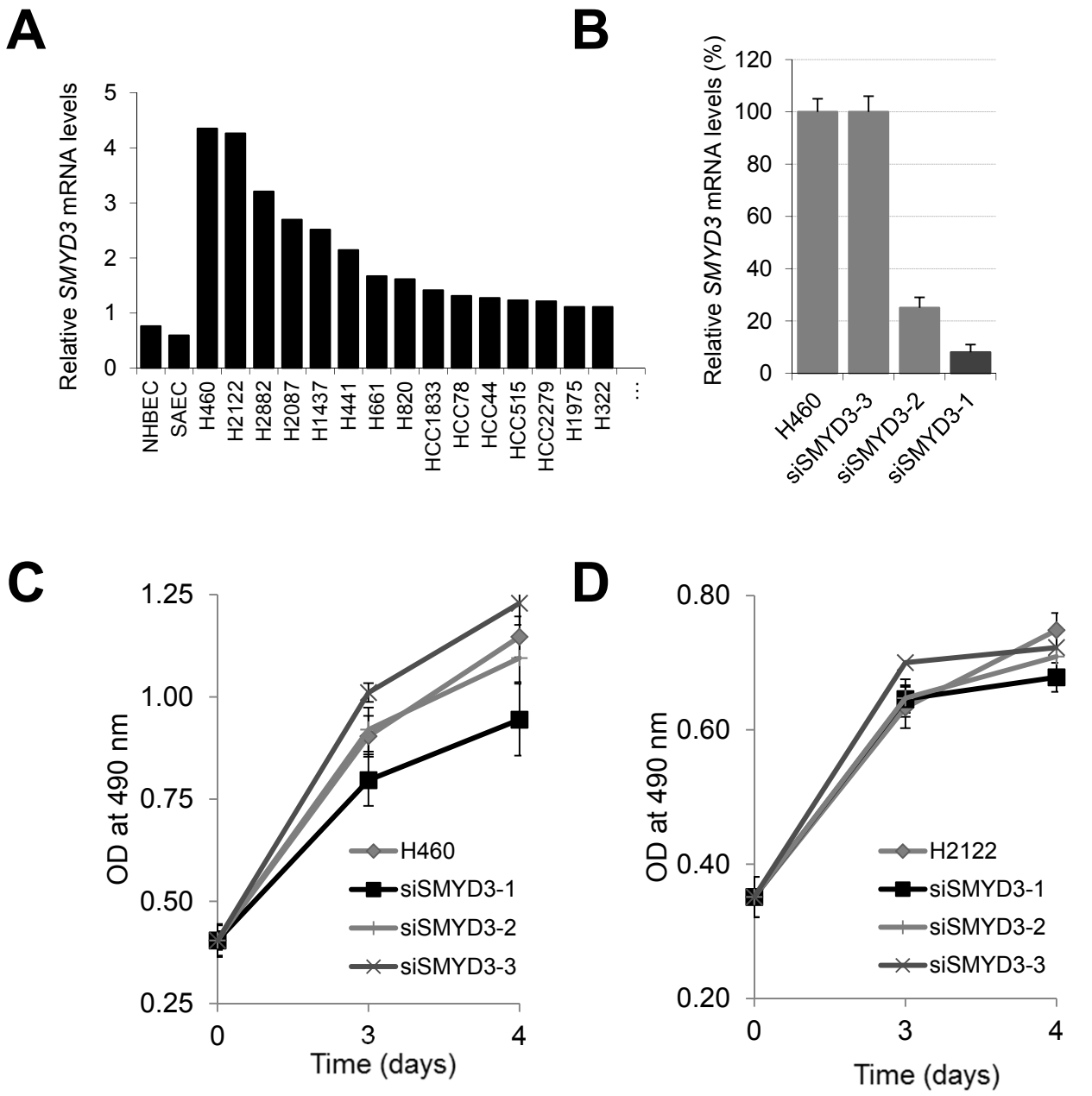
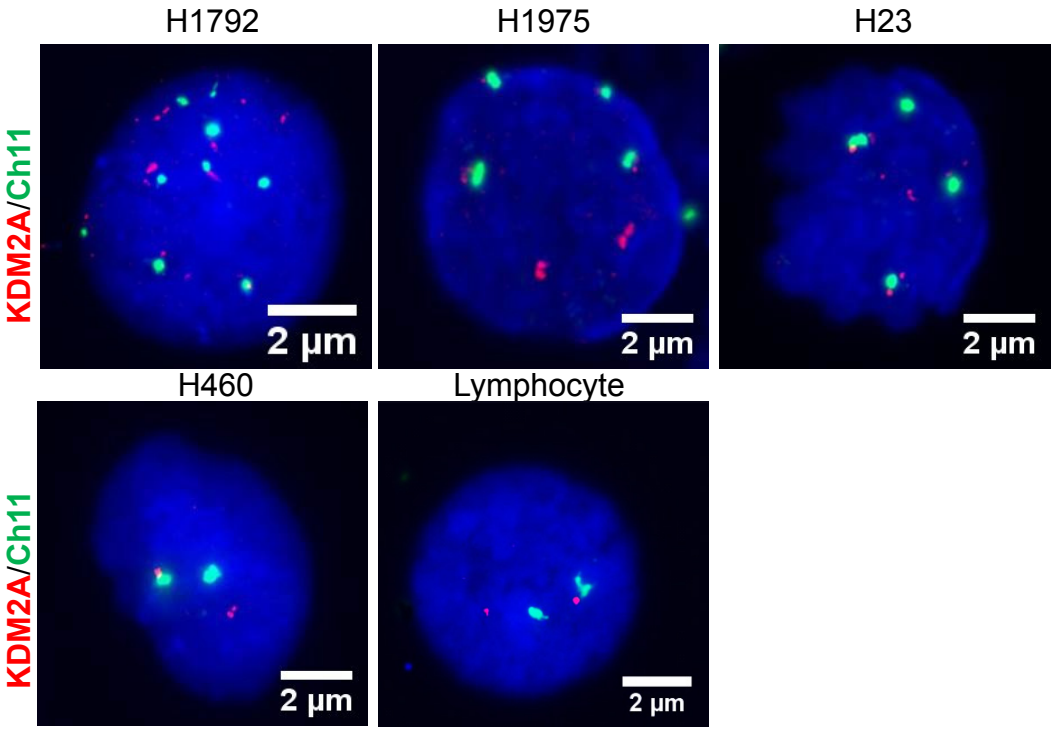


Figure S1. **SMYD3 knockdown did not have any significant effect on cell proliferation of SMYD3-overexpressing H460 and H2122 cells.** (**A**) H460 and H2122 cells displayed the highest *SMYD3* mRNA expression levels across 54 NSCLC cell lines. Control normal cell lines are presented in columns 1 and 2: NHBEC, Normal human bronchial epithelial cells; SAEC, Normal small airway epithelial cells. (**B**) Knockdown efficacy of SMYD3 by three independent siRNAs (siSMYD3-1, 3-2, and 3-3) was analyzed by quantitative RT-PCR. (**C** and **D**) SMYD3 knockdown had no significant effect on the proliferation of H460 (**C**) and H2122 (**D**) cells. Cell proliferation was measured by MTS assays (at 490 nm).

Supplemental Figure 2

A



B

FBXL11 (chr11:66644073-66781717)

Cancer Subset	In Peak?	Nearest Peak	#Genes in Peak	Q-value	Frequency of Amplification		
					Overall	Focal	High-level
all_cancers	No	chr11:69104194-69265651	3	1.49E-17	0.1718	0.0747	0.0176
Lung SC	Yes	chr11:29631919-104127195	675	1.0	0.225	0.075	0.025
all_epithelial	No	chr11:69104194-69265651	3	4.04E-16	0.2355	0.1035	0.0233
all_lung	No	chr11:68689617-69265651	4	2.0E-5	0.2726	0.1021	0.0194
Lung NSC	No	chr11:68766043-69265651	4	2.46E-5	0.2756	0.1037	0.0191
Breast	No	chr11:68933687-69265651	3	5.77E-4	0.3251	0.1893	0.0535
Esophageal squamous	No	chr11:68230745-68388280	3	0.0323	0.4773	0.4318	0.0682

Figure S2. (**A**) **Analysis of *KDM2A* gene by fluorescence *in situ* hybridization (FISH) showed that *KDM2A gene* signal numbers were increased in all three KDM2A-overexpressing cell lines (H1792, H1975, and H23) as compared to H460 cell line and a normal lymphocyte**. FISH analysis of normal lymphocytes is shown as control. Red and green signals indicate the *KDM2A* gene (chromosome 11q13.2) and chromosome (Ch) 11 centromere, respectively. Scale bars indicate 2 µm. (**B**) **The *KDM2A* (*FBXL11*) gene appeared to be significantly amplified in a subset of NSCLC tumors.** Although KDM2A gene is not in peak regions in several types of cancer, its low Q-values (a typical threshold is 0.25) suggest that amplifications at this locus are significantly enriched by selective pressures. Overall frequency measures the fraction of cancers which exhibit any amplification/deletion at that gene. Focal frequency measures the fraction of cancers which exhibit amplifications/deletions spanning less than half a chromosome arm in length. High-level frequency measures the fraction of cancers that show amplification of greater than 1 copy. All these numbers are likely to be underestimates due to the effects of contaminating normal cells in many of the cancer samples and the limited resolution of the copy number platform. Lung SC: small cell lung carcinoma; **Lung NSC; non-small cell lung carcinoma.** Most of this legend is directly from **the *Source*:** http://www.broadinstitute.org/tumorscape/pages/portalHome.jsf

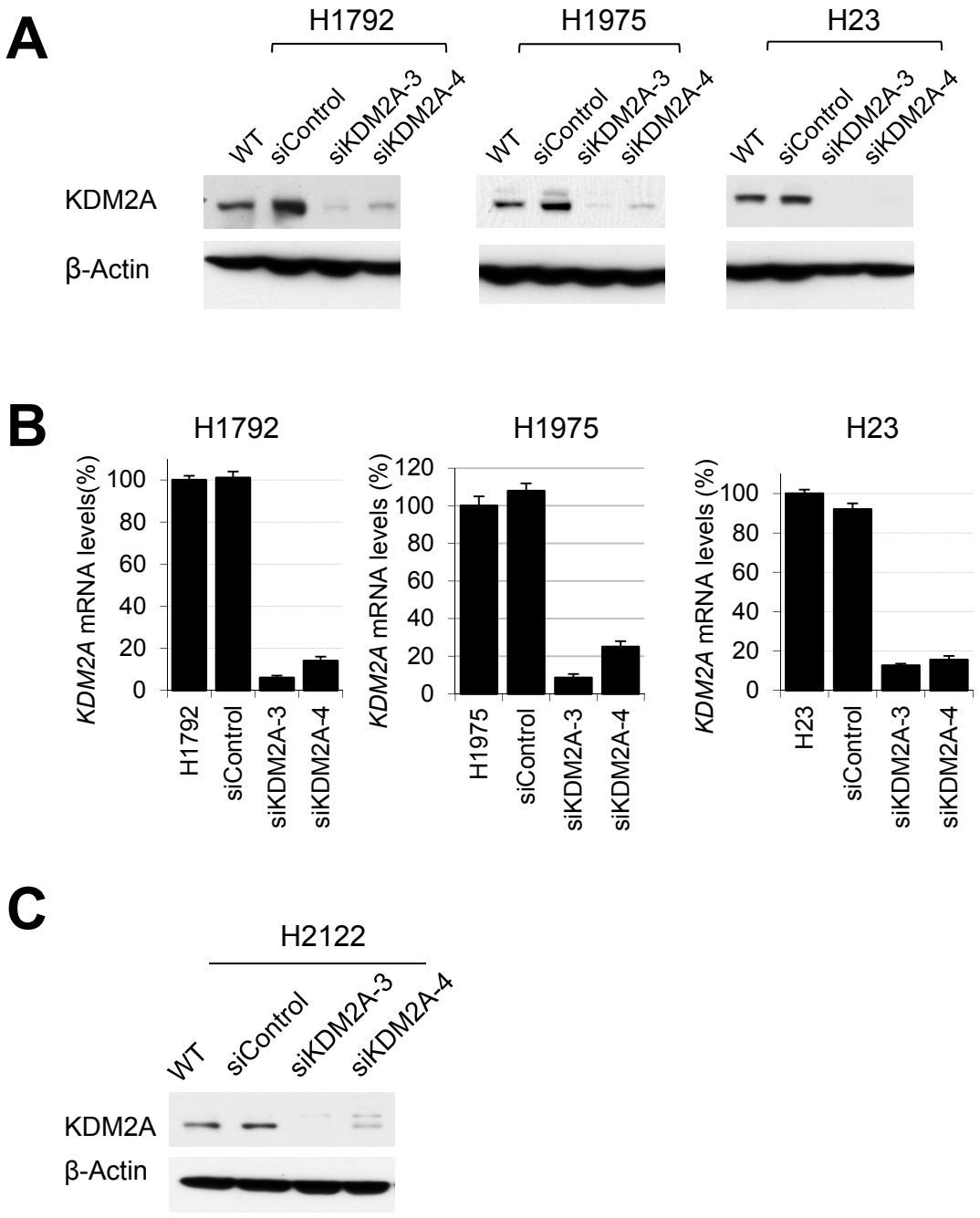


Figure S3. **The efficacy of KDM2A knockdown**. (**A** and **B**) After siRNA treatment, KDM2A protein and mRNA levels in KDM2A-overexpressing NSCLC cell lines (H1975, and H1792 and H23) were measured by Western blot analysis (**A**) and quantitative RT-PCR (**B**), respectively. (**C**) After siRNA treatment, KDM2A protein levels in the cell line (H2122) with low KDM2A levels were assessed by Western blot analysis.

