Figure S1. MYC induces metabolic changes. A, heatmap of the metabolites regulated by MYC in the presence or absence of AHR. B, description of the metabolites shown in (A).

Figure S2. AHR regulates metabolic pathways in the absence of MYC. A, heatmap of the metabolic changes driven by AHR in *myc-/-* + MYC rat fibroblasts. B, description of the metabolites shown in (A). C, heatmap of the metabolic changes driven by AHR in *myc-/-* rat fibroblasts. D, description of the metabolites shown in (C). E-I, relative mRNA expression of *L2HGDH* and *MDH2* (E), *ADHEF1* and *D2HGDH* (F), *HGAH* (G), *UMPS* (H), and *LDHA* (I), according to our RNA-seq. J, qPCR for rat *LDHA* upon AHR knockdown. K, rat *LDHA* promoter showing AHR and MYC binding sites. Asterisks represent p-value <0.05.

Figure S3. Glycolysis in the absence of AHR. A, schematic representation of the glycolysis pathway. B, relative amounts of the glycolytic metabolites found in the LC/MS metabolomic screening in the presence or absence of MYC and AHR in rat fibroblasts normalized by the *myc* -/- condition. C, relative mRNA levels of the enzymes involved in glycolysis found by RNA-seq in MYC-expressing cells 48 h after transfection with control or *AHR* siRNAs. Asterisks represent p-value <0.05. Asterisks in C-E represent p-value <0.05 in both *AHR* siRNA conditions relative to siCtrl.

Figure S4. TCA cycle and pyrimidine biosynthesis pathway in the absence of AHR. A, schematic representation of the TCA cycle pathway. B, relative amounts of the TCA cycle metabolites found in the LC/MS metabolomic screening in the presence or absence of MYC and AHR in rat fibroblasts normalized to the *myc-/-* condition. C, relative mRNA levels of the enzymes involved in TCA cycle found by RNA-seq in MYC-expressing cells 48 h after transfection with control or *AHR* siRNAs. D, relative amounts of the pyrimidine metabolites found in the LC/MS metabolomic screening in the presence or absence of MYC and AHR in rat fibroblasts normalized to the *myc-/-* condition. E, relative mRNA levels of the enzymes involved in pyrimidine biosynthesis found by RNA-seq in MYC-expressing cells 48 h after transfection with control

or *AHR* siRNAs. Asterisks represent p-value <0.05. Asterisks in C and E represent p-value <0.05 in both *AHR* siRNA conditions relative to siCtrl.

Figure S5. AHR is necessary for viability of GBM cells. A-B, mRNA levels of *ARNT, MYC,* and *MAX* in grade II, III or IV/GBM gliomas from patients whose tumor data are archived in the TCGA (A) and CGGA (B) databases. C, Western blot of LN229 and SF188 72 h after infection with an *AHR* shRNA lentiviral vector. AHR silencing induces cell cycle arrest, as indicated by increased expression of p27 and decreased expression of cyclin A1, and apoptosis, as indicated by cleaved PARP1 and cleaved caspase 3. D, relative proliferation of GBM9 72 h after transfection with control or *AHR* siRNA. Upper panel shows *AHR* silencing by Western blot. E, qPCR for *AHR*, *CAD*, *DHODH*, and *UMPS* in LN229 72 h after infection with a lentiviral vector containing an *AHR* shRNA. Asterisks represent p-value <0.05.

Figure S6. AHR, MYC and MAX bind to *LDHA*, *CAD*, *DHODH* and *UMPS* promoters. A, table displaying the coordinates in the hg19/human reference genome of the optimal IDR peaks found in the ChIP-seq experiments for AHR (ENCSR412ZDC) and MYC (ENCSR000EZD) deposited in the ENCODE database. B, representation of the signals and optimal IDR peaks of the ChIP-seq experiments for AHR (ENCSR412ZDC), ARNT (ENCSR029IBC), MYC (ENCSR000EZD) and MAX (ENCSR000EZF) deposited in the ENCODE database on the *CYP1A1* (*bona-fide* AHR target gene), *LDHA* (*bona-fide* MYC target gene), *CAD*, *DHODH* and *UMPS* genes. C, schematic representation of the human *LDHA* gene promoter regions showing the presence of XRE (AHR binding sites) or E-box (MYC binding sites).

