

## 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                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( $n$ ) 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 checked="" type="checkbox"/> | <input 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. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> 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 type="checkbox"/>            | <input checked="" type="checkbox"/> 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

Data 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](#)

Data presented in the manuscript will be made available to investigators following request.

## 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

Fecal samples were collected from 34 healthy controls (aged 18 to 73, with no psychological or cognitive impairments) and from 39 patients with Crohn's disease (CD) at Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (key resources table).

Reporting on race, ethnicity, or other socially relevant groupings

None

Population characteristics

All patients were diagnosed according to European Crohn's and Colitis Organization (ECCO) guidelines, including radiologic, endoscopic, clinical symptoms, and pathology. The patients were without antibiotics and probiotics in the month prior to sample collection. Other exclusion criteria included: history of bowel resection; pregnant or lactating women; age <18, or age > 75. The baseline characteristics of the participants are shown in Supplemental Table 1.

Recruitment

The study involved the collection of fecal samples from two distinct groups: healthy controls and patients diagnosed with Crohn's disease (CD). A total of 34 healthy controls, aged between 18 to 73 years and free from psychological or cognitive impairments, were recruited. Additionally, 39 patients with CD were included, all diagnosed according to the European Crohn's and Colitis Organization (ECCO) guidelines, encompassing radiological, endoscopic, clinical, and pathological assessments.

Ethics oversight

Informed consent was obtained from all participants. The experimental protocol was approved by the Clinical Research Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Approval No. 20210622-31) and the Clinical Research Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University (Approval No. V1.0, 20210221). Human colonic biopsies and organoid culture: Colon biopsies were collected from three individuals (2 males, 1 female) during routine colonoscopy at the First Affiliated Hospital of Guangdong Pharmaceutical University. Normal mucosal tissues adjacent to intestinal polyps were obtained with informed consent. These primary tissues were used to establish the human colonic organoid lines described in this study.

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://www.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 determine sample size. The sample sizes were selected based on previous experience and published literature. For in vitro and in vivo experiments, the minimum of sample size was 3 in all the cases. The sample size is stated in the figure legends.

Data exclusions

No data exclusion was performed.

Replication

All the experiments were replicated. The number of replicates is stated in figure legends.

Randomization

Animals of the indicated ages were randomized in the described groups. For all in vitro experiments, experimental treatment group allocation was random.

Blinding

Histology analyses were performed blinded and the investigators were blinded to group allocation during data collection. For other experiments, the investigators were not blinded to group allocation during the data collection, but were blinded to data 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                                           |
|-------------------------------------|-----------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines       |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Animals and other organisms |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                                 |

## Methods

| n/a                                 | Involved in the study                              |
|-------------------------------------|----------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Flow cytometry |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging    |

## Antibodies

### Antibodies used

Anti-mouse CD3 (Flow cytometry) (Rat, Clone 17A2), FITC conjugated, eBioscience, Cat# 11-0032-82, 1/200 dilution  
 Anti-mouse CD4 (Flow cytometry) (Rat, Clone GK1.5), eFluor™ 450 conjugated, eBioscience, Cat# 48-0041-82, 1/200 dilution  
 Anti-mouse CD8a (Flow cytometry) (Rat, Clone 53-6.7), APC conjugated, Tonbo Biosciences, Cat# 20-0081, 1/200 dilution  
 Anti-human/mouse CD11b (Flow cytometry) (Rat, Clone M1/70), PerCP-Cy5.5 conjugated, MultiSciences, Cat# F41011b04, 1/200 dilution  
 Anti-mouse F4/80 (Flow cytometry) (Rat, Clone BM8.1), PE conjugated, MultiSciences, Cat# F21480A02, 1/200 dilution  
 Anti-mouse CD11c (Flow cytometry) (Armenian Hamster, Clone N418), APC conjugated, Biolegend, Cat# 117309, 1/200 dilution  
 Anti-mouse Ly-6G (Flow cytometry) (Rat, Clone 1A8), FITC conjugated, eBioscience, Cat# 11-9668-80, 1/200 dilution  
 TruStain FcXTM (anti-mouse CD16/32) Antibody (Fc block) (Rat, clone 93), BioLegend, Cat# 101320, 1/200 dilution  
 PPARα Mouse mAb (ChIP), Santa Cruz Biotechnology, Cat# sc-398394  
 IL-6 Rabbit pAb (Immunofluorescence), Proteintech, Cat# 21865-1-AP, 1/50 dilution  
 Occludin Rabbit pAb (Immunofluorescence), Proteintech, Cat# 13409-1-AP, 1/100 dilution  
 MUC2 Rabbit pAb (Immunofluorescence), Proteintech, Cat# 27675-1-AP, 1/100 dilution  
 Anti-Ki67 Rabbit mAb (Immunofluorescence), Abcam, Cat# ab16667, 1/250 dilution  
 Phospho-STAT1 (Tyr701) Rabbit pAb (Immunofluorescence), MCE, Cat# HY-P80856, 1/200 dilution  
 HOPX Rabbit pAb (Immunofluorescence), ABclonal, Cat# A15537, 1/100 dilution  
 LGR5 Rabbit pAb (Immunofluorescence), Affinity, Cat# DF2816, 1/400 dilution  
 HMGS2 Rabbit pAb (Immunofluorescence), ABclonal, Cat# A14244, 1/100 dilution  
 PPAR alpha Rabbit pAb (western blot), Affinity, Cat# AF5301, 1/1000 dilution  
 HMGS2 Rabbit pAb (western blot), ABclonal, Cat# A14244, 1/2000 dilution  
 YAP1 Rabbit mAb (western blot), ABclonal, Cat# A21216, 1/1000 dilution  
 Beta Actin Mouse mAb (western blot), Proteintech, Cat# 66009-1, 1/50000 dilution  
 GAPDH Mouse mAb (western blot), Proteintech, Cat# 60004-1, 1/100000 dilution  
 IL-6 Rabbit pAb (western blot), Servicebio, Cat# GB11117-100, 1/500 dilution  
 IL-1 beta Rabbit pAb (western blot), Servicebio, Cat# GB11113-100, 1/800 dilution  
 TNF alpha Rabbit pAb (western blot), Elabscience, Cat# E-AB-33121, 1/600 dilution

