SUPPLEMENTARY MATERIALS AND METHODS

Cell culture and reagents

The human multiple myeloma (MM) cell lines LME-1, MM1.S, XG-1, XG-3, LP-1, ANBL-6, UM-3, RPMI-8226, and B-cell malignancy cell lines (BCMCLs) JEKO-1, REC, GRANTA-519 (mantle cell lymphoma; MCL), RAJI, RAMOS (Burkitt lymphoma; BL), KMH2, L428, L540 (Hodgkin lymphoma; HL), RIVA, U2932 and HBL-1 (diffuse large B-cell lymphoma; DLBCL) were cultured at 37°C, 5% CO_2 in Iscove's modified Dulbecco medium (IMDM; Invitrogen Life Technologies, Carlsbad, CA) supplemented with 2 mM of L-glutamine (Gln), 100 U/mL of penicillin, 100 µg/mL of streptomycin (P/S; Gibco, Thermo Fisher Scientific, Waltham, MA), and 10% fetal calf serum (FCS; HyClone, GE Healthcare Life Sciences, Pittsburgh, PA) unless stated otherwise. XG-1, XG-3, and ANBL-6 were cultured in the presence of 1 ng/mL interleukin-6 (IL-6; Prospec Inc., Rehovot, Israel), which was removed before using these cell lines in experiments. In galactose-adaptation experiments, cells were cultured for 4 days at 37°C, 5% CO_2 in supplemented (Gln, P/S, 10% FCS) RPMI-1640 or in supplemented (Gln, P/S, 10% FCS) glucose-free RPMI-1640 with 11.1 mM galactose (Sigma Aldrich), prior to metabolic and viability analyses. The generation of CRISPR/Cas9 Knock out (KO) HMCL clones and MCL-1-overexpressing HCML has been described previously[1]. The following (small-molecule) inhibitors were used: MK2206 (AKT inhibitor; MedChemExpress, Monmouth Junction, NJ), GSK2110813 (AKT inhibitor; Selleck Chemicals, Houston, TX), sodium dichloroacetate (DCA; MedChemExpress). 2-deoxy-D-glucose (2-DG; Sigma Aldrich, St. Louis, MO).

Isolation of primary MM plasma cells, human peripheral blood mononuclear cells (PBMNCs), and purification of human peripheral blood B cells

Primary MM plasma cells were obtained from the bone marrow samples of two newly diagnosed patients with plasmacytosis of >80% (percent CD138+ CD38+ cells of mononuclear cells). Plasma cells were enriched by Ficoll-Paque (Cytiva Life Sciences, Marlborough, MA)

density centrifugation and overnight culture in supplemented IMDM (Gln, P/S, 10% FCS) with 1 ng/mL interleukin-6. Purity of primary MM plasma cells was assessed by flow-cytometry staining for CD138 and CD38 and was confirmed >95% prior to further experiments. PMBNCs from were isolated by Ficoll-Paque density centrifugation of buffy coats (obtained from 500 ml whole blood, Sanquin, Amsterdam, The Netherlands) from three healthy donors. To remove remaining red blood cells, cell pellets were resuspended in 10 ml 1x lysis buffer (Red Blood Cell Lysis Buffer, BioVision, San Fransisco, CA) and incubated for 10 min, in the dark at room temperature. B cells were purified using MACs cell separation (Pan B cell isolation Kit, Miltenyi Biotec, Bergisch Gladbach, Germany) according to manufacturer's protocol. B-cell purity was > 95% for all donors as confirmed by flowcytometry staining for CD19 (clone SJ25C1, BD Biosciences, Franklin Lakes, NJ). The isolated PMBNCs and purified B cells were cultured in at a density of 1x10e6/mL in 6 well-plates in supplemented MDM (Gln, P/S, 10% FCS) at 37°C, 5% CO_2 and activated with CpG oligodeoxynucleotides (5 μg/mL, CpG ODN 2006, Invivogen, Toulouse, France) for 48 hours prior to Seahorse XF metabolic profiling assays.

Metabolic profiling

The XF Cell Mito Stress Test and XF Glycolysis stress test were used to determine mitochondrial function (oxygen consumption rate; OCR) and glycolytic rate (extracellular acidification rate; ECAR), respectively, according to the manufacturer's protocol. For both protocols, XF Cell culture plates (Agilent, Santa Clara, CA) were precoated with Poly-D- lysine (50 µg/ml, Sigma Aldrich). For cell lines and for primary MM samples 50,000 cells were used per measurement, and for PBMNCs/purified B cells 100,000 cells were used. 5 to 6 replicate measurements were performed per sample/per analysis. For Seahorse analyses, cells were spun down in 50 µl of appropriately supplemented (according to the specific metabolic profiling assay) base medium (Dulbecco's modified eagle medium (DMEM); 31.6 mM NaCl, 45 µM phenol red, pH 7.4) in the precoated plates after which the volume was adjusted to 175 µl using supplemented base medium. The plates were then incubated for 1 hour at 37°C in a non-CO_2

incubator, after which OCR and ECAR were measured on a seahorse 96XFe analyser (Agilent). In the XF Glycolysis stress test basal medium was supplemented with 2 mM glutamine and the following compounds were injected during the assay at the final concentrations of 10mM glucose (A), 1.5 µM oligomycin (B) and 100mM 2-DG (C). Glycolysis was calculated by subtracting the non-glycolytic acidification (last ECAR value before injection A) from the highest ECAR value after injection A. The glycolytic reserve was calculated by subtracting the glycolysis from the glycolytic capacity (highest ECAR value after injection B – the non-glycolytic acidification). Glycolytic reserve as a % was calculated by dividing the glycolytic capacity by the glycolysis x 100.

