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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	no software used
Data analysis	Github URLs to the repositories containing source code and documentation of all the software used in this manuscript are specified in the supplementary material. In addition all the software is publicly available together with detailed description and further documented at https://depmap.sanger.ac.uk/programmes#analytics.

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 upon request. 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

Due to their large size, the raw and processed datasets presented in our manuscript are available for the editorial office and the reviewers as encrypted compressed

files at the following URLs:
Gene essentiality matrices
Link: https://cog.sanger.ac.uk/cmp/download/essentiality_matrices.zip

Raw sgRNA counts
Link: https://cog.sanger.ac.uk/cmp/download/raw_sgrnas_counts.zip
[Passwords required to decrypt these zipped folder are included in the cover letter we enclosed to the Revised version of our submission].

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Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	not applicable
Data exclusions	not applicable
Replication	not applicable
Randomization	not applicable
Blinding	not applicable

Reporting for specific materials, systems and methods

Materials & experimental systems

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

Methods

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

Antibodies

Antibodies used

WRN (8H3) Mouse mAb #4666; Cell Signalling Technologies
MLH1 mouse mAb #3515; Cell Signalling Technologies
MSH3 mouse mAb #sc-271080; Santa Cruz Biotechnology
WRN rabbit polyclonal #PA5-27319; Thermo Fisher
Anti-flag M2 rat mAb #F3165; Sigma Aldrich
B-actin rabbit mAb #4970; Cell Signalling Technologies
IRDye® 800CW Donkey-anti-Mouse Antibody #926-32212; LI-COR
IRDye® 680LT Donkey anti-Rabbit IgG (H + L) #925-68023; Li-COR
Anti-Mouse IGG HRP linked secondary antibody #NA931; GE Healthcare

Validation

Manufacturers Statement:

WRN (8H3) Mouse mAb detects endogenous levels of total WRN protein. Species Reactivity: Human, Mouse. Product Citations: Pal, D., Pertot, A., et al. (2017), 'TGF-β reduces DNA ds-break repair mechanisms to heighten genetic diversity and adaptability of CD44+/CD24- cancer cells.', Elife; Li, K., Wang, R., et al. (2010), 'Acetylation of WRN protein regulates its stability by inhibiting

ubiquitination.', PLoS One, 5 (4), pp. e10341; Shiratori, M., Sakamoto, S., et al. (1999), 'Detection by epitope-defined monoclonal antibodies of Werner DNA helicases in the nucleoplasm and their upregulation by cell transformation and immortalization.', J Cell Biol, 144 (1), pp. 1-9

MLH1 (4C9C7) Mouse mAb detects endogenous levels of total MLH1 protein. Species Reactivity: Human, Monkey. Product Citations: Yan, J., Shun, M. C., et al. (2018), 'HIV-1 Vpr Reprograms CLR4DCAF1 E3 Ubiquitin Ligase to Antagonize Exonuclease 1-Mediated Restriction of HIV-1 Infection.', MBio, 9 (5); Kashyap, T., Argueta, C., et al. (2018), 'Selinexor reduces the expression of DNA damage repair proteins and sensitizes cancer cells to DNA damaging agents.', Oncotarget, 9 (56), pp. 30773-30786

MSH3 (B-4) is a mouse monoclonal antibody raised against amino acids 61-360 of MSH3 of human origin. Species Reactivity: Human, Mouse and rat. Product citations: Germini, D.E., et al. 2016. Detection of DNA repair protein in colorectal cancer of patients up to 50 years old can increase the identification of Lynch syndrome? Tumour Biol. 37: 2757-2764.

