nature portfolio

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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	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on 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 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)
☒	☐	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

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	no software was used
Data analysis	no software was used

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

MS data are available at PRIDE EBI-EMBL database with identifier PXD008932.
ChIP-seq data for BRD4 is deposited at GEO (GSE196461)
Token code: obepawuefrodlit

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data where this information has been collected, and consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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

Life sciences study design

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

Sample size	A minimum of two biological replicates have been perform in all in vitro experiments including 3 technical replicates. For the in vivo experiments we included the minimum number of animals to obtain significant results.
Data exclusions	There is no data exclusion in none of the experiments described in the manuscript-
Replication	All results included in the manuscript were totally reproducible.
Randomization	In all in vivo experiments, animals were randomly ascribed to the different experimental groups
Blinding	Blinding was not relevant since all measurements are objective

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
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used

BRD4 Rabbit 1:1000 Abcam ab128874
IKKα Rabbit 1:1000 Cell signaling #2682s
p-IKKα(16A6) Rabbit 1:1000 Cell signaling #2697
H4 Rabbit 1:1000 Abcam ab-10158
H4k5Ac Rabbit 1.1000 Active Motif 39169
Tubulin Mouse 1:10000 Sigma T6074
Lamin B Goat 1:1000 Santa Cruz sc-6216
STAT3 Rabbit 1:1000 Cell signaling #12640s
p-STAT3(S727) Mouse 1:1000 Cell signaling sc-71792
p-STAT3(Y705) Rabbit 1:1000 Cell signaling #9145s
cCAS3 Rabbit 1:1000 Cell signaling #9661s
PARP1 Mouse 1:1000 From Dr. Yélamos (IMIM)
p-ERK1/2 Rabbit 1:1000 Cell signaling #9102s
ERK1/2 Mouse 1:1000 Milipore 13-6200
BRD4 ChIP Rabbit 2µg/IP Diagenode C15410337

Validation

All are commertially validated antibodies

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

CRC cell lines HCT116 (KRAS mutated), Caco2 (KRAS and BRAF WT) and HT29 (BRAF mutated) were obtained from the American Type Culture Collection (ATCC, USA). WT and IKKα KO MEFs were kindly provided by Michael Karin (UCSD, La Jolla) and HeLa S3 cells were kindly provided by Dr. Shannon Lauberth, UCSD

Authentication

Cell lines were obtained from ATCC or provided by trusted researchers

Mycoplasma contamination

All cell lines used were tested negative for mycoplasm contamination

Commonly misidentified lines
(See ICLAC register)

Name any commonly misidentified cell lines used in the study and provide a rationale for their use.

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

In vivo experiments were performed using athymic Nude Mice.

Wild animals

Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.

Reporting on sex

We did not consider the possibility that experimental differences were associated with gender in this tumor type.

Field-collected samples

For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.

Ethics oversight

Animal work was conducted according to the guidelines from the Animal Care Committee at the Generalitat de Catalunya. The Committee for Animal Experimentation at the Institute of Biomedical Research of Bellvitge (Barcelona) approved these studies. In all the experiment, animals were sacrificed at 21 days of treatment or at the humanitarian endpoint in the case of the long-term survival experiment (the criterium used were evidences of animal distress or presence of tumors biger than 3000 mm3, aprox)

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

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.

ChIP-seq data for BRD4 is deposited at GEO (GSE196461)
Token code: obepawuefrodlit

Files in database submission	*Provide a list of all files available in the database submission.*
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	A minimum of two independent (biological) replicates were performed for each experimental condition
Sequencing depth	Raw single-end 50-bp sequences were filtered by quality (Q >30) and length (length > 20 bp) with Trim Galore. Total filtered sequences, which ranged between 32 and 55 million per sample, were aligned against the reference genome (mm10 release) with Bowtie2.
Antibodies	BRD4 Rabbit 1:1000 Abcam ab128874
Peak calling parameters	Peaks from biological replicates were merged using bedtools. Peaks that were detected in the input samples were filtered out, as well as the mouse black regions downloaded from the ENCODE portal (ENCFF547MET) (https://www.encodeproject.org/). Peak annotation was performed with ChIPseeker and Annotatr packages
Data quality	MACS2 software was run for each replicate considering unique alignments (q-value < 0.1)
Software	Peak annotation was performed with ChIPseeker and Annotatr packages; and functional enrichment analysis with enrichR, using the latest version of GO annotations. Peaks heatmaps and multiple coverage correlation across bigwig files were performed with Deeptools.