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Reporting Summary

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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	BD CellQuest Pro, BD FACS Accuri C6 and LSRFortessa-FACS Diva (BD) softwares were used to collect flow cytometry data. Zeiss Zen software was used to collect microscopy data.
Data analysis	Flow cytometric analyses were performed with FlowJo software (FlowJo 7.6.5). Fiji software was used to analyze image data. Graph Pad Prism 8 was used for the statistical analyses of the experimental studies. For the clinical studies, the calculations were performed with SPSS (version 20.0, SPSS Inc) for Windows, R version 3.6.0 (https://www.R-project.org/), survival analysis was performed using the R packages survival (https://CRAN.R-project.org/package=survival) and survminer (https://CRAN.R-project.org/package=survminer). For analysis of mass-spectometry data, acquired raw data files were processed using Proteome Discoverer 2.4.1.15 SP1 for DDA experimental data or Skyline version 20.1.0.155 for PRM experimental data or using Mascot version 2.3.02 (Matrix Science, London, UK) and Phenyx (GeneBio, Geneva, Switzerland) as search engines. RNA-Seq data were quality controlled using FastQC v0.11.3 (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/) and trimmed using the Trim Galore v0.4.1 wrapper (https://www.bioinformatics.babraham.ac.uk/projects/trim_galore/). Reads were aligned to the GRCm38 mouse reference genome using Tophat v2.0.12 (Trapnell et al 2009). Reads with a minimum map quality of 20 were imported into Seqmonk 1.45.4 (http://www.bioinformatics.babraham.ac.uk/projects/seqmonk).

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. 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

The RNA sequencing datasets (from vascular smooth muscle cells) are available in the Gene Expression Omnibus with accession codes GSE117963 and GSE17858. All other relevant data are available from the corresponding authors upon reasonable request. Source data of Figures 1, 2, 3, 4 and Extended Data figures 1, 2, 5, 6, 7 and 8 are included within the paper. Supplemental Information is available for this paper.

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	For experimental atherosclerosis studies power calculations were performed to determine sample size using data from previous experiments in our lab, and are included in the approved study plan by the Animal Ethics Committee of the Medical University of Vienna.
Data exclusions	One mouse was excluded due to low plasma cholesterol despite atherogenic diet feeding and two other mice (in different studies) as mathematic outliers (abnormally big plaque size in the aortic root and thoracic aorta); the mathematical criteria for the latter was: > mean +2.3xSD, which were defined a priori.
Replication	All attempts at replication were successful. Where appropriate pooled data of all independent experiments are shown.
Randomization	Where appropriate, the mice were selected at random. Otherwise, animals from different experimental groups of each study were co-housed (in a similar ratio) to eliminate cage to cage effects. In all studies mice were matched for sex and age.
Blinding	Where appropriate data collection was performed in a blind manner.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Anti mouse APRIL antibodies (clones Apry-1-1 and 108), anti-CD16/32 antibody (clone 93; eBiosciences), anti-B220 PercP-Cy5.5 (clone RA3-6B2; eBiosciences), anti-CD23 FITC (clone B3B4; eBiosciences), anti-CD43 PE (clone S7; BD Biosciences), anti-IgM APC (clone II/41; eBiosciences), anti-CD21 biotinylated (clone 7E9; Biolegend), anti-CD11b APC (clone M1/70; eBiosciences), anti-CD5 (clone 53-7.3; eBiosciences), CD11b-APC (clone M1/70; eBiosciences), anti-Ly6C-FITC (clone HK1.4; Biolegend), anti-Ly6G-PE (clone 1A8; Biolegend), anti-flag M2 antibody (Sigma), biotinylated rat anti-mouse IgG1 (cloneA85-1; BD Biosciences), anti-mouse IgM (Sigma; M8644) or anti-mouse IgG1 (Biolegend; RMG1-1) or anti-mouse IgG2b (BD Biosciences; R9-91) or anti-mouse IgG2c (STAR135) or anti-mouse IgG3 (BD Biosciences; R2-38) or anti-mouse IgA (BD Biosciences; C10-3), anti-mouse IgM antibody conjugated to alkaline phosphatase (Sigma; A9688), biotinylated anti-mouse IgG1 (BD Biosciences; A85-1), biotinylated anti-mouse IgG2b (BD Biosciences; R12-3), anti-mouse IgG2c (JIR 115-065-208), anti-mouse IgG3 (BD