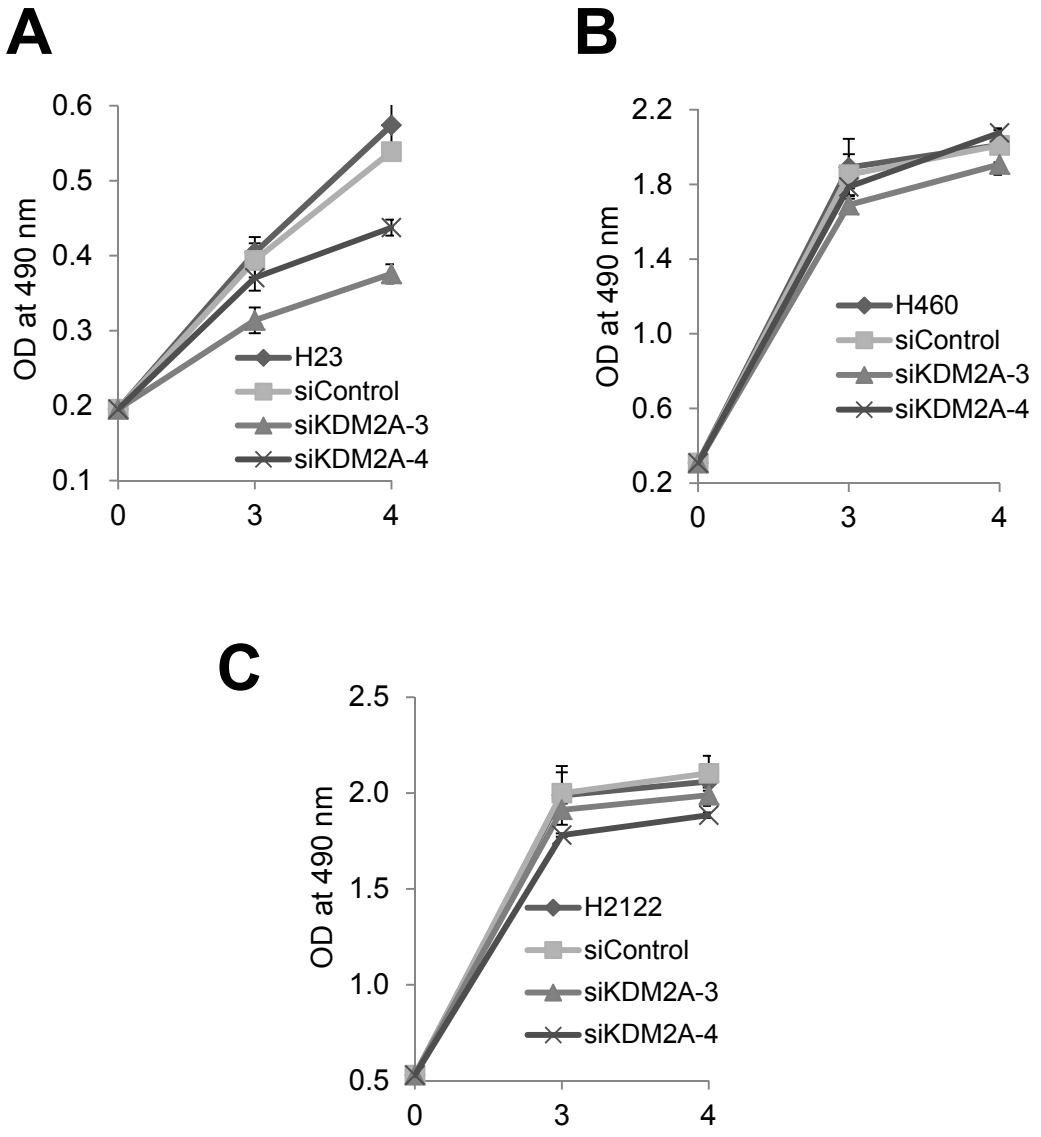


Figure S4. (**A-C**) Knockdown of KDM2A decreased the proliferation of the KDM2A-overexpressing NSCLC cell line H23 (**A**) but did not affect the proliferation of two NSCLC cell lines with low KDM2A levels, i.e., H460 (**B**) and H2122 (**C**). Cells were treated with siControl (siLuciferase), siKDM2A-3 or siKDM2A-4. Cell proliferation was measured by MTS assay.

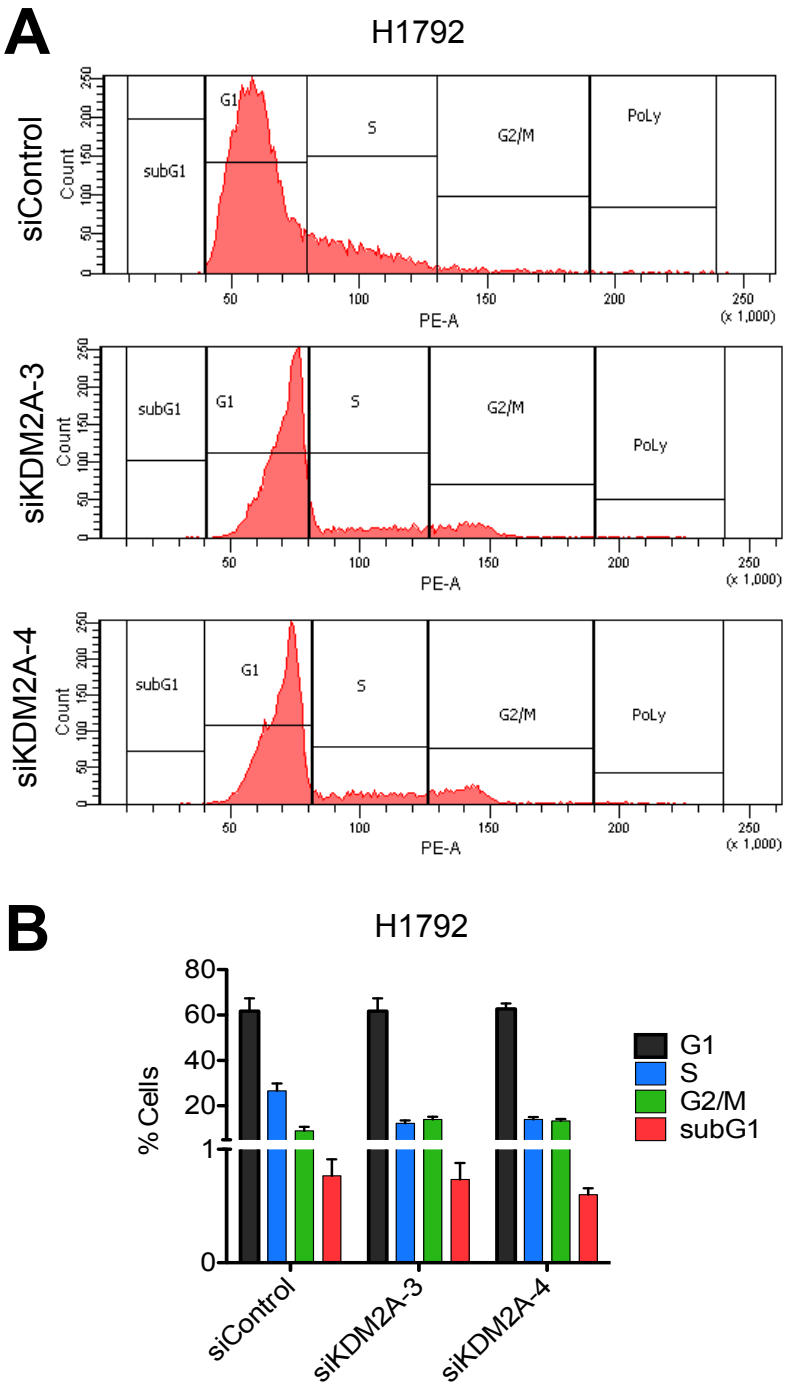


Figure S5. KDM2A knockdown reduced S phase percentages but did not affect sub-G1 population in H1792 cells. H1792 cells were treated with siControl (siLuciferase), siKDM2A-3 or siKDM2A-4 at a final concentration of 50 nM. Forty eight hours later, cells were harvested, fixed in cold 75 % ethanol for 30 min at 4 °C, and washed 2 times in PBS. Then, cells were incubated at 37°C for 30 min in a buffer containing 50 µg/ml propidium iodine, 5 mM $MgCl_2$, 10 mM TRIS-HCl pH 7.0, 25 µg/ml RNaseA. DNA contents were analyzed using flow cytometry. The distribution (**A**) and percentages (**B**) of cells in sub-G1, G1, S, and G2/M phase of the cell cycle are shown. The sub-G1 peaks indicate cells with a lower DNA content.

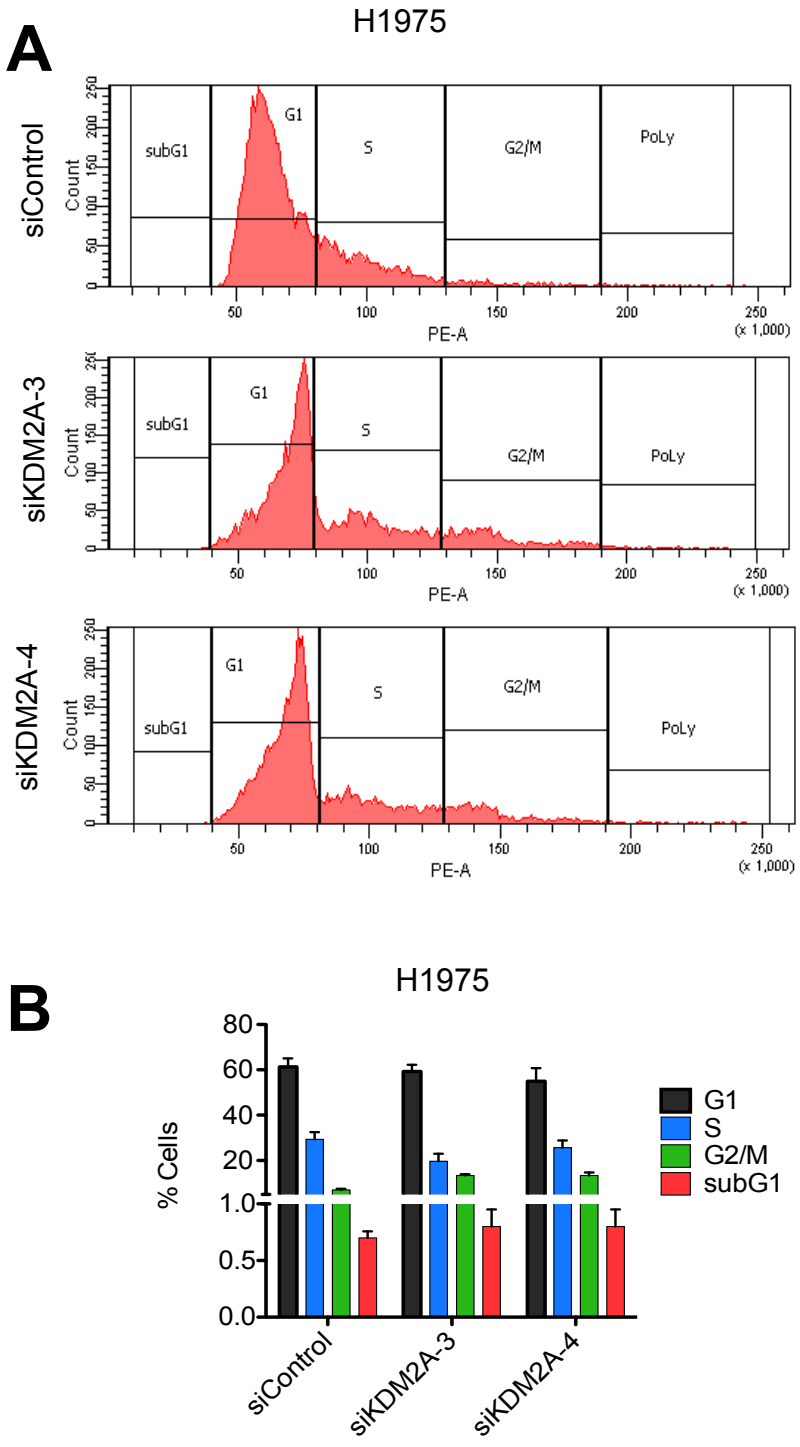


Figure S6. KDM2A knockdown reduced S phase percentages but did not affect sub-G1 population in H1975 cells. H1975 cells were treated with siControl (siLuciferase), siKDM2A-3 or siKDM2A-4 at a final concentration of 50 nM. The distribution (**A**) and percentages (**B**) of cells in sub-G1, G1 , S and G2/M phase of the cell cycle were analyzed as in **Figure S5**.

