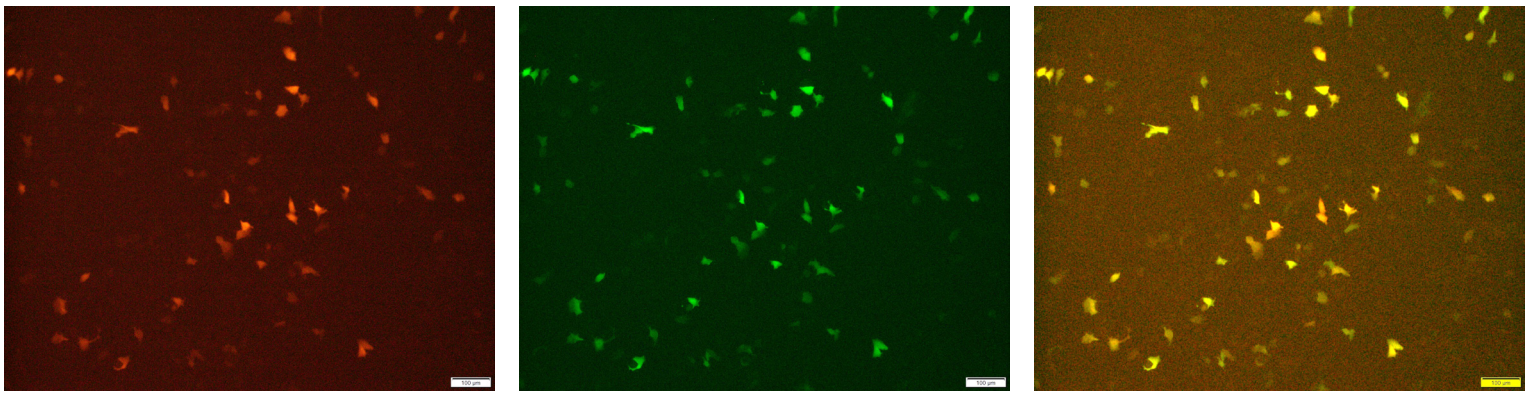
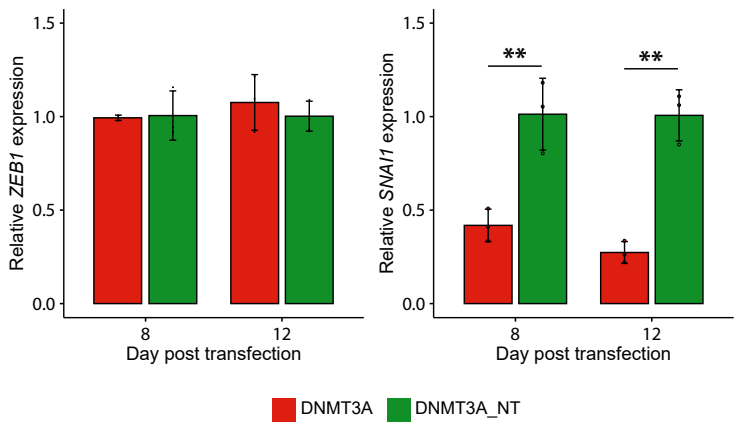
SUPPLEMENT FIGURES