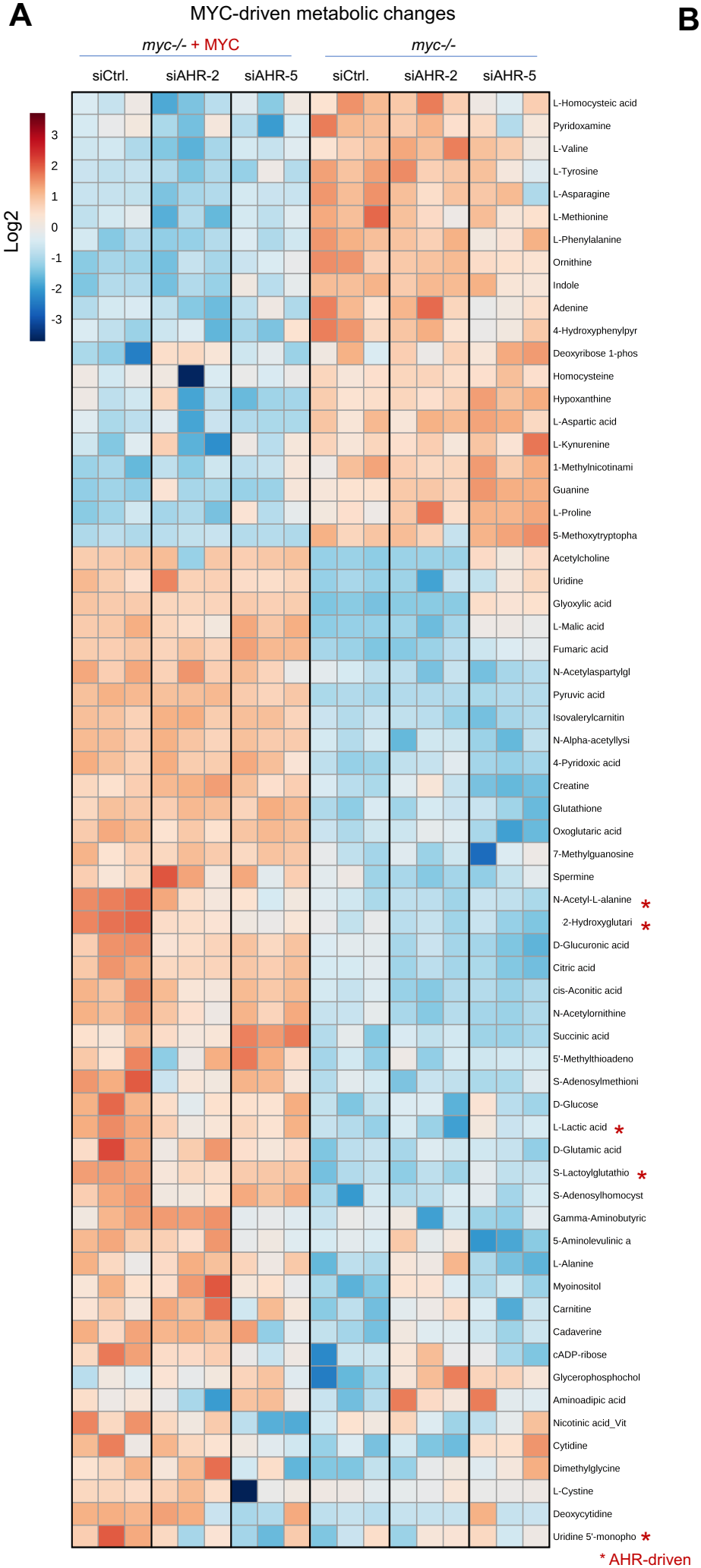
Figure S7. A, Relative amounts of the pyrimidine metabolites found in the LC/MS metabolomic screening upon *AHR* knockdown in the SF188. B, qPCR for *SCL28A1-3 and SLC29A1-3* in SF188 72 h after infection with a lentiviral vector containing an *AHR* shRNA. C-D, Relative proliferation of SF188 (C) and *myc-/-* + MYC (D) rat cells upon *AHR* silencing in the presence of uridine. Uridine addition did not rescue proliferation of these cells upon *AHR* knockdown.

Table S1. Antibodies, siRNA, shRNA, and primers used in this study.

Table S2. TIC values for LC/MS metabolomics in HO15.19.

Table S3. TIC values for LC/MS metabolomics in SF188.

A

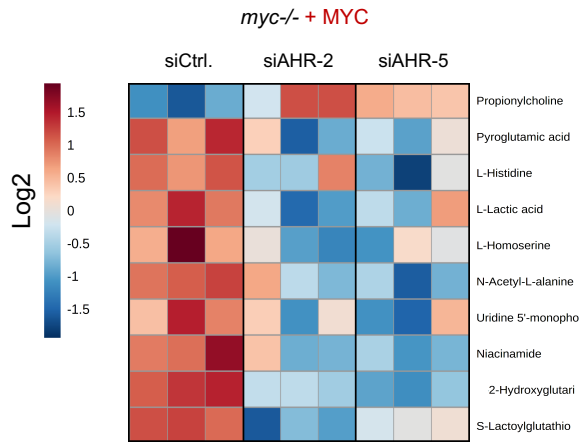


B

MYC-driven metabolic changes	
Pathway	**Metabolite**
AA	N-Acetyl-L-alanine
	N-Alpha-acetyllysine
	L-Cystine
	L-Alanine
	L-Proline
	L-Tyrosine
	L-Valine
	L-Phenylalanine
	L-Asparagine
	L-Methionine
	L-Aspartic acid
Alpha-aminoadipate pathway	Aminoadipic acid
Arginine metabolism	Creatine
Fatty acid transport	Isovalerylcarnitine
Fatty acid transport	Carnitine
Glucosaminoacids	D-Glucuronic acid
Glutaminolysis	D-Glutamic acid
Glycolysis	Pyruvic acid
	D-Glucose
	L-Lactic acid
Glyoxalase cycle	S-Lactoylglutathione
Glyoxylate cycle	Glyoxylic acid
Methionine-Glutathione metabolism	Acetylcholine
	S-Adenosylhomocysteine
	Glutathione
	5'-Methylthioadenosine
	S-Adenosylmethionine
	Dimethylglycine
	Homocysteine
Neurotransmitter	N-Acetylaspartylglutamic acid
	Gamma-Aminobutyric acid
	L-Homocysteic acid
Nicotinamide metabolism	1-Methylnicotinamide
Nucleotide synthesis	Deoxyribose 1-phosphate
Oncometabolite	2-Hydroxyglutaric acid
Phenylalanine metabolism	4-Hydroxyphenylpyruvic acid
Phospholipid	Myoinositol
	Glycerophosphocholine
Polyamine metabolism	Cadaverine
	Spermine
Porphyrins metabolism	5-Aminolevulinic acid
Purines	7-Methylguanosine
	cADP-ribose
	Adenine
	Hypoxanthine
	Guanine
Pyrimidines	Deoxycytidine
	Uridine
	Cytidine
	Uridine 5'-monophosphate
TCA cycle	cis-Aconitic acid
	L-Malic acid
	Oxoglutaric acid
	Fumaric acid
	Citric acid
	Succinic acid
Trp derivative	L-Kynurenine
	Indole
	5-Methoxytryptophan
Urea cycle	N-Acetylornithine
	Ornithine
Vitamin B3	Nicotinic acid_Vit B3
Vitamin B6 metabolism	4-Pyridoxic acid
	Pyridoxamine