For the XF Cell Mito Stress test, the base medium was supplemented with 25 mM D-glucose,1mM sodium pyruvate and 2mM glutamine (unless stated otherwise in the figure legends), during the assay, the following compounds were injected to final concentrations of 1.5 µM oligomycin (A), 2 µM FCCP (B) and 1.25 µM Rotenone + 2.5 µM Antimycin A (C). Basal respiration was calculated by subtracting the non-mitochondrial respiration rate (lowest OCR value after injection C) from the last OCR value before injection A. The spare respiratory capacity was calculated by subtracting the basal respiration from the maximal respiration (highest OCR value after injection B – the non-mitochondrial respiration rate). The spare respiratory capacity as a % was calculated by dividing the maximum respiration by the basal respiration value x 100.

Antibodies

Antibodies used in this study are: rabbit-anti-HK2 (Biorbyt, Cambridge, UK), rabbit-anti-PKM2 (clone D78A4), rabbit-anti-Phospho-FoxO1 (Thr24)/FoxO3a (Thr32), rabbit-anti-FoxO1 (clone C29H4), FoxO3a (clone 75D8), rabbit-anti-Phospho-Akt (Ser473) (clone D9E) XP, rabbit-anti-Akt1/2/3 (clone C67E7) (Cell signaling technologies, Beverly, MA), mouse-anti-PDH1 (clone 9H9AF5, Abcam, Cambridge, UK), rabbit-anti-Phospho-PDH-E1α (Ser293) (Sigma-Aldrich), mouse-anti β-actin (clone C4, Millipore, Burlington, USA).

2-NBDG assay

For the fluorescent glucose analog 2-NBDG flow cytometry assay, 100,000 cells were incubated in supplemented RPMI-1640 without glucose for 20 minutes at 37°C, 5% CO_2. 2-NBDG was added at a final concentration of 25 μM and incubated for 30 minutes at 37°C, 5% CO_2, or on ice as a negative control, after which the samples were analyzed by flow cytometry.

REFERENCES

1. Bloedjes TA, de Wilde G, Maas C, et al. AKT signaling restrains tumor suppressive functions of FOXO transcription factors and GSK3 kinase in multiple myeloma. *Blood Adv*. 2020;4(17):4151–4164.

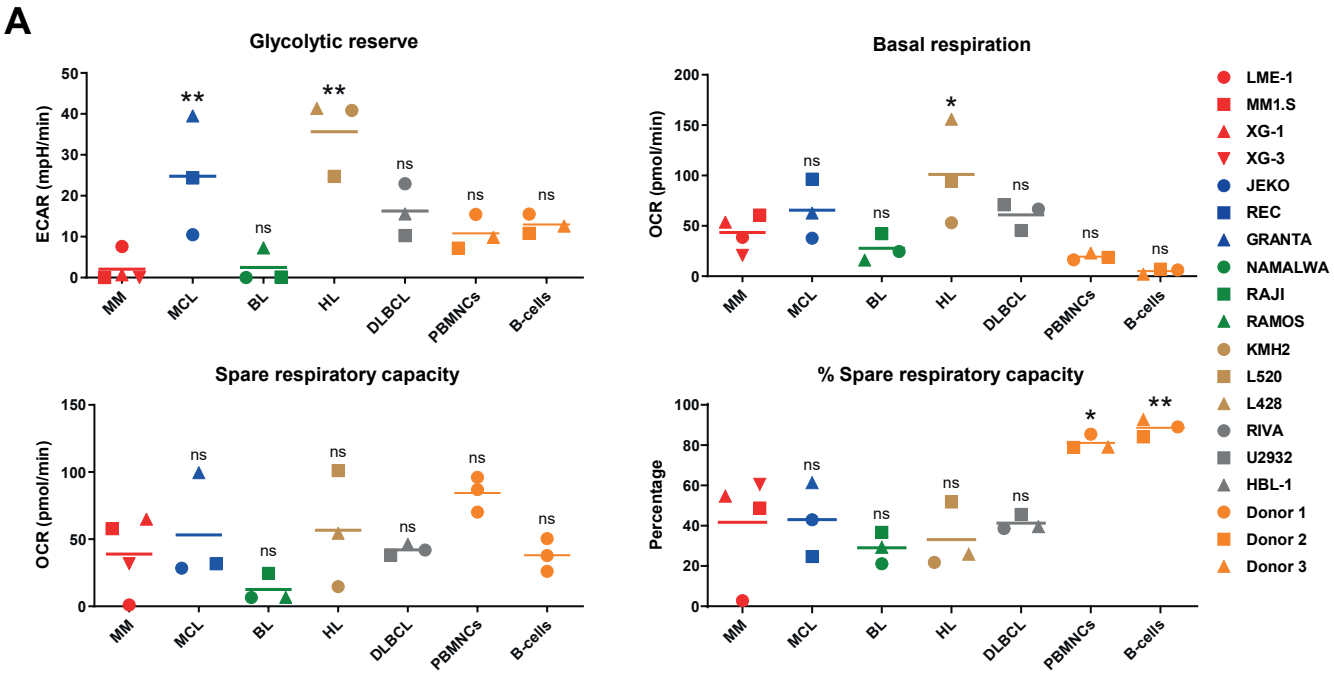
SUPPLEMENTARY TABLE S1. Leading edge genes from several metabolic GSEAs.
The leading-edge genes that contribute to core enrichment in the GSEAs for glycolysis - (HALLMARK_GLYCOLYSIS, KEGG_GLYCOLYSIS, REACTOME_GLYCOLYSIS or TCA cycle - (BIOCARTA_KREB_PATHWAY, GO_CITRATE_METABOLIC_PROCESS, MOOTHA-TCA, KEGG_CITRATE_CYCLE_TCA_CYCLE) or OXPHOS gene sets (KEGG_OXIDATIVE_PHOSPHORYLATION, HALLMARK_OXIDATIVE_PHOSPHORYLATION) (Fig 3B and Suppl. Fig. 3A-C) were combined in the LE_GLYCOLYSIS, LE_TCA_CYCLE or LE_OXPHOS gene sets.