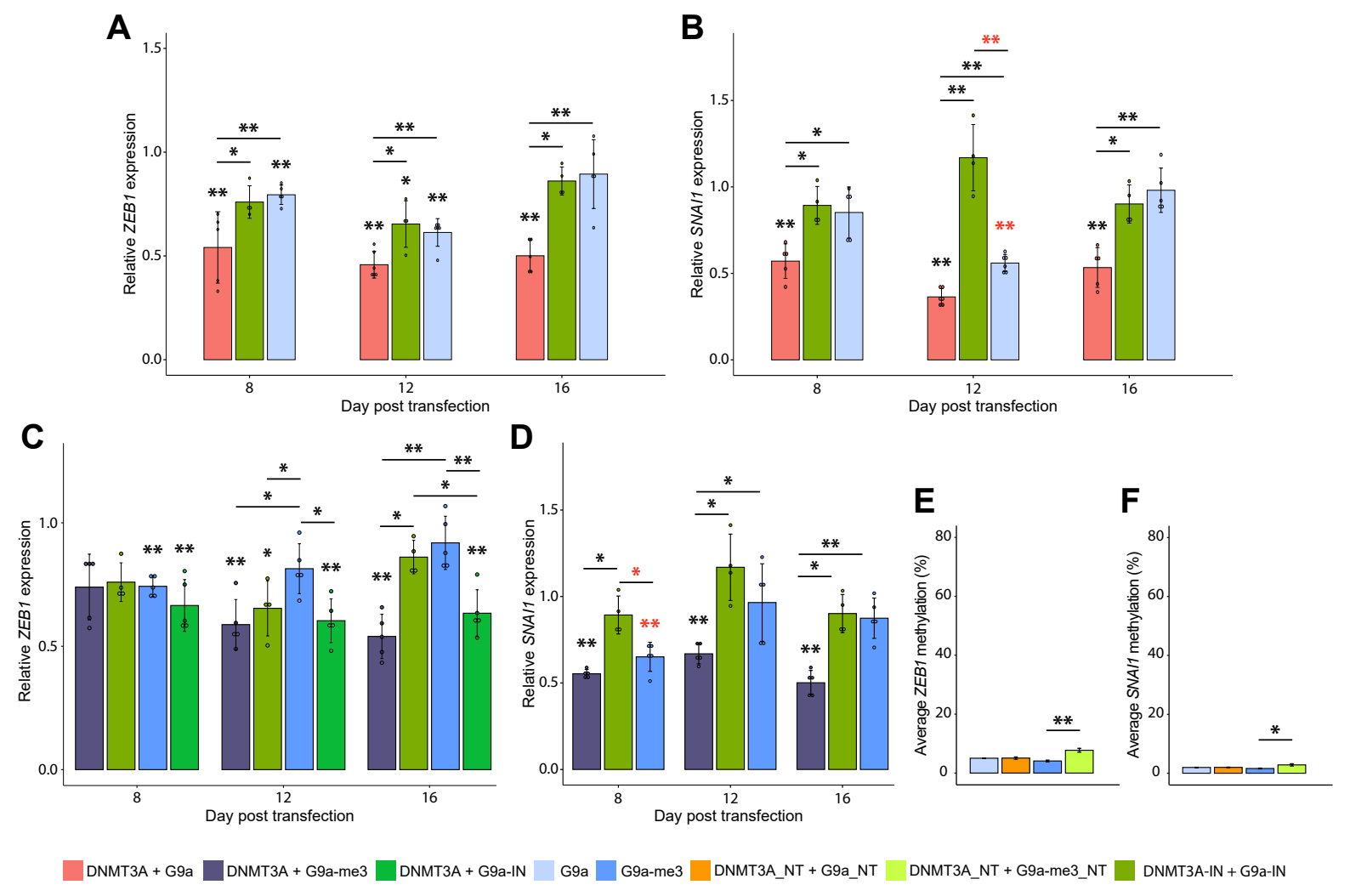
A



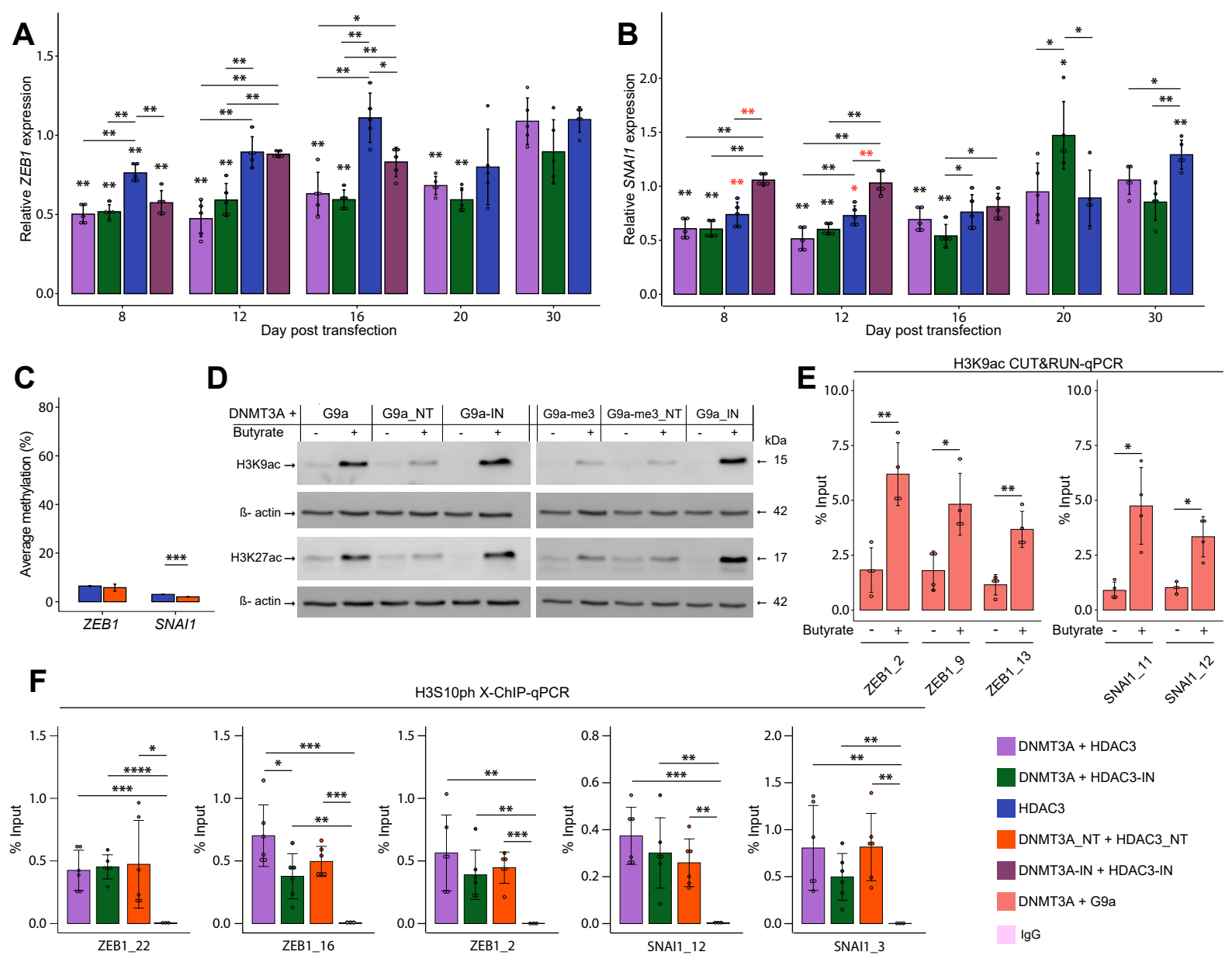
B



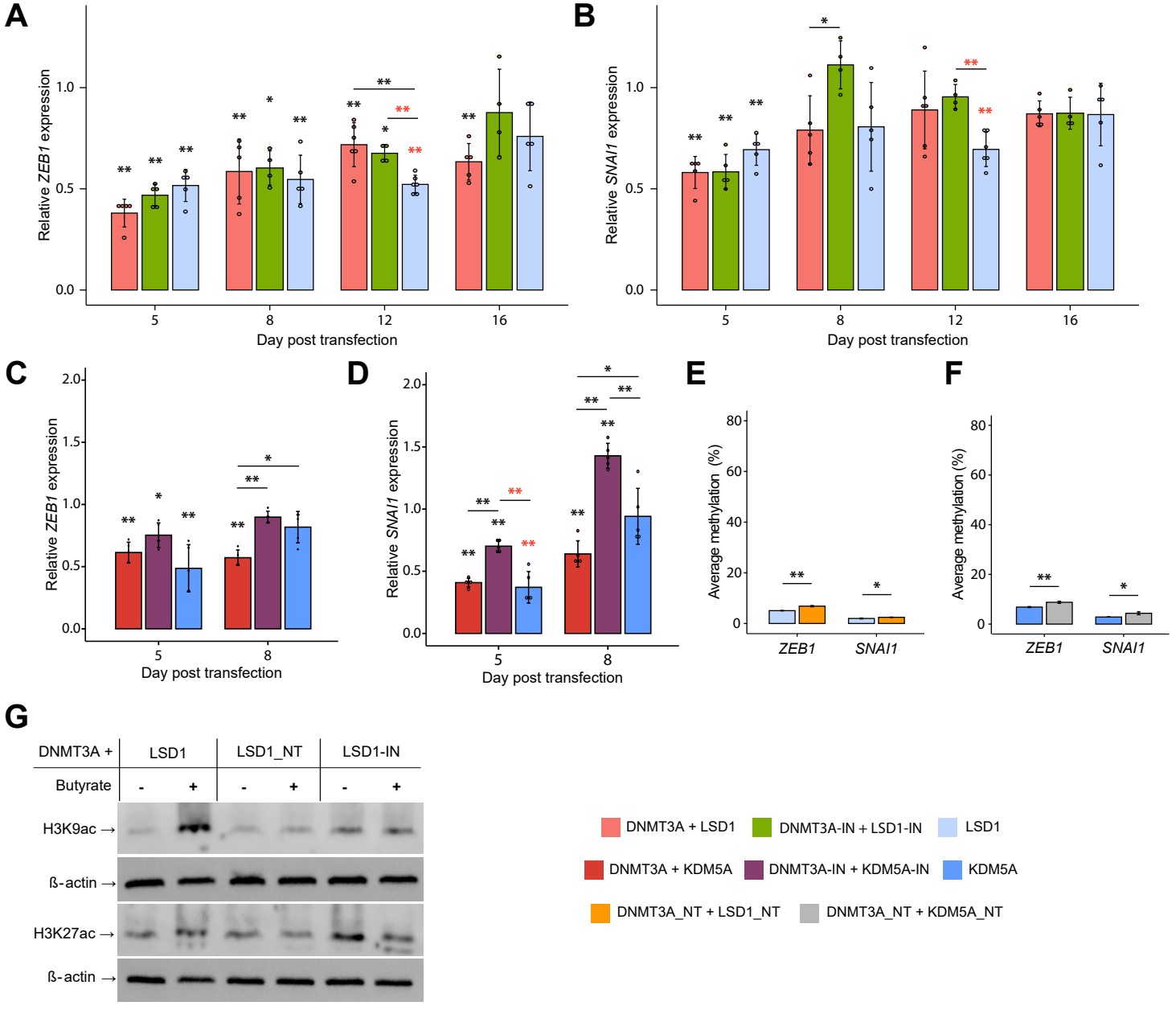
Supplementary Figure 1. Double transfection efficiency in the HepG2 cell line and the influence of *SNAI1* gene transcription change on *ZEB1* transcription. (A) Efficiency of double transfection in HepG2 cells with DNMT3A and G9a. The mRuby3 fluorescent marker was used for DNMT3A-dCas9, while mClover3 was used for G9a-dCas9 construct. Approximately 85% of the cells were co-transfected with both fusion constructs. **(B)** Analysis of *SNAI1* and *ZEB1* transcriptional activity on days 8 and 12 following epigenetic editing of *SNAI1* with DNMT3A-dCas9 revealed a significant decrease in *SNAI1* transcription, whereas *ZEB1* transcription remained unchanged. ImageJ was used for fluorescence image analysis and quantification of double-transfected cells. Error bars represent ± SD (n = 3). Statistical significance for gene expression analysis was determined using a *t*-test, **P< 0.01.


A
Relative ZEB1 expression
1.5
1.0
0.5
0.0
8
12
16
Day post transfection
B
Relative SNAI1 expression
1.5
1.0
0.5
0.0
8
12
16
Day post transfection
C
Relative ZEB1 expression
1.0
0.5
0.0
8
12
16
Day post transfection
D
Relative SNAI1 expression
1.5
1.0
0.5
0.0
8
12
16
Day post transfection
E
Average ZEB1 methylation (%)
80
60
40
20
0
F
Average SNAI1 methylation (%)
80
60
40
20
0
DNMT3A + G9a
DNMT3A + G9a-me3
DNMT3A + G9a-IN
G9a
G9a-me3
