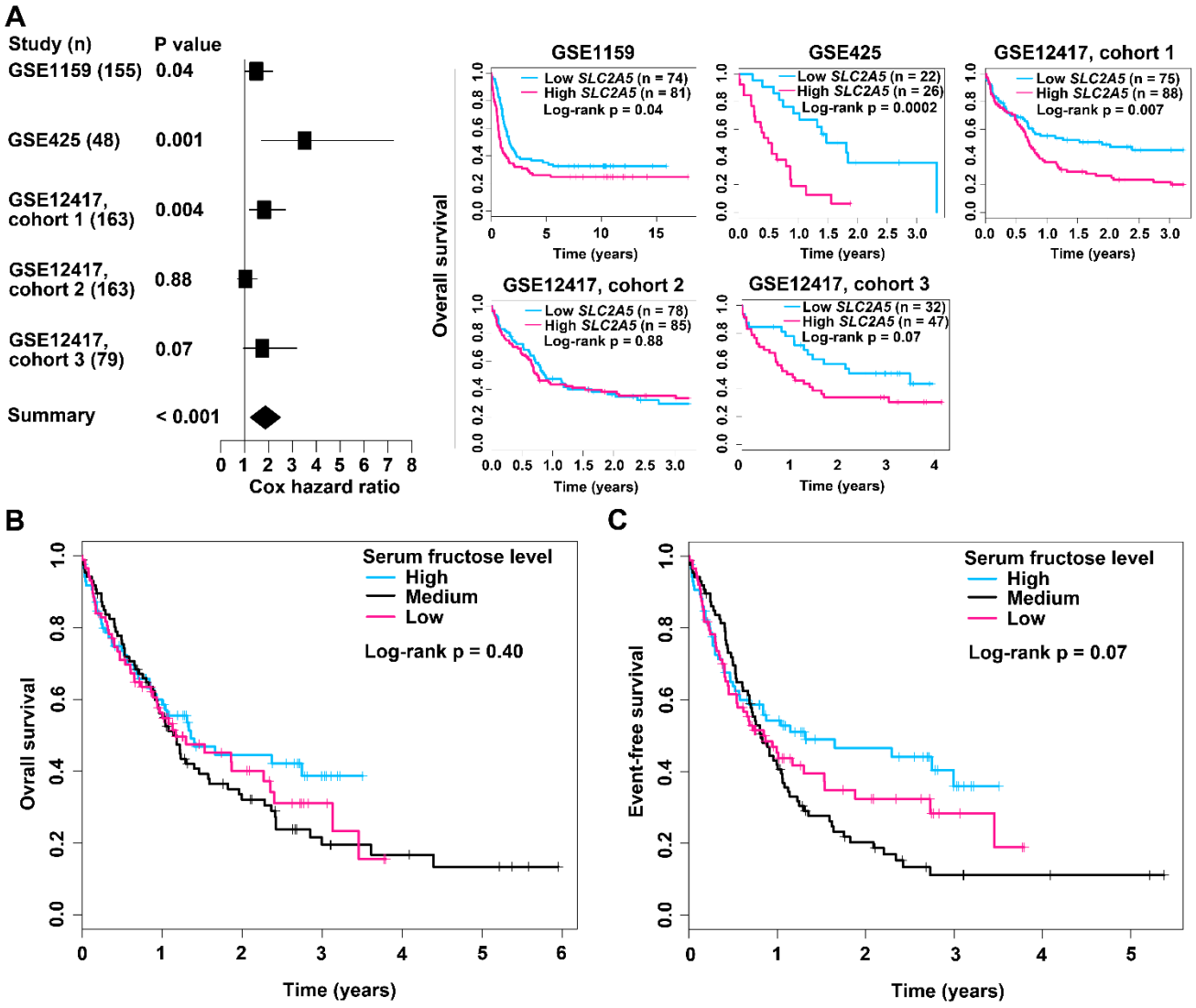

Figure S2. Related to Figure 2. The prognostic value analysis of different *SLC2A5* expression levels and distinct serum fructose concentrations in AML patients.

(A) (Left) Meta-analysis of Cox hazard ratio of *SLC2A5* expression levels in 5 data sets. The categorical values of *SLC2A5*, divided by the mean *SLC2A5* in each data set, were used in the analysis. (Right) Kaplan-Meier survival curves of AML patients of 5 data sets. Patients of each data set were divided into 2 groups using the mean *SLC2A5* expression as the cut-off value.

(B) Overall survival of 3 groups of AML patients divided by distinct serum fructose concentrations.

(C) Event-free survival of 3 groups of AML patients divided by distinct serum fructose concentrations.

