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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Proteomic mass spectrometry data was acquired using Xcalibur software (Thermo Scientific). Confocal microscopy images were collected with Zeiss ZEN software. Epifluorescence images were collected with Nikon NIS-Elements software. Microarray CEL intensity files were generated by GeneChip Command Console Software. Chromatin immunoprecipitation data and RNA sequencing data were collected with Illumina HCS1.5/RTA1.13 and CASAVA 1.6. Metabolomics data were acquired with MassHunter Data Acquisition (LC-MS/MS) or MassHunter ChemStation (GC-MS). Described in Methods.
Data analysis	Proteomic mass spectrometry data was processed with MaxQuant v1.5.3.15 using the Andromeda search engine; statistical and bioinformatics analyses were done using Perseus (MaxQuant environment) or the R framework (R version 4.4.2; R studio version 1.1.383). Microarray data was processed with Transcriptome Analysis Software 4.0. Gene set enrichment analysis was performed with GSEA v2.2.0. Histone modification proteomics data was analyzed with Skyline software v3.5. RNA sequencing data was analyzed with STAR v2.5. ChIP-sequencing data was processed and analyzed with Trimmomatic 0.36, BWA aln 0.7.17, homer 4.8.3, and rgt-THOR v0.11.2. Metabolomics data were processed with MS-DIAL (LC-MS/MS) or BinBase (GC-MS). Databases used for metabolomics analysis were HILIC m/z-RT, CSH m/z-RT, MoNA, NIST 17, LipidBlast, and BinBase. Other data analyses were performed with Microsoft Excel, GraphPad Prism v7.04, or R. Described in Methods. Bioluminescence data was processed with Living Image v4.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Proteomic data is available online at http://maxqb.biochem.mpg.de/mxdb/project/show/9373012627500 (username: review2; password: 5kcGES) and have been deposited to the ProteomeXchange Consortium (http://proteomecentral.proteomexchange.org/cgi/GetDataset?ID=PXD006396) via the PRIDE partner repository with the dataset identifier PXD006396 (username: reviewer40116@ebi.ac.uk; password: XsCmGwHJ). Raw and processed data is available in the Gene Expression Omnibus (GEO) database (microarray data: GSE112497; DNA methylation array: GSE126672; RNA-sequencing data: GSE124014; ChIP-sequencing data: GSE124015). The MaxQuant quantitative proteomics software package and Perseus data analysis software environment are freely available: http://www.biochem.mpg.de/5111733/software. Supplementary data is available online.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to determine sample size. Animal experimental numbers were based on previous experience with the models. Other experiments were repeated in triplicate unless noted.
Data exclusions	No collected data were excluded.
Replication	All attempts at replication were successful. Experimental results were confirmed with biological triplicates unless otherwise noted. DNA methylation array analysis was performed in biological duplicate and cytokine arrays in technical duplicate.
Randomization	Animals were not randomized for experiments as all animal studies used inbred lines purchased from the same supplier at the same time and were of identical age and sex. We study ovarian cancer and therefore used only female mice.
Blinding	Investigators were blinded while assessing end-point outcome during animal experiments. Due to feasibility, investigators were not blinded during other experiments.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☐	☒ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Primary antibodies: Nicotinamide N-methyltransferase (NNMT); Santa Cruz Biotechnology; sc-376048; Lot J2511; IB: 1:1000; IHC: 1:200 Fibronectin (Fn1); Millipore; MAB1937; IB: 1:2000; IF: 1:200 Smooth muscle actin (SMA); Abcam; ab7817; IB: 1:1000; IF: 1:200 Cartilage oligomeric matrix protein (COMP); Thermo Fisher Scientific; MA1-20221; Lot RH22496911; IB: 1:500; IHC: 1:100 Histone H3 (total H3); Bioss Antibodies; bs-0349R; IB: 1:2000

Histone H3 lysine 27 trimethylation (H3K27me3); Cell Signaling Technologies; 9733; Lot 14; IB: 1:1000; IHC: 1:200; ChIP-seq: 1:100
Beta-actin (ACTB); Sigma; A5441; Lot 127M4857V; IB: 1:2000
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH); Cell Signaling Technologies; Lot 10; 2118; IB: 1:2000
Histone H3 lysine 4 trimethylation (H3K4me3); Cell Signaling Technologies; 9751T; Lot 10; IB: 1:1000
Acetylated alpha tubulin (Ac-α-Tub); Cell Signaling Technologies; 5335T; Lot 4; IB: 1:1000
Alpha Tubulin (α-Tub); Millipore; 05-829; Lot DAM159178; IB: 1:1000
Acetylated Histone H3 lysine 9 (H3K9Ac); Epigenetek; A-4022; Lot 705658; IB: 1:1000
Snail Family Transcriptional Repressor 1 (Snai1); Cell Signaling Technologies; 3879P; Lot 12; IB: 1:1000
Phospho-Histone H3 (Ser10); Cell Signaling Technologies; 9701S; Lot 16; IB: 1:1000; IF: 1:200

