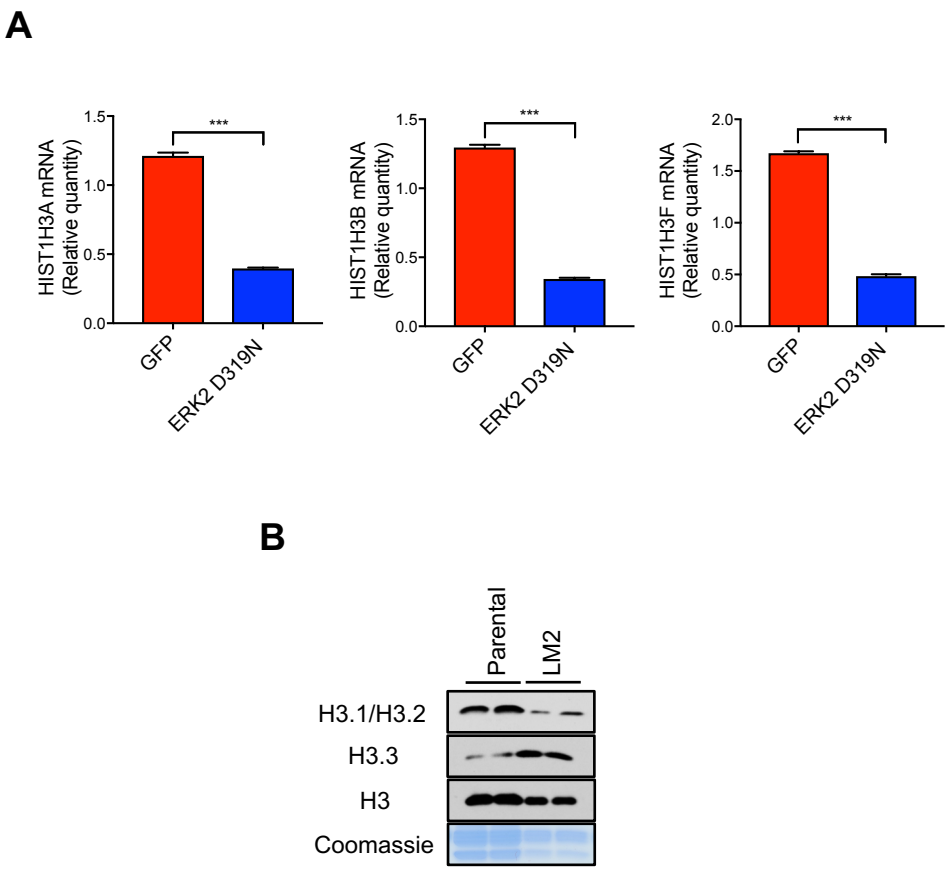


**Figure S1. mRNA of canonical H3 histones is reduced by metastatic signaling (related to Figure 1)**

(A) mRNA levels of H3.1 encoding genes *HIST1H3A, HIST1H3B* and *HIST1H3F* evaluated by qPCR in MCF-10A expressing ERK2 D319N inducibly for 3 days (n = 4). All values are expressed as mean ± SEM (***p < 0.001).

(B) Levels of histone H3 variants in chromatin extracts and Coomassie Blue stain of total histones in histone extracts of the MDA-MB-231 parental versus the more metastatic LM2 clone; representative images (n = 4).

