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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	The code used for sequencing data collection can be found on github: https://github.com/tdido. The FACS data collection was done by: BD FACSDiva version 6.1.3.
Data analysis	The code used for analyzing the COMRADES data can be found on github: https://github.com/gkudla/hyb. Additional analysis softwares used to analyze the data: hyb package version: Nov 20 2013; Java Treeview version: 1.1.6r2; R-chie version: R4RNA 0.1.4; GraphPad Prism version 7.

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

All sequencing data sets have been deposited in ArrayExpress under accession number: E-MTAB-6427

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	COMRADES experiment was independently performed 3 times in different days, thus meeting the standards of next-generation sequencing studies.
Data exclusions	No data were excluded from the analyses. all attempts at replication were successful.
Replication	All experiments were repeated at least 3 times
Randomization	The data was not randomized since the experiments did not include allocation of samples to groups
Blinding	Data was not blinded, since the crosslinked and control libraries undergo different order of processing steps

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	Flavivirus group antigen antibody against the NS1 envelope protein, Novus biologicals, D1-4G2-4-15 (4G2), lot: T1650A04, diluted 1:100. Goat anti-Mouse IgG secondary antibody, Alexa Fluor 488, Eugene, A11029, lot: 1550911, dilution: 1:1,000.
Validation	Flavivirus group antigen antibody against NS1 was validated by (Chavali PL et al, Science. 2017 Jul 7;357(6346):83-88). Secondary antibody is commonly used and established antibody. Both Flavivirus group antigen antibody against NS1 and the secondary antibody were validated by the authors by positive and negative staining of cells inoculated / not inoculated with Zika virus respectively.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	JEG-3 and Hela cells were purchased from ATCC; VERO cells were purchased from Sigma
Authentication	Cell lines were purchased from commercial providers and were not authenticated by the authors
Mycoplasma contamination	All cell lines were tested negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

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	Jeg-3 cells pre-inoculated with ZIKV were stained according to BD Cytofix/Cytoperm kit protocol, using a primary monoclonal antibody: D1-4G2-4-15 (4G2), and a secondary antibody Alexa Fluor 488 (A-11029, Thermo Fisher Scientific).
Instrument	LSRFortessa, BD Biosciences
Software	Data collection was done using BD FACSDiva. Data analysis was done using Flowjo
Cell population abundance	Cell population abundance is shown in supplementary Fig. 9h. Initial gating based on FCS-SSC values resulted in collecting 88 +/-4% of the entire cell population
Gating strategy	Gating strategy is shown in supplementary Fig. 9h-j. ZIKV virus positive cells are defined as ZIKV positive gating divided by all cells gating

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