Figure S1

A

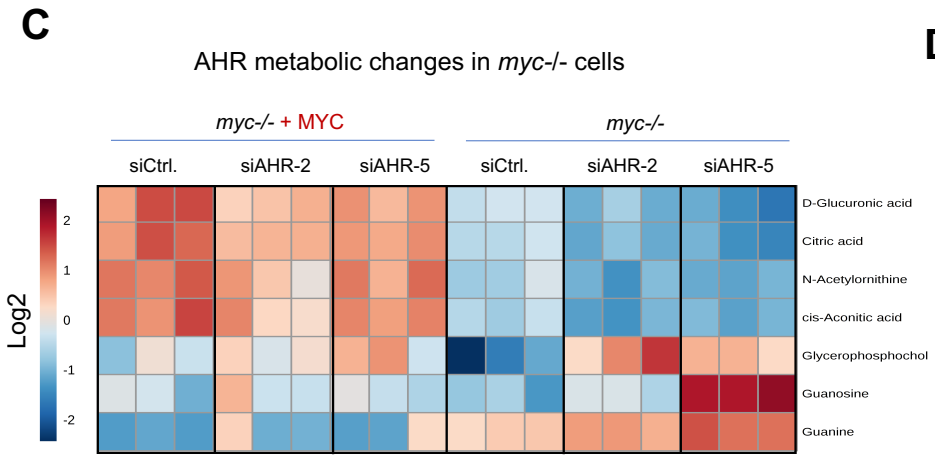


B

AHR-driven in myc-/- + MYC cells		
Pathway	**Metabolite**	
Choline metabolite	Propionylcholine	
Glutathione metabolism	Pyroglutamic acid	
Aminoacid	L-Histidine	
Glycolysis	Lactate	*
Transsulfuration pathway	L-Homoserine	
Aminoacid	N-Acetyl-L-alanine	*
Pyrimidines	UMP	*
Vitamin B	Niacinamide	
Oncometabolite	2-Hydroxyglutarate	*
Glyoxalase cycle	S-Lactoylglutathione	*

* Increased by MYC, downregulated by AHR

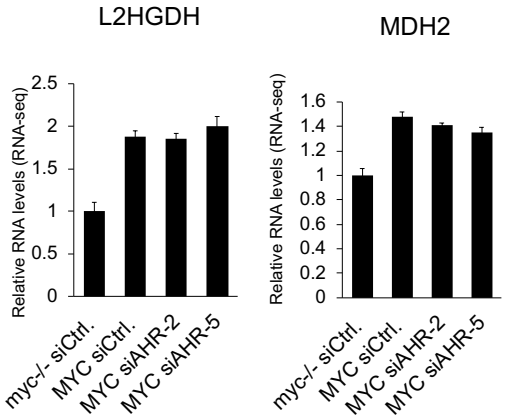
C



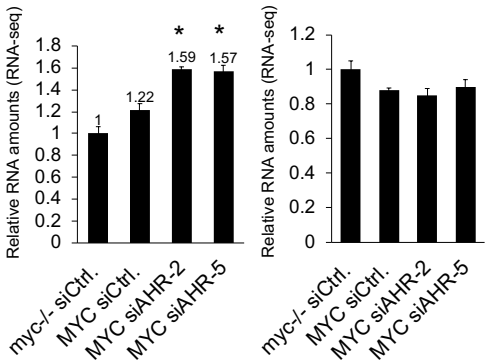
D

AHR-driven MYC-independent metabolic changes	
Pathway	**Metabolite**
Glucosaminoacids	D-Glucuronic acid
Phospholipid	Glycerophosphocholine
Purines	Guanosine
	Guanine
TCA cycle	Citric acid
	cis-Aconitic acid
Urea cycle	N-Acetylornithine