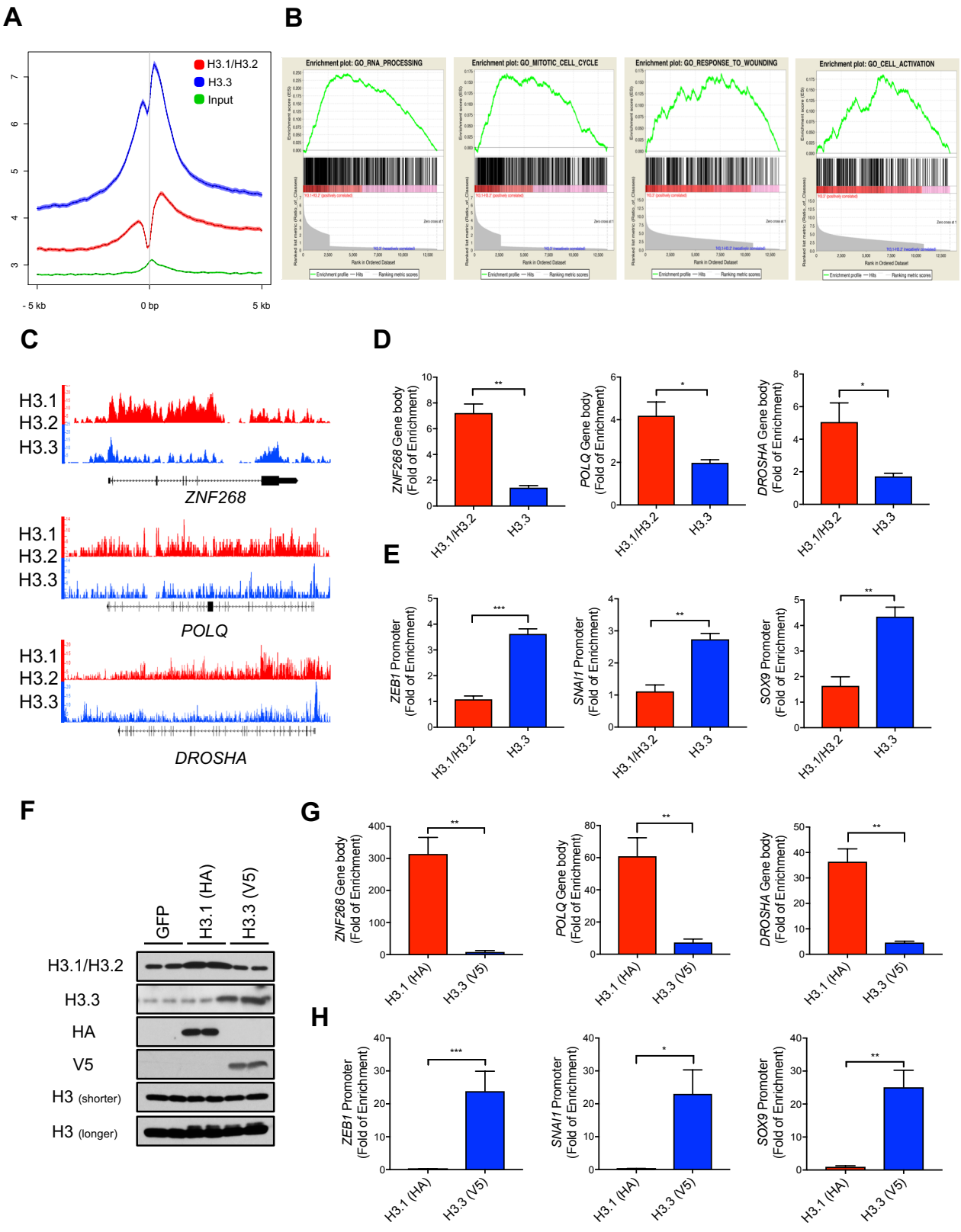


**Figure S2. Histone H3 variants regulate distinct genetic programs in metastatic cells (related to Figure 2)**

(A-C) Summary of H3.1/H3.2 and H3.3 ChIP-seq analysis in LM2 cells displayed as: an average plot of H3.1/H3.2 and H3.3 distribution across transcriptional starting sites (TSS) (A), GSEA

enrichment plots evaluating H3.1/H3.2 enrichment in GO-term gene sets for RNA processing and mitotic cell cycle, and H3.3 enrichment in GO-term gene sets for response to wounding and cell activation (B), H3.1/H3.2 and H3.3 signal tracks for genes *ZNF257*, *POLQ* and *DROSHA* (C).
(D and E) Validation of the H3.1/H3.2 ChIP-seq top targets *ZNF268*, *POLQ* and *DROSCHA* (D), and the H3.3 ChIP-seq top targets *ZEB1*, *SNAI1* and *SOX9* (E) by ChIP-qPCR in LM2 cells (n = 3).
(F) Validation of antibody specificity for histone H3 variants in LM2 cells expressing a HA-tagged version of H3.1 or a V5-tagged version of H3.3; “shorter” and “longer” indicates shorter/longer film exposures, representative images (n = 4).
(G and H) Validation of the H3.1/H3.2 ChIP-seq top targets *ZNF268*, *POLQ* and *DROSCHA* (G), and the H3.3 ChIP-seq top targets *ZEB1, SNAI1* and *SOX9* (H) by ChIP-qPCR in LM2 cells expressing a HA-tagged version of H3.1 or a V5-tagged version of H3.3 (n = 3).
All values are expressed as mean ± SEM (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

