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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	cutadapt 1.7.1, STAR 2.4.0, bwa 0.7.12, samtools 1.1
Data analysis	R 3.1.3, Bioconductor 3.0, CLIPanalyze (https://bitbucket.org/leslielab/clipanalyze)

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

Accession codes:
GSE116561: Superset of this study. RNA-Seq dataset, GSE116348; Differential iCLIP dataset, GSE116466 ; PolyA-Seq dataset, GSE116468 .

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	In the experiments of this study, more than three biologically independent samples were used in order to statistically test uncovered effects. The sample sizes were chosen in order to detect certain level of effect size of the related measurements. Sample sizes were indicated in Figure legends and Methods
Data exclusions	No data were excluded. Raw reads from high-throughput sequencing of iCLIP dataset were pre-processed to remove PCR duplicates.
Replication	Experiments were performed on more than three biologically independent samples. All attempts of replication were successful.
Randomization	Experiments were performed using equal number of wild-type and miR-155-deficient primary immune cells. Covariates were controlled by using B6 mice (wild-type and miR-155-deficient) of the same genetic background.
Blinding	Blinding is not used in this study. Instead, appropriate controls were included to achieve unbiased conclusions.

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

Antibodies

Antibodies used	Antibody against Argonaute 2 protein was generated in lab as described in Methods. Aicda-specific antibody is a gift from J. Chaudhuri (MSKCC). Other antibodies are commercially available, including Inpp5d (BioLegend, #656601, Lot:B208319), Spi1 (Cell Signaling, #2258S, Lot:3), Tab2 (LifeSpan, #LS-C498046, Lot:107509), Jarid2 (Cell Signaling, #13594T, Lot:1), Uqcrfs1 (LifeSpan, #LS-C185466, Lot:123920), Hif1a (SIGMA, #ABE279, Lot:3022947), and Actb (Sigma, #A3853, Lot:048M4754V) antibodies.
Validation	Primary citation for Argonaute 2 antibody: Loeb, G.B. et al. Transcriptome-wide miR-155 binding map reveals widespread noncanonical microRNA targeting. Molecular Cell 48, 760-770 (2012). Citation for Aicda antibody: Yen W.F. et al. BRCT-domain protein BRIT1 influences class switch recombination. PNAS 114 (31), 8354-59 (2017). Commercially available antibodies are validated products (see vendors' website for details).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Mouse B16 melanoma cell line (ATCC)
Authentication	This cell line was purchased from ATCC, authenticated by the vendor, and has been carefully maintained.
Mycoplasma contamination	B16 cell line tested negative for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	Male and female C57BL/6J mice (wild-type and miR-155-deficient) were purchased from The Jackson Laboratory with age ranging from 8-week to 12-week old. Mice of both sexes with age of ~2-6 months were used in the study. Usage of mice followed the guidelines of Animal Care Committee of MSKCC.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the filed.