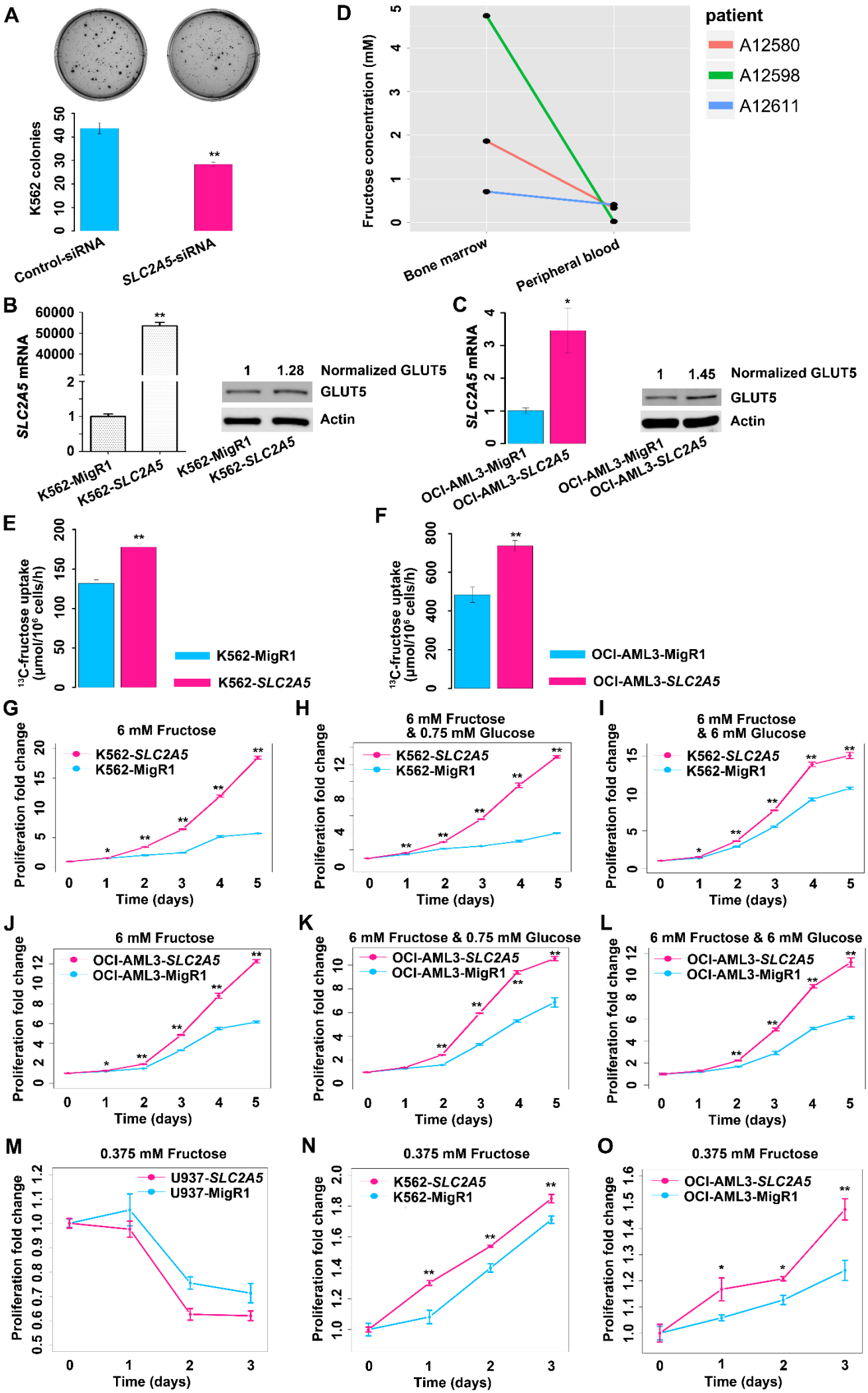
A
K562 colonies
Control-siRNA
SLC2A5-siRNA
D
Fructose concentration (mM)
Bone marrow
Peripheral blood
patient
A12580
A12598
A12611
B
SLC2A5 mRNA
K562-MigR1
K562-SLC2A5
1
1.28
Normalized GLUT5
GLUT5
Actin
C
SLC2A5 mRNA
OCI-AML3-MigR1
OCI-AML3-SLC2A5
1
1.45
Normalized GLUT5
GLUT5
Actin
E
13C-fructose uptake (µmol/10^6 cells/h)
K562-MigR1
K562-SLC2A5
F
13C-fructose uptake (µmol/10^6 cells/h)
OCI-AML3-MigR1
OCI-AML3-SLC2A5
G
6 mM Fructose
K562-SLC2A5
K562-MigR1
Proliferation fold change
Time (days)
H
6 mM Fructose & 0.75 mM Glucose
I
6 mM Fructose & 6 mM Glucose
J
6 mM Fructose
OCI-AML3-SLC2A5
OCI-AML3-MigR1
K
6 mM Fructose & 0.75 mM Glucose
L
6 mM Fructose & 6 mM Glucose
M
0.375 mM Fructose
U937-SLC2A5
U937-MigR1
N
0.375 mM Fructose
O
0.375 mM Fructose

Figure S3. Related to Figure 3. Enhanced fructose utilization mediated by *SLC2A5* promotes AML cell growth.

