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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	Flow cytometry data: data acquisition was performed on BD LSRII flow cytometer using Diva software (BD Biosciences) or Beckman Coulter CyAn ADP flow cytometer with Summit software. For RNAseq of murine tumours: sequenced using on the Illumina Hiseq2000/Hiseq2500 Machine For IHC: for individual images, cellSens Entry software (Olympus). For digital processing, slides were scanned using the Aperio ScanScope (Aperio, Vista, CA). Cell growth kinetics in vitro were analysed using the IncuCyte System (Essen BioScience). For RT-qPCR: LightCycler 480 thermocycler (Roche). For western blot: Odyssey CLx imaging system

Data analysis	Statistical analyses were performed using GraphPad Prism 7/8 (GraphPad Software Inc., La Jolla, CA). Flow cytometry data analysis was performed using FlowJo software version 9.9. For images: ImageJ software 1.48v For the mouse RNA-Seq/human TCGA analysis: R software version 3.4.2, Tophat2 (Tophat version 2.1.0 / Bowtie version 1.0.0), edgeR R package version 3.20.5, biomaRt R package, NMF R-package version 0.20.6, Ingenuity Pathway analysis version 01-06 (QIAGEN), flexgsea-r R package and R2 Genomics Analysis and Visualization Platform (http://r2.amc.nl/) were used. Principal component analysis was performed using the prcomp-function in R (version 3.4.2) For ChIP-sequencing: Easeq software was used for visualisation. For power calculations and group size determination: G*Power software (version 3.1).

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

The RNA sequencing datasets have been deposited in the Gene Expression Omnibus (GEO, NCBI) repository under accession number GSE112665.

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	Sample size was based on previous experience with the mouse models (Coffelt et al., 2015; Doornebal et al., 2013) or otherwise determined using G*Power software version 3.1. For immunohistochemistry, flow cytometry and RT-qPCR experiments, ≥3 biological replicates were used. For the intervention experiment assessing metastasis, ≥ 9 mice were used. To exclude bias towards one particular GEMM in the analyses for Figure 1, we have performed the same analyses on the average of the neutrophil levels and serum cytokine values per model. This demonstrated the same correlations between the assessed values and p53 status of the tumour, thus excluding bias towards one or several particular models.
Data exclusions	Mice with skin tumours (in the models in which Keratin-14 (K14) drives expression of Cre recombinase, skin tumours can arise, since K14 is also expressed in the skin) were excluded from the study, based on assessment of H&E stainings of the tumour. For orthotopic transplantation of cancer cell lines, samples were excluded when not properly transplanted in the mammary fat pad (e.g. in the skin adjacent to the mammary gland). For metastasis scoring in the KEP-tumour based metastasis model, mice that died because of reasons not related to metastasis were excluded (surgery-related or local recurrance of the primary tumour after surgery). In the WEP cell line-based metastasis model, samples were excluded when smaller tumours, due to their invasive behaviour, grew through the skin before the end of the experiment (1200 - 1500 mm3 tumour size), to allow all tumours sufficient time to metastasize. For RT-PCR analysis, samples were run in technical duplicate and if the difference between the Ct values of the duplo was bigger than 1 cycle, samples were discarded. Exclusion criteria were pre-determined before the experiments.
Replication	In vitro experiments were repeated in at least 2 - 3 independent experiments and showed comparable results between experiments.
Randomization	For intervention studies, mice were randomly distributed over the two treatment arms when tumours reached the size indicated in the figures. The first animal was assigned randomly in the treatment or control group, after which each subsequent animal was placed in the next group.
Blinding	Tumour measurements and post mortem analyses were performed in a blinded fashion. Assessment of IHC counts were performed by 2 or more independent researchers in a blinded fashion.

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: Biological samples derived from the mouse model are available upon reasonable request and after signing of a standard MTA.

Antibodies

Antibodies used:

For a list of used antibodies, also see Supplemental Table 1.