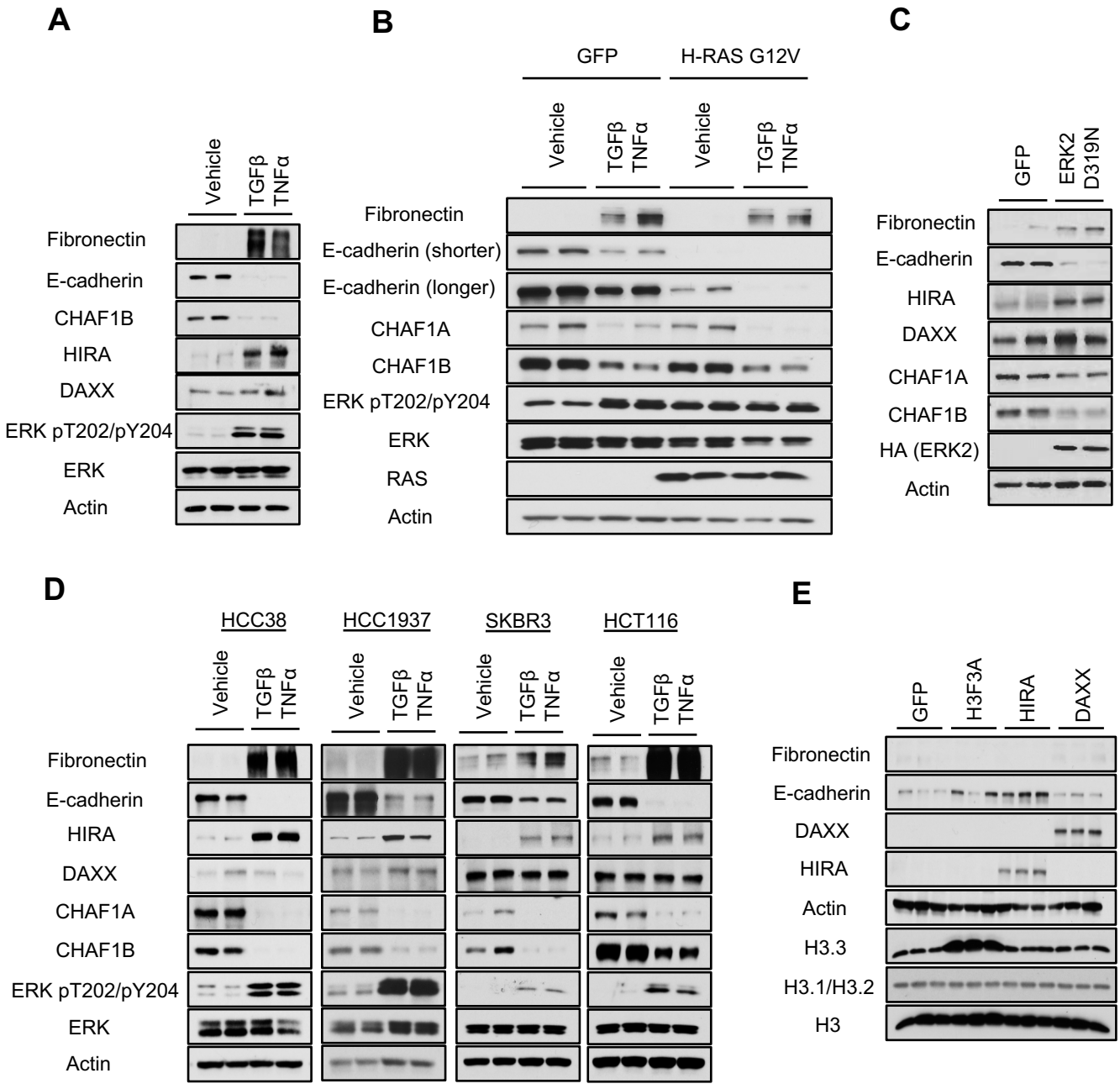


**Figure S3. Metastatic signaling suppresses the CAF-1 complex and increases HIRA in a variety of cell models (related to Figure 3)**

(A-D) Levels of the histone H3 chaperones in NMuMG with TGFβ + TNFα for 10 days (A), MCF-10A transformed by induction of oncogenic H-RAS and treated with TGFβ + TNFα for 5 days (B), MCF-10A expressing ERK2 D319N for 6 days after transduction (C), HCC38, HCC1937, SKBR3 and HCT116 treated with TGFβ + TNFα for 10 days (D); "shorter" and "longer" indicates shorter/longer film exposure, representative images (n = 4).

(E) EMT induction determined by the protein levels of the mesenchymal marker fibronectin and the epithelial marker E-cadherin after 14 days of expression of H3F3A or HIRA or DAXX in MCF-10A; representative images (n = 3).

