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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 *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	Images were captured through Zeiss LSM980, Leica DM4000. Cell sorting was performed using BD FACSAriaFusion(BD Biosciences) with FlowJo software. Smart-seq2 data was assessed with an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA) and sequencing was performed on a NovaSeq X Plus platform. Single cell sequencing was done with a 10X genomics pipeline and analysis is described below. Spatial transcriptomics data was obtained using the Stereo-seq technology. Measurement of mouse retinal morphology and function was performed using SPECTRALIS system (Heidelberg Engineering, Germany), Celeris-Diagnosys system, Micron IV camera (Phoenix Research Labs, Pleasanton, CA, USA), STRIA TECH Optodrum Plus. En-face OCTA images of patients were captured using the Topcon DRI OCT Triton SS OCT Angio™ system (Topcon Corp., Tokyo, Japan).
Data analysis	ZEN(blue edition), ImageJ were used for imaging analysis. All computational analysis in this study was performed using open-source packages FASTQ files were processed using Cell Ranger and SAW. Single-cell RNA-seq, Smart-seq2 and spatial transcriptomics data analysis was performed in R using the following packages: Seurat, pheatmap, scales, ggplot2, clusterProfiler, etc. Spatial transcriptomics data was also performed using the following package Stereopy. Protein-protein interaction networks was analyzed using the STRINGdatabase (v11.0, http://string-db.org) Spatial transcriptomics dotplots were visualized using BGI stereomap system. FACS data was analysed using FlowJo software. Statistical analysis was performed in R. All analyses were conducted using publicly available software as detailed in methods.

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

All the raw and analyzed data associated with aLARM cells sequencing and identification have been uploaded to the Gene Expression Omnibus repository (GSE301932, GSE301934, GSE324535, GSE324526, GSE333417) .

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	Details regarding the recruited eyes for the OCTA study are provided in the Methods section and source data files. Post-mortem donor eyes were sourced from donors aged 55–75 years, with equal numbers of males and females.
Reporting on race, ethnicity, or other socially relevant groupings	No race, ethnicity, or other socially constructed or socially relevant categorization was used in this manuscript.
Population characteristics	The study population included eyes without retinal disease and eyes with age-related macular degeneration (AMD) diagnosed according to the American Academy of Ophthalmology (AAO) 2025 Age-Related Macular Degeneration Preferred Practice Pattern.
Recruitment	Participants were recruited among patients undergoing OCTA examination. Written informed consent was obtained from all participants.
Ethics oversight	This study was approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun-Yat Sen University (No: 2024KYPJ082), registered at www.medicalresearch.org.cn (MR-44-25-043663) and ClinicalTrials.gov (Identifier: NCT06803082).

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 statistical methods were used to predetermine the sample size. Experiments were performed using at least three biological replicates except spatial transcriptomics. In accordance with IACUC guidelines and based on our prior experience with the models, we used an appropriate number of animals for in vivo experiments to obtain statistically significant results. For immunofluorescence, Hematoxylin & eosin staining and TEM on retinal section, at least three sections of each retina and at least three retinae of each group were used. In every section, at least three images were captured in the center, mid-periphery, and periphery area, respectively. For immunofluorescence on whole mounts, at least six images were captured in the center, mid-periphery, and periphery areas of each retina respectively. At least six retinae or RPE-sclera complex from at least six mice were used in each group for analysis. Representative images were shown in the according Figures. In experiments including qPCR and western blot, samples were collected from three retinae or RPE-sclera complex of at least three individual mice. All in vitro experiments were performed in triplicate and repeated independently for at least three times. For normally distributed data, two-sided unpaired Student's t-test for two groups or one-way ANOVA with Tukey's post hoc test were used for over three groups. For non-normal data, Mann-Whitney U test or Kruskal–Wallis test with Dunn's post hoc test were applied.
Data exclusions	No data excluded from analysis unless described in the manuscript.
Replication	All experiments and micrographs described were replicated at least three times independently with biological replicates showing similar results. Experimental replicates are indicated in the figure legends. Except one biological sample was used for spatial transcriptomics.
Randomization	Animals were randomly assigned to experimental groups before treatment. For human samples, participants and donor tissues were included according to predefined inclusion and exclusion criteria, and analyses were performed without selective allocation to experimental conditions.