Supplemental Figure 7

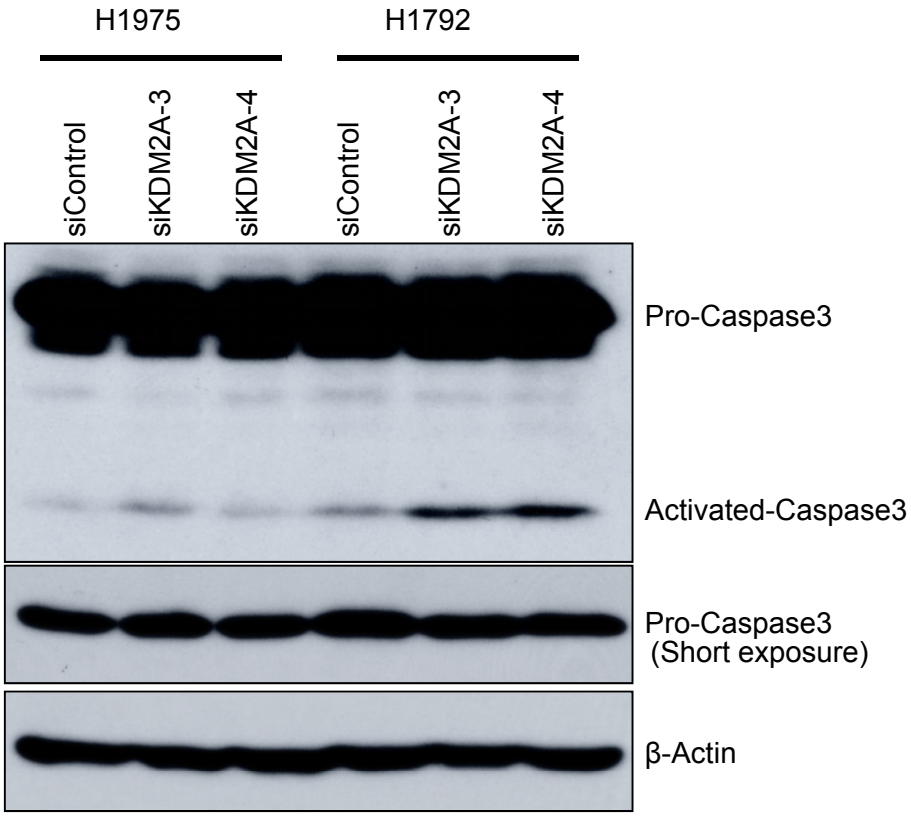


Figure S7. **KDM2A knockdown did not have any significant effect on activated and total caspase 3 in H1792 and H1975 cells**. Total and activated cellular levels of caspase 3 in siControl- and siKDM2A-treated H1792 and H1975 cells were examined by Western blot analysis. β-Actin was used as internal loading controls.

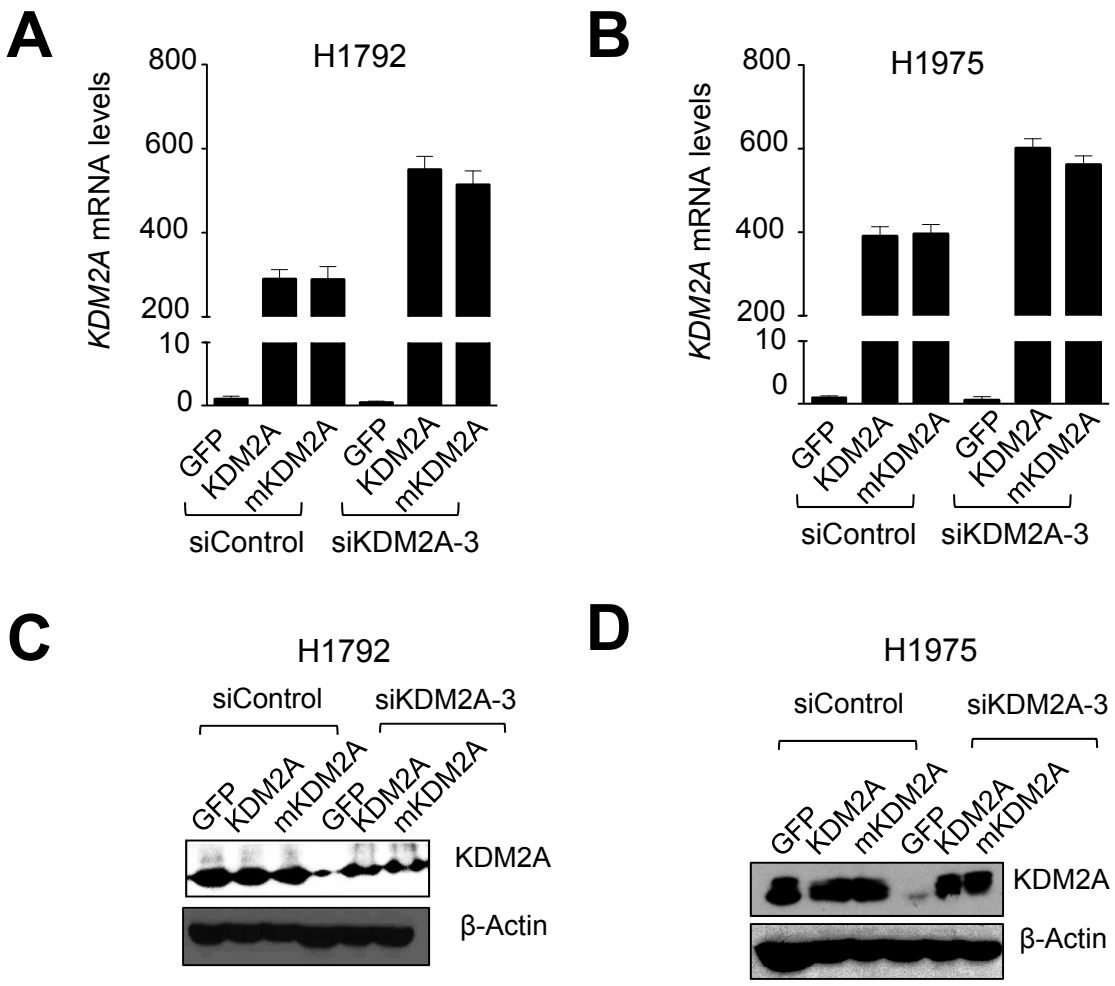


Figure S8. KDM2A and its catalytic mutant were transiently expressed in H1792 (**A and C**) and H1975 (**B and D**), which were treated with siControl or siKDM2A-3. KDM2A mRNA (**A and B**) and protein (**C and D**) levels were quantified by RT-PCR and Western blot analysis, respectively. Transient expression of KDM2A and mKDM2A (H212A) in siControl-treated cells did not increase their proteins levels as compared to GFP control, although KDM2A and mKDM2A mRNA levels appeared to be highly increased. A possible reason for no obvious effect of increased mRNA levels of KDM2A and mKDM2A on their protein levels in H1792 and H1975 cells is that cellular KDM2A protein levels may be saturated by high endogenous KDM2A expression in these cells.

Supplemental Figure 9

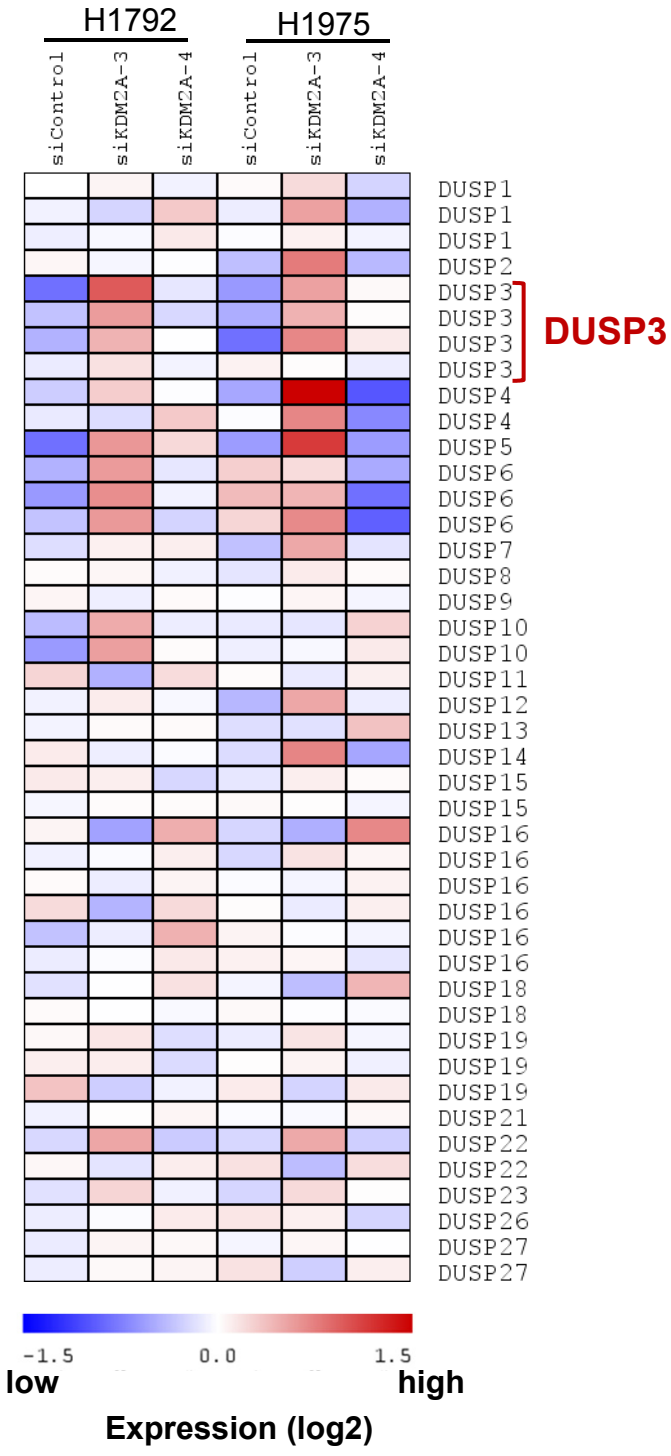


Figure S9. Of the DUSP family members, DUSP3 mRNA levels were consistently up-regulated by KDM2A knockdown in H1792 and H1975 cells. H1792 and H1975 cells were treated with siControl RNA or two different siKDM2As (siKDM2A-3 and -4) and harvested 48 h later. The mRNA levels in KDM2A knockdown cells were measured by Affymetrix U133P and compared with those of siControl-treated cells in a heat map.

Supplemental Figure 10

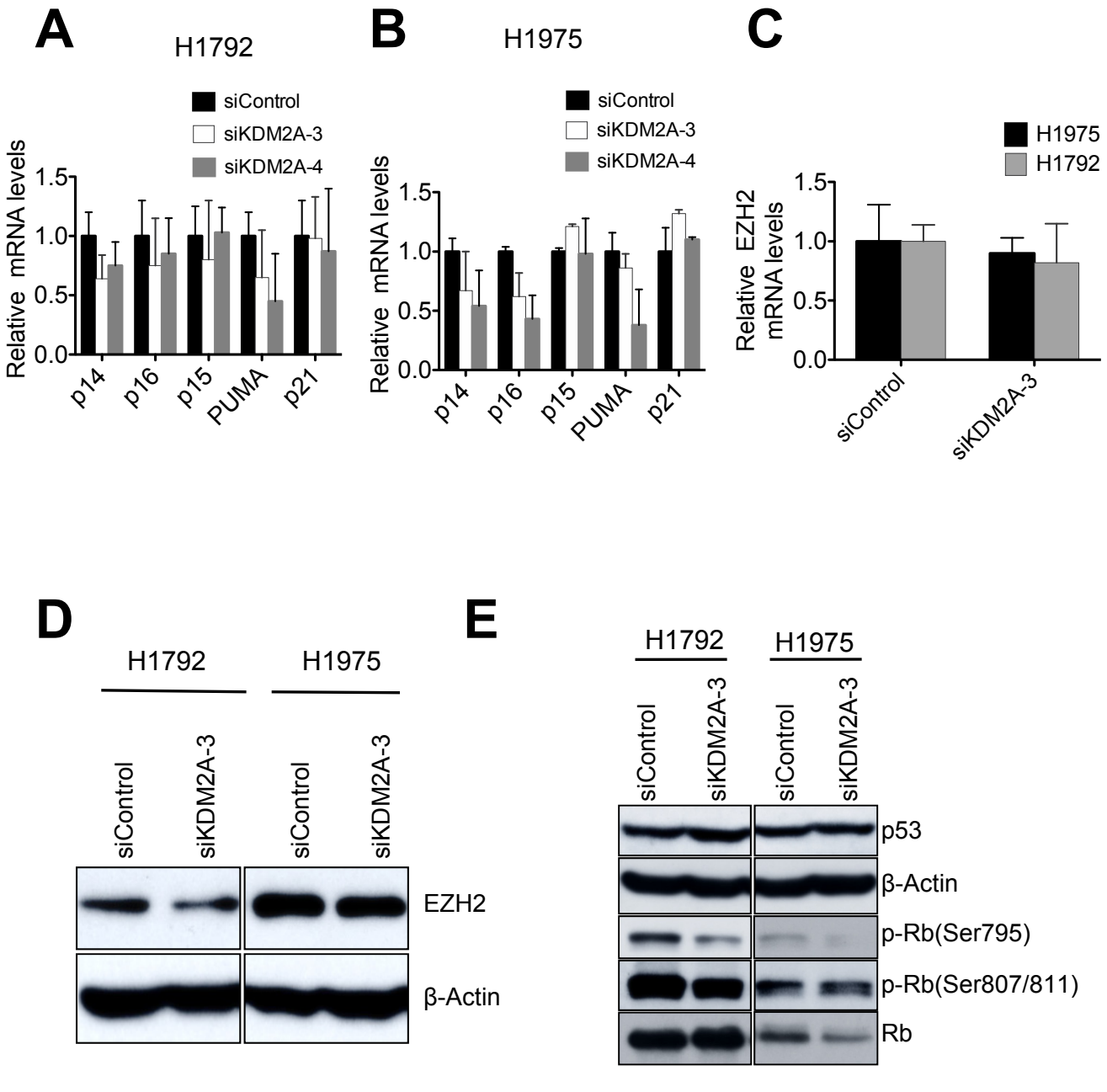


Figure S10. **KDM2A knockdown had no significant effect on *p14^{ARF}*, *p16^{Ink4a}*, *p15^{Ink4b}*, *PUMA*, *p21^{CIP1}*, *EZH2* and *p53* expression levels and slightly decreased in phosphorylated Rb-Ser795 in H1792 and H1975 cells**. (**A−C**) H1792 and H1975 cells were treated with siControl or siKDM2As, and mRNA levels of *p14^{ARF}*, *p16^{Ink4a}*, *p15^{Ink4b}*, *PUMA*, *p21^{CIP1}* (**A** and **B**) and EZH2 (**C**) were quantified by qRT-PCR. (**D**) EZH2 protein levels were not changed by KDM2A knockdown. (**E**) The levels of total p53 and phosphorylated Rb upon KDM2A knockdown in H1792 and H1975 cells were examined by Western blot analysis.

