

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  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of all covariates tested   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), 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	Flow cytometry data were acquired on a BD FASaria II, BD LSRII flow cytometer and Attune NxT flow cytometer (ThermoFisher Scientific). EP data were acquired with LabChart Pro v8 (AD Instruments). Optical mapping data were collected and focused onto an 80×80 charge-coupled device camera (RedShirtImaging SMQ Camera and MacroScope IIA). Blood pressures were measured with a non-invasive tail cuff system (Kent Scientific Corporation). Intracellular calcium transients were recorded using a Nikon Eclipse Ti-U inverted microscope (Nikon Instruments) and a NeuroCCDSM camera (RedShirtImaging). Confocal microscopy was executed with a Zeiss LSM800 Airyscan. Blots were scanned with an Azure Biosystems Sapphire Biomolecular imager. ELISA data were acquired with a SpectraMax iD3 (Molecular Devices) and a Tecan Spark plate reader. Real-time qPCR data was acquired with a Bio-Rad CFX96 Real-Time system. Histological slides were scanned with the NanoZoomer 2.0RS digital slide scanner (Hamamatsu).
Data analysis	Human thoracic lymph node sizes were analyzed using Slicer v5.2.2 software. Flow cytometry data were analyzed with FlowJo v10 software. EP data were analyzed using LabChart Pro v8 software (AD Instruments). Optical mapping data were analyzed with Matlab. Intracellular calcium transients were analyzed with Neuroplex (RedShirtImaging) and Clampfit v9.2 software (Molecular Devices). Confocal, histological and blotting images were analyzed with ImageJ software (National Institutes of Health). Densitometric analyses were performed with Image Lab software (Bio-Rad). Real-time qPCR data were analyzed with Bio-Rad CFX Manager v3.1. scRNAseq data were processed and analyzed using Seurat v3.1, edgeR v3.34.1 and GSEA v4.2.2.

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](#)

Raw and processed mouse scRNA-seq data as well as processed human scRNA-seq data are available at the NCBI's Gene Expression Omnibus database under accession no. GSE224959. Raw human scRNA-seq data are accessible at the controlled access repository Data Use Oversight System (DUOS; <https://duos.broadinstitute.org>) under accession no. DUOS-000150 under the restrictions listed by this system.

## 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

Analysis of thoracic lymph node size was undertaken on a cohort of sex-matched patients with AF or sinus rhythm. To explore the prevalence of anti-ADRB1 in humans with and without AF, no matching for sex was attempted. No sex- and gender-based analyses were performed.

Reporting on race, ethnicity, or other socially relevant groupings

No socially constructed or socially relevant categorization variables were used in this manuscript.

Population characteristics

Key baseline characteristics are presented in Supplementary Tables 1 and 2.

Recruitment

Analysis of thoracic lymph node size was undertaken as a substudy from the Oxford Risk Factors And Non-Invasive Imaging (ORFAN) Study. A cohort of age- and sex-matched patients with AF or sinus rhythm undergoing coronary computed tomography were randomly identified from the registry arm of the ORFAN study. To explore the prevalence of anti-ADRB1 in humans with and without AF, stored frozen plasma samples were randomly selected from patients who had participated in one of two ethically approved clinical trials; all patients freely gave their written informed consent. For the sinus rhythm group, samples were selected at random from patients (n=152) who participated in the Statin Therapy in Cardiac Surgery (STICS) trial (ClinicalTrials.gov no. NCT01573143). All patients in this trial were confirmed by ECG to be in sinus rhythm at the time this sample was taken (baseline sample, prior to planned cardiac surgery and prior to trial group allocation). For the AF group, samples were selected at random from patients (n=41) participating in the LOSE-AF trial (ClinicalTrials.gov no. NCT03713775). All patients were confirmed by ECG to be in AF at the time this baseline sample was acquired. Whilst known risk factors for AF were present in patients in both trials, the inclusion/exclusion criteria differed and patients in LOSE-AF were required to have elevated body mass index to enter the study. No matching for baseline characteristics was attempted.