(A) Colony formation of K562 cells without or with suppressed *SLC2A5* expression. Cells were seeded at a density of 3000/well and fed with complete medium containing 6 mM fructose. Colonies were analyzed at day 30.

(B) Analysis of the expression of *SLC2A5*/GLUT5 in K562 cells transfected with the control MigR1 retrovirus (K562-MigR1) or MigR1-*SLC2A5* retrovirus (K562-*SLC2A5*) by Q-PCR and western blot respectively.

(C) Analysis of the expression of *SLC2A5*/GLUT5 in OCI-AML3 cells transfected with the control MigR1 retrovirus (OCI-AML3-MigR1) or MigR1-*SLC2A5* retrovirus (OCI-AML3-*SLC2A5*) by Q-PCR and western blot respectively.

(D) Fructose concentrations in paired peripheral blood and bone marrow samples from 3 AML patients.

(E) Uptake of ^{13}C-labeled fructose by K562-MigR1 and K562-*SLC2A5* cells.

(F) Uptake of ^{13}C-labeled fructose by OCI-AML3-MigR1 and OCI-AML3-*SLC2A5* cells.

(G-I) Proliferation of K562-MigR1 and K562-*SLC2A5* cells in complete media containing 6 mM fructose without glucose or with distinct levels of glucose.

(J-L) Proliferation of OCI-AML3-MigR1 and OCI-AML3-*SLC2A5* cells in complete media containing 6 mM fructose without glucose or with distinct levels of glucose.

(M) Proliferation of U937-MigR1 and U937-*SLC2A5* cells under 0.375 mM fructose condition.

(N) Proliferation of K562-MigR1 and K562-*SLC2A5* cells under 0.375 mM fructose condition.

(O) Proliferation of OCI-AML3-MigR1 and OCI-AML3-*SLC2A5* cells under 0.375 mM fructose condition.