- Flow cytometry:
CD45 eFluor 605NC eBioscience/ThermoFisher 93-0451 1:100
CD45 BUV395 30-F11 BD Biosciences 564279 1:200
CD11b BV650 M1/70 BioLegend 101239 1:400
CD11b APC M1/70 eBioscience/ThermoFisher 17-0112-81 1:400
CD11b APC-eFluor 780 M1/70 eBioscience/ThermoFisher 47-0112-82 1:400
Ly6G APC 1A8 eBioscience/ThermoFisher 17-9668-82 1:400
Ly6G FITC 1A8 BD Biosciences 561105 1:400
Ly6C eFluor 450 HK1.4 eBioscience/ThermoFisher 48-5932-82 1:400
F4/80 APC-eFluor 780 BM8 eBioscience/ThermoFisher 47-4801-82 1:400
F4/80 APC BM8 eBioscience/ThermoFisher 17-4801-82 1:400
F4/80 FITC BM8 eBioscience/ThermoFisher 11-4801-82 1:400
cKIT PE 2B8 eBioscience/ThermoFisher 12-1171-82 1:200
cKIT PE-Cy7 2B8 eBioscience/ThermoFisher 25-1171-82 1:200
CD3 PE-Cy7 145-2C11 eBioscience/ThermoFisher 25-0031-82 1:200
CD4 APC-eFluor 780 GK1.5 eBioscience/ThermoFisher 47-0041-82 1:200
CD8 APC-eFluor 780 53-6.7 eBioscience/ThermoFisher 47-0081-82 1:400
CD8 PerCP-eFluor 710 53-6.7 eBioscience/ThermoFisher 46-0081-82 1:400
Gamma delta-TCR FITC GL3 BD Biosciences 553177 1:400
CD19 APC-eFluor 780 eBio1D3 eBioscience/ThermoFisher 47-0193-82 1:200
CD34 eFluor 450 RAM34 eBioscience/ThermoFisher 48-0341-82 1:100
CD16/32 PerCP-eFluor 710 93 eBioscience/ThermoFisher 46-0161-82 1:200
Sca-1 PE D7 eBioscience/ThermoFisher 12-5981-82 1:100
CD45R APC-eFluor 780 RA3-6B2 eBioscience/ThermoFisher 47-0452-82 1:200
CD5 APC-eFluor 780 53-7.3 eBioscience/ThermoFisher 47-0051-82 1:200
CD127 APC-eFluor 780 A7R34 eBioscience/ThermoFisher 47-1271-82 1:200
Ter119 APC-eFluor 780 TER-119 eBioscience/ThermoFisher 47-5921-82 1:200
CCR2 AF700 475301 R&D Systems FAB5538N 1:200
CCR6 BV421 29-2L17 BioLegend 129817 1:200
CD206 AF488 MR5D3 AbD Serotec/Bio-Rad MCA2235 1:200
CSF-1R PE AFS98 eBioscience/ThermoFisher 12-1152-82 1:200
CXCR4 PerCP-eFluor 710 2B11 eBioscience/ThermoFisher 46-9991-82 1:200
MHC-II APC-eFluor 780 M5/114.15.2 eBioscience/ThermoFisher 47-5321-82 1:200
CD68 BV421 Y1/82A BD Biosciences 564943 1:200
CD14 BUV737 M5E2 BD Biosciences 564444 1:400
CD206 FITC 15-2 BioLegend 321103 1:200
CD168 APC GHI/61 BioLegend 333609 1:200
HLA-DR BV650 G46-6 BD Biosciences 564231 1:200
- Western blotting:
:p53 1C12 Cell Signalling 2524 1:1000
p21 SX118 BD Biosciences 556430 1:1000
Wnt1 10C8 EMD Millipore MABD168 1:1000
Wnt6 Polyclonal (EPR9244) Abcam Ab154144 1:1000
Wnt7a Polyclonal Novus Biologicals NBP2-20913 1:1000
Porcupine Polyclonal Novus Biologicals NBP1-79322 1:1000
Non-phospho- β-catenin - 8E7 EMD Millipore 05-665 1:1000
β-actin D6A8 Cell Signalling 8457 1:5000