Supplemental Figure 11

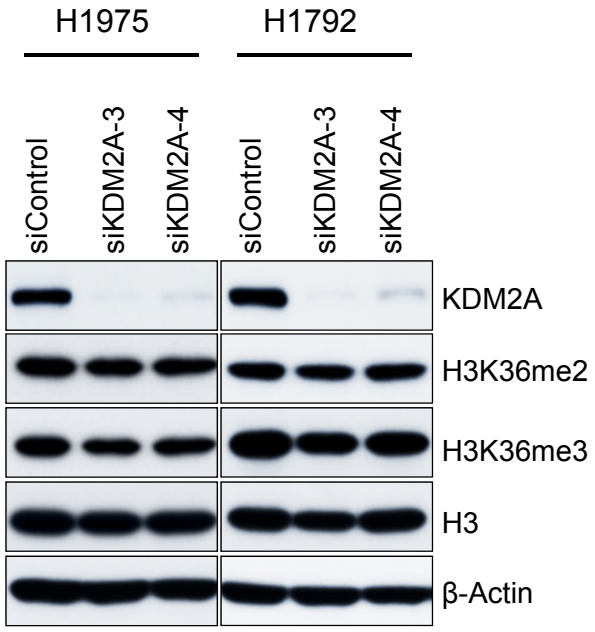


Figure S11. **KDM2A knockdown did not affect total cellular levels of H3K36me2 in H1792 and H1975 cells**. Total cellular levels of H3K36me2 in siControl- and siKDM2A-treated H1792 and H1975 cells were examined by Western blot analysis. H3 and β-Actin were used as internal loading controls.

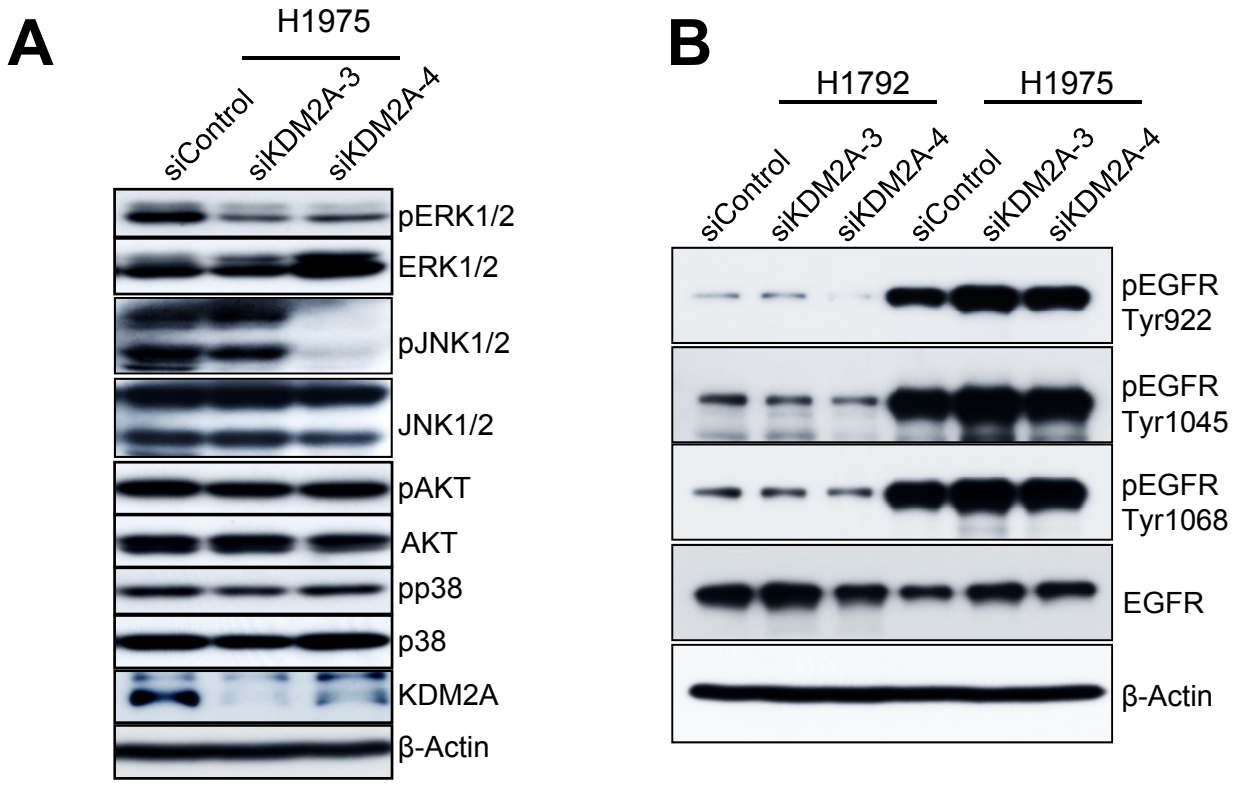


Figure S12. KDM2A knockdown decreased phospho-ERK1/2 and to a lesser extent phospho-JNK1/2 levels. (**A**) KDM2A knockdown downregulated phospho-ERK1/2 and to a lesser extent phospho-JNK1/2 in H1975 cells, but did not affect phospho-p38 nor phospho-AKT levels. Phosphorylated forms of ERK1/2, JNK1/2, p38 and AKT in siControl- and siKDM2A-treated H1975 cells were examined by Western blot analysis. Total ERK1/2, JNK1/2, p38 and AKT were used as internal loading controls. (**B**) KDM2A knockdown had no obvious effect on phosphorylation levels of EGFR. Phosphorylated forms of EGFR in KDM2A-depleted cells and control cells were examined by Western blot analysis. Total EGFR and β-Actin were used as internal loading controls. Phosphorylated forms of EGFR were higher in H1975 cells than in H1792 cells, because L858R mutation in H1795 cells results in a constitutive activation of EGFR.

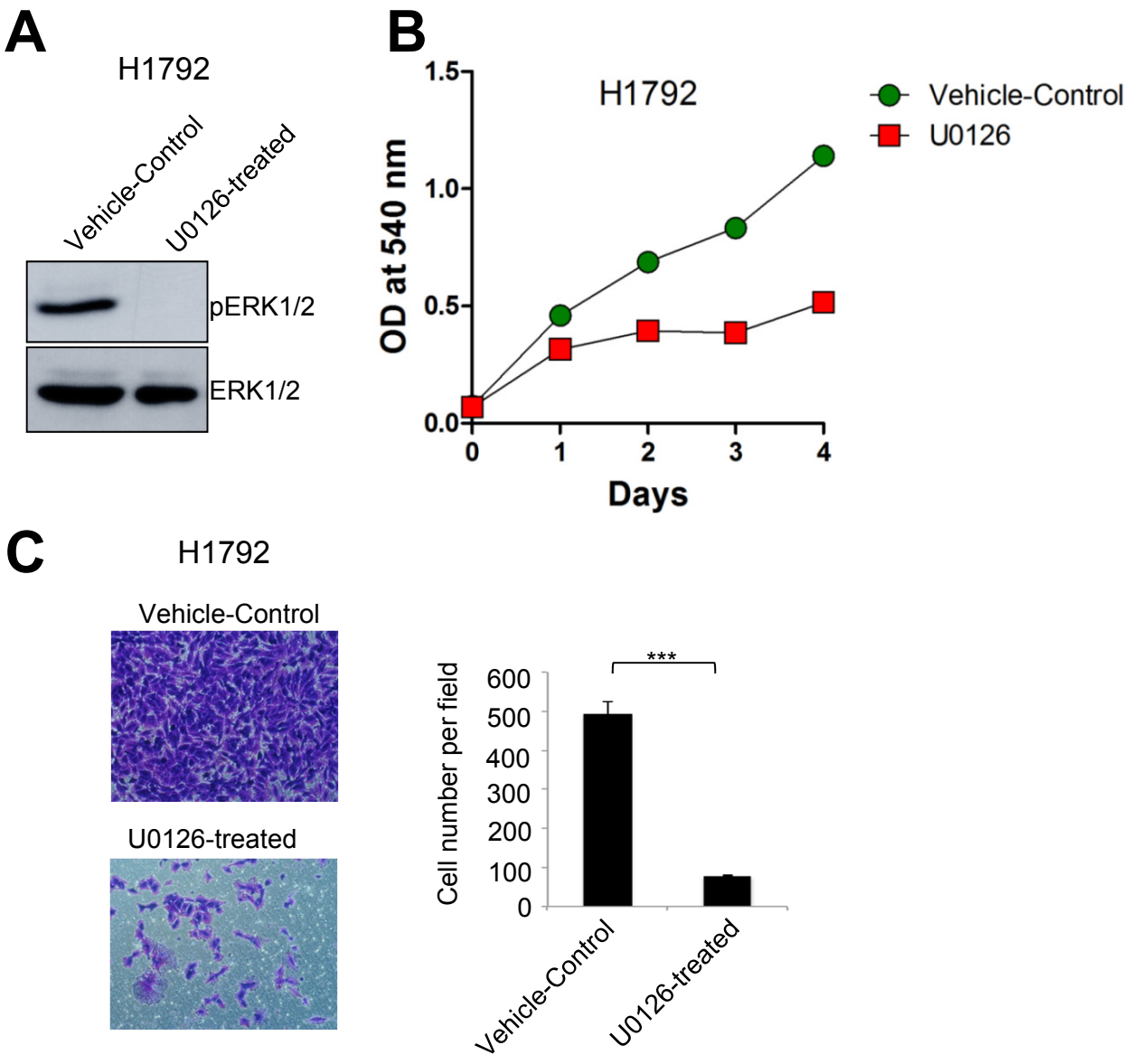


Figure S13. Inhibition of ERK1/2 phosphorylation by the MEK inhibitor U0126 reduced the proliferation and invasion of KDM2A-overexpressing cells. (**A**) U0126 inhibitor decreased phosphorylated ERK1/2 levels. H1792 cells were continuously treated with 10 μM U0126, a MEK inhibitor that consequently impedes ERK1/2 phosphorylation. Phosphorylated ERK1/2 levels of in vehicle - or U0126- treated H1792 cells were examined by Western blot analysis. Total ERK1/2 was used as internal loading control. (**B and C**) Inhibition of ERK1/2 phosphorylation decreased the proliferation and invasion of KDM2A-overexpressing H1792 cells. Cell proliferation and invasion was measured by MTS assay (**B**) and Boyden Chamber invasion assay (**C**), respectively.

