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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	The scRNA-seq, scATAC-seq and spatial transcriptome data generated in this study were performed on the 10× Chromium platform or BD Rhapsody using XXX or Next GEM single cell ATAC Gel Beads V1.1 (scATAC-seq) or Visium Spatial Gene Expression Slide & Reagent Kit (spatial transcriptome) according to the manufacturer's protocols including sample preparation, library preparation and instrument and sequencing settings. ST-seq were conducted by Shanghai XuRan Biotechnology Co., Ltd. (Shanghai, China). ChIP-seq and scATAC-seq was conducted by LC-Biotechnology (Hangzhou, China). CITE-seq and scRNA-seq were conducted by NovelBio Bio-Pharm Technology Co.,Ltd. (Shanghai, China). All fluorescence images were captured on a confocal microscope (Zeiss LSM880) with ZEN 3.1 blue edition software. LC-MS experiments were conducted by Novogene Co., Ltd. (Beijing, China). Some diagram images were created with BioRender.com.
Data analysis	Raw scRNA-seq data were processed using the Cell Ranger (v.3.1.0) software (10× Genomics) for read alignment, barcode assignment and unique molecular identifier (UMI) counting, based on corresponding reference genomes (human GRCh38, mouse mm10-3.0.0, monkey macFas5). Cells were filtered with a UMI count greater than 200 and a mitochondrial percentage less than 20%. Filtered data were then log normalized and scaled, with cell-cell variation due to UMI counts and percent mitochondrial reads regressed out using Seurat (v.3.2.3). To avoid batch effects among samples and experiments, Seurat's canonical correlation analysis (CCA) integration tool was used to integrate single-cell data. Dimensionality reduction was performed with "RunUMAP" function and visualized by Uniform Manifold Approximation and Projection (UMAP). Cell clustering was performed by "FindClusters" function at a resolution of 0.2 and the top 30 principal components (PCs) were used to define cell identity. Marker genes for each cluster were performed using the Wilcoxon rank-sum test ("FindAllMarkers" function with default parameters) and each cell clusters were annotated based on known maker genes the top gene list.

Spatial transcriptomics data were processed using Space Ranger (v.1.1.0) software (10× Genomics) was used to process, align and summarize UMI counts against the GRCh38 human reference genome and macFas5 monkey reference genome respectively for each spot on the Visium spatial transcriptomics array. Raw spot count matrices were filtered out to keep only spots overlaying tissue sections. In order to account for variability in total spot RNA content, count matrices were normalized using regularized negative binomial regression (SC Transform). Dimensionality reduction was performed using PCA and for each slide. Clustering was performed using Louvain clustering algorithm (resolution=1.0) and clusters were visualized using UMAP algorithm. Clusters distributions were visualized in spatial context over H&E images.
scATAC-seq data were processed using Cell Ranger ATAC (v.1.2.0) software (10× Genomics), which generated a count matrix for open chromatin regions in single cells after barcode processing, alignment, duplicate marking, peak calling and cell calling. Human reference genome version GRCh38 and monkey custom reference genome macFas5 were used in alignment process, respectively. Downstream analyses were performed with the ArchR workflow (version 1.0.1). In brief, we filtered out cells with less than 1,000 unique fragments and transcriptional start site (TSS) enrichment score below 4 so that the remaining cells had adequately sequenced reads and high signal-to-background ratio. Then, we filtered doublets with the ratio of predicted doublets to filter based on the number of pass-filter cells less than 1. Finally, scATAC-seq clustering was performed by using Seurat's "FindClusters" function. We used SVD on the TF-IDF matrix to generate a lower-dimensional representation of the data by retaining the first 50 dimensions. We then used these reduced dimensions as input into a Seurat object and then final clusters were identified by Seurat's SNN graph clustering "FindClusters" with a resolution of 0.3.
Raw sequencing data of ChIP-seq were cleaned to filter adapters and low quality reads using FASTQC (v0.11.5) and the unique mapped reads were harvested by mapping the cleaned reads to genome with no more than two mismatches by Bowtie 2. MACS2 (v2.1.1) was used to call peak, giving a robust and high resolution ChIP-Seq peak predictions. Peaks were annotated related genes using Homer (v4.10). deepTools (v2.4.1) was used to plot gene coverage of the reads near TSS and TES. ChIPseeker (v1.5.1) was used to depict the reads distribution on chromosomes. Homer (v4.10) was used to search motif and analyze transcription factors.
CITE-seq:Fastq files were processed via the standard Rhapsody analysis pipeline (BD Biosciences) on Seven Bridges (https://www.sevenbridges. com) according to the manufacturer's recommendations. The resulting unique molecular identifier (UMI) count matrices were imported into R (v.4.0.0) and processed with the R package Seurat (v.4.0.4). To account for differences in sequencing depth across cells, both layers were normalized independently using Seurat defaults. RNA UMI counts were log-normalized, while antibody UMI counts were centered using log ratio normalization to account for unspecific binding background signal. Subsequently, both normalized matrices were concatenated and integration across patients was performed using Harmony.
Statistical analyses were performed using GraphPad Prism 7.0.