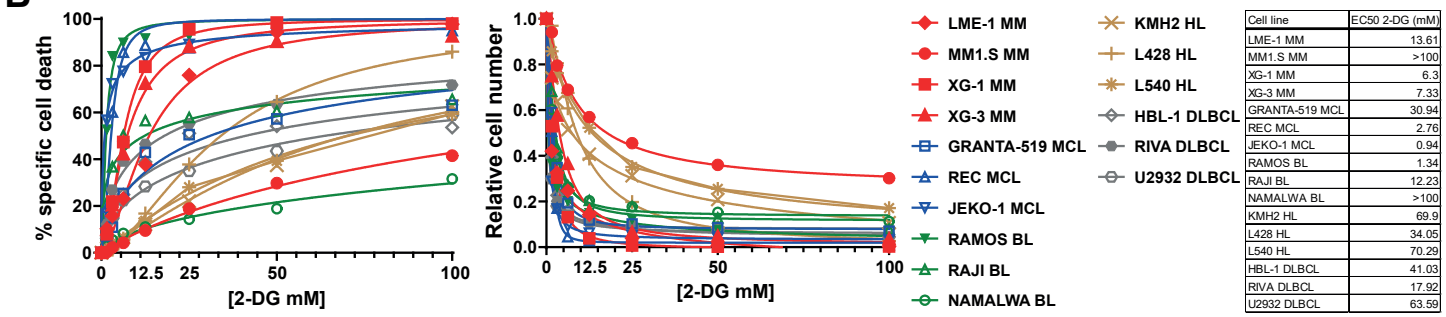
REACTOME_ GLYCOLYSIS	KEGG_ GLYCOLYSIS	HALLMARK_ GLYCOLYSIS	LE_ GLYCOLYSIS
AAAS	ADH1C	ABCB6	AAAS
ENO2	AKR1A1	AKR1A1	ABCB6
GAPDHS	ALDH1B1	ALG1	ADH1C
HK3	ALDH3A2	ANGPTL4	AKR1A1
NDC1	ALDOA	ARPP19	ALDH1B1
NUP107	BPGM	ARTN	ALDH3A2
NUP153	DLAT	AURKA	ALDOA
NUP160	DLD	B4GALT2	ALG1
NUP188	ENO2	CDK1	ANGPTL4
NUP205	ENO3	CENPA	ARPP19
NUP210	FBP1	CHST6	ARTN
NUP214	G6PC2	CLN6	AURKA
NUP35	HK1	COG2	B4GALT2
NUP37	HK3	CYB5A	BPGM
NUP62	LDHA	DEPDC1	CDK1
NUP93	LDHC	DLD	CENPA
NUP98	PDHA1	DSC2	CHST6
PFKFB1	PDHA2	ENO2	CLN6
PFKL	PDHB	FKBP4	COG2
PFKM	PFKL	G6PD	CYB5A
PGP	PFKM	GAPDHS	DEPDC1
PPP2R1B	PGAM1	GOT1	DLAT
PPP2R5D	PGK1	GOT2	DLD
PRKACA	PGM1	GPC1	DSC2
SEH1L	PGM2	HOMER1	ENO2
TPI1	PKM	HS2ST1	ENO3
	TPI1	KIF20A	FBP1
		LDHC	FKBP4
		MDH1	G6PC2
		MED24	G6PD
		MIF	GAPDHS
		MIOX	GOT1
		NASP	GOT2
		NSDHL	GPC1
		PAXIP1	HK1
		PC	HK3
		PFKFB1	HOMER1
		POLR3K	HS2ST1
		PPFIA4	KIF20A
		PRPS1	LDHA
		PSMC4	LDHC
		RPE	MDH1
		SAP30	MED24
		SDC1	MIF
		SDC2	MIOX
		SDC3	NASP
		SLC25A10	NDC1
		SLC37A4	NSDHL
		SRD5A3	NUP107
		STC1	NUP153
		STMN1	NUP160
		TALDO1	NUP188
		TFF3	NUP205
		TPI1	NUP210
		TPST1	NUP214
		TXN	NUP35
		VLDLR	NUP37
			NUP62
			NUP93
			NUP98
			PAXIP1
			PC
			PDHA1
			PDHA2
			PDHB
			PFKFB1
			PFKL
			PFKM
			PGAM1
			PGK1
			PGM1
			PGM2
			PGP
			PKM
			POLR3K
			PPFIA4
			PPP2R1B
			PPP2R5D
			PRKACA
			PRPS1
			PSMC4
			RPE
			SAP30
			SDC1
			SDC2
			SDC3
			SEH1L
			SLC25A10
			SLC37A4
			SRD5A3
			STC1
			STMN1
			TALDO1
			TFF3
			TPI1
			TPST1
			TXN
			VLDLR

BIOCARTA_ KREB_ PATHWAY	GO_ CITRATE_ METABOLIC_ PROCESS	MOOTHA_ TCA	KEGG_ CITRATE_ CYCLE_ TCA_CYCLE	LE_ TCA_CYLCE
ACO2	ACLY	ACO2	ACLY	ACLY
CS	ACO1	CS	ACO1	ACO1
FH	ACO2	FH	ACO2	ACO2
MDH1	CS	IDH3A	CS	CS
SUCLA2	IREB2	IDH3B	DLAT	DLAT
		IDH3G	DLD	DLD
		MDH2	FH	FH
		SDHB	IDH3A	IDH3A
		SDHC	IDH3B	IDH3B
		SDHD	MDH1	IDH3G
		SUCLA2	MDH2	IREB2
		SUCLG1	PC	MDH1
			PDHA1	MDH2
			PDHA2	PC
			PDHB	PDHA1
			SDHB	PDHA2
			SDHD	PDHB
			SUCLA2	SDHB
			SUCLG1	SDHC
			SUCLG2	SDHD
				SUCLA2
				SUCLG1
				SUCLG2