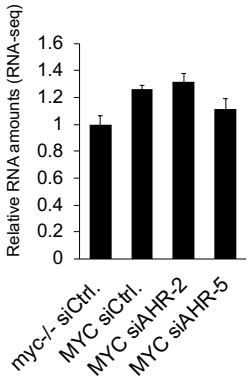
E L-2-Hydroxyglutarate production



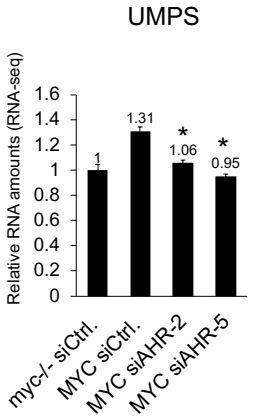
F D-2-Hydroxyglutarate production



G S-Lactoyl-glutathione prodution

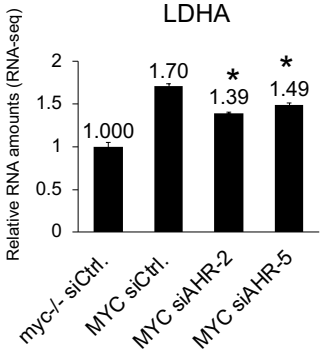


H UMP production

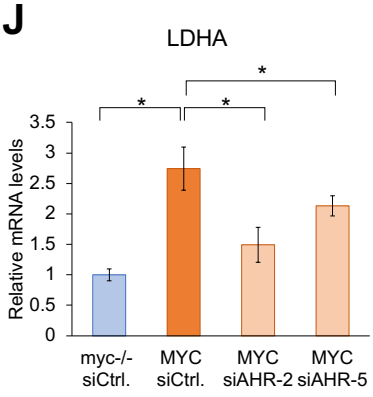


*RNA-seq showed that IDH1 and IDH2 are wild type in this rat fibroblasts

I Lactate and L-2-Hydroxyglutarate production



J



K

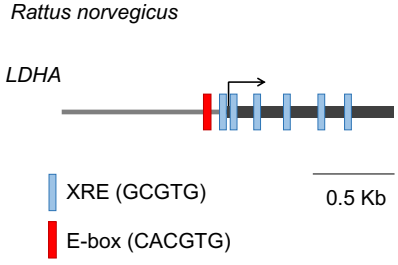


Figure S2

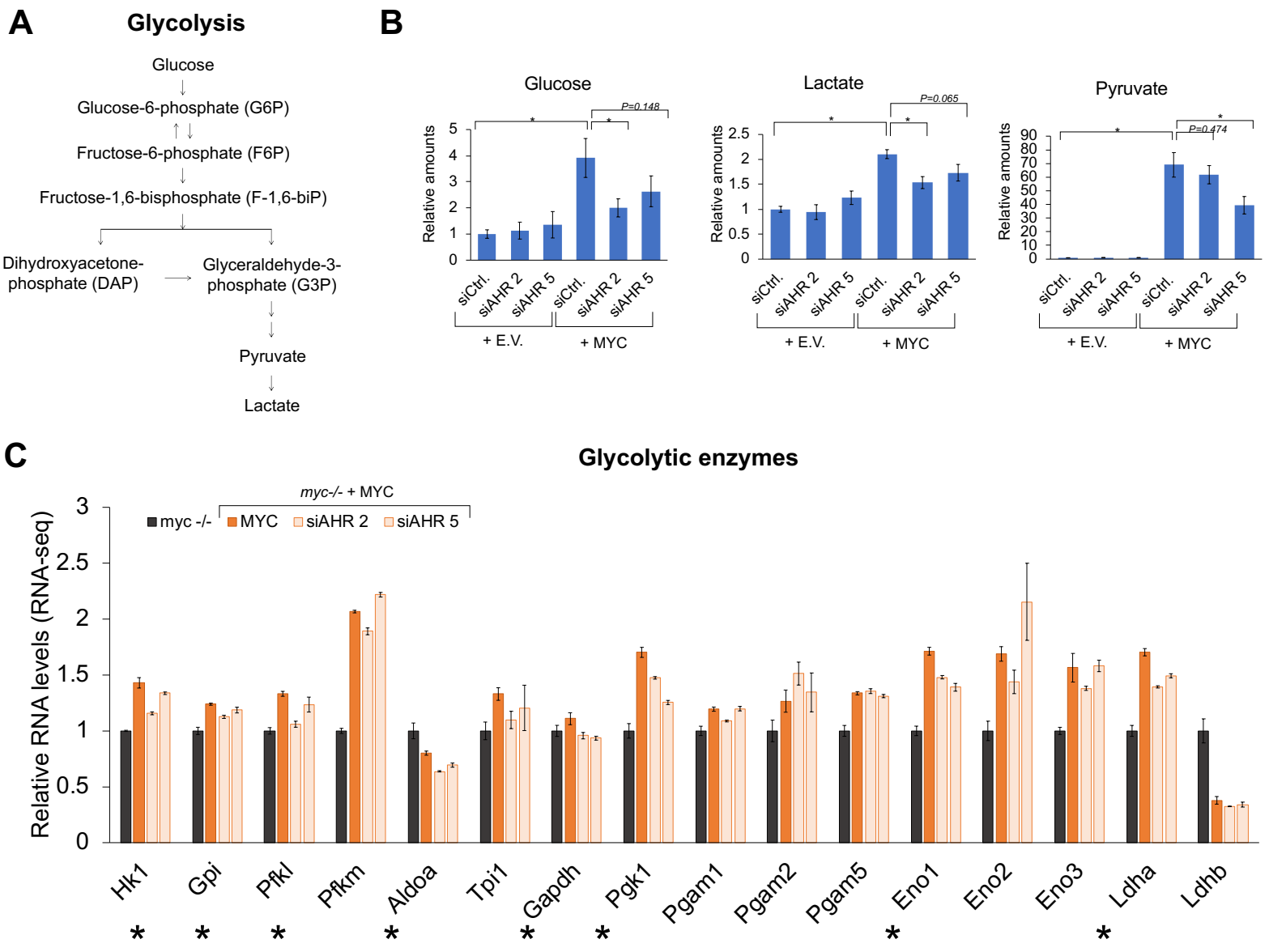

A
Glycolysis
Glucose
Glucose-6-phosphate (G6P)
Fructose-6-phosphate (F6P)
Fructose-1,6-bisphosphate (F-1,6-biP)
Dihydroxyacetone-phosphate (DAP)
Glyceraldehyde-3-phosphate (G3P)
Pyruvate
Lactate
B
Glucose
Lactate
Pyruvate
Relative amounts
P=0.148
P=0.065
P=0.474
siCtrl.
siAHR 2
siAHR 5
+ E.V.
+ MYC
C
Glycolytic enzymes
myc-/- + MYC
myc -/-
MYC
siAHR 2
siAHR 5
Relative RNA levels (RNA-seq)
Hk1
Gpi
Pfkl
Pfkm
Aldoa
Tpi1
Gapdh
Pgk1
Pgam1
Pgam2
Pgam5
Eno1
Eno2
Eno3
Ldha
Ldhb