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 data that support the findings of this study have been deposited into Gene Expression Omnibus (GEO) with accession number: Human: GSE223639, Monkey: GSE223641, Mouse: GSE223640, ChIP: GSE223642,CITE-seq: GSE272956. All other data that support the findings of this study are available from the corresponding author on reasonable request . The following secure token has been created to allow review while it remains in private status: kviviuooxpgtvkf or ctgjomowzjwjdej.All code for generating the figures in the single-cell transcriptome analysis section is available at https://github.com/fwenwen/NETs/tree/main.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Because this study focused on endometritis and endometrial hyperplasia, tissue samples in this study were only from women.
Population characteristics	All human endometrial tissue samples used in this study were obtained from Tongde Hospital of Zhejiang Province. All individuals including endometritis, endometrial hyperplasia and control subjects, females; age: 25-55 years old) gave their informed consent for tissue collection.
Recruitment	We recruited all endometrial hyperplasia and endometritis patients or control patients from Tongde Hospital of Zhejiang Province and obtained their informed consent for tissue collection. For human sample collection, resected tissue was subjected to post-surgical histological examinations to confirm the pathological phenotype of the tissue. There is no self-selection biases. The study excluded all adolescent women and postmenopausal women. All participants were informed of the purpose of the study, they were required to provide written informed consent before experiments. The patients were not compensated.
Ethics oversight	All experimental procedures were approved by the by the Ethics Institutional Review Board of Tongde Hospital of Zhejiang Province (Study number: 2020-002, 2021-013) and Research and Ethical Committee of Affiliated Hospital of Nanjing University of Chinese Medicine (2020-NL-094-02) and in accordance with NIH Laboratory Animal Care Guidelines.

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	Using G-power software 3.1, sample size is estimated by the significance level (0.05), effect size (base on the data in our previous study) and a given power (usually 0.8). We also conducted power analysis after the experiment and found enough power value (>0.8) in each statistical analysis.
Data exclusions	No data were excluded.
Replication	All experimental findings were reproduced in multiple independent experiments. The number of independent experiments and biological replicates in each data panel is indicated in the figure legends.
Randomization	Mice/cells were assigned randomly into experimental groups and processed in an arbitrary order. For volunteer, endometrial hyperplasia and endometritis participants, people were randomly chosen.
Blinding	All mice and subsequent samples were labelled only with mouse ID numbers and did not indicate genotype or type of treatment. Genotype or treatment type were decoded after the data acquisition and quantification analysis were complete.

