**SUPPLEMENTARY INFROMATION**

# Arginine is an epigenetic regulator targeting TEAD4 to modulate OXPHOS in prostate cancer cells

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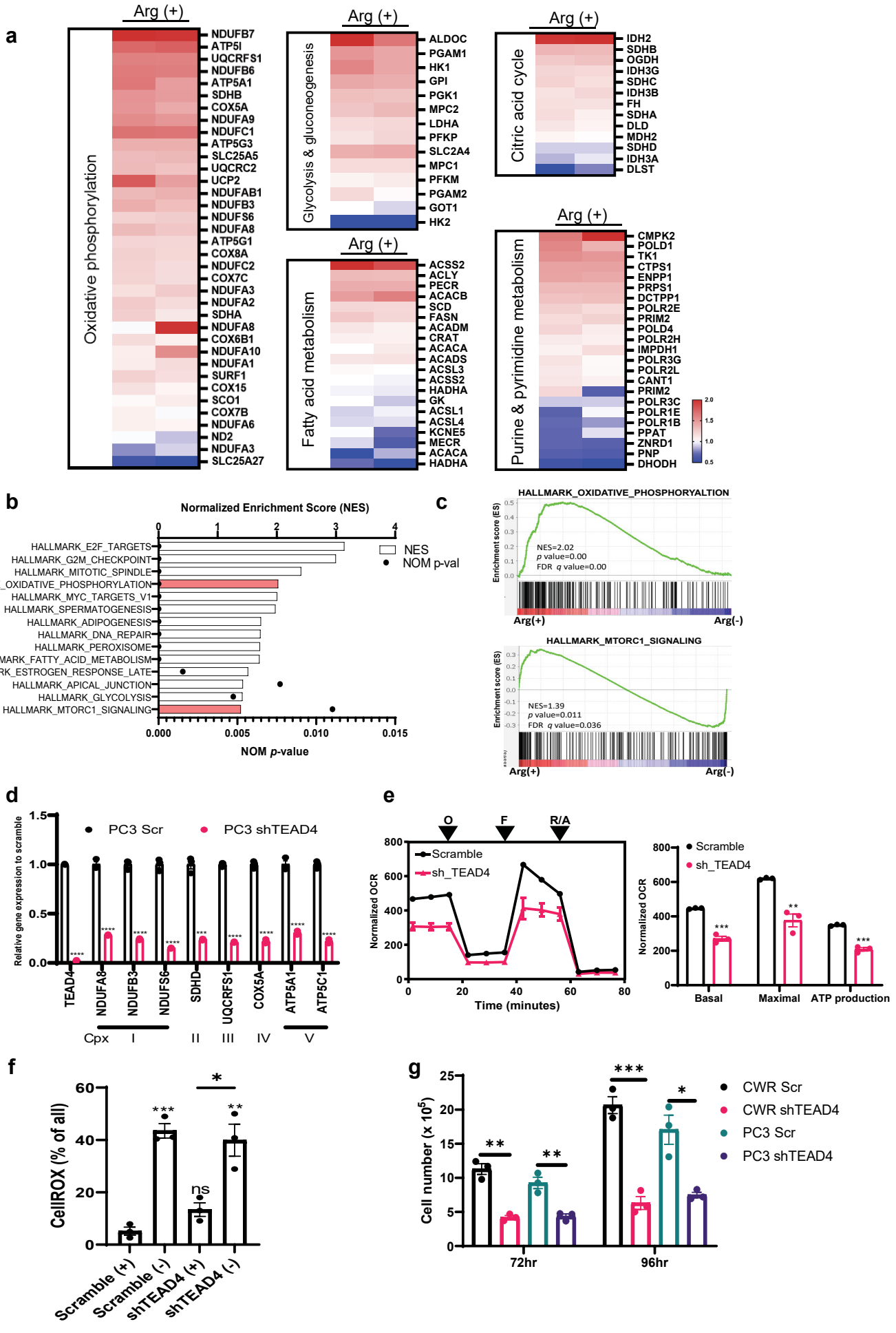
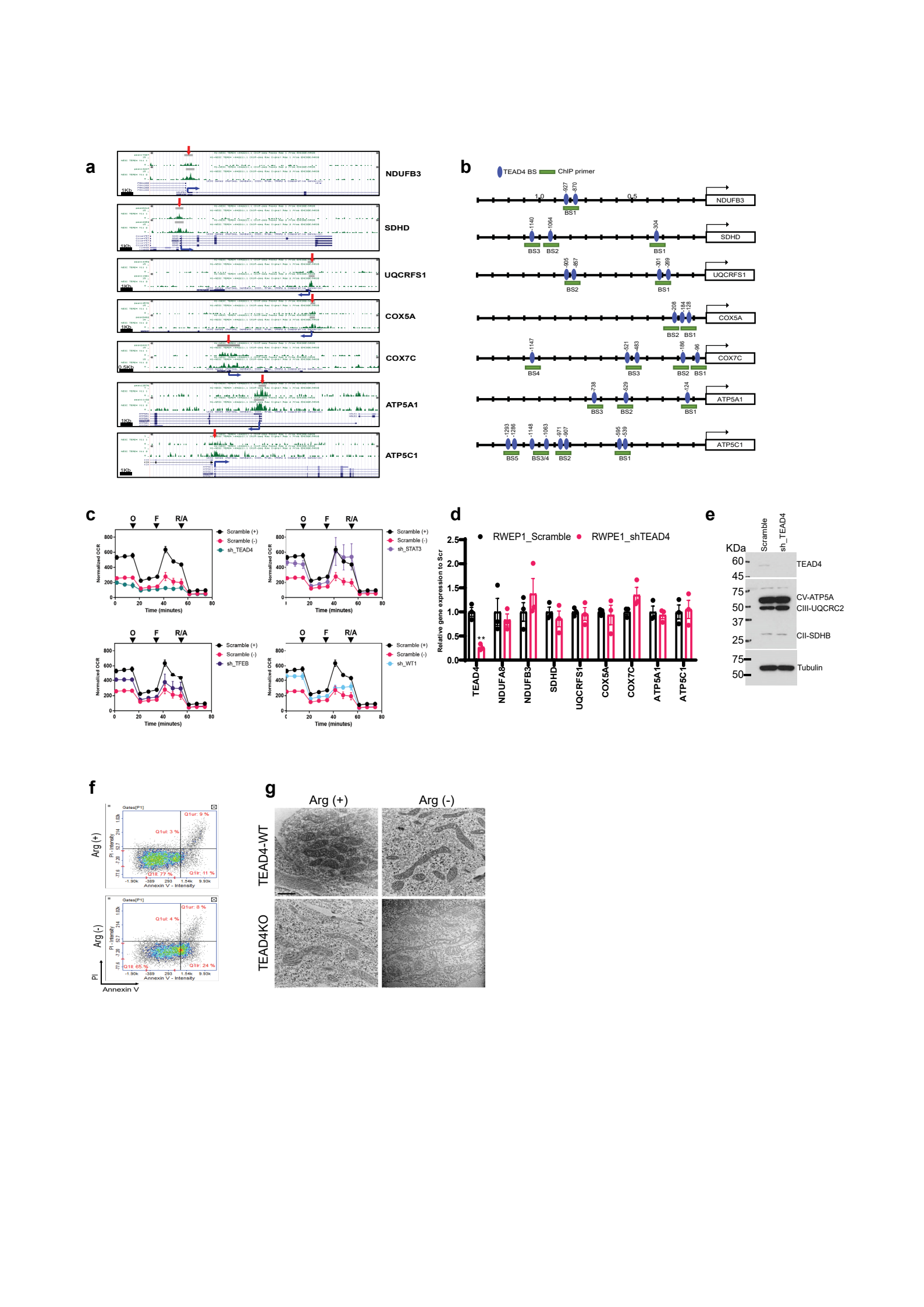
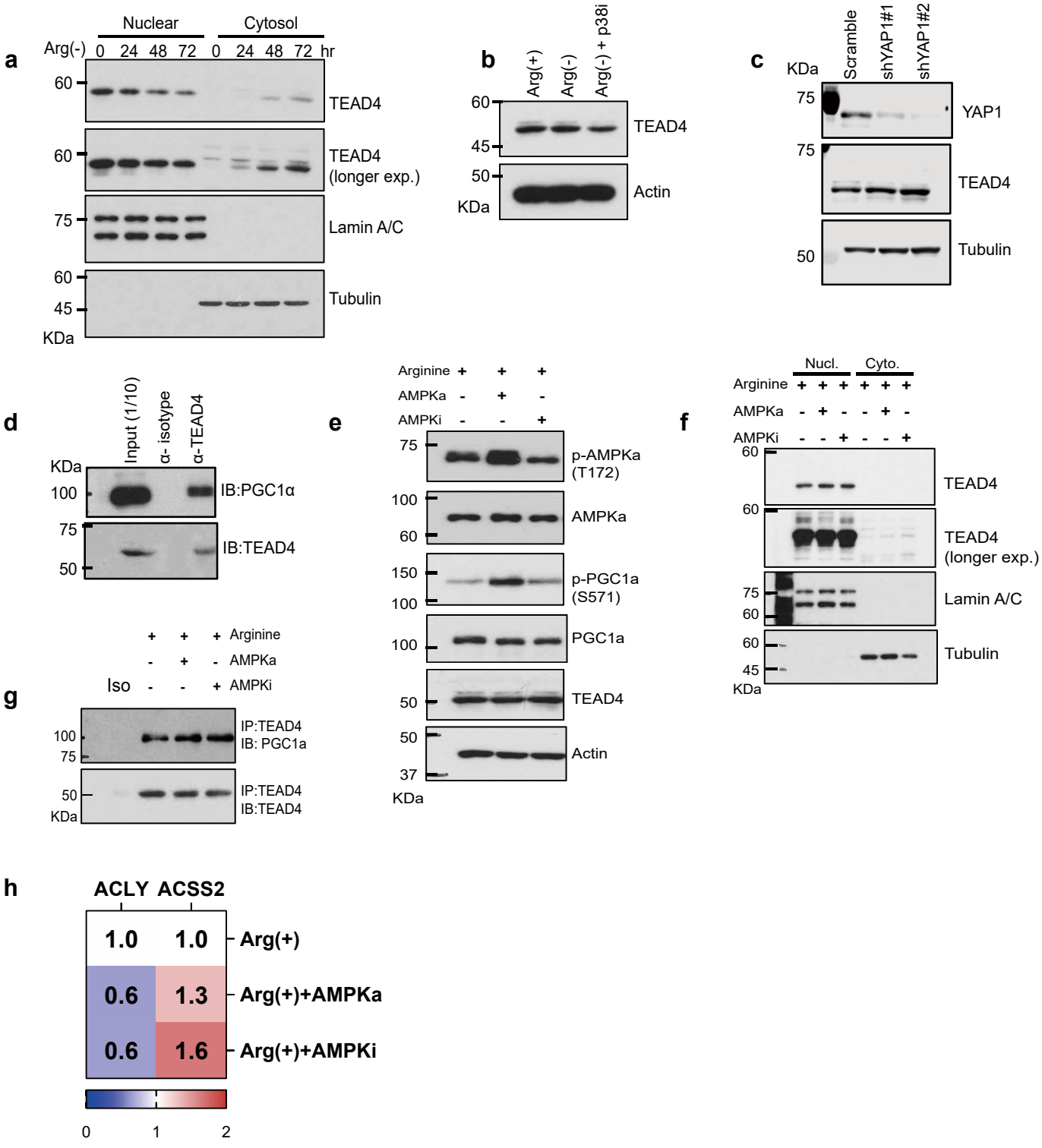

