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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.

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	Micro-CT acquisition was performed on u-CT (MI Labs) with Acquisition 7.45 software. Image reconstruction and visualization used performed with MI Labs REC-7.09. Analysis was performed with Microview version 2.5. Quantification of IHC, clonogenic growth, was performed with FIJI (ImageJ). Compusyn software (ComboSyn, Inc.) was used for determination of synergy. CBioportal and was used for enumerating mutation frequency in the indicated human genomic data sets. Oncomine was used for establishing genotype dependent associations with tumor stage, grade, frequency of metastasis, and size in the indicated human genomic data sets.
Data analysis	Statistical analyses were performed using Prism Software version 7. All statistical methods are indicated in the figure legends and in the methods. Reads from RNA-Seq were mapped using STAR aligner (v2.5.2b). FeatureCounts (v1.5.0-p1) was used to quantify alignments against the mouse genomic annotations from Gencode (vM11). Differentially expressed genes were identified with DESeq2 (v1.14.0). Single sample gene set enrichment analysis (ssGSEA) was performed at https://genepattern.broadinstitute.org/gp/ using the ssGSEAProjection module. BAM files were indexed using samtools (v.1.9) and quantified using Integrative Genomics Viewer (v.2.4.10). Sashimi plots were generated using Integrative Genomics Viewer (v.2.4.10)

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

All data generated or analysed during this study are included in this published article (and its supplementary information files) with the exception of raw RNA-Seq data associated with Extended Data Fig. 2e,f which have been deposited publicly in the Gene Expression Omnibus under accession number XXXXX

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	No statistical methods were used to predetermine sample sizes. The size of each animal cohort was determined by estimating biologically relevant effect sizes between control and treated groups and then using the minimum number of animals that could reveal statistical significance using the indicated tests of significance.
Data exclusions	In analysis of Cdkn2a reads from RNA-Seq datasets, outliers were excluded based on pre-established criteria (greater than Q3 + 1.5x interquartile range or less than Q1 - 1.5x interquartile range). No other data were excluded from analyses
Replication	Cell culture experiments described were repeated with at least 3 independent replicates and on at least two separate occasions with significant results in the same direction as those represented in the figures. Independent experiments (or experimental groups) were combined as indicated and when appropriate (e.g. when multiple cell lines with the same genotype had the same phenotype).
Randomization	All animal studies were randomized in 'Control' or 'Treated' groups. However, all animals housed within the same cage were generally placed within the same treatment group.
Blinding	For analysis of tumour grades sample identity and group identity were blinded from histopathological assessment.

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	A subset of the tumor tissue micro-arrays (TMA) are unique and not available commercially. Other TMAs were obtained from BioMax.