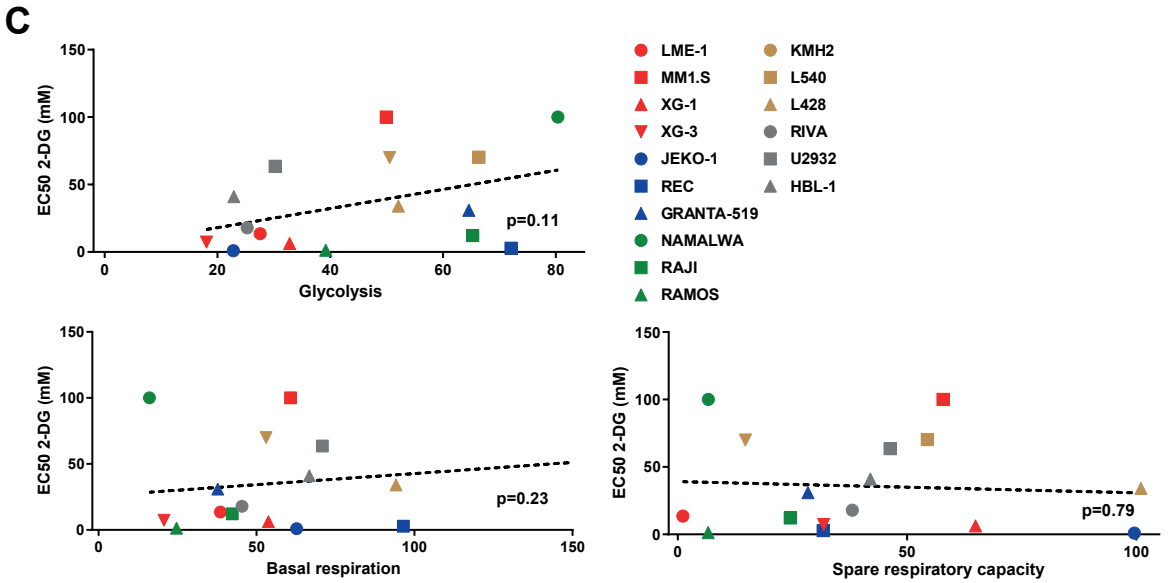
KEGG_ OXIDATIVE_ PHOSPHORYLATION	HALLMARK_ OXIDATIVE_ PHOSPHORYLATION	LE_ OXPHOS
ATP5F1B	ABCB7	ABCB7
ATP5F1C	ACAA2	ACAA2
ATP5F1E	ACADM	ACADM
ATP5MC1	ACAT1	ACAT1
ATP5MC3	AFG3L2	AFG3L2
ATP5ME	AIFM1	AIFM1
ATP5MF	ALAS1	ALAS1
ATP5PD	ALDH6A1	ALDH6A1
ATP5PF	ATP5F1B	ATP5F1B
ATP5PO	ATP5F1C	ATP5F1C
ATP6V0A2	ATP5F1E	ATP5F1E
ATP6V1A	ATP5MC1	ATP5MC1
ATP6V1B2	ATP5MC3	ATP5MC3
ATP6V1C1	ATP5ME	ATP5ME
ATP6V1D	ATP5MF	ATP5MF
ATP6V1E1	ATP5PD	ATP5PD
ATP6V1H	ATP5PF	ATP5PF
COX11	ATP5PO	ATP5PO
COX15	ATP6V1C1	ATP6V0A2
COX17	ATP6V1D	ATP6V1A
COX5A	ATP6V1E1	ATP6V1B2
COX5B	ATP6V1H	ATP6V1C1
COX6A1	BCKDHA	ATP6V1D
COX6C	BDH2	ATP6V1E1
COX7A2	COX11	ATP6V1H
COX7B	COX15	BCKDHA
COX7B2	COX17	BDH2
COX7C	COX5A	COX11
COX8A	COX5B	COX15
CYC1	COX6A1	COX17
NDUFA1	COX6C	COX5A
NDUFA10	COX7A2	COX5B
NDUFA2	COX7B	COX6A1
NDUFA4	COX7C	COX6C
NDUFA5	COX8A	COX7A2
NDUFA6	CS	COX7B
NDUFA8	CYB5A	COX7B2
NDUFA9	CYC1	COX7C
NDUFAB1	CYCS	COX8A
NDUFB1	DECR1	CS
NDUFB10	DLAT	CYB5A
NDUFB2	DLD	CYC1
NDUFB3	ECHS1	CYCS
NDUFB4	ECI1	DECR1
NDUFB6	ETFA	DLAT
NDUFB8	ETFB	DLD
NDUFB9	FH	ECHS1
NDUFC2	GLUD1	ECI1
NDUFS1	GOT2	ETFA
NDUFS2	GPI	ETFB
NDUFS5	HADHB	FH
NDUFS6	HCCS	GLUD1
NDUFS7	HSD17B10	GOT2
NDUFV1	HSPA9	GPI
NDUFV2	HTRA2	HADHB
PPA1	IDH1	HCCS
PPA2	IDH3A	HSD17B10
SDHA	IDH3B	HSPA9
SDHC	IDH3G	HTRA2
SDHD	IMMT	IDH1
UQCR10	ISCA1	IDH3A
UQCR11	LDHA	IDH3B
UQCRC1	LDHB	IDH3G
UQCRC2	LRPPRC	IMMT
UQCRFS1	MDH1	ISCA1
	MDH2	LDHA
	MRPL15	LDHB
	MRPL35	LRPPRC
	MRPS11	MDH1
	MRPS12	MDH2
	MRPS15	MRPL15
	MRPS30	MRPL35
	MTRR	MRPS11
	MTX2	MRPS12
	NDUFA1	MRPS15
	NDUFA2	MRPS30
	NDUFA4	MTRR
	NDUFA5	MTX2
	NDUFA6	NDUFA1
	NDUFA8	NDUFA10
	NDUFA9	NDUFA2
	NDUFAB1	NDUFA4
	NDUFB1	NDUFA5
	NDUFB2	NDUFA6
	NDUFB3	NDUFA8
	NDUFB4	NDUFA9
	NDUFB6	NDUFAB1
	NDUFB8	NDUFB1
	NDUFC2	NDUFB10
	NDUFS1	NDUFB2
	NDUFS2	NDUFB3
	NDUFS6	NDUFB4
	NDUFS7	NDUFB6
	NDUFV1	NDUFB8
	NDUFV2	NDUFB9
	NNT	NDUFC2
	OAT	NDUFS1
	OGDH	NDUFS2
	OPA1	NDUFS5
	PDHA1	NDUFS6
	PDHB	NDUFS7
	PDHX	NDUFV1
	PDP1	NDUFV2
	POLR2F	NNT
	PRDX3	OAT
	RHOT1	OGDH
	SDHA	OPA1
	SDHC	PDHA1
	SDHD	PDHB
	SLC25A11	PDHX
	SLC25A12	PDP1
	SLC25A20	POLR2F
	SLC25A4	PPA1
	SLC25A5	PPA2
	SUCLA2	PRDX3
	SUCLG1	RHOT1
	TIMM10	SDHA
	TIMM13	SDHC
	TIMM17A	SDHD
	TIMM50	SLC25A11
	TIMM8B	SLC25A12
	TOMM70	SLC25A20
	UQCR10	SLC25A4
	UQCR11	SLC25A5
	UQCRC1	SUCLA2
	UQCRC2	SUCLG1
	UQCRFS1	TIMM10
	VDAC1	TIMM13
	VDAC2	TIMM17A
	VDAC3	TIMM50
		TIMM8B
		TOMM70
		UQCR10
		UQCR11
		UQCRC1
		UQCRC2
		UQCRFS1
		VDAC1
		VDAC2
		VDAC3

