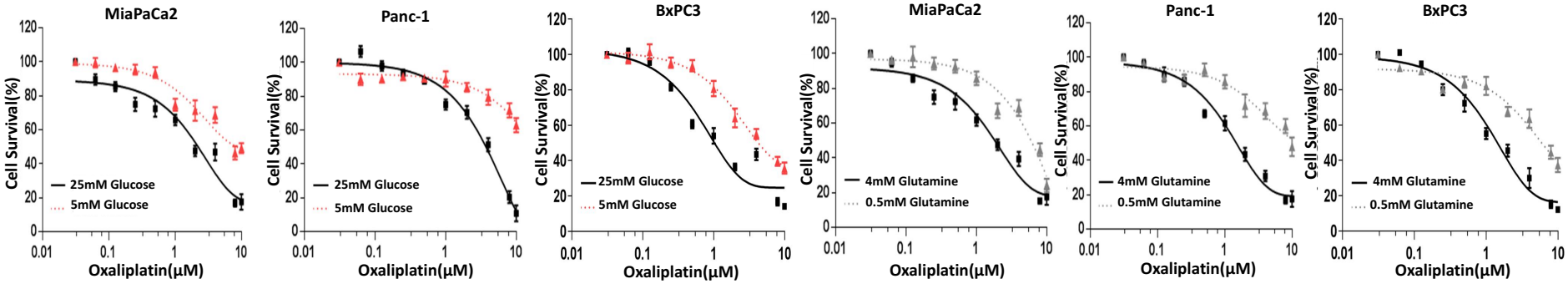
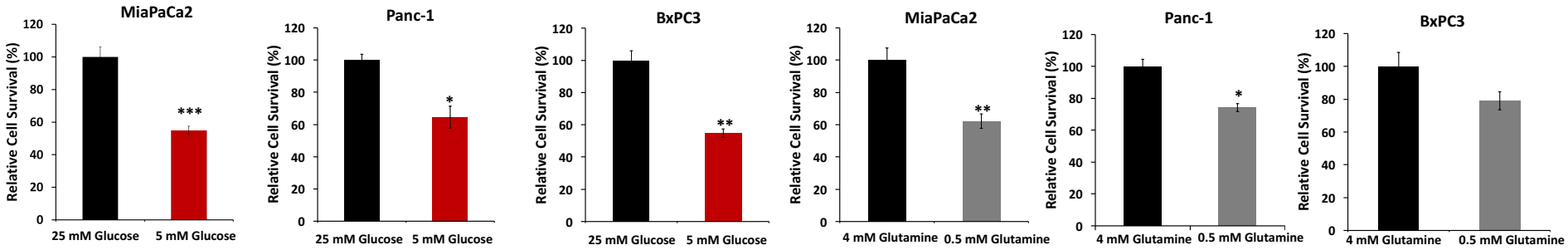
A



Oxaliplatin IC50 Values(±SEM),μM

	25 mM Glucose	5mM Glucose	Fold Difference 5 mM VS 25mM	p-value(two-tailed)	4mM Glutamine	0.5mM Glutamine	Fold Difference 0.5 mM VS 4mM	p-value(two-tailed)
MiaPaCa2	1.82 (0.041)	8.22 (0.53)	4.51	< 0.0047	1.63 (0.034)	5.41 (0.037)	5.61	< 0.001
Panc-1	3.25 (0.027)	>10	>10	NA	1.52 (0.033)	>10	>10	< 0.0032
BxPC3	1.37 (0.064)	6.98 (0.06)	5.09	< 0.0026	1.44 (0.068)	8.653 (0.012)	6.09	< 0.001

B



C

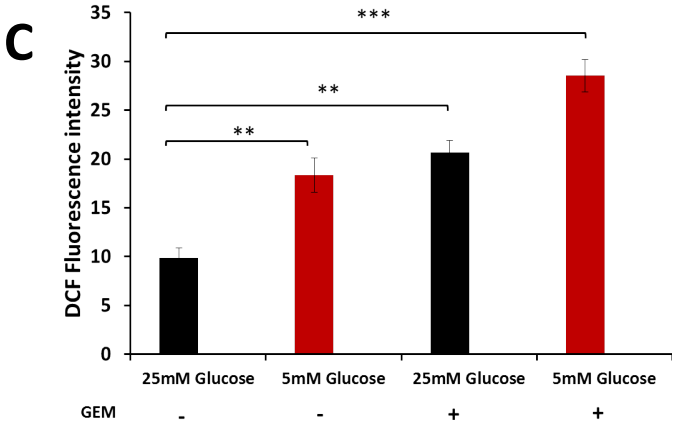


Figure S1

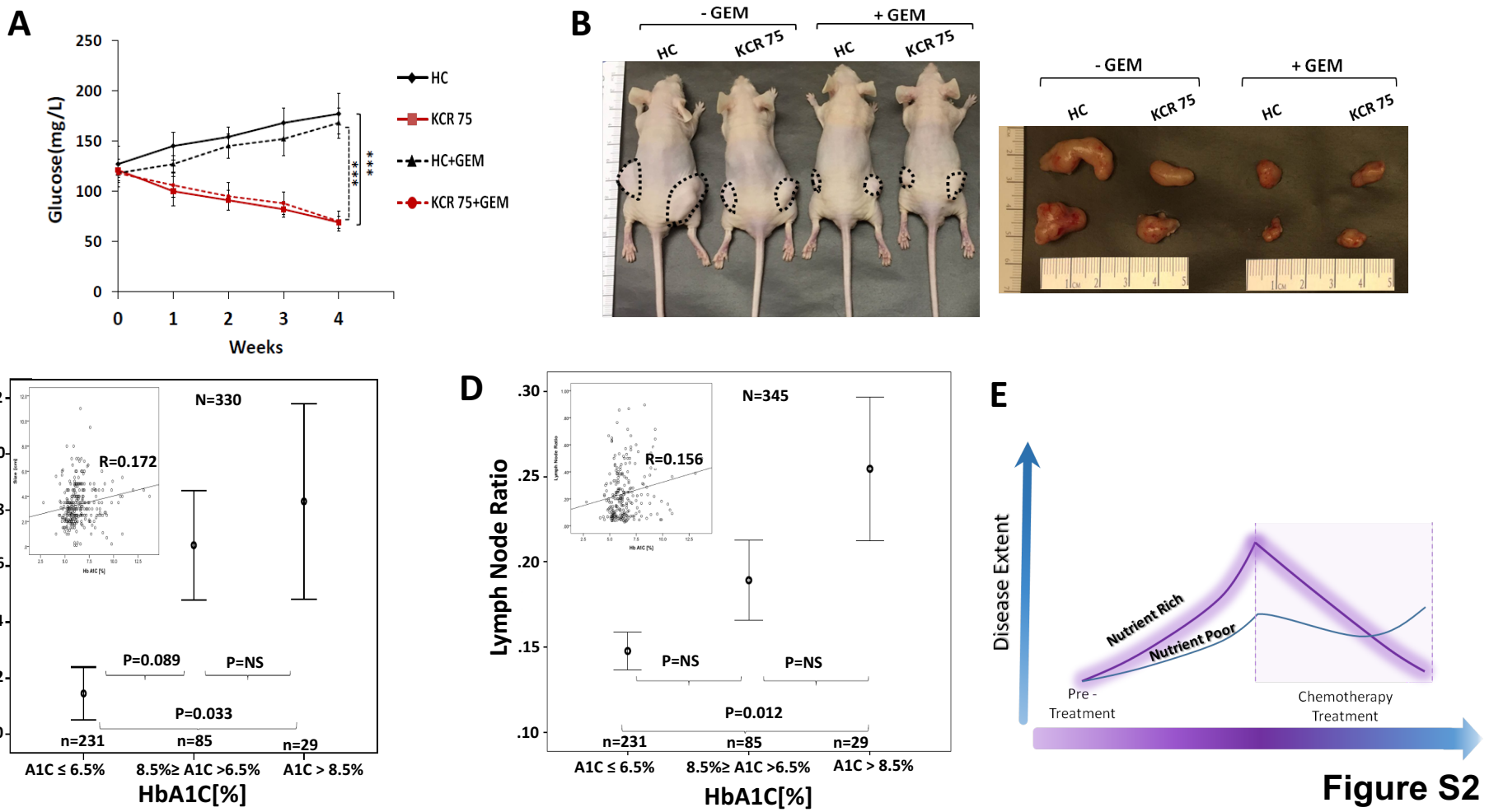

A
Glucose(mg/L)
Weeks
HC
KCR 75
HC+GEM
KCR 75+GEM
***
***
B
- GEM
+ GEM
HC
KCR 75
C
Size[cm]
N=330
R=0.172
P=0.089
P=NS
P=0.033
n=231
n=85
n=29
A1C ≤ 6.5%
8.5%≥ A1C >6.5%
A1C > 8.5%
HbA1C[%]
D
Lymph Node Ratio
N=345
R=0.156
P=NS
P=NS
P=0.012
n=231
n=85
n=29
A1C ≤ 6.5%
8.5%≥ A1C >6.5%
A1C > 8.5%
HbA1C[%]
E
Disease Extent
Nutrient Rich
Nutrient Poor
Pre - Treatment
Chemotherapy Treatment

