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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	No software was used for data collection.
Data analysis	PRISM 6.0 (GraphPad Software) and FlowJo (Tree Star Inc.) were used for data analyses.

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 the subject-level data that support the findings in this study are available from Dr. Weyand (Corresponding author) upon reasonable request.

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	The sample size was calculated to ensure 80% power for detecting a group difference of 2.0 standard deviations.
Data exclusions	All the available samples and animals were included in the analyses. No data was excluded.
Replication	Appropriate sample size, duplicative experiments, and a combination of flow cytometry with western blotting for protein detection, were applied for verifying the data reproducibility. All attempts were successful.
Randomization	N/A for in vitro studies. Experimental mice were randomly assigned into control and treatment groups.
Blinding	As a rule, the investigator measuring the sample was blinded to the group assignment to ensure the objectivity of the measurement.

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	All the materials are available from the commercial sources. The AMPK activator A769662 was purchased from APExBIO (Houston, TX). The AMPK activator Metformin, the mTORC1 inhibitor Rapamycin and the metabolite Succinate were obtained from Sigma-Aldrich (St. Louis, MO). The fatty acid synthase (FAS) inhibitor C75 and the AMPK inhibitor Compound C were purchased from Cayman Chemical (Ann Arbor, MI). The PFKFB3 inhibitor 3PO was from EMD Millipore (Burlington, MA). The human NMT1 cDNA ORF Clone and the appropriate control were purchased from Origene (Rockville, MD). Human NMT1 siRNA and control siRNA, human AMPKα siRNA and control siRNA, the pyruvate kinase M2 (PKM2) activator ML265, the PKM2 inhibitor Shikonin, the metabolites Pyruvate and Malic acid, were bought from Santa Cruz Biotechnology (Santa Cruz, CA). Nucleofection kits from Lonza (Walkersville, MD) were used for cell transfections. Lysosomes were isolated with the Lysosome enrichment kit for cultured cells (Thermo Fisher Scientific, Waltham, MA). Concentrations of cellular free fatty acids were determined with Free Fatty Acid Quantification Assay Kits (Abcam, Burlingame, CA).

Antibodies

Antibodies used	For flow cytometry, FITC or PE-Cy7 anti-human CD4 antibody (BioLegend, Clone RPA-T4, 1:50), APC anti-human CD8 antibody (BioLegend, Clone SK1, 1:50), PE-Cy7 anti-human CD19 antibody (BioLegend, Clone HIB19, 1:50), APC anti-human CD14 antibody (BD, Clone M5E2, 1:50), APC-Cy7 anti-human CD45RA antibody (BioLegend, Clone HI100, 1:50), APC anti-human CD28 antibody (BioLegend, Clone CD28.2, 1:50), PE anti-human CD95 antibody (BioLegend, Clone DX2, 1:50), PE or PE-Cy7 anti-human T-bet antibody (eBioscience, Clone eBio4B10, 1:50), APC anti-human RORγt antibody (eBioscience, Clone AFKJS-9, 1:50), PE anti-human FoxP3 antibody (BioLegend, Clone 259D, 1:50), Phospho-AMPK alpha-1,2 (Thr172) antibody (Thermo Fisher Scientific, 44-1150G, 1:100) plus Alexa Fluor® 488 anti-rabbit IgG (Thermo Fisher Scientific, A-11034, 1:200), PE anti-human phospho-S6 protein antibody (Cell Signaling, Clone D57.2.2E, 1:50), rabbit anti-human NMT1 antibody (Abcam, ab84666, 1:100) plus Alexa Fluor® 488 anti-rabbit IgG (Thermo Fisher Scientific, A-11034, 1:200), mouse anti-human NMT2 antibody (Novus Biologicals,