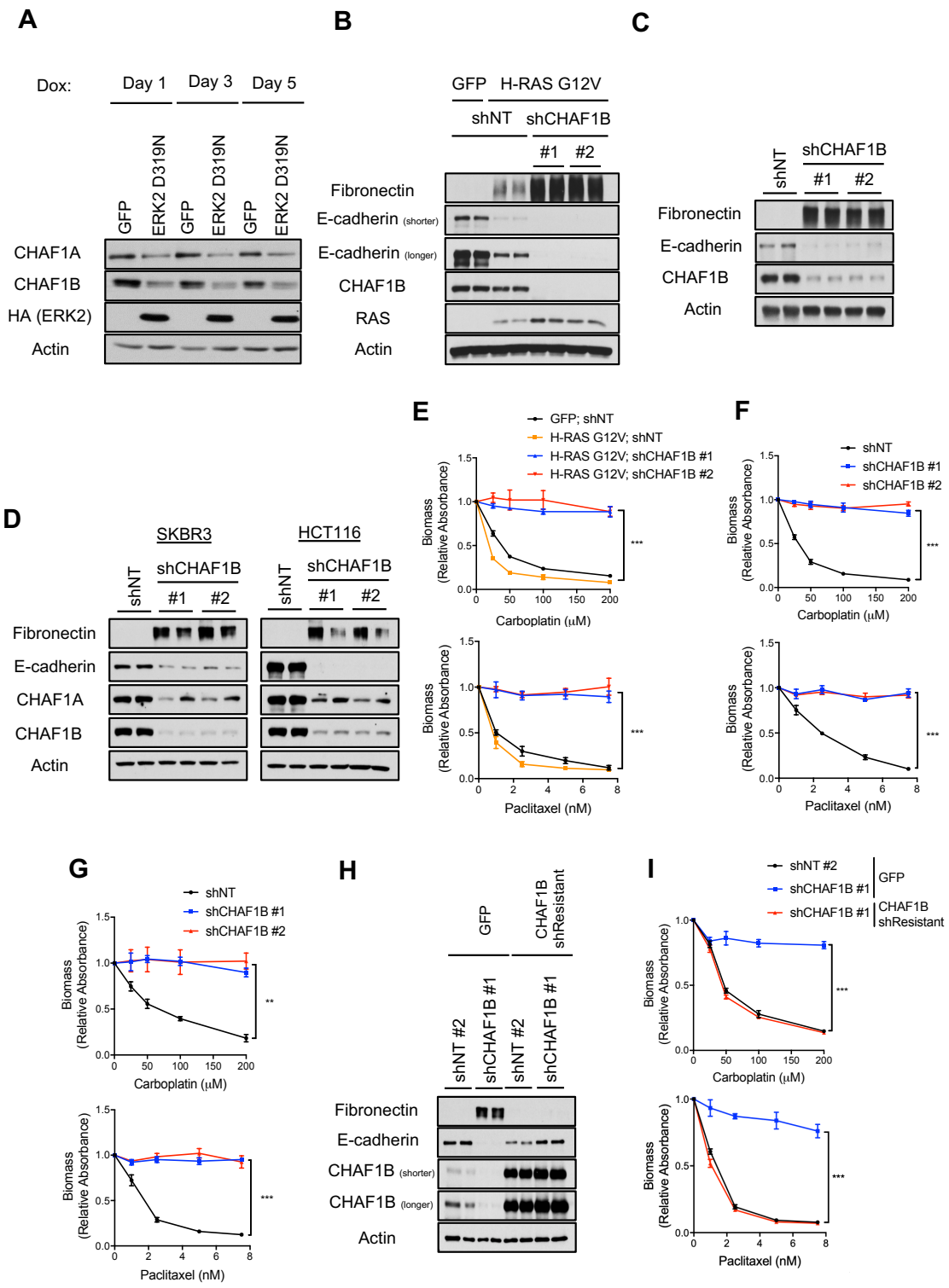


**Figure S4. Suppression of the CAF-1 complex promotes aggressiveness of cancer cells (related to Figure 4)**

(A) Time-course analysis of CAF-1 complex protein levels in MCF-10A expressing ERK2 D319N inducibly for 1, 3 or 5 days; representative images (n = 4).

(B-D) EMT induction determined by protein levels of the mesenchymal marker fibronectin and the epithelial marker E-cadherin in MCF-10A cells transformed by induction of oncogenic H-RAS and with CHAF1B knockdown for 5 days (B), NMuMG with CHAF1B knockdown for 10 days (C),

SKBR3 and HCT116 both with CHAF1B knockdown for 10 days (D); “shorter” and “longer” indicates shorter/longer film exposures, representative images (n = 4).
(E-G) Viability of MCF-10A cells transformed by induction of oncogenic H-RAS with CHAF1B knockdown for 5 days (E), SKBR3 with CHAF1B knockdown for 10 days (F), and HCT116 with CHAF1B knockdown for 10 days (G) treated with the chemotherapeutic drugs carboplatin and paclitaxel (n = 4).
(H) EMT induction determined by protein levels of the mesenchymal marker fibronectin and the epithelial marker E-cadherin in MCF-10A with CHAF1B knockdown and overexpression of a shRNA-resistant *CHAF1B* cDNA; representative images (n = 4).
(I) Viability of MCF-10A with CHAF1B knockdown and a shRNA-resistant CHAF1B cDNA treated with the chemotherapeutic drugs carboplatin and paclitaxel (n = 4).
All values are expressed as mean ± SEM (**$p < 0.01$, ***$p < 0.001$).

