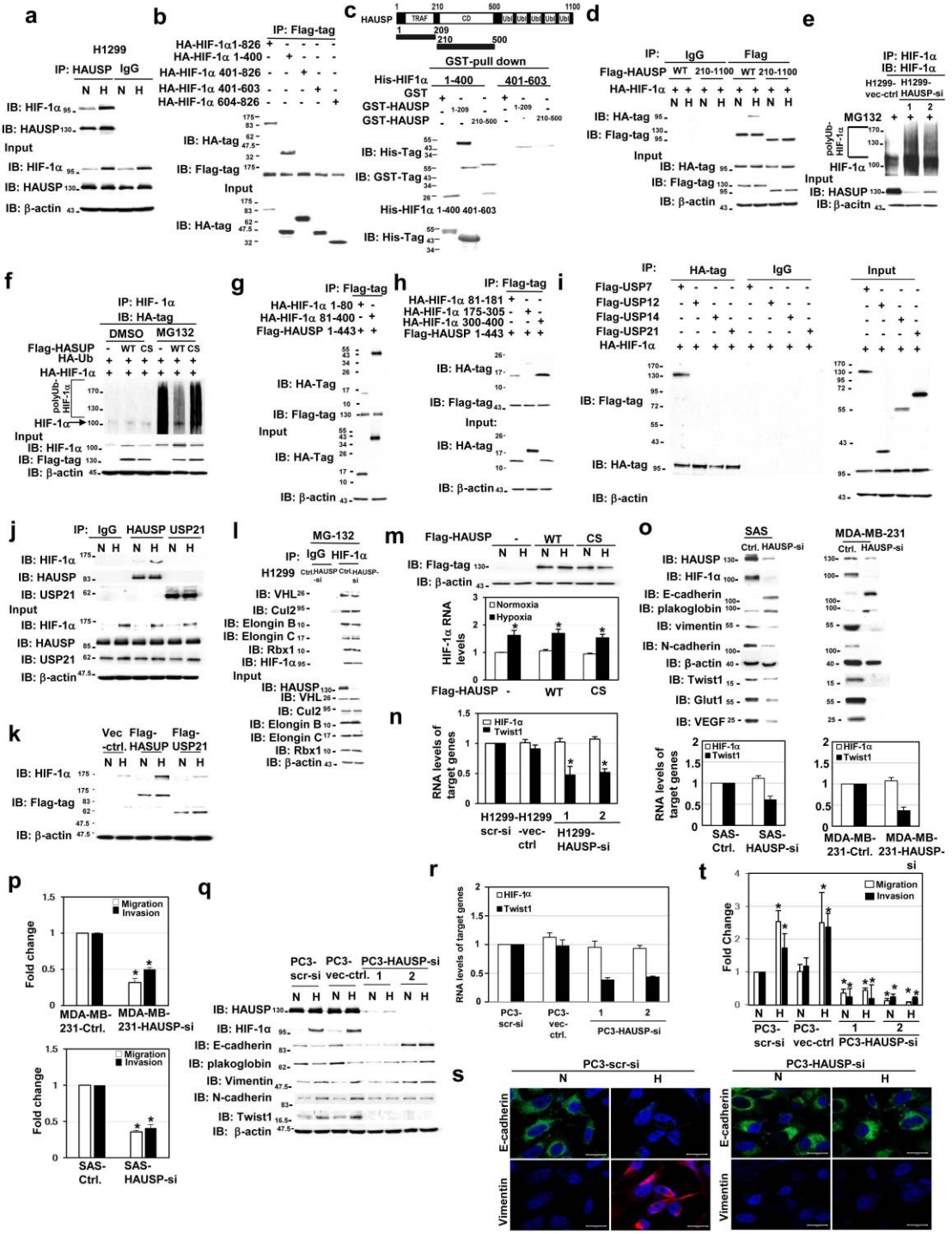
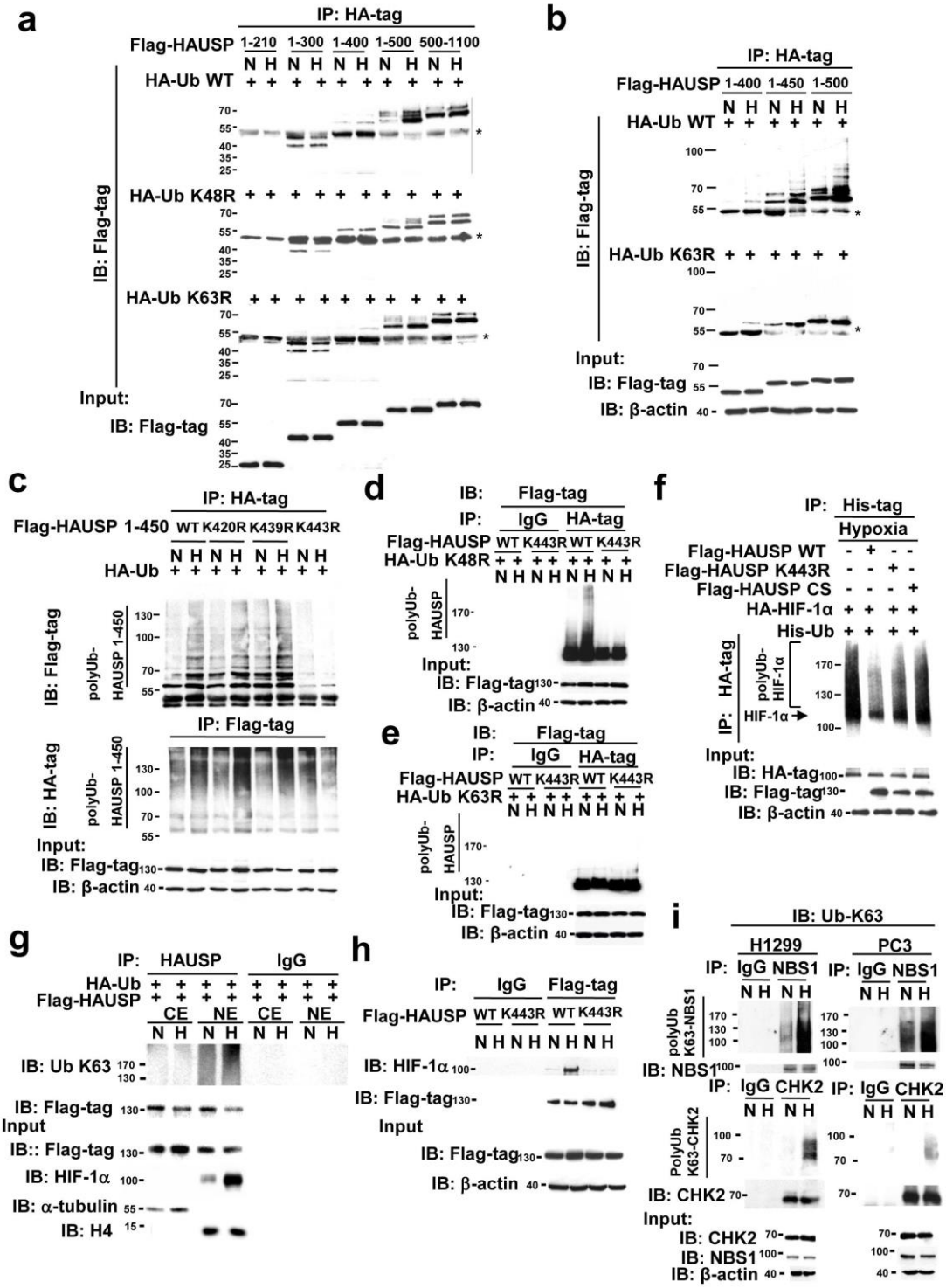


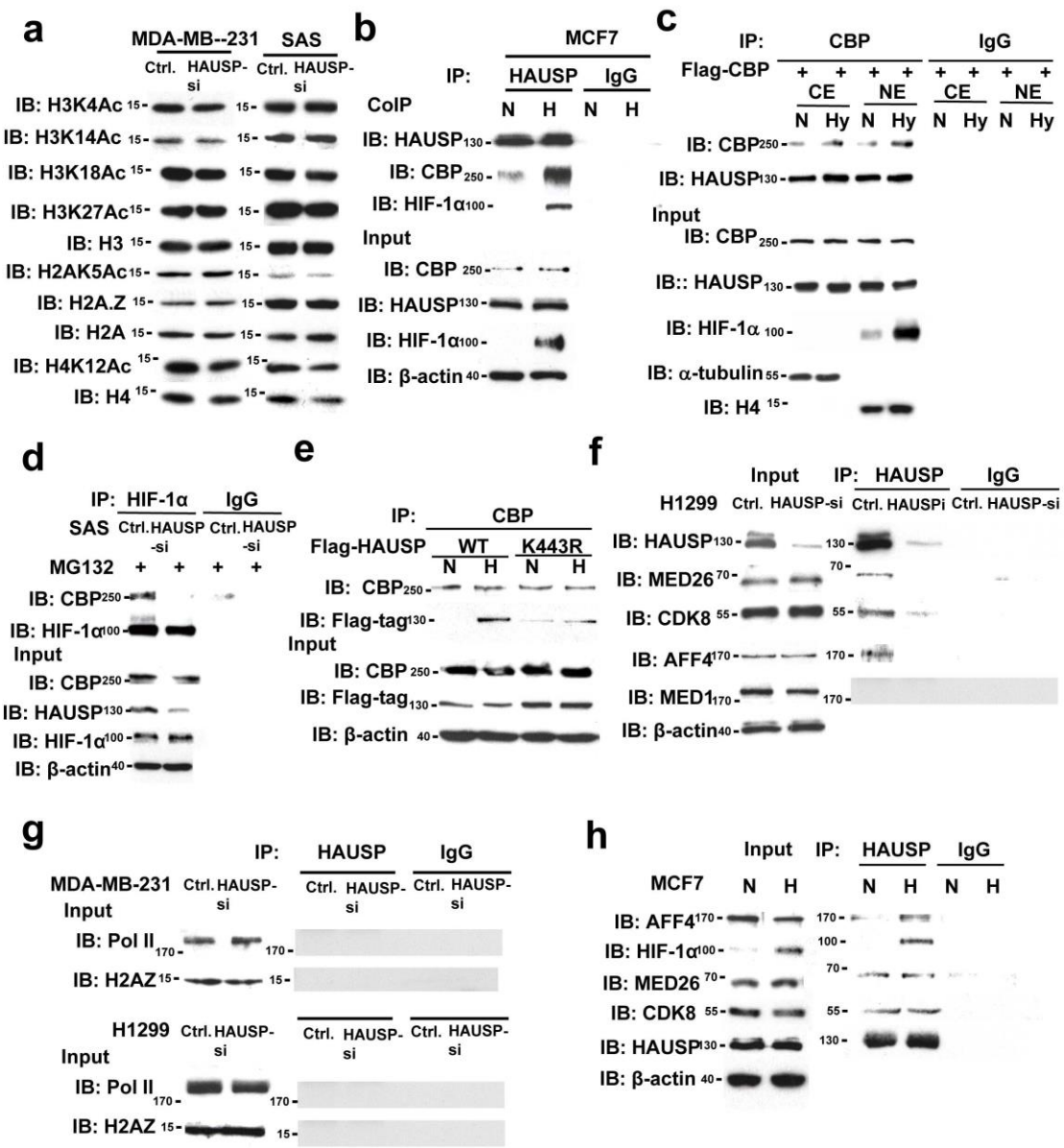
**Supplementary Figure 1. Demonstration of interaction between HAUSP and HIF-1α and various functional characterizations of HAUSP. (a)-(d)** Demonstration of interaction between HAUSP and HIF-1α and mapping of their interacting domains by co-immunoprecipitation assays. **(e) & (f)** HAUSP levels