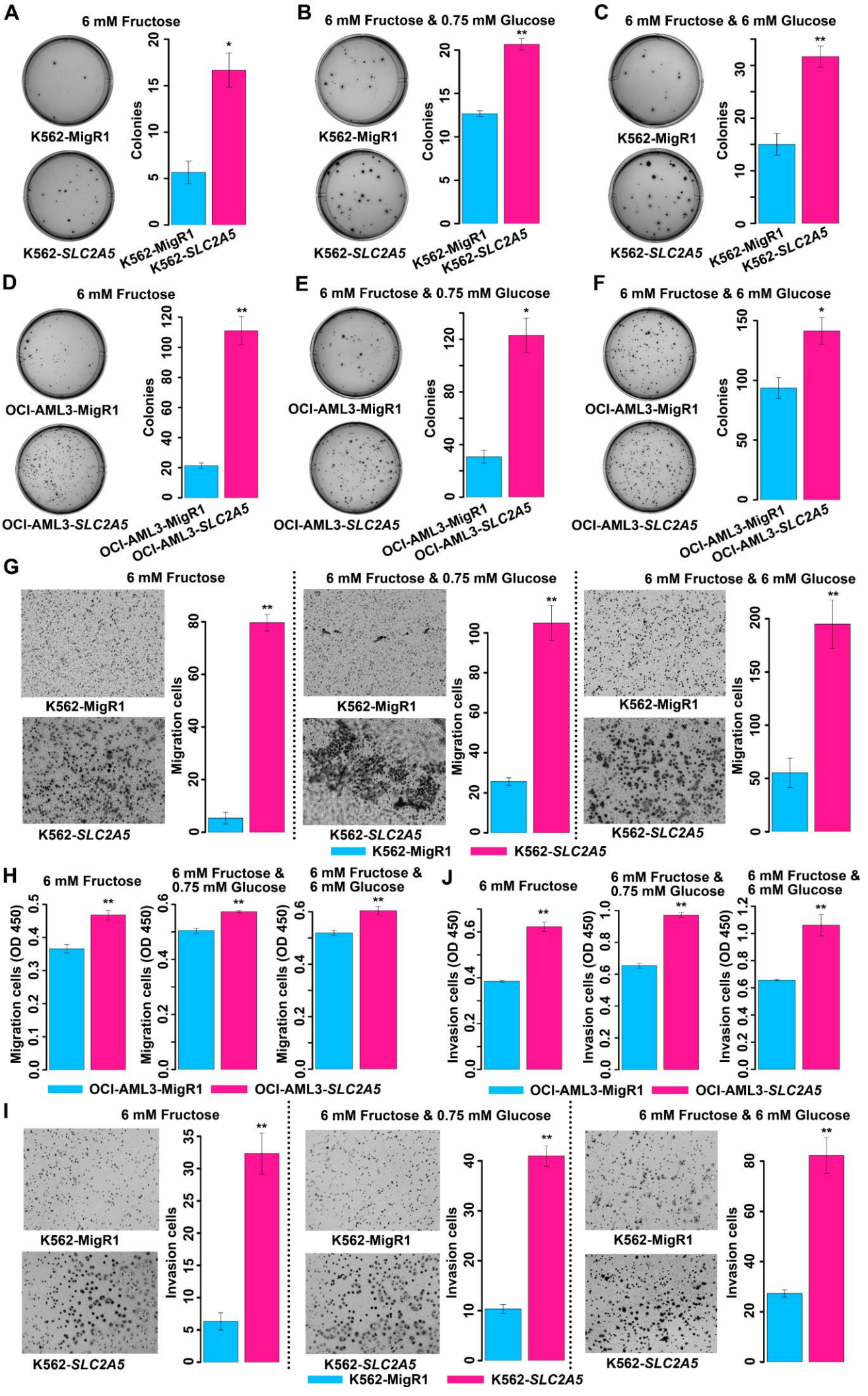
A
6 mM Fructose
K562-MigR1
K562-SLC2A5
Colonies
K562-MigR1
K562-SLC2A5
B
6 mM Fructose & 0.75 mM Glucose
K562-MigR1
K562-SLC2A5
Colonies
K562-MigR1
K562-SLC2A5
C
6 mM Fructose & 6 mM Glucose
K562-MigR1
K562-SLC2A5
Colonies
K562-MigR1
K562-SLC2A5
D
6 mM Fructose
OCI-AML3-MigR1
OCI-AML3-SLC2A5
Colonies
OCI-AML3-MigR1
OCI-AML3-SLC2A5
E
6 mM Fructose & 0.75 mM Glucose
OCI-AML3-MigR1
OCI-AML3-SLC2A5
Colonies
OCI-AML3-MigR1
OCI-AML3-SLC2A5
F
6 mM Fructose & 6 mM Glucose
OCI-AML3-MigR1
OCI-AML3-SLC2A5
Colonies
OCI-AML3-MigR1
OCI-AML3-SLC2A5
G
6 mM Fructose
K562-MigR1
K562-SLC2A5
Migration cells
6 mM Fructose & 0.75 mM Glucose
K562-MigR1
K562-SLC2A5
Migration cells
6 mM Fructose & 6 mM Glucose
K562-MigR1
K562-SLC2A5
Migration cells
K562-MigR1
K562-SLC2A5
H
6 mM Fructose
6 mM Fructose & 0.75 mM Glucose
6 mM Fructose & 6 mM Glucose
Migration cells (OD 450)
OCI-AML3-MigR1
OCI-AML3-SLC2A5
J
6 mM Fructose
6 mM Fructose & 0.75 mM Glucose
6 mM Fructose & 6 mM Glucose
Invasion cells (OD 450)
OCI-AML3-MigR1
OCI-AML3-SLC2A5
I
6 mM Fructose
K562-MigR1
K562-SLC2A5
Invasion cells
6 mM Fructose & 0.75 mM Glucose
K562-MigR1
K562-SLC2A5
Invasion cells
6 mM Fructose & 6 mM Glucose
K562-MigR1
K562-SLC2A5
Invasion cells
K562-MigR1
K562-SLC2A5

Figure S4. Related to Figure 3. Enhanced fructose utilization mediated by *SLC2A5* increases colony growth and migratory/invasive tendency of AML cells.

(A-C) Colony formation of K562-MigR1 and K562-*SLC2A5* cells in soft agar fed with complete media containing 6 mM fructose without glucose or with distinct levels of glucose. Cells were seeded at a density of 1,600/well (A) or 1,200/well (B) or 800/well (C). Colonies were assayed at day 23 (P and Q) or day 16 (R).

(D-F) Colony formation of OCIAML3-MigR1 and OCIAML3-*SLC2A5* cells in soft agar fed with complete media containing 6 mM fructose without glucose or with distinct levels of glucose. Cells were seeded at a density of 4,000/well (D) or 3,000/well (E) or 2,000/well (F). Colonies were assayed at day 16.

(G) Migration of K562-MigR1 and K562-*SLC2A5* cells fed with complete medium containing 6 mM fructose without glucose or with distinct levels of glucose.

(H) Migration of OCI-AML3-MigR1 and OCI-AML3-*SLC2A5* cells fed with complete medium containing 6 mM fructose without glucose or with distinct levels of glucose.

(I) Invasion of K562-MigR1 and K562-*SLC2A5* cells fed with complete medium containing 6 mM fructose without glucose or with distinct levels of glucose.

(J) Invasion of OCI-AML3-MigR1 and OCI-AML3-*SLC2A5* cells fed with complete medium containing 6 mM fructose without glucose or with distinct levels of glucose.

Error bars represent mean ± SEM. * $p < 0.05$, ** $p < 0.01$ (Student's t test).