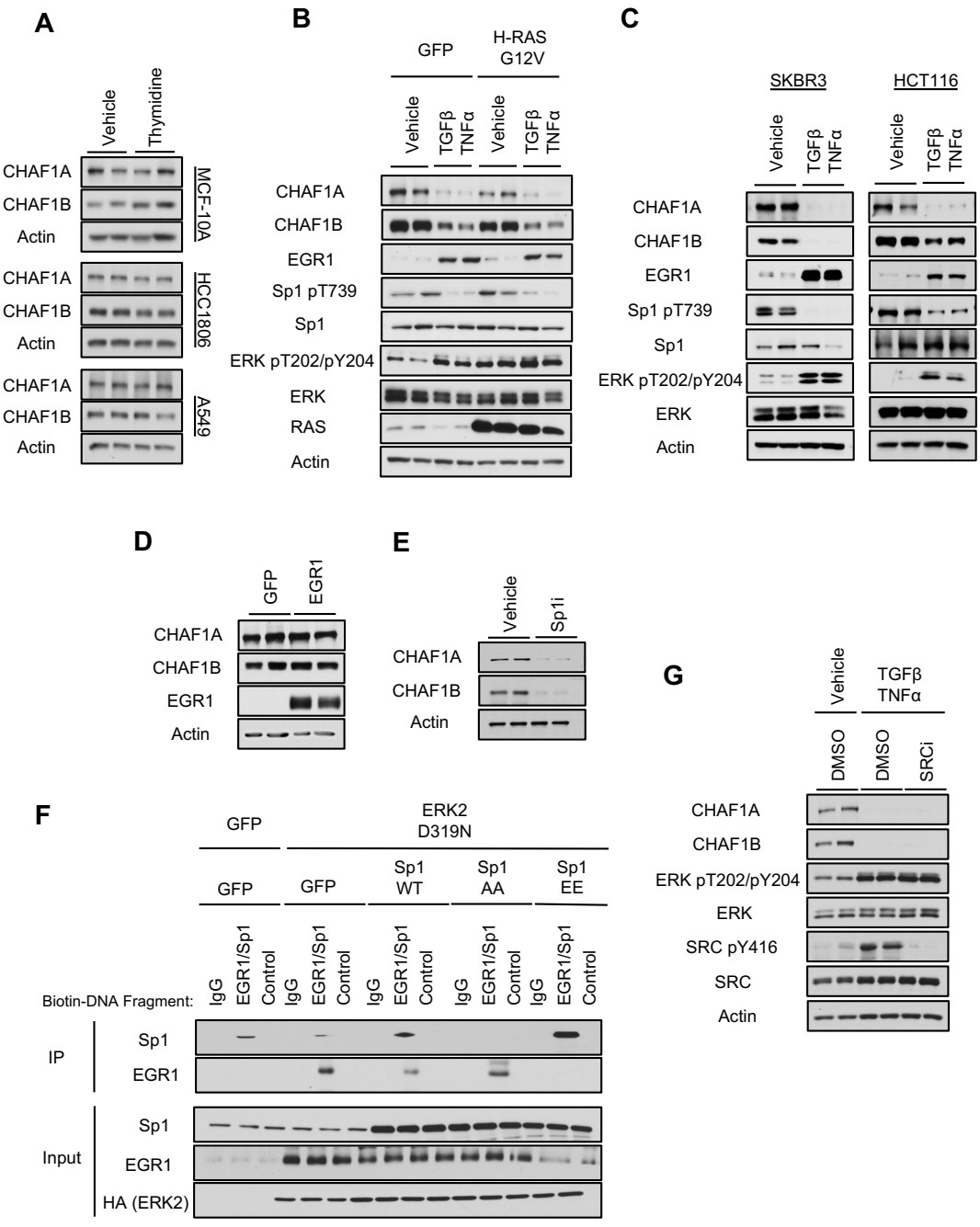


**Figure S5. CAF-1 levels are not acutely regulated by cell cycle or SRC activation (related to Figure 5)**

(A) CAF-1 complex protein levels in MCF-10A, HCC1806 and A549 treated with thymidine for 24 hours; representative images (n = 4).

(B and C) Protein levels of EGR1, Sp1 pT739 and ERK2 pT202/pY204 phosphorylation in MCF-10A cells transformed by induction of oncogenic H-RAS and treated with TGFβ + TNFα for 5 days (B), and SKBR3 and HCT116 treated with TGFβ + TNFα for 10 days (C); representative images (n = 4).

(D and E) CAF-1 complex protein levels in MCF-10A expressing EGR1 for 3 days (D), and MCF-10A treated with the Sp1 inhibitor mithramycin A for 24 hours (E); representative images (n = 4).

(F) Binding of Sp1 and/or EGR1 to biotinylated DNA fragments of either the CHAF1B promoter containing the overlapping Sp1/EGR1 site or a scrambled control in lysates from MCF-10A expressing inducible ERK2 D319N and either Sp1 WT or the Sp1 T453/T739 phosphorylation site mutants for 3 days; IgG control for the immunoprecipitation of the DNA fragments with streptavidin; representative images (n = 4).
(G) CAF-1 complex protein levels in MCF-10A treated with the SRC inhibitor KX2-391 and TGFβ + TNFα for 24 hours; representative images (n = 4).