correlated with the polyubiquitinated HIF-1α levels in H1299 cells in knockdown or overexpression experiments under MG132 treatment. MG132 was used to inhibit proteasome-mediated HIF-1α degradation. **(g)-(h)** Further mapping of the domain in HIF-1α that interacted with the a.a. 1-443 domain of HAUSP by co-expressing experiments in 293T cells using co-immunoprecipitation assays. **(i)-(k)** Characterizations of other USP family members that did not interact with or stabilize HIF-1α. **(l)** Co-immunoprecipitation assays showed that knockdown of HAUSP in H1299 cells did not affect the interaction between HIF-1α and the VHL/E3 ubiquitin ligase complex in H1299 cells. **(m) & (n)** Overexpression or knockdown of HAUSP did not affect the mRNA levels of HIF-1α under hypoxia by real time PCR analysis**.** No HAUSP-transfected (normoxia) or H1299 scrambled-siRNA sample was used as the control for statistical analysis. **(o) & (p)** Knockdown of HAUSP reversed EMT, decreased HIF-1α target gene expression with no alteration in HIF-1α mRNA levels, and decreased the *in vitro* migration and invasion activity in two cell lines. The scrambled-siRNA controls were used as the controls for statistical analysis for either SAS or MDA-MD-231 cells. **(q)** Western blot analysis of epithelial and mesenchymal markers under normoxia and hypoxia in HAUSP-knockdown PC3 and control PC3 cells (PC3 scrambled-siRNA control cells and PC3 vector control cells). **(r)** Knockdown of HAUSP reduced the *Twist1* mRNA levels but did not affect the endogenous *HIF-1α* mRNA levels in PC3 cells. The PC3 scrambled-siRNA controls were used as the controls. Green fluorescence: E-cadherin; red fluorescence: vimentin. **(s)** & **(t)** Knockdown of HAUSP reversed the EMT marker changes by immunofluorescence assay or decreased the *in vitro* migration and invasion activity induced by hypoxia in PC3 cells. The PC3 scrambled-siRNA control clone was used as the control. Anti-IgG antibodies were used as negative controls in co-immunoprecipitation assays. For **(m)-(p), (r) & (t)**, data from three independent experiments are expressed as mean ± s.d. The asterisk (*) indicates statistical significance ($P<0.05$) between experimental and control clones/transfections, t-test. N: normoxia, H: hypoxia.



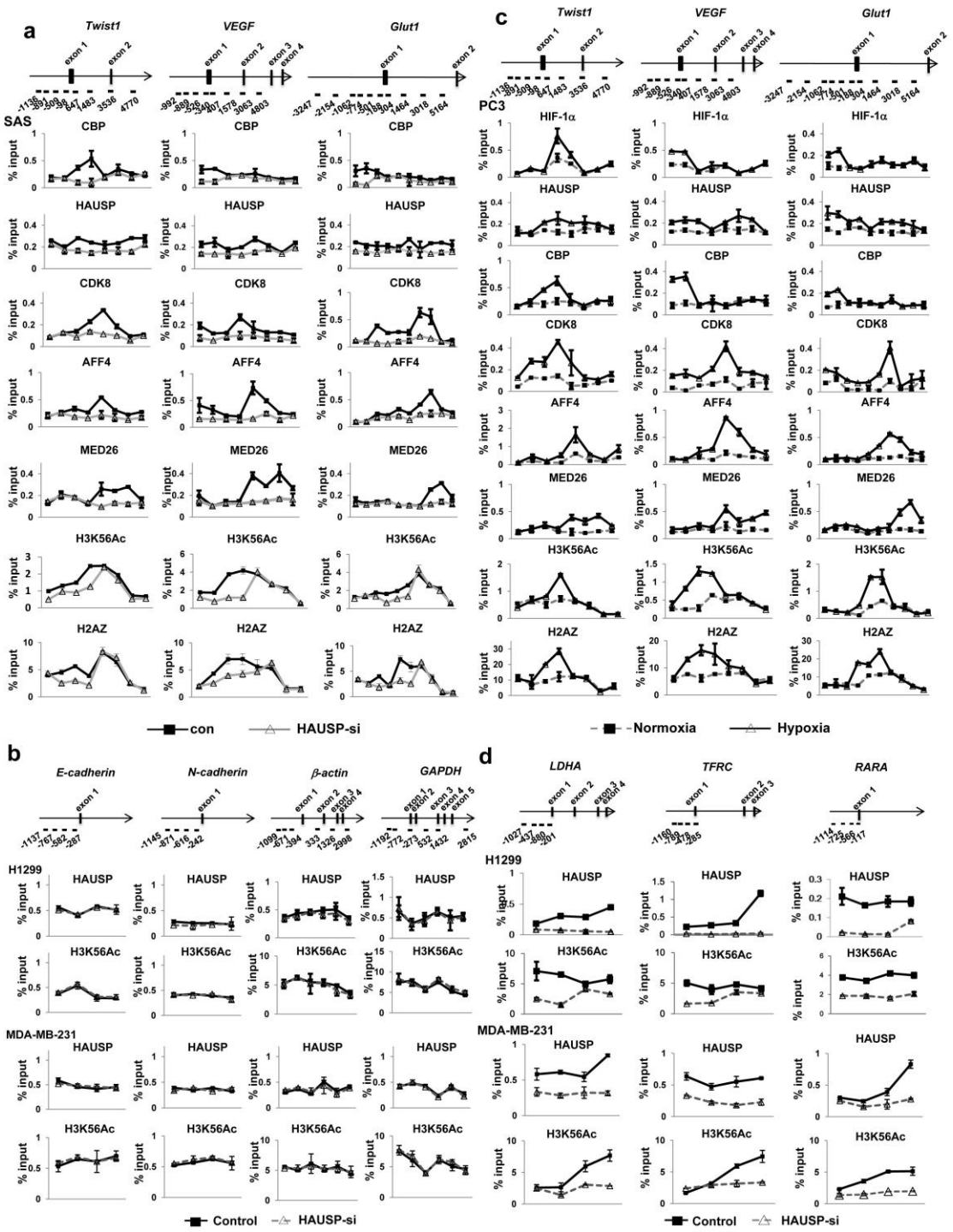

**Supplementary Figure 2. Increase in the deubiquitinase activity of HAUSP by**

**hypoxia and mapping of the K63-polyubiquitinated site of HAUSP. (a) & (b)** Domain mapping experiments showed that the a.a. 400-450 domain in HAUSP is K63-linked polyubiquitinated under hypoxia, as demonstrated by expressing different truncation mutants of HAUSP and HA-Ub in 293T cells followed by the pull-down with anti-HA antibodies. The asterisk (*) indicates heavy chain. **(c)** K443 was the site responsible for hypoxia-induced K63-linked polyubiquitination. Co-expression of HA-ubiquitin and Flag-tagged HAUSP1-450 (wild type, K420R, K439R, or K443R) mutants followed by co-immunoprecipitation experiments showed that the polyubiquitination levels of HAUSP1-450$^{K443R}$ mutant was significantly less than the wild type or other mutants. **(d)** Western blot assays showed that the K48R ubiquitin was conjugated to the full-length wild type HAUSP, but not the HAUSP$^{K443R}$ mutant, by co-immunoprecipitation experiments in 293T cells. **(e)** Western blot assays showed that the K63R ubiquitin was not able to be conjugated into either wild type or mutant HAUSP by co-immunoprecipitation experiments in 293T cells. **(f)** The HAUSP$^{K443R}$ mutant had a significantly less ability to deubiquitinate polyubiquitinated HIF-1α compared to the wild-type HAUSP under hypoxia, as demonstrated by expressing HA-HIF-1α and Flag-HAUSP vector (wild type, K443R, or CS mutant) in 293T cells followed by Western blot analysis. **(g)** Hypoxia-induced K63-linked polyubiquitination of HAUSP was located in the nucleus and further increased under hypoxia as demonstrated by expressing Flag-HAUSP and HA-ubiquitin in 293T cells followed by anti-HAUSP antibodies pull down using Western blot analysis. The cytoplasmic and nuclear fractions were isolated according to the methods described in the method section. **(h)** Co-immunoprecipitation assays using the HAUSP wild type vs. the HAUSP$^{K443R}$ mutant to interact with HIF-1α under hypoxia were shown. Flag-HAUSP (wild type or mutant) was expressed in 293T cells followed by co-immunoprecipitation of endogenous HIF-1α with anti-Flag antibodies. N: normoxia, H: hypoxia. **(i)** Increased K63-linked polyubiquitination status of CHK2 and NBS1 under hypoxia in two different cell lines. Anti-CHK2 or NBS1 antibodies were used to pull down CHK2 or NBS1 under normoxia or hypoxia followed by blotting with antibodies against K63 polyubiquitin chain. Anti-IgG antibodies were used as negative controls in co-immunoprecipitation assays.