Figure S2

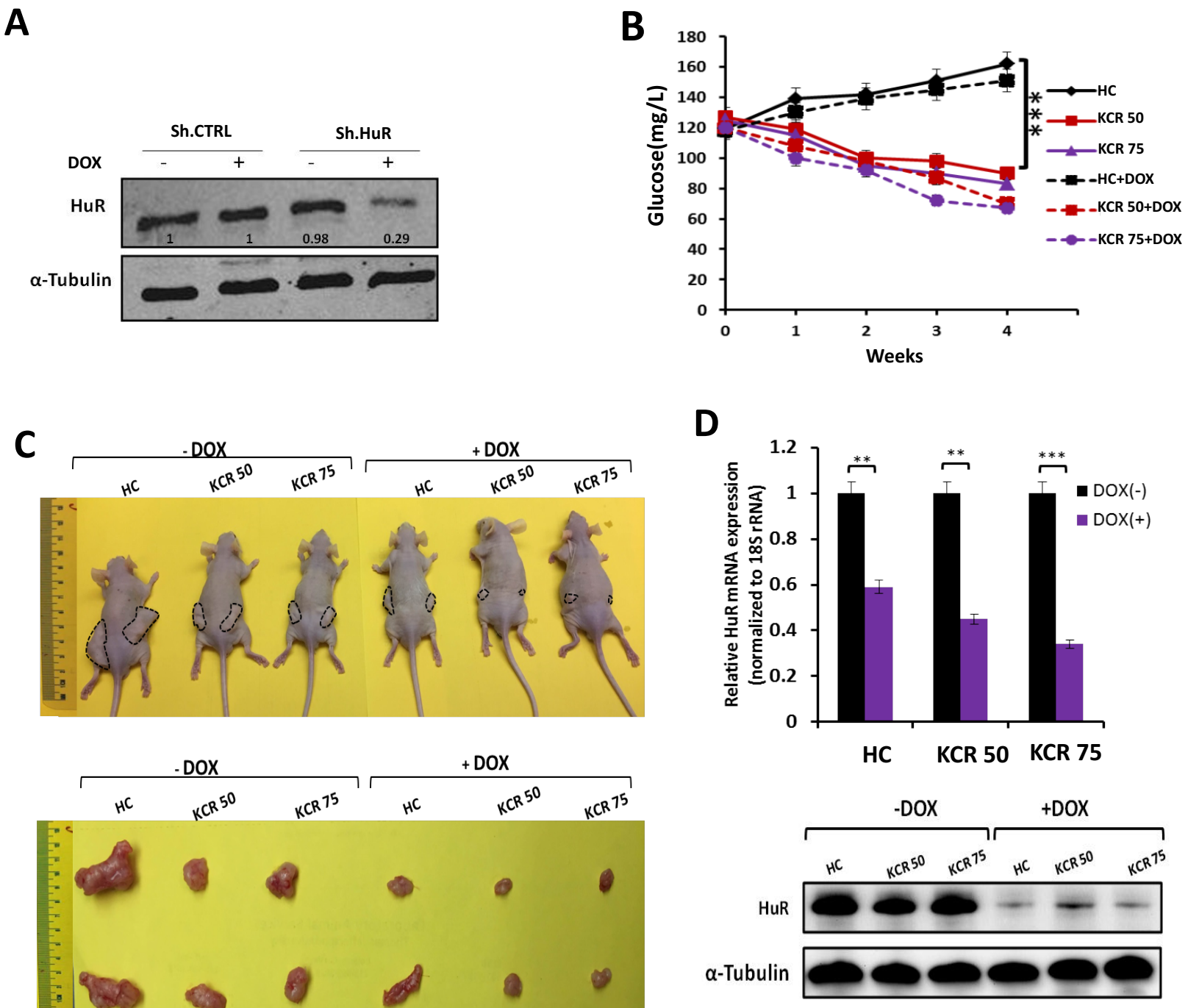
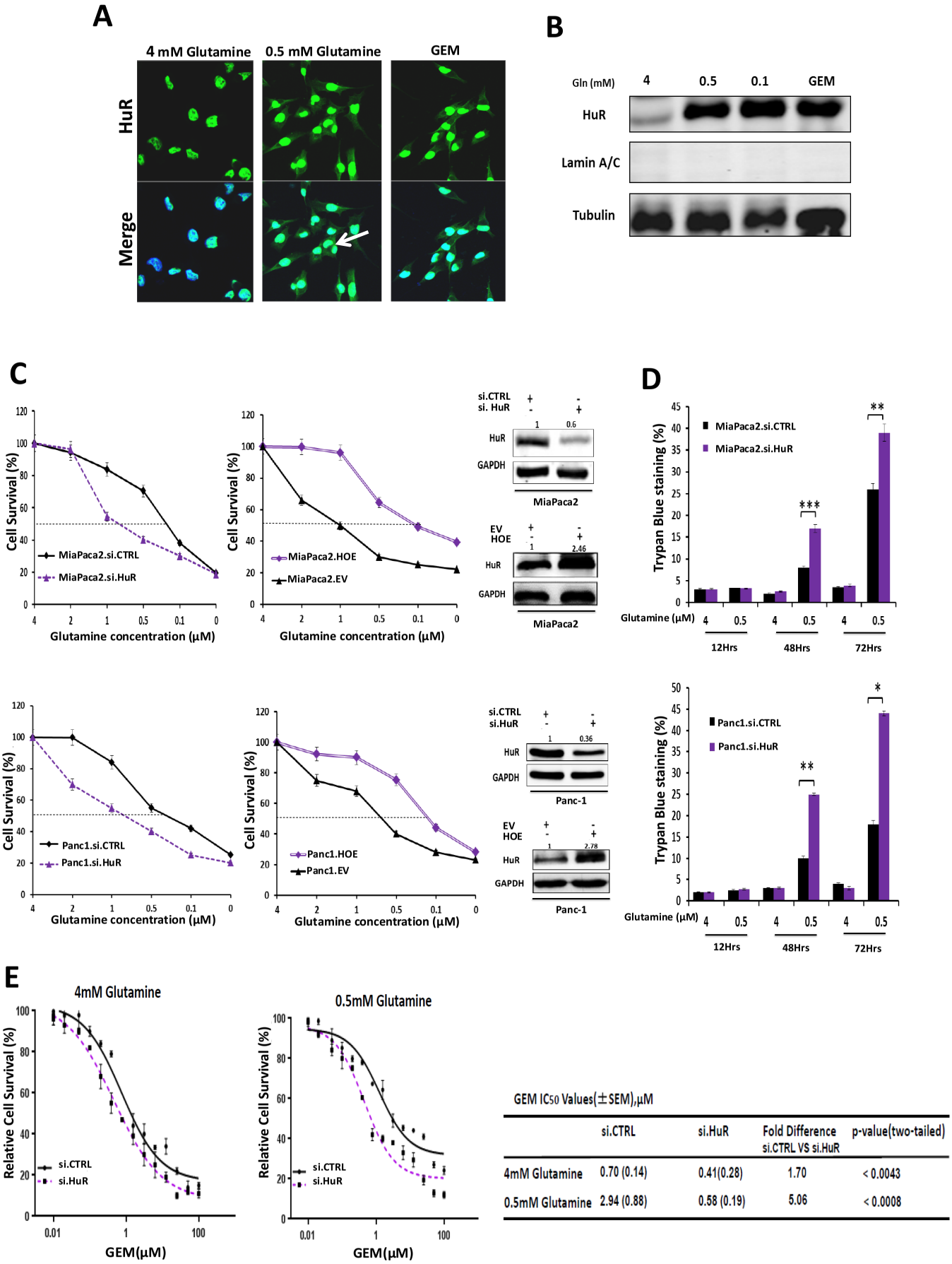