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

Methods

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

Antibodies

Antibodies used

Rabbit polyclonal anti-NKCC1 (1:1000, Abcam,ab140986)
Mouse monoclonal anti-myeloperoxidase (1:200, Abcam, ab90810)
Rabbit monoclonal anti-myeloperoxidase (1:200, Abcam, ab208670)
Rabbit monoclonal anti-CD45 (1:200, Abcam, ab40763)
Mouse monoclonal anti-β-actin (1:1000, Abmart, M20011)
Rabbit polyclonal anti-neutrophil elastase (1:200, Bioss, bs-6982R)
Mouse monoclonal anti-CD15 (1:1000, Cell Signaling Technology, 4774)
Mouse monoclonal anti-NKCC1(1:200, Santa Cruz Biotechnology, sc-514774)
Mouse monoclonal anti-neutrophil elastase (1:200, Santa Cruz Biotechnology, sc-55549)
Mouse monoclonal anti-PCNA (1:200,Santa Cruz Biotechnology,sc-56)
Rabbit monoclonal anti-Estrogen Receptor alpha (Use 4 µg for 25 µg of chromatin, Abcam, ab32063)
Goat anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488 (1:500, Thermo Fisher Scientific, A11034)
Goat anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 555 (1:500, Thermo Fisher Scientific, A21424)
Anti mouse Ly6G (Clone: 1A8) (bioXcell, BE0075-1)
Anti human/monkey CD20 (bioXcell, BE0276)
Fixable viability dye eFlour506 (Invitrogen , 65-0866-18)
Anti-human CD45 (BD, 563792)
Anti-human CD3 (BD, 563800)
Anti-human CD19 (Biolegend, 302208)
Anti-human CD11b (BD, 562399)

Anti-human CD14 (Biolegend, 301834)
Anti-human CD66b (Biolegend, 305110)
Anti-human CD56 (BD , 557919)
Anti-mouse CD45 (Miltenyi Biotec , 130-110-665)
Anti-mouse CD45 (Biolegend , 103116)
Anti-mouse CD3 (BD , 553061)
Anti-mouse CD19 (BD ,563235)
Anti-mouse Nkp46 (eBioscience, 50-3351-82)
Anti-mouse CD11b (Biolegend , 101216)
Anti-mouse Ly6G (BD , 560602)
Anti-mouse Ly6C (Biolegend, 128041)
Anti-Histone H3 (citrulline R17) (Abcam , ab219407)
Anti-Neutrophil Elastase antibody (Abcam, Ab254178)
PCNA (PC10) Mouse mAb (Cell Signaling Technology , 2586)
Anti-Myeloperoxidase antibody (Abcam, Ab208670)
HMGN2 (D9B9) XP® Rabbit mAb (Cell Signaling Technology, 9437S)
Rabbit monoclonal anti-HMGN2 (Abcam, ab124997)
Anti-huamn CD45 (Clone: 2D1) (Biolegend , 368507)
Anti-human CD15 (Clone: MMA) (eBioscience, 48-0158-42)
BD Abseq Immune Discovery Panel (BD,625970)
Anti-CD36 (Clone: CLB-IVC7)(BD,940224)
Anti-CD206 (Clone: 19.2)(BD,940068)
Anti-CD32 (Clone: FLI8.26)(BD,940069)
Anti-CD69 (Clone: FN50)(BD,940019)
Anti-CD141 (Clone: 1A4)(BD,940079)
Anti-CD43 (Clone: 1G10)(BD,940278)
Anti-CD102 (Clone: CBR-IC2/2)(BD,940241)
Anti-CD110 (Clone: 1G10)(BD,940278)
Anti-CD140a (Clone: αR1)(BD,940246)
Anti-CD59 (Clone: p282 (H19))(BD,940301)
Anti-CD15(Clone: W6D3)(BD,940274)
Anti-CD66 (Clone: B1.1/CD66)(BD,940048)
Mouse monoclonal anti-Ac-lysine (1:200,Santa Cruz Biotechnology, sc-32268)
E-Cadherin Rabbit mAb (1:1600,Cell Signaling Technology, 3195S)