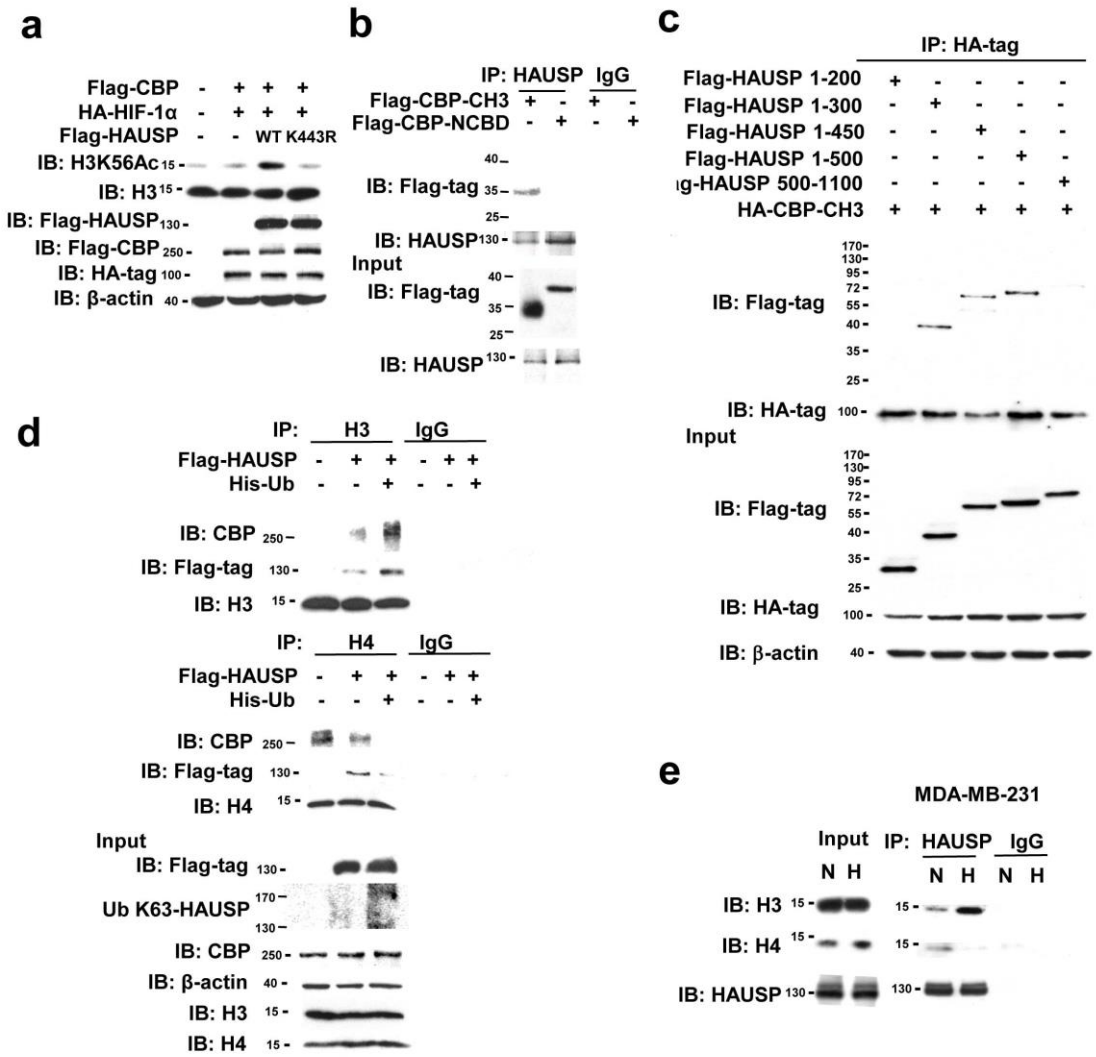

**Supplementary Figure 3. Screening of various histone marks in control vs. HAUSP knockdown cell lines and co-immunoprecipitation experiments. (a)** Screening of various histone marks in control vs. HAUSP knockdown cell lines (SAS,

MDA-MB-231) by Western blot analysis. **(b)** Co-immunoprecipitation assays showed the increased the interaction between HAUSP and CBP under hypoxia in MCF7 cells. N: normoxia, H: hypoxia. **(c)** Co-immunoprecipitation assays showed that the increased interaction between HAUSP and CBP under hypoxia occurred in the nuclear fraction as demonstrated by expressing Flag-CBP in 293T cells followed by the pull-down with anti-CBP antibodies**.** CE: cytoplasmic extract, NE: nuclear extract. **(d)** Knockdown of HAUSP in SAS cells decreased the interaction between HIF-1α and CBP by co-immunoprecipitation assays. **(e)** Decreased interaction between $HAUSP^{K443R}$ mutant and CBP (compared to wild-type HAUSP) under hypoxia was detected by expressing Flag-HAUSP (wild type or K443R mutant) in 293T cells followed by the pull-down with anti-CBP antibodies using co-immunoprecipitation assays. **(f)** Co-immunoprecipitation assays showed the interaction between HAUSP and CDK8, MED26, AFF4, but not between HAUSP and MED1 in H1299 cells. Knockdown of HAUSP abolished all the interactions. **(g)** No interaction between HAUSP and the Pol II subunit or H2A.Z in two cell lines (MDA-MB-231, H1299) by co-immunoprecipitation assays. **(h)** Increased interaction between HAUSP and AFF4 under hypoxia by co-immunoprecipitation assays. No difference in the interaction between HAUSP and MED26 or CDK8 under normoxia vs. hypoxia was observed. N: normoxia, H: hypoxia. Anti-IgG antibodies were used as negative controls in co-immunoprecipitation assays.



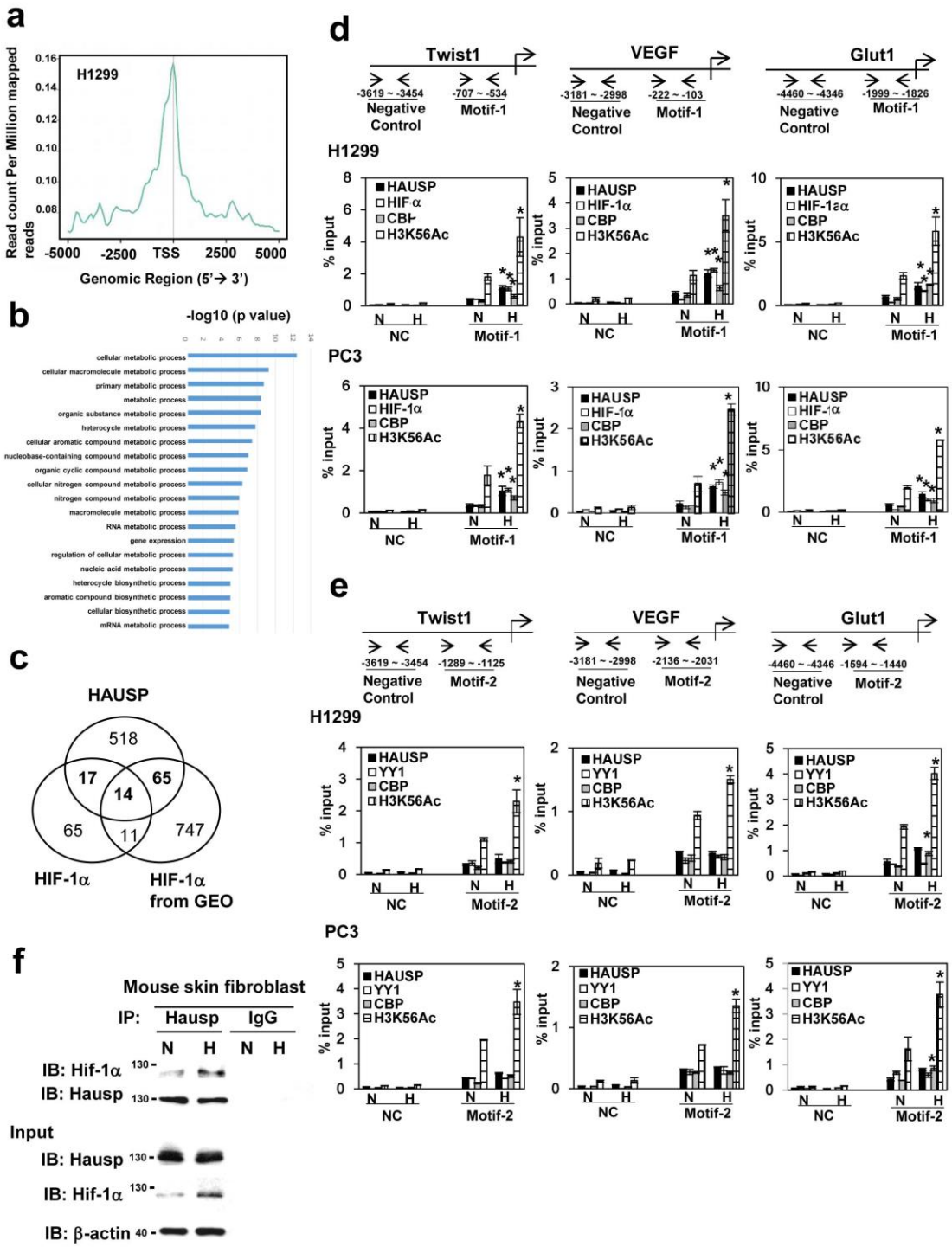

**Supplementary Figure 4. qChIP assays of the binding of various proteins as well as the levels of H3K56Ac and H2A.Z on the promoters of various genes. (a)**

qChIP levels of the binding of various proteins and histone marks on the promoters/gene body of three genes (*Twist1, VEGF, Glut1*) between control and HAUSP knockdown clone in SAS cells. Different regions located in the promoters and inside the gene body of three genes were shown underneath the plotting of genes. The different numbers indicated the starting nucleotide positions in the regions (labeled by brackets) before and after the initiation site. **(b)** No difference of the qChIP levels of H3K56Ac in the various promoter regions of *E-cadherin, N-cadherin, β-actin,* and *GAPDH* genes in two different cell lines (H1299, MDA-MB-231). **(c)** qChIP levels of the binding of various proteins and histone marks on the promoters/gene body of three genes (*Twist1, VEGF, Glut1*) between normoxia and hypoxia in PC3 cells. Different regions located in the promoters and inside the gene body of three genes were shown underneath the plotting of genes. The different numbers indicated the starting nucleotide positions in the regions (labeled by brackets) before and after the initiation site. **(d)** qChIP levels of HAUSP binding and H3K56Ac levels on the promoter of three HIF-1α target genes (*LDHA, TFRC, RARA*) between control and HAUSP knockdown clone in two cell lines (H1299, MDA-MB-231). For the qChIP analysis in **(a)**, **(b), (c), & (d)**, data from three independent experiments are expressed as mean ± s.d., *t*-test.

