

Reporting Summary

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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 (<i>n</i>) 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 type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
<input type="checkbox"/>	<input checked="" type="checkbox"/> A description of all covariates tested
<input type="checkbox"/>	<input type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
<input type="checkbox"/>	<input 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 type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
<input type="checkbox"/>	<input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
<input 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 type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), 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	FACS Aria I (BD Biosciences), SH800S cell sorter (Sony Biotechnology) , BD FACSymphony, BD LSR Fortessa flow cytometer, LAS-4000 mini luminescent image analyzer, Fluidigm Biomark HD
Data analysis	Microsoft Excel v16.95.1; Microsoft Word v16.95.1; Adobe Photoshop v23; inForm v2.4.8; phenoptr (version not mentioned); phenoptrReports v0.2.8; Ilastik v1.3.2; ImageJ v1.48V; FlowJo v10.6.01; GraphPad v8 and v10; Cell Ranger v5.0.0; R v4.0.2, v4.1.2 and v4.3.1; Seurat v4.0.1 and v5.0.1; SingleCellExperiment v1.24.0; harmony v1.2.0; nt-core/rnaseq v3.4; STAR 2.7.11b; Salmon v1.10.0; GSVA v1.50.5; PROGENy v1.24.0; CellPhoneDB v2.1.7; Python v.3.8.18 and v3.11.8; biomaRt v2.58.2; ktplots v.2.2.0; HISAT v2.2.1; htseq-count 0.11.1; DESeq2 v1.42.0; EnhancedVolcano v1.20.0; clusterProfiler v4.10.1; enrichplot v1.22.0; ComplexHeatmap 2.18.0; pheatmap v1.0.2; ggplot2 v3.4.4; ggalluvial v0.12.5; ggVennDiagram v1.4.13; tidyverse 2.0.0; Xenium Ranger v3.1.1; Squidpy v1.2.2; Scanpy v1.10.1; XeniumExplorer v3.2.0; RStudio v2023.9.1.494; Jupyter Notebook 7.3

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 data necessary to support the conclusions of this paper are included in the article and the Supplementary Materials. The data discussed in this publication have been deposited in NCBI's Gene Expression Omnibus and are accessible through the GEO Series accession numbers listed in the manuscript. The codes used for the analysis of the sequencing data in this manuscript are available at: https://github.com/msaliutina/OSMR_RNA-Seq

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender	The information of the patients whose tissues were used in this study can be found in Supplementary Table 5.
Population characteristics	The information of the IBD and CAC patient samples including age, gender, detailed on the inflammation type can be found in supplementary table 5 and 6. No significant association with age and gender was observed in this study.
Recruitment	Mucosal samples from IBD patients were collected at the Charité University Hospital during surgery. These surgeries were conducted for medical reasons, and the current study did not influence any medical decisions.
Ethics oversight	All patient samples were obtained with written informed consent and in compliance with IRB protocols (protocol number EA1/200/17) at Charité – Universitätsmedizin Berlin. The samples were collected from patients undergoing intestinal resection and processed within 2-4 hours post-collection. For in situ hybridization (ISH) analysis in Fig. S7a, additional samples were sourced from patients at the Mayo Clinic, enrolled in an observational study approved by the Mayo Clinic Institutional Review Board (IRB 10-006628). Informed consent was obtained in accordance with institutional guidelines. Collection procedures strictly adhered to the guidelines of the World Medical Association, including the Declaration of Helsinki and its subsequent amendments

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	For pre-clinical and in vitro studies, no formal sample size calculation was performed. Instead, sample sizes were determined based on prior experience with the respective model systems. For example, group sizes of n = 6–18 mice in colitis and colitis-associated cancer (CAC) models were deemed sufficient to yield statistically meaningful data, accounting for the known inter-individual variability among mice.
Data exclusions	Gene expression datasets: All samples which passes RNA sequencing quality controls were used. Biological experiment: Except in cases of major experimental error, all data were included in the analyses.
Replication	Replication was confirmed through independent biological replicates and experimental repeats, as specified in the respective figure legends.
Randomization	Mice were randomly assigned to groups by genotype and treatment prior to the initiation of the experiment.
Blinding	Mice were assigned unique experimental identifiers based on treatment group and genotype at the outset of each study. All subsequent experimental procedures and analyses were conducted using these identifiers to maintain consistency. Histological assessments were performed by two independent investigators blinded to the experimental design and group allocations.