a
Arg (+)
Oxidative phosphorylation
NDUFB7
ATP5I
UQCRFS1
NDUFB6
ATP5A1
SDHB
COX5A
NDUFA9
NDUFC1
ATP5G3
SLC25A5
UQCRC2
UCP2
NDUFAB1
NDUFB3
NDUFS6
NDUFA8
ATP5G1
COX8A
NDUFC2
COX7C
NDUFA3
NDUFA2
SDHA
NDUFA8
COX6B1
NDUFA10
NDUFA1
SURF1
COX15
SCO1
COX7B
NDUFA6
ND2
NDUFA3
SLC25A27
Glycolysis & gluconeogenesis
ALDOC
PGAM1
HK1
GPI
PGK1
MPC2
LDHA
PFKP
SLC2A4
MPC1
PFKM
PGAM2
GOT1
HK2
Fatty acid metabolism
ACSS2
ACLY
PECR
ACACB
SCD
FASN
ACADM
CRAT
ACACA
ACADS
ACSL3
ACSS2
HADHA
GK
ACSL1
ACSL4
KCNE5
MECR
ACACA
HADHA
Citric acid cycle
IDH2
SDHB
OGDH
IDH3G
SDHC
IDH3B
FH
SDHA
DLD
MDH2
SDHD
IDH3A
DLST
Purine & pyrimidine metabolism
CMPK2
POLD1
TK1
CTPS1
ENPP1
PRPS1
DCTPP1
POLR2E
PRIM2
POLD4
POLR2H
IMPDH1
POLR3G
POLR2L
CANT1
PRIM2
POLR3C
POLR1E
POLR1B
PPAT
ZNRD1
PNP
DHODH
b
Normalized Enrichment Score (NES)
HALLMARK_E2F_TARGETS
HALLMARK_G2M_CHECKPOINT
HALLMARK_MITOTIC_SPINDLE
HALLMARK_OXIDATIVE_PHOSPHORYLATION
HALLMARK_MYC_TARGETS_V1
HALLMARK_SPERMATOGENESIS
HALLMARK_ADIPOGENESIS
HALLMARK_DNA_REPAIR
HALLMARK_PEROXISOME
HALLMARK_FATTY_ACID_METABOLISM
HALLMARK_ESTROGEN_RESPONSE_LATE
HALLMARK_APICAL_JUNCTION
HALLMARK_GLYCOLYSIS
HALLMARK_MTORC1_SIGNALING
NES
NOM p-val
NOM p-value
c
HALLMARK_OXIDATIVE_PHOSPHORYALTION
Enrichment score (ES)
NES=2.02
p value=0.00
FDR q value=0.00
Arg(+)
Arg(-)
HALLMARK_MTORC1_SIGNALING
NES=1.39
p value=0.011
FDR q value=0.036
d
PC3 Scr
PC3 shTEAD4
Relative gene expression to scramble
TEAD4
NDUFA8
NDUFB3
NDUFS6
SDHD
UQCRFS1
COX5A
ATP5A1
ATP5C1
Cpx I
II
III
IV
V
e
O
F
R/A
Scramble
sh_TEAD4
Normalized OCR
Time (minutes)
Basal
Maximal
ATP production
f
CellROX (% of all)
Scramble (+)
Scramble (-)
shTEAD4 (+)
shTEAD4 (-)
ns
g
Cell number (x 10^5)
CWR Scr
CWR shTEAD4
PC3 Scr
PC3 shTEAD4
72hr
96hr