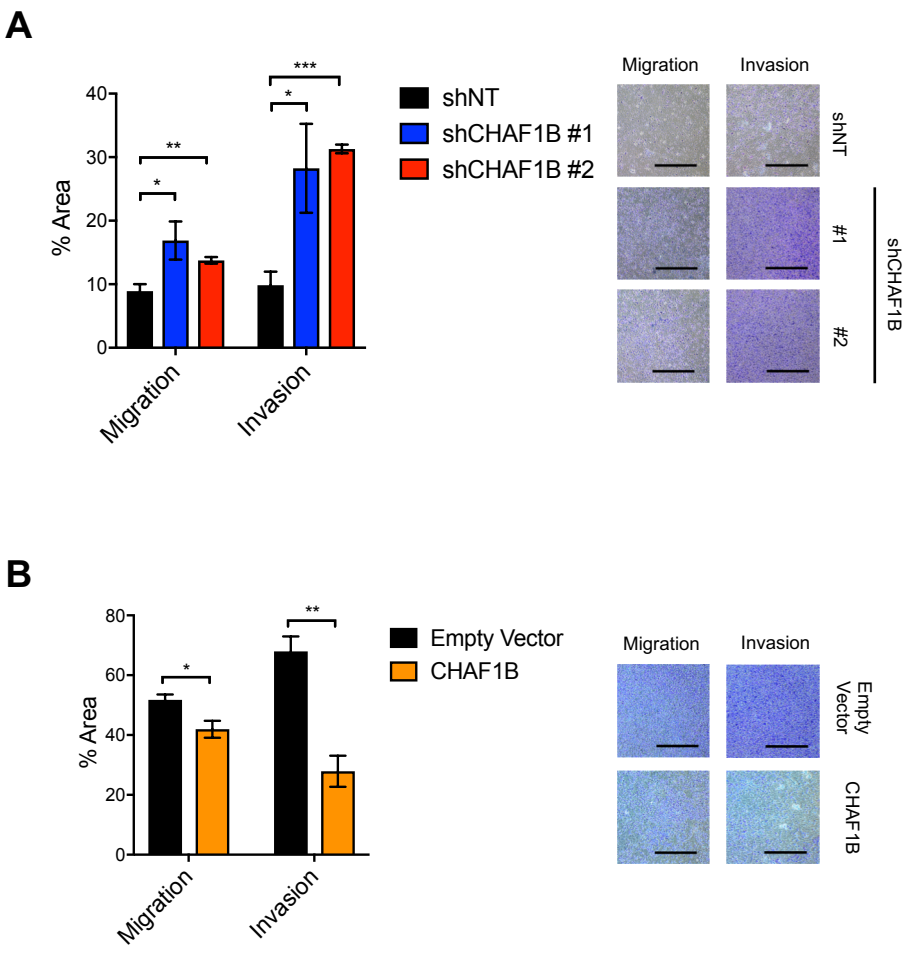


**Figure S6. CAF-1 levels dictates metastatic-like properties of cancer cells (related to Figure 6)**

(A and B) Quantification of migration and invasion of MDA-MB-231 parental cells with CHAF1B knockdown for 10 days (A), and LM2 overexpressing CHAF1B for 10 days (B) evaluated by transwell assays (left); representative images (right) (n = 4), scale bar = 1 mm.

All values are expressed as mean ± SEM (*p < 0.05, **p < 0.01, ***p < 0.001).

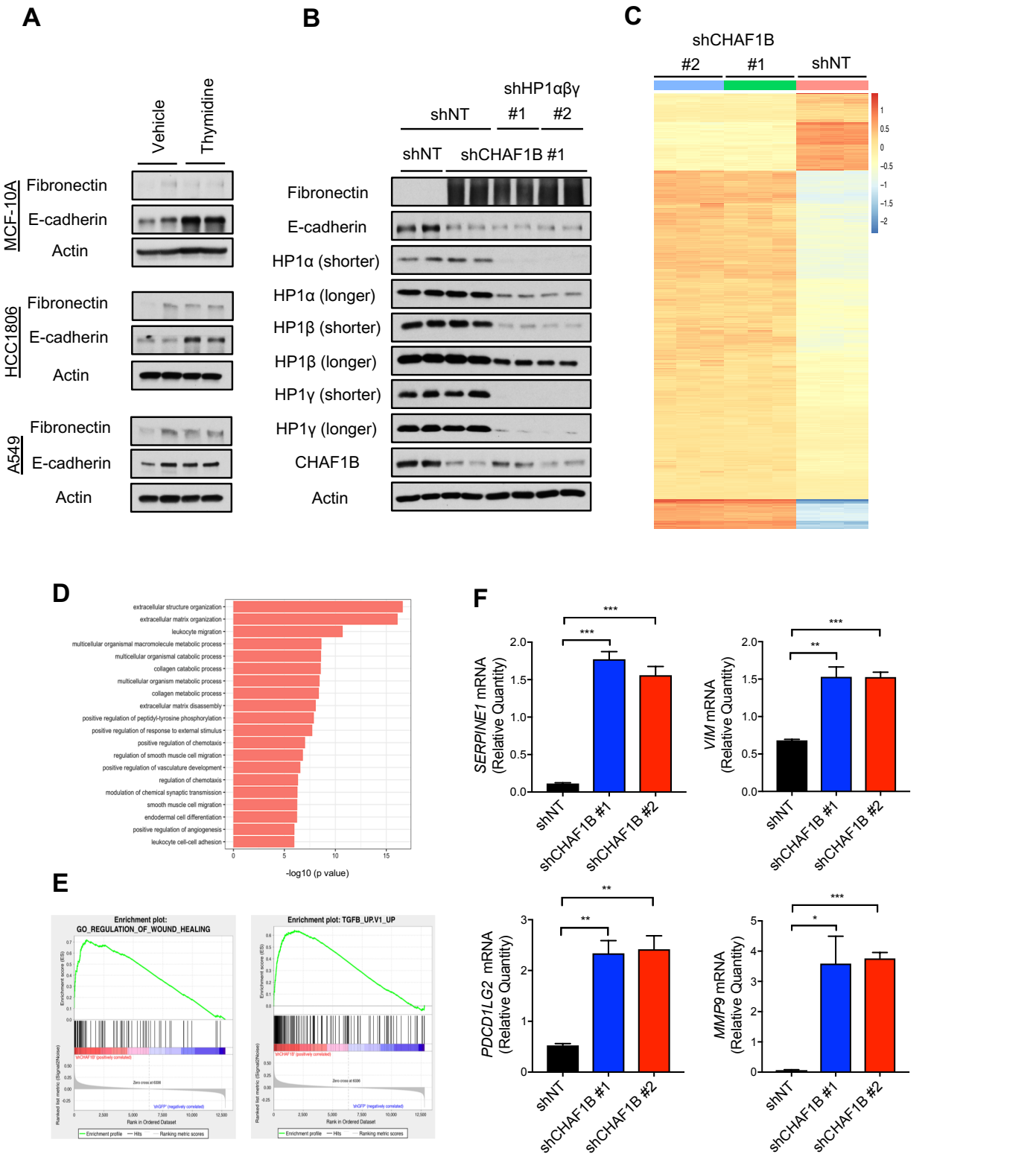


**Figure S7. Suppression of the CAF-1 complex triggers a pro-metastatic transcriptional reprogramming (related to Figure 7)**

(A) EMT induction determined by protein levels of the mesenchymal marker fibronectin and the epithelial marker E-cadherin in MCF-10A, HCC1806 and A549 treated with thymidine for 7 days; representative images (n = 4).

