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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.	Sample sizes used throughout were consistent with those used in previous studies.

2. Data exclusions

Describe any data exclusions.	No exclusion of data was made.

3. Replication

Describe whether the experimental findings were reliably reproduced.	Experimental findings were reliably reproduced. Number (n) of biological and experimental replicates is stated in the figure legends. All attempts at replication were successful for the experiments described in the manuscript.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.	Mice/cell lines were allocated into groups according to genotype of interest.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.	Investigators were blinded during data collection and analysis where possible. This included enumeration of micronuclei numbers, and single RNAseq analysis upto the point of grouped analyses.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒	A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	A statement indicating how many times each experiment was replicated
☐	☒	The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒	A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒	The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒	A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒	Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	FACs data were collected using FACS DIVA 8.0.1 and analysed using FlowJo v.7.6.5 software (Tree Star). Graphical data was plotted and statistical analysis was performed using Prism (Graphpad Software Inc). Fixed and live images were captured with iVision or Micromanager and where stated in the methods, were deconvolved using Volocity software (PerkinElmer).

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	No restrictions on availability of unique materials

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	The following previously validated antibodies were used for immunofluorescence: phospho-Histone H2A.X (Ser139) (2577, Cell signalling, validated www.cellsignal.com), Lamin B1 (ab16048, Abcam, validated Robijns et al, Sci Rep, 2016.) and Retinoblastoma (554136, BD Biosciences, validated Mittnacht and weinberg, Cell, 1991). cGAS (D1D3G, Cell Signalling) was used for endogenous staining and was validated using siRNA of cGAS in human cells both by immunoblot and immunofluorescence.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	C57BL/6J Rnaseh2b-/- p53-/- and Rnaseh2b+/+ p53-/- MEFs were generated from individual E10.5 embryos. C57BL/6NTac cGas−/− MEFs and C57BL/6J (p53+/+) MEFs were generated from E13.5 embryos. U2OS cells were purchased from the European Collection of Authenticated Cell Cultures (ECACC, Cat no. 92022711).
b. Describe the method of cell line authentication used.	MEF lines were validated by PCR genotyping. U2OS cells were sourced from a well recognised cell repository.
c. Report whether the cell lines were tested for mycoplasma contamination.	All cells were mycoplasma-free, with regular checks performed using the Lonza-Mycoalert Mycoplasma Detection Kit.
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No commonly misidentified cell lines were used in this study.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.	Cell lines used: C57BL/6J Rnaseh2btm1d/+ (referred to as Rnaseh2b+/−), C57BL/6J Rnaseh2btm2-hgu-A174T (referred to as Rnaseh2bA174T/A174T)(Mackenzie, K. J. et al, EMBO, 2016), Trp53tm1tyj/J (referred to as p53+/-)(Jacks, T. et al, Current biology, 1994) and 57BL/6NTac-Mb21d1tm1a(EUCOMM)Hmgu/IcsOrl (referred to as cGas−/−)(Bridgeman, A. et al. Science, 2015).

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.	N/A