**Supplementary Figure 1 Arginine epigenetically modulates mitochondrial OXPHOS genes** (a) Heat map of Affymertrix microarray analysis shows arginine (Arg+) globally induced metabolic pathways, including oxidative phosphorylation pathway, glucose, fatty acid and DNA metabolic pathways in PC3 prostate cancer cells. The color key indicates the fold change to control. (b) Gene set enrichment assay (GSEA) of PC3 microarray data was performed using hallmark gene set collection. Normalized enrichment scores (NES) for pathways indicates the significantly difference in arginine stimulation group. (c) GSEA shows the genes associated with oxidative phosphorylation (upper panel) and mTORC1 pathway (lower panel) are enriched in arginine stimulation Arg (+) group. (d) Real-time PCR analysis of OXPHOS genes expression after silencing of TEAD4 *via* shRNA in PC3 cells. (e) Seahorse assay for mitochondrial respiration activities after silencing TEAD4 *via* shRNA in PC3 cells. O: oligomycin, F: FCCP, R/A: rotenone /antimycin. (f) Advance image cytometer analysis shows silencing of TEAD4 increased cellular ROS production in PC3 cells. (g) Cell number after silencing of TEAD4 by shRNA in CWR22Rv1 and PC3 cells at different time points in the presence of arginine. Data are presented as mean values + SEM of independent experiments (n=3 in d-g). *$p$< 0.05, **$p$ < 0.01, ***$p$< 0.001, ****$p$ < 0.0001, ns: not significant, using unpaired two-tailed Student's t test. Source data are provided as a Source Data file.


a
NDUFB3
SDHD
UQCRFS1
COX5A
COX7C
ATP5A1
ATP5C1
b
TEAD4 BS
ChIP primer
NDUFB3
SDHD
UQCRFS1
COX5A
COX7C
ATP5A1
ATP5C1
c
O
F
R/A
Normalized OCR
Time (minutes)
Scramble (+)
Scramble (-)
sh_TEAD4
sh_STAT3
sh_TFEB
sh_WT1
d
RWEP1_Scramble
RWPE1_shTEAD4
Relative gene expression to Scr
TEAD4
NDUFA8
NDUFB3
SDHD
UQCRFS1
COX5A
COX7C
ATP5A1
ATP5C1
e
Scramble
sh_TEAD4
KDa
TEAD4
CV-ATP5A
CIII-UQCRC2
CII-SDHB
Tubulin
f
Arg (+)
Arg (-)
PI
Annexin V
g
Arg (+)
Arg (-)
TEAD4-WT
TEAD4KO

**Supplementary Figure 2 Arginine targets TEAD4 to modulate the mitochondrial functions** (a) TEAD4 ChIP-seq distribution at representative OXPHOS genes loci from ENCODE database (ENCFF000OWA and ENCFF000OWD), visualized by UCSC Genome Browser ( https://genome.ucsc.edu ). (b) Predication of TEAD4 binding sites (BS in blue) on OXPHOS promoter regions by FIMO program. The green box indicates the target sites of ChIP-qPCR. (c) Individual shRNA plot for seahorse assay in Figure 3c. (d) TEAD4 was knock-down in non-arginine auxotrophic epithelial prostate cells, RWPE1, *via* lentivirus shRNA infection for 24 hours, following antibiotics selection for one week. OXPHOS genes expression was determined by quantitative real-time PCR and the protein level was evaluated by immunoblot (e). (f) Apoptosis analysis by double staining of annexin V and propidium iodide (PI) staining after arginine deprivation for 48-hours. (g) Ultrastructure of mitochondrial morphology after 48-hours arginine deprivation in wild type (WT) or TEAD4 knock-out (TEAD4KO) cells (scale bar=500nm). Data are presented as mean values + SEM of independent experiments (n=3 in d). $^{**}p < 0.01$, using unpaired two-tailed Student's t test. Source data are provided as a Source Data file.