A
Sh.CTRL
Sh.HuR
DOX
- + - +
HuR
1 1 0.98 0.29
α-Tubulin
B
Glucose(mg/L)
180
160
140
120
100
80
60
40
20
0
0 1 2 3 4
Weeks
HC
KCR 50
KCR 75
HC+DOX
KCR 50+DOX
KCR 75+DOX
C
- DOX
+ DOX
HC
KCR 50
KCR 75
D
Relative HuR mRNA expression (normalized to 18S rRNA)
1.2
1
0.8
0.6
0.4
0.2
0
**
**
***
DOX(-)
DOX(+)
HC
KCR 50
KCR 75
-DOX
+DOX
HuR
α-Tubulin

Figure S3



GEM IC_{50} Values(±SEM),μM

	si.CTRL	si.HuR	Fold Difference si.CTRL VS si.HuR	p-value(two-tailed)
4mM Glutamine	0.70 (0.14)	0.41(0.28)	1.70	< 0.0043
0.5mM Glutamine	2.94 (0.88)	0.58 (0.19)	5.06	< 0.0008

Figure S4

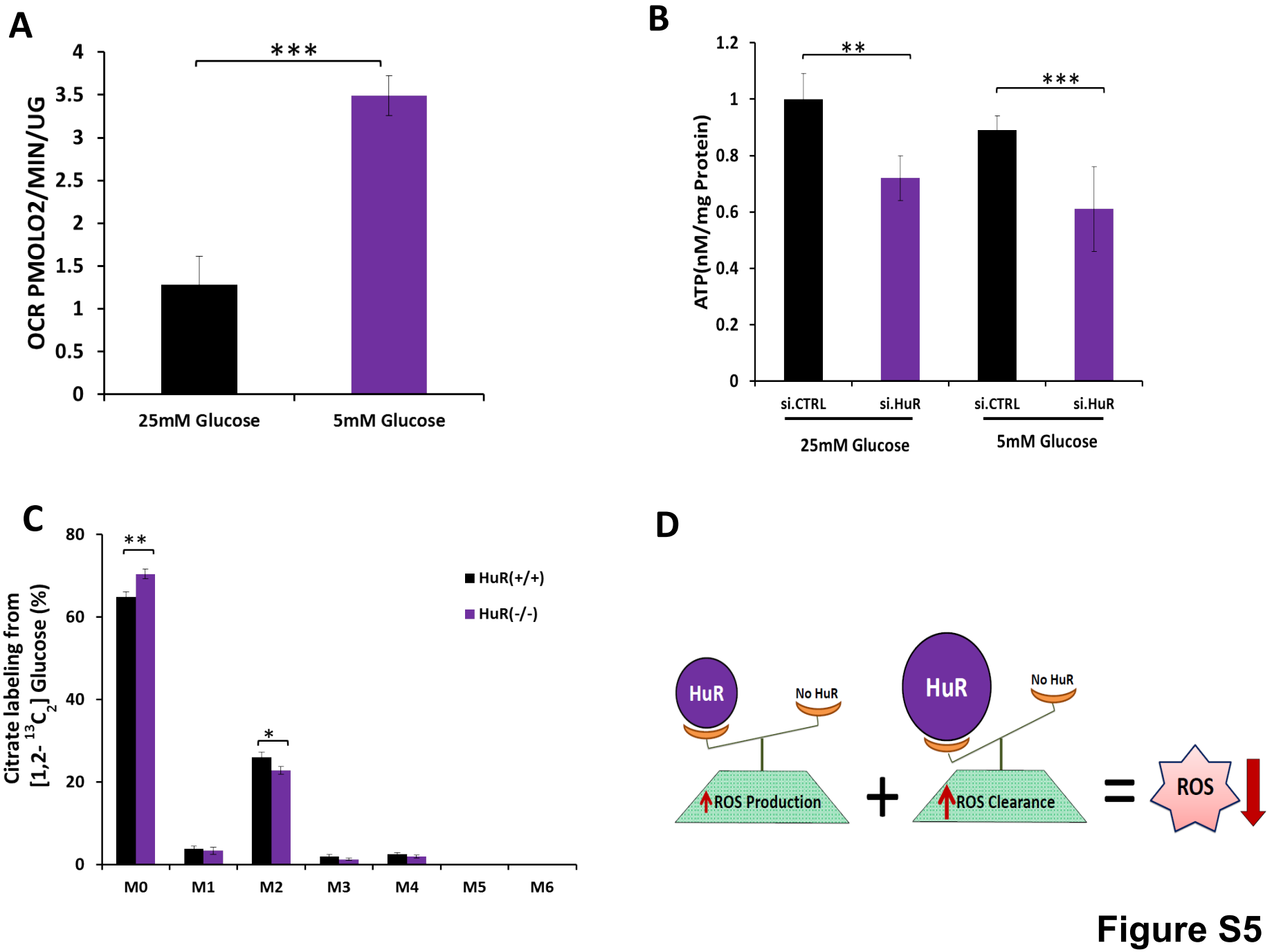

A
OCR PMOLO2/MIN/UG
4
3.5
3
2.5
2
1.5
1
0.5
0
***
25mM Glucose
5mM Glucose
B
ATP(nM/mg Protein)
1.2
1
0.8
0.6
0.4
0.2
0
**
***
si.CTRL
si.HuR
si.CTRL
si.HuR
25mM Glucose
5mM Glucose
C
Citrate labeling from [1,2-13C2] Glucose (%)
80
60
40
20
0
**
*
HuR(+/+)
HuR(-/-)
M0
M1
M2
M3
M4
M5
M6
D
HuR
No HuR
ROS Production
+
HuR
No HuR
ROS Clearance
=
ROS