(B) Induction of EMT determined by protein levels of the mesenchymal marker fibronectin and the epithelial marker E-cadherin in MCF-10A with CHAF1B knockdown as well as HP1 knockdown for 10 days; “shorter” and “longer” indicates shorter/longer film exposures, representative images (n = 4).
(C-E) Summary of RNA-seq analysis in MCF-10A with CHAF1B knockdown for 3 days (*n*=3): a heatmap representation of differentially expressed genes (up regulated genes are indicated with red and down regulated genes are indicated with blue) (C), GSEA analysis of the > 2-fold changed mRNAs (D), GSEA enrichment plots for the wound healing and TGFβ GO-term gene sets (E).
(F) Relative mRNA levels of *SERPINE1*, *VIM*, *MMP9* and *PDCD1LG2* evaluated by qPCR in MCF-10A with CHAF1B knockdown for 3 days (n = 3). All values are expressed as mean ± SEM (*p < 0.05, **p < 0.01, ***p < 0.001).

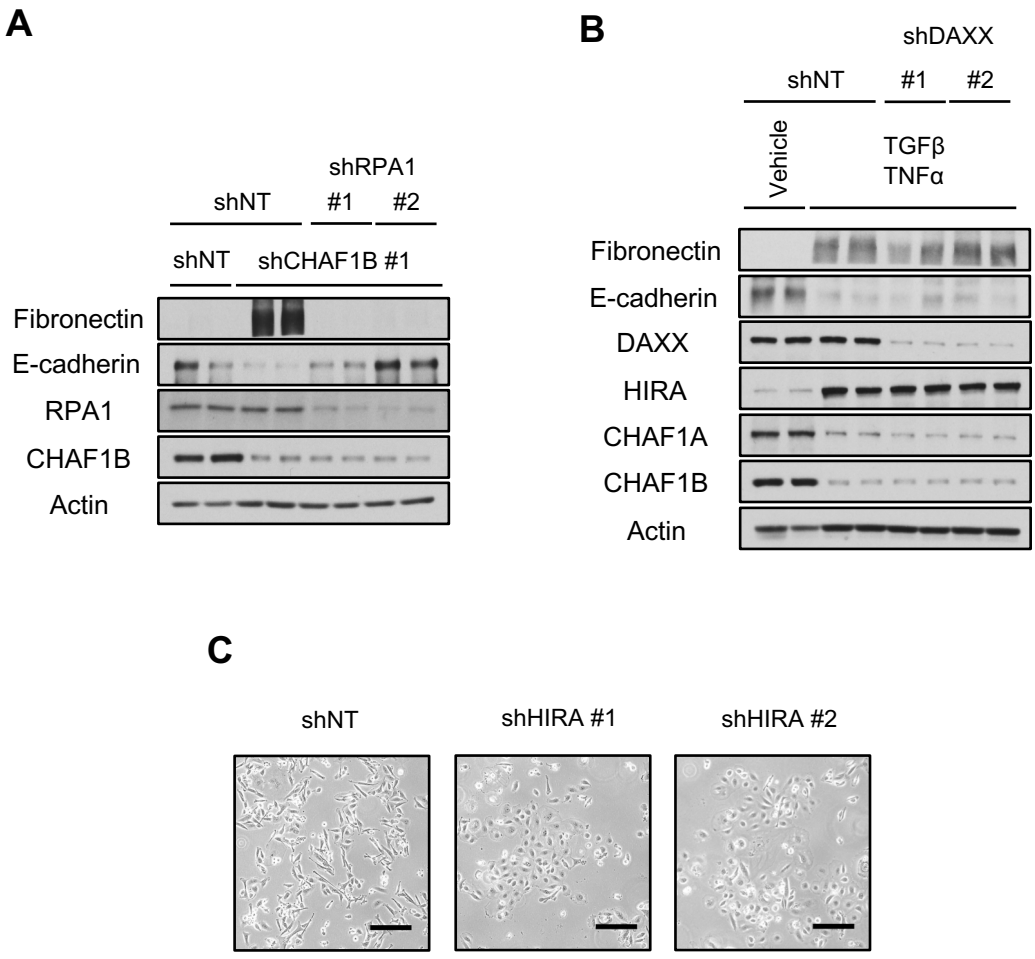


**Figure S8. DAXX does not mediate the pro-metastatic effects of CAF-1 suppression (related to Figure 8)**

(A and B) EMT induction determined by the protein levels of the mesenchymal marker fibronectin and the epithelial marker E-cadherin in MCF-10As with both CHAF1B and RPA1 knockdown (A), and in MCF-10As with DAXX knockdown treated with TGFβ + TNFα for 5 days (B); representative images (n = 4).

