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
- 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: Microsoft Excel (v16.5) for database management.
- Data analysis: Data were analyzed using Microsoft Excel and Graphpad Prism 8.3. Statistical analyses were done using Graphpad Prism 8.3.

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

Source data file is provided with this paper. Other data that support the findings of this study are available from the corresponding authors (K.S. and R.W.S.) upon reasonable request. Genbank accession codes are indicated in the Methods section and in the data availability section.
Human research participants

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

Reporting on sex and gender

| N/A |
|-----|

Population characteristics

| N/A |
|-----|

Recruitment

| N/A |
|-----|

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

No sample-size calculations were performed. >5 animals were sufficient to detect effect previously (Sliepen Nat Comm 2019).

Data exclusions

No data was excluded from analyses, except for a few outliers in the data underlying Fig 3f. (see source data for Fig. 3f).

Replication

Experiments were repeated and/or performed duplicate or triplicate. Repeats showed similar results.

Randomization

Rabbits were randomly distributed among the groups.

Blinding

Experiments were analyzed by unblinded investigators due for pragmatic reasons.

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**
AR4A, AT1209, AT1211, AR3C, AP33, AR3B, HC84.26 were produced in the lab. CBH-4B, 4D, 4G were provided by Steven Foung (Stanford University, USA). All other antibodies were produced using transient transfection using plasmids expressing the antibody heavy and light chains. Goat-anti-human IgG Jackson Immunoresearch (cat# 109-035-170).

**Validation**
AR4A, AT1209, AT1211, AR3C, AP33, AR3B, HC84.26 antibody plasmids were validated by sequencing.

**Eukaryotic cell lines**

**Policy information about** cell lines and Sex and Gender in Research

**Cell line source(s)**
HEK293 cell lines were obtained from Thermo Fisher or ATCC as described in the methods. Ramos B cells were obtained from dr. Li Wu and dr. Vineet N. KewalRamani via the NIH AIDS Reagent Program.

**Authentication**
None of the cell lines were validated.

**Mycoplasma contamination**
All cell lines were tested negative for mycoplasma.

**Commonly misidentified lines**
No commonly misidentified cell lines were used.

(See ICLAC register)

**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**
New Zealand White rabbits, female, start age/weight; 2.5-3kg

**Wild animals**
No wild animals were used in this study

**Reporting on sex**
All rabbits were female

**Field-collected samples**
No field collected samples were used in this study.

**Ethics oversight**
All immunization procedures complied with all relevant ethical regulations and protocols of the Covance Institutional Animal Care and Use Committee (IACUC, study C0096-19) and the Pocono Institutional Animal Care and Use Committee (IACUC).

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

**Flow Cytometry**

**Plots**

- 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**
lgM-negative Ramos B cell lines were previously transfused with AR3C as described in the methods. Cells were then sorted for GFP+ IgG + lgM-. Cells were frozen until use.

**Instrument**
LSR Fortessa (BD Biosciences)

**Software**
FlowJo 8.1. Data visualization with Graphpad Prism 8.3

**Cell population abundance**
Single cell line was used (so 100%).

**Gating strategy**
Cell line expressing AR3C was sorted was as indicated in Figure S11

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