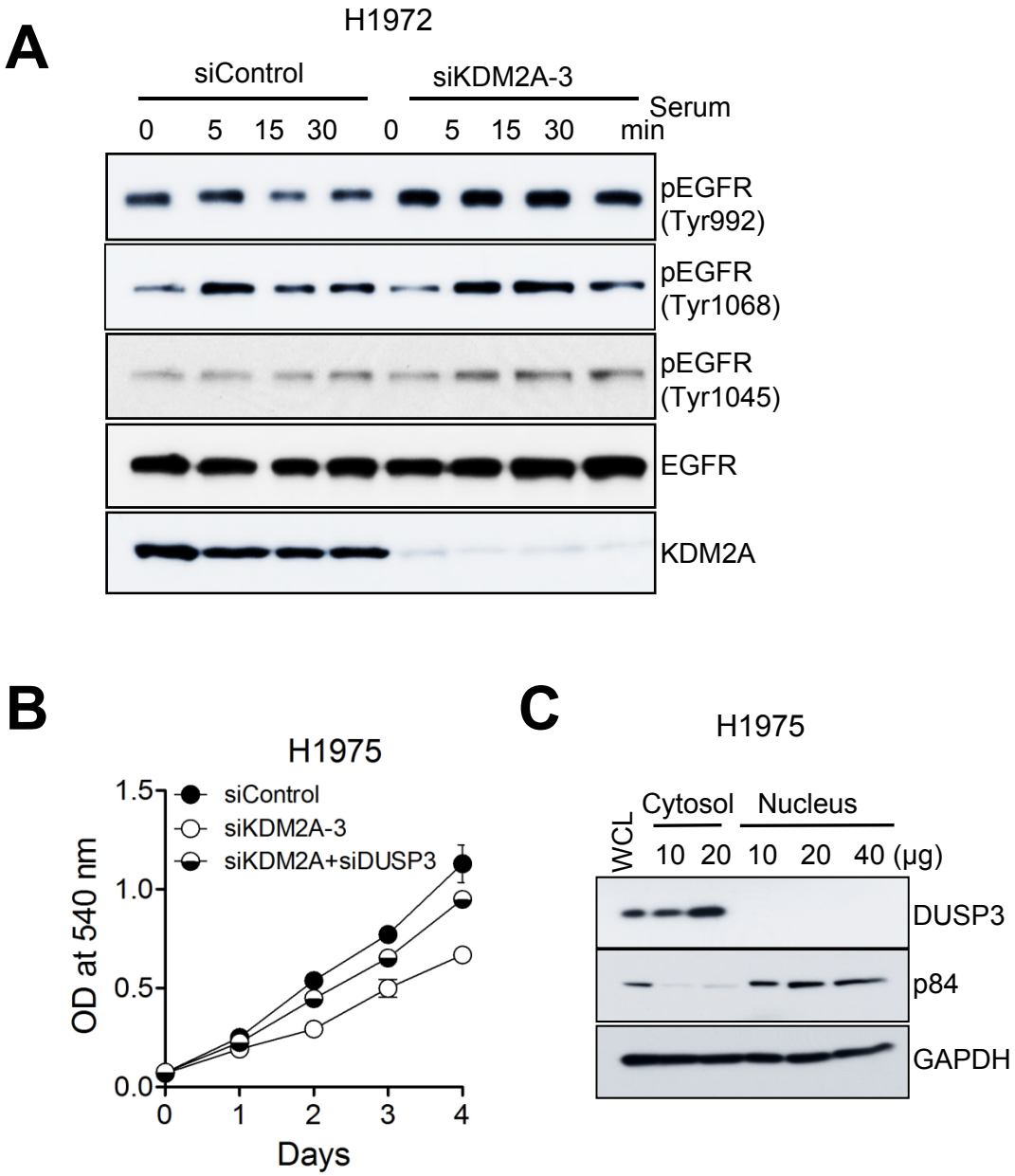


Figure S14. (**A**) **KDM2A knockdown did not have any obvious effect on phosphorylation levels of EGFR during serum activation**. KDM2A-depleted H1792 cells and control cells were stimulated with 10% serum for 0, 5, 15 or 30 minutes after 18 hours of serum starvation. Subsequently, protein extracts were examined by Western blot analysis using antibodies to phosphorylated forms of EGFR. Total EGFR and β-Actin were used as internal loading controls. (**B**) **DUSP3 knockdown restored defective proliferation of KDM2A-depleted H1975 cells**. (**C**) **DUSP3 was localized in cytosol in H1975 cells**. Cytoplasmic and nuclear fractions of H1975 cells were examined by Western blot analysis. p84 and GAPDH were used as a nuclear marker and a loading control, respectively. WCL, whole cell lysates.

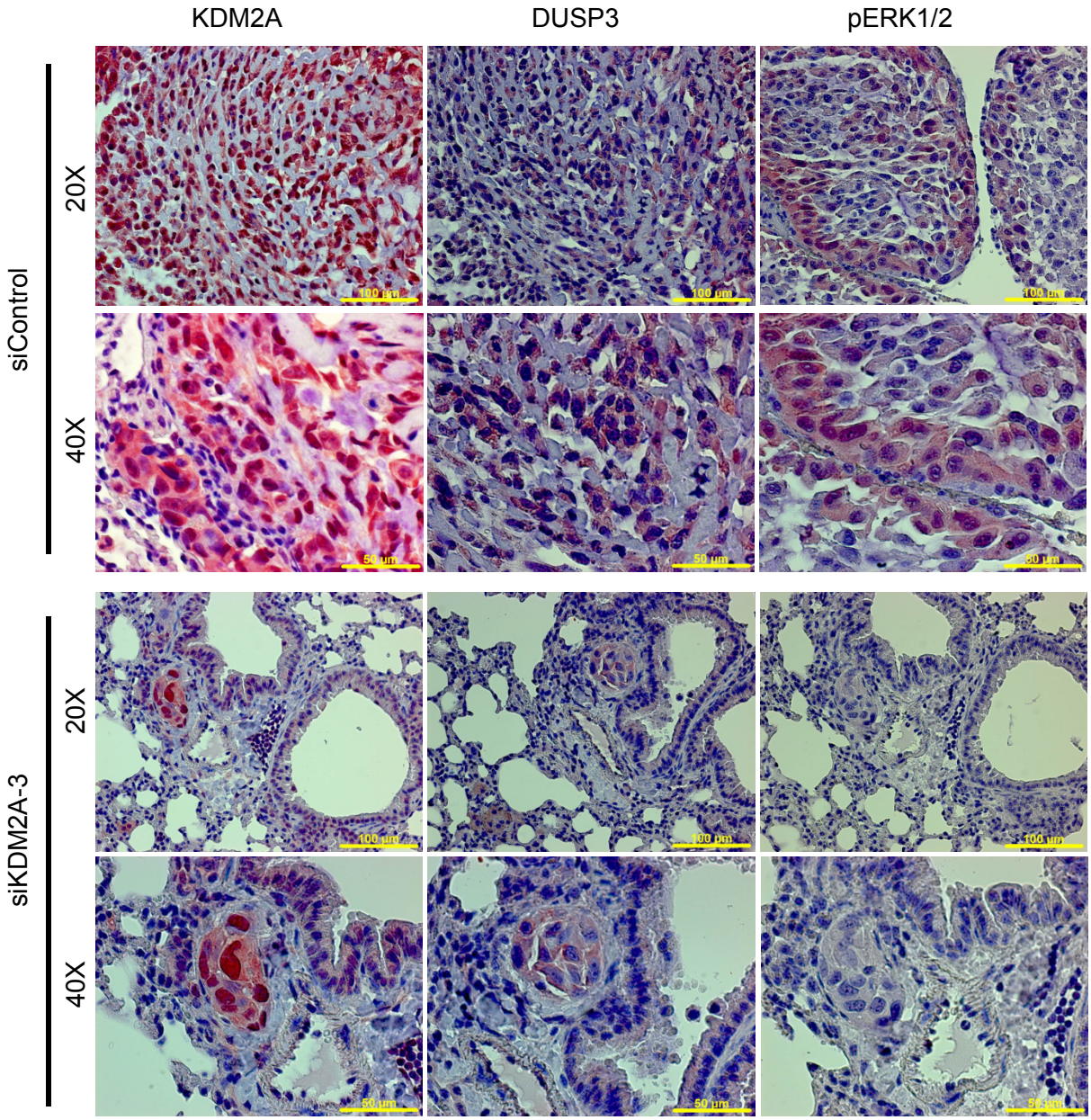
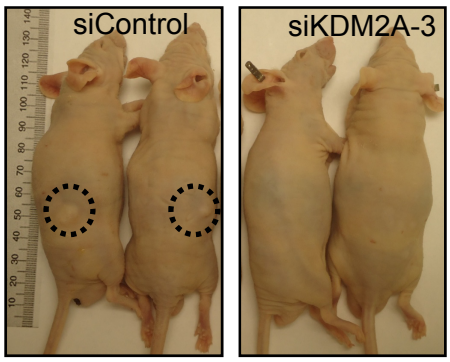


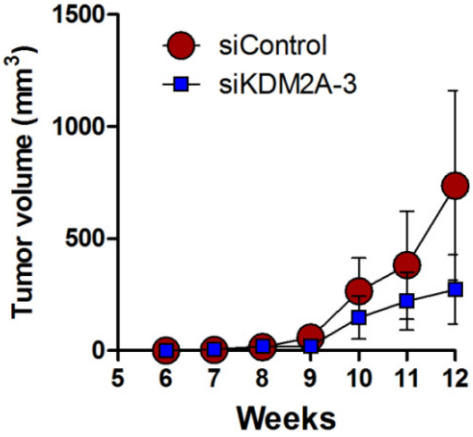
Figure S15 : **Representative images of immunohistochemical staining of KDM2A, DUSP3, and phospho-ERK1/2 (pERK1/2) in tumor tissues in orthotopic lung mouse model** (related to **Figure 7, C and D, and Table 3**). siControl- or siKDM2A-transfected H1792 cells were injected into the lungs of mice. For KDM2A, DUSP3, and pERK1/2, stained areas in siKDM2A-3 group were much smaller than those in siControl group, indicating that KDM2A knockdown dramatically decreases tumor sizes. 20 x and 40 x magnification are shown. Scale bars indicate 50 μm (20 x) or 100 μm (40 x).

Supplemental Figure 16

A



B



C

Treatment	Total #	Mouse # with tumors (s.c injection)
siControl	9	7
siKDM2A-3	9	4

D

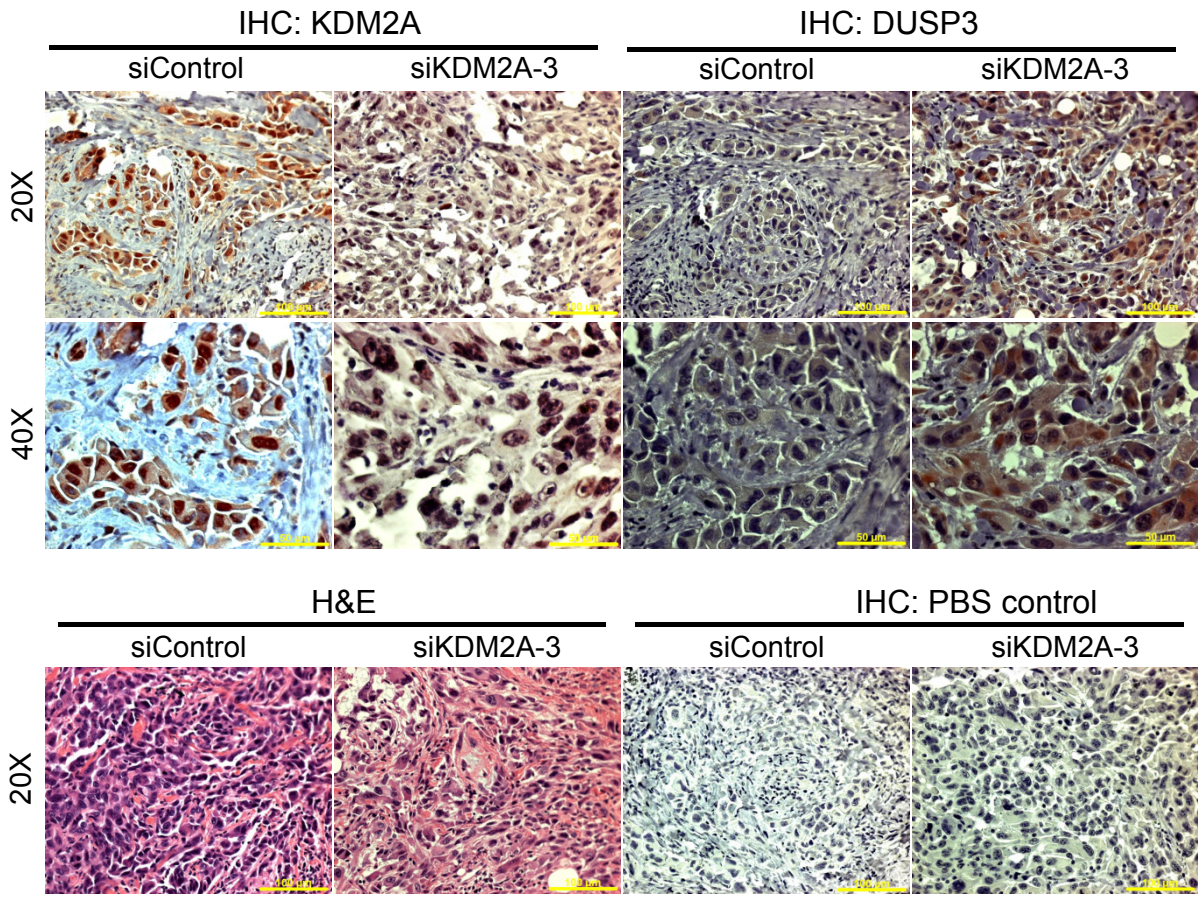


Figure S16. siRNA-mediated knockdown of KDM2A moderately decreased tumorigenicity of H1792 cells in a subcutaneous mouse xenograft model. (**A**) H1792 cells (2 x 10^6) transfected with either siControl or siKDM2A in H1792 cells were injected subcutaneously into 9 nude mice. Representative images of nude mice in siControl and siKDM2A group are shown. Pictures were taken 11 weeks after subcutaneous injection. Dotted circles indicate tumor-containing areas. (**B**) Tumor volumes were monitored and plotted for 11 weeks. (**C**) Numbers of tumor-bearing mouse at the 11^{th} week are shown. (**D**) Representative images of immunohistochemical staining of KDM2A and DUSP3 in tumor tissues obtained from each group of nude mice. These images shows that KDM2A and DUSP3 levels in tumors from siKDM2A group are lower and higher than in those from siControl group, respectively. PBS control indicates IHC staining without the use of primary antibody. 20 x and 40 x magnification are shown. Scale bars indicate 50 μm (20 x) or 100 μm (40 x).