Figure S3

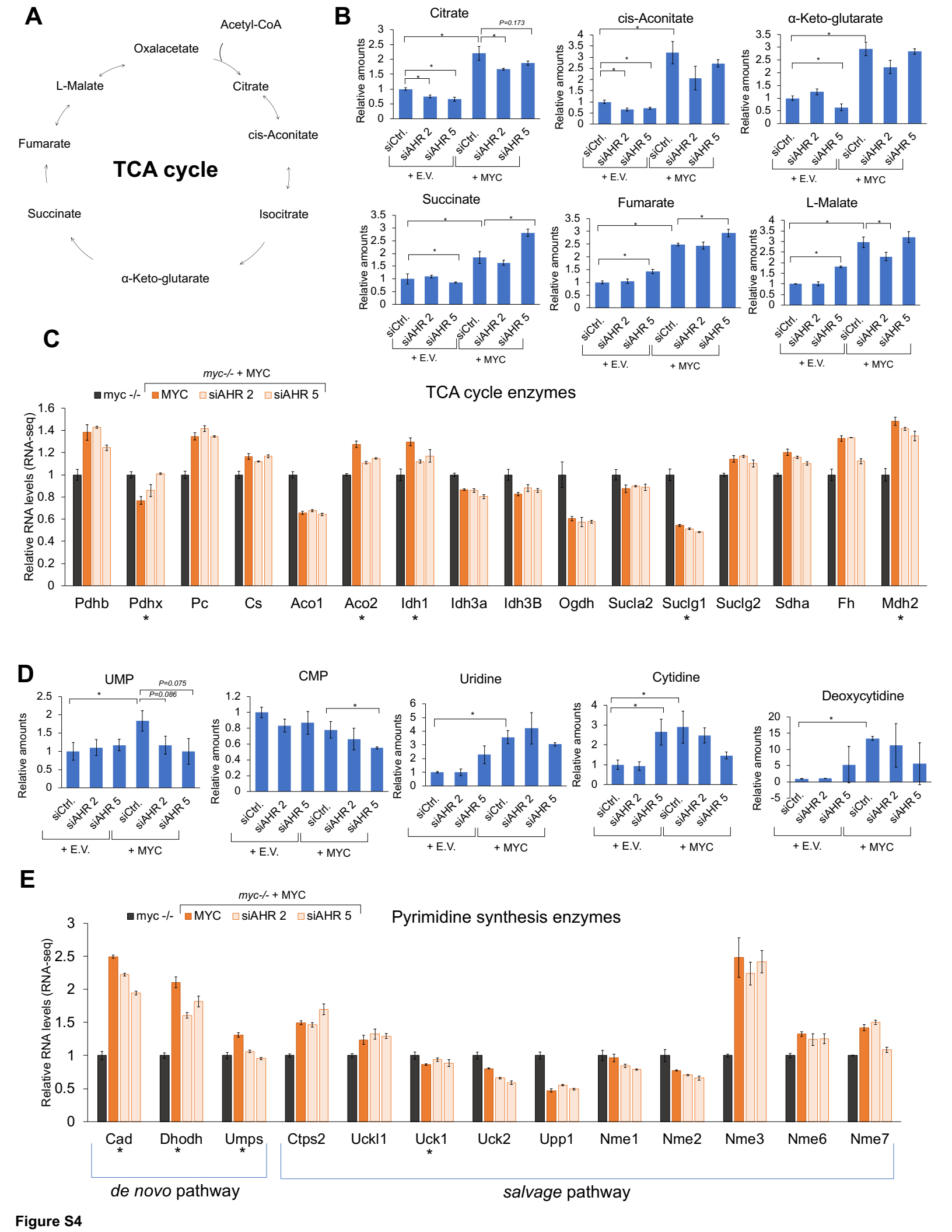
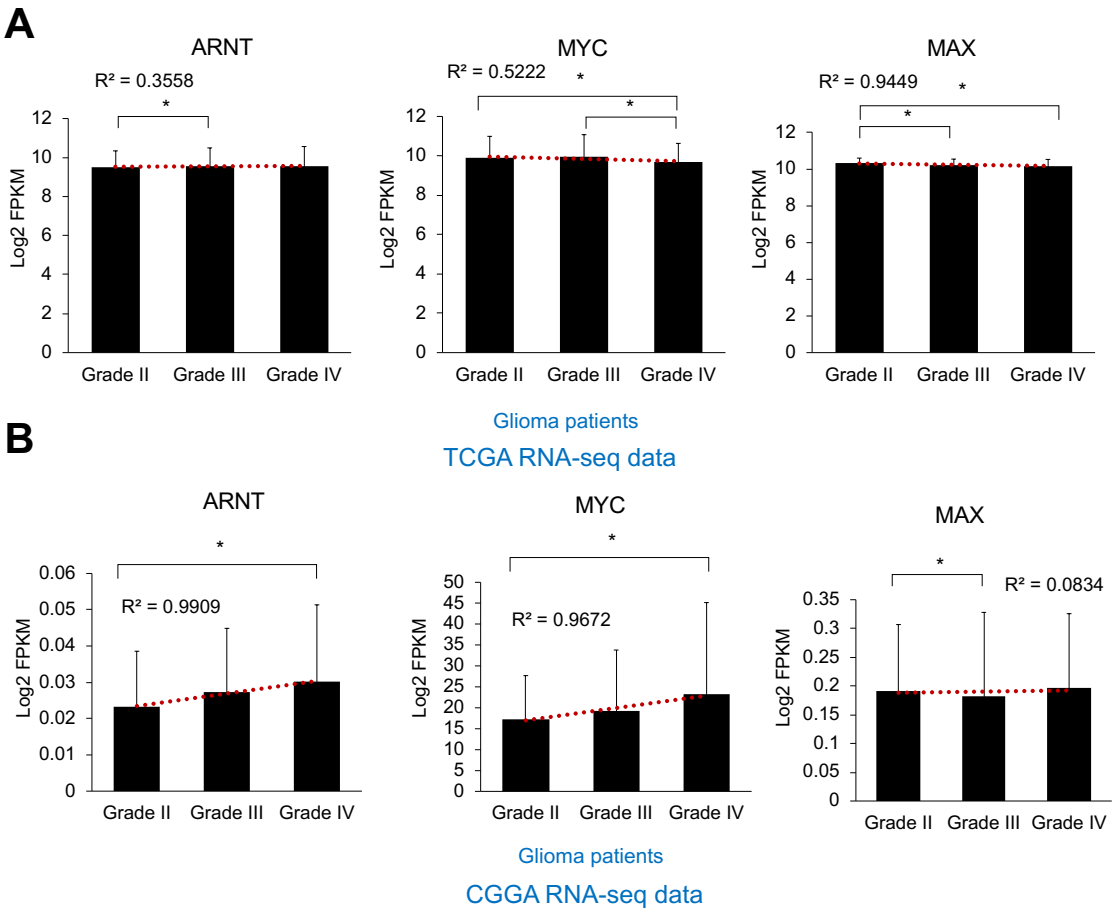
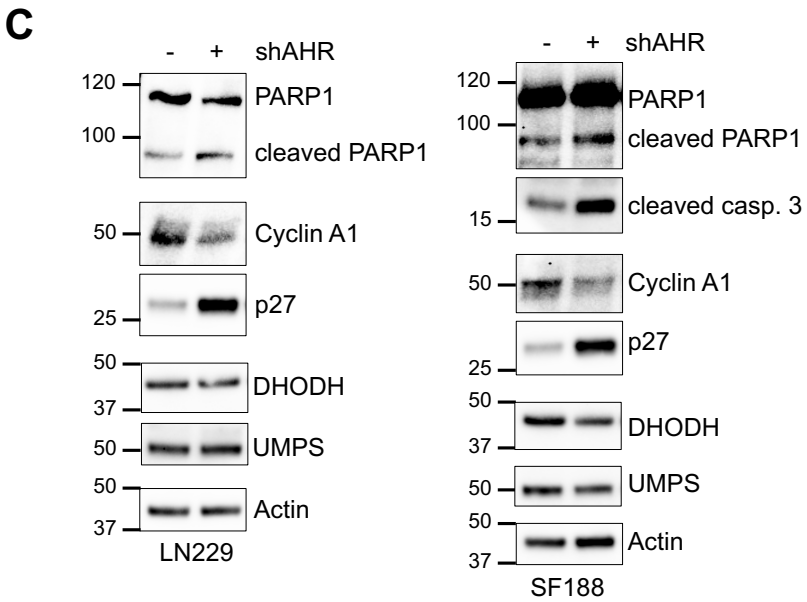
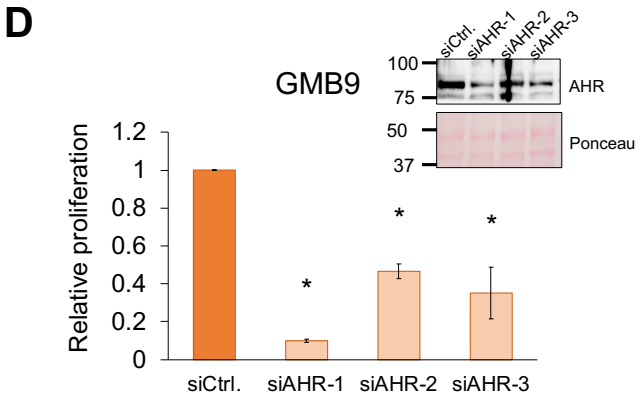