Normal Rabbit IgG; Cell Signaling Technologies; 2729; Lot 8; IF: 1:200

Anti-mouse IgG, HRP-linked Antibody; Cell Signaling Technology; #7076; Lot 33
Anti-rabbit IgG, HRP-linked Antibody; Cell Signaling Technology; #7074; Lot 28
Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 647; Invitrogen A-21244; Lot 1959073
Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 555; Invitrogen A-21422; Lot 1931963

IB=immunoblotting dilution IF=immunofluorescence dilution IHC=immunohistochemistry dilution
Provided in Supplementary Table S13.

Validation

We relied on data provided from manufacturer and cited literature for validation of antibodies (see below list). For tissue immunohistochemistry and immunofluorescence for NNMT and H3K27me3, we performed isotype control staining (Extended Data Fig. 3b and Extended Data Fig. 10j).

Manufacturer validation:
NNMT: immunoblotting of Caki-1, Sol8, and A549 cells; IHC of human liver, uterine cervix, and kidney.
Smooth muscle actin (SMA): immunoblotting of HeLa, A431, Jurkat, and HEK293 cells; IF of mouse primary colon myofibroblasts.
COMP: immunoblotting of Raji and HepG2 lysates.
Histone H3 (Bioss): Immunoblotting of K562 lysates.
H3K27me3: Immunoblotting of HCT116, NIH/3T3, C6, and COS lysates; IF of HeLa cells; IHC of human lymphoma; ChIP with chromatin from HeLa cells.
Beta-actin: Immunoblotting of HeLa, Jurkat, COS7, NIH/3T3, PC-12, RAT2, CHO, MDBK, and MDCK cell lysates.
GAPDH: Immunoblotting of HeLa, NIH/3T3, C6, HUVEC, and L929 cells.
H3K4me3: Immunoblotting of HeLa, H-4-II-E, COS, and NIH/3T3 lysates, including with competitor histone peptides.
Acetylated alpha tubulin: Immunoblot of HeLa cells, untreated or treated with 400 nM TSA.
Alpha tubulin: Immunoblot of A431 cells.
H3K9Ac: Immunoblot of lysates from HCT116, HeLa, NIH/3T3, Rat2, and COS cells.
Snai1: Immunoblot of HCT116, HeLa, NIH/3T3, Rat2, and COS cells.
Phospho-Histone H3 (Ser10): Immunoblot of TSA or calyculin A treated NIH/3T3 cells; IF of mitotic HeLa cells; IHC of human tonsil and 4T1 syngeneic mouse tumors.

References:
NNMT IB: Strom et al. N1-methylnicotinamide is a signalling molecule produced in skeletal muscle coordinating energy metabolism. Sci Rep. 2018 Feb 14;8(1):3016. doi: 10.1038/s41598-018-21099-1. PMID: 29445118

NNMT IHC: Win et al. Nicotinamide N-methyltransferase overexpression is associated with Akt phosphorylation and indicates worse prognosis in patients with nasopharyngeal carcinoma.Tumour Biol. 2013 Dec;34(6):3923-31. doi: 10.1007/s13277-013-0980-z. Epub 2013 Jul 11. PMID: 23838801

Fibronectin IB: Manzano et al. Human renal mesangial cells are a target for the anti-inflammatory action of 9-cis retinoic acid. Br J Pharmacol. 2000 Dec;131(8):1673-83. PMID: 11139446

COMP IHC: Frolova et al. Control of organization and function of muscle and tendon by thrombospondin-4. Matrix Biol. 2014 Jul;37:35-48. doi: 10.1016/j.matbio.2014.02.003. Epub 2014 Mar 1. PMID: 24589453

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

HeyA8: Gordon Mills, Oregon Health and Science University, Portland, OR
CAOV3: American Type Culture Collection
TYKnu: Gottfried Koneczny, University of California, Los Angeles
ID8: Katherine Roby, University of Kansas Medical Center, Kansas City, KS
3T3: American Type Culture Collection
293T: Lucy Godley, University of Chicago, Chicago, IL
WI-38: American Type Culture Collection
Described in Methods.

Authentication

All cell lines were regularly authenticated with IDEXX Bioresearch short tandem repeat marker profiling. See Methods.