Blinding

For histological analysis of samples, investigators were blinded to the group identifer until the completion of data collection of the image analysis. Investigators were not blinded to treatment groups for other in vivo or in vitro experiments, as such knowledge is essential to conduct the experiments.

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

We report all antibodies used in this manuscript in the supplementary table 2, including information on manufacturer, catalog number and usage.

Validation

1. anti-Iba1 antibody, WAKO 019-19741, Polyclonal, IF Validated by manufacturer for immunofluorescence; specificity confirmed in microglial cells.
2. anti-Tip47 antibody, Santa Cruz sc-393461, Clone E-5, IF Validated by manufacturer; reactivity confirmed in mouse and human samples.
3. anti-CD36 antibody, Abcam ab80080, Clone MF3, WB, IF Validated by manufacturer; knockout validated; widely cited in literature.
4. anti-β-actin antibody, Cell Signaling Technology 3700S, Clone 8H10D10, WB Validated as loading control; reactivity confirmed across species.
5. anti-NLRP3 antibody, Cell Signaling Technology 15101S, Clone D4D8T, WB, IF Validated by manufacturer; knockout validated; specific band observed at expected molecular weight.
6. anti-IL-1β antibody, Santa Cruz sc-52012, Clone 11E5, WB, IF Validated by manufacturer; reactivity confirmed in murine samples.
7. Anti-Lrp1 Antibody, Abcam ab92544, Clone EPR3724, WB, IF Validated by manufacturer; reactivity confirmed in mouse and human tissues.
8. Anti-P2rx7 antibody, Santa Cruz sc-514962, Clone D-1, WB, IF Validated by manufacturer; specific signal blocked by peptide competition.
9. anti-Abca1 antibody, Abcam ab66217, Clone HJ1, WB, IF Validated by manufacturer; reactivity confirmed in multiple species.
10. anti-CD11b antibody, Abcam ab8878, Clone M1/70, IF Validated by manufacturer for immunohistochemistry; widely used in microglia/macrophage staining.
11. anti-Tmem119 antibody, Abcam ab209064, Clone 28-3, IF Validated by manufacturer; specific for microglial cells in mouse brain.
12. Anti-NG2 Antibody, Merck Millipore AB5320, Polyclonal, IF Validated by manufacturer for oligodendrocyte precursor cell labeling.
13. BODIPY, MCE HY-W090090, IF Validated by manufacturer for lipid droplet staining.
14. anti-ZO-1 antibody, Santa Cruz sc-33725, Clone R40.76, IF Validated by manufacturer; reactivity confirmed in tight junction staining.
15. anti-IL-1R1 antibody, R&D AF771-SP, Polyclonal, IF Validated by manufacturer; reactivity confirmed in mouse tissues.
16. OxLDL-Dil, Invitrogen L34358, IF Validated by manufacturer for cell labeling and tracing.
17. Anti-p21-antibody, Santa Cruz sc-6246, Clone F-5, WB Validated by manufacturer; specific band at expected molecular weight.
18. Anti-αSMA-antibody, Abcam ab5694, Polyclonal, WB, IF Validated by manufacturer; reactivity confirmed in smooth muscle cells.
19. Anti-oxLDL-antibody, Bioss bs-1698R, Polyclonal, WB Validated by manufacturer; specificity confirmed by peptide blocking.
20. Anti-PPARγ-antibody, Cell Signaling Technology 2435S, Clone C26H12, WB Validated by manufacturer; knockout validated; specific band observed.
21. WGA, ThermoFisher Scientific W11261, IF Validated by manufacturer for lectin staining of glycoproteins.
22. LIVE/DEAD™ Fixable Green Dead Cell Stain Kit, Invitrogen L34970, Flowcytometry Validated by manufacturer for viability discrimination in flow cytometry.
23. Endosomal Marker Antibody Sampler Kit, Cell Signaling Technology 12666T, IF Each antibody in the kit is validated by manufacturer for endosomal compartment staining.
24. Brilliant Violet 421™ anti-mouse/human CD11b antibody, Biolegend 101236, Clone M1/70, Flowcytometry Validated by manufacturer for flow cytometry; specificity confirmed by positive/negative populations.
25. APC Rat Anti-Mouse CD45(30-F11) antibody, BD Pharmingen™ 559864, Clone 30-F11, Flowcytometry Validated by manufacturer; widely used for hematopoietic cell identification.
26. PE anti-mouse CD36 antibody, Biolegend 102606, Clone HM36, Flowcytometry Validated by manufacturer for flow cytometry; specificity confirmed in mouse macrophages.
27. anti-CD36 Antibody, Clone FA6-152, Abcam ab17044, CD36-blocking Validated by manufacturer; mouse IgG1 isotype control, Clone MOPC-21, Selleck A2106 as isotype control antibody.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	All cell lines used in this study were obtained from commercial suppliers: HMC3 (Procell, CL-0620), and bEnd.3 (Procell, CL-0598).
Authentication	Cell line authentication was performed by the suppliers which used STR profiling; no additional authentication was carried out by the authors.
Mycoplasma contamination	Negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