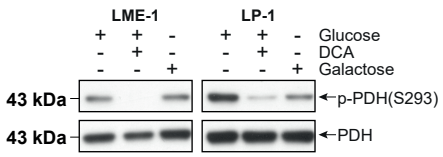
SUPPLEMENTARY FIGURE 1

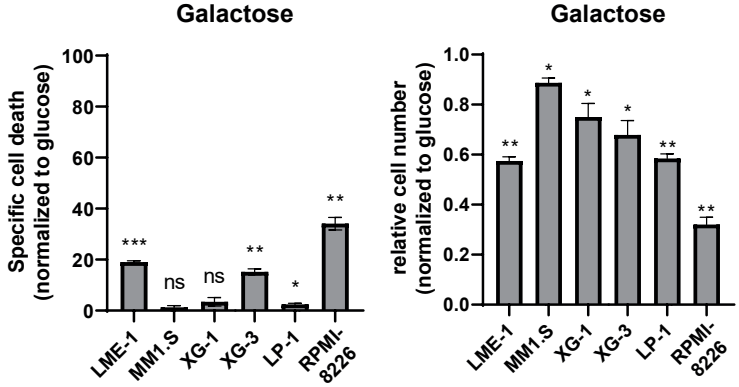




Cell line	EC50 2-DG (mM)
LME-1 MM	13.61
MM1.S MM	>100
XG-1 MM	6.3
XG-3 MM	7.33
GRANTA-519 MCL	30.94
REC MCL	2.76
JEKO-1 MCL	0.94
RAMOS BL	1.34
RAJI BL	12.23
NAMALWA BL	>100
KMH2 HL	69.9
L428 HL	34.05
L540 HL	70.29
HBL-1 DLBCL	41.03
RIVA DLBCL	17.92
U2932 DLBCL	63.59