A
Acetyl-CoA
Oxalacetate
L-Malate
Citrate
Fumarate
cis-Aconitate
TCA cycle
Succinate
Isocitrate
α-Keto-glutarate
B
Citrate
cis-Aconitate
α-Keto-glutarate
Succinate
Fumarate
L-Malate
Relative amounts
P=0.173
siCtrl.
siAHR 2
siAHR 5
+ E.V.
+ MYC
C
myc -/-
MYC
siAHR 2
siAHR 5
myc-/- + MYC
TCA cycle enzymes
Relative RNA levels (RNA-seq)
Pdhb
Pdhx
Pc
Cs
Aco1
Aco2
Idh1
Idh3a
Idh3B
Ogdh
Sucla2
Suclg1
Suclg2
Sdha
Fh
Mdh2
D
UMP
CMP
Uridine
Cytidine
Deoxycytidine
P=0.075
P=0.086
Relative amounts
E
Pyrimidine synthesis enzymes
Relative RNA levels (RNA-seq)
Cad
Dhodh
Umps
Ctps2
Uckl1
Uck1
Uck2
Upp1
Nme1
Nme2
Nme3
Nme6
Nme7
de novo pathway
salvage pathway

Figure S4


A
ARNT
R² = 0.3558
MYC
R² = 0.5222
MAX
R² = 0.9449
Log2 FPKM
Grade II
Grade III
Grade IV
Glioma patients
TCGA RNA-seq data
B
ARNT
R² = 0.9909
MYC
R² = 0.9672
MAX
R² = 0.0834
Glioma patients
CGGA RNA-seq data


C
shAHR
PARP1
cleaved PARP1
Cyclin A1
p27
DHODH
UMPS
Actin
LN229
cleaved casp. 3
SF188