Supplemental Figure 17

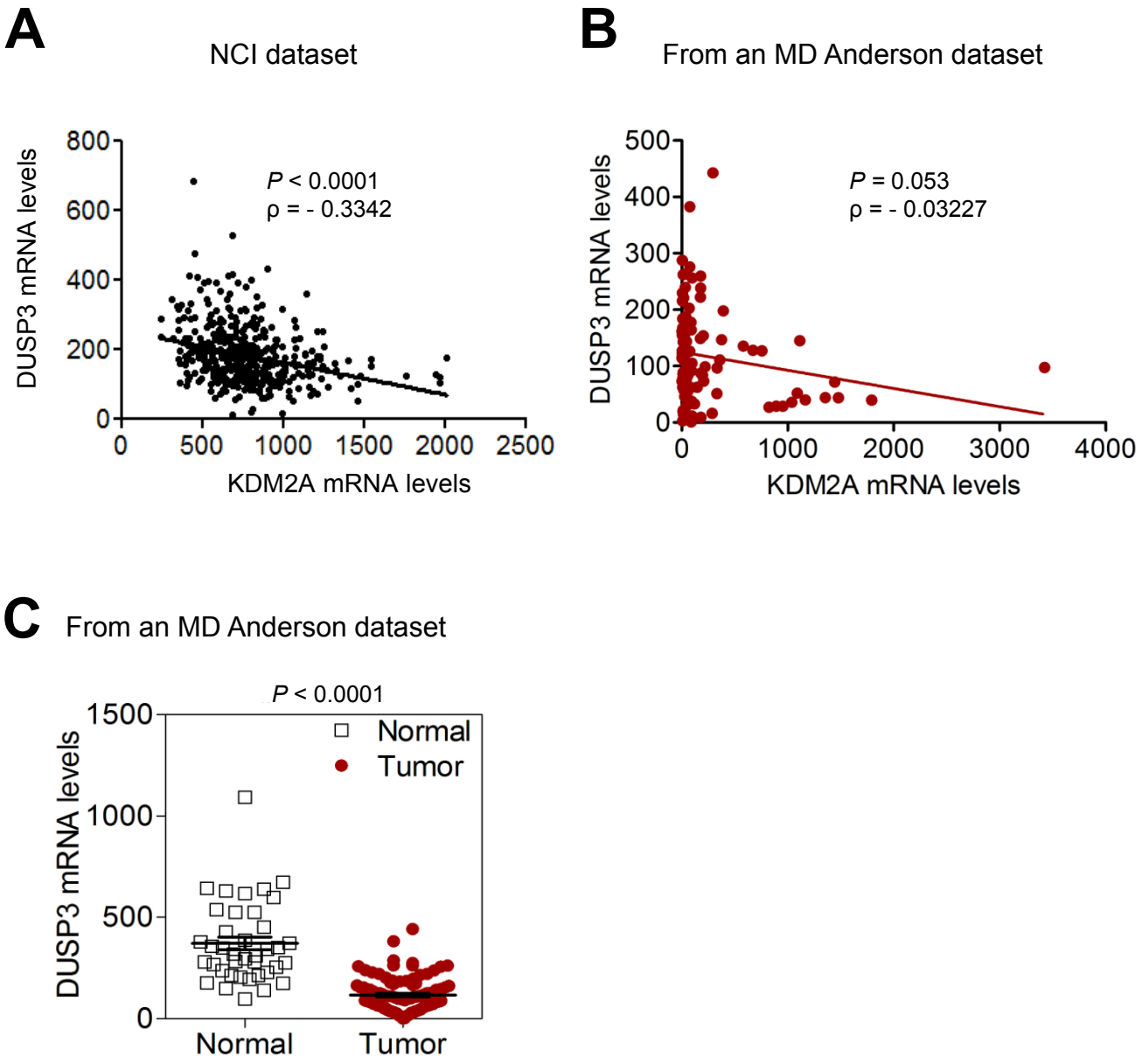


Figure S17. (**A**) ***DUSP3*** **mRNA levels were inversely related to** ***KDM2A*** **mRNA levels** in the publicly available NCI Director's Challenge Consortium patient set (444 lung adenocarcinoma samples). (**B**) ***DUSP3*** **mRNA levels were inversely associated with** ***KDM2A*** **mRNA levels in tumors in the 98 NSCLC patients** from UT MD Anderson Cancer Center. (**C**) ***DUSP3*** **mRNA levels were down-regulated in NSCLC samples**. *DUSP3* mRNA levels were analyzed in 103 NSCLC tumors (stages I, II, and III) from UT MD Anderson Cancer Center and 40 adjacent normal lung tissues. DUSP3 mRNA levels were evaluated by quantitative RT-PCR.

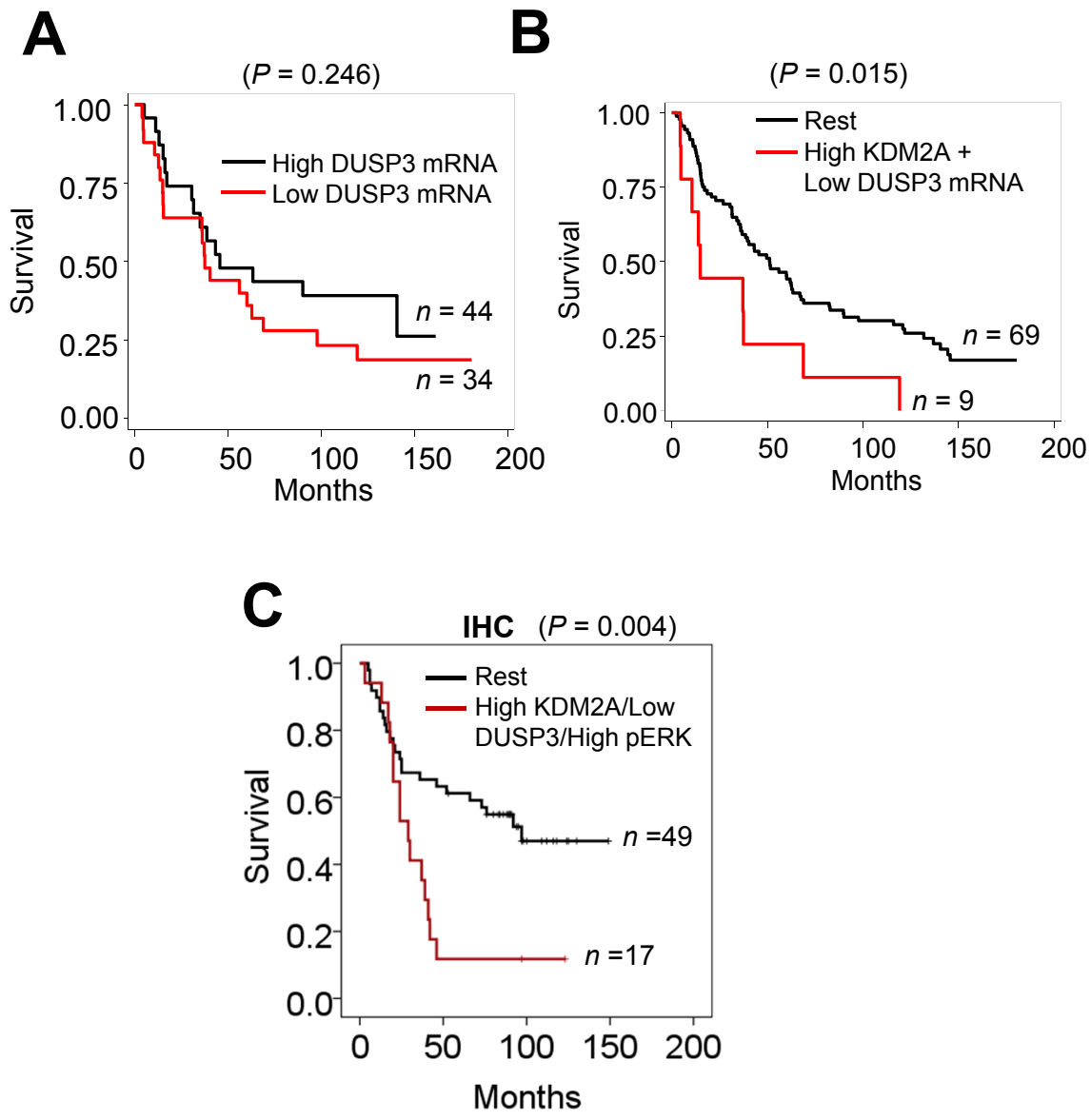


Figure S18: (**A & B**) **Low *DUSP3* mRNA levels showed a trend for poor survival** (**A**), **and low *DUSP3* mRNA levels with high *KDM2A* mRNA levels were associated with poor survival** (**B**). Kaplan-Meier survival analysis were performed using NSCLC tumor samples with patient history from UT MD Anderson Cancer Center. Tumors were classified as "high DUSP3" or "low DUSP3" by an cut-off value that is the mean of normal value in 40 normal lung tissues. Survival rates were compared between high KDM2A plus low DUSP3 and rest. (**C**) **Survival rate of high KDM2A levels with low DUSP3 and high pERK1/2 levels was lower than that of rest**. On the basis of IHC, Kaplan-Meier survival analysis were carried out using human lung tumor samples.

Supplemental Table 1: Bioinformatic analysis of whole-genome Affymetrix data of 54 NSCLC cell lines. Results showed that the histone lysine demethylase KDM2A and the histone methyltransferase SMYD3 had the largest normalized SD within histone demethylases and methyltransferases examined, respectively. Normalized SD indicates standard deviation normalized to the mean. MAX and MIN represent the maximum and minimum values that were normalized to the mean.

Rank	Histone modifiers	Unigene	Affy Probe Set	Normalized SD	MAX	MIN
	Histone demethylases					
1	KDM2A, FBXL11	Hs.124147	208988_at	**0.83**	4.24	0.15
2	KDM5D, JARID1D, SMCY	Hs.80358	206700_s_at	**0.74**	3.84	0.49
3	KDM1B, LSD2	Hs.709336	227021_at	**0.72**	4.47	0.36
4	KDM3C, JMJD1C	Hs.413416	221763_at	**0.66**	3.12	0.23
5	KDM7A, JHDM1D	Hs.308710	221778_at	**0.56**	3.35	0.35
6	KDM3A, JMJD1A	Hs.557425	212689_s_at	**0.54**	3.19	0.25
7	KDM2B, FBXL10	Hs.524800	226215_s_at	**0.43**	2.74	0.28
8	KDM5B, JARID1B	Hs.443650	211202_s_at	**0.42**	1.99	0.30
9	KDM5C, JARID1C, SMCX	Hs.631768	202383_at	**0.41**	2.42	0.49
10	JARID2	Hs.269059	203297_s_at	**0.38**	2.33	0.33
11	KDM5A, JARID1A	Hs.76272	202040_s_at	**0.38**	1.83	0.39
12	JMJD6	Hs.514505	212723_at	**0.38**	1.94	0.26
13	PHF2	Hs.211441	212726_at	**0.37**	2.25	0.45
14	KDM3B, JMJD1B	Hs.730776	201643_x_at	**0.31**	1.73	0.42
15	KDM1A, LSD1	Hs.591518	212348_s_at	**0.31**	1.71	0.53
16	KDM6B, JMJD3	Hs.223678	41387_r_at	**0.28**	1.78	0.51
17	PHF8	Hs.133352	212916_at	**0.26**	1.98	0.64
18	KDM6A, UTX	Hs.522616	203990_s_at	**0.25**	1.72	0.60
19	KDM4C, JMJD2C, GASC1	Hs.709425	209984_at	**0.24**	1.88	0.53
20	KDM4B, JMJD2B	Hs.654816	212495_at	**0.21**	1.77	0.63
21	KDM4A, JMJD2A	Hs.155983	203205_at	**0.18**	1.53	0.70
22	KDM4D, JMJD2D	Hs.503598	242788_at	**0.13**	1.26	0.70
23	JMJD5	Hs.145717	220070_at	**0.13**	1.35	0.78
	Methyltransferase					
1	SMYD3	Hs.567571	218788_s_at	**0.90**	4.35	0.20
2	PRMT6	Hs.26006	223275_at	**0.87**	5.01	0.12
3	EZH2	Hs.444082	203358_s_at	**0.65**	2.80	0.19
4	PRMT3	Hs.152337	213320_at	**0.59**	3.50	0.41
5	SUV420H1	Hs.632120	222759_at	**0.56**	2.77	0.18
6	PRMT1	Hs.20521	206445_s_at	**0.53**	3.29	0.39
7	MLL3	Hs.647126	222415_at	**0.53**	2.52	0.34
8	SETD8	Hs.443735	220200_s_at	**0.51**	2.20	0.36
9	MLL5	Hs.592262	223190_s_at	**0.49**	3.20	0.39
10	PRMT7	Hs.712584	219408_at	**0.47**	3.18	0.55
11	CARM1	Hs.371416	212512_s_at	**0.46**	2.80	0.39
12	PRMT2	Hs.154163	228725_x_at	**0.44**	2.34	0.29
13	PRMT5	Hs.367854	217786_at	**0.42**	2.48	0.33
14	SFRS17A	Hs.522572	203624_at	**0.41**	2.66	0.45
15	SETD7	Hs.480792	224928_at	**0.40**	1.91	0.13
16	EHMT1	Hs.495511	225461_at	**0.40**	2.58	0.40
17	MLL	Hs.258867	226981_at	**0.35**	1.82	0.29
18	PRMT8	Hs.504530	230839_at	**0.33**	3.16	0.76
19	MLL4	Hs.92236	203419_at	**0.32**	2.41	0.52
20	DOT1L	Hs.713643	226201_at	**0.30**	2.21	0.57
21	SUV39H1	Hs.522639	218619_s_at	**0.30**	2.61	0.61
22	ASH2L	Hs.521530	209517_s_at	**0.29**	2.09	0.60
23	MLL2	Hs.120228	231974_at	**0.19**	1.53	0.57
24	NSD1	Hs.106861	225654_at	**0.16**	1.41	0.68
25	SUV420H2	Hs.590982	224431_s_at	**0.13**	1.29	0.79
26	EHMT2	Hs.709218	229079_at	**0.10**	1.28	0.72
27	SUV39H2	Hs.554883	219262_at	**0.09**	1.32	0.85

Supplemental Table 2: Characteristics of three NSCLC cell lines with high KDM2A levels (H1975, H23 and H1792) and two NSCLC cell lines with low KDM2A levels (H460 and H2122).

