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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	All sequence data was generated in this study.
Data analysis	For the single-cell RNA-seq data, demultiplexing and alignment were performed using Cell Ranger (v6.1.2). Empty droplets were removed using DropletUtils (v1.14.2) R package. Quality control was performed using scatter (v1.22.0) R package. Normalization was performed using scran (v1.22.1) R package. Batch correction was performed using harmony (v0.1.1) R package. UMAP plot was generated using Seurat (v4.3.0) R package. Expression density was calculated using Nebulosa (v1.4.0) R package. Gene set enrichment analysis was performed using escape (v.1.5.1) R package. Cell communication analysis was performed using CellChat (v.1.6.1) R package. For the exosomal small RNA-seq data, raw sequences were quality-checked using FASTQC (v0.11.4) and trimmed using Trimmomatic (v0.39). Mapping was performed using Bowtie1 (v1.3.1). The miRNA alignment was performed using miRDeep2 (v2.0.1.2). Differential expression analyses were performed using DEseq2 (v1.40.2) R package. Target gene prediction was performed using TargetScan (v8.0). Functional enrichment was performed using DAVID. For the small RNA-seq data, low-quality sequences were trimmed using Trimmomatic (v0.39). Then trimmed seuqences were mapped using Bowtie1 (v1.3.1) and alinged to the miRNAs in miRBase 22.1 using miRDeep2. Differential expression analyses were performed using DEseq2 (v1.40.2) R package. Target gene prediction was performed using TargetScan (v8.0) tool. Functional enrichment was performed using DAVID.

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 raw and processed data for scRNA-seq of BALF cells are available from the Gene Expression Omnibus under super series accession GSE247257. All raw data for small RNA-seq of BALF exosomes are available from the Sequence Read Archive under the accession PRJNA640269.

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	NA
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

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	Thirty-six 4-week-old piglets after lactating were used in this study. They were separated into negative (n = 12), NA8 (n = 6), JA142 (n = 12), and NA10 (n = 6) groups depending on PRRSV infection plan.
Data exclusions	No data was excluded.
Replication	To verify reproducibility of our findings, we performed each major experiment multiple times in order to generate biological replicates. All attempts at replication were successful. For pig studies, 3 pigs were used for each virus infection. All attempts at replication of the pig experiments were successful.
Randomization	The pigs were randomly assigned to receive each virus infection.
Blinding	The investigators were blinded to group allocation during data collection and analysis.

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	The following antibodies were used for flow cytometry: porcine MHC-II (MSA3, cat.: WS0589S-100, Kingfischer Biotech), porcine CD163 (2A10/11, cat.: MCA2311GA, Bio-Rad), CD172α (Sirpα, 74-22-15, cat.: MCA6100PE, Bio-Rad), Zombie Green live-dead fixable dye (cat.: 423112, BioLegend), rat APC anti-mouse IgG1 (cat.: 406610, BioLegend), rat PerCP/Cy5.5 anti-mouse IgG2a (cat.: 407112, BioLegend), porcine CD3 (PPT3, cat.: MCA5951F, Bio-Rad), porcine CD4α (74-12-4, cat.: 561474, BD), porcine CD8α (76-2-11, cat.: 559584, BD), porcine CD25 (K231.3B2, cat.: MCA1736GA, Bio-Rad), FoxP3 (FJK-16s, cat.: 11-5773-82, eBioscience), porcine CD335 (VIM-KM1, cat.: MCA5972GA, Bio-Rad), porcine IFN-γ (P2G10, cat.: 561481, BD), IL17 (eBio64DEC17, cat.: 17-7179-42, eBioscience), porcine TCR1 δ (PGBL22A, cat.: WS0621S-100, Kingfischer Biotech)
Validation	All antibodies used were validated by the suppliers they were acquired from and were used at the optimized conditions according to the manufacturer's recommendations.

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	In vivo experiments were performed using 4-week-age old three-way hybrid pig((YorkshireXLandrace)XDuroc).
Wild animals	No wild animals used in the study.
Reporting on sex	Sex was not considered in this study.
Field-collected samples	No field-collected samples used in this study
Ethics oversight	Animal experiments in this study were approved by the Jeonbuk National University Institutional Animal Care and Use Committee (JBNU-IACUC), Republic of Korea (approval number JBNU 2021-0172) and were conducted according to the guidelines of th JBNU-IACUC.

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

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	Bronchoavleolar lavage cells (BAL cells) were collected by lavaging the lungs after the necropsy with FACS buffer (3% FBS in PBS and 0.02% sodium azide). Collected BAL cells were quantified and washed with FACS buffer before staining. Cells were divided into each panels and stained with antibodies according to the manufacturer's recommendation
Instrument	BD Accuri C6 Plus
Software	FlowJo
Cell population abundance	Flow cytometry was used for analysis. No cell sorting was conducted.
Gating strategy	Preliminary gating strategy consisted of FSC-A/FSC-H and FSC-A/SSC-A gates to identify single cells and exclude doublets.

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