a
Nuclear
Cytosol
Arg(-) 0 24 48 72 0 24 48 72 hr
60
TEAD4
60
TEAD4
(longer exp.)
75
Lamin A/C
60
45
Tubulin
KDa
b
Arg(+)
Arg(-)
Arg(-) + p38i
60
TEAD4
45
50
Actin
KDa
c
KDa
Scramble
shYAP1#1
shYAP1#2
75
YAP1
75
TEAD4
50
Tubulin
d
Input (1/10)
α- isotype
α-TEAD4
KDa
100
IB:PGC1α
75
IB:TEAD4
50
e
Arginine + + +
AMPKa - + -
AMPKi - - +
75
p-AMPKa
(T172)
100
AMPKa
60
150
p-PGC1a
(S571)
100
100
PGC1a
50
TEAD4
50
Actin
37
KDa
f
Nucl.
Cyto.
Arginine + + + + + +
AMPKa - + - - + -
AMPKi - - + - - +
60
TEAD4
60
TEAD4
(longer exp.)
75
60
Lamin A/C
60
Tubulin
45
KDa
g
+ + + Arginine
- + - AMPKa
Iso - - + AMPKi
100
75
IP:TEAD4
IB: PGC1a
50
IP:TEAD4
IB:TEAD4
KDa
h
ACLY ACSS2
1.0 1.0 Arg(+)
0.6 1.3 Arg(+)+AMPKa
0.6 1.6 Arg(+)+AMPKi
0
1
2

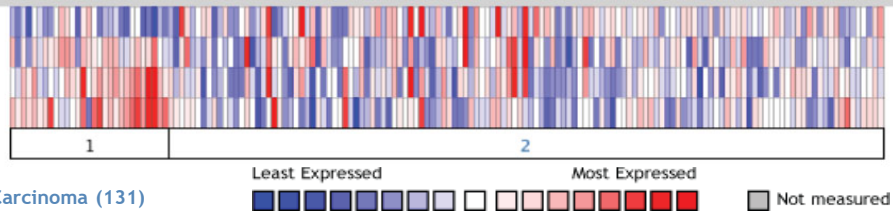
**Supplementary Figure 3 Arginine mediated nuclear retention of TEAD4** (a) Immunoblotting shows TEAD4 location after arginine deprivation at different time pointed (related to figure 4e). (b) Immunoblotting of total TEAD4 expression after treatment (related to figure 4f). (c) YAP1 was knocked down by two individual YAP1 shRNA clones via lentivirus transduction for 24 hours, following antibiotics selection for one week. Total TEAD4 protein expression was evaluated by immunoblotting. (d) The interaction of TEAD4 with PGC1a was evaluated by immunoprecipitation. Total lysate was first incubated with isotype or TEAD4 antibody overnight and then pull-down by magnetic beads. Interaction was evaluated by PGC1a antibody. 10% of total protein as internal control. (e) In the presence of arginine, cells were treated with either AMPK activator, Metformin (10mM), or AMPK inhibitor, Dorsomorphin (10μM), for 24hours. The downstream target, phosphor-PGC1a (S571) was confirmed by immunoblot. However, the total level of TEAD4 was not affected. (f) The immunoblot of cell fractionation shows AMPK did not affection TEAD4 translocation in the presence of arginine. (g) The immunoprecipitation shows AMPK did not affect the interaction of TEAD4 with PGC1a in the presence of arginine. (h) The quantitative real-time PCR shows AMPK did not correlate with the expression of ACLY or ACSS2 in the presence of arginine. The color key indicates the relative gene expression to control. Source data are provided as a Source Data file.

**a**

## Comparison of TEAD1, TEAD2, TEAD3 and TEAD4 in Taylor Prostate 3

Over-expression in Prostate Carcinoma vs. Normal
log2 median-centered intensity

| P-value | Fold Change | Gene |
|---|---|---|
| 4.55E-5 | 1.13 | TEAD4 |
| 0.998 | -1.10 | TEAD2 |
| 1.000 | -1.21 | TEAD3 |
| 1.000 | -1.47 | TEAD1 |



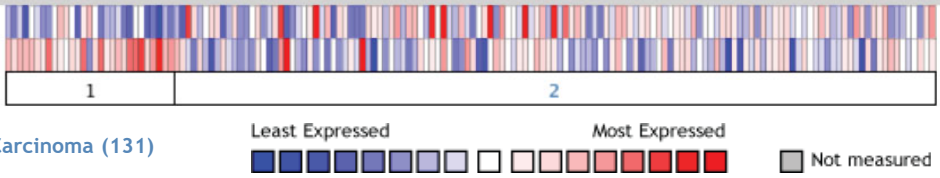

1. Prostate Gland (29) 2. Prostate Carcinoma (131)

**b**

## Comparison of TEAD4 and YAP1 in Taylor Prostate 3

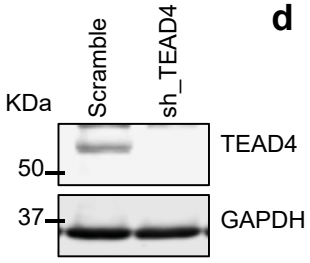
Over-expression in Prostate Carcinoma vs. Normal
log2 median-centered intensity

| P-value | Fold Change | Gene |
|---|---|---|
| 4.55E-5 | 1.13 | TEAD4 |
| 1.000 | -1.29 | YAP1 |