Ethics oversight

Analysis of thoracic lymph node size was undertaken as a substudy from the Oxford Risk Factors And Non-Invasive Imaging (ORFAN) Study (Ethics committee reference 15/SC/0545, Confidentiality Advisory Group reference 20/CAG/0157). To explore the prevalence of anti-ADRB1 in humans with and without AF, patients were randomly selected from one of two ethically approved clinical trials (STICS trial, ClinicalTrials.gov no. NCT01573143 and LOSE-AF trial, ClinicalTrials.gov no. NCT03713775); all patients freely gave their written informed consent.

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](https://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

Sample size was approximated based on prior experiments and available data (DOI:10.1126/science.abq3061) without statistical predetermination.

Data exclusions

No data were excluded.

Replication

All data were acquired during at least two independent experiments. All replication attempts were successful.

Randomization

Animals were randomly assigned to experimental groups. For in vitro experiment, cells were randomly distributed in different groups.



## 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

Antibodies for flow cytometry:

B220 (BioLegend, 103222, clone RA3-6B2), CD3 (BioLegend, 100206, 100209, clone 17A2, dilution 1:100), CD4 (BioLegend, 100434, clone GK1.5), CD11b (BioLegend, 101212, clone M1/70), CD11c (BioLegend, 117318, clone N418), CD19 (BioLegend, 115520, 115555, clone 6D5), CD45 (BioLegend, 103128, 103147, clone 30-F11), CD64 (BioLegend, 139306, clone X54-5/7.1), CD115 (BioLegend, 135513, clone AFS98), CD138 (BioLegend, 142510, clone 281-2), CD317 (BioLegend, 127038, clone 551/927), CXCR5 (BioLegend, 145506, clone L138D7), Fas (BioLegend, 152612, clone SA367H8), GL7 (BioLegend, 144604, clone GL7), Ly6C (BioLegend, 128036, clone HK1.4), Ly6G (BioLegend, 127606, 127641, clone 1A8), MHCII (BioLegend, 107632, clone M5/114.15.2), NK1.1 (BioLegend, 108736, clone PK136), TACI (BioLegend, 133404, clone 8F10), XCR1 (BioLegend, 148225, clone ZET), CD80 (BioLegend, 104714, clone 16-10A1), CD23 (BioLegend, 101614, clone B3B4), CD21/CD35 (BioLegend, 123420, clone 7E9), IgD (BioLegend, 405725, clone 11-26c.2a) and IgG (BioLegend, 406620, clone RMG1-1), all dilution 1:300, unless otherwise mentioned. DAPI or LIVE/DEAD Fixable Aqua Dead Cell Stain (Life Technologies, L-34966) was used as a cell viability marker.

Antibodies for immunocytochemistry, immunofluorescence, antigen immunoblotting, Western blotting and ELISA:

Rabbit anti-mouse ADRB1 (Alomone Labs, AAR-023, 1:400), donkey anti-rabbit IgG Alexa Fluor 647 (ThermoFisher Scientific, A-31573, 1:1000), goat anti-mouse IgG Alexa Fluor 568 (ThermoFisher Scientific, A-11004, 1:1000), goat anti-mouse IgM Alexa Fluor 555 (ThermoFisher Scientific, A-21426, 1:100), WGA Alexa Fluor 488 (ThermoFisher Scientific, W11261, 1:100), anti-mouse Troponin I antibody (Abcam, ab47003, 1:200), goat anti-rabbit IgG Alexa Fluor 488 (ThermoFisher Scientific, A-11008, 1:100), goat anti-mouse IgM IRDye 800CW (LI-COR, 926-32280, 1:2500), anti-mouse p2808 RyR2 (Badrilla, A-010-30, 1:1000), anti-mouse RyR2 (ThermoFisher Scientific, PA5-87416, 1:15000), anti-mouse GAPDH (Cell Signaling, 2118, 1:5000), HRP-conjugated secondary antibodies (Cell Signaling, 7074, 1:5000), HRP-conjugated goat anti-mouse IgM (Abcam, ab97230, 1:10000), HRP-conjugated goat anti-mouse IgG (Abcam, ab205719, 1:10000).

### Validation

All antibodies used for flow cytometry, immunocytochemistry, immunofluorescence, antigen immunoblotting, Western blotting and ELISA were previously validated for the respective application by the distributor. The use of each antibody for imaging or cytometric application can be accessed on the manufacturer's website.