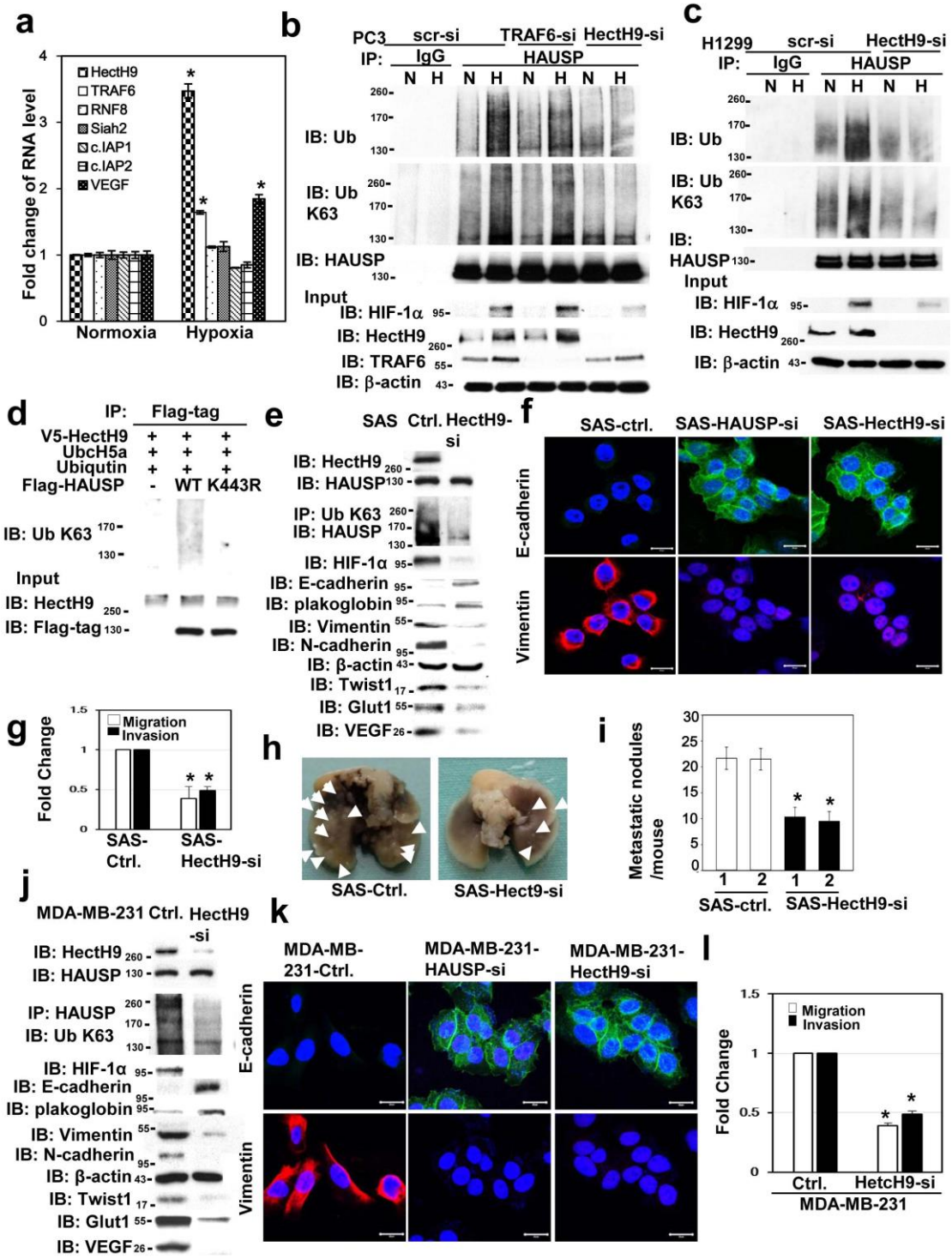



**Supplementary Figure 5. Demonstration of the histone acetylase activity of**

**HAUSP and mapping of its interaction domains with CBP or H3-binding. (a)** Overexpression of wild type HAUSP, but not the HAUSP$^{K443R}$ mutant, together with HIF-1α and CBP in 293T cells increased the H3K56Ac levels by Western blot analysis. **(b)** Co-immunoprecipitation assays showed the interaction between HAUSP and the CBP CH3 domain, but not the NCBD domain when two different domains of CBP were respectively expressed in 293T cells followed by the pull-down with anti-HAUSP antibodies. **(c)** Domain mapping experiments showed that a.a. 200-300 region of HAUSP interacted with the CBP CH3 domain by expressing different truncation mutants of HAUSP and the HA-CBP CH3 domain in 293T cells followed by the pull-down with anti-HA antibodies in Western blot analysis. **(d)** Co-immunoprecipitation assays showed the increased binding of the CBP-polyubiquitinated HAUSP complex to histone 3 under hypoxia, but decreased binding of the CBP-polyubiquitinated HAUSP complex to histone 4 under hypoxia. Flag-HAUSP and His-Ub vectors were expressed in 293T cells followed by pull down using anti-H3 or anti-H4 antibodies. **(e)** The interaction between H3/H4 and HAUSP during hypoxia


a
H1299
Read count Per Million mapped reads
Genomic Region (5'→ 3')
b
-log10 (p value)
cellular metabolic process
cellular macromolecule metabolic process
primary metabolic process
metabolic process
organic substance metabolic process
heterocycle metabolic process
cellular aromatic compound metabolic process
nucleobase-containing compound metabolic process
organic cyclic compound metabolic process
cellular nitrogen compound metabolic process
nitrogen compound metabolic process
macromolecule metabolic process
RNA metabolic process
gene expression
regulation of cellular metabolic process
nucleic acid metabolic process
heterocycle biosynthetic process
aromatic compound biosynthetic process
cellular biosynthetic process
mRNA metabolic process
c
HAUSP
518
17
65
14
65
11
747
HIF-1α
HIF-1α from GEO
d
Twist1
VEGF
Glut1
-3619 ~ -3454
-707 ~ -534
-3181 ~ -2998
-222 ~ -103
-4460 ~ -4346
-1999 ~ -1826
Negative Control
Motif-1
H1299
PC3
HAUSP
HIF-1α
CBP
H3K56Ac
% input
NC
e
-3619 ~ -3454
-1289 ~ -1125
-3181 ~ -2998
-2136 ~ -2031
-4460 ~ -4346
-1594 ~ -1440
Motif-2
YY1
f
Mouse skin fibroblast
IP:
Hausp
IgG
IB: Hif-1α
IB: Hausp
Input
IB: β-actin

**Supplementary Figure 6. ChIP-seq results of HAUSP and HIF-1α and qChIP analysis of various factors binding to motifs-1 and 2 in various gene promoters.** **(a)** The distrubtion of HAUSP binding around the TSS site using ChIP-seq analysis. **(b)** GO analysis of the 532 genes that showed binding by HAUSP. **(c)** Overlapping set of genes bound by HAUSP and HIF-1α (the set performed in this report as well as the public HIF-1α ChIP-seq data set). **(d) & (e)** qChIP results of the *Twist1, VEGF*, and *Glut1* gene promoters under similar analysis (as in Fig. 6) of motif-1 and motif-2 sites bound by HAUSP, HIF-1α, CBP, and H3K56Ac in H1299 and PC3 cells. The binding of various factors to motif-1 or motif-2 sites under normoxia was used as controls. For **(d) & (e),** data from three independent experiments are expressed as mean ± s.d. The asterisk (*) indicated statistical significance ($P<0.05$) between hypoxia and normoxia. *t*-test. **(f)** Co-immunoprecipitation assay showed that HIF-1α was expressed in mouse skin fibroblast under normoxia and interacted with HAUSP. Anti-IgG antibodies were used as negative controls in co-immunoprecipitation assays.


a
Fold change of RNA level
HectH9
TRAF6
RNF8
Siah2
c.IAP1
c.IAP2
VEGF
Normoxia
Hypoxia
b
PC3
scr-si
TRAF6-si
HectH9-si
IP:
IgG
HAUSP
N H N H N H N H
IB: Ub
IB: Ub K63
IB: HAUSP
Input
IB: HIF-1α
IB: HectH9
IB: TRAF6
IB: β-actin
c
H1299
scr-si
HectH9-si
IP:
IgG
HAUSP
N H N H N H
IB: Ub
IB: Ub K63
IB: HAUSP
Input
IB: HIF-1α
IB: HectH9
IB: β-actin
d
IP: Flag-tag
V5-HectH9
UbcH5a
Ubiqutin
Flag-HAUSP
- WT K443R
IB: Ub K63
Input
IB: HectH9
IB: Flag-tag
e
SAS Ctrl. HectH9-si
IB: HectH9
IB: HAUSP
IP: Ub K63
IB: HAUSP
IB: HIF-1α
IB: E-cadherin
IB: plakoglobin
IB: Vimentin
IB: N-cadherin
IB: β-actin
IB: Twist1
IB: Glut1
IB: VEGF
f
SAS-ctrl.
SAS-HAUSP-si
SAS-HectH9-si
E-cadherin
Vimentin
g
Fold Change
Migration
Invasion
SAS-Ctrl.
SAS-HectH9-si
h
SAS-Ctrl.
SAS-Hect9-si
i
Metastatic nodules /mouse
SAS-ctrl.
SAS-HectH9-si
j
MDA-MB-231 Ctrl. HectH9-si
IB: HectH9
IB: HAUSP
IP: HAUSP
IB: Ub K63
IB: HIF-1α
IB: E-cadherin
IB: plakoglobin
IB: Vimentin
IB: N-cadherin
IB: β-actin
IB: Twist1
IB: Glut1
IB: VEGF
k
MDA-MB-231-Ctrl.
MDA-MB-231-HAUSP-si
MDA-MB-231-HectH9-si
E-cadherin
Vimentin
l
Fold Change
Migration
Invasion
Ctrl.
HetcH9-si
MDA-MB-231