DNMT3A_NT + G9a_NT
DNMT3A_NT + G9a-me3_NT
DNMT3A-IN + G9a-IN

Supplementary Figure 2. Changes in *ZEB1* and *SNAI1* transcription and promoter DNA methylation following epigenetic targeting with DNMT3A and G9a/G9a-me3. Combined targeting with DNMT3A and G9a significantly reduced **(A)** *ZEB1* and **(B)** *SNAI1* transcription from day 8 post-transfection compared with the catalytically inactive CRISPR interference control. G9a alone repressed *SNAI1* transcription on day 12. In contrast, DNMT3A and G9a-me3 significantly reduced **(C)** *ZEB1* transcription on day 16, coincident with loss of CRISPR interference, while **(D)** *SNAI1* transcription *was* reduced from day 8. G9a-me3 alone selectively repressed *SNAI1* transcription on day 8. Average DNA methylation levels at the *ZEB1* **(E)** and *SNAI1* **(F)** CpG islands following transfection with G9a or G9a-me3 alone did not show a *de novo* increase in DNA methylation. Error bars represent ± SD (n = 3-5), the Mann-Whitney U test was used for gene expression analysis, while the *t*-test was used for DNA methylation analysis, *P< 0.05, **P< 0.01. Asterisks above bars indicate comparisons with the non-targeting (NT) control, whereas asterisks in line plots indicate comparisons between DNMT3A + G9a-me3 and DNMT3A + G9a_IN. Red asterisks highlight the effect of G9a or G9a-me3 alone on gene transcription and the synergistic effect of the DNMT3A and G9a-me3 combination on DNA methylation level.