β-actin A1978 Sigma A2228 1:5000
GAPDH - 6C5 HyTest 5G4 1:5000
Donkey-anti-mouse IgG IRDye 680RD LiCor 926-68072 1:10000
Donkey-anti-rabbit IgG IRDye 800CW LiCor 926-32213 1:10000
- Immunohistochemistry:
Ly6G 1A8 BD Biosciences 551459 1:150
F4/80 CI:A3-1 AbD Serotec/Bio-Rad MCA497GA 1:400
CD8 4SM15 eBioscience/ThermoFisher 14-0808-82 1:2000
CD4 4SM95 eBioscience/ThermoFisher 14-9766-82 1:1000
Foxp3 FJK-16s eBioscience/ThermoFisher 14-5773-82 1:400
Cytokeratin-8 Troma-I DSHB University of Iowa TROMA-I 1:600
Goat-anti-Rat IgG - 3052-08 SouthernBiotech 3052-08 1:100
- Chromatin immunoprecipitation:
p53 5 µg 1C12 Cell Signalling 2524

Validation

Antibodies for flow cytometry were validated for target species (mouse or human) using FMO or isotype controls where necessary.
Antibodies used for IHC were validated for mouse by the Pathology facilities at the NKI.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Mouse cell lines were generated in house.
MCF-7 and HEK293T cells were provided by the Schumacher lab (Netherlands Cancer Institute).

Authentication

Mouse tumour-derived cell lines were checked for purity using genotyping.
MCF-7 cells were not authenticated, but the TP53-WT and TP53-KO cells were made from the same parental line.

Mycoplasma contamination

Cells were routinely tested for mycoplasma contamination and only negative cells were used.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified lines were used in this study.

Animals and other organisms

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

Laboratory animals

The following mouse models were used in this study: Keratin14 (K14)-cre;Cdh1F/F;Trp53F/F, K14cre;Trp53F/F, K14cre;Brca1F/F;Trp53F/F, Whey Acidic Protein (Wap)-cre;Trp53F/F, Wap-cre;Brca1F/F;Trp53F/F, Wap-cre;Brca1F/F;Trp53F/F;Col1a1invCAG-Met-IRES-Luc/+ (Wap-cre;Brca1F/F;Trp53F/F;Met), Wap-cre;Brca1F/F;Trp53F/F;Col1a1invCAG-Myc-IRES-Luc/+ (Wap-cre;Brca1F/+;Trp53F/F;Myc), Wap-cre;Brca1F/F;Trp53F/F;Col1a1invCAG-Myb2-IRES-Luc/+ (Wap-cre;Brca1F/F;Trp53F/F;Myb2), Wap-cre;Trp53F/F;Col1a1invCAG-ESR1-IRES-Luc/+ (Wap-cre;Trp53F/F;HA-ESR1), Wap-cre;Cdh1F/F;Col1a1invCAG-AktE17K-IRES-Luc/+ (Wap-cre;Cdh1F/F;AktE17K), Wap-cre;Cdh1F/F;Col1a1invCAG-Pik3caE545K-IRES-Luc/+ (Wap-cre;Cdh1F/F;Pik3caE545K), Wap-cre;Cdh1F/+;Col1a1invCAG-Fgfr2ex1-15-IRES-Luc/+ (Wap-cre;Cdh1F/+;Fgfr2ex1-15), Wap-cre;Cdh1F/F;Col1a1invCAG-Fgfr2ex1-15-IRES-Luc/+ (Wap-cre;Cdh1F/F;Fgfr2ex1-15), Wap-cre;Cdh1F/F;T2/Onc;Rosa26Lox66SBLox71/+ (Wap-cre;Cdh1F/F;SB), Wap-cre;Map3k1F/F;PtenF/F, Mouse mammary tumour virus LTR (MMTV)-NeuT40. All mouse models were on FVB/N background, except MMTV-NeuT and Wap-cre;Cdh1F/F;SB, which were on Balb/c and a mixed genetic (C57BL/6J and FVB/N) background, respectively. Mice developed tumours between 3 and 18 months of age. For tumour inoculation experiments, FVB/N mice were used of 8 - 10 weeks of age. All used mice were female. All materials were derived from one or more of the above models.

Wild animals

This study did not involve wild animals.