Figure S5

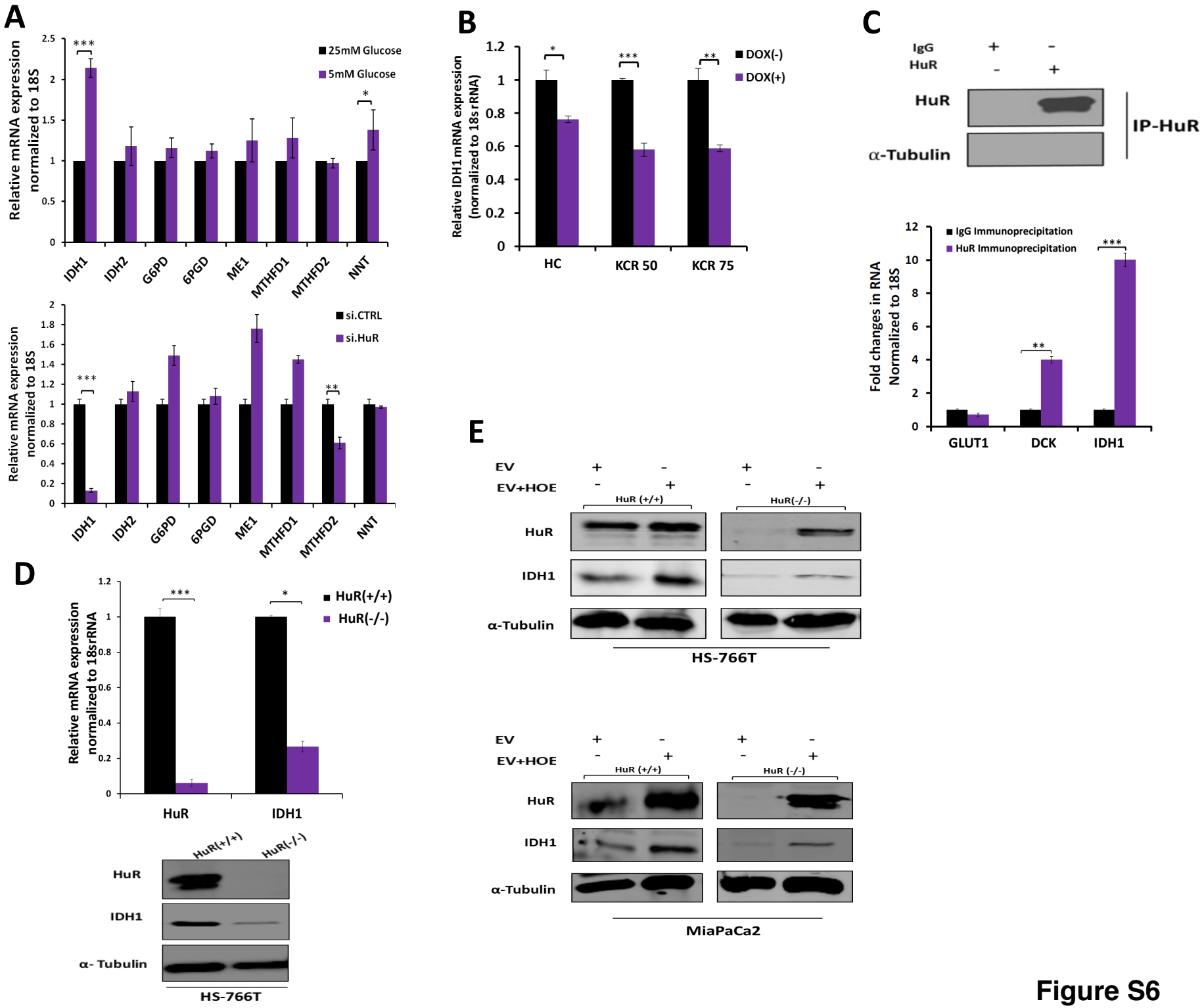
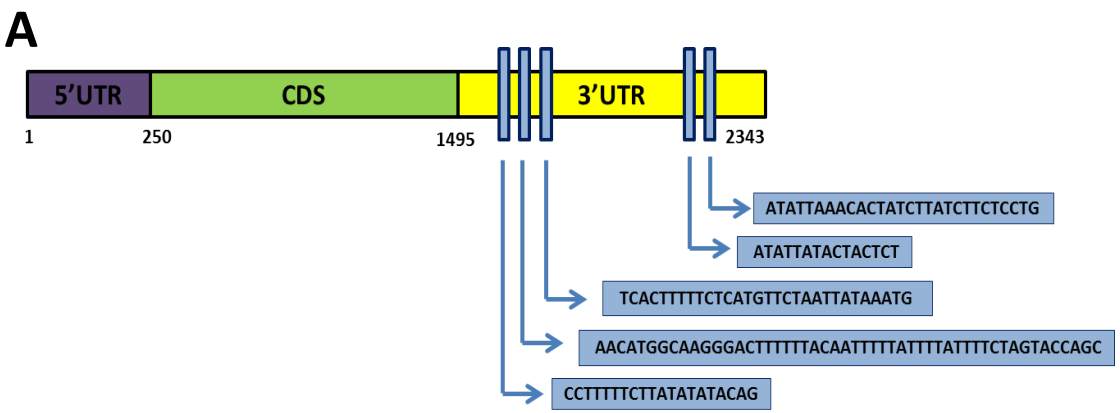
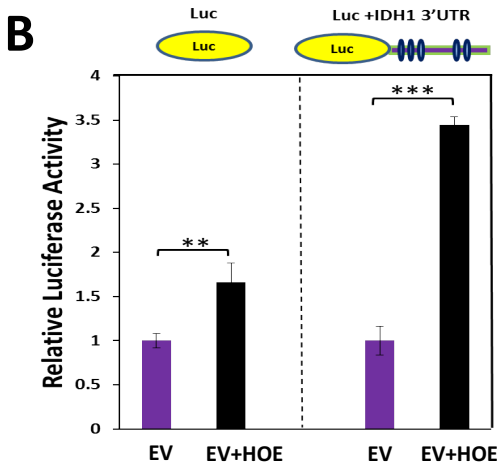
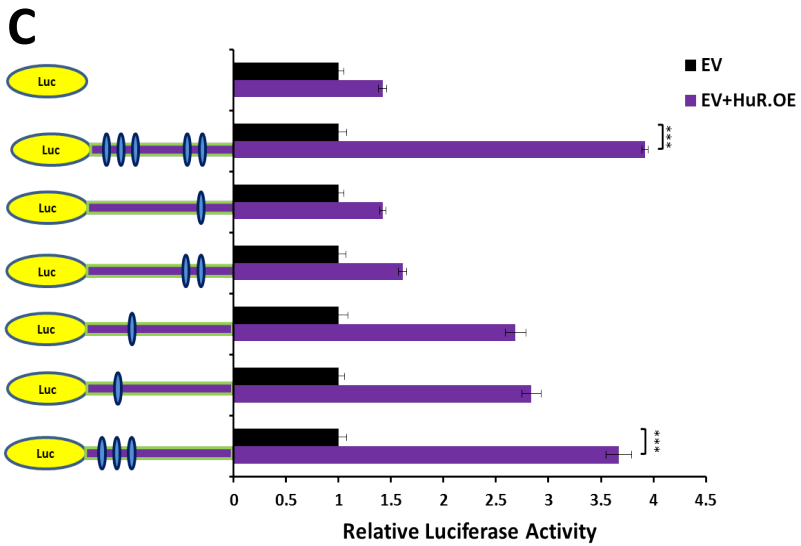
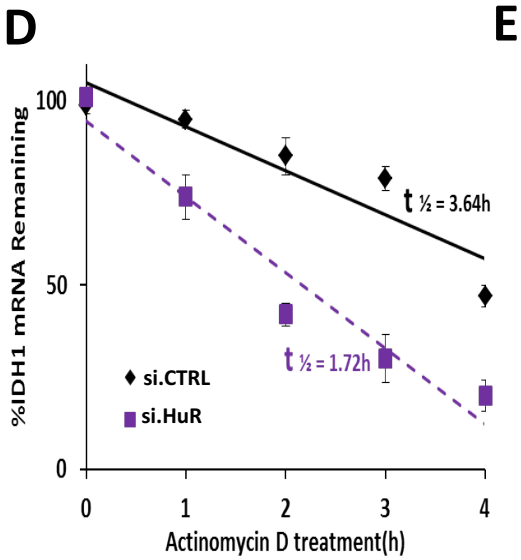

A
Relative mRNA expression normalized to 18S
25mM Glucose
5mM Glucose
IDH1
IDH2
G6PD
6PGD
ME1
MTHFD1
MTHFD2
NNT
si.CTRL
si.HuR
B
Relative IDH1 mRNA expression (normalized to 18s rRNA)
DOX(-)
DOX(+)
HC
KCR 50
KCR 75
C
IgG
HuR
IP-HuR
α-Tubulin
IgG Immunoprecipitation
HuR Immunoprecipitation
Fold changes in RNA Normalized to 18S
GLUT1
DCK
IDH1
D
Relative mRNA expression normalized to 18srRNA
HuR(+/+)
HuR(-/-)
HuR
IDH1
α- Tubulin
HS-766T
E
EV
EV+HOE
HuR (+/+)
HuR(-/-)
HuR
IDH1
α-Tubulin
HS-766T
HuR (+/+)
HuR (-/-)
MiaPaCa2

Figure S6


A
5'UTR
CDS
3'UTR
1
250
1495
2343
ATATTAAACACTATCTTATCTTCTCCTG
ATATTATACTACTCT
TCACTTTTTCTCATGTTCTAATTATAAATG
AACATGGCAAGGGACTTTTTTACAATTTTTATTTTATTTTCTAGTACCAGC
CCTTTTTCTTATATATACAG


B
Luc
Luc +IDH1 3'UTR
Relative Luciferase Activity
EV
EV+HOE
EV
EV+HOE


C
EV
EV+HuR.OE
Relative Luciferase Activity


D
%IDH1 mRNA Remaining
si.CTRL
si.HuR
t ½ = 3.64h
t ½ = 1.72h
Actinomycin D treatment(h)

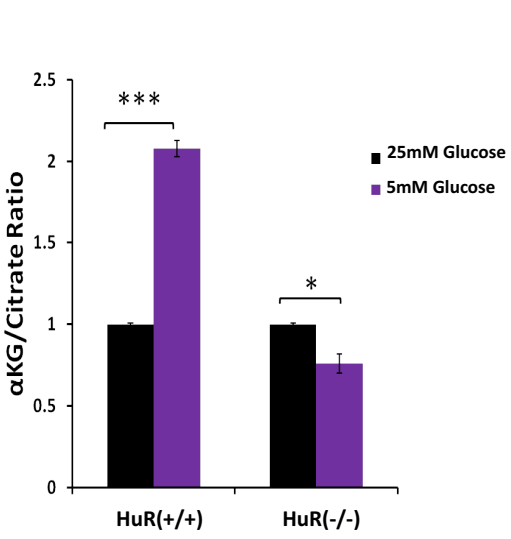

E
αKG/Citrate Ratio
25mM Glucose
5mM Glucose
HuR(+/+)
HuR(-/-)