Biosciences; R40-82), anti-mouse IgA (BD Biosciences; C10-1), anti-mIgG2a-biot (rat; clone R19-15; BD), anti-flag antibody (Biolegend; clone L5), mouse anti-APRIL biotinylated antibody (clone 2C8), anti-HSPG2 (clone: A7L6; Merck Millipore), anti-CD31 (clone: EPR3094; Abcam), goat anti-rat AF488 (Life Technologies), goat anti-rabbit AF647 (Life Technologies), goat anti-mouse AF555 (Life Technologies), MB47 antibody (provided by Dr. Witztum's lab UCSD), Anti-hAPRIL antibodies Mahya-1 (mouse IgG1, AG-20B-0078PF-C100) and 110 (mouse IgG1) were provided by Adipogen. Aprily1, Aprily2, Aprily3, Aprily5, Aprily6, Aprily8, Aprily9 and Aprily10 (mouse IgG1) were custom-made by NanoTools (Teningen, Germany), mouse anti-APRIL biotinylated antibody clone 2C8, rabbit anti-ApoB antibody (Abcam; ab20737)

Validation

The validation of the commercially available antibodies used for flow cytometry and confocal microscopy were performed by antibody suppliers per quality assurance literature provided by each supplier. Extensive validation data for the antibodies that were developed by us are either included in previous publications (which are cited in the manuscript) or are included in the manuscript.

Animals and other organisms

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

Laboratory animals	Ldlr-/-, Apoe-/- and Bcma-/- and Apoe-/- Hspg2d3/d3 mice were on C57BL/6J background. Female and male mice were included in the studies at the age of 8 weeks or more.
Wild animals	This study did not involve wild animals
Field-collected samples	This study did not involve samples collected from the field
Ethics oversight	All experimental studies were approved by the Animal Ethics Committee of the Medical University of Vienna (Austria) 66.009/0281-/WFV/3b/2014, 66.009/0223-WF/II/3b/2014 and 66.009/0398-V/3b/2019 or have been regulated under the Animals (Scientific Procedures) Act 1986 Amendment Regulations 2012 following ethical review by the University of Cambridge Animal Welfare and Ethical Review Body (PPL PA4BDF775).

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Patients from the ICARAS (Inflammation and Carotid Artery-Risk for Atherosclerosis Study) clinical study described in Schillinger, M., et al. Inflammation and Carotid Artery--Risk for Atherosclerosis Study (ICARAS). Circulation 111, 2203-2209 (2005). Patients from the LURIC study, including exclusion and inclusion criteria are described in Winkelmann, B.R., et al. Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. Pharmacogenomics 2, S1-73 (2001). Patients from the FAST-MI study are described in Puymirat, E. et al Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation 10.1161/CIRCULATIONAHA.117.030798, (2017).
Recruitment	ICARAS: In this single-center study, 1268 consecutive patients who underwent duplex ultrasound investigations of the extracranial carotid arteries were prospectively enrolled between March 2002 and March 2003. A total of 1268 patients were enrolled in the study. Of these, 203 patients (16%) were lost to clinical follow-up and for 280 patients (22%) no serum sample for the measurement of APRIL levels was available, leaving 785 patients for the final analysis. The 483 patients who had to be excluded from analysis did not differ significantly from the subjects who were included with respect to baseline and demographic parameters (age, sex, frequency of risk factors for atherosclerosis, and cardiovascular comorbidities. LURIC: Patients from the LURIC study, including exclusion and inclusion criteria are described in Winkelmann, B.R., et al. Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. Pharmacogenomics 2, S1-73 (2001). The exclusion and inclusion criteria for patients from the FAST-MI study are described in Puymirat, E. et al Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation 10.1161/CIRCULATIONAHA.117.030798, (2017).
Ethics oversight	The ICARAS study complied with the Declaration of Helsinki and was approved by the review board and the institutional ethics committee of the Medical University of Vienna. The LURIC study was approved by the institutional review board of the ethics committee of the Landesärztekammer Rheinland-Pfalz (No. 1997-203). All patients gave their written informed consent. The FAST-MI study was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Antoine University Hospital and the Commission Nationale Informatique et Liberté.