Table S3. Related to Figure 3. Fructose concentrations in unpaired peripheral blood and bone marrow samples from patients with hematological malignancies.

Patient ID	Disease	Sample	Fructose (mM)	Fructose, median (range) (mM)	Wilcoxon p value
619	NHL	Peripheral blood	0.925	0.176 (0-1.456)	0.007
620	NHL	Peripheral blood	0.527		
621	NHL	Peripheral blood	0		
622	NHL	Peripheral blood	0.030		
623	AML	Peripheral blood	0.210		
624	NHL	Peripheral blood	0.138		
625	AML	Peripheral blood	0		
626	MM	Peripheral blood	0.143		
627	AML	Peripheral blood	1.043		
629	ALL	Peripheral blood	1.456		
630	AML	Bone marrow	5.162	1.492 (0.337-5.168)	
631	NHL	Bone marrow	1.192		
632	AML	Bone marrow	1.492		
633	AML	Bone marrow	5.168		
634	NHL	Bone marrow	0.618		
635	NHL	Bone marrow	0.337		
636	AML	Bone marrow	2.707		

Abbreviation: NHL, Non-Hodgkin's lymphomas; MM, Multiple myeloma; ALL, Acute lymphoblastic leukemia.

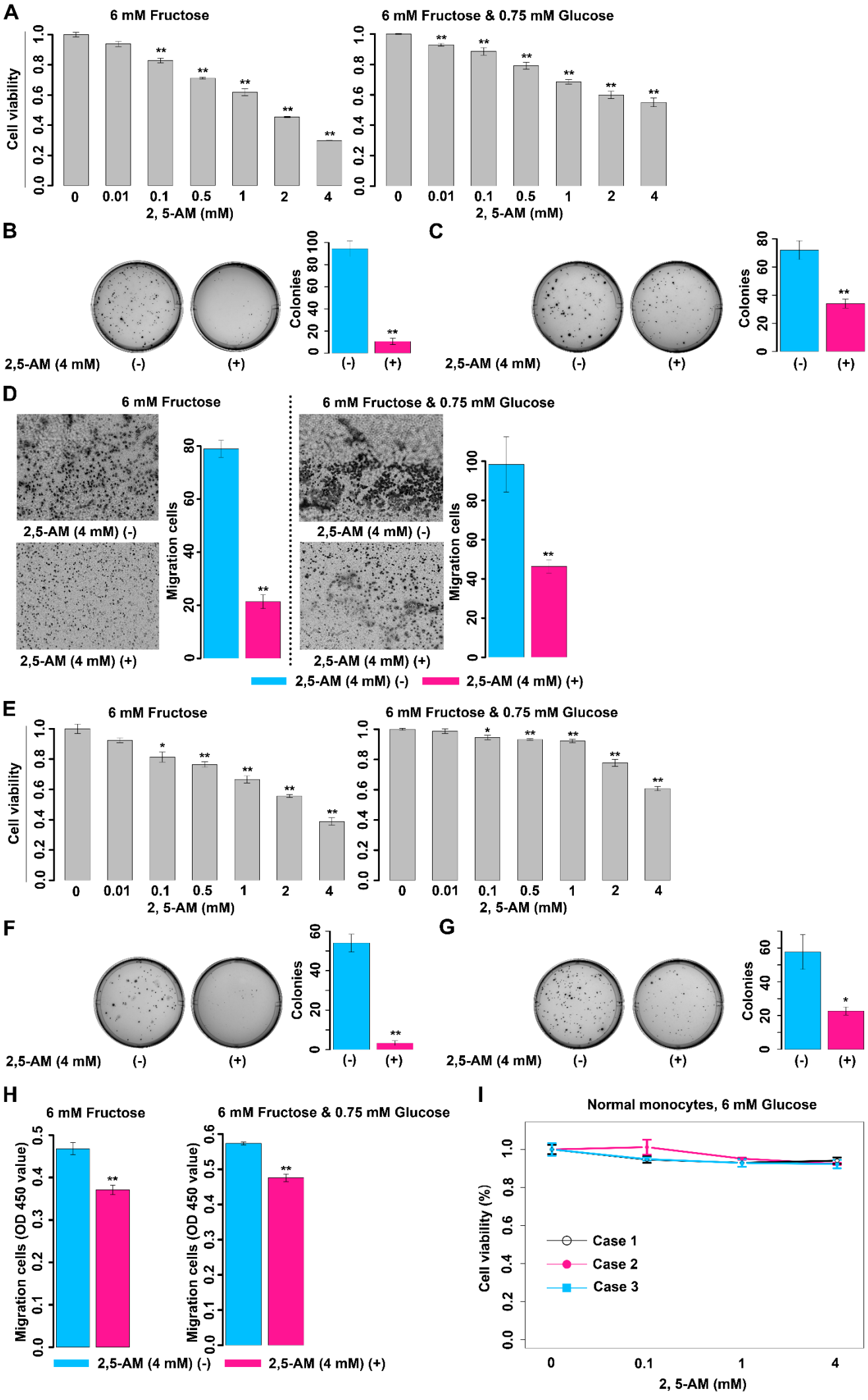
A
6 mM Fructose
6 mM Fructose & 0.75 mM Glucose
Cell viability
2, 5-AM (mM)
B
C
Colonies
2,5-AM (4 mM)
(-)
(+)
D
6 mM Fructose
6 mM Fructose & 0.75 mM Glucose
2,5-AM (4 mM) (-)
2,5-AM (4 mM) (+)
Migration cells
E
F
G
H
Migration cells (OD 450 value)
I
Normal monocytes, 6 mM Glucose
Cell viability (%)
Case 1
Case 2
Case 3