**Supplementary Figure 7. The role of HectH9 in mediating K63-linked HAUSP polyubiquitination and inducing EMT and *in vivo* metastatic activity. (a)** Expression of HectH9 and TRAF6 was induced by hypoxia using real-time PCR analysis. The mRNA levels of each gene under normoxia were used as the controls for statistical analysis. **(b)** Western blot analysis showed the decreased K63-linked polyubiquitination levels of HAUSP in PC3 cells under HectH9 knockdown when extracts were immunoprecipitated by anti-HAUSP antibodies followed by blotting with anti-Ub or anti-K63-Ub antibodies. scr-si: scrambled siRNA control. Knockdown of HectH9, but not TRAF6, significantly decreased the induction of HIF-1α by hypoxia in PC3 cells using Western blot analysis. **(c)** The *in vitro* ubiquitination assay by incubating HectH9, Ubc5a, ubiquitin, and Flag-HAUSP showed that HectH9 mediated K63-lined polyubiquitination of HAUSP WT, but not the $HAUSP^{K443R}$ mutant. **(d)** Western blot analysis showed the decreased K63-linked polyubiquitination levels of HAUSP in H1299 cells under HectH9 knockdown when extracts were immunoprecipitated by anti-HAUSP antibodies followed by blotting with anti-Ub or anti-K63-Ub antibodies. scr-si: scrambled siRNA control. Knockdown of HectH9 significantly decreased the induction of HIF-1α by hypoxia in H1299 cells using Western blot analysis. scr-si: scrambled siRNA control. N: normoxia, H: hypoxia. **(e)-(i)** Knockdown of HectH9 reversed EMT, decreased the expression of HIF-1α targets, and decreased the *in vitro* migration/invasion and *in vivo* metastatic activity in SAS cells. **(j)-(l)** Knockdown of HectH9 reversed EMT, decreased the expression of HIF-1α targets, and decreased the *in vitro* migration/invasion activity in MDA-MB-231 cells. For **(a), (g)**, & **(l)**, data from three independent experiments are expressed as mean ± s.d. For (i), data are presented as the mean ± s.d. (n=6 mice/group). The asterisk (*) indicated statistical significance ($P<0.05$) between experimental and control treatment, *t*-test. Anti-IgG antibodies were used as negative controls in co-immunoprecipitation assays.

**Supplementary Table 1. Univariate analysis for probability of overall survival in 190 patients of resected stage I lung adenocarcinoma**

| | N (%) of cases | Median (months) | HR | 95% CI | *P* value |
|---|---|---|---|---|---|
| Age at operation, years | | | | | |
| < 65 | 98 (51.6) | 87.4 | 1 | | |
| > 65 | 92 (48.4) | 76.0 | 1.071 | 0.687-1.670 | 0.762 |
| Gender | | | | | |
| Male | 102 (53.7) | 87.3 | 1 | | |
| Female | 88 (46.3) | 72.3 | 0.739 | 0.468-1.168 | 0.193 |
| Extent of pulmonary resection | | | | | |
| Sublobar resection | 42 (22.1) | 68.3 | 1 | | |
| Anatomical resection | 148 (77.9) | –* | 0.704 | 0.426-1.163 | 0.168 |
| Tumor size | | | | | |
| ≤3 cm | 113 (59.5) | –* | 1 | | |
| > 3 to ≤5 cm | 77 (40.5) | 55.9 | 1.846 | 1.183-2.881 | 0.006 |
| T status | | | | | |
| T1 | 54 (28.4) | –* | 1 | | |
| T2a | 136 (71.6) | 72.3 | 1.615 | 0.943-2.766 | 0.078 |
| HIF-1α overexpression | | | | | |
| No | 91 (47.9) | –* | 1 | | |
| Yes | 99 (52.1) | 67.5 | 1.533 | 0.975-2.410 | 0.062 |
| HectH9 overexpression | | | | | |
| No | 79 (41.6) | –* | 1 | | |
| Yes | 111 (58.4) | 57.8 | 2.930 | 1.742-4.929 | <0.001 |
| HIF-1α and HectH9 co-overexpression | | | | | |
| No | 112 (58.9) | –* | 1 | | |
| Yes | 78 (41.1) | 63.4 | 1.927 | 1.234-3.010 | 0.003 |

HR, hazard ratio; CI, confidence interval. *Median survival was not reached.

**Supplementary Table 2. Association between HIF-1α and HectH9 expression in lung cancer patients**

| Variables | HIF-1α overexpression | | *P* value |
|---|---|---|---|
| | No | Yes | |
| HectH9 overexpression | | | |
| No | 58 (63.7%) | 21 (21.2%) | <0.001 |
| Yes | 33 (36.3%) | 78 (78.8%) | |

**Supplementary Table 3. Multivariate analysis for probability of overall survival in 190 patients of resected stage I lung adenocarcinoma**

| | HR | 95% CI | *P* value |
|---|---|---|---|
| Tumor size | | | |
| ≤ 3 cm | 1 | | |
| > 3 to ≤ 5 cm | 1.967 | 1.144-3.381 | 0.014 |
| T status | | | |
| T1 | 1 | | |
| T2a | 1.050 | 0.548-2.013 | 0.882 |
| HIF-1α and HectH9 co-overexpression | | | |
| No | 1 | | |
| Yes | 2.088 | 1.329-3.280 | 0.001 |

HR, hazard ratio; CI, confidence interval

**Supplementary Table 4. Sequence of the oligonucleotides and restriction enzymes used for plasmid construction**

| Constructions | Sequence (5'→3') | Restriction Enzyme site |
|---|---|---|
| HA-HIF-1a 1-400 | F: ATAAGAATGCGGCCGCTCACAGCAAAGTTAAAGCATCAGGT | *Not*I |
| | R: CGCGGATCCAAATGGAGGGCGCCGGCGGC | *BamH*I |
| HA-HIF-1a 401-826 | F: ATAAGAATGCGGCCGCTCACTGGAATACTGTAACTGTGCTT | *Not*I |
| | R: CGCGGATCCAACAGACTCAAATACAAGAACCTA | *BamH*I |
| HA-HIF-1a 401-603 | F: ATAAGAATGCGGCCGCTCACTGGAATACTGTAACTGTGCTT | *Not*I |
| | R: CGCGGATCCAAGCCCCAGCCGCTGGAGAC | *BamH*I |
| HA-HIF-1a 604-826 | F: ATAAGAATGCGGCCGCTCAGTTAACTTGATCCAAAGCTCTG | *Not*I |
| | R: CGCGGATCCAACAGACTCAAATACAAGAACCTA | *BamH*I |
| Flag-HAUSP WT | F: CCCAAGCTTAACCACCAGCAGCAGCAGCAG | *Hind*III |
| | R: CGCGGATCCTCAGTTATGGATTTTAATGGCCTT | *BamH*I |
| Flag-HAUSP 1-450 | F: CCCAAGCTTAACCACCAGCAGCAGCAGCAG | *Hind*III |
| | R: CGCGGATCCTCATGGTGGCAATGTTAGGAATTT | *BamH*I |
| Flag-HAUSP 1-210 | F: CCCAAGCTTAACCACCAGCAGCAGCAGCAG | *Hind*III |
| | R: CGCGGATCCTCACTTCTTYGAATCCCACGCAACTC | *BamH*I |
| Flag-HAUSP 1-300 | F: CCCAAGCTTAACCACCAGCAGCAGCAGCAG | *Hind*III |
| | R: CGCGGATCCTCAACAAAGCTCCTGAACATCATG | *BamH*I |
| Flag-HAUSP 1-400 | F: CCCAAGCTTAACCACCAGCAGCAGCAGCAG | *Hind*III |
| | R: CGCGGATCCTCATGGTGGCAATGTTAGGAATTT | *BamH*I |
| Flag-HAUSP 1-500 | F: CCCAAGCTTAACCACCAGCAGCAGCAGCAG | *Hind*III |
| | R: CGCGGATCCTCAATAATTGTGCTCAATTGCTTCCTC | *BamH*I |
| Flag-HAUSP 500-1100 | F: CCCAAGCTTGGGGGTCACGATGACGACCTGTCT | *Hind*III |
| | R: CGCGGATCCTCAGTTATGGATTTTAATGGCCTTTTC | *BamH*I |
| GST-HAUSP 1-209 | F: CGCGGATCCAACCACCAGCAGCAGCAGCAG | *BamH*I |
| | R:ATAAGAATGCGGCCGCTCACTTCTTTGAATCCCACGCAACTC | *Not*I |
| GST-HAUSP 210-500 | F: CGCGGTCCCACACAGGCTACGTCGGCTTA | *BamH*I |
| | R:ATAAGAATGCGGCCGCTCAATAATTGTGCTCAATTGCTTCCTC | *Not*I |
| His-HIF-1a 1-400 | F: CGGGGTACCATGGAGGGCGCCGGCGG | *Kpn*I |
| | R: CGCGGATCCTCACAGCAAAGTTAAAGCATCAG | *BamH*I |
| His-HIF-1a 401-603 | F: CGCGGATCCGCCCCAGCCGCTGGAGA | *BamH*I |
| | R: CCGCTCGAGTCACTGGAATACTGTAACTGTGC | *Xho*I |
| HA-HIF-1a 1-80 | F: CGGGGTACCATGGAGGGCGCCGGCGG | *Kpn*I |
| | R: AAGGAAAAAAGCGGCCGCTCAAATATCCAAATCACCAGCATCC | *Not*I |
| HA-HIF-1a 81-400 | F: CGGGGTACCGAAGATGACATGAAAGCACA | *Kpn*I |

| | | |
|---|---|---|
| | R: AAGGAAAAAAGCGGCCGCTCACAGCAAAGTTAAAGCATCAG | *Not*I |
| HA-HIF-1a 81-180 | F: CGGGGTACCGAAGATGACATGAAAGCACA | *Kpn*I |
| | R: AAGGAAAAAAGCGGCCGCTCATCTTCCTCGGCTAGTTAG | *Not*I |
| HA-HIF-1a 175-305 | F: CGGGGTACCCTAACTAGCCGAGGAAGA | *Kpn*I |
| | R: AAGGAAAAAAGCGGCCGCTCAGTACTGTCCTGTGGTGAC | *Not*I |
| HA-HIF-1a 300-400 | F: CGGGGTACCGTCACCACAGGACAGTAC | *Kpn*I |
| | R:AAGGAAAAAAGCGGCCGCTCACAGCAAAGTTAAAGCATCAG | *Not*I |
| Flag-USP21 | F: CCGGAATTCAATGCCCCAGGCCTCTGAGCACCGCCTG | *EcoR*I |
| | R: CGGGGTACCTCACAGGCACCGGGGTGGCTCCTGCATC | *Kpn*I |
| HA-CBP 8 | F: ATAAGATCTCTGACCGCTTTGTTTATACCTGCAATGAGTGC | *Bgl*II |
| | R: AAGCGGCCGCCTACCCGGGTGGTGCTGAGGTAGGAGAAGGCAA | *Not*I |
| HA-CBP 8ΔZnF | F: ATAAGATCTCTTGGGGGCTAGGCCTAGATGATGAGGGCAGC | *Bgl*II |
| | R: AAGCGGCCGCCTACCCGGGTGGTGCTGAGGTAGGAGAAGGCAA | *Not*I |