A
Relative ZEB1 expression
Day post transfection
B
Relative SNAI1 expression
Day post transfection
C
Average methylation (%)
ZEB1
SNAI1
D
DNMT3A +
G9a
G9a_NT
G9a-IN
G9a-me3
G9a-me3_NT
G9a_IN
Butyrate
kDa
H3K9ac
ß- actin
H3K27ac
ß- actin
E
H3K9ac CUT&RUN-qPCR
% Input
Butyrate
ZEB1_2
ZEB1_9
ZEB1_13
SNAI1_11
SNAI1_12
F
H3S10ph X-ChIP-qPCR
% Input
ZEB1_22
ZEB1_16
ZEB1_2
SNAI1_12
SNAI1_3
DNMT3A + HDAC3
DNMT3A + HDAC3-IN
HDAC3
DNMT3A_NT + HDAC3_NT
DNMT3A-IN + HDAC3-IN
DNMT3A + G9a
IgG

Supplement Figure 3. Effects of acetylation on gene expression, DNA methylation, and histone modifications. Co-transfection with DNMT3A and HDAC3 showed no synergistic effect on **(A)** *ZEB1* or **(B)** *SNAI1* transcription, while HDAC3 alone repressed *SNAI1* on days 8 and 12. Further, HDAC3 alone did not induce *de novo* DNA methylation **(C)** at *ZEB1* or *SNAI1* CpG islands. **(D)** Butyrate treatment increased global H3K9ac and H3K27ac levels, as shown by western blot in co-transfections with DNMT3A+G9a/G9a-me3. **(E)** Butyrate increased H3K9ac at multiple regions within *ZEB1* and *SNAI1* CpG islands in DNMT3A and G9a co-transfections, as shown by CUT&RUN-qPCR. **(F)** DNMT3A and HDAC3 co-transfection did not alter H3S10 phosphorylation at either locus. Error bars are ± SD (n = 3-5), statistical significance was assessed using the Mann-Whitney U test for gene expression analysis, while the *t*-test was used for DNA methylation, X-ChIP-qPCR, and CUT&RUN-qPCR analysis, *P< 0.05, **P< 0.01, ***P< 0.001, ****P< 0.0001. Asterisks above bars indicate comparisons with NT control, and a red asterisk denote effect of HDAC3 alone on gene transcription.


A
Relative ZEB1 expression
1.0
0.5
0.0
5
8
12
16
Day post transfection
B
Relative SNAI1 expression
1.0
0.5
0.0
5
8
12
16
Day post transfection
C
Relative ZEB1 expression
2.0
1.5
1.0
0.5
0.0
5
8
Day post transfection
D
Relative SNAI1 expression
2.0
1.5
1.0
0.5
0.0
5
8
Day post transfection
E
Average methylation (%)
80
60
40
20
0
ZEB1
SNAI1
F
Average methylation (%)
80
60
40
20
0
ZEB1
SNAI1
G
DNMT3A +
LSD1
LSD1_NT
LSD1-IN
Butyrate
-
+
-
+
-
+
H3K9ac →
ß-actin →
H3K27ac →
ß-actin →
DNMT3A + LSD1
DNMT3A-IN + LSD1-IN
LSD1
DNMT3A + KDM5A
DNMT3A-IN + KDM5A-IN
KDM5A
DNMT3A_NT + LSD1_NT
DNMT3A_NT + KDM5A_NT

Supplementary Figure 4. Regulation of *ZEB1* and *SNAI1* transcription following DNMT3A co-targeting with LSD1 or KDM5A. Co-targeting of DNMT3A and LSD1 at **(A)** *ZEB1* or **(B)** *SNAI1* did not further reduce transcription compared with the catalytically inactive CRISPR interference control. LSD1 alone reduced *ZEB1* and *SNAI1* transcription on day 12. Co-targeting of DNMT3A and KDM5A significantly reduced **(C)** *ZEB1* transcription on day 8 and **(D)** *SNAI1* transcription on days 5 and 8 relative to the CRISPR interference control. KDM5A alone selectively reduced *SNAI1* transcription on day 5. **(E)** LSD1 or **(F)** KDM5A alone did not induce *de novo* DNA methylation at the *ZEB1* or *SNAI1* CpG islands. **(G)** Western blot analysis showed increased global H3K9ac and H3K27ac following DNMT3A and LSD1 co-transfection along with butyrate treatment. Error bars are ± SD (n = 3-5), the Mann-Whitney U test was used for gene expression analysis, while the *t*-test was used for DNA methylation analysis, *P< 0.05, **P< 0.01. Asterisks above each bar indicate comparisons with the NT control. Red asterisks denote effects of LSD1 or KDM5A alone on *ZEB1* and *SNAI1* gene transcription.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Upgrade of the modular CRISPR/dCas9 toolbox with the new multi-guide cassette

The *ZEB1* and *SNAI1* gene loci were targeted simultaneously with 9 different gRNAs at the same time (*ZEB1* with 6 gRNAs and *SNAI1* with 3 gRNAs). For that purpose, the multi-guide system from Josipović et al. (2019)[1] was upgraded to receive more than six different gRNA molecules at the same time. Five different gRNAs for *ZEB1* were cloned into each pSgMxG plasmid for SpCas9 gRNA molecules (x = 1, 2, 3, 4, and 5). Next, Esp3I assembly of plasmids for cloning of individual gRNA molecules into the final BsaI assembled constructs was done as described in Josipović et al. (2019)[1]. For the last position with ends "IV-Z", Multi-guide_IV-Z annealed oligonucleotide (Supplementary Table S1) was used, containing two BsaI restriction sites, leaving "B-A" sticky ends. Since each pSg-x1-6 empty plasmid also contains two BsaI restriction sites leaving "B-A" compatible ends, the remaining 3 gRNAs for *SNAI1* and last gRNA for *ZEB1* gene locus were assembled in pSg-x4 and then cloned with BsaI in final construct. The resulting plasmid then contained 9 different gRNA molecules along with dCas9 fusion.