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

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	Whole spleens were isolated and single cell suspensions were obtained using cell strainers with 100 µm diameter. Erythrocytes were lysed with erythrocyte lysis buffer. Flow cytometry analysis of splenic and peritoneal B and T cell subsets was performed using directly conjugated antibodies on mechanically obtained single cell suspensions of freshly isolated spleens and peritoneal cells. Peripheral blood from the vena cava was diluted with PBS + 2% dextran (Sigma) and incubated for at least 30 minutes at 37oC to concentrate the RBCs at the bottom of the tube. The upper clear phase was collected, and cells were stained with directly conjugated antibodies HUVECs were stained in DPBS (Sigma) supplemented with 10% FBS (Gibco) with 0.5µg/ml of either murine flag-tagged APRIL4 or amino-terminal flag-tagged bacterial alkaline phosphatase (BAP) fusion protein (Sigma) for 30 minutes at 4oC, followed by staining with 1µg/ml of anti-flag M2 antibody (Sigma) for 20 minutes at 4oC. Then cells were stained with 1µg/ml of a biotinylated rat anti-mouse IgG1 (cloneA85-1; BD Biosciences) for 20 minutes at 4oC and streptavidin-APC (eBiosciences) for 20 minutes at 4oC. HEK 293 wild-type cells were stained for 20 min on ice with 50 µl of Flag-ACRP-mAPRIL A88 (DYKDDDDKGPGQVQLH-[aa 18-111 of mACRP30]-LQ-[aa 88-232 of mAPRIL]) in FACS buffer (PBS+ 5% FCS) at 1000 ng/ml final and 5-fold dilutions, either alone or after preincubation with Apry1-1 at 25 µg/ml, or after preincubation with liquemine (DrossaPharm, Basel, Switzerland) at 10 I.U./ml final concentration. Then cells were stained with biotinylated anti-Flag M2 (1:500; Sigma F9291) followed by PE-coupled streptavidin. HEK 293 wild-type cells were stained with 5% rat serum in PBS+0.5% BSA (buffer) for 15 min on ice. After washing with buffer, cells were incubated with 1, or 3 or 6 µg/ml of Fc-human APRIL-A88 for 30 min on ice. After washing cells were incubated with human native LDL at 25 or 75 or 225 µg/ml for 30 min on ice. Then, cells were incubated with 4% PFA for 20 min at room temperature. After washing with buffer, cells were stained with the monoclonal MB47 antibody (provided by Dr. Witztum's lab UCSD) at 0.5µg/ml for 20 min on ice, followed by an anti-mIgG2a-biot (rat; clone R19-15; BD) for 15 min on ice and PE-coupled streptavidin for 15 min on ice (1:400; eBiosciences).
Instrument	FACS Calibur (BD) or FACS Accuri C6 (BD) or LSRFortessa (BD)
Software	BD CellQuest Pro, BD FACS Accuri C6 and LSRFortessa-FACS Diva (BD) softwares were used to collect flow cytometry data
Cell population abundance	not applicable
Gating strategy	FSC/SSC gating was used to identify live cells. B cell subsets were defined as: follicular/trantitional stage 2 B cells: B220+CD43-CD21+CD23+, marginal zone B cells: B220+CD43-CD21highCD23-, transitional stage 1 (T1) B cells: B220+CD43-CD21lowCD23-, newly formed (NF)B cells: B220+CD43-CD21l-CD23-, B-1 B cells: B220lowIgM+CD43+; peritoneal B-1a: B220lowCD11bintCD5+, B-1b: B220lowCD11bintCD5- and CD23+ B-2: B220highCD11b-CD5-CD23+ cells; CD4+ T cells : as CD3+CD4+CD8- and CD8+ T cells: CD3+CD8+CD4-, peripheral inflammatory monocytes as: CD11b+B220-Ly6G-Ly6Chigh, intermediate monocytes: CD11b +B220-Ly6G-Ly6Cint and resident monocytes: CD11b+B220-Ly6G-Ly6Clow.

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