**Supplementary Table 5. Schemes of plasmid constructions for constructs used.**

| Plasmid | Template | Vector | Restriction enzyme site (F/R) |
|---|---|---|---|
| pCMV-HA-HIF-1a WT | pcDNA3-HA- HIF-1a | pCDNA3 | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a 1-400 | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a 401-826 | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a 401-603 | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a 604-826 | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a 1-80 | pCMV-HA- HIF-1a WT | pCMV-HA | *Kpn*I / *Not*I |
| pCMV-HA-HIF-1a 81-400 | pCMV-HA- HIF-1a WT | pCMV-HA | *Kpn*I / *Not*I |
| pCMV-HA-HIF-1a 81-180 | pCMV-HA- HIF-1a WT | pCMV-HA | *Kpn*I / *Not*I |
| pCMV-HA-HIF-1a 175-305 | pCMV-HA- HIF-1a WT | pCMV-HA | *Kpn*I / *Not*I |
| pCMV-HA-HIF-1a 300-400 | pCMV-HA- HIF-1a WT | pCMV-HA | *Kpn*I / *Not*I |
| pCMV-HA-HIF-1a S239A | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a S282A | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pCMV-HA-HIF-1a S366A | pCMV-HA- HIF-1a WT | pCMV-HA | *Not*I / *BamH*I |
| pFlag-CMV2-HAUSP WT | pCMV-HA- HIF-1a WT | pIRES | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-210 | pCMV-Flag-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-300 | pCMV-Flag-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-400 | pCMV-Flag-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-450 | pCMV-Flag-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-500 | pCMV-Flag-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 500-1100 | pCMV-Flag-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-450 K420R | pFlag-CMV2-HAUSP 1-450 | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-450 K439R | pFlag-CMV2-HAUSP 1-450 | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP 1-450 K443R | pFlag-CMV2-HAUSP 1-450 | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-HAUSP K443R | pFlag-CMV2-HAUSP WT | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV2-Usp21 | gDNA | pFlag-CMV2 | *EcoR*I / *Kpn*I |
| pGEX4T1-HAUSP 1-209 | pCMV-HA- HIF-1a WT | pGEX4T1 | *BamH*I / *Not*I |
| pGEX4T1-HAUSP 210-500 | pCMV-HA- HIF-1a WT | pGEX4T1 | *BamH*I / *Not*I |
| pET32a-His-HIF-1a 1-400 | pcDNA-HA- HIF-1a WT | pET32a | *Kpn*I / *BamH*I |
| pET32a-His-HIF-1a 401-603 | pcDNA-HA- HIF-1a WT | pET32a | *BamH*I / *Xho*I |
| pCMV-HA-CBP CH3 | pFlag-CMV2-CBP 1680-1892 | pFlag-CMV2 | *Bgl*II / *Not*I |
| pCMV-HA-CBP CH3ΔZZ | pFlag-CMV2-CBP 1680-1892 | pFlag-CMV2 | *Bgl*II / *Not*I |
| pCMV-HA-CBP CH3ΔZZ-TAB2 | pFlag-CMV2-CBP 1680-1892 | pFlag-CMV2 | *Bgl*II / *Not*I |
| pCMV-HA-CBP 8 C1710S | pCMV-HA-CBP 1702-1892 | pFlag-CMV2 | *Bgl*II / *Not*I |

| | | | |
|---|---|---|---|
| pCMV-Flag-CBP | pIRES-Flag-CBP | pFlag-CMV2 | *Hind*III / *BamH*I |
| pCMV-Flag-CBPΔZZ | pIRES-Flag-CBP | pFlag-CMV2 | *Hind*III / *BamH*I |
| pCMV-Flag-CBPΔZZ-TAB2 | pIRES-Flag-CBP | pFlag-CMV2 | *Hind*III / *BamH*I |
| pFlag-CMV6-Usp12 | gDNA | pFlag-CMV6 | *Sgf*I/*Mlu*I |
| pFlag-CMV6-Usp14 | gDNA | pFlag-CMV6 | *Sgf*I/*Mlu*I |
| pFlag-CMV2-Usp21 | gDNA | pFlag-CMV2 | *EcoR*I / *Kpn*I |

**Supplementary Table 6. List of proteins tested by and characteristics of the corresponding antibodies**

| Protein | Assay | Origin | Dilution | Incubation period |
|---|---|---|---|---|
| HIF-1α | WB | #610958, BD Biosciences | 1:250 | 4℃, Overnight |
| HIF-1α | IP | #610958, BD Biosciences | 5 μl | 4℃, Overnight |
| HIF-1α | CHIP | PA3-16521, Thermo scientific | 5 μl | 4℃, Overnight |
| E-cadherin | WB | #4065, Cell signaling | 1:500 | 4℃, Overnight |
| vimentin | WB | V-6630, Sigma-Aldrich Corp. | 1:1000 | 4℃, Overnight |
| N-cadherin | WB | #610921, BD Biosciences | 1:500 | 4℃, Overnight |
| plakoglobin | WB | Ab11506, Abcam | 1:1000 | 4℃, Overnight |
| GLUT-1 | WB | #07-1401, Millipore | 1:1000 | 4℃, Overnight |
| VEGF | WB | 19003-1-AP, Proteintech | 1:1000 | 4℃, Overnight |
| β-actin | WB | A-5441, Sigma-Aldrich Corp. | 1:10000 | 4℃, Overnight |
| Flag | WB | F3165, Sigma-Aldrich Corp. | 1:1000 | 4℃, 1 hour |
| Flag | IP | F3165, Sigma-Aldrich Corp. | 5 μl | 4℃, Overnight |
| HA | WB | #2367, Cell signaling Technology, Inc. | 1:1000 | 4℃, 1 hour |
| HA | IP | #2367, Cell signaling Technology, Inc. | 5 μl | 4℃, Overnight |
| HA | IP | 05-904, Millipore | 5 μl | 4℃, Overnight |
| TWIST | WB | Sc-15303, Santa cruz Biotechnology, Inc. | 1:500 | 4℃, Overnight |
| HAUSP | WB | A300-033A, Bethyl | 1:1000 | 4℃, Overnight |
| HAUSP | IP | A300-033A, Bethyl | 5 μl | 4℃, Overnight |
| USP21 | WB | BML-PW0585, Enzo | 1:1000 | 4℃, Overnight |
| USP21 | IP | Sc-79305, Santa cruz Biotechnology, Inc. | 5 μl | 4℃, Overnight |
| Ubiquitin | WB | BML-PW8810, Enzo | 1:1000 | 4℃, Overnight |
| Ubiquitin, Lys48-Specific | WB | #05-1307, Millipore | 1:1000 | 4℃, Overnight |
| Ubiquitin, Lys63-Specific | WB | #05-1308, Millipore | 1:500 | 4℃, Overnight |
| Ubiquitin, Lys63-Specific | WB | #05-1308, Millipore | 1:500 | 4℃, Overnight |
| VHL | WB | #2738, Cell signaling Technology, Inc. | 1:1000 | 4℃, Overnight |
| HectH9 | WB | #5695, Cell signaling Technology, Inc. | 1:1000 | 4℃, Overnight |
| TRAF6 | WB | TA300591, OriGene Technologies, Inc. | 1:1000 | 4℃, Overnight |
| HectH9 | IHC | NBP1-83127, Novus | 1:500 | 4℃, Overnight |
| HIF-1 | IHC | Sc-10790, Santa Cruz | 1:250 | 4℃, Overnight |
| CBP | WB | GTX307050, Genetex | 1:20 | 4℃, Overnight |
| CBP | CHIP | #7389, Cell signaling Technology, Inc. | 5 μl | 4℃, Overnight |
| CDK8 | WB, CHIP | Sc-1521, Santa cruz Biotechnology, Inc. | 10 μl | 4℃, Overnight |

| | | | | |
|---|---|---|---|---|
| AFF4 | CHIP | A302-538A, Bethyl | 5 μl | 4℃, Overnight |
| H3K56Ac | CHIP | #17-10259, Millipore | 3 μl | 4℃, Overnight |
| H2AZ | CHIP | PA5-21923, Thermo scientific | 3 μl | 4℃, Overnight |
| H4K5Ac | CHIP | #17-10045, Millipore | 3 μl | 4℃, Overnight |
| H3K4Ac | WB | #07-539, upstate | 1:250 | 4℃, Overnight |
| H3K9Ac | WB | #06-942, upstate | 1:500 | 4℃, Overnight |
| H3K14Ac | WB | #06-911, millipore | 1:500 | 4℃, Overnight |
| H3K56Ac | WB | #17-10259, Millipore | 1:500 | 4℃, Overnight |
| H4K5Ac | WB | ab51997, abcam | 1:500 | 4℃, Overnight |
| H4K12Ac | WB | ab61238, abcam | 1:500 | 4℃, Overnight |
| H3 | WB | #9715, Cell signaling Technology, Inc. | 1:500 | 4℃, Overnight |
| H2AZ | WB | #2718, Cell signaling Technology, Inc. | 1:500 | 4℃, Overnight |
| H2A | WB | #2578, Cell signaling Technology, Inc. | 1:500 | 4℃, Overnight |
| H3K18Ac | WB | ab1191, abcam | 1:500 | 4℃, Overnight |
| H3K27Ac | WB | ab4729, abcam | 1:500 | 4℃, Overnight |
| H2AK5Ac | WB | ab1764, abcam | 1:500 | 4℃, Overnight |
| MED1 | WB | A300-793A, Bethyl | 1:500 | 4℃, Overnight |
| RNA pol II | WB | A300-653A, Bethyl | 1:500 | 4℃, Overnight |
| MED26 | WB | Sc-48776, Santa cruz Biotechnology, Inc. | 1:500 | 4℃, Overnight |
| CDK8 | WB | Sc-1521, Santa cruz Biotechnology, Inc. | 1:500 | 4℃, Overnight |
| AFF4 | WB | A302-539A, Bethyl | 1:500 | 4℃, Overnight |
| CBP | IP | GTX307050, Genetex | 50 μl | 4℃, Overnight |
| YY1 | CHIP | ab12132, abcam | 5 μl | 4℃, Overnight |
| HectH9 | IP | R960-25, ThermoFisher scientific | 5 μl | 4℃, Overnight |