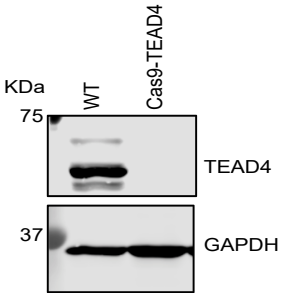


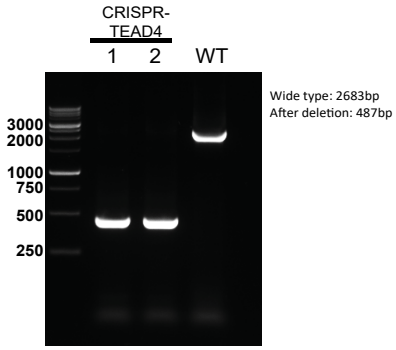

1. Prostate Gland (29) 2. Prostate Carcinoma (131)

**c**

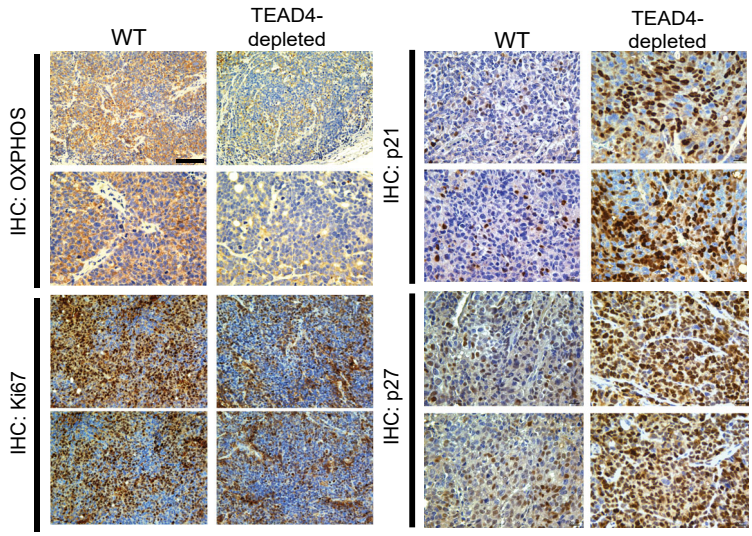



**d**




**e**



**Supplementary Figure 4 TEAD4 could be a potential target for cancer therapy** (a) Oncomine database (www.oncomine.org) shows TEADs expression in Taylor Prostate cancer library. (b) Oncomine database shows TEAD4 and YAP1 expression in Taylor prostate cancer library. (c) Western blotting shows the knock-down efficiency of shRNA_TEAD4 CWR22Rv1 cells before subcutaneous injection. (d) Knock-out efficiency of CRISPR-Cas9 TEAD4 (left panel) CWR22Rv1 cells before subcutaneous injection as well as PCR confirmation (right panel). (e) IHC staining of pan-OXPHOS protein, CDK inhibitors, p21 and p27, and proliferation marker, Ki67 in mouse tumor samples (scale bar=50μm). Source data are provided as a Source Data file.

**Supplementary Table 1 Target OXPHOS genes in TEAD4 ChIP-seq datasets from the ENCODE dataset**

| Complex | I | | II | III | IV | V |
|---|---|---|---|---|---|---|
| Targets | NDUFA1 | NDUFB1 | SDHA | UQCR10 | COX10 | ATP5B |
| | NDUFA2 | NDUFB2 | SDHAF1 | UQCR11 | COX11 | ATP5C1 |
| | NDUFA3 | NDUFB3 | SDHAF2 | UQCRB | COX14 | ATP5D |
| | NDUFA4 | NDUFB5 | SDHAF3 | UQCRC1 | COX15 | ATP5E |
| | NDUFA4L2 | NDUFB6 | SDHAF4 | UQCRC2 | COX16 | ATP5O |
| | NDUFA5 | NDUFB7 | SDHAP1 | UQCRFS1 | COX17 | ATP5F1 |
| | NDUFA6 | NDUFB9 | SDHAP3 | UQCRH | COX18 | ATP5G1 |
| | NDUFA7 | NDUFB10 | SDHB | UQCRHL | COX19 | ATP5G2 |
| | NDUFA8 | NDUFB11 | SDHC | UQCRQ | COX20 | ATP5G3 |
| | NDUFA9 | NDUFC1 | SDHD | CYC1 | COX4I1 | ATP5H |
| | NDUFA10 | NDUFC2 | | | COX5A | ATP5I |
| | NDUFA11 | NDUFC2- | | | COX5B | ATP5J |
| | NDUFA12 | KCTD14 | | | COX6A1 | ATP5J2 |
| | NDUFA13 | NDUFS1 | | | COX6B1 | ATP5J2- |
| | NDUFAB1 | NDUFS3 | | | COX6C | PTCD1 |
| | NDUFAF1 | NDUFS4 | | | COX7A2 | ATP5L |
| | NDUFAF2 | NDUFS5 | | | COX7A2L | ATP5L2 |
| | NDUFAF3 | NDUFS6 | | | COX7B | ATP5S |
| | NDUFAF4 | NDUFS7 | | | COX7C | ATP5SL |
| | NDUFAF5 | NDUFS8 | | | COX8A | |
| | NDUFAF6 | NDUFV1 | | | | |
| | NDUFAF7 | NDUFV2 | | | | |
| | | NDUFV3 | | | | |

