nature portfolio

Corresponding author(s): Ryan A. Flynn

Last updated by author(s): Nov 11, 2025

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	Data collection was performed in LAS X v3.5.2 18963, Nikon Denoise.ai software v3.6, Li-COR Image Studio software v6.1, Zeiss Zen v2.1, BD Biosciences LSRFortessa v3, and MO. Control v1.6.1.
Data analysis	Statistical analysis was performed in Microsoft 365 Excel v2507, GraphPad PRISM v10, R v4.3.3, DESeq2 v1.42.1, ImageJ 1.53t v1.8.0_322 (64-bit), CFX Masetro Software v2.3, FlowJo (v10, BD), and Geneious Primer v2019.1.1.

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 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

All data are presented in the main text or Supplementary Materials.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	No statistical methods were used to determine the sample size. All sample sizes were determined based on optimization experiments, previous experience, and published literature. For imaging sample sizes, we referenced Jonathan et al., Cell 2025 PMID: 40020667; For glycoRNA sample sizes, we referenced Yixuan et al., Cell 2024 PMID: 39173631; for flow cytometry sample sizes, we referenced Benson et al., Nat Biotechnol 2025 PMID: 40269321; for mouse experiments, we referenced Andew et al., Elife 2022 PMID: 36197001; for zebra fish experiments, we used at least 30 embryos per condition in each repeat.
Data exclusions	No data was excluded in this study.
Replication	All experiments were performed at least two or three times as independent experiments and were successfully replicated. This is indicated in the figure legends for each experiments.
Randomization	No randomization was performed in this study. Sex- and age-matched mice were assigned to different experimental groups.
Blinding	No blinding was performed in this study. All results and analysis were based on objective quantification of the data collected through automated instrumentation.

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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

All antibodies used in this study are commercially available and used extensively. These antibodies and their clones names/CAT# are included in the methods section of this manuscript.
anti-ds-RNA 9D5 (2.5 µg/mL for IF, Ab00458-23.0-BT, Ab00458-2.0, Absolute Antibody)
10E4 (1 µg/mL for IF, 360255-S, F58-10E4, Amsbio)
3G10 (1 µg/mL for IF, 360260-S, F69-3G10, Amsbio)
DDX21 (2.5 µg/mL for IF, NB100-1718, Novus Biological)
hRNP-U (2.5 µg/mL for IF, 14599-1-AP, Proteintech)
HS2ST1 (1:1000 dilution for WB, sc-376530, G-10, Santa Cruz)
HS6ST1 (1:1000 dilution for WB, sc-398231, C-9, Santa Cruz)
NDST1 (1:1000 dilution for WB, sc-100790, FF-2, Santa Cruz)
EXT2 (1:1000 dilution for WB, sc-514092, A-2, Santa Cruz)
EXT1 (1:1000 dilution for WB, sc-515144, A-7, Santa Cruz)
phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (1:500 dilution for WB, 4370S, D13.14.4E, Cell Signaling Technology)
p44/42 MAPK (Erk1/2) (1:500 dilution for WB, 4696S, L34F12, Cell Signaling technology)
GAPDH (1:1000 dilution for WB, sc-47724, 0411, Santa Cruz)
VEGFA (1 µg/mL for IF, 1:1000 dilution for WB, 2 µg/mL for IP, 66828-1-lg, 2E2H9, Proteintech)
VEGFA (1:1000 dilution for WB, AF293-NA, R&D system)
WNT3A (1:500 dilution for WB, 26744-1-AP, Proteintech)
VEGFR2 (2.5 µg/mL for IF, AF357-SP, R&D system)
PECAM-1 (1:300 dilution for IF, 3528, 89C2, Cell Signaling Technology)
ERG (1:500 dilution for IF, ab92513, EPR3864, Abcam)
IB4 (1:500 dilution for IF, 132450, Invitrogen)
mVEGF164 (1:500 dilution for IF, AF-493-NA, R&D Systems)
GFP (1:1000 dilution for WB, 1:200 dilution for IF, A11122, Invitrogen)
HA (1:1000 dilution for WB, sc-7392, Santa Cruz)