Figure S7

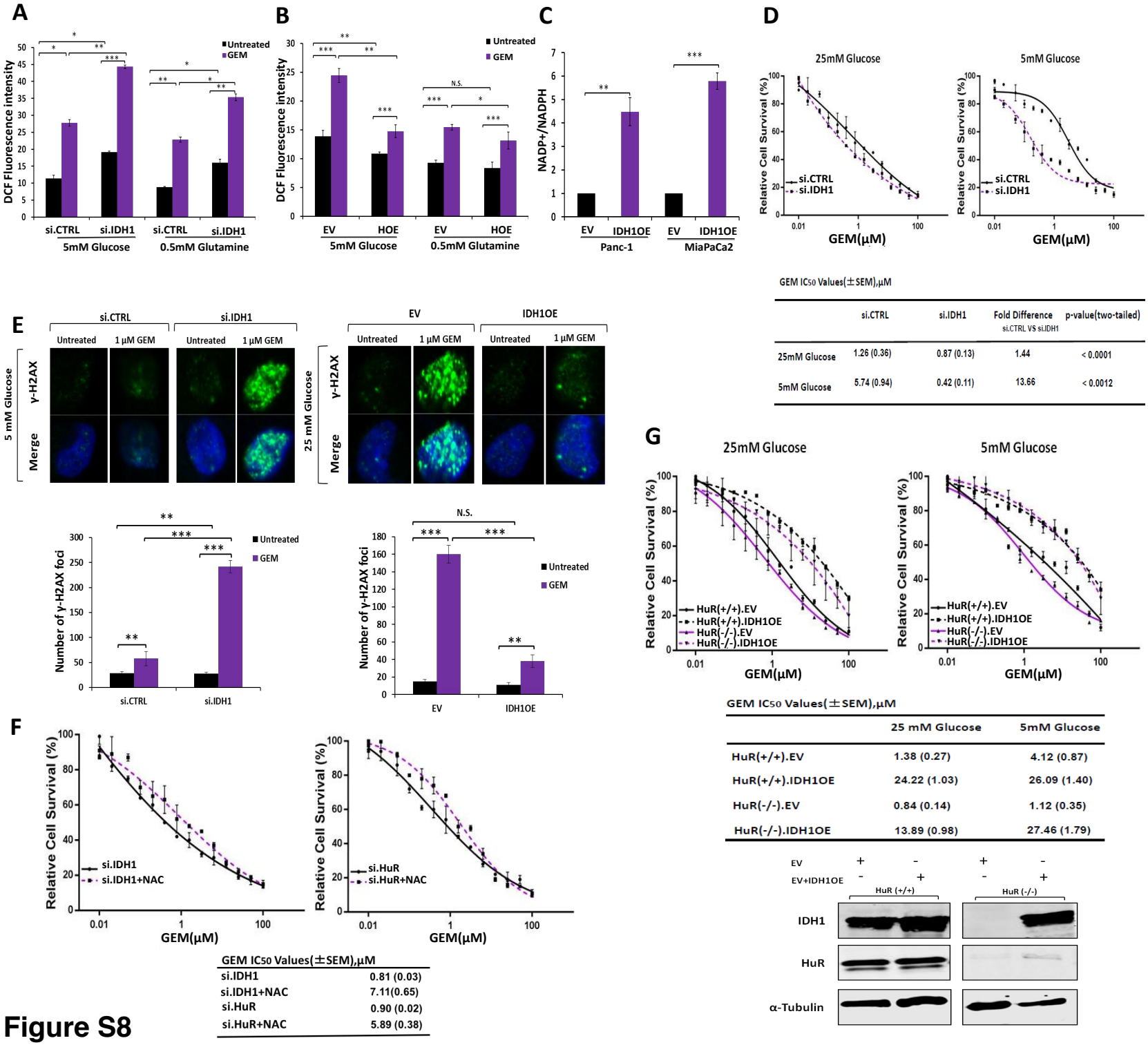

A
DCF Fluorescence intensity
Untreated
GEM
si.CTRL
si.IDH1
si.CTRL
si.IDH1
5mM Glucose
0.5mM Glutamine
B
DCF Fluorescence intensity
Untreated
GEM
N.S.
EV
HOE
EV
HOE
5mM Glucose
0.5mM Glutamine
C
NADP+/NADPH
EV
IDH1OE
EV
IDH1OE
Panc-1
MiaPaCa2
D
25mM Glucose
5mM Glucose
Relative Cell Survival (%)
si.CTRL
si.IDH1
GEM(μM)
GEM IC50 Values(±SEM),μM
si.CTRL
si.IDH1
Fold Difference si.CTRL VS si.IDH1
p-value(two-tailed)
25mM Glucose
1.26 (0.36)
0.87 (0.13)
1.44
< 0.0001
5mM Glucose
5.74 (0.94)
0.42 (0.11)
13.66
< 0.0012
E
si.CTRL
si.IDH1
EV
IDH1OE
Untreated
1 μM GEM
5 mM Glucose
25 mM Glucose
γ-H2AX
Merge
Number of γ-H2AX foci
Untreated
GEM
si.CTRL
si.IDH1
EV
IDH1OE
F
Relative Cell Survival (%)
si.IDH1
si.IDH1+NAC
si.HuR
si.HuR+NAC
GEM(μM)
GEM IC50 Values(±SEM),μM
si.IDH1
0.81 (0.03)
si.IDH1+NAC
7.11(0.65)
si.HuR
0.90 (0.02)
si.HuR+NAC
5.89 (0.38)
G
25mM Glucose
5mM Glucose
Relative Cell Survival (%)
HuR(+/+).EV
HuR(+/+).IDH1OE
HuR(-/-).EV
HuR(-/-).IDH1OE
GEM(μM)
GEM IC50 Values(±SEM),μM
25 mM Glucose
5mM Glucose
HuR(+/+).EV
1.38 (0.27)
4.12 (0.87)
HuR(+/+).IDH1OE
24.22 (1.03)
26.09 (1.40)
HuR(-/-).EV
0.84 (0.14)
1.12 (0.35)
HuR(-/-).IDH1OE
13.89 (0.98)
27.46 (1.79)
EV
EV+IDH1OE
HuR (+/+)
HuR (-/-)
IDH1
HuR
α-Tubulin

Figure S8

Supplemental Tables

Table S1: Nomenclature used throughout manuscript to describe genetically modified cell lines.

Name	Transfection procedure
MiaPaCa2.si.CTRL	siRNA transfection of scrambled control
MiaPaCa2.si.HuR	siRNA transfection against HuR
MiaPaCa2.si.IDH1	siRNA transfection against IDH1
Panc-1.si.CTRL	siRNA transfection of scrambled control
Panc-1.si.HuR	siRNA transfection against HuR
MiaPaCa2.EV	Plasmid transfection of empty vector
MiaPaCa2.HOE	Plasmid transfection of HuR
Panc-1.EV	Plasmid transfection of empty vector
Panc-1.HOE	Plasmid transfection of HuR
MiaPaCa2.IDH1OE	Plasmid transfection of IDH1
MiaPaCa2.sh.CTRL	shRNA stable transfection of scrambled control
MiaPaCa2.sh.HuR	shRNA stable transfection against HuR [doxycycline inducible suppression of HuR]
Mia.HuR(-/-)	CRISPR/Cas9-mediated knockout of HuR using a guide RNA targeting HuR in MiaPaca2 cells
Mia.HuR(+/+)	CRISPR/Cas9- scrambled control in MiaPaca2cells
HS.HuR(-/-)	CRISPR/Cas9-mediated knockout of HuR using a guide RNA targeting HuR in HS-766T cells
HS.HuR(+/+)	CRISPR/Cas9- scrambled control in HS-766T cells
Mia.HuR(-/-).EV	Stable overexpression of empty vector in CRISPR/Cas9 mediated knockout of HuR in MiaPaca2 cells
Mia.HuR(-/-).IDH1OE	Stable overexpression of IDH1 in CRISPR/Cas9 mediated knockout of HuR in MiaPaca2 cells