Validation

All antibodies were validated for the indicated species and applications by manufacturer's references.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Endometrial epithelial cell line was purchased from Qingqi (Shang hai) Biotechnology Development Co.Ltd. HL-60 cell cell line was purchased from Wuhan Pricella Biotechnology Co., Ltd.
Authentication	All the cell lines were authenticated by short tandem repeat profiling prior to use
Mycoplasma contamination	All cell lines tested 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	The neutrophil cell-specific Pad4 knockout mice, neutrophil-specific Esr1 knockout mice,epithelial cell-specific Slc12a2 knockout mice, Hmgn2 knockout mice, Timm8b knockout mice, and eight-week-old female C57BL/6 mice were purchased from GemPharmatech Co. Ltd.and maintained in specific pathogen-free conditions at GemPharmatech Co. Ltd. and the Experimental Animal Center at Nanjing University with access to food and water ad libitum. Healthy female cynomolgus monkeys ranging from 3 to 5 years in age were raised in the monkey breeding base of Changchun Biotechnology Development Co., Ltd., Guangxi, China.
Wild animals	None
Reporting on sex	Because this study focused on endometrial hyperplasia, we used female animals.
Field-collected samples	Uterine tissues were isolated in the indicated time in figure lengend. All samples were separated and fixed with paraformaldehyde for paraffin embedding or single-cell suspension preparation.
Ethics oversight	All mouse procedures were approved by the National Institutes of Medicine Guidelines for the Care and Use of Laboratory Animals

Ethics oversight	and the Nanjing University Animal Care and Use Committee (IACUC-2012011) and Laboratory Animal Ethics Review Zhejiang Academy of Traditional Chinese Medicine (2022-044).The sample collection of cynomolgus monkeys and research conduction in this study were approved by the Research Ethics Committee of Changchun Biotechnology Development Co., Ltd. (Approval Number: 200010).

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

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	The data have been deposited in the GEO repository (GSE223642).
Files in database submission	GSM696970 medium[IP], GSM6969741 estradiol[IP], GSM6969742 aspirin[IP], GSM6969743 medium[input],GSM6969744 estradiol[input],GSM6969745 aspirin[input].
Genome browser session (e.g. UCSC)	ftp://ftp.ensembl.org/pub/release-101/fasta/homo_sapiens/dna//Homo_sapiens.GRCh38.dna.primary_assembly.fa.gz

Methodology

Replicates	The information including medium[IP], estradiol[IP], aspirin[IP], medium[input],estradiol[input],aspirin[input].
Sequencing depth	1. medium, total: 31616601, unique: 2046622, length of reads: 150bp, paired-end; 2. estradiol, total: 36978357, unique: 1033874, length of reads: 150bp, paired-end; 3. aspirin, total: 35004547, unique: 3402969, length of reads: 150bp, paired-end.
Antibodies	Rabbit monoclonal anti-Estrogen Receptor alpha (Use 4 µg for 25 µg of chromatin, Abcam, ab32063)
Peak calling parameters	MACS2: -g hs -q 0.05 --keep-dup all
Data quality	All identified peaks in the study were called with the qval threshold of 0.05.
Software	FastQC (v0.11.5) Bowtie2 (v2.4.1) Homer (v4.10) MACS2 (v2.1.1) deepTools(v2.4.1) ChIPseeker (v1.5.1)

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	Endometrial tissues were minced into approximately 3 mm pieces and digested into a single-cell suspension by a tissue dissociation kit (Miltenyi Biotec) in a gentleMACS OcboDissociator (Miltenyi Biotec) according to the manufacturer's protocol. The suspension was filtered by a 40 µM strainer to discard cell clumps. Then, the cells were washed twice and centrifuged at 300 × g for 5 min at 4°C. Next, the supernatant was discarded. The cells were stained, for 30 min at 4°C. Then the cells were washed twice with 0.5% BSA in PBS and passed through a 70-µm cell strainer.
Instrument	FACS Aria II (BD Biosciences)
Software	FACS Diva software (BD Biosciences) was used to collect the data.
Cell population abundance	The cells were identified by antibody fluorescence.

Gating strategy | FSC-A and SSC-A were used to identify the starting cell population.

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