SUPPLEMENTARY TABLES

Supplementary Table S1. Sequences of primers and custom oligonucleotides used for molecular cloning

Primer/custom oligonucleotide	Sequence (5'→3')	Use
Gblock-G9a-SET_S	CATGAACCCCGACAACAGCGACGAAGACA AGCTTGGTCTCTCCATGGTGCCTAAGAAGA AAAGAAAAGTTGGTGGCGGATCCGCAGCC ATAGCTGAAGTTCTGCTGAACGCTAGATGT GACCTGCACGCAGTCAATTATCACGGCGA CACTCCACTGCATATTGCCGCAAGAGAAAG TTACCACGACTGCGTGCTGCTGTTCCTGAG CCGCGGCGCAAACCCTGAGCTGAGAAACA AGGAGGGCGATACCGCCTGGGACCTCACC CCTGAGCGCTCTGATGTTTGGTTCGCTCTC CAACTGAACCGGAAACTCAGGCTGGGGGT CGGCAACAGGGCTATCAGGACCGAAAAGA TCATCTGTCGGGATGTGGCAAGAGGCTAT GAAAATGTCCCTATACCCTGTGTTAATGGT GTGGATGGCGAGCCATGCCCTGAAGATTA CAAGTATATCAGCGAGAACTGCGAGACTTC TACCATGAACATAGACAGAAACATTACACA CCTCCAGCATTGTACTTGCGTCGATGATTG CTCAAGCTCAAATTGCCTCTGCGGGCAACT CAGCATTCGCTGTTGGTATGATAAGGATGG AAGGCTGCTCCAGGAGTTTAATAAGATAGA ACCACCTCTCATATTTGAGTGTAATCAGGC TTGTAGCTGCTGGAGAAACTGCAAGAATAG AGTGGTTCAAAGCGGAATCAAAGTCAGGC TGCAACTCTACAGGACCGCTAAGATGGGA TGGGGTGTGAGAGCCCTCCAGACCATTCC ACAAGGCACTTTCATATGCGAATATGTCGG AGAGCTGATCAGCGATGCAGAAGCAGACG TTCGGGAGGACGATAGCTACCTGTTCGAC CTGGACAACAAAGATGGGGAAGTCTATTGT ATAGACGCAAGATACTATGGCAACATCTCC CGGTTCATTAACCATCTGTGTGACCCAAAC ATCATCCCTGTGAGAGTGTTCATGCTGCAT CAGGATCTGAGGTTCCCTAGGATCGCATTC TTCAGCTCCCGCGATATACGCACAGGCGA GGAACTCGGCTTTGACTACGGAGATCGGT TTTGGGACATAAAGTCTAAGTACTTTACCT GTCAGTGCGGTAGCGAAAAATGCAAACATT CTGCTGAGGCAATAGCTCTCGAACAATCAA GACTGGCTCGGCTCGATCCACACCCTGAA CTCCTGCCTGAACTCGGCAGCCTGCCTCC CGTGAACTCCGGAGTGAGACCCTCGAGGT CTTCCTAAGGGATGCGGAAGGTCAGGATG GATCCATGTCACGCAGGAAGCAGAGCAAT CCTAGGCAAATCAAGCGGTCCCTCGGCGA TATGGAGGCTCGGGAGGAAGTCCAGCTCG	Custom-synthesized gene fragment for G9a-SET domain

	TCGGTGCTTCTCACATGGAACAAAAGGCAA CAGCACCCGAGGCCCCCAGTCCCGGCGG AGGGTCCATGAGCCGCAGGAAGCAGAGTA ACCCTCGCCAAATAAAGCGCAGTCTCGGG GATATGGAGGCTCGCGAGGAAGTGCAACT GGTTGGAGCATCCCACATGGAGCAGAAAG CTACAGCCCCCGAGGCACCCTCTCCATCC GGATAACCTGGGCTTTCTGGATGTCCAGG ATCCTAATAGAACGCATGAGAAAGCCCCC GGAAGATCACCTTCCGGGGGCTTTTTTATT GCGCGTCGGCCGCGGACACCAGCTTGGA CTTCTA	
Gblock-G9a-SET_A	TAGAAGTCCAAGCTGGTGTCCGCGGCCGA CGCGCAATAAAAAAGCCCCCGGAAGGTGA TCTTCCGGGGGCTTTCTCATGCGTTCTATT AGGATCCTGGACATCCAGAAAGCCCAGGT TATCCGGATGGAGAGGGTGCCTCGGGGG CTGTAGCTTTCTGCTCCATGTGGGATGCTC CAACCAGTTGCACTTCCTCGCGAGCCTCC ATATCCCCGAGACTGCGCTTTATTTGGCGA GGGTTACTCTGCTTCCTGCGGCTCATGGA CCCTCCGCCGGGACTGGGGGCCTCGGGT GCTGTTGCCTTTTGTTCCATGTGAGAAGCA CCGACGAGCTGGACTTCCTCCCGAGCCTC CATATCGCCGAGGGACCGCTTGATTTGCC TAGGATTGCTCTGCTTCCTGCGTGACATGG ATCCATCCTGACCTTCCGCATCCCTTAGGA AGACCTCGAGGGTCTCACTCCGGAGTTCA CGGGAGGCAGGCTGCCGAGTTCAGGCAG GAGTTCAGGGTGTGGATCGAGCCGAGCCA GTCTTGATTGTTCGAGAGCTATTGCCTCAG CAGAATGTTTGCATTTTTCGCTACCGCACT GACAGGTAAAGTACTTAGACTTTATGTCCC AAAACCGATCTCCGTAGTCAAAGCCGAGTT CCTCGCCTGTGCGTATATCGCGGGAGCTG AAGAATGCGATCCTAGGGAACCTCAGATC CTGATGCAGCATGAACACTCTCACAGGGAT GATGTTTGGGTCACACAGATGGTTAATGAA CCGGGAGATGTTGCCATAGTATCTTGCGTC TATACAATAGACTTCCCCATCTTTGTTGTCC AGGTCGAACAGGTAGCTATCGTCCTCCCG AACGTCTGCTTCTGCATCGCTGATCAGCTC TCCGACATATTCGCATATGAAAGTGCCTTG TGGAATGGTCTGGAGGGCTCTCACACCCC ATCCCATCTTAGCGGTCCTGTAGAGTTGCA GCCTGACTTTGATTCCGCTTTGAACCACTC TATTCTTGCAGTTTCTCCAGCAGCTACAAG CCTGATTACACTCAAATATGAGAGGTGGTT CTATCTTATTAAACTCCTGGAGCAGCCTTC CATCCTTATCATACCAACAGCGAATGCTGA GTTGCCCGCAGAGGCAATTTGAGCTTGAG CAATCATCGACGCAAGTACAATGCTGGAG GTGTGTAATGTTTCTGTCTATGTTCATGGTA GAAGTCTCGCAGTTCTCGCTGATATACTTG TAATCTTCAGGGCATGGCTCGCCATCCACA	