Cell Line	KDM2A mRNA (Affy 208988_at)	KDM2A mRNA* (qRT-PCR)	Histology	Gender	K-RAS	EGFR
H1975	4.2	17.1	Adeno	F	WT	L858R,T790M
H23	3.7	20.7	Adeno	M	12TGT	WT
H1792	3.5	30.3	Adeno	M	12TGT	WT
H460	0.6	4.9	LC	M	12TGT	WT
H2122	0.5	2	Adeno	F	12TGT	WT

*Relative KDM2A mRNA levels were measured by quantitative RT-PCR.
Adeno, Adenocarcinoma; LC, Large cell; BA, Bronchoalveolar

Supplemental Table 3: List of genes that are up- and down-regulated by KDM2A knockdown in H1792 and H1975 cells

The order of genes in the list is based simply on the mean of fold changes in expression that were induced by two siKDM2As (siKDM2A-3 and -4) in H1792 and H1975 cells.

Gene.Symbol	UniGene.ID	AffyID	H1792		H1975		MEAN
			siKDM2A-3	siKDM2A-4	siKDM2A-3	siKDM2A-4	
Upregulated genes							
TIMM17A	Hs.20716	215171_s_at	5.73	5.56	10.88	8.51	7.67
LOC729680	Hs.130652	228977_at	7.65	4.50	14.15	4.07	7.59
TMEM65	Hs.187646	241342_at	5.89	3.33	9.04	3.74	5.50
SPFH2	Hs.125849	221543_s_at	6.74	4.11	5.04	4.47	5.09
UPF3B	Hs.103832	218757_s_at	4.43	4.43	6.27	4.24	4.84
MAP3K8	Hs.432453	202424_at	7.85	1.51	5.61	2.22	4.30
CRLF3	Hs.370168	205474_at	3.67	3.14	4.76	3.14	3.67
RPIA	Hs.469264	212973_at	3.83	3.56	4.25	2.83	3.62
CDC42SE2	Hs.508829	228993_s_at	3.04	1.55	6.65	2.83	3.52
RNF170	Hs.491626	226104_at	4.36	2.57	3.54	3.50	3.49
IFNGR1	Hs.520414	211676_s_at	4.69	2.08	3.60	3.31	3.42
TCFL5	Hs.646274	235694_at	3.47	2.47	4.31	3.29	3.39
LRRC57	Hs.234681	229232_at	3.25	2.19	4.44	3.64	3.38
HERPUD2	Hs.651273	202944_at	2.65	3.87	1.76	5.01	3.32
E2F5	Hs.445758	221586_s_at	3.64	3.15	3.09	3.32	3.30
LOC201725	Hs.380920	204639_at	1.65	3.08	3.55	4.53	3.20
BRWD1	Hs.190548	239363_at	4.00	1.78	4.99	1.80	3.14
TMEM134	Hs.288761	218531_at	3.37	3.13	2.59	3.37	3.12
REV3L	Hs.232021	208070_s_at	3.11	2.81	2.91	3.44	3.07
ANKRD10	Hs.525163	218093_s_at	2.76	3.22	3.10	2.97	3.01
LOC201725	Hs.380920	226342_at	1.69	3.39	2.77	4.08	2.98
PDSS2	Hs.486095	241985_at	4.06	2.72	3.10	1.87	2.94
ZNF652	Hs.463375	205594_at	3.36	3.02	2.11	3.17	2.92
GPR157	Hs.31181	227970_at	3.09	2.41	3.59	2.52	2.90
Protocadherin-7	Hs.479439	228640_at	2.96	2.35	1.97	4.31	2.90
DKFZP564J0863	Hs.356719	224893_at	4.09	2.79	2.09	2.58	2.88
TRPC1	Hs.250687	205802_at	3.55	2.29	3.15	2.36	2.84
HDAC3	Hs.519632	216326_s_at	3.17	2.60	2.84	2.72	2.83
PLEKHA8	Hs.233495	227247_at	2.64	2.94	2.35	3.38	2.83
C16orf46	Hs.203594	200760_s_at	2.91	1.81	3.50	3.05	2.81
GLS	Hs.116448	203159_at	2.02	2.23	2.16	4.80	2.81
Paxillin	Hs.446336	201087_at	4.04	2.21	2.71	2.10	2.77
KIAA1826	Hs.266782	205226_at	2.84	1.82	3.94	2.29	2.72
MOBK1B	Hs.196437	214812_s_at	2.41	2.76	2.24	3.32	2.68
AGPAT5	Hs.624002	232007_at	2.21	4.10	1.98	2.36	2.66
NUP98	Hs.524750	213490_s_at	2.25	1.89	4.29	2.18	2.65
C5orf33	Hs.81907	228594_at	2.54	2.06	3.29	2.57	2.61
TATDN3	Hs.530538	228867_at	2.59	2.08	3.17	2.40	2.56
LOC339290	Hs.643553	221206_at	2.75	1.85	2.99	2.52	2.53

SARS	Hs.531176	225163_at	2.53	1.55	4.28	1.63	2.50
YPEL2	Hs.463613	222785_x_at	2.95	1.99	1.73	3.17	2.46
IHPK2	Hs.595983	223165_s_at	2.15	2.07	2.02	3.59	2.46
RKHD1	Hs.436495	91816_f_at	2.42	2.65	2.69	2.01	2.44
LOC728923	Hs.647112	216705_s_at	2.32	2.02	1.83	3.38	2.39
TMEM41A	Hs.634586	225991_at	2.07	2.41	2.36	2.61	2.36
SATB2	Hs.516617	235147_at	2.02	2.04	2.60	2.77	2.36
PDCD4	Hs.232543	219831_at	2.78	2.58	1.92	2.15	2.36
DOCK4	Hs.133299	229355_at	2.66	1.56	3.06	2.05	2.33
FBXL20	Hs.462946	235089_at	3.08	2.21	1.86	2.09	2.31
C9orf80	Hs.536958	239363_at	2.18	2.32	2.24	2.47	2.30
GSTP1	592542 /// Hs.593	225446_at	2.31	2.89	1.60	2.36	2.29
FLJ21986	Hs.189652	203216_s_at	2.70	2.55	2.25	1.61	2.28
C14orf28 /// SYPL2	Hs.528366	235369_at	2.93	1.58	2.02	2.56	2.27
ARL6IP5	Hs.518060	212593_s_at	3.82	2.12	1.54	1.56	2.26
ALG5	Hs.507769	218203_at	2.20	2.08	2.52	2.16	2.24
DUSP3	Hs.651126	202730_s_at	3.51	1.62	2.22	1.56	2.23
FAM123B	Hs.314225	235069_at	2.49	2.89	1.93	1.57	2.22
FBXL17	Hs.112143	212956_at	1.81	1.75	1.69	3.55	2.20
MGC2752	Hs.541177	219851_at	3.56	1.65	1.92	1.58	2.18
R3HDM2	Hs.443673	223391_at	2.55	2.05	1.81	2.22	2.16
ITGB8	Hs.592171	228324_at	2.14	2.52	1.61	2.35	2.15
TFDP2	Hs.379018	228088_at	1.99	1.50	3.09	2.00	2.15
LOC92482	Hs.651309	225087_at	2.53	2.57	1.60	1.86	2.14
SLC6A8	Hs.540696	203580_s_at	2.44	1.94	1.81	2.37	2.14
ATXN1	Hs.434961	205003_at	3.22	2.05	1.50	1.70	2.12
GNPDA1	Hs.633853	220985_s_at	1.98	1.57	2.79	2.13	2.12
GKAP1	Hs.522255	219171_s_at	1.95	1.61	2.69	2.20	2.11
LOC652968	---	235037_at	2.96	1.72	1.70	2.05	2.11
KIAA1600	Hs.192619	203097_s_at	2.83	1.55	1.98	1.99	2.09
TBC1D9	Hs.480819	212696_s_at	2.32	1.97	2.28	1.76	2.08
MYO6	Hs.149387	201415_at	2.43	1.97	1.99	1.91	2.08
ZNF281	Hs.59757	241968_at	2.41	1.59	1.90	2.33	2.06
TRIM4	Hs.50749	225802_at	2.42	2.07	1.67	2.07	2.06
ABCC5	Hs.368563	231894_at	1.95	1.53	2.36	2.36	2.05
ZNF236	Hs.189826	217865_at	2.35	2.27	1.57	1.98	2.04
RAB8B	Hs.389733	204451_at	2.58	1.97	1.49	2.10	2.04
TMEM8	Hs.288940	202662_s_at	2.58	1.77	1.83	1.94	2.03
NAGA	Hs.75372	225471_s_at	2.35	2.23	1.74	1.78	2.02
KDELC1	Hs.408629	226431_at	1.60	1.80	2.21	2.47	2.02
C9orf41	Hs.567688	226189_at	1.87	1.64	2.44	2.11	2.02
YES1	Hs.194148	1555824_a_at	2.66	1.60	1.58	2.13	1.99
ALS2CR13	Hs.471130	225991_at	2.84	1.50	1.59	2.02	1.99
RAPGEF2	Hs.113912	220189_s_at	2.18	1.64	2.15	1.96	1.98
PDGFRL	Hs.458573	230129_at	1.57	3.10	1.50	1.76	1.98
ADA	Hs.255479	228390_at	2.32	1.64	2.06	1.89	1.98
SPTBN1	Hs.503178	228452_at	2.36	1.88	2.06	1.53	1.96

PMS2	Hs.632637	212040_at	2.48	1.81	1.81	1.71	1.95
C16orf63	Hs.514179	218203_at	1.68	1.71	2.09	2.24	1.93
MARCH9	Hs.632709	205027_s_at	2.15	1.85	1.76	1.95	1.93
TGM2	Hs.517033	224704_at	2.18	1.60	1.75	2.14	1.92
TBC1D15	Hs.284630	223591_at	1.74	1.68	2.21	2.04	1.92
MGC7036	Hs.488173	225238_at	1.97	1.88	2.05	1.75	1.91
MAP2K2	Hs.465627	201042_at	1.97	1.68	2.08	1.87	1.90
MLLT3	Hs.591085	223066_at	1.58	1.55	1.86	2.59	1.90
ZNF613	Hs.183390	216199_s_at	1.50	1.73	1.73	2.61	1.89
MSI2	Hs.585782	208706_s_at	1.84	1.62	2.12	1.98	1.89
SNAPAP	Hs.32018	208756_at	1.85	1.75	2.02	1.94	1.89
PPP2R3A	Hs.518155	209019_s_at	1.81	1.54	1.58	2.62	1.89
EIF5	Hs.433702	226155_at	1.65	1.60	2.34	1.94	1.88
C5	Hs.494997	1552882_a_at	1.62	1.78	2.04	2.07	1.88
PANK1	Hs.376351	206036_s_at	1.77	1.54	1.85	2.34	1.88
VPS26B	Hs.334684	229034_at	2.13	1.54	2.15	1.68	1.87
GSS	Hs.82327	226633_at	2.09	1.82	1.71	1.88	1.87
AKT2	Hs.631535	91816_f_at	2.05	2.27	1.57	1.59	1.87
REL	Hs.631886	228391_at	2.68	1.63	1.53	1.57	1.85
CDKL3	Hs.105818	202219_at	1.77	1.70	1.59	2.35	1.85
SGPP1	Hs.24678	225380_at	1.62	1.62	2.10	2.03	1.84
C10orf89	Hs.281004	225276_at	1.53	1.83	2.37	1.64	1.84
JMY	Hs.482605	244362_at	1.97	1.67	1.70	2.02	1.84
MTHFS	Hs.459049	225483_at	1.51	1.61	1.92	2.31	1.84
TGOLN2	Hs.593382	229907_at	1.87	1.63	1.69	2.15	1.84
ULBP2	Hs.651271	212414_s_at	1.54	1.87	1.79	2.12	1.83
PINK1	Hs.389171	210242_x_at	2.03	1.68	1.68	1.93	1.83
TEAD3	Hs.485205	225237_s_at	1.91	1.50	2.19	1.70	1.82
YY1AP1	Hs.584927	226381_at	1.68	1.57	1.65	2.38	1.82
FZD1	Hs.94234	223384_s_at	2.00	1.63	1.70	1.94	1.81
MGAT4B	Hs.567419	204918_s_at	2.04	1.52	1.94	1.73	1.81
CYP4V2	Hs.237642	203232_s_at	1.82	1.51	1.64	2.21	1.79
MAML3	Hs.586165	226454_at	1.72	1.53	1.80	2.13	1.79
DEGS1	Hs.299878	202382_s_at	1.52	1.57	2.04	2.04	1.79
C6orf120	Hs.591375	1568864_at	1.87	1.64	1.65	1.99	1.79
TFPI	Hs.516578	204484_at	1.90	1.61	1.59	2.00	1.77
FRMD4A	Hs.330463	228785_at	1.86	1.67	1.83	1.73	1.77
PNPO	Hs.631742	238542_at	1.80	1.73	1.63	1.93	1.77
LOC91461	Hs.408542	229354_at	1.62	1.86	1.51	2.05	1.76
FZD2	Hs.142912	226363_at	1.96	1.56	1.67	1.82	1.75
PTCH1	Hs.494538	201299_s_at	1.63	1.79	1.93	1.64	1.75
SLC7A6	Hs.334848	211630_s_at	1.78	1.54	2.16	1.51	1.75
EIF3S2	Hs.530096	233528_s_at	1.66	1.53	2.08	1.68	1.74
CHERP	Hs.631627	229299_at	1.83	1.58	1.98	1.54	1.73
C17orf39	Hs.187422	201536_at	1.94	1.51	1.87	1.59	1.73
RNF135	Hs.29874	221786_at	2.14	1.52	1.54	1.68	1.72
RNF4	---	213258_at	1.69	1.50	2.10	1.57	1.72