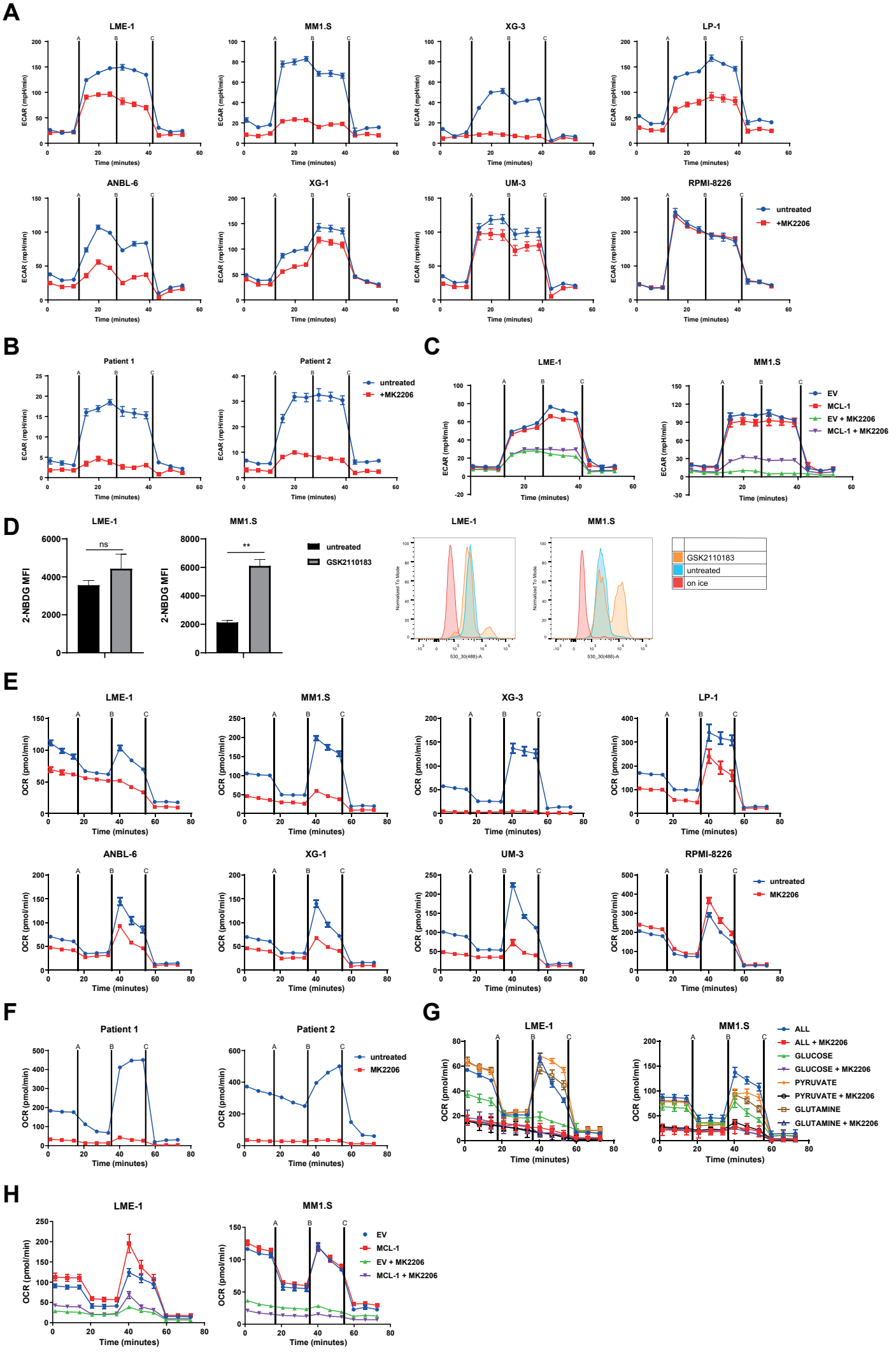




SUPPLEMENTARY FIGURE 1. 2-deoxy-D-glucose (2-DG) and galactose treatment reduces viability but does not not correlate with metabolic function in HMCLs

(A) Seahorse FX real-time metabolic profiling of HMCLs (red symbols), BCLs (blue, green, brown and grey symbols), activated PBMNCs and purified B cells (orange symbols). Mean values for Glycolytic reserve, based on extracellular acidification rates (ECAR), and mean values for basal respiration, spare respiratory capcity and % spare respiratory capacity based on oxygen consumption rates (OCR) are depicted (one-way ANOVA with Bonferroni's multiple comparisons test; HMCLs versus BCLs, *p<0.05, **p<0.01, ns = not significant, n=5 measurements for the HMCLs and BCLs, n=3 donors for PBMNCs and B-cells)**. (B)** Percent specific cell death (left panel) and relative cell numbers (middle panel) of HMCLs (red symbols and lines) and BCLs (blue, green, brown and grey symbols and lines) treated with increasing concentrations of 2-DG (1.56, 3.12, 6.25, 12.5 25, 50 and 100 mM) for 3 days. Corresponding EC50 values (cell death) are depicted in the table (right panel). Mean values of 3 independent experiments are shown. **(C)** Linear regression analysis of the mean glycolysis, basal respiration, and spare respiratory capacity values (y-axis) versus the EC50 specific cell death values for 2-DG (x-axis) in HMCLs (red symbols) and BCLs (blue, green, brown and grey symbols). **(D)** Immunoblot analysis of total and phosphorylated (Ser293) pyruvate dehydrogenase (PDH), in the HMCLs LME-1 and LP-1 incubated with 25 mM DCA for 20 hours, cultured in galactose-containing glucose-free medium for 20 hours, or left untreated. **(E)** Percent specific cell death of HMCLs incubated with galactose or glucose for 4 days (left panel, normalized to the glucose condition) and relative cell numbers, (right panel, normalized to the glucose condition). Mean values ± SEM of 3 independent experiments are shown, (one-sample t-test, *p<0.05, **p<0.01).

