

Reporting Summary

Nature Portfolio 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 Portfolio policies, see our [Editorial Policies](#) 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                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), 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 | Zen Black v2.3 SP1 software was used to acquire imaging data.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Data analysis   | Custom R and MATLAB code used for analysis. R versions: 4.3.1; MATLAB versions: R2021b and R2023b. Other software/packages used for bioinformatics analyses: Seurat v4.4.0 and 5.0.1; HOMER v4.5 and v4.11, fgsea v1.26, TrimGalore v0.4.5 and 0.6.7, FastQC v0.11.5 and v0.12.1, cutadapt v1.15 and v4.0, bowtie2 v2.3.4.1 and v2.3.5.1, Picard v2.16, deepTools v3.3.0 and v3.5.1, clusterProfiler v4.10.0, DESeq2 v1.42, featureCounts v1.6.1. Additional software/plugins used for image analysis: CellProfiler v4.2.5, TrackMate v7.11.1, Fiji v2.14, Spectronaut v18.5. All code used for analysis and plotting is available at <a href="https://github.com/mvhunter1/Hunter_2024">github.org/mvhunter1/Hunter_2024</a> . |

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Raw and processed RNA-seq, ChIP-seq, and ATAC-seq data generated in this study have been deposited to the Gene Expression Omnibus (GEO) under accession

number GSE253803. Human melanoma scRNA-seq data was obtained from GEO accession number GSE115978. The TurboID proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD060265. All other relevant data supporting the key findings of this study are available within the article and its Supplementary Information files or from the corresponding authors upon request.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

|                                                                    |                                            |
|--------------------------------------------------------------------|--------------------------------------------|
| Reporting on sex and gender                                        | No human data was generated in this study. |
| Reporting on race, ethnicity, or other socially relevant groupings | No human data was generated in this study. |
| Population characteristics                                         | No human data was generated in this study. |
| Recruitment                                                        | No human data was generated in this study. |
| Ethics oversight                                                   | No human data was generated in this study. |

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

## 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](https://www.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     | While no formal power calculation was performed, in all cases we aimed for the sample size to be as large as possible within the technical confines of the experiment and availability of animals.                                                    |
| Data exclusions | No data was excluded from the analysis other than quality control filtering.                                                                                                                                                                          |
| Replication     | RNA-seq and ATAC-seq data has not been replicated due to technical/cost limitations, however 3 technical replicates were performed for each condition in all experiments. For all other experiments, at least n=3 biological replicates were assayed. |
| Randomization   | No randomization was done as in all cases there was only one experimental group.                                                                                                                                                                      |
| Blinding        | No blinding was done as in all cases there was only one experimental group.                                                                                                                                                                           |

## 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                                           |
|-------------------------------------|-----------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines       |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                                 |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> ChIP-seq    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

|                 |                                                                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibodies used | Primary antibodies used were: rabbit anti-HMGB2 (abcam, ab124670 - for HMGB2 IF), rabbit anti-HMGB2 (Millipore Sigma, HPA053314 - for HMGB2 Western blot), rabbit anti-HMGB1 (abcam, ab18256), rabbit anti-HMGA1 (abcam, ab129153), mouse anti-α- |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

tubulin (Millipore Sigma, CP06), chick anti- $\beta$ -tubulin (Novus Biologicals, NB100-1612), mouse anti-acetylated tubulin (Millipore Sigma, 6793), rabbit anti-acetylated tubulin (Cell Signaling Technologies, CST 5335), rat anti-tyrosinated tubulin (Millipore Sigma, MAB1864-I), mouse anti-polyglutamylated tubulin (Millipore Sigma, T9822), mouse anti-GFP (abcam, ab1218), rabbit anti-H3Ac (Millipore Sigma, 06-599), mouse anti-Annexin V (Santa Cruz, sc-74438), rabbit anti-cleaved caspase-3 (CST 9661), rabbit anti-cleaved PARP (CST 5625), rabbit anti-YAP (CST 14074), mouse anti-Twist (abcam 50887), rabbit anti-Snail (CST 3879), rabbit anti-SMAD3 (abcam ab40854), rabbit anti-SYNE2 (abcam ab204308), rabbit anti-S100a6 (abcam ab204028), mouse anti-BRAF[V600E] (abcam ab228461), rabbit anti-acetylated tubulin (abcam ab179484), rabbit anti-HMGB2 (abcam ab67282 - for ChIP-seq only), rabbit anti-V5 (abcam ab9116), rabbit anti-H3K4me3 (Epiccypher 13-0041). All primary antibodies were used at 1:200.