**Supplementary Table 2 Primer list For ChIP-histone H3 acetylation on OXPHOS promoter region**

| Promoter region | Forward primer sequence (5' to 3') | Reverse primer sequence (5' to 3') |
|---|---|---|
| NDUFB3-pro | GAT GCT ACC TGG TTT ACG AGA G | GGA GGC AAA GTG CTA GAT GAA |
| NDUFS6-pro | GAA CCA CTG GGT ACT CCT AAT C | TGC AGC CTC ATG CAG TT |
| SDHD-pro | CTA ACT AGT CTC CCG TAC CCT T | GCT CAG GTG CCA GGT ATA TAA G |
| UQCRFS1-pro | CAA GAT GTG AAG CAG GGT AAT C | GAG CTC TGT GCA TCC TCT AA |
| COX5A-pro | TGT GGC TCA TGC CTG TAAT C | ACC ACG CCT GGC TAA TTT |
| COX7C-pro | CCC TTC TAG TGC TCC TTG ATA C | TTC CCA ACA TGG CTG AGT T |
| ATP5A1-pro | ACC ACA ACT CCC AGA AAT CC | CCG CCA CTT TAC TAG GAA CTC |
| ATP5C1-pro | GGT ACA GTG TAG GTG CTC AAT AA | AGA AAC AGG GTG GTT AGG ATT C |

**Supplementary Table 3 Primer list for ChIP-TEAD4 on OXPHOS promoter region**

| TEAD4 binding site | Forward primer sequence (5' to 3') | Reverse primer sequence (5' to 3') |
|---|---|---|
| NDUFB3_TEAD4_BS1 | GGA GGA AGG GAT CTA CCA ACT A | GGG TCA AGG CTG ACA ACA T |
| SDHD_TEAD4_BS1 | GGA CAG GAG AGC CAT AAC TTT G | ACC TTC CTT GGT GGT CCT |
| SDHD_TEAD4_BS2 | TGA ACC AAC TAG GGA ACC AAT TA | ATG GAA GAA TTA CCT TGT CTA GGG |
| SDHD_TEAD4_BS3 | AGA TCC TCG TCC CTA CAG ATT | TTG GTT CCC TAG TTG GTT CAC |
| UQCRFS1_TEAD4_BS1 | GCGAT TACTA TGTGC TGGAC T | GGCCG ACTTT ACGAT CCTTT A |
| UQCRFS1_TEAD4_BS2 | ACT CTA GAC TCA GTT CTC TGC T | TTG GCC TCA GTT TGA TCC TAA T |
| COX5A_TEAD4_BS1 | ACA AGA TCA CGG TCG GTT G | CCT TGT CTC TGG TCA GGT G |
| COX5A_TEAD4_BS2 | GCT GGG ATT ACA GGC ATG A | CCC AGG AGG GCA CTT AAT C |
| COX7C_TEAD4_BS1 | CGA AAC TAC ATT TCC CAC AAT CC | CTT GAG GAA ACG CGA CAA AG |
| COX7C_TEAD4_BS2 | AGG GAT GGG TTT ATT GTC CTT T | CCC GAA GGA TTG TGG GAA AT |
| COX7C_TEAD4_BS3 | TTC CCT GCC CTT TGT TCT T | GCA CAA AGG ACT TCA GAG AGA |
| COX7C_TEAD4_BS4 | GGC ATG GTT GTT CTC TTC CA | ATT GCC TCA CGT GTC TCA TTT A |
| ATP5A1_TEAD4_BS1 | CCT GGG AAC TGC TGC TTA G | TGG TCC TGG CAT TCG TTA TAC |
| ATP5A1_TEAD4_BS2 | AGC TGG GAA TCT TTA ACC TGA G | TCA GAC CCT CTG AGT CGA AA |
| ATP5A1_TEAD4_BS3 | ATG ACT CTT CTA GGC CTC CTT | ACC TAG GTG ATG GGA TGA TAG T |
| ATP5C1_TEAD4_BS1 | CCG GGC GTC TAG TAT TGC | CAG CCT GTG TTC TGC GA |
| ATP5C1_TEAD4_BS2 | AGA CTC CTT GAG CCA CTC TAT | CTT ACC AAC CGT GTG GTC TT |
| ATP5C1_TEAD4_BS3 | GCA TTC AAT CAA CCA CCT CTT T | TAG AGT GGC TCA AGG AGT CT |
| ATP5C1_TEAD4_BS4 | CTT CCT TCA CTT GCA GAA ACA C | GTG CAG GCT AGT GAT GTG AT |
| ATP5C1_TEAD4_BS5 | CAC CCA GTC TAC TGC ACT TTA T | TGC AAG TGA AGG AAG AGG TAT T |