D
GMB9
siCtrl.
siAHR-1
siAHR-2
siAHR-3
AHR
Ponceau
Relative proliferation

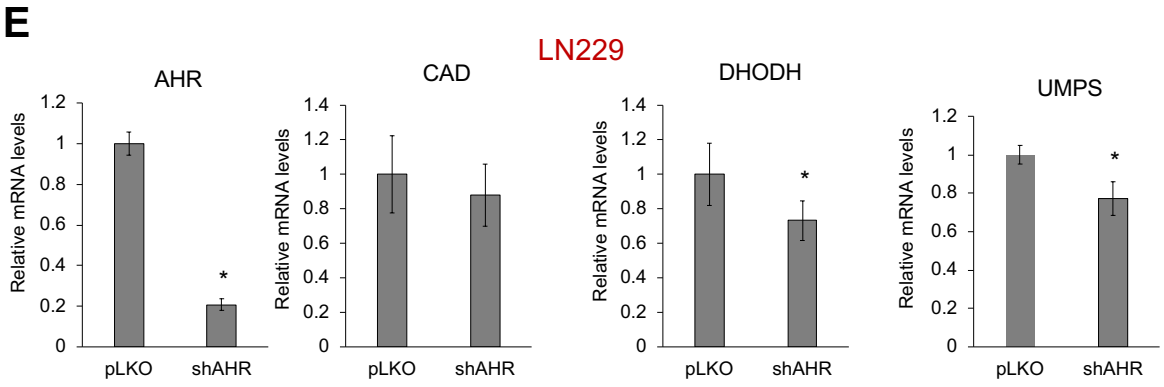

E
LN229
AHR
CAD
DHODH
UMPS
Relative mRNA levels
pLKO
shAHR

Figure S5

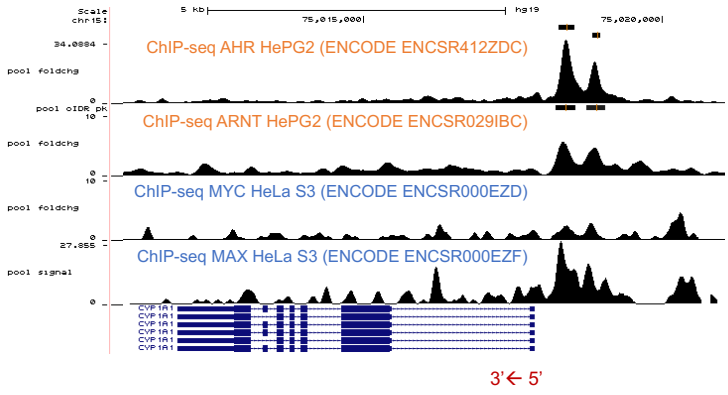
A

	hg19/Human ChIP-seq ENCODE					
	AHR optimal IDR peaks (HepG2)			MYC optimal IDR peaks (HeLa-S3)		
Gene	**Coordinates**	**Eboxes**	**HRE**	**Coordinates**	**Eboxes**	**HRE**
CAD	No peak	NA	NA	chr2:27440241-27440422	2	0
DHODH	chr16:72042582-72042997	1	4	chr16:72042486-72042829 chr16:72042686-72043029	0 1	2 3
UMPS	chr3:124449022-124449437 chr3:124449742-124450157 chr3:124449952-124450367	0 0 0	0 1 0	chr3:124449087-124449430 chr3:124449302-124449645	0 0	0 0

B

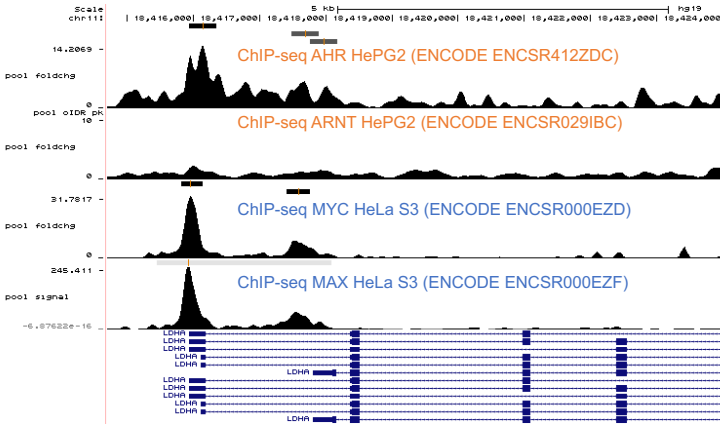
CYP1A1

(*bona-fide* AHR-ARNT target gene)

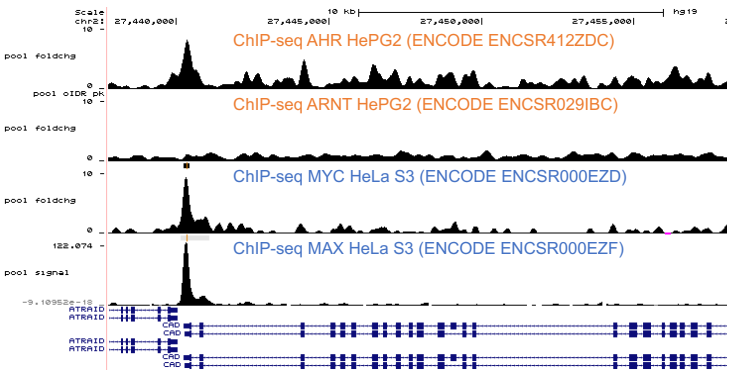


LDHA

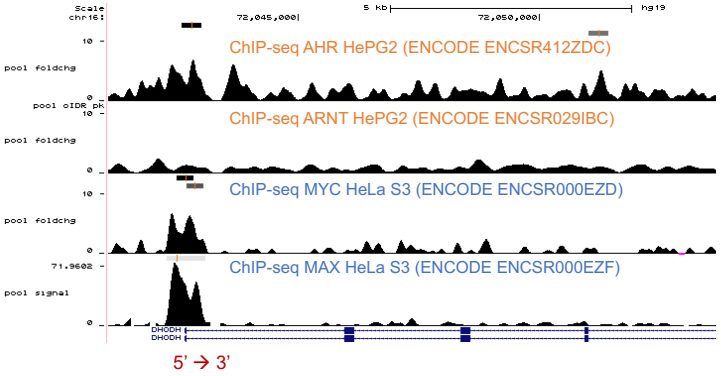
(*bona-fide* MYC-MAX target gene)