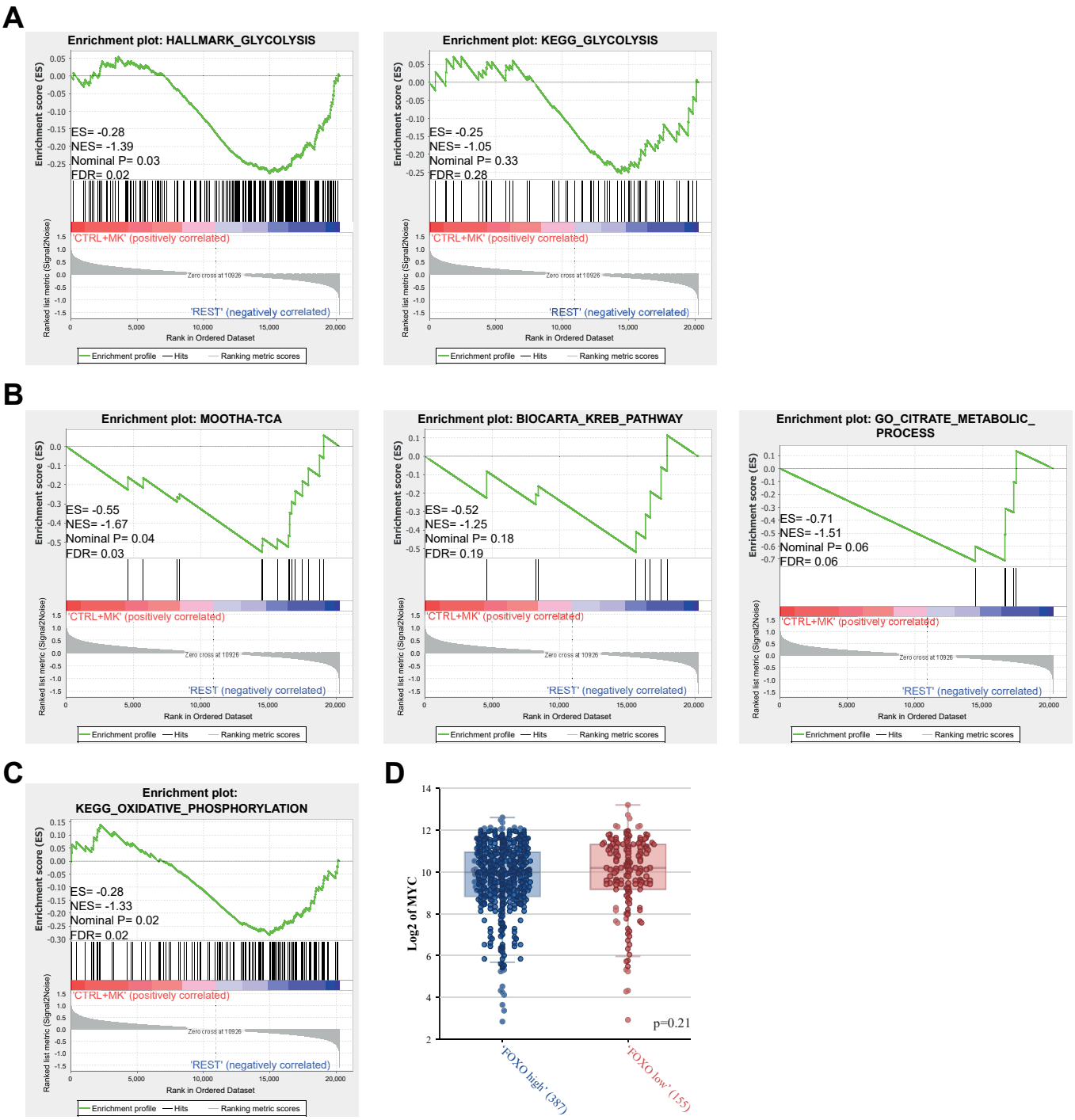
SUPPLEMENTARY FIGURE 2



SUPPLEMENTARY FIGURE 2. AKT sustains glycolysis and OXPHOS in MM cells

Seahorse XF glycolysis stress test profiles of HMCLs **(A)** and primary plasma cells from MM patients (n=2) **(B)** incubated with 2.5 µM MK2206 (AKT inhibitor) for 20 hours (red symbols and lines) or left untreated (blue symbols and lines). Means ± SEM (n=5-6 measurements) of the extracellular acidification rate (ECAR) values are shown, Seahorse XF glycolysis stress test injections are indicated (A=glucose, B=oligomycin, C=2-DG). **(C)** Seahorse XF glycolysis stress test profiles of HMCLs overexpressing MCL-1 (red and purple symbols and lines) or empty vector (EV) (blue and green symbols and lines) indicate that MCL-1 does not rescue AKT inhibitor-induced decrease in ECAR. HMCLs were treated with 2.5 µM MK2206 for 20 hours or left untreated, means ± SEM of the ECAR values are depicted. **(D)** Glucose analog (2-NBDG) uptake assay in LME-1 and MM1.S cells incubated with 2.5 µM GSK2110183 (AKT inhibitor) for 20 hours (grey bars), or left untreated (black bars). Bar graph depicts mean fluorescent intensity (MFI) (t-test, *p<0.05, **p<0.01, n=3) (left panel), representative flow cytometry histograms are shown (right panel). Seahorse XF mitochondrial stress test profiles of HMCLs **(E)** and primary plasma cells from MM patients (n=2) **(F)** treated with 2.5 µM MK2206 for 20 hours (red symbols and lines) or left untreated (blue symbols and lines). Means ± SEM of the oxygen consumption rate (OCR) values are depicted, Seahorse FX mitochondrial stress test injections are indicated (A=oligomycin, B=FCCP, C=rotenone & antimycin A). **(G)** Seahorse XF mitochondrial stress test profiles of LME-1 (left panel) and MM1.S (right panel) using glucose, pyruvate or glutamine as sole carbon sources, or in the presence of the combination of glucose, pyruvate and glutamine (green, yellow, brown and blue symbols and lines, respectively). Cells were treated with 2.5 µM MK2206 for 20 hours (red, purple, black and dark blue symbols and lines). Carbon sources were injected at time point t=0. Means ± SEM of the OCR values (n=5-6 measurements) are depicted. **(H)** Seahorse XF mitochondrial stress test profiles of HMCLs overexpressing MCL-1 (red and purple symbols and lines) or empty vector (EV) control cell lines (blue and green symbols and lines). MCL-1 does not restore the AKT inhibitor-induced decrease in OCR. HMCLs were incubated with 2.5 µM MK2206 for 20 hours, or left untreated. Means ± SEM (n=5-6 measurement) of the OCR values are depicted.