## 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

Wildtype C57BL/6 (stock 000664), B6.129S2-Ighmtm1Cgn/J ( $\mu$ MT, stock 002288), B6.C(Cg)-Cd79atm1(cre)Reth/EhobJ (Mb1-Cre, stock 020505), B6.129-Prdm1tm1Clme/J (Prdm1-fl/+, stock 008100), B6.FVB-Tg (Myh6-cre) 2182Mds/J (Myh6-Cre, stock 011038), Gt (ROSA) 26Sortm4 (ACTB-tdTomato,-EGFP)Luo/J (mTmG-fl/+, stock 007576), B6.129S2-H2dAb1-Ea/J (MHCII-/-, stock 003584) and ADRB1tm1Bkk ADRB2tm1Bkk/J (ADRB1-/-, stock 003810) were purchased from Jackson Laboratory. All experiments were performed with 8- to 12-week-old animals and using age-matched groups. All animals were housed under 12-hour dark/light cycle under free access to food and water with a room temperature 21-23 °C.

### Wild animals

No wild animals were used in the study.

### Reporting on sex

All experiments were performed on male animals.

### Field-collected samples

No field collected samples were used in the study.

### Ethics oversight

Animal protocols were approved by the Institutional Animal Care and Use Committee at Massachusetts General Hospital (protocol

## Ethics oversight

no. 2014N000078). All animal experiments were performed in compliance with relevant ethical regulations and all efforts were made to avoid suffering of animals.

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

Mouse peripheral blood was collected by retro-orbital bleeding using heparinized capillary tubes, and red blood cells were lysed with 1× red blood cell lysis buffer (Biolegend). For organ harvest, an incision was made in the right atrium and mice were perfused through the left ventricle with 10 mL of ice-cold PBS. Mediastinal and iliac lymph nodes were carefully excised using a dissection microscope. Lymph nodes were then plunged and filtered through a 40-µm cell strainer. For analysis of the bone marrow, the epiphyses of the tibia were carefully opened and flushed with FACS buffer (1× PBS supplemented with 0.5% BSA). The collected bone marrow cells were then filtered through a 40-µm cell trainer. Left atrial tissues were excised using a dissection microscope, minced into small pieces and enzymatically digested with 450 U/mL collagenase I, 125 U/mL collagenase XI, 60 U/mL DNase I and 60 U/mL hyaluronidase (all Sigma-Aldrich) for 30 min at 37°C under agitation. After digestion, tissues were washed and filtered through a 40-µm cell strainer and subsequently centrifuged to obtain single-cell suspensions.

## Instrument

Flow cytometry data were acquired on a BD FASARIA II, BD LSRII flow cytometer and Attune NxT flow cytometer (ThermoFisher Scientific).

## Software

FACS Diva v6.1 software (BD Biosciences) and Attune Cytometric v5.3.0 software (ThermoFisher Scientific) were used for data collection. Data were analyzed with FlowJo v10 software.

## Cell population abundance

n/a

## Gating strategy

All cell populations were pre-gated on viable and single cells. Blood B cells were gated as CD19+ B220+ CD3-, T cells as CD19- B220- CD3+, neutrophils as CD19- B220- CD3- CD11b+ CD115low/int Ly6G+ and monocytes as CD19- B220- CD3- CD11b+ CD115high Ly6G- Ly6Clow/high. Tissue pDC were gated as CD45+ CD19- CD3- Ly6G- NK1.1- CD11cint CD317+, cDC1 as CD45+ CD19- CD3- Ly6G- NK1.1- CD317- CD11c+ MHCII+ XCR1+ and cDC2 as CD45+ CD19- CD3- Ly6G- NK1.1- CD317- CD11c+ MHCII+ CD11b+. Tissue B cells were gated as B220+, germinal center B cells as B220+ GL7+ Fas+, follicular helper T cells as CD3+ CD4+ PD1+ CXCR15+ and plasma cells as CD138+ TACI+, age-associated B cells as CD23- CD21- CD35-, follicular B cells as CD23+ CD21+ CD35+, plasmablasts as CD138+ B220+ CD19+, naive B cells as IgG- IgD+ and class-switched activated B cells as IgG+ IgD-.

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