Table S2. Patient Cohort Characteristics

	Total (N= 107)	HG (n=86)	NG (n=21)	P
	N(%)	N(%)	N(%)	
Gender				
Male	56 (52%)	45 (52%)	11 (52%)	*NS*
Female	51 (48%)	41 (48%)	10 (48%)	
Race				
White/European	95 (89%)	76 (89%)	19 (90%)	
African American	9 (8%)	8 (9%)	1 (5%)	*NS*
Asian	2 (2%)	1 (1%)	1 (5%)	
Other	1 (1%)	1 (1%)	0 (0%)	
BMI	28.0 (±6.1)	28.3 (±6.3)	26.9 (±4.7)	*NS*
Age	65.9 (±10.4)	65.9(±10.0)	65.9 (±12.3)	*NS*
Procedure				
Classic Whipple	17 (16%)	13 (15%)	4 (19%)	
PPPD	64 (60%)	49 (57%)	15 (71%)	*NS*
Distal Pancreatectomy	23 (21%)	22 (26%)	1 (5%)	
Total Pancreatectomy	3 (3%)	2 (2%)	1 (5%)	
Histopathology				
Tumor Size	3.5 (±1.5)	3.7 (±1.5)	3.0 (±1.2)	*§*
High Tumor Grade	20 (19%)	14 (16%)	6 (29%)	*NS*
Metastatic Lymph Nodes	75 (70%)	60 (70%)	15 (71%)	*NS*
LNR	0.16 (±0.18)	0.15 (±0.17)	0.19 (±0.21)	*NS*
Involved Surgical Margins	35 (33%)	28 (32%)	7 (33%)	*NS*
Perineural Invasion	95 (89%)	80 (93%)	15 (71%)	*

Categorical parameters are presented as absolute count and percentages in parenthesis. Continuous parameters are presented as means (±SD). PPPD, *Pylorus Preserving Pancreatoduodenectomy.* Lymph node ratio was calculated as number of metastatic lymph nodes/total number of lymph nodes recovered from the surgical specimen. NS, Non-Significant. Statistical significance of $P<0.05$ is marked with an asterisk (*).§ - Statistical trend ($P = 0.1$-0.05).

Table S4. List of Enzymes directly involved in the anti-oxidant defense response.

Gene Name	Gene Symbol	Classification/Pathway
6-phosphogluconate dehydrogenase	6PGD	NADPH regeneration/Pentose Phosphate
Glucose-6-phosphate dehydrogenase	G6PD	NADPH regeneration/Pentose Phosphate
Isocitrate Dehydrogenase 1	IDH1	NADPH regeneration/Krebs
Isocitrate Dehydrogenase 2	IDH2	NADPH regeneration/Krebs
Malic Enzyme 1	ME1	NADPH regeneration/Krebs
Methylenetetrahydrofolate dehydrogenase 1	MTHFD1	NADPH regeneration/Folate
Methylenetetrahydrofolate dehydrogenase 2	MTHFD2	NADPH regeneration/Folate
Nicotinamide Nucleotide Transhydrogenase	NNT	NADPH regeneration/NAD
Catalase	CAT	Antioxidants/Catalses/free radical detoxification
Glutamate-cysteine ligase catalytic subunit	GCLC	Antioxidants/Glutathione synthesis
Glutamate-cysteine ligase modifier subunit	GCLM	Antioxidants/Glutathione synthesis
Glutathione peroxidase1	GPx1	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione peroxidase2	GPx2	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione peroxidase3	GPx3	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione peroxidase4	GPx4	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione peroxidase5	GPx5	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione peroxidase6	GPx6	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione peroxidase7	GPx7	Antioxidants/Glutathione Peroxidases/free radical detoxification
Glutathione S-transferase	GST	Antioxidants/Glutathione synthesis/free radical detoxification
Glutathione synthetase	GSS	Antioxidants/Glutathione synthesis/free radical detoxification
Superoxide dismutase 1 or Copper–zinc SOD	SOD1	Antioxidants/Superoxide Metabolism
Superoxide dismutase 2 or Manganese SOD	SOD2	Antioxidants/Superoxide Metabolism
Superoxide dismutase 3 or Extracellular SOD	SOD3	Antioxidants/Superoxide Metabolism
Glutaredoxin1	GRX1	Redox
Glutaredoxin2	GRX2	Redox
Glutaredoxin3	GRX3	Redox
Glutaredoxin4	GRX4	Redox
Glutaredoxin5	GRX5	Redox
Glutathione Reductase	GR	Redox
peroxiredoxin 1	PRDX1	Redox
peroxiredoxin 2	PRDX2	Redox
peroxiredoxin 3	PRDX3	Redox
peroxiredoxin 4	PRDX4	Redox
peroxiredoxin 5	PRDX5	Redox
peroxiredoxin 6	PRDX6	Redox
Thioredoxin reductase 1	TXNRD1	Redox
Thioredoxin reductase 2	TXNRD2	Redox
Thioredoxin reductase 3	TXNRD3	Redox
Thioredoxin1	TXN 1	Redox
Thioredoxin2	TXN 2	Redox

Table S5: Results of RNA sequencing in PDA cell lines (HS-766T and MiaPaCa2) with each modulated by CRISPR/Cas9 to delete HuR expression.

	HS			Mia		
Gene Symbol	Log2 Fold Change (HuR(+/+)vsHuR(-/-); <=0 is down in HuR(-/-)	pValue	FDR	Log2 Fold Change (HuR(+/+)vsHuR(-/-); <=0 is down in HuR(-/-)	pValue	FDR
IDH1	-6.18610	0.00000	0.00000	-4.19733	0.00078	0.00738
ELAVL1	-4.50754	0.00000	0.00000	-2.47939	0.00000	0.00000
GPx3	0.78045	0.00418	0.02155	-1.25985	0.00001	0.00022
GRX3	0.56216	0.00112	0.00720	-0.54306	0.00413	0.02847
SOD2	0.55764	0.00030	0.00235	0.64184	0.00021	0.00250
GCLM	0.18137	0.48910	0.71718	-1.24421	0.00000	0.00000
GPx4	0.07350	0.62605	0.82867	0.56763	0.00676	0.04182
GRX1	0.29823	0.20110	0.40651	2.16108	0.00009	0.00119
ME1	0.37969	0.14378	0.32453	0.79444	0.00748	0.04514
SOD1	0.03521	0.94323	1.00000	-0.53206	0.00449	0.03027
GCLC	-0.77948	0.00022	0.00181	-0.55723	0.02518	0.11359
GRX5	-1.17113	0.00000	0.00000	0.41264	0.02221	0.10353
GSS	0.52491	0.01112	0.04694	0.12923	0.69909	0.90211
MTHFD2	-1.76775	0.00000	0.00000	-0.32393	0.04243	0.16438
PRDX1	0.70918	0.00001	0.00007	-0.00554	1.00000	1.00000
PRDX4	-0.76080	0.00004	0.00039	-0.31095	0.14998	0.38087
GR	0.20379	0.31774	0.55050	-0.07234	0.70778	0.90693
6PGD	0.40346	0.02157	0.07888	-0.48224	0.01065	0.05932
CAT	0.43410	0.12796	0.29958	-0.06134	0.91541	1.00000
G6PD	0.53432	0.03641	0.11827	0.42565	0.07038	0.22997
GPx1	-0.11793	0.63938	0.83796	0.20981	0.49977	0.76698
GPx2	-1.09321	0.63351	0.83478	not expressed		
GPx5	not expressed			not expressed		
GPx6	not expressed			not expressed		
GPx7	0.85049	0.35606	0.59151	not expressed		
GRX2	0.48896	0.16192	0.35076	0.09539	0.74649	0.93214
GRX4	not expressed			not expressed		
GST	0.21470	0.99988	1.00000	-0.15027	0.75125	0.93478
IDH2	-0.67838	0.01454	0.05802	0.22542	0.37173	0.65304
MTHFD1	0.26363	0.13023	0.30274	0.14841	0.44003	0.71723
NNT	0.29714	0.21809	0.42893	-0.23764	0.81422	0.96562
PRDX2	0.12871	0.43486	0.66898	-0.01078	0.91246	1.00000
PRDX3	0.09033	0.63888	0.83761	-0.09467	0.73893	0.92743
PRDX5	0.19037	0.32529	0.55776	-0.28408	0.25664	0.53159
PRDX6	0.29760	0.09558	0.24295	0.19599	0.27485	0.55494
SOD3	not expressed			not expressed		
TXN1	0.13121	0.39574	0.63202	-0.14490	0.39908	0.67966
TXN2	-0.31790	0.31745	0.55006	-0.47557	0.45790	0.73389
TXNRD1	0.14478	0.32651	0.55926	-0.26647	0.04211	0.16362
TXNRD2	1.31332	0.01732	0.06679	0.24360	0.51546	0.77717
TXNRD3	0.35552	0.54112	0.76008	-0.09352	0.85046	0.98524

ELAVL1(HuR) is included as a **reference gene** since it is the target of CRISPR/Cas9 editing and It is the only non-anti-oxidant gene in this table.