Antibodies

Antibodies used	Primary Antibodies used for Immunohistochemistry and Immunofluorescence: Rb [Abcam; ab181616], Lot GR3188052-5, 1:200, Commercially verified by Abcam, using Knockout Validation GFP [Cell Signaling; 2956], Lot: 4 , 1:100 Commercially verified by Cell Signaling, using HCC827 cells, untransfected or GFP-transfected. phosphorylated Mek 1/2 [Cell Signaling; cs2338], Lot: 9, 1:50 Commercially verified by Cell Signaling, using A375 cells, untreated or treated with Raf1 Kinase Inhibitor 1 phosphorylated Erk 1/2 [Cell Signaling; cs4370], Lot: 17 1:800 Commercially verified by Cell Signaling, using human lung carcinoma, untreated or λ phosphatase-treated BrdU [BD Transduction Laboratories; 347580], lot: 36576, 1:50, Commercially verified by BD Ki67 [Vector Laboratories; VP-RM04], lot: X0302, 1:1000, Commercially verified by Vector Labs (*product sheet says human but here's one of 37 citations used in mouse Zheng et al. (2008) Nature https://www.nature.com/articles/nature07443 Nkx2-1 [Abcam; ab76013], Lot: GR76790-21, 1:250, Commercially verified by Abcam, using Human lung carcinoma and thyroid carcinoma tissue Hmga2 [Biocheck; 59170AP], Lot: RN-31993, 1:300, Chiou et al. (2018) Scientific Reports, https://www.nature.com/articles/s41598-018-32159-x Foxa2 [santa cruz sc-6554] lot 1715 1:250, Spc [Millipore; AB3786], lot: 2965119, 1:200, Commercially validated by Millipore, using staining for localization of prosurfactant protein C in adult mouse lung. CC10 [Santa Cruz; sc-9772], lot:1613, 1:50 García-Sanmartín, J. et al. 2015. Histology and histopathology. phospho-Rb Ser807/811 [Cell Signaling; cs8516], Lot: 6 1:100 Commercially verified by Cell Signaling, using human colon carcinoma tissue Cdk2 [Abcam; ab32147], Lot: GR292523-18, 1:100, Commercially verified by Abcam, using Knockout Validation Cdk4 [Abcam; ab199728]. Lot: GR207212-2, 1:100 Commercially verified by Abcam, using Knockout Validation Secondary Antibodies used for Immunofluorescence: Invitrogen; Anti-rabbit-Alexa594 [A21207] Lot: 1890862, 1:200, Commercially verified by ThermoFisher Anti-mouse-Alexa647 [A31571] Lot: 423849, 1:200, Commercially verified by ThermoFisher Primary Antibodies used for Immunoblots: Total Erk 1/2 [Cell Signaling; cs4696], Lot:22, 1:1000, Commercially verified by Cell Signaling using analysis of extracts from NIH/3T3, PC12 and COS cells Cdk1 [Gift from L. Busino/Michele Pagano], 1:4000 Cdk4 [Abcam; ab199728], GR207212-2,1:1000, Commercially verified by Abcam, using Knockout Validation Cdk6 [Abcam; ab151247], no lot info: 1:1000, commercially verified by Abcam using 293T, A431, H1299, HeLa, HepG2, MOLT4 and Raji whole cell lysates; HeLa cells; Human SW480 xenograft tissue Cyclin D1 [Abcam; 16663], GR129539-3, 1:2000, Commercially verified by Abcam, using Knockout Validation Cyclin E1 [Bioss Antibodies; bs-0573R], Lot: 9B10X4, 1:3000 Cited by Lv, H., Ren, J., et al. 2012 PLoS ONE E2f1 [Abcam; ab179445], Lot Gr155150-19, 1:1000, Commercially verified by Abcam using NIH 3T3, HeLa, HepG2, T47D, Human spleen and fetal muscle lysates; E2F1-DDDDK tag transfected 293T lysate; HepG2 cells Beta-Actin [Sigma Aldrich; A2066], 102M4771, 1:10000, Commercially verified by Sigma Hsp90 [BD Transduction Laboratories; 610418]. Lot: 8179654, 1:10000, Commercially verified by BD phospho- Rb Ser780 [Cell Signaling; cs3509], unknown lot#, Antibodies that are not listed twice were used for both IHC and immunoblot.
Validation	When possible, antibodies were validated beyond the manufacturers data sheet specification by staining slides (IHC) or blots (western) with known deficiencies for expression of the antigen.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Murine cell lines were generated from primary mouse tumors and propagated using standard techniques. Human lung adenocarcinoma cell lines were obtained from ATCC or NIH Cell line repository. HEK293FT cells used for lentivirus production were obtained from Invitrogen. GreenGo cells used for titering lentivirus were obtained from Tyler Jack's Laboratory and are a derivative of NIH3T3 cells.
Authentication	Mouse cell lines were authenticated for genotype. Human and mouse lung cancer cell lines were tested for the expected, genotype-associated protein expression patterns by western blot. HEK293FT cells used for lentivirus production were validated by verifying high titter virus production was possible. NIH3T3-GreenGo cells were validated by measuring Cre-induced GFP expression.
Mycoplasma contamination	Human cells were tested negative by the cell line repository or the manufacturer. Mouse cell lines were not tested.
Commonly misidentified lines (See ICLAC register)	We have not used any commonly misidentified cell lines in this study.

Animals and other organisms

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

Laboratory animals	Species: Mus musculus

Laboratory animals	Strain and Sex : KrasLSL-G12D, p53flox, RbXTR, and Rosa26FlpO-ER strains are maintained on a mixed 129sv/Jae, C57Bl6J background (Male and Female), tumors initiated by 20 weeks of age. Xenograft recipient mice: CrTac:NCr-Foxn1nu (Males); NOD Rag1-/-;Il2rg-/- (Males), Age = 6-12 weeks.
Wild animals	N/A
Field-collected samples	N/A

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	Cells were isolated from culture dishes using trypsin-EDTA, washed 3x with PBS and fixed according to the APC BrdU Flow Kit (BD Pharmingen).
Instrument	Attune acoustic focusing cytometer
Software	FlowJo v10
Cell population abundance	Greater than 20,000 total events/cells were acquired.
Gating strategy	All events were separated based on APC and 7-AAD staining and gated as shown. BrdU negative cells were used to establish thresholds for gates. Clear separtaion between G1 and G2/M populations were established by assuming that G2/M cells would be twice as bright for 7-AAD than G1 cells.

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