Figure S5. Related to Figure 5. Response of K562-*SLC2A5*, OCI-AML3-*SLC2A5* and normal monocytes to pharmacological blockage of fructose utilization.

(A) Suppressed proliferation of K562-*SLC2A5* cells treated with the fructose analogue 2,5-AM. Two carbon source conditions, 6 mM fructose and 6 mM fructose plus 0.75 mM glucose, were tested. P values were obtained by comparison with the proliferation of K562-*SLC2A5* cells in 0 mM 2,5-AM.

(B-C) The colony growth of K562-*SLC2A5* cells in soft agar under the condition of 6 mM fructose (B) or 6 mM fructose plus 0.75 mM glucose (C) with or without 2,5-AM treatment. Cells were seeded at a density of 2,000/well (B) or 1,500/well (C). Colonies were assayed at day 26.

(D) Migration assay of K562-*SLC2A5* cells with or without 2,5-AM treatment in medium containing 6 mM fructose or 6 mM fructose plus 0.75 mM glucose.

(E) Suppressed proliferation of OCI-AML3-*SLC2A5* cells treated with the fructose analogue 2,5-AM. Two carbon source conditions, 6 mM fructose and 6 mM fructose plus 0.75 mM glucose, were tested. P values were obtained by comparison with the proliferation of OCI-AML3-*SLC2A5* cells in 0 mM 2,5-AM.

(F-G) The colony growth of OCI-AML3-*SLC2A5* cells in soft agar under the condition of 6 mM fructose (F) or 6 mM fructose plus 0.75 mM glucose (G) with or without 2,5-AM treatment. Cells were seeded at a density of 4,000/well (F) or 3,000/well (G). Colonies were assayed at day 18 (F) or day 20 (G).

(H) Migration assay of OCI-AML3-*SLC2A5* cells with or without 2,5-AM treatment in medium containing 6 mM fructose or 6 mM fructose plus 0.75 mM glucose.

(I) Influence of the fructose analogue 2,5-AM on the glucose-induced proliferation of normal monocytes.

Error bars represent mean ± SEM. * $p < 0.05$, ** $p < 0.01$(Student's t test).

Table S4. Related to Figure 5. Combination indices for combination of fructose analogue 2,5-AM and Ara-C in AML cell lines as computed by CompuSyn.

Cell line	Carbon source	Agent combination	Combination index			
			ED50	ED75	ED90	ED95
U937	6 mM Fructose	2,5-AM + Ara-C	0.84	0.74	0.64	0.59
OCI-AML3	6 mM Fructose	2,5-AM + Ara-C	0.66	0.61	0.59	0.58
HL-60	6 mM Fructose	2,5-AM + Ara-C	0.48	0.29	0.17	0.12
K562	6 mM Fructose	2,5-AM + Ara-C	0.36	0.30	0.25	0.22
U937	6 mM Fructose + 0.75 mM Glucose	2,5-AM + Ara-C	0.96	0.71	0.65	0.65
OCI-AML3	6 mM Fructose + 0.75 mM Glucose	2,5-AM + Ara-C	0.92	0.84	0.75	0.72
HL-60	6 mM Fructose + 0.75 mM Glucose	2,5-AM + Ara-C	0.69	0.39	0.22	0.15
K562	6 mM Fructose + 0.75 mM Glucose	2,5-AM + Ara-C	0.18	0.25	0.35	0.44