SOLO	Hs.30977	1558279_a_at	1.65	1.78	1.63	1.79	1.71
PIK3C2B	Hs.497487	221542_s_at	1.95	1.53	1.53	1.84	1.71
TNRC6A	Hs.407740	219673_at	1.67	1.63	1.74	1.81	1.71
SLC18A2	Hs.369009	209815_at	1.98	1.52	1.75	1.58	1.71
DYRK4	Hs.439530	234192_s_at	1.67	1.71	1.51	1.89	1.70
PXK	Hs.190544	241262_at	1.55	1.53	1.64	2.04	1.69
ITPR2	Hs.512235	226272_at	1.80	1.73	1.61	1.60	1.69
C6orf61	Hs.279008	203831_at	1.64	1.73	1.54	1.83	1.69
MSL3L1	Hs.307924	226649_at	1.74	1.63	1.51	1.81	1.68
TOP1MT	Hs.528574	207551_s_at	1.93	1.72	1.50	1.55	1.67
SEPT6 /// N-PAC	Hs.387255	222653_at	1.90	1.50	1.56	1.68	1.66
C11orf1	Hs.17546	228728_at	1.51	1.58	1.55	1.98	1.66
PS1TP4	Hs.355655	209454_s_at	1.63	1.61	1.61	1.77	1.65
RNF130	Hs.484363	209250_at	1.68	1.64	1.51	1.76	1.65
MAP3K4	Hs.390428	227983_at	1.51	1.55	1.75	1.61	1.61

Downregulated genes

NHLRC2	Hs.594372	219353_at	0.49	0.49	0.49	0.59	0.51
GPR107	Hs.512461	211979_at	0.57	0.48	0.44	0.45	0.49
FLJ25006	Hs.151761	1553292_s_at	0.37	0.44	0.44	0.58	0.46
ZNF302	Hs.436350	228393_s_at	0.33	0.48	0.48	0.53	0.46
EMP2	Hs.531561	225078_at	0.37	0.50	0.47	0.46	0.45
ZBTB41	Hs.529439	226962_at	0.49	0.48	0.39	0.44	0.45
LIFR	Hs.133421	225571_at	0.40	0.42	0.38	0.57	0.44
UBE3B	Hs.374067	212403_at	0.45	0.47	0.30	0.48	0.43
UBE2N	Hs.524630	212751_at	0.27	0.47	0.33	0.61	0.42
NANOS1	Hs.591918	228523_at	0.48	0.46	0.36	0.38	0.42
UGCGL2	Hs.193226	235749_at	0.37	0.37	0.50	0.41	0.41
RDX	Hs.263671	212397_at	0.43	0.43	0.36	0.43	0.41
ARHGAP19	Hs.80305	37577_at	0.38	0.49	0.31	0.44	0.41
RP11-93B10.1	Hs.612782	228654_at	0.33	0.38	0.47	0.42	0.40
FLJ11184	Hs.267446	218513_at	0.38	0.22	0.58	0.42	0.40
SDC4	Hs.632267	202071_at	0.36	0.36	0.27	0.57	0.39
DYNC1LI2	Hs.369068	224614_at	0.38	0.38	0.26	0.47	0.37
GRPEL2	Hs.511816	226881_at	0.34	0.42	0.37	0.36	0.37
CLCN3	Hs.481186	201734_at	0.39	0.38	0.21	0.51	0.37
RAPH1	Hs.471162	225188_at	0.40	0.31	0.24	0.49	0.36
CDK6	Hs.119882	224847_at	0.35	0.51	0.23	0.35	0.36
PSMD12	Hs.646575	202353_s_at	0.26	0.26	0.43	0.38	0.33
RNASEL	Hs.518545	229285_at	0.41	0.18	0.35	0.34	0.32
WDR67	Hs.492716	1556429_a_at	0.27	0.32	0.39	0.31	0.32
CANX	Hs.651169	238034_at	0.28	0.26	0.31	0.38	0.31
ZC3H5	Hs.584768	228357_at	0.22	0.44	0.22	0.30	0.30
CDK6	Hs.119882	224851_at	0.28	0.35	0.24	0.30	0.29
NEK7	Hs.24119	212530_at	0.32	0.34	0.19	0.31	0.29
DCBLD1	Hs.583022	226609_at	0.33	0.31	0.18	0.33	0.29
FBXL11(=KDM2A)	Hs.124147	208989_s_at	0.20	0.24	0.20	0.33	0.24

Supplemental Table 4: Clinical characteristics of the NSCLC tumor set from UT MDACC (*n* = 98). N0, No regional lymph nodes; N1, Metastasis in hilar lymph nodes; N2, Metastasis in ipsilateral mediastinal lymph nodes. There is no significant difference in gender, age, smoking status, stage, and NSCLC histology between patients with high KDM2A and those with low KDM2A.

UT MDACC set	KDM2A high	KDM2A low	*P* value
Patients	14/98 (14%)	84/98 (86%)	
Gender			
Female	12/14 (85.7%)	74/84 (88.1%)	
Male	2/14 (14.3%)	10/84 (11.9%)	0.80
Age	64.14 (8.65)	66.24 (11.26)	0.51
Smoking			
Never	1/12 (8.3%)	12/82 (14.6%)	
Ex-Smoking	4/12 (33.3%)	42/82 (51.2%)	
Current smoking	7/12 (58.3%)	28/82 (34.1%)	0.27
Pathology			
Adenocarcinoma	6/14 (42.9%)	46/84 (54.8%)	
Squamous cell ca	6/14 (42.9%)	31/84 (36.9%)	
Large cell ca	1/14 (7.1%)	3/84 (3.6%)	
BAC	0/14 (0%)	3/84 (3.6%)	
NOS (plemorphi,sarcomatoid)	1/14 (7.1%)	1/74 (1.2%)	0.19
Stage			
IA	1/14 (7.1%)	16/84 (19.0%)	
IB	4/14 (28.6%)	31/84 (36.9%)	
IIA	1/14 (7.1%)	0/84 (0%)	
IIB	4/14 (28.6%)	15/84 (17.9%)	
IIIA	2/14 (14.3%)	16/84 (19.0%)	
IIIB	2/14 (14.3%)	6 (7.1%)	0.12
N0	6/14 (42.9%)	53/84 (63.1%)	
N1-2	8/14 (57.1%)	31/84 (36.9%)	0.15

Supplemental Table 5: Clinical characteristics of an NSCLC patient set (*n* = 96) that was analyzed by IHC (related to **Tables 1, 5, 6, Figure 8G, and Figure 9, B-E**). Statistical differences in gender, age, smoking status, stage, and NSCLC histology were analyzed between high and low group of KDM2A, DUSP3, and pERK1/2.

Clinico-pathological parameter		***n* = 96**	**Enzymes**								
			KDM2A			**DUSP3**			**pERK1/2**		
			low	**high**	***P*-value**	**low**	**high**	***P*-value**	**low**	**high**	***P*-value**
Age	**≤50**	17	11	6	0.1	12	4	0.245	7	10	0.214
	>50	79	38	41		59	21		31	43	
Sex	**Male**	80	43	37	0.181	60	20	0.405	32	44	0.558
	Female	16	6	10		11	5		6	9	
Tumor Size	**T1**	3	2	1	0.117	2	1	0.162	1	2	0.079
	T2	75	37	38		55	20		34	38	
	T3	9	4	5		6	3		2	5	
	T4	5	4	1		4	1		1	4	
Node Status	**N0**	48	26	22	**0.031**	33	17	**0.018**	24	22	**0.011**
	N1	25	15	10		18	6		10	14	
	N2	17	6	11		14	2		4	11	
	N3	2	0	2		2	0		0	2	
Stage	**I**	40	22	18	0.06	27	15	**0.016**	22	17	**0.001**
	II	27	15	12		20	6		11	14	
	III	24	9	15		20	3		5	17	
	IV	5	3	2		4	1		0	5	
Metastasis	**No**	85	44	41	0.232	60	25	**0.029**	36	44	0.066
	Yes	11	5	6		11	0		2	9	

Supplemental Table 6: Primer list

Gene	Application	Sequence (5'-3')	
DUSP3 F-a-region	ChIP-PCR	GCCTGTAATCCCAGCACTTT	
DUSP3 R-a-region	ChIP-PCR	GCACCATGCCCAGCTAAT	
DUSP3 F-b-region	ChIP-PCR	CCTTCCAGCAACCCTAGAATTAG	
DUSP3 R-b-region	ChIP-PCR	GAGAGTCATCGTCGTGCTTAAA	
DUSP3 F-c-region	ChIP-PCR	TTCAGGGAAGGAAGTTACCG	
DUSP3 R-c-region	ChIP-PCR	TGGAGTCTCAGGGGTCCTC	
DUSP3 F-d-region	ChIP-PCR	TCGCGAGTCTTGGGTTG	
DUSP3 R-d-region	ChIP-PCR	GCAGGGTTCCAGTTCCTT	
GPR107 F	ChIP-PCR	GAGTGTGAAGCGCCTAGAAA	
GPR107R	ChIP-PCR	GGGCCACTGATTGAACTGAT	
GPR157 F	ChIP-PCR	GAACTTCCAAGCACCTGAGC	
GPR157R	ChIP-PCR	GGAGCCGAGAGCATCAATAG	
TMEM65 F	ChIP-PCR	CCAAAAGTTTGTATGAGCCATTT	
TMEM65 R	ChIP-PCR	TGCCAGAAGCAAGATCAGAA	
TIMM17 F	ChIP-PCR	GACCTTAACGCCCTCCTCTC	
TIMM17 R	ChIP-PCR	GGGCAAGAGAAATGCAAAGA	
KDM2A F	RT-PCR	CAAGGCACTTGAAGGAAAGC	
KDM2A R	RT-PCR	CAGCAGCCAATTCTCGTACA	
DUSP3 F	RT-PCR	CCCCTGAAACCCCGTATTTAC	
DUSP3 R	RT-PCR	CCTGTTCCATCACTTCCCAG	
GPR157 F	RT-PCR	CCAACTGCATCATGTTCGTC	
GPR157R	RT-PCR	CCTGAGATTCTCCTGGCTTG	
TMEM65 F	RT-PCR	TGCCCAAGAAAAATTGGAAG	
TMEM65 R	RT-PCR	CAGCAGCTGCCATAGTTGAA	
TIMM17 F	RT-PCR	CGAATTGTGGATGACTGTGG	
TIMM17 R	RT-PCR	TCCAGGGATCTTCCTTTCCT	
GPR107 F	RT-PCR	CATCTGAACACCTTTGGCTTC	
GPR107R	RT-PCR	TCATTCTTTGTACGGTCTAGGC	
18s F	RT-PCR	TCAACTTTCGATGGTAGTCGCCGT	
18s R	RT-PCR	TCCTTGGATGTGGTAGCCGTTTCT	
EZH2 F	RT-PCR	CGCAAGGGTAACAAAATTCG	
EZH2 R	RT-PCR	AAAACAGCTCTTCGCCAGTC	
P14 F	RT-PCR	GATGTCGCACGGTACCTG	
P14 R	RT-PCR	TCTCTGCTTCTTTCAATCGGG	
P15 F	RT-PCR	GGACTAGTGGAGAAGGTGCG	Kotake et al.
P15 R	RT-PCR	GGGCGCTGCCCATCATCATG	Kotake et al.
P16 F	RT-PCR	ATCGCGATGTCGCACGGTACCTG	
P16 R	RT-PCR	ATCTAAGTTTCCCGAGGTTTCTC	
PUMA F	RT-PCR	CGACCTCAACGCACAGTAC	
PUMA R	RT-PCR	CCTAATTGGGCTCCATCTCG	
P21 F	RT-PCR	GCACCTCACCTGCTCTGCTGCA	
P21 R	RT-PCR	GGCTTCCTCTTGGAGAAGATC	

Kotake, Y., Cao, R., Viatour, P., Sage, J., Zhang, Y., and Xiong, Y. 2007. pRB family proteins are required for H3K27 trimethylation and Polycomb repression complexes binding to and silencing $p16^{INK4alpha}$ tumor suppressor gene. *Genes Dev.* 21:49-54.