**Supplementary Table 4 Primer list for qPCR assay**

| Genes | Forward primer sequence (5' to 3') | Reverse primer sequence (5' to 3') |
|---|---|---|
| NDUFA8 | CCT TTA CCG GAG AAT CCC TAT C | CCA CGG ACC CAT CTT TAC TT |
| NDUFAB1 | TAT AGC GAC ATG CCT CCT TTG | GAA AGC TTC TCT GGG TCA ATC T |
| NDUFB3 | GGA CAT GAG CAT GGA CAT CAT A | GCC AGC TTC TTC TGG ATA GTT |
| NDUFS6 | CAC ACT GGC CAG GTT TAT GA | GGG CTG CTC TGC TAT CAA AT |
| SDHD | CGA GAG GGT TGT CAG TGT TT | CCA GTG ACC ATG AAG AGT GAG |
| UQCRFS1 | CCG ATA TTC CAG AAG GCA AGA A | TGG GTC CCT CAA CTG TGA TA |
| COX5A | GCT CGC TGG GTA ACA TAC TT | GGG CTC TGG AAC CAT ATC ATA G |
| COX7C | GTC CGT AGG AGC CAC TAT GA | GTG TAG CAA ATG CAG ATC CAA AG |
| ATP5A1 | GAG GAC TGT GTG GTG CTA TTC | CTT TCC CAG CTG CTG TTA GT |
| ATP5C1 | GAG GAC TGT GTG GTG CTA TTC | CTT TCC CAG CTG CTG TTA GT |
| ACSS1 | GGT ACT GGG AGA CAG TAG AGA G | CCC AGG CAT CAC CGT ATT T |
| ACSS2 | GCT GCA GTC TTC TCA TCA CTA C | GAA ACC CTT CTC CTG ACA CTT C |
| ACLY | AAC ATC CTG GCC TCC AAA C | CGT GGT CCG AGA GAT GAT ATT G |
| HAT1 | TAT TGC TGG TAG CCT GTC AAC | CCT CAA CAT CAT CTG CCT CTA C |
| KAT2A | GGG TTT CTC CAA GGA CAT CAA | GAT TCA GCT CAC ACT CCA TCA G |
| KAT2B | GCC GTG TTA TTG GTG GTA TCT | TAG CCC TTG ACT TGC TCA TTT |
| KAT3A | GGA CCC AGA GTC ATT ACC TTT C | GAG AGG TCC ATG GGA TTC TTT AC |
| KAT3B | GCA GCA ACA GGT GCT TAG TA | CAG GGA TGG GTT GTG GAT TAG |
| KAT5 | TCC TCC AGG CAA TGA GAT TTA C | AGA CAC AGG TTC TGG GAA TAA C |
| KAT6A | ATG GAT GTG CCT TCC GTA TC | TCG TAA CTG CTT GGG TTC TC |
| KAT6B | AAA GGG ACA CCC GAG TTA TG | CTA GAG GAG GAG GAG TGA GAA A |
| KAT7 | CTG ACC CAA GGA GTT CTG TTA TG | AGC ACT AGT ACC ACG CTT AGA |
| KAT8A | CGA TCA CCA AGG TGA AGT ATG T | CTT GGG CTG TTT CCC ATA GT |
| KAT9 | CCA AAC GTG GGA CTA GAA AGA G | CGA ATC ACC AGG GTA GGA TAG A |
| TEAD1 | CTG AGT CGC AGT TAC CAC CA | AGC CTG GAG CCT TTT CAA G |
| TEAD2 | ACA TGA TGA ACA GCG TCC TG | CAG CAG TTC CTG GGT GTC TC |
| TEAD3 | CAT CGA GCA GAG CTT CCA G | CGT GCA ATC AAC TCA TTT CG |
| TEAD4 | GCC TTC CAC AGT AGC ATG G | AAA GCT CCT TGC CAA AAC C |
| YAP1 | GCA AAT TCT CCA AAA TGT CAG G | CGG GAG AAG ACA CTG GAT TT |

**Supplementary references for Bioinformatic packages**

**ChIP-seq analysis[1-8] and Motif analysis[9-11]**


1. Bolger, A.M., Lohse, M. & Usadel, B. Trimmomatic: a flexible trimmer for Illumina sequence data. Bioinformatics 30, 2114-2120 (2014).
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