	CCATTAACACAGGGTATAGGGACATTTTCA TAGCCTCTTGCCACATCCCGACAGATGATC TTTTCGGTCCTGATAGCCCTGTTGCCGACC CCCAGCCTGAGTTTCCGGTTCAGTTGGAG AGCGAACCAAACATCAGAGCGCTCAGGGG TGAGGTCCCAGGCGGTATCGCCCTCCTTG TTTCTCAGCTCAGGGTTTGCGCCGCGGCT CAGGAACAGCAGCACGCAGTCGTGGTAAC TTTCTCTTGCGGCAATATGCAGTGGAGTGT CGCCGTGATAATTGACTGCGTGCAGGTCA CATCTAGCGTTCAGCAGAACTTCAGCTATG GCTGCGGATCCGCCACCAACTTTTCTTTTC TTCTTAGGCACCATGGAGAGACCAAGCTTG TCTTCGTCGCTGTTGTCGGGGTTCATG	
G9a_Y1067F_S	ACAAGGCACTTTCATATGCGAATTTGTCGG AGAGCT	Mutation Y1067F for the construction of G9a_me3
G9a_Y1067F_A	AGCTCTCCGACAAATTCGCATATGAAAGTG CCTTGT	
G9a_Y1154F_S	GAGGAACTCGGCTTTGACTTCGGAGATCG G	Construction of catalytically inactive G9a
G9a_Y1154F_A	CCGATCTCCGAAGTCAAAGCCGAGTTCCT C	
HDAC3_Fw	TTCGTCTCTGGAGGAGGATCTATGGCCAA GACCGTCGCCTATTTCTACG	PCR amplification of HDAC3
HDAC3_Rev	TTCGTCTCTCGAAAATCTCCACATCGCTTT CCTTGTC	
HDAC3_noBsaI_S	ATTACGGTCTGTATAAGAAGATGATCGTCT TC	BsaI restriction site I mutagenesis in HDAC3
HDAC3_noBsaI_A	GCAGGACCAGGCTATGGG	
HDAC3_Fw	TTCGTCTCTGGAGGAGGATCTATGGCCAA GACCGTCGCCTATTTCTACG	BsaI restriction site II mutagenesis in HDAC3
HDAC3_noBsaI_Rev	TTCGTCTCTCGAAAATCTCCACATCGCTTT CCTTGTCATTGTCATGATCTCCATC	
HDAC3_R265P_S	CTGTGATCCATTGGGCTGCTTTAACCTCAG C	Construction of catalytically inactive HDAC3
HDAC3_R265P_A	GCTGAGGTTAAAGCAGCCCAATGGATCAC AG	
KDM5A_Fw	TACGTCTCTGGAGGAGGATCTATGGCGGG CGTGGGGC	PCR amplification of KDM5A (1-797)
KDM5A_Rev	TACGTCTCACGAATCCGGACACAGATGCA CATGTCTCAGCTTCTTTTACAGC	
KDM5A_noBsaI_S	CAGGAAAAGGAACTGGGTCCCTTTTGAAGT CACATTATGA	BsaI restriction site mutagenesis in KDM5A
KDM5A_noBsaI_A	TCATAATGTGACTTCAAAAGGGACCCAGTT CCTTTTCCTG	
KDM5A_H483A_S	CTTCTCTTCTTTTTGCTGGGCCATTGAGGA TCACTGGAGT	Construction of catalytically inactive KDM5A
KDM5A_H483A_A	ACTCCAGTGATCCTCAATGGCCCAGCAAAA AGAAGAGAAG	
RIOX1_Fw	AAGAAGACTTGGAGGAGGATCTATGGATG GGCTCCAGGCC	PCR amplification of RIOX1
RIOX1_Rev	TTGAAGACTTCGAAATTTAGGGCTAGAGGC ATCTTAGTG	

RIOX1_noBsaI_1_S	CGGTCCGGGTGGTGGAAACCTCGGCC	BsaI restriction site I mutagenesis in RIOX1
RIOX1_noBsaI_1_A	GGCCGAGGTTTCCACCACCCGGACCG	
RIOX1_noBsaI_2_S	CAACGGACGACGCGAAACCCTGAACCC	BsaI restriction site II mutagenesis in RIOX1
RIOX1_noBsaI_2_A	GGGTTCAGGGTTTCGCGTCGTCCGTTG	
RIOX1_noEsp3I_S	CTCCCTGCGTCTGCTCTGTCCGCAG	Esp3I restriction site mutagenesis in RIOX1
RIOX1_noEsp3I_A	CTGCGGACAGAGCAGACGCAGGGAG	
RIOX1_H339A_S	AGGGCTTTGCCCCCGCCTACGACGACATCG	Construction of catalytically inactive RIOX1
RIOX1_H339A_A	CGATGTCGTCGTAGGCGGGGGCAAAGCCCT	
RIOX1_H404A_S	CTGTATTTTCCTCGGGGCTTCATTGCCCAAGCTGAATGC	
RIOX1_H404A_A	GCATTCAGCTTGGGCAATGAAGCCCCGAGGAAAATACAG	
LSD1_Fw	TACGTCTCTGGAGCCATGGTCTTATCTGGGAAGAAGGCGGCAG	PCR amplification of LSD1
LSD1_Rev	TACGTCTCTCGAATCCGGACATGCTTGGGGACTGCTGTGC	
LSD1_noBsaI_S	TATAGGCTCTGGGGTGTCAGGCTTGGCAG	BsaI restriction site mutagenesis in LSD1
LSD1_noBsaI_A	CTGCCAAGCCTGACACCCCAGAGCCTATA	
LSD1_K661A_S	ATGGGATTTGGCAACCTTAACGCCGTGGTGTTGTGTTTTGATCGG	Construction of catalytically inactive LSD1
LSD1_K661A_A	CCGATCAAAACACAACACCACGGCGTTAAGGTTGCCAAATCCCAT	
Multi-guide_IV-Z_S	CGCTTGACAGAGACCGATTGTCGCACCTGATTGCCCGGTCTCAGGTA	Multi-guide_IV-Z oligonucleotide
Multi-guide_IV-Z_A	ACCTTACCTGAGACCGGGCAATCAGGTGCGACAATCGGTCTCTGTCA	