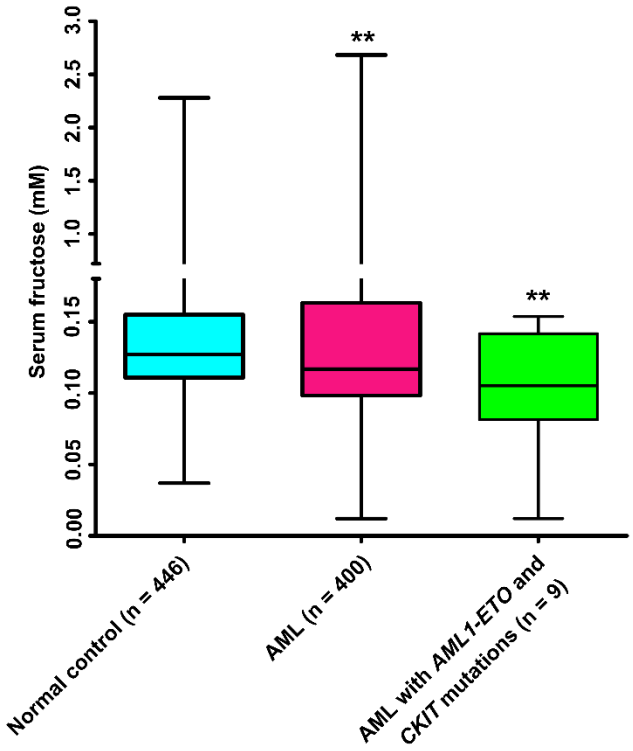

Figure S6. Related to Figure 6. Serum fructose concentrations in normal controls, patients with AML, and patients with AML harboring *AML1-ETO* and *C-KIT* mutations.

**p < 0.01 versus normal controls (Wilcoxon rank-sum test).

Table S5. Related to Figure 6. Description of the parameters among 5 mouse groups 17 days after leukemic cell transplantation.

Mouse group	PB blasts (%)	BM blasts (%)	Blasts in spleen (%)	WBC ($\times 10^9$/L)	RBC ($\times 10^{12}$/L)	HGB (g/L)	PLT ($\times 10^9$/L)	Spleen weight (g)
Normal controls (n = 6)	0	0	0	5.35 ± 0.09	9.53 ± 0.05	143.50 ± 1.10	1165.83 ± 17.06	0.09 ± 0.0008
Vehicle (n = 8)	82.33 ± 0.63	73.10 ± 1.36	89.57 ± 0.46	122.55 ± 1.93	4.65 ± 0.13	71.14 ± 1.88	345.33 ± 5.13	0.47 ± 0.004
2,5-AM (n = 8)	69.28 ± 1.53	61.85 ± 1.10	88.48 ± 0.30	79.63 ± 1.31	5.96 ± 0.07	91.63 ± 1.53	392.50 ± 4.62	0.42 ± 0.003
Ara-C (n = 6)	55.10 ± 0.99	56.82 ± 0.75	NA	56.03 ± 1.24	4.72 ± 0.22	71.67 ± 3.23	289.83 ± 10.25	NA
2,5-AM & Ara-C (n = 6)	41.66 ± 1.69	46.78 ± 1.04	89.48 ± 0.56	36.40 ± 1.66	8.04 ± 0.25	119.83 ± 3.53	487.25 ± 20.67	0.38 ± 0.005

All the parameter values were shown as mean ± standard error of mean.

PB, peripheral blood; BM, bone marrow; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet.

Supplemental experimental procedures

Cell Proliferation and Viability Assays

AML cells were harvested, rinsed twice in PBS and seeded into a 96-well plate at a density of 10,000 cells/well. For normal monocytes, cells were washed twice in PBS after thawing in a 37℃ water bath and then seeded into a 96-well plate at a density of 50,000 cells/well. Cells were grown in glucose-free RPMI 1640 (life technologies) containing 10% dialyzed FBS (dFBS, life technologies) (for AML cells) or 10% dFBS plus 5% human serum (Sigma) (for normal monocytes). For determination of the effect of fructose on cell proliferation, fructose solution was added in cells at a concentration range from 0 mM to 6 mM under defined glucose levels. For determination of the inhibitive effect of 2,5-anhydro-D-mannitol (2,5-AM) on fructose-induced cell proliferation, AML cells fed with 6 mM fructose, 6 mM fructose plus 0.75 mM glucose or 6 mM glucose were treated in a proper concentration range for this reagent. 2,5-AM and Ara-C were also used together to investigate their synergistic effects on AML cells. The drug concentration range for these experiments was set according to the suggested algorithm of CompuSyn software (ComboSyn, Inc., Paramus, NJ). Cell proliferation and cell viability were measured using a Cell Counting Kit-8 (CCK-8, Dojindo Laboratories) following the manufacturer's protocol at the time point(s) indicated in the figures or figure legends.

Overexpression of *SLC2A5* in AML Cells

A restriction endonuclease site of NcoI was added to the 2 ends of *SLC2A5* complementary DNA (cDNA) by polymerase chain reaction (PCR) with the following primers: 5'-CATGCCATGGAGCAACAGGATCAGAGC-3' and 5'-CATGCCATGGACTGTTCCGAAGTGACAGG-3'. The cDNA was then subcloned into MigR1 with the unique internal NcoI site. The insertion of the cDNA sequence into the vector was verified by Sanger sequencing. The retrovirus was produced as follows: empty MigR1 vector or MigR1 vector containing *SLC2A5* was cotransfected with VSVG and gag/pol plasmids into HEK293T cell using Lipofectamine 3000 (Life Technologies) following the manufacturer's instruction. Virus-containing supernatants were collected and filtered (0.45 μm filter) to remove cells. Subsequently, AML cells were infected with the control MigR1 virus or MigR1 virus expressing *SLC2A5* in the presence of 8 μg/mL polybrene. The green fluorescent protein (GFP)-positive cells were sorted 48 hours after infection using flow cytometry.