β-Actin (13E5) Rabbit mAb #4970 detects endogenous levels of total β-actin protein. This antibody may cross-react with the γ-actin (cytoplasmic isoform). It does not cross-react with α-skeletal, α-cardiac, α-vascular smooth, or γ-enteric smooth muscle isoforms. Species Reactivity: Human, Mouse, Rat, Monkey, Bovine, Pig. CPT1A-mediated succinylation of S100A10 increases human gastric cancer invasion. In Journal of Cellular and Molecular Medicine on 1 January 2019 by Wang, C., Zhang, C., et al. Cytotoxic phenanthroline derivatives alter metallostasis and redox homeostasis in neuroblastoma cells. In Oncotarget on 20 November 2018 by Naletova, I., Satriano, C., et al. We did not perform additional validation of this antibody.

Monoclonal ANTI-FLAG® M2 antibody. Anti Flag M2 antibody is used for the detection of Flag fusion proteins.This monoclonal antibody is produced in mouse and recognizes the FLAG sequence at the N-terminus, Met N-terminus, and C-terminus. The antibody is also able to recognize FLAG at an internal site. The GOLD domain-containing protein TMED7 inhibits TLR4 signalling from the endosome upon LPS stimulation. Sarah L Doyle et. al Nature communications, 3, undefined (2012-3-20). Analysis of orthologous groups reveals archease and DDX1 as tRNA splicing factors. Johannes Popow et. al. Nature, 511(7507), undefined (2014-5-30). We used untransfected control cell lysate to demonstrate antibody specificity against FLAG tagged proteins.

Monoclonal Anti-α-Tubulin (mouse IgG1 isotype) is derived from the B-5-1-2 hybridoma produced by the fusion of mouse myeloma cells and splenocytes from an immunized mouse. Tubulin is the major building block of microtubules. Species reactivity human, Chlamydomonas, African green monkey, chicken, kangaroo rat, bovine, mouse, rat, sea urchin. Tubulin acetyltransferase aTAT1 destabilizes microtubules independently of its acetylation activity. Kalebic N, et.al. Molecular and Cellular Biology 33(6), 1114-1123, (2013). Increased expression of αTubulin is associated with poor prognosis in patients with pancreatic cancer after surgical resection Lin C, et al. Oncotarget 7(37), 60657-60657, (2016). We did not perform additional validation of the antibody.

IRDye® 800CW Donkey-anti-Mouse Antibody. The antibody was isolated by affinity chromatography using antigens coupled to agarose beads. Based on ELISA, this antibody reacts with the heavy and light chains of mouse IgG and with the light chains of mouse IgM and IgA. This antibody was tested by ELISA and/or solid-phase absorbed to ensure minimal cross-reaction with bovine, chicken, goat, guinea pig, horse, human, rabbit, and sheep serum proteins, but the antibody may cross-react with immune-globulins from other species. The conjugates has been specifically tested and qualified for western blot and in-cell western assay applications. We did not perform additional validations of this secondary antibody.

IRDye® 680LT Donkey anti-Rabbit IgG (H + L). The antibody was isolated from antisera by immunoaffinity chromatography using antigens coupled to agarose beads. Based on immunoelectrophoresis, the antibody reacts with the heavy chains on rabbit IgG and with the light chains common to most rabbit immunoglobulins. No reactivity was detected against non-immunoglobulin serum proteins. This antibody has been tested by ELISA and/or solid-phase adsorbed to ensure minimal cross-reaction with bovine, chicken, goat, guinea pig, Syrian hamster, horse, human, mouse, rat and sheep serum proteins, but the antibody may cross-react with immunoglobulins from other species. The conjugates has been specifically tested and qualified for western blot applications. We did not perform additional validations on this secondary antibody.

Anti-Mouse IGG HRP linked secondary antibody #NA931; GE Healthcare
Highly species-specific; optimized for use with our range of ECL™ Detection Reagents; recommended dilutions to minimize background.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

All cell lines (324) are part of the Cell Model Passport Collection (https://cellmodelpassports.sanger.ac.uk/).