CAD



DHODH



UMPS

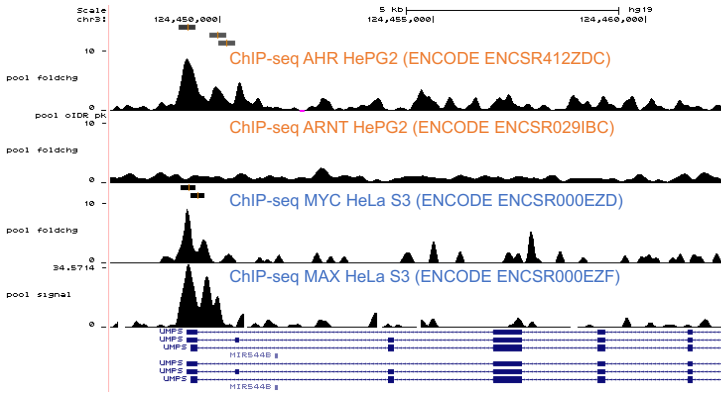


Figure S6

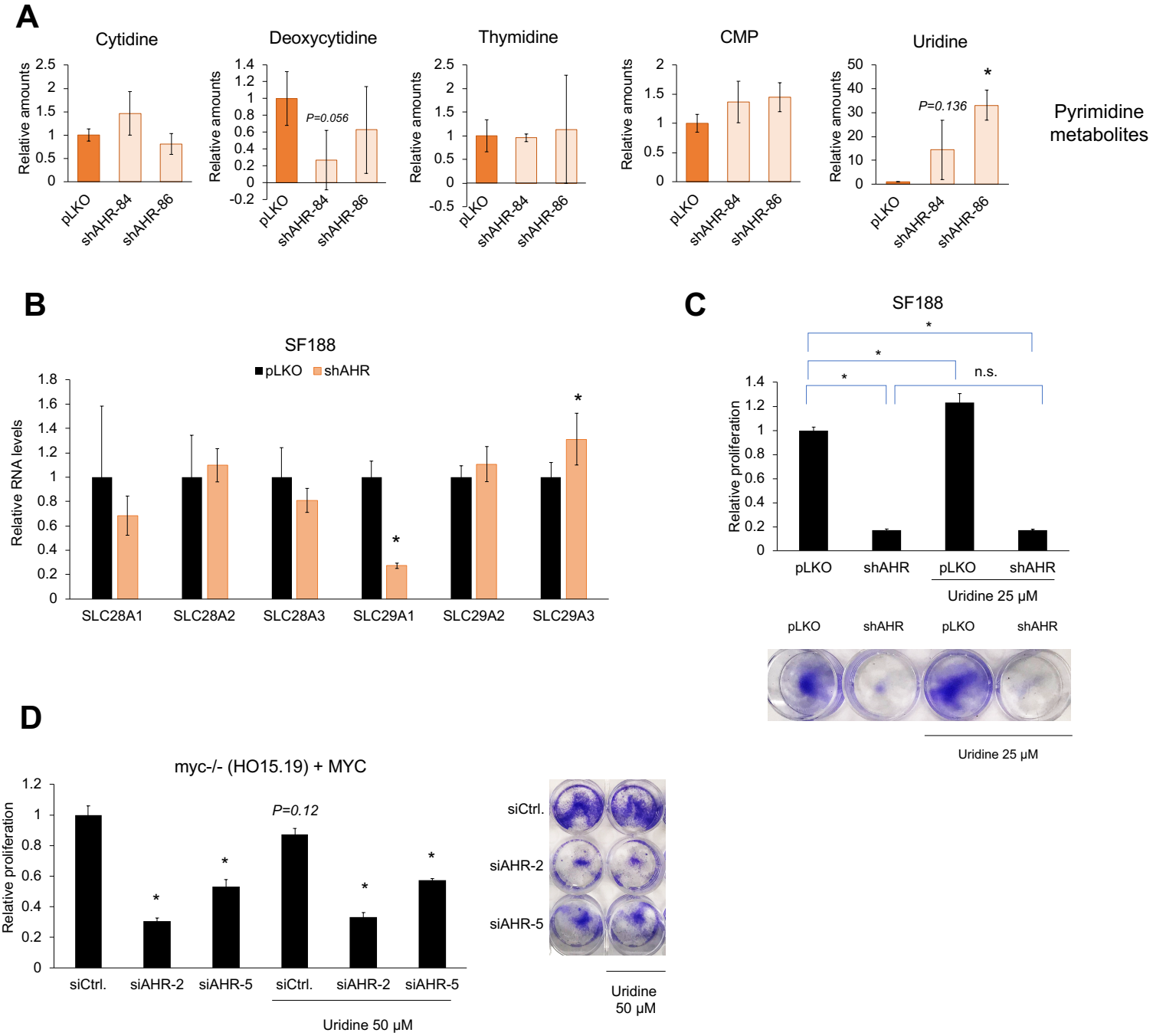

A
Cytidine
Deoxycytidine
Thymidine
CMP
Uridine
Relative amounts
P=0.056
P=0.136
pLKO
shAHR-84
shAHR-86
Pyrimidine metabolites
B
SF188
pLKO
shAHR
Relative RNA levels
SLC28A1
SLC28A2
SLC28A3
SLC29A1
SLC29A2
SLC29A3
C
SF188
Relative proliferation
n.s.
pLKO
shAHR
Uridine 25 μM
D
myc-/- (HO15.19) + MYC
P=0.12
siCtrl.
siAHR-2
siAHR-5
Uridine 50 μM

Figure S7