## Validation

All antibodies are commonly used in our lab and have been validated by the suppliers.

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

## Cell line source(s)

A375, SK-MEL-5, Panc-1, MiA-PaCa-2, HTB-4, HTB-9 and HEK 293T cells were obtained from ATCC.

## Authentication

A375, SK-MEL-5, Panc-1, MiA-PaCa-2, HTB-4, HTB-9 and HEK 293T cells were authenticated using Short Tandem Repeat profiling at ATCC.

## Mycoplasma contamination

Cells were routinely tested to be free of mycoplasma.

Commonly misidentified lines  
(See [ICLAC](#) register)

None of the cell lines used in this study are commonly misidentified.

## Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

## Laboratory animals

Zebrafish (*Danio rerio*) - Genotype: casper; mitfa-BRAV600E; p53-/-; mitfa-/- . Age: 6-12 months. Mouse (*Mus musculus*): athymic, 6-8 week old females.

## Wild animals

No wild animals were used in the study.

## Reporting on sex

Sex was not a variable in the zebrafish studies and thus was not controlled for. Female mice were used for mouse experiments.

## Field-collected samples

No field-collected samples were used in the study.

## Ethics oversight

All animal procedures were approved by the Memorial Sloan Kettering Cancer Center Institutional Animal Care and Use Committee (protocol #12-05-008).

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

## Plants

## Seed stocks

No plant material was used in the study.

## Novel plant genotypes

No plant material was used in the study.

## Authentication

No plant material was used in the study.

## 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 ChIP data has been added to our existing GEO repository GSE253803.

## Files in database submission

FASTQ and bed files.

Genome browser session  
(e.g. [UCSC](#))

No longer applicable.

## Methodology

|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Replicates              | 2 replicates were performed for each experimental group and negative control.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Sequencing depth        | The libraries were sequenced on an Illumina NovaSeq 6000, with ~30-40 million 100 bp paired-end reads per library.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Antibodies              | anti-HMGB2: abcam 67282<br>anti-V5: abcam 9116<br>rabbit anti-H3K4me3: Epicypher 13-0041                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Peak calling parameters | To ascertain enriched regions, MACS2 was used with a p-value setting of 0.001 and run against a matched control for each condition. A peak atlas was created by combining the superset of all peaks using the 'merge' function in the BEDTools suite v2.29.2. Read density profiles were created using deepTools 'bamCoverage' v3.3.0, normalized to 10 million uniquely mapped reads and with read pileups extended to 200 bp. Version 1.6.1 of featureCounts was used to build a raw counts matrix and DESeq2 was used to calculate differential enrichment for all pairwise contrasts for experiments with replicates. |
| Data quality            | For single sample data, MACS2 was run by swapping bams of different conditions to find differential regions. Peak-gene associations were created by assigning all intragenic peaks to that gene, while intergenic peaks were assigned using linear genomic distance to transcription start site.                                                                                                                                                                                                                                                                                                                          |
| Software                | TrimGalore (v 0.4.5), cutadapt (v 1.15), FastQC (v 0.11.5), bowtie2 (v 2.3.4.1), PicardTools (v 2.16.0), MACS2 (v 2.2.9.1), BEDTools (v 2.29.2), deepTools (v 3.3.0), featureCounts (v 1.6.1), HOMER (v 4.5).                                                                                                                                                                                                                                                                                                                                                                                                             |