Supplementary Table S2. Sequences of gRNA molecules

gRNA molecule	Target site sequence (5'→3') including PAM (underlined)
ZEB1_gRNA01	CACTCACCGTTATTGCGCCGCGG
ZEB1_gRNA02	TACACGTACATTTCGGACCGAGG
ZEB1_gRNA03	TCGGCGCCGGCTAACGGTCCAGG
ZEB1_gRNA04	CGGCCGGCGGCGGTAAAGTTGGG
ZEB1_gRNA05	AGGTACCCACTTAACGCCGCCGG
ZEB1_gRNA06	TAGCAGCCCCGCGCGTCCGTCGG
SNAI1_gRNA01	GCATTCATTGCGCCGCGGCACGG
SNAI1_gRNA02	CTTCGCTCGACGTCCCGCCCCGG
SNAI1_gRNA03	ACACCGCACGTGGCTCTCGGCGG
NT-gRNA	GTAGGCGCGCCGCTCTCTAC

Supplementary Table S3. Sequences of pyrosequencing assays used for methylation analysis

Assay name	Assay sequence 5'→3' (analysed CpG sites are bold and underlined)
ZEB1_A1	G**CG**C**CG**GGATGGGC**CG**GTGTG**CG**TG**CG**CCT**CGCG**CT
ZEB1_A2	C**CG**GA**CG**CA**CG**GAG**CG**CTGAAGC**CG**GATAATGGGGCTTGGATGG**CG**
ZEB1_A3	G**CGCGCG**TGTG**CGCG**GG**CG**C**CG**GCTGTG**CGCG**C**CGCG**GG**CG**GACAGG GTT**CG**GC**CG**G**CG**G**CG**
ZEB1_A4	**CG**C**CG**CTGC**CG**GAGC**CGCG**C**CGCG**GC**CG**CT**CG**
ZEB1_A5	**CGCG**GAGGCAGGA**CG**C**CG**C**CG**AG
SNAI1_A1	C**CG**GG**CG**CTGAGC**CG**GTGGG**CGCGCG**G**CG**TCCTGC**CG**
SNAI1_A2	**CG**CCA**CGCG**G**CGCG**AGCC**CG**GCCAGCAGC**CG**G**CG**CACCTGCT**CG**
SNAI1_A3	**CGCG**AAT**CG**G**CG**ACCCCAGTGCCT**CG**ACCACTATGC**CGCG**

Supplementary Table S4. Sequences of PCR and pyrosequencing primers

Primer	Sequence (5'→3')	Use
ZEB1_Pyro_Fw	TTGGGTTTAGAGATYGGGAAGTATTATAGA	PCR amplification of ZEB1_A1 and ZEB1_A2 fragment
ZEB1_Pyro_Rev_Btn	[Btn]CCCTTAACACAACAACACAAATCAATA	
ZEB1_Pyro_Seq1	GGTAGAYGAGGTTTTT	Pyrosequencing of ZEB1_A1
ZEB1_Pyro_Seq2	GGGAAGTTGTTATTTGGG	Pyrosequencing of ZEB1_A2
ZEB1_Pyro_Fw3	GTTGYGTGGGGTTTGT	PCR amplification of the ZEB1_A3 fragment
ZEB1_Pyro_Rev3_Btn	[Btn]ACCCRCRAATCCCAACTTTACC	
ZEB1_Pyro_seq3	GTTGYGTGGGGTTTGT	Pyrosequencing of ZEB1_A3
ZEB1_Pyro_Fw4	GTGGAGTGGGAAAGTAGAAAGTAGTG	PCR amplification of the ZEB1_A4 fragment
ZEB1_Pyro_Rev4	[Btn]CTCCACCCRAAACCAAAAAAATAACC	
ZEB1_Pyro_Seq4	GTAGTGTTTTTTGTTTTTTTTYGTTGT	Pyrosequencing of ZEB1_A4
ZEB1_Pyro_Fw5	GYGGYGGGTGTGGTTAG	PCR amplification of ZEB1_A5 fragment
ZEB1_Pyro_Rev5	[Btn]CATCACCTTCCTTACACCTAAAAACTC	
ZEB1_Pyro_Fw5	GYGGYGGGTGTGGTTAG	Pyrosequencing of ZEB1_A5
SNAI1_Pyro_Fw1	GGAGGAAATTTTYGTTTTTTTTTAAGTT	PCR amplification of
SNAI1_Pyro_Rev1_Btn	[Btn]AAACCTCTACRAAATAAAACCCC	

		the SNAI1_A1 fragment
SNAI1_Pyro_Seq1	GTTAGAAGYGTTTAGATTA	Pyrosequencing of SNAI1_A1
SNAI1_Pyro_Fw2	GTTTYGGATAGTTTTAGTAT	PCR amplification of the SNAI1_A2 fragment
SNAI1_Pyro_Rev2_Btn	[Btn]CCACRCCCCTTTATCACCTC	
SNAI1_Pyro_seq2	GAGGAGTTTTYGTTYGGGTTTTTAT	Pyrosequencing of SNAI1_A2
SNAI1_Pyro_Fw3	GGAGTATTTAAGGGAGTTGG	PCR amplification of the SNAI1_A3 fragment
SNAI1_Pyro_Rev3_Btn	[Btn]CTAAAACCCAAAACCCCTC	
SNAI1_Pyro_seq3	GTTTTTTTGYGTTATTGTTG	Pyrosequencing of SNAI1_A3