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	Eight- to twelve-week-old C57BL/6J (GemPharmatech, Nanjing, China), Nlrp3-/- (Strain: #021302), Cx3cr1-GFP (Strain: #005582)and CD36 cKO mice were used in this study. The CD36 cKO mice were constructed by crossing CD36fl/fl mice (Strain: #032276) and Cx3cr1cre mice (Strain: #025524).
Wild animals	The study did not involve wild animals
Reporting on sex	Both male and female mice were included in the study
Field-collected samples	The study did not involve fieldwork
Ethics oversight	All the experiments were carried out in accordance with the ARVO Statement and followed the guidelines of Animal Care and Use Committee of Zhongshan Ophthalmic Center (Ethics ID: Z2024001).

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov, Identifier: NCT06803082.
Study protocol	The full study protocol is available on ClinicalTrials.gov.
Data collection	Participants were recruited at the Clinical Research Center of Zhongshan Ophthalmic Center, Guangzhou, China.
Outcomes	The primary outcome measure was pre-defined prior to database lock and statistical analysis as the density of hyperreflective foci (HRF; number/mm^2) on the RPE en face structural image derived from a fovea-centered 3×3 mm macular scan acquired using a Topcon OCT/OCTA system.

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA

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	Retinal single-cell suspensions were prepared as previously described with minor modifications. Briefly, mouse eyeballs were enucleated and retinae were carefully dissected. Retinal tissues were transferred into RPMI-1640 medium supplemented with HEPES buffer and mechanically dissociated by gentle trituration using wide-bore pipette tips. The resulting cell suspension was passed through a 70-µm cell strainer (BD Biosciences) to remove debris and cell aggregates. Cells were washed with phosphate-buffered saline (PBS) containing 1% fetal bovine serum (FBS) and incubated with fluorochrome-conjugated antibodies against CD45, CD11b, and CD36 and Live/Dead dye for 30 min at room temperature in the dark.
Instrument	FACSAriaFusion(BD Biosciences)
Software	FlowJo software
Cell population abundance	Single-cell suspensions isolated from mouse retinas were first gated on FSC/SSC to exclude debris and select the total cell population. From this gate, CD45int and live cells (CD45-APC+, Live/Dead-FITC–) accounted for approximately 10% of the total cells. Within this CD45int live population, ~60% were CD11b+ viable cells. Among $CD11b^+$ cells, ~20% were $CD36^+$ and ~30% were $CD36^-$. These frequencies were consistently observed across independent experiments.
Gating strategy	Cells were first selected based on forward scatter (FSC) and side scatter (SSC) to exclude debris and identify the main cell population. Subsequently, viable CD45int cells were gated and from this CD45int live population, Live/Dead-FITC negative were gated. Subsequently, CD11b-BV421 and CD36-PE double-positive cells were identified as the target population (CD11b +CD36+). All gates were set based on blank controls and isotype controls to ensure specificity. The gating strategy was provided in Fig.S4 and Fig.S10.

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