Abbreviations: WB, Western blot; IP, Immunoprecipitation; mmab, mouse monoclonal antibody; rmab, rabbit monoclonal antibody; rpab, rabbit polyclonal antibody; gpab, goat polyclonal antibody

**Supplementary Table 7. Sequence of the oligonucleotides for real-time PCR**

| Target | Sequence (5'→ 3') |
|---|---|
| HIF-1a | F: TTTTTCAAGCAGTAGGAATTGGA |
| | R: GTGATGTAGTAGCTGCATGATCG |
| Twist1 | F: AGCTACGCCTTCTCGGTCT |
| | R: CCTTCTCTGGAAACAATGACATC |
| HectH9 | F: TTGGACCGCTTCGATGGAATA |
| | R: TGAAGTTCAACACAGCCAAGAG |
| TRAF6 | F: GATGCAGAGGAATCACTTGGC |
| | R: GGTCTTGTCTTACAAGGCGAC |
| RNF8 | F: CCCGGCTTCTTCGTCACAG |
| | R: ACCTCGCACCCATCTTCCA |
| Siah2 | F: CATCAGGAACCTGGCTATGG |
| | R: GGACGGTATTCACATATGTC |
| c.IAP1 | F: AGAGGAGAAGGAAAAACAAGCT |
| | R: ATCCAGGATAGGAAGCACACA |
| c.IAP2 | F: TTCCACACACTCATTACTTCC |
| | R: TCTGGAGTTTACAGGATTTGATG |
| VEGF | F: GTACCCTGATGAGATCGAGT |
| | R: GTGATGTTGGACTCCTCAGT |
| mTwist1 | F: AGCGGGTCATGGCTAACG |
| | R: AGCTCGTCGCTCTGCAGG |
| mGlut1 | F: CGGAACTCCATGCTGATGATG |
| | R: CCACATACATGGGCACAAAGC |
| Vegf | F: AAGCCAGCACATAGGAGAGATGA |
| | R: CTGTCTTTCTTTGGTCTGCATTCA |
| m18S | F: TTCGTATTGCGCCGCTAGA |
| | R: CTTTCGCTCTGGTCCGTCTT |
| HAUSP K444R | F: CCCAATTGGTGAAAGAGCTTA |
| Typing primer | R: CTGGAAACTCAAACCTGTTCAA |

**Supplementary Table 8. Sequence of the oligonucleotides for ChIP assays**

| Target | Sequence (5'→ 3') |
|---|---|
| Twist1 (-1136~-1024) | F: CCTCTTTGGGGCTCTTCGTT |
| | R: TCTAGGGCATCCAGTGGACA |
| Twist1 (-891~-767) | F: TGAAATGGCCACAGGGTCTC |
| | R: TTCGGTGGAAGGAAACCCAG |
| Twist1 (-509~-399) | F: CACTTTTCTTGGCATGCCCC |
| | R: GGTGATGTCTCATCTCGCCC |
| Twist1 (-98~-29) | F: GGGACTGGAAAGCGGAAACT |
| | R: TGTCATTGGCCTGACGTGAG |
| Twist1 (647~800) | F: GTCCGCAGTCTTACGAGGAG |
| | R: TTGAGGGTCTGAATCTTGCTC |
| Twist1 (1483~1677) | F: AACAGCCGCAGAGACCTAAA |
| | R: CACGCCCTGTTTCTTTGAAT |
| Twist1 (3536~3640) | F: GGAAGGCGATTATGTGTTGG |
| | R: ATGCTTTCCCTCATCCTCCT |
| Twist1 (4770~4897) | F: CATGGTTTGGCAAAGTCAGA |
| | R: ATCATGAGAGCGGGACAAAC |
| VEGF (-992~-900) | F: GCCAGACTCCACAGTGCATA |
| | R: CTGAGAACGGGAAGCTGTGT |
| VEGF (-889~-787) | F: TTGGTGCCAAATTCTTCTCC |
| | R: GCCTGCAGACATCAAAGTGA |
| VEGF (-526~-470) | F: GCGTCTTCGAGAGTGAGGAC |
| | R: CACACGCACACACTCACTCA |
| VEGF (-340~-285) | F: AAAGAGGGAACGGCTCTCAG |
| | R: AGGGAGCAGGAAAGTGAGGT |
| VEGF (407~517) | F: ACAGGGGCAAAGTGAGTGAC |
| | R: CTGTCTGTCTGTCCGTCAGC |
| VEGF (1578~1649) | F: GCTTGCTGTCACTGCCACT |
| | R: AGCAATCCACCCCAAAACTT |
| VEGF (3063~3146) | F: CTAGCAGGGTCTGGTGTTCC |
| | R: CTCCAGCTCTCACCAACTCC |
| VEGF (4803~4935) | F: TGGATCCTCCCATTTCTCTG |
| | R: CCACGCCAGATTTAGGTCAG |
| Glut1 (-3247~-3093) | F: CATTTGGGAGCCTCTGTGAT |
| | R: GAGAAGGCCCCAGGAAATAG |

| | |
|---|---|
| Glut1 (-2154~-1980) | F: TGGGAAAAGGCATAGACTGG |
| | R: ATGCACGAATGAGTGAGCAG |
| Glut1 (-1062~-925) | F: CTTGAGCCCAGGAGTTTGAG |
| | R: GGAGAGGTGCAATTTCCAGA |
| Glut1 (-774~-634) | F: TGGTGAAACCCCGTCTCTAC |
| | R: CACGATCTCGGCTCACTGTA |
| Glut1 (-501~-370) | F: TGGTTCAAACCCGAGGTCTA |
| | R: GGGACGCCTTCCTCTACTTC |
| Glut1 (-188~-46) | F: TCCATGCAGTAGACGCTGTT |
| | R: TGGAAAGCTGGACTGGAGTT |
| Glut1 (304~426) | F: CTGGCAAGAGGCAAGAGGTA |
| | R: ACTCCCACTGCGACTCTGAC |
| Glut1 (1464~1570) | F: CCTGCAGGGCATCTTTGTAG |
| | R: GGAGGAAAGGAGGTGGAAAG |
| Glut1 (3018~3102) | F: TTTCCCCTCCAAATCTTGTG |
| | R: TGCAGGTCAAATCAGCAGTC |
| Glut1 (5164~5294) | F: GGAGCCTTGGTTTCCTTCTC |
| | R: CCCAGACTGGCCTTACAAAG |
| E-cadherin (-1137~-992) | F: AAACTGAGGCTTTGGGAGGT |
| | R: TTCTGAACTCAGGCGATCCT |
| E-cadherin (-767~-640) | F: CGCCTGTAGTCCCAGCTACT |
| | R: GACGGAGTCTCGCTCTGTCT |
| E-cadherin (-582~-479) | F: ATGGCTCACACCTGAAATCC |
| | R: GCGCTGTGTCTCCCTGTATT |
| E-cadherin (-287~-212) | F: GAGTGAGACCCCATCTCCAA |
| | R: GGGCTTTTACACTTGGCTGA |
| N-cadherin (-1145~-1059) | F: TGCACTCTCAAACTCCCAGA |
| | R: CTCCCACCCTTGAGGATGTA |
| N-cadherin (-871~-765) | F: TTAGGCTCCCAAGGAGACAC |
| | R: GGGCAGGAACTTGATTGGTA |
| N-cadherin (-616~-499) | F: CTACAGCCGCAGCTTGGT |
| | R: CCGCTCCCCTCTCCTATTC |
| N-cadherin (-242~-132) | F: CCGGAGAACAGTCTCCAACT |
| | R: ACCCACAAAGAGCAGCAGTC |
| KDM3A (-1257~-1032) | F: GCCCAGTATTTTCAAGCTTCC |
| | R: CCAGCTGAAAGAAGGCAGAA |
| KDM3A (-495~-333) | F: CCAGTAACTCCACGCCTTTC |