Supplementary Table S5. Sequences of ChIP-qPCR primers

Primer	Sequence (5'→3')	ChIP-qPCR assay
ZEB1_ChIP_Fw2	GTGCCAAGGGAAACACACAC	ZEB1_2
ZEB1_ChIP_Rev2	GCAACCACCACCACATGTTC	
ZEB1_ChIP_Fw4	CTTTTCCCTCGCCCCTCAAT	ZEB1_4
ZEB1_ChIP_Rev4	AACCTTGTTGCTAGGGACCG	
ZEB1_ChIP_Fw9	CGCGCTTTTCTCTTTCGGT	ZEB1_9
ZEB1_ChIP_Rev9	CATCCAAGCCCCATTATCCG	
ZEB1_ChIP_Fw13	TTTCTGGTTATCTCGGGGCG	ZEB1_13
ZEB1_ChIP_Rev13	CTCTCGCCACAGGAACTGTC	
ZEB1_ChIP_Fw16	CGCTCGCTCTCCCTGAAC	ZEB1_16
ZEB1_ChIP_Rev16	TAGGCGGAGAGAGACCAGG	
ZEB1_ChIP_Fw20	ATCTGTCAGCCGATGCTTCT	ZEB1_20
ZEB1_ChIP_Rev20	GCTAAGGTATCCACAGGCCAT	
ZEB1_ChIP_Fw22	GGAAGTGAGACAAGCACCGT	ZEB1_22
ZEB1_ChIP_Rev22	GCTAGAAGTTCCGCTTGCCA	
SNAI1_ChIP_Fw3	GGTTCTTCTGCGCTACTGCT	SNAI1_3
SNAI1_ChIP_Rev3	GAGGAAAGAGCGCGGCATAG	
SNAI1_ChIP_Fw5	CCAGTGCCTCGACCACTATG	SNAI1_5
SNAI1_ChIP_Rev5	CCTCCAACGCACCTGGATTA	
SNAI1_ChIP_Fw11	TCCCTGGAAGCTGCTCTCT	SNAI1_11
SNAI1_ChIP_Rev11	ATCAAGGGAAAAGGCCCGAG	
SNAI1_ChIP_Fw12	GTGCTCTTGGCTAGCTGGG	SNAI1_12
SNAI1_ChIP_Rev12	AAATGCCACGGCCTTTTTGCS	

Supplementary Table S6. List of locus-specific proteins associated with the *SNAI1* (S) or *ZEB1* (Z) CpG islands that and enriched by immunoprecipitation of dCas9 fusion proteins following S or Z transfections with DNMT3A-dCas9 and G9a-dCas9. Proteins were identified by mass spectrometry, with protein accession numbers, protein and gene names, and normalized mass spectrometry intensities provided. Fold changes in protein abundance between the *ZEB1* and *SNAI1* loci are reported. In addition, ratios comparing protein intensities in the MOCK negative control with the lowest detected intensities in samples transfected with dCas9 fusion constructs are included.

Accession	Protein Name	Gene Name	Fold Change (S/Z)	Normalized Intensity (S)	Normalized Intensity (Z)	Ratio (MOCK/ Sample)
Q71UI9	Histone H2A.V	*H2AZ2*	Only detected in S	38497.81328	0	0.323
V9HWN7	Fructose-bisphosphate aldolase	*HEL-S-87p*	Only detected in S	15406.0607	0	Not in MOCK
P62906	60S ribosomal protein L10a	*RPL10A*	3.824	310360.0335	81159.36942	Not in MOCK
J3KRX5	60S ribosomal protein L17 (Fragment)	*RPL17*	3.053	416777.8782	136508.5452	0.154
P39019	40S ribosomal protein S19	*RPS19*	2.738	951537.5204	347509.4806	Not in MOCK
I3L303	40S ribosomal protein S15a	*RPS15A*	1.820	123037.0825	67605.9726	Not in MOCK
A8MPY5	SRSF protein kinase 3	*SRPK3*	1.624	639274.3714	393711.1265	0.228
P62314	Small nuclear ribonucleoprotein Sm D1	*SNRPD1*	1.578	38773.27086	24578.28935	Not in MOCK
B0AZU3	cDNA, FLJ79533, highly similar to Bcl-2-associated transcription factor 1	*BCLAF1*	1.522	483677.6498	317691.3817	0.027
Q1ZYL5	Tropomyosin 1 alpha variant 6	*TPM1*	1.488	346159.5264	232602.3517	0.170
Q9Y2W1	Thyroid hormone receptor-associated protein 3	*THRAP3*	1.384	168060.4711	121426.4181	Not in MOCK
A0A7I2V649	Poly(A) binding protein cytoplasmic 1	*PABPC1*	1.377	328409.3726	238490.8496	0.132
P42766	60S ribosomal protein L35	*RPL35*	1.352	1147868.987	849104.6034	0.278
P49207	60S ribosomal protein L34	*RPL34*	1.332	260621.3684	195646.1547	Not in MOCK
B4DS01	cDNA FLJ59402, highly similar to Eukaryotic translation initiation factor 4B	*EIF4B*	1.323	95899.90109	72485.92044	Not in MOCK

Q9Y3U8	60S ribosomal protein L36	*RPL36*	0.774	627305.7622	810906.0626	0.068
K9JA46	Epididymis luminal secretory protein 52	*EL52*	0.732	198949.117	271834.7097	0.050
F5H5D3	Tubulin alpha chain	*TUBA1C*	0.659	1013747.959	1539431.448	0.148
Q6FHZ0	Malate dehydrogenase	*MDH2*	0.650	105167.1486	161703.4712	0.375
Q59GK9	60S ribosomal protein L21 (Fragment)	*RPL21*	0.640	565550.1182	883413.7525	0.400
P30050	60S ribosomal protein L12	*RPL12*	0.607	230668.1618	379716.9421	Not in MOCK
P62979	Ubiquitin-40S ribosomal protein S27a	*RPS27A*	0.583	1333651.216	2288440.529	0.173
A0A024RD80	Heat shock protein 90kDa alpha (Cytosolic), class B member 1, isoform CRA_a	*HSP90AB1*	0.561	1732573.247	3085785.871	0.094
A0A0A0MR02	Voltage dependent anion channel 2 (Fragment)	*VDAC2*	0.344	19559.01772	56870.36184	Not in MOCK
B4DIT7	cDNA FLJ58187, highly similar to Protein-glutamine gamma-glutamyltransferase 2	*TGM2*	0.323	114746.2248	354990.6414	Not in MOCK

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