Significant Fold Change:
FDR <=0.05
log2 fold change +/- 0.58
pvalue <=0.05

Supplemental Methods

Detailed Mouse studies

Treatment groups for mouse experiments are detailed in the text, and included various dietary modifications, and/or gemcitabine treatment. For gemcitabine administration, the drug was suspended in normal saline at 5mg/mL and administered i.p. to mice at 100 mg/kg; vehicle was prepared at a volume of 20µl/g of 0.9%NaCl. For relevant experiments, drug was injected biweekly into the peritoneal cavity once the tumor diameter reached 50 mm^3.

Mouse diets were modified to alter peripheral glucose levels and simulate nutrient withdrawal experiments performed *in vitro*, and nutrient withdrawal present in the PDA tumor microenvironment in patients. Prior mouse xenograft studies demonstrate that differences in peripheral glucose levels *in vivo* translate into even greater discrepancies within the mouse tumor microenvironment (15,16). Mice were therefore fed normal chow (NC) until tumors reached 50 mm^3, and assigned one of the following diets: high carbohydrate diet (HC), ketogenic and calorie restricted diet at 75% of their average daily calorie intake (KCR75), and a ketogenic and calorie restricted diet at 50% of their caloric intake (KCR50). Specific dietary formulas were as follows: 1) HC (Bio-serve; F3155), carbohydrate 68%, protein 12.6%, fat 4.1%, 3.5 kcal/gm; 2) KCR (Bio-serve; F3666), carbohydrate 3.2%, protein 8.6%, fat 75.1%, 7.24 kcal/gm. Mice involved in calorie restricted experiments were singly caged for optimal dietary control, with no ill effects observed from this intervention. For *in vivo* experiments involving doxycycline (DOX) inducible gene suppression, the antibiotic was integrated into the chow formula at 200 mg/kg (HC+DOX; Bio-serve; F6987)(KC+DOX; Bio-serve; F7106). Serum glucose levels were tracked once per week using the AlphaTrak glucometer system (Abbott). Upon termination of mouse experiments, mice were euthanized using carbon dioxide inhalation followed by cervical dislocation, and

tumors harvested.

Bioenergetics analysis

Cells were seeded at 20,000 cells per well within 24 well Seahorse cell culture plates and allowed to grow for 24 hours. Using the Seahorse XF24 Extracellular Flux Analyzer, baseline measurements of the O2 consumption rate (OCR) were recorded followed by leak dependent OCR (after addition of 500ng/mL oligomycin), maximal OCR (after addition of 100nM FCCP), and non-mitochondrial OCR (Antimycin 1uM). Measurements were normalized to total cellular protein/well using the BCA protein assay (Thermo Fisher Scientific).

Evaluation of IDH1 mRNA in pancreas clinical specimens

Previously reported microarray expression (21) data was downloaded from GEO (accession number: GSE71729). The dataset contains 46 normal pancreatic tissue samples, 145 primary pancreatic adenocarcinomas, and 61 metastatic pancreatic adenocarcinomas. Paired t-tests were performed to compare the differences between the three conditions. P values < 0.05 were considered statistically significant.

Immunohistochemistry (IHC)

Each sample was re-reviewed by an experienced surgical pathologist (W.J.) to confirm the histological diagnosis of PDA. TMAs were cut to 4μm thick sections and assayed with antibodies against HuR (Santa Cruz Biotechnologies; 5261 clone 3A2, 1:400) and IDH1 (Abcam; ab 184615, 1:100). All immunolabeled samples were given a total IHC score by a surgical pathologist, equivalent to the labeling intensity score (1, negative staining; 2, weak staining; 3, moderate staining; or 4, strong staining) multiplied by a score reflecting the percentage of labeled cells (0-10%=1, 10-50%=2, 50%-80%=3, >80%=4)(15). HuR staining was evaluated separately for cytoplasmic and nuclear staining. A total cellular HuR score was also

calculated, and equaled the sum of cytoplasmic and nuclear HuR scores. IHC scores were categorized for each protein, into tiered groups to facilitate statistical analyses. IDH1 scores were grouped as high (IHC score > 6), moderate (IHC score = 6) or low (IHC score < 6). HuR scores above 6 and 8 were categorized as high scores for cytoplasmic and total HuR scores, respectively; remaining samples were categorized as low. Associations between IDH1 and HuR IHC scores were determined using a $\chi 2$ test. P values < 0.05 were considered as statistically significant.

RNA sequencing

RNA seq was performed on MiaPaCa2 and HS-766T modulated genetically by CRISPR/Cas9 to knockout HuR, along with the appropriate isogenic control cells. Cells were plated in 100mm^3 dishes in triplicate, and incubated in 5mM glucose media for 24 hours (low glucose culture conditions). Total RNA was extracted using the RNeasy mini kit (Qiagen). The RNA was then deep sequenced on an Illumina NextSeq 500 machine. Sequence libraries were constructed following the manufacture's protocol; 2x75 bp paired-end reads and ~80 million reads were generated for each sample, and quality trimming on raw reads was performed using Cutadapt prior to sequence mapping (http://journal.embnet.org/index.php/embnetjournal/article/view/200). Sequence reads were aligned to the hg19 human genome build using the STAR aligning program (1). A two-pass alignment was performed and only those reads mapping uniquely to the human genome were maintained for further analysis. Quantification of all genes and their isoforms was performed using the RSEM algorithm, and the DESeq2 package was used to determine differentially expressed genes (2). Bioinformatics was performed for each of the two cell lines, comparing the expression levels of genes in the HuR (-/-) genes, compared to the isogenic control samples HuR

(+/+). P values and false-discovery rates (FDR) were calculated for each gene. Genes with gene expression changes that surpassed a log2 fold change +/- 0.58, FDR values <=0.05 and p values <=0.05 were identified as significantly changed from the control cell line to the HuR-knockout cell line. FPKM values for all genes in the coding transcriptome are provided, but the analysis for this study focused on 40 well characterized transcripts encoding enzymes directly involved in antioxidant defense. A heatmap including those genes that are significantly different in isogenic lines was generated using the ggplot2 program in R. Raw data are provided in Table S3.

Clinical outcome data

For the clinical correlation analysis, we analyzed records from 724 consecutive patients with PDA resected at Thomas Jefferson University Hospital between 2002 and 2014, after obtaining IRB approval. For the first analysis (Figure S2C and S2D), patients were grouped into 3 categories based on the Position Statement of the American Diabetes Association 2014 (HbA1C≤6.5%, 6.5%<HbA1C≤8.5%, HbA1C>8.5%). A total of 345 patients had available information. Parametric and non-parametric correlation studies were performed, along with ANOVA and post-hoc Bonferroni tests for HbA1C group comparisons. These tests were applied to determine the correlation of elevated HbA1C levels and pathologic features that are routinely reported on pathologic reports of resected specimens. Lymph node ratio (the number of regional lymph node metastases to total lymph nodes examined) was used as a surrogate marker of lymph node metastases.

In a separate survival analysis, disease free survival (DFS) data were available for a total of 107 patients who underwent pancreatic resection for localized disease at Thomas Jefferson University Hospital, and also received adjuvant gemcitabine (Table S2). An expanded definition of poor glycemic control was used, to optimize the sample size of the cohort with available data.

Patients were categorized into high glucose (HG, n=86) if they carried an existing diagnosis of diabetes or had a pre-operative HgbA1C > 6.0%. The remaining patients were categorized as having normal glucose (NG, n=21). Kaplan-Meier survival analysis and Cox multivariate hazard models were used for comparisons of survival. Adjusted covariates included tumor size, regional lymph node metastases, tumor grade, and glycemic status. P values < 0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS, Ver.20, SPSS Inc., Chicago, IL, USA).