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

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

Brilliant Violet 785™ anti-mouse CD19 Antibody, Biolegend, Cat# 115543, RRID:AB_11218994, Clone: 6D5, Rat IgG2a, κ, 1:300;
Brilliant Violet 711™ anti-mouse CD8a Antibody, Biolegend, Cat# 100748, RRID:AB_2562100, Clone: 53-6.7, Rat IgG2a, κ, 1:600;
Brilliant Violet 650™ anti-mouse NK-1.1 Antibody, Biolegend, Cat# 108736, RRID:AB_2563159, Clone: PK136, Mouse IgG2a, κ, 1:400;
Pacific Blue™ anti-mouse CD3 Antibody, Biolegend, Cat# 100214, RRID:AB_493645, Clone: 17A2, Rat IgG2b, κ, 1:200;
APC/Cyanine7 anti-mouse Ly-6G/Ly-6C (Gr-1) Antibody, Biolegend, Cat# 108424, RRID:AB_2137485, Clone: RB6-8C5, Rat IgG2b, κ, 1:400;
Alexa Fluor® 700 anti-mouse CD45 Antibody, Biolegend, Cat# 103128, RRID:AB_493715, Clone: 30-F11, Rat IgG2b, κ, 1:3000;
Alexa Fluor® 647 anti-mouse/human CD11b Antibody, Biolegend, Cat# 101218, RRID:AB_389327, Clone: M1/70, Rat IgG2b, κ, 1:500;
PE/Cyanine7 anti-mouse Ly-6C Antibody, Biolegend, Cat# 128018, RRID:AB_1732082, Clone: HK1.4, Rat IgG2c, κ, 1:800;
PE/Cyanine5 anti-mouse/human CD44 Antibody, Biolegend, Cat# 103010, RRID:AB_312961, Clone: IM7, Rat IgG2b, κ, 1:600;
PE/Dazzle™ 594 anti-mouse CD11c Antibody, Biolegend, Cat# 117348, RRID:AB_2563655, Clone: N418, Armenian Hamster IgG, 1:600;
PE anti-mouse CD170 (Siglec-F) Antibody, Biolegend, Cat# 155506, RRID:AB_2750235, Clone: S17007L, Rat IgG2a, κ, 1:500;
PerCP anti-mouse CD4 Antibody, Biolegend, Cat# 100538, RRID:AB_893325, Clone: RM4-5, Rat IgG2a, κ, 1:300;
Alexa Fluor® 488 anti-mouse I-A/I-E Antibody, Biolegend, Cat# 107616, RRID:AB_493523, Clone: M5/114.15.2, Rat IgG2b, κ, 1:500;
FITC anti-mouse CD326 (Ep-CAM) Antibody, Biolegend, Cat# 118208, RRID:AB_1134107, Clone: G8.8, Rat IgG2a, κ, 1:300;
APC anti-mouse Podoplanin Antibody, Biolegend, Cat# 127410, RRID:AB_10613649, Clone: 8.1.1, Syrian Hamster IgG, 1:600;
PE anti-mouse CD31 Antibody, Biolegend, Cat# 102408, RRID:AB_312903, Clone: 390, Rat IgG2a, κ, 1:400;
PE/Cyanine7 anti-mouse CD54 Antibody, Biolegend, Cat# 116121, RRID:AB_2715949, Clone: YN1/1.7.4, Rat IgG2b, κ, 1:300;
BD Horizon™ BV510 Mouse Anti-Ki-67, BD Bioscience, Cat# 563462, RRID:AB_2738221, Clone: B56, Mouse IgG1, κ, 1:200;
Brilliant Violet 785™ anti-mouse CD127 (IL-7Rα) Antibody, Biolegend, Cat# 135037, RRID:AB_2565269, Clone: A7R34, Rat IgG2a, κ, 1:300;
Brilliant Violet 711™ anti-mouse CD90.2 (Thy1.2) Antibody, Biolegend, Cat# 105349, RRID:AB_2800564, Clone: 30-H12, Rat IgG2b, κ, 1:800;
Brilliant Violet 650™ anti-mouse CD45 Antibody, Biolegend, Cat# 103151, RRID:AB_2565884, Clone: 30-F11, Rat IgG2b, κ, 1:1000;