ATCC: hTERT-RPE-1, MDA-MB-468, MDA-MB-436, MDA-MB-415, NCI-H1355, NCI-H1299, NCI-H1155, M059J, LS-411N, Hs-746T, Hs-683, HPAF-II, HCC70, HCC38, LS-513, LS-180, LS-1034, LNCaP-Clone-FGC, LN-229, KLE, KATOIII, JHU-029, NCI-H2087, NCI-H2170, NCI-H358, NCI-H2405, NCI-H1755, NCI-H1650, NCI-H1568, NCI-H2023, NCI-H1993, NCI-H1975, NCI-H1944, NCI-H1915, NCI-H1869, LS-123, T84, A375, A253, A2058, A172, 769-P, UWB1.289, Detroit562, SW837, SW48, SW620, COLO-320-HSR, AGS, FADU, ES-2, HCC1143, DBTRG-05MG, HCC1954, HCC1937, HCC1806, HCC1395, HCC1187, AU565, AsPC-1, ARH-77, CHP-212, Caov-4, SCC-9, SCC-4, RL95-2, RKO, SK-PN-DW, SK-N-SH, SK-N-FI, SK-N-DZ, SK-N-AS, SK-MES-1, SJSA-1, NCI-H650, NCI-H520, PANC-10-05, PANC-08-13, PANC-04-03, PANC-03-27, PANC-02-03, OV-90, SNU-16, SNU-1, NCI-N87, SW1088, SW1573, SW1990, SW626, TOV-21G, TOV-112D, T98G, UACC-893, SU8686, U-87-MG, SNU-C1, LNZTA3WT4, BE2-M17, C2BBe1, MC-IXC, MM1S.

Cancer Science Institute of Singapore: OVCA420, Hey, DOV13.

CLS: RCC-FG2.

DSMZ: L-363, MFM-223, MFE-296, MFE-280, LXF-289, LP-1, LOU-NH91, LCLC-97TM1, MHH-ES-1, SU-DHL-10, SCC90, SU-DHL-5, ROS-50, TC-71, SU-DHL-8, OACM5-1, OCI-AML2, PA-TU-8988T, PA-TU-8902, OPM-2, OCI-LY-19, OCI-AML3, 22RV1, CAL-72, CAL-51, CAPAN-1, CAL-27, CAL-33, CL-11, DK-MG, DAN-G, COLO-824, COLO-680N, COLO-678, 23132-87, 42-MG-BA, BHY, 8-MG-BA, KYSE-70, KYSE-520, KYSE-510, KYSE-450, KYSE-410, KYSE-270, KYSE-150, KYSE-140, JIMT-1, FLO-1, EVSA-T, ESS-1, EPLC-272H, EGI-1, EFO-27, EFO-21, GAMG, HCC-78, HCC-15.

Duke University Medical Center: D-542MG, D-502MG, D-423MG, D-247MG.

ECACC: BICR10, BxPC-3, COLO-684, PSN1, PEO4, PEO1, PE-CA-PJ15, OV-56, OE33, OE21, OAW-42, SK-GT-4, BICR22, BICR78, MOG-G-UVW, MIA-PaCa-2, COR-L23, MDST8, MDA-MB-361, KYAE-1, HuP-T4, HuP-T3, GP5d, ESO51, ESO26, DOK, HT55, COLO-205, A2780ADR, A2780cis.

IARC: EW-22, EW-16, EW-7, EW-1.

Unknown source: DiFi, HSC-39, PCI-30, PCI-4B, TMK-1,PL4.

ICLC: A2780, CAS-1, OC-314, IST-MEL1, GI-ME-N.

JCRB: MCAS, YH-13, VMRC-LCD, TYK-nu, T-T, TGW, TE-9, TE-8, TE-5, TE-10, SAS, RMG-I, RKN, RERF-LC-Sq1, RERF-GC-1B, RCM-1, SUIT-2, SNG-M, SKN-3, SK-MG-1, SF126, SCH, OVMIU, EBC-1, Ca9-22, Becker, AM-38, LU-65, LK-2, KYSE-220, KURAMOCHI, KS-1, KP-N-YN, OVISE, OSC-20, OSC-19, KP-3, NUGC-3, no-11, no-10, NMC-G1, NH-12, GB-1, KP-1N, HSC-4, HSC-3, HO-1-u-1, HEC-1, HARA, IM-95, KON, KNS-62, KNS-42, KMS-11, KINGS-1, IM-9, LoVo, LU-99A, KCLB, SNU-81, SNU-61, SNU-C5.