| | |
|---|---|
| | R: GGAGGAGCGATAGTGCTCTG |
| KDM3A (-71~155) | F: TGTGAGGCAACAAATGGAAA |
| | R: TCATTGGCTGAAACACAGGA |
| Twist1 (-3619~-3454) | F: CCCTCTGGAGTGTTCAAAGC |
| | R: CTGTTTGTTGGCTCCGAGTT |
| Twist1 (-1289~-1125) | F: TAAGGGATGGACCTGAAACG |
| | R: GCCCCAAAGAGGGTGTTAAT |
| Twist1 (-707~-534) | F: CGTCAGACTGGGTCGTTGTA |
| | R: TCAGGTAGACGAACCCCTTG |
| VEGF (-3181~-2998) | F: TTGGAGGTGACAGGACATCA |
| | R: CAGTTCAGAAGGAGCCAAGG |
| VEGF (-2136~-2031) | F: GGCTCTTTTAGGGGCTGAAG |
| | R: GTAGACATCTTGGGGCAGGA |
| VEGF (-222~-103) | F: TTCAGGCTGTGAACCTTGG |
| | R: GAGCCTCAGCCCTTCCAC |
| Glut1 (-4460~-4346) | F: CAGGGAGGAGGATGAATGAA |
| | R: CAGTCAATCCCGTGGACTTT |
| Glut1 (-1999~-1826) | F: CTGCTCACTCATTCGTGCAT |
| | R: CTGGTTCTCCCAAGTGGAAA |
| Glut1 (-1594~-1440) | F: GCAGGACTGGAGGACAAAAG |
| | R: CTATGCTCAGCCTGGAAAGC |
| β-ACTIN (-1099~-931) | F: TGACAAGGACAGGGTCTTCC |
| | R: CACCGTCCGTTGTATGTCTG |
| β -ACTIN (-671~-458) | F: GACTTCTAAGTGGCCGCAAG |
| | R: CTGCAGAAGGAGCTCTTGGA |
| β -ACTIN (-394~-173) | F: AGTGCCCAAGAGATGTCCAC |
| | R: AGAGCGAGAGCGAGATTGAG |
| β -ACTIN (333~521) | F: CGGGGTCTTTGTCTGAGC |
| | R: GCAGTTAGCGCCTTGAGTC |
| β -ACTIN (1326~1534) | F: AGAAAATCTGGCACCACACC |
| | R: AACGGCAGAAGAGAGAACCA |
| β -ACTIN (2998~3168 | F: AAACTGGAACGGTGAAGGTG |
| | R: AGAGAAGTGGGGTGGCTTTT |
| GAPDH (-1192~-1029) | F: GGCTGGTGTCAGGTTATGCT |
| | R: TCTTCTGGTAGGAGGGCAGA |
| GAPDH (-772~-604) | F: AGGTTTCCAGGAGTGCCTTT |
| | R: CACGGAAGGTCACGATGTC |

| | |
|---|---|
| GAPDH (-273~-27) | F: CAATTCCCCATCTCAGTCGT |
| | R: TAGTAGCCGGGCCCTACTTT |
| GAPDH (532~695) | F: GGGTCTTTGCAGTCGTATGG |
| | R: TTTCTGGGGACTAGGGGAAG |
| GAPDH (1432~1647) | F: CCCACACACATGCACTTACC |
| | R: CCCACCCCTTCTCTAAGTCC |
| GAPDH (2815~3190) | F: CTCCCACCTTTCTCATCCAA |
| | R: TGGACTGTGGTCTGCAAAAG |

**Supplementary Table 9. Lentivirus used in RNAi experiments**

| Target | Sequence | Clone ID |
|---|---|---|
| Scrambled control | CCTAAGGTTAAGTCGCCCTCG | |
| HAUSP (USP7) | CGTGGTGTCAAGGTGTACTAA | TRCN0000010845 |
| HectH9 (HUWE1) | CGACGAGAACTAGCACAGAAT | TRCN0000073306 |
| TRAF6 | GCCACGGGAAATATGTAATAT | TRCN0000007348 |

## Supplementary Notes

## (: containing full blots of regular figures)

Fig. 1a

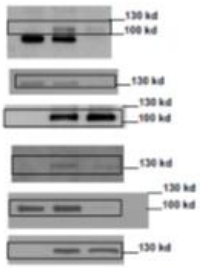



Fig. 1b

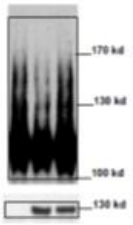



Fig. 1c

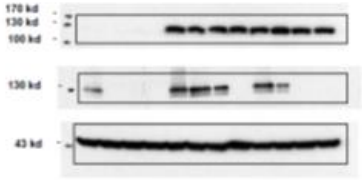



Fig. 1d

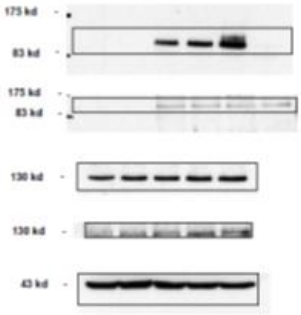



Fig. 1e

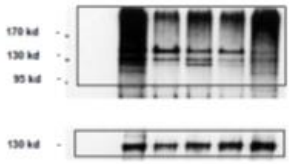



Fig. 1f


Fig. 1h

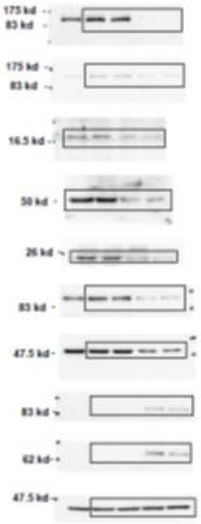



Fig. 2a

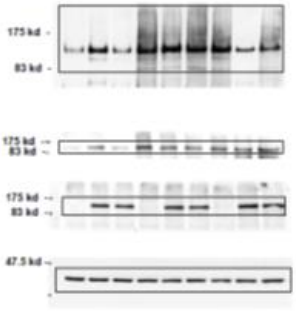



Fig. 2b

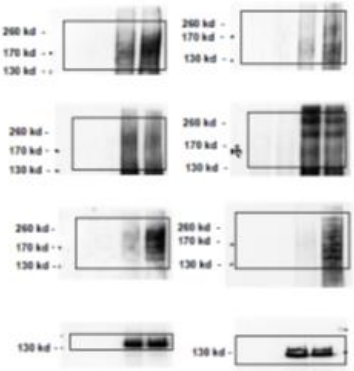


Fig. 2c

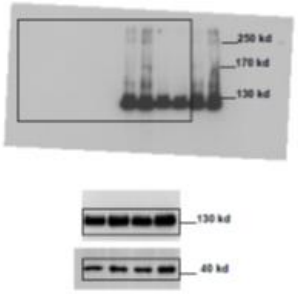



Fig. 2e

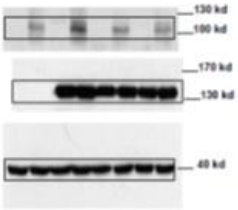



Fig. 2f

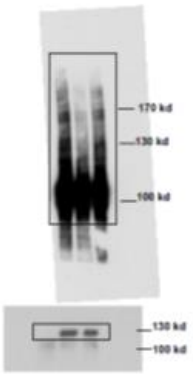



Fig. 3a

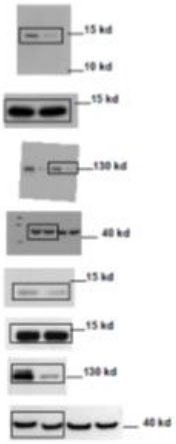



Fig. 3b

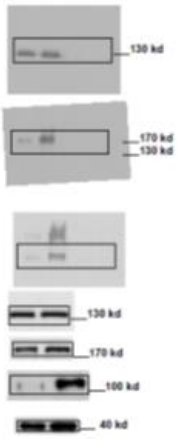



Fig. 3c

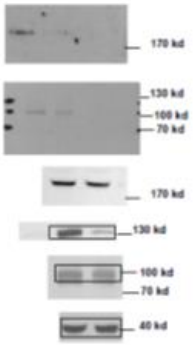



Fig. 3d

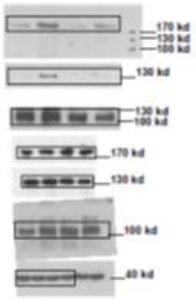
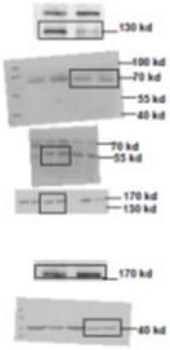



Fig. 3e



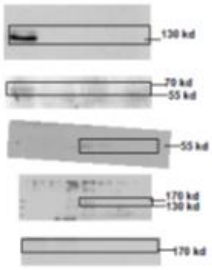




Fig. 3f

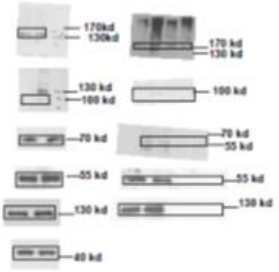


Fig. 3g

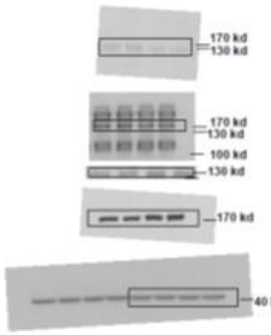



Fig. 5b

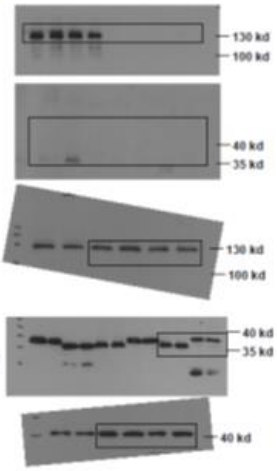



Fig. 5c

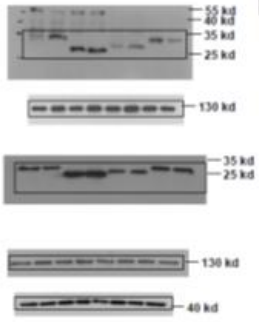



Fig. 5d

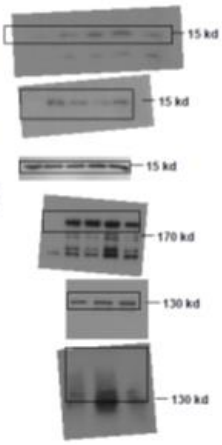



Fig. 5e

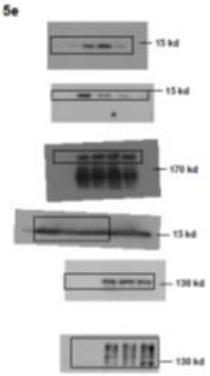



Fig. 7d

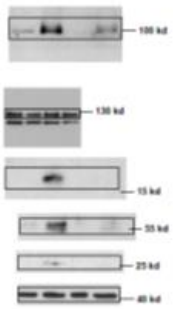



Fig. 7e

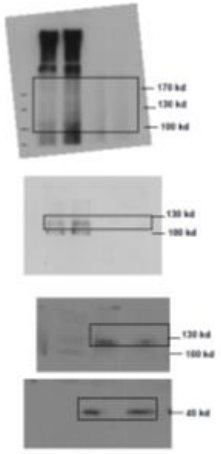



Fig 8e