Biotin anti-mouse F4/80 Antibody, Biolegend, Cat# 123105, RRID:AB_893499, Clone: BM8, Rat IgG2a, κ, 1:1000;
APC/Cyanine7 anti-mouse FcεR1α Antibody, Biolegend, Cat# 134325, RRID:AB_2572063, Clone: MAR-1, Armenian Hamster IgG, 1:300;
PE-Cyanine5 anti-mouse TCR gamma/delta, eBioscience, Cat# 15-5711-82, RRID:AB_468804, Clone: eBioGL3, Armenian Hamster IgG, 1:800;
PE/Dazzle™ 594 anti-mouse CD4 Antibody, Biolegend, Cat# 100456, RRID:AB_2565845, Clone: GK1.5, Rat IgG2b, κ, 1:300;
BD Horizon™ BUV737 Rat Anti-Mouse CD3 Molecular Complex, BD Bioscience, Cat# 612803, RRID:AB_2738781, Clone: 17A2, Rat IgG2b, κ, 1:300;
BD Horizon™ BV421 Mouse Anti-Mouse RORγt, BD Bioscience, Cat# 562894, RRID:AB_2687545, Clone: Q31-378, Mouse IgG2a, κ, 1:100;
Brilliant Violet 605™ anti-mouse IL-17A Antibody, Biolegend, Cat# 506927, RRID:AB_11126144, Clone: TC11-18H10.1, Rat IgG1, κ, 1:150;
Alexa Fluor® 700 anti-mouse IFN-γ Antibody, Biolegend, Cat# 505823, RRID:AB_2561299, Clone: XMGI.2, Rat IgG1, κ, 1:200;
Gata-3 Monoclonal Antibody (TWAJ), PE, eBioscience, Cat# 12-9966-42, RRID:AB_1963600, Clone: TWAJ, Rat IgG2b, κ, 1:300;
PE/Cyanine7 anti-T-bet Antibody, Biolegend, Cat# 644824, RRID:AB_2561761, Clone: 4B10, Mouse IgG1, κ, 1:100;
IL-22 Monoclonal Antibody (1H8PWSR), PE, eBioscience, Cat# 12-7221-82, RRID:AB_10597428, Clone: 1H8PWSR, Rat IgG1, κ, 1:250;
EOMES Monoclonal Antibody (Dan11mag), Alexa Fluor™ 488, eBioscience, Cat# 53-4875-80, RRID:AB_2802207, Clone: Dan11mag, Rat IgG2a, κ, 1:100;
Polyclonal goat anti-mouse OSMRβ biotin conjugated antibody, R&D Systems, Cat# BAF662, Lot# DZZ011021, 1:200;
Biotin anti-phycoerythrin (PE) Antibody, Biolegend, Cat# 408104, RRID:AB_2561761, Clone: PE001, Mouse IgG1, κ, 1:200;
Streptavidin, PE, Miltenyi Biotec, Cat# 130-106-789, RRID:AB_2661577, 1:1000;
PE/Cyanine7 anti-mouse CD31 Antibody, Biolegend, Cat# 102418, RRID:AB_830756, Clone: 390, Rat IgG2a, κ, 1:800;
Brilliant Violet 421™ anti-mouse CD326 (Ep-CAM) Antibody, Biolegend, Cat# 118225, RRID:AB_2563983, Clone: G8.8, Rat IgG2a, κ, 1:300;
Anti-Human OSMR-β PE, Invitrogen, Cat# 12-1303-42, RRID:AB_1633423, Clone: AN-V2, Mouse IgG1, 1:100;
Alexa Fluor® 700 anti-human CD45 Antibody, Biolegend, Cat# 505823, RRID:AB_2561299, Clone: HI30, Mouse IgG1, κ, 1:400;
APC anti-human CD326 (EpCAM) Antibody, Biolegend, Cat# 505823, RRID:AB_2561299, Clone: 9C4, Mouse IgG2b, κ, 1:100;
Biotin anti-mouse FcεR1α Antibody, Biolegend, Cat# 134303, RRID:AB_1626100, Clone: MAR-1, Armenian Hamster IgG, 1:1000;
Biotin anti-mouse CD19 Antibody, DRFZ Berlin, Clone: 1d3, Mouse IgG1, 1:1000;
Biotin anti-mouse CD11c Antibody, DRFZ Berlin, Clone: N418, Mouse IgG1, 1:1000;
Biotin anti-mouse Ly6G/C (Gr1) Antibody, DRFZ Berlin, Clone: RB6-8C5, Mouse IgG1, 1:1000;