Kyoto Prefectural University of Medicine: KP-N-YS

Ludwig Institute for Cancer Research, Brussels branch: BB30-HNC, LB771-HNC, LB1047-RCC.

Massachusetts General Hospital: JHU-022, JHU-011.

NCI: M14, SK-MEL-2, SF539, SF295, SF268, RPMI-8226, OVCAR-8, OVCAR-5, OVCAR-4, SNB75, T47D, OVCAR-3, U251, NCI-H322M, HCC2998, DU-145, HOP-62, Hs-578-T, HT-29, NCI-H3122, NCI-H23, NCI-H226, MDA-MB-231, MCF7, KM12, IGROV-1, HCT-116, HCT-15, A549.

NCI-Navy Medical Oncology Branch: NCI-H3118.

RIKEN: PC-14, OVK-18, OCUB-M, NB69, TE-15, TE-4, TGBC11TKB, MKN28, MKN1, MDA-MB-453, GI-1, GCIY, EC-GI-10, HGC-27, LC-1-sq, KP-4, JHOS-4, JHOS-2.

St Jude Children's Research Hospital: NB7, NB6, NB5, NB17, NB13, NB10, ES8, ES5, ES4.

The University of Hong Kong: PCI-6A, PCI-38, PCI-15A.

University of Pennsylvania Health System: HCE-4.

University of Michigan: HCT116 Parental, HCT116-Ch3, HCT116-Ch5 and HCT116-Ch3+Ch5.

Baylor Charles A. Sammons Cancer Center: HCT116-Ch2.

Authentication

Each of the cell lines have been tested using a panel of 16 STRs (AmpFLSTR Identifiler KIT, ABI), which includes the 9 currently used by most of the cell line repositories (ATCC, Riken, JCRB and DSMZ).

Mycoplasma contamination

All cell lines were tested for mycoplasma contamination and only cell lines that were negative were included in the study.

Commonly misidentified lines
(See ICLAC register)

This study includes the following commonly misidentified lines:

Ca9-22 - STR matches JCRB reference (JCRB0625) & RIKEN (RCB1976).

MKN28 - noted as derivative of MKN74 in Cell Model Passports (https://cellmodelpassports.sanger.ac.uk/passports/SIDM00260); Clinical information matches MKN74.

KP-1N - known misidentification issue; Cell Model Passports data for both KP-1N & Panc-1 identical (https://cellmodelpassports.sanger.ac.uk/passports/SIDM00583).

OVMIU - known misidentification issue; Cell Model Passports data for both OVMIU and OVSAYO are identical (https://cellmodelpassports.sanger.ac.uk/passports/SIDM00465).

SK-MG-1 - STR profile matches JCRB profile which internally matches to Marcus; Cell Model Passports data for both SK-MG-1 and Marcus are identical; removed from core collection set.

Misidentified lines have been noted in Supplementary Table 1 and on the Cell Model Passport (https://cellmodelpassports.sanger.ac.uk). Mis-identification does not impact tissue of origin or genomic data used for analyses.

Animals and other organisms

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

Laboratory animals	Mus musculus, non-obese diabetic/severe combined immunodeficient (NOD-SCID), female, 5- to 6- week-old.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the fields.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cell lines were fixed with 4% formaldehyde & resuspended in PBS before running through analyzers.
Instrument	Becton Dickinson LSRFortessa flow analyser
Software	FlowJo
Cell population abundance	Cells were not sorted; only analyzed.
Gating strategy	Gates were set for each cell line based on a negative control sample that had no treatment.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.