### Validation

IL-6 Polyclonal antibody, Xiao Y, 2021, Cancer Cell, 39(3):423-437  
 F4/80 Polyclonal antibody, Pan T, 2021, Theranostics, 11(3):1192-1206  
 Occludin Polyclonal antibody, Zhao M, 2018, EMBO Mol Med, 10(8):e8736  
 MUC2 Polyclonal antibody, Bai R, 2020, EMBO J, 39(13):e103325  
 Occludin Polyclonal antibody, Zhao Z, 2021, Acta Pharm Sin B, 11(9):2859-2879  
 Beta Actin Monoclonal antibody, Qian H, 2020, Nature, 582(7813):550-556  
 ZO-1 Polyclonal antibody, Wang Z, 2023, Redox Biol, 60:102618  
 GAPDH Monoclonal antibody, Zhou R, 2022, Nature, 612(7940):519-527  
 IL-6 rabbit polyclonal antibody, Deng Z, 2020, Oxid Med Cell Longev, 2020:4964202  
 IL-1 beta rabbit polyclonal antibody, Yang L, 2022, Food Sci Nutr, 10(5):1357-1367  
 Histone H3 Mouse Monoclonal Antibody, Xu D, 2020, J Pineal Res, 69(4):e12690  
 TNF alpha Polyclonal Antibody, Fischer A, 2022, 23(4):518-531

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

### Cell line source(s)

293T cells were purchased from ATCC.

|                                                                      |                                                                                                    |
|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Authentication                                                       | The cell lines were authenticated by manufacturers.                                                |
| Mycoplasma contamination                                             | All the Cell lines were tested for mycoplasma contamination by PCR. All the results were negative. |
| Commonly misidentified lines<br>(See <a href="#">ICLAC</a> register) | None                                                                                               |

## 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      | Germ-free (GF) C57BL/6J mice were bred and housed at the Shenzhen Gnotobio Biotechnology Co., Ltd. GF status was confirmed through 16S qPCR analysis before use in relevant experiments, which were also carried out at Shenzhen Gnotobio Biotechnology Co., Ltd. Wild-type C57BL/6J (WT) mice were purchased from the Model Animal Research Center of Nanjing University (Nanjing, China). Nlrp3 <sup>-/-</sup> mice, Ahr-flox mice and Villin-Cre mice were purchased from Cyagen Biosciences Inc (Suzhou, China). Ppara-flox mice were kindly provided by Dr. Aijuan Qu from Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Capital Medical University. Hmgcs2-flox mice were a gift from Dr. Kai Xia from National-Local Joint Engineering Research Center for Stem Cells and Regenerative Medicine, Zhongshan School of Medicine, Sun Yat-sen University. The Bmi1-P2A-CreERT2 mice, Lgr5-CreERT2 mice, H11-CAG-LSL-tdTomato mice and Hopx-CreERT2 mice were purchased from GemPharmatech Co., Ltd (Nanjing, China). Unless otherwise stated, all experiments utilized 6-8-week-old male or female mice. No significant sex-dependent differences were observed in the reported experiments. The mice were housed in a specific-pathogen-free (SPF) facility at Zhejiang University, where they were maintained under controlled conditions of temperature (22 ± 2 °C) and humidity (50 ± 10%), with a constant 12-hour light/dark cycle. They had free access to a regular chow diet (P1101F-25, Suzhou SHUANGSHI) and water throughout the study. |
| Wild animals            | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Reporting on sex        | The research process with the method of male and female in half, so the study not only applies to one gender.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Field-collected samples | Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Ethics oversight        | The ethical guidelines of the Animal Experimentation Ethics Committee of Zhejiang University (No. 27248) and IACUC of Gnotobio (JTAW20240615-1) were followed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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

## Plants

|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Seed stocks           | <i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>                                                                                                                                                                                                                                                                                          |
| Novel plant genotypes | <i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i> |
| Authentication        | <i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>                                                                                                                                                                                                                                       |

## 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 | 1 x 10 <sup>6</sup> cLPMCs were incubated with 1 mg of anti-CD16/32 antibody (BioLegend, 101320) for 10 min to block non-specific binding of immunoglobulin to the Fc receptors. Subsequently, cells were stained for live cells using the Live/Dead Fixable Aqua Dead Cell Stain Kit (BD Biosciences, 564995) for 30 minutes. Following this, the appropriate amount of pre-diluted fluorescent-labeled antibodies (eBioscience, 11-0032-82, 48-0041-82, 11-9668-80; MultiSciences, F41011b04, F21480A02; Tonbo Biosciences, 20-0081; Biolegend, 117309) was added to each tube as per the manufacturer's recommendations. The cells were then incubated in the dark at 4 °C for 30 minutes and washed twice with PBS. |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                           |                                                              |
|---------------------------|--------------------------------------------------------------|
| Instrument                | BD FACSVers                                                  |
| Software                  | FlowJo V10                                                   |
| Cell population abundance | Abundance is reported in figures and methods where relevant. |
| Gating strategy           | The gating strategy is detailed in Extended Data Fig. 1l.    |

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