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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	Gromacs 2018.8 with Plumed 2.5.1 was used for the molecular dynamics simulations. The program patch for VcMD simulation is available upon request. BD Accuri C6 Plus was used for flow cytometry data collection. Keyence BZ-X800 microscope was used for cell image data and immunohistochemistry data collection. JEOL JEM-2100F electron microscope was used for CNT data collection. Bio-Rad iMark was used for ELISA data collection. Wako OptimaShot CL-420a was used for immunoblot data collection.
Data analysis	CD-HIT 4.5.4 and lxml 4.6.3 were used for in silico screen. numpy 1.16.6 and Scikit-learn 0.20.3 were used to analyze molecular dynamics trajectories. GraphPad Prism (8.4.3) was used for statistical analysis. FlowJo (10.7.1) was used for flow cytometry data analysis. BZ-X800 analyzer was used for cell image analysis.

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

The protein structure information was downloaded from the Protein Data Bank Japan (https://pdbj.org) and AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk). Representative structures for each binding mode generated by the MD simulations have been submited to the Biological Structure Model Archive (BSM-Arc) under BSM-ID BSM00031 (https://bsma.pdbj.org/entry/31). Source data are provided with this paper. All data supporting of this study are available from the corresponding author on reasonable request.

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 method was used to predetermine sample size. Sample size was determined based on our previous studies and common practice in the field.
Data exclusions	Exclusion criteria were not used in this study.
Replication	Each experiment was repeated twice or more with similar results.
Randomization	Animals and cells were randomized among group. Healthy volunteers were grouped by Siglec-14 genotype and then were randomized.
Blinding	In silico study, in vitro study using cell lines, and in vivo study were not performed in a blinded manner as the investigator need to know the treatment groups to compare the study. All data were acquired and analyzed by software with objective standard, thus blinding was not relevant to these experiments. Human peripheral blood mononuclear cell (PBMC) study was performed in a double-blinded manner not to identify individuals.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	anti-human siglec-5/14 (clones SY2, Original, IHC: 2 ug/ml, Blocking: 10 ug/ml) isotype control mouse IgG1 (clone MG1-45, BioLegend, Blocking: 10 ug/ml) biotinylated anti-human siglec-5/14 (clones SY1, SY2, Original, FACS: 2 ug/ml) biotinylated isotype control mouse IgG1 (clone MOPC-21, BioLegend, FACS: 2 ug/ml) streptavidin-PE (405204, BioLegend, FACS: 2 ug/ml)

FITC-anti-human CD14 (clone M5E2, BioLegend, FACS: 2 ug/ml)
FITC-anti-human CD43 (clone 1G10, BD bioscience, FACS: 2 ug/ml)
FITC-anti-mouse Siglec-F (clone S17007L, BioLegend, FACS: 2 ug/ml)
FITC-isotype control rat IgG2a (clone RTK2758, BioLegend, FACS: 2 ug/ml)
FITC-isotype control mouse IgG1 (clone MOPC21, BioLegend, FACS: 2 ug/ml)
PE-anti-human Tim1 (clone 1D12, BioLegend, FACS: 2 ug/ml)
PE-anti-human Tim4 (clone 9F4, BioLegend, FACS: 2 ug/ml)
PE-anti-human Siglec-3 (clone P67.6, BioLegend, FACS: 2 ug/ml)
PE-anti-human Siglec-9 (clone K8, BioLegend, FACS: 2 ug/ml)
PE-anti-mouse Tim4 (clone RMT4-54, BioLegend, FACS: 2 ug/ml)
PE-isotype control mouse IgG1 (clone MOPC-21, BioLegend, FACS: 2 ug/ml)
PE-isotype control rat IgG2a (clone RTK2758, BioLegend, FACS: 2 ug/ml)
anti-human siglec-5 (AF1072, R&D systems, WB: 1:2000 dilution)
anti-human caspase-1 (3866, Cell Signaling Technology, WB: 1:1000 dilution)
anti-beta-actin (4967, Cell Signaling Technology, WB: 1:1000 dilution)
anti-IkappaB-alpha (4814, Cell Signaling Technology, WB: 1:1000 dilution)
anti-Syk (2712, Cell Signaling Technology, WB: 1:1000 dilution)
HRP-anti-rabbit IgG (211-032-171, Jackson ImmunoResearch, WB: 1:5000 dilution)
HRP-anti-goat IgG (705-035-003, Jackson ImmunoResearch, WB: 1:5000 dilution)
human IL-1beta ELISA DuoSet kit (DY201, R&D systems)
human IL-8/CXCL8 DuoSet kit (DY208, R&D systems)
anti-human CD68 (76437, Cell Signaling Technology, IHC: 1:500 dilution)
Alexa Fluor 568-anti-rabbit IgGs (A11011, Thermo Fischer Scientific, IHC: 1:500 dilution)
Alexa Fluor 488-anti-mouse IgGs (A32723, Thermo Fischer Scientific, IHC: 1:500 dilution)
Alexa Fluor 647-anti-mouse IgGs (Poly4053, BioLegend, FACS: 2 ug/ml)

Validation

SY1 and SY2, neutralizing anti-human siglec-5/14 monoclonal antibodies generated in this study, were validated as described in the manuscript (Extended Data Fig. 6 and Supplementary Fig. 13). Regarding commercially available antibodies, the validation is described in technical data sheets provided by the manufactures and/or on their websites.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	NIH-3T3 (ATCC) Jurkat cells (Cell Resource Center for Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University) THP-1 cells (Cell Resource Center for Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University) Lenti-X 293T cells (632180, Takara Bio)
Authentication	None of the cell lines were authenticated in the lab.
Mycoplasma contamination	The cell lines were tested negative for mycoplasma by PCR using Mycoplasma Detection Set (6601, Takara-Bio).
Commonly misidentified lines (See ICLAC register)	No misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	C57BL/6J mice (8-12 weeks, female) and BALB/c mice (6-8 weeks, female) were purchased from CLEA Japan.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The animal study was approved by the institutional review committee of Shiga University of Medical Science (2022-6-12) and Ritsumeikan University (BKC2020-001).

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	PBMCs were collected from healthy volunteers (20-50-year-old male and female) and were grouped based on siglec-14 genotype.
Recruitment	Healthy volunteers were recruited via campus poster announcement. Informed consent was obtained from all volunteers for the study protocol. Participants were paid 3,000 yen.
Ethics oversight	The human study was approved by the institutional ethics committee of Ritsumeikan University (BKC-2019-077).

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	Human PBMCs were prepared from healthy volunteers by density graduation centrifugation with Lymphoprep (Axis Shield). These cells were stained with FITC-anti-CD14 mAb. Particle recognition was analyzed by measuring side scatter intensity.
Instrument	BD Accuri C6 Plus
Software	FlowJo 10.7.1
Cell population abundance	No sorting was performed by flow cytometry.
Gating strategy	Using FSC/SSC gating, debris was removed. Gating strategy for CNT recognition was shown in Supplementary Figs. 6 and 12. Human peripheral lymphocytes and monocytes were gated by FSC/SSC intensity (Supplementary Fig. 1) and monocytes were confirmed to be CD14-positive (Fig. 4).

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