Validation

All antibodies are commercially available and validated by the manufacturer. We selected the antibodies used in this study due to the validation provided by each manufacturer for their use in immunoblotting and immunoflurescence labeling. 9D5, anti-DDX21, and anti-hRNP-U, used for the key csRNP live cell labeling in this paper, have been validated in our previous work (Jonathan et al., Cell 2025 PMID: 40020667).
9D5 validated by the manufacturer with the notes - species reactivity human, applications immunofluorescence
10E4 validated by the manufacturer with the notes - species reactivity human, applications flow cytometric analysis, Immunohistochemistry, ELISA
3G10 validated by the manufacturer with the notes - species reactivity human, applications flow cytometric analysis, Immunohistochemistry, ELISA
DDX21 validated by the manufacturer with the notes - species reactivity human, applications immunofluorescence, western blot
hRNP-U validated by the manufacturer with the notes - species reactivity human, applications immunofluorescence, western blot
HS2ST1 validated by the manufacturer with the notes - species reactivity human, applications western blot
HS6ST1 validated by the manufacturer with the notes - species reactivity human, applications western blot
NDST1 validated by the manufacturer with the notes - species reactivity human, applications western blot
EXT2 validated by the manufacturer with the notes - species reactivity human, applications western blot
EXT1 validated by the manufacturer with the notes - species reactivity human, applications western blot
phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) validated by the manufacturer with the notes - species reactivity human, applications western blot
p44/42 MAPK (Erk1/2) validated by the manufacturer with the notes - species reactivity human, applications western blot
GAPDH validated by the manufacturer with the notes - species reactivity human, applications western blot
VEGFA validated by the manufacturer with the notes - species reactivity human, applications western blot, immunoprecipitation, immunofluorescence
WNT3A validated by the manufacturer with the notes - species reactivity human, applications western blot
VEGFR2 validated by the manufacturer with the notes - species reactivity human, applications western blot, immunoprecipitation
PECAM1, ERG, IB4 validated by PMID: 36197001
mVEGF164 validated by the manufacturer with the notes - species reactivity mouse, applications immunohistochemistry
GFP and HA validated by the manufacturer with the notes - species reactivity human, applications western blot

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

HEK293, HUVEC, U2OS and keratinocyte cell lines were obtained from ATCC. MOLM-13 cell line was obtained from Sanger Intitute Cancer Cell Collection.

Authentication

Cell lines have been checked for morphology by the supplier. No further validation was performed in lab.

Mycoplasma contamination

Cell lines are routinely tested for Mycoplasma in the lab.

Commonly misidentified lines
(See ICLAC register)

No misidentified cell lines were used.

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	C57BL/6J mice are purchased directly from the Jackson laboratory and P6 pups were used in experiments. Zebrafih (Danio rerio) AB/Tübingen (TAB5/14) genetic background are used. Embryos collected for injection 30 minutes after combining the males and females and were harvested at 24 hpf
Wild animals	The study did not involve wild animals.
Reporting on sex	Findings are applicable to male and female mice. Sex is not a relevant variable in zebrafish embryos, as sex determination occurs at developmental stages beyond those analyzed in this study.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The animal studies were approved by the Boston Children's Hospital Institutional Animal Care and Use Committee (IACUC). Zebrafish lines were housed in AAALAC-approved facilities and maintained according to protocols approved by the Massachusetts Institute of Technology Committee on Animal Care.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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	MOLM-13 cells were directly counted. U2OS cells were gently lifted with Accutase (Sigma-Aldrich) for 3 minutes at 37°C, quenched with growth media, and then counted. For each condition, 50,000 cells were used. For antibody staining, MOLM-13 cells were blocked as per the manufacturer's protocol with Human TruStain FcX in FACS buffer for 15 minutes on ice. 1 µg/mL of recombinant human IgG1 Fc, Siglec-7 Fc chimera protein, and Siglec-11 Fc chimera protein were precomplexed with 0.5 µg/mL of donkey anti-human IgG AF647 secondary antibody in FACS buffer for 45 minutes on ice. Precomplexed antibodies were then added to bind cells on ice for 45 minutes. For live cell periodate labeling of cell surface glycans, cells were washed twice with cold PBS + Ca + Mg and then incubated at 4°C in cold PBS + 1 mM sodium periodate for 5 minutes at 1 million cells per mL. Cells were then quenched with 1 mM glycerol added to the PBS, and then cells were washed twice with cold PBS. Cells were then incubated at 4°C in cold FACS buffer + 25 µM aminooxy-biotin (Cayman Chemical) + 10 mM aniline for 30 minutes at 1 million cells per mL. Cells were mixed via pipetting halfway through the incubation. Cells were then washed once with cold 1x PBS and blocked as per the manufacturer's protocol with Human TruStain FcX in FACS buffer for 15 minutes on ice. Cells were then stained for 30 minutes on ice with Strep-AF647 at 1 µg/mL. After staining, all cells were spun at 4°C for 3 minutes at 400x g and supernatant was discarded. Cells were washed once with 150 µL of FACS buffer, spun under the same conditions, and finally resuspended in FACS buffer containing 0.1 µg/mL DAPI.
Instrument	BD Biosciences LSRFortessa 3
Software	FlowJo Software

Cell population abundance	at least 30,000 events collected per samples
Gating strategy	For Extended Figure 1D, the gating strategy was as follows: FSC-A/SSC-A of all events. The gate captures the major density of events so that events with very low or very high FSC and SSC are eliminated. Single cell FSC-A and FSC-H gating on singlets to exclude doublets. Live cell gating (with DAPI viability marker) is placed on live cells (DAPI negative) to exclude dead cells.

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