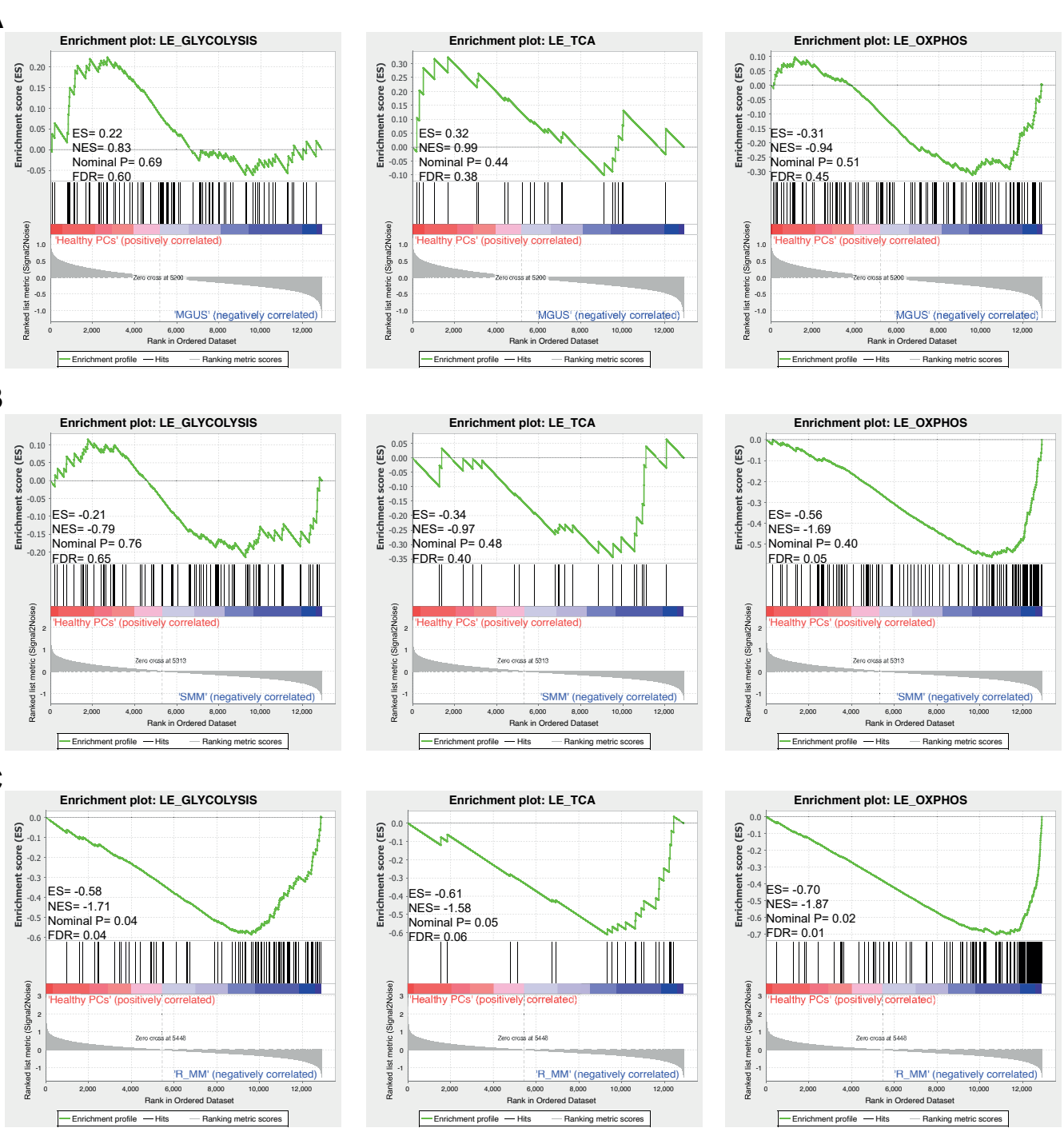
SUPPLEMENTARY FIGURE 3



SUPPLEMENTARY FIGURE 3. FOXO represses the expression of genes involved in glycolysis, the TCA-cycle and OXPHOS

(A-C) Gene set enrichment analysis (GSEA) of Cas9-control (CTRL) HMCL clones treated overnight with 2.5 µM MK2206 ('CTRL+MK') versus the combination of untreated CTRL clones and FOXO knockout clones, either treated overnight with 2.5 µM MK2206 or left untreated ('REST'). Datasets from the HMCLs LME1, MM1.S and XG-3 were combined for GSEA. Enrichment plots for HALLMARK_GLYCOLYSIS, KEGG_GLYCOLYSIS, MOOTHA_TCA, BIOCARTA_KREBB_PATHWAY, GO-CITRATE_METABOLIC_PROCESS and KEGG_OXIDATIVE_PHOSPHORYLATION gene sets are shown. FDR, ES, NES and p-values are shown in the plots. **(D)** MM patient groups defined by k-means clustering were labeled as 'FOXO high' (n=387) and 'FOXO low' (n=155). Depicted are the normalized Log2 transformed microarray gene expression levels of MYC as boxplots for the 'FOXO high'and 'FOXO low' patient groups (each circle represents the mRNA levels of a different patient, p=0.21, ANNOVA)

SUPPLEMENTARY FIGURE 4



SUPPLEMENTARY FIGURE 4. FOXO repressesed metabolic genes are upregulated in MM disease progression.

(A-C) GSEA enrichments plots show enrichment of the FOXO-regulated LE_GLYCOLYSIS, LE_TCA_CYCLE and LE_OXPHOS gene sets (see table S1) in plasma cells from MGUS patients (MGUS, n=21), smouldering MM patients (SMM, n=23) or relapsed MM patients (R_MM, n=27) compared to plasma cells from healthy donors (Healthy PCs, n=15). FDR, ES, NES and p-value, are depicted in the plots.