Supplemental Figure Legends

Figure S1, related to Figure 1: Low nutrient conditions promote PDA chemoresistance. (A) Survival of PDA cell lines treated with the indicated doses of oxaliplatin. IC_{50} values are provided. Cell survival was calculated by measurement of dsDNA content using PicoGreen**.** (B) Survival of PDA cells under the indicated conditions in the absence of chemotherapy by trypan blue staining. (C) ROS levels in MiaPaCa2 cells by DCF fluorerscence under the indicated culture conditions for 24 hours. Gemcitabine (GEM 1μM) was administered at the time of nutrient withdrawal. Error bars represent ± SEM of triplicate wells from a representative experiment. (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Figure S2, related to Figure 2: Low nutrient conditions induce PDA resistance to gemcitabine in mice and patients. (A) Peripheral glucose levels were higher in mice fed a high carbohydrate (HC) diet, than mice fed a ketogenic and calorie restricted diet (75% of the average caloric intake, KCR75). Mice were treated with GEM as indicated. (B) Representative images of subcutaneous MiaPaca2 tumors, at the termination of the experiment (day 55). (C) Association of HbA1C levels and tumor size in resected PDA, with a corresponding correlation analysis (small panel). (D) Association of HbA1C levels and metastatic lymph node ratio in resected PDA, with a corresponding correlation analysis (small panel). (E) Schematic illustrating the effect of austere nutrient conditions on PDA cell growth and chemoresistance.

Figure S3, related to Figure 3: Dox-induced HuR silencing, along with a calorie restricted diet, suppresses PDA xenograft growth. (A) Immunoblot of HuR protein expression of MiaPaCa2 cells modified with a doxycycline (DOX) inducible sh.HuR plasmid. Cells were

cultured in vitro and treated with 0 or 2 μg/ml of DOX for 5 days. (B) Peripheral glucose levels in mice fed a high carbohydrate (HC) diet, a ketogenic diet with 75% caloric intake (KCR75), or a ketogenic diet with 50% caloric intake (KCR50); mice were fed DOX as indicated. Each data point represents the mean ± SEM (n=8 per group). (C) Representative images of excised tumors of MiaPaCa2.sh.HuR and MiaPaCa2.sh.CTRL cells. Mice were fed an HC diet, KCR75 diet, or KCR50 diet. (D) qPCR-mRNA and immunoblot-protein validation of HuR suppression in MiaPaCa2.sh.HuR and MiaPaCa2.sh.CTRL cells. Each data point represents the mean ± SEM of three independent experiments * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure S4, related to Figure 3: Low glutamine levels induce HuR nucleocytoplasmic shuttling. (A) Immunofluorescence demonstrates HuR subcellular localization to the cytoplasm (green cytoplasmic signal) when MiaPaCa2 cells are cultured in low glutamine media for 24 hours. GEM is used as a positive control that induces cytoplasmic HuR translocation (28). Magnification 40x. (B) Immunoblot of cytoplasmic MiaPaCa2 lysates incubated for 24 hours. GEM is used as a positive control. (C) PicoGreen cell survival assay at 5 days in MiaPaCa2 cells with declining levels of glutamine in the media. HuR overexpression or silencing was performed, along with siRNA controls. Representative immunoblots are shown. (D) Trypan blue staining in MiaPaCa2 and Panc-1 cells after HuR silencing, with cells cultured in high and low glutamine conditions. (E) PicoGreen cell survival assay in MiaPacCa2 cells under the indicated conditions, with declining levels of GEM. Each data point represents the mean ± SEM of three independent experiments * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure S5, related to Figure 4: HuR detoxifies reactive oxygen species (A) Baseline oxygen consumption rates (OCR) in MiaPaca2 cells cultured as indicated for 24 hours. (B) ATP production levels in MiaPaCa2 cells cultured for 24 hours under the indicated conditions. (C) **C**itrate fractions with the indicated amounts of ^{13}C. The M2 fraction reveals glucose-derived carbon. Preparations were derived from MiaPaca2 CRISPR HuR(+/+) or HuR(-/-) cells cultured in 5mM glucose for 24 hours in the presence of [1,2-$^{13}C_6$]glucose tracer. Each data point represents the mean ± SEM of three independent experiments. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. (D) Schematic depicting HuR's general influence on ROS levels. Despite enhanced mitochondrial function (yielding increased ROS production), increased ROS clearance likely yields a net reduction of intracellular ROS.

Figure S6, related to Figure 5: HuR regulates IDH1 mRNA. (A) In top panel**,** MiaPaCa2 cells were cultured in 25Mm and 5 mM glucose media for 24 hours, In bottom panel MiaPaCa2 cells after HuR silencing were cultured in 5 mM glucose media for 24 hours and the expression of transcripts encoding enzymes that generate NADPH was measured by RT-qPCR. (B) qPCR-mRNA expression of IDH1 in MiaPaCa2.sh.HUR xenografts after doxycycline treatment, related to Figures S3C and S3D. (C) HuR RNP-IP. Abundance of IDH1 mRNA bound to HuR. GLUT1 and DCK serve as negative and positive controls, respectively (10,22). MiaPaCa2 cells were cultured in low glutamine (0.5 mM) for 24 hours. (D) HuR and IDH1 mRNA levels in HS-766T CRISPR HuR(+/+) or HuR(-/-) cells; immunoblot of IDH1 and HuR protein in the same cells. (E) Transient overexpression of HuR (or control empty vector) in Mia.HuR(-/-) and HS.HuR(-/-) cells (with CRISPR deletion of HuR), restored IDH1 expression in these cells, confirming HuR's importance for IDH1 expression. Each data point represents the mean ± SEM of three

independent experiments. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure S7, related to Figure 5: IDH1 3'UTR deletion constructs confirmed HuR binding to the IDH1 transcript. (A) Schematic highlighting computationally predicted HuR binding sites in the 3'UTR of the IDH1 mRNA transcript**.** (B) MiaPaCa2 cells were co-transfected with an overexpression plasmid (HuR or empty vector) and luciferase reporter constructs (luciferase control or luciferase fused with IDH1 3′ UTR). Cells were cultured in 5mM glucose media for 24 hours. (C) IDH1 3'UTR deletion series localizing the HuR binding region to the upstream 192bp of the IDH1 3'UTR, containing three predicted binding sites. Luciferase activity was tested after HuR overexpression. (D) MiaPaCa2 cells were cultured in 5mM glucose for 24 hours and IDH1 mRNA was measured after treatment with a transcription inhibitor (actinomycin D). IDH1 transcript levels were normalized to 18S. (E) αKG/citrate ratios measured by GC/MS, in Mia.HuR(-/-) or Mia.HuR(+/+) cells cultured under the indicated conditions for 24hours. Each data point represents the mean ± SEM of three independent experiments. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure S8, related to Figure 6 and Figure 7: IDH1 expression protects PDA cells under stress, and rescues HuR-deficient PDA cells under stress. (A) IDH1 silencing. ROS levels in MiaPaCa2.si.IDH1 cells, as measured by DCF fluorescence. Cells were cultured under the indicated conditions for 48 hours, and GEM (1μM) for the last18 hours, as indicated. (B) IDH1 overexpression. ROS levels in MiaPaCa2.IDH1OE cells, as measured by DCF fluorescence. Culture conditions were the similar to Figure S8B. (C) IDH1 overexpression. $NADP^+$/NADPH ratio in Panc-1.IDH1OE and MiaPaCa2.IDH1OE cells cultured in 5 mM glucose media for 24

hours. (D) PicoGreen cell survival and drug sensitivity assays in MiaPaCa2 cells treated with GEM. (E) γ-H2AX foci. MiaPaCa2 cells were cultured in 5mM and 25mM glucose for 48 hours, and either GEM (1μM) or vehicle for the last 18 hours, as indicated. Each data point represents the mean ± SEM of three independent experiments. (F) PicoGreen cell survival and drug sensitivity assays in MiaPaCa2 cells with IDH1 or HuR silencing. Cells were cultured in 5 mM glucose and treated with n-acetyl cysteine (NAC)(0.5mM/ml). (G) PicoGreen cell survival and drug sensitivity assays in MiaPaCa2 cells treated with GEM. IDH1 overexpression (or empty vector) was performed in Mia.HuR(-/-) knockout cells or Mia.HuR(+/+). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.