(C) Morphology of LM2 cells with HIRA knockdown; representative images (n = 4), scale bar = 200 μm.

**Table S5. Human primers used for mutagenesis, related to STAR Methods**

| Target | | Primer Sequence |
|---|---|---|
| *CHAF1B* T195C/C204A | Forward | AACGCACAACATTGACTGCTTTGGTGTGACGAGCAAGATTGG |
| | Reverse | CCAATCTTGCTCGTCACACCAAAGCAGTCAATGTTGTGCGTT |
| *CHAF1B* C198T/C207T (after T195C/C204A) | Forward | GAGAAAAACGCACAACATTAACTGCTTTAGTATGACGAGCAAGATTGG |
| | Reverse | CCAATCTTGCTCGTCATACTAAAGCAGTTAATGTTGTGCGTTTTTCTC |
| *CHAF1B* T192A/A201G (after T95C/C198T/ C204A/C207T) | Forward | CCAGTTGGAGAAAAACGCACAACATTAACTGCCTTAGTGTGTCGAGCAAGATTGGACAAAAATTCCAC |
| | Reverse | GTGGAATTTTTGTCCAATCTTGCTCGACACACTAAGGCAGTTAATGTTGTGCGTTTTTCTCCAACTGG |
| *Sp1* T453A | Forward | CCCCACTGTTGGTGCCCGGATGATGATGG |
| | Reverse | CCATCATCATCCGGGCACCAACAGTGGGG |
| *Sp1* T453E | Forward | TTGGGCCCCACTGTTGGCTCCCGGATGATGATGGGAC |
| | Reverse | GTCCCATCATCATCCGGGAGCCAACAGTGGGGCCCAA |
| *Sp1* T739A | Forward | AGGGCTGAAGGAGCGGCAGTGCCACTG |
| | Reverse | CAGTGGCACTGCCGCTCCTTCAGCCCT |
| *Sp1* T739E | Forward | GGTAATAAGGGCTGAAGGCTCGGCAGTGCCACTGCCTTC |
| | Reverse | GAAGGCAGTGGCACTGCCGAGCCTTCAGCCCTTATTACC |

**Table S6. Human primers used for gene expression qPCR analysis, related to STAR methods**

| Gene | | Primer Sequence |
|---|---|---|
| *ACTB* | Forward | CATGTACGTTGCTATCCAGGC |
| | Reverse | CTCCTTAATGTCACGCACGAT |
| *TBP* | Forward | GAGCCAAGAGTGAAGAACAGTC |
| | Reverse | GCTCCCCACCATATTCTGAATCT |
| *CHAF1A* | Forward | CAGCCAGACAGTCTTGTGGAC |
| | Reverse | GTCGTTCTGAATGGCCTTCAA |
| *CHAF1B* | Forward | GCGTGGACACCAATGTCAG |
| | Reverse | GCTCCGGCTCCTTGTTATCAT |
| *ZEB1* | Forward | TTACACCTTTGCATACAGAACCC |
| | Reverse | TTTACGATTACACCCAGACTGC |
| *SNAI1* | Forward | ACAAGCACCAAGAGTCCG |
| | Reverse | ATGGCAGTGAGAAGGATGTG |
| *FOSL1* | Forward | GCCCACTGTTTCTCTTGAGC |
| | Reverse | GGAGATAGGGTTGGGTGGAT |
| *SOX9* | Forward | ACTTGCACAACGCCGAG |
| | Reverse | CTGGTACTTGTAATCCGGGTG |
| *MMP9* | Forward | CGAACTTTGACAGCGACAAG |
| | Reverse | CACTGAGGAATGATCTAAGCCC |
| *SERPINE1* | Forward | GTGGACTTTTCAGAGGTGGAG |
| | Reverse | GAAGTAGAGGGCATTCACCAG |
| *VIM* | Forward | CGTGAATACCAAGACCTGCTC |
| | Reverse | GGAAAAGTTTGGAAGAGGCAG |
| *PDCD1LG2* | Forward | GGACGAAGGACAGTACCAATG |
| | Reverse | GCTCTACCTCATCTGTTTCTGG |

**Table S7. Human primers used for ChIP-qPCR analysis, related to STAR methods**

| Target | | Primer Sequence |
|---|---|---|
| *ZEB1* promoter | Forward | AGGCGTGGGACTGATGGTAG |
| | Reverse | TGGCTGATTCTCCCTGTACC |
| *SNAI1* promoter | Forward | CGCTCCGTAAACACTGGATAA |
| | Reverse | GCACATCACTGGGGAGGAAG |
| *SOX9* promoter | Forward | CAGGAGGCAAAGACCAAAAC |
| | Reverse | CACATCGACCTTGAGCTCTG |
| *ZNF268* gene body | Forward | CCTGTTGATCCTGCTCTTCTG |
| | Reverse | GAATAAAGACCCCTTGGATTCAG |
| *POLQ* gene body | Forward | GCAGTCCCTTACTGGCAATG |
| | Reverse | TGGAGAGTGAGAACCCCTTC |
| *DROSHA* gene body | Forward | TCCATAAAAGGGCAGTTTCAC |
| | Reverse | ATGCTTCTCCCATCCTGTTG |