Field-collected samples

This study did not involve field-collected samples.

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.

The data of the ChIP-seq experiments were used to assess specific loci, and not to make statements on genome-wide chromatin binding of p53. For this reason we did not upload the files to GEO. The data is available upon request.

Files in database submission

See above.

Genome browser session
(e.g. UCSC)

https://genome.ucsc.edu/cgi-bin/hgTracks?hgS_doOtherUser=submit&hgS_otherUserName=sprekovic&hgS_otherUserSessionName=p53%20mm10

Methodology

Replicates	Two cell lines, derived from spontaneous mouse tumours, Wap-cre;Cdh1F/F;Akt-E17K and Wap-cre;Cdh1F/F;Pik3ca-E545K, were used. Of each of these lines, three cell lines from three individual mouse tumours were used as biological replicates.
Sequencing depth	Number of reads per sample were approximately between 1.0x10^7 - 2.0x10^7. Details of sequencing metric (total number of reads and number of unmapped reads) per sample are available upon request. Single-end, 65-bp reads were used.
Antibodies	p53 antibody (clone 1C12, #2524, Lot 13, Cell Signalling) was used for ChIP experiments.
Peak calling parameters	Peak calling over input control was performed using and MACS 2.0 peak caller (callpeak -t P1.bam -c InputP1.bam -f BAM -g mm -n P1tumor -B -q 0.01).
Data quality	Quality control measurements including count in peaks for all the samples, plots indicating all the called peaks and their respective fold enrichments and q-values, Venn diagrams showing the overlap of peaks are available upon request.
Software	Data was visualized using Easeq software.

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	Flow cytometry analysis was performed as previously described6. Briefly, tissues were collected in ice-cold PBS and blood was collected in tubes containing heparin. Tumours and lungs were mechanically chopped using a McIlwain tissue chopper (Mickle Laboratory Engineering). Tumours were digested for 1 hour (h) at 37°C in 3 mg/mL collagenase type A (Roche) and 25 µg/mL DNase (Sigma) in serum-free DMEM medium. Lungs were digested for 30 minutes (min) at 37°C in 100 µg/mL Liberase TM (Roche). Enzyme reactions were stopped by addition of cold DMEM/8% Fetal Calf Serum (FCS) and suspensions were dispersed through a 70 µm cell strainer. Bone marrow was collected from the tibia and femurs of both hind legs and flushed using RPMI/8% FCS through a 70 µm cell strainer. Single-cell suspensions were treated with NH4Cl erythrocyte lysis buffer. Before staining, cell suspensions were subjected to Fc receptor blocking (rat anti-mouse CD16/32, BD Biosciences) for 15 min at 4°C, except for bone marrow (to allow assessment of CD16/32 expression). Cells were stained with conjugated antibodies for 30 min at 4°C in the dark in PBS/0.5% BSA. 7AAD (1:20; eBioscience) or Fixable Viability Dye eFluor 780 (1:1000; eBioscience) was added to exclude dead cells. For intracellular cytokine staining, single-cell suspensions were stimulated in IMDM containing 8% FCS, 100 IU/mL penicillin, 100 mg/mL streptomycin, 0.5% β-mercaptoethanol, 50 ng/ml PMA, 1 mM ionomycin and Golgi-Plug (1:1,000; BD Biosciences) for 3h at 37°C. Surface antigens were stained first, followed by fixation and permeabilization using the Cytofix/ Cytoperm kit (BD Biosciences) and staining of intracellular proteins.
Instrument	All experiments were performed using a BD LSR II flow cytometer using Diva software or the Beckman Coulter CyAn ADP flow cytometer using Summit software.
Software	The software used to collect data was Diva software (BD Biosciences) and data analysis was performed using FlowJo software version 9.9.
Cell population abundance	No sorting of cells was performed.
Gating strategy	The morphologic gate (FSC/SSC) was used to included all cells and excluding debris. Doublets (using FSC-H/FSC-A and SSC-H/SSC-A) and dead cells were excluded. Immune cells were then gated based on their specific markers, indicated in relevant figures. Gating strategies are shown in Extended Data Fig. 2 and 3.

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