GLUT5 Expression Assay by Western Blot

Cells were washed twice with PBS (Life Technologies) and lysed in RIPA buffer (Sigma-Aldrich) containing 1% protease inhibitor cocktail (vol/vol, Sigma-Aldrich) on ice. Supernatants of cell lysates were obtained by centrifugation at 13,000 rpm for 15 minutes. Protein extracts were denatured by addition of sample buffer (Bio-rad) followed by boiling for 10 minutes, resolved by SDS-PAGE, and then transferred to PVDF membranes (Bio-rad). Subsequently, the membranes were blocked in Odyssey® Blocking buffer (Li-cor) and then incubated with GLUT5 or Actin primary antibodies. Primary antibodies were detected with fluorescent secondary antibodies (Li-cor).

Quantitative Real-time PCR (Q-PCR)

The expression of *SLCA2A5* was measured by Q-PCR. 18S rRNA was used as the internal control. The assay was conducted using Platinum® SYBR® Green qPCR SuperMix on a Roche Light Cycler® 480 Ⅱ PCR machine (Roche, Indianapolis, Indiana, US). The primers for human *SLCA2A5* were 5'-TCTGTAACCGTGTCCATGTTTC-3' (forward primer) and 5'-CATTAAGATCGCAGGCACGATA-3' (reverse primer). The primers for mouse *SLCA2A5* were 5'-TCTCTTCCAACGTGGTCCCTA -3' (forward primer) and 5'-GAGACTCCGAAGGCCAAACAG-3' (reverse primer). The primers for human 18S rRNA were 5'-CGGCGACGACCCATTCGAAC-3' (forward primer) and 5'- GAATCGAACCCTGATTCCCCGTC-3' (reverse primer). The primers for mouse 18S rRNA were 5'-GCAATTATTCCCCATGAACG-3' (forward primer) and 5'-GGCCTCACTAAACCATCCAA-3' (reverse primer).

Microarray Data and Gene Mutation Data Analysis

For the gene expression data sets including GSE 9476, GSE 37307, GSE 1159 and GSE 12417, raw data (CEL files) were

downloaded from the NCBI Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/). These data were normalized using MAS 5.0 algorithm (Gautier et al., 2004) followed with $\log_2$ transformation. For the data set GSE 425, online normalized data were used directly. Kaplan-Meier survival analysis and meta-analysis were performed using Bioconductor package "survcomp" (Schroder et al., 2011). All the analyses were performed with the use of R (version 2.15.0, www.r-project.org) and Bioconductor packages (Gentleman et al., 2004). TCGA gene mutation data were downloaded from the Cancer Genome Atlas database (http://cancergenome.nih.gov/).

Colony Formation Assay in Soft Agar

The colony formation assay was performed as previously described with minor changes (Rivera et al., 2012). Briefly, cells were harvested and rinsed twice in PBS to completely remove residual media. Then, cells were seeded on 0.35% top agarose (Sigma-Aldrich) overlaided onto solidified 0.7% agarose in glucose-free RPMI 1640 containing 10% dFBS and additive sugar(s) as indicated in figures. Cultures were fed every week. Colonies were analyzed at the time point indicated in figures or figure legends.

Migration and Invasion Assay

AML cell migration was assessed in Corning Transwell Permeable Supports with polycarbonate membranes (24-well plate, 8 μm pore size). AML cells were harvested, rinsed twice in PBS, resuspended in glucose-free and serum-free RPMI 1640 containing sugar(s) as indicated in figures, and seeded into the upper chambers of the transwell plates at a density of 2×10^5/well. The lower chamber of each well was filled with complete medium containing 10% dFBS and sugar(s) as indicated in figures. After incubation of 16 hours, migrating U937 and OCI-AML3 cells were measured using the CCK-8 kit. The migrating K562 cells were detected using the protocol previously reported (Dutta et al., 2010).

Invasion assays were performed using the Corning Biocoat Martrigel Invasion Chamber (24-well plate, 8 μm pore size). The Matrigel was rehydrated prior to use by adding warm glucose-free RPMI 1640 to the interior of the insert. AML cells were resuspended in glucose-free and serum-free RPMI 1640 containing sugar(s) as indicated in figures, and seeded into the upper chambers at a density of 1×10^6/well. After incubation for 16 hours, invading U937 and OCI-AML3 cells were counted using the CCK-8 kit, while invading K562 cells were detected using the protocol previously reported (Dutta et al., 2010).

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