NBP2-01676, 1:100) plus Alexa Fluor® 594 anti-mouse IgG (Thermo Fisher Scientific, A-11032, 1:200), BODIPY™ 493/503 (Thermo Fisher Scientific, D3922, 3 μM), PerCP-Cy5.5 anti-human IFN-γ antibody (BioLegend, Clone 4S.B3, 1:50) plus APC anti-human IL-17 antibody (eBioscience, Clone eBio64DEC17, 1:50). For western blot, anti-NMT1 antibody (Abcam, ab84666, 1:1000), anti-phospho-AMPKα (Thr172) (Cell Signaling Technology, 40H9, 1:1000), anti-AMPKα-1, 2 antibody (Abcam, 34.2, 1:1000), anti-AMPKβ-1,2 antibody (Thermo Fisher Scientific, E.427.6, 1:1000), anti-AMPKγ-1 antibody (Labome, Y308, 1:1000), anti-mTOR (7C10) antibody (Cell Signaling Technology, 2983S, 1:1000), anti-phospho-p70 S6 Kinase (Thr389) antibody (Cell Signaling Technology, 9205S, 1:1000), anti-p70 S6 Kinase antibody (Santa Cruz Biotechnology, B-5, 1:500), anti-phospho-S6 ribosomal protein (Ser235/236) antibody (Santa Cruz Biotechnology, 50.Ser 235/236, 1:500), anti-S6 ribosomal protein antibody (Santa Cruz Biotechnology, C-8, 1:500) and anti-β-actin antibody (Cell Signaling Technology, 8H10D10, 1:1000). For AMPKbeta immunoprecipitation and immunoblots, anti-human AMPKβ1 antibody (Cell Signaling Technology, 12063S, 1:50) and HRP-Streptavidin (Cell Signaling Technology, 3999S, 1:2000).

Validation

The antibodies used for flow cytometry were verified with flow cytometry or immunofluorescence experiments. The antibodies used for western blot were verified with western blot experiments. All relevant data are available on the manufacturers' websites.

Animals and other organisms

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

Laboratory animals

NOD.Cg-PrkdcscidIl2rgtm1Wjl/SzJ (NSG) mice, 50 female and 28 male, 8-12 weeks old.

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve field-collected samples.

Human research participants

Policy information about studies involving human research participants

Population characteristics

Patients with RA were 56.4±14.9 years old, 78.1% female and 20.7% untreated. Patients with PsA were 55.6±11.1 years old, 39.4% female and 12.1% untreated. Patients with SLE were 49.7±13.9 years old and 100% female, while patients with GPA were 42.8±19.8 years old, 83.3% female, 50% positive for anti-myeloperoxidase and 50% positive for anti-proteinase 3 antibodies.

Recruitment

Patients with a diagnosis of RA (n=155) who were positive for rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies were recruited into the study. Patients with a diagnosis of psoriatic arthritis (PsA, n=33), systemic lupus erythematosus (SLE, n=6) and granulomatosis with polyangitis (GPA, n=6) served as controls. Individuals with cancer, uncontrolled medical disease or any other inflammatory syndrome were excluded. Age-matched healthy donors without a personal or family history of cancer or autoimmune disease were enrolled as healthy controls.

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

Peripheral blood mononuclear cells (PBMC) were isolated by gradient centrifugation with Lymphocyte Separation Medium (Lonza, Walkersville, MD) and cultured in RPMI 1640 medium supplemented with 10% FCS (Hyclone, Logan, UT) plus Pen/Strep/Glutamine. Naïve CD4+ CD45RA+ T cells were purified from fresh PBMCs using an EasySep™ Human naïve CD4 T Cell Enrichment Kit (STEMCELL Technologies, Vancouver, Canada).

Instrument

LSR II flow cytometer (BD Biosciences).

Software

FlowJo software from Tree Star Inc. was used for data analyses.

Cell population abundance

The purity of cell population was consistently > 95% determined by flow cytometry.

Gating strategy

Fluorescence minus one (FMO) was used to define the positive and negative populations for all experiments.

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