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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	Microsoft Excel, PRISM-ImageJ (FIJI). PreSens (OXY-4 mini version 2.30FB) and VisiSens software.
Data analysis	IMARIS (IMARIS 7.6 F1 workstation; Bitplane Scientific Software) MATLAB ImageJ (FIJI) Graphpad Prism software R: A language and environment for statistical computing Bioinformatics: Raw reads were analyzed using QIIME 1.0 under standard protocols, and resulting joined reads were aligned to the Greengenes database. The data were loaded into R, and the phyloseq package was used for further processing. Differential abundance of these genera between the culture conditions was quantified by using the DESeq2 package.

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The main data supporting the findings of this study are available within the Article and its Supplementary Information. The raw data generated in this study are available from the corresponding author upon 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	All experiments were carried out with n=3–6 independent biological replicates per experiment (details are provided in Methods and in the figure legends). Sample sizes were determined on the basis of previous experimental experience as well as the power of the statistical test performed.
Data exclusions	No data were excluded from the analyses.
Replication	16S rRNA sequencing data that has been done once with n=4. All other experiments have been reproduced at least twice, with similar results. All experiments were reproducible as assessed in multiple Intestine Chip culture devices per experiment. We did not have cases of irreproducibility.
Randomization	Intestine Chips were randomly allocated into the experimental groups.
Blinding	All 16S rRNA sequencing data collection was done blindly. For other assays, investigators were not blinded to the identities of the samples. However, all experimental and control samples were collected/analyzed at the same time under the same condition, and the quantification was carried out with the same software settings.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Mouse monoclonal to ZO1 (1:200; Life Technologies 33-9100, Clone: ZO1-1A12; Lot: Q1215680) Mouse monoclonal to VE-cadherin/CD144 (1:200; BD Biosciences 555661, Clone: 55-7H1; Lot: 6273648) Rabbit polyclonal to Villin (1:100; Life Technologies PA5-29078, Lot: T12636343A) Rabbit polyclonal to Muc2 (1:100; Santa Cruz Biotechnology sc-15334, Clone: H-300; Lot: F1915) Mouse monoclonal to HIF-1a (1:100; Abcam ab16066; Clone: mgc3; Lot: GR271167) For immunofluorescence, Donkey anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, DyLight 488 (1:500; ThermoFisher SA5-10166, Lot: SC2352413A), Donkey anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, DyLight 488 (1:500; ThermoFisher SA5-10038, Lot: SC2357051A), Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 555 (1:500; ThermoFisher A31570, Lot: 1850121) and Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 555 (1:500; ThermoFisher A31572, Lot: 1837922) secondary antibodies were used.
Validation	ZO1: recommended for immunofluorescence staining by the provider. we performed control experiments, including no primary antibody (negative) controls and comparison to experimental group staining patterns. VE-Cadherin/CD144: recommended for immunofluorescence staining by the provider, and the vendor demonstrated positive staining for CD144 in Human Vein Endothelial Cells (HUVECs). Villin: recommended for immunofluorescence staining by the provider. we performed control experiments, including no primary antibody (negative) controls and comparison to experimental group staining patterns.

Muc2: recommended for detection of Mucin 2 of mouse, rat and human origin by immunofluorescence and immunohistochemistry. The vendor demonstrated positive staining of methanol-fixed SW480 cells showing cytoplasmic localization.

HIF-1a: recommended for immunofluorescence staining by the provider. The vendor demonstrated positive staining for U251, A2058 and HeLa cells.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Caco2 BBE human colorectal carcinoma cell; human intestinal microvascular endothelial cells (HIMECs).
Authentication	Cells were obtained from the Harvard Digestive Disease Center and from ScienCell (company), and validated via phenotype analysis.
Mycoplasma contamination	Caco2 cells received from the Harvard Digestive Disease Center were negative for mycoplasma contamination; HIMECs were negative for mycoplasma, as described in the ScienCell data sheet.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	Five C57/Bl6 4–6-week-old mice of mixed sex.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	Animal experiments were performed under IACUC approval (ID# IS00000187-3; Microbial Effect on Mammalian Host)

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	Cells isolated from human intestinal organoids were derived from resected tissue of a 15-year-old patient diagnosed with ulcerative colitis, and collected from grossly unaffected (macroscopically normal) areas of the terminal ileum during an endoscopy procedure. Infant fecal samples were collected throughout hospitalization from premature infants born prior to 32 weeks of gestation.
Recruitment	The ileal biopsies were derived from resected tissue of a patient undergoing endoscopy for gastrointestinal complaints. Infants were recruited from those who were admitted to the Brigham and Women's Newborn Intensive Care Unit at birth. Infants were followed until discharge.
Ethics oversight	For the ileal biopsies, informed consent and developmentally-appropriate assent were obtained at Boston Children's Hospital from the donors' guardian and the donor, respectively. All methods were carried out in accordance with the Institutional Review Board of Boston Children's Hospital (Protocol# IRB-P00000529) approval. For infant fecal samples, informed consent from guardians was obtained at Brigham and Women's Hospital. All methods were carried out in accordance with a protocol approved by the Partner's Human Research Committee, the Institutional Review Board (IRB) of Partners HealthCare overseeing research at Brigham and Women's Hospital (protocol no. 2016-P-001020).

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