Mycoplasma contamination	All cell lines were regularly tested and found to be Mycoplasma-negative (IDEXX Bioresearch). Described in Methods.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Studies used either 6 week old female nude mice (Harlan; xenograft models) or 6 week old female C57BL/6 mice (Harlan; syngeneic model). Described in Methods.
Wild animals	The study did not use wild animals.
Field-collected samples	The study did not use field-collected samples.
Ethics oversight	All animal experiments were approved by the University of Chicago Institutional Animal Care and Use Committee. Described in Methods.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Information on the patient cohort are provided in Supplementary Tables S1 and S12. All patients were females with high-grade (grade 3) serous-papillary ovarian cancer. The mean age at diagnosis was 61.0 (range: 33-88).
Recruitment	Patients were recruited from the pool of patients at the University of Chicago and may be biased based on individuals that seek care at the University of Chicago and consent to participate in a research study (95% of all patients consent). The patient cohort is representative of the general patient population at this institution with ovarian cancer.
Ethics oversight	All human tissue samples were collected with informed consent under University of Chicago Institutional Review Board-approved protocols and in accordance with the Declaration of Helsinki. Described in Methods.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	To review GEO accession GSE124015: Go to https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_geo_query_acc.cgi-3Facc-3DGSE124015&d=DwIBAg&c=Nd1gv_ZWYNIRyZYZmXb18oVfc3lTqv2smA_esABG70U&r=96FXrG_VhLfzIMLx4ONnlVQHTtvHqR7ONp2wm9cfrmo&m=elmfJ_3swjx2ns9XUQAVrpNBGYCWU3y2L1N_TaH-B5U&s=tnPRRGCkuFzS3WvTL8jmm6Hq91fF2tXZidgFtLWJfAM&e= Enter token ahcbmqemtjqljod into the box
Files in database submission	H3K27me3 ChIP raw data files: GSM3518717 3T3 Ctrl Replicate 1 GSM3518718 3T3 Ctrl Replicate 2 GSM3518719 3T3 Ctrl Replicate 3 GSM3518720 3T3 NNMT Replicate 1 GSM3518721 3T3 NNMT Replicate 2 GSM3518722 3T3 NNMT Replicate 3 GSM3518723 3T3 Ctrl Input GSM3518724 3T3 NNMT Input .BED file: GSE124015_NNMTvsCtrl_H3K27me3.bed.gz
Genome browser session (e.g. UCSC)	http://genome.ucsc.edu/cgi-bin/hgTracks?hgS_doOtherUser=submit&hgS_otherUserName=kmhernan&hgS_otherUserSessionName=eckert%2Dnnmt%2Dsession

Methodology

Replicates	All experiments were performed in biological triplicate (integrated replicates presented in Figure 3; individual replicates presented in Extended Data Figure 8).

Sequencing depth	H3K27-Ctrl-1 Total=71169601 Length=50 FilteredAlignments=59652136 single-end H3K27-Ctrl-2 Total=61228085 Length=50 FilteredAlignments=52016584 single-end H3K27-Ctrl-3 Total=58424516 Length=50 FilteredAlignments=49508418 single-end H3K27-NNMT-1 Total=42322971 Length=50 FilteredAlignments=35089088 single-end H3K27-NNMT-2 Total=51431612 Length=50 FilteredAlignments=42920606 single-end H3K27-NNMT-3 Total=40713864 Length=50 FilteredAlignments=33787186 single-end Ctrl-Input Total=52031719 Length=50 FilteredAlignments=40874779 single-end NNMT-Input Total=49995714 Length=50 FilteredAlignments=38411786 single-end
Antibodies	Tri-Methyl-Histone H3 (Lys27) (C36B11) Rabbit monoclonal antibody (Cell Signaling #9733); Lot number 14.
Peak calling parameters	Peak calling parameters: rgt-THOR --merge –rmdup
Data quality	Alignments were filtered by mapping quality >= 5 to remove low quality, and unmapped reads. PCR duplicates were not considered during peak detection. THOR tests for differential binding between two treatments and is able to model replicates. Differentially bound peaks were filtered by adjusted P-value < 0.05 and within 5kb of a TSS (H3K27 – 21659).
Software	Reads were preprocessed with Trimmomatic 0.36 (parameters: ILLUMINACLIP:TruSeq3-SE.fa:2:30:10 SLIDINGWINDOW:4:15 MINLEN:36) to remove low quality data and adapters before aligning to GRCm38 with BWA aln 0.7.17. Alignments were filtered and PCR duplicates were marked using sambamba 0.6.5 (parameters: -F "mapping_quality > 5"). Differential binding was performed with rgt-THOR 0.11.2 (parameters: --merge –rmdup) which can handle replicates. Here, each histone mark was run separately to compare the control and NNMT groups with both the control and NNMT “input” samples provided to remove background noise. Peaks were annotated with homer 4.8.3 and filtered to only keep peaks with an adjusted P-value < 0.05 and within 5kb of a TSS. We integrated the histone binding data with expression data by matching gene symbols of the filtered peaks (based on TSS) and differentially expressed genes (adjusted P-val < 0.05). Peak heatmaps were created by averaging the signals across the treatments and plotting different sets of genes using deepTools 3.1.0.