Biotin anti-mouse F4/80 Antibody, DRFZ Berlin, Clone: F4/80, Mouse IgG1, 1:1000;
 Streptavidin, APC-Vio® 770, Miltenyi Biotec, Cat# 130-106-794, RRID:AB_2661586, 1:250;
 Zombie Aqua™ Fixable Viability Kit, Biolegend, Cat# 423102, 1:400;
 eBioscience™ Fixable Viability Dye eFluor™ 780, eBioscience, Cat# 65-0865-18, 1:1000;
 eBioscience™ Calcein AM Viability Dye (UltraPure Grade), eBioscience, Cat# 65-0853-78, 1:500; β-Actin (13E5) Rabbit mAb, Cell Signaling Technology, Cat# 4970, RRID:AB_2223172, Clone: 13E5, Rabbit IgG, 1:1000;
 Anti-rabbit IgG, HRP-linked Antibody, Cell Signaling Technology, Cat# 7074, RRID:AB_2099233, Goat, 1:2000;
 STAT3 (D3Z2G) Rabbit mAb, Cell Signaling Technology, Cat# 12640, RRID:AB_2629499, Clone: D3Z2G, Rabbit IgG, 1:1000;
 STAT1 (D1K9Y) Rabbit mAb, Cell Signaling Technology, Cat# 14994, RRID:AB_2737027, Clone: D1K9Y, Rabbit IgG, 1:1000;
 Phospho-Stat3 (Tyr705) (D3A7) XP Rabbit mAb, Cell Signaling Technology, Cat# 9145, RRID:AB_2491009, Clone: D3A7, Rabbit IgG, 1:1000;
 Phospho-Stat1 (Tyr701) (D4A7) Rabbit mAb, Cell Signaling Technology, Cat# 7649, RRID:AB_10950970, Clone: D4A7, Rabbit IgG, 1:1000;
 Biotin anti-mouse NGAL (Lipocalin-2), Biolegend, Cat# 532304, RRID:AB_2686952, Clone: M0417A8, Rat IgG2a, λ, 1:300;
 Purified anti-mouse NGAL (Lipocalin-2), Biolegend, Cat# 532202, RRID:AB_2650711, Clone: M047A10, Rat IgG2a, κ, 1:5000;
 Recombinant Mouse NGAL (Lipocalin-2) (ELISA Std.), Biolegend, Cat# 563601;
 Mouse S100A8/S100A9 Heterodimer DuoSet, R&D Systems, Cat# DY8596-05

Validation

All staining antibodies used in this study were commercially validated, with detailed validation information available on the respective manufacturers' websites. The anti-mouse OSMR antibody was additionally verified using endothelial cells isolated from Cdh5-Cre OSMRfl/fl mice.

Eukaryotic cell lines

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

Cell line source(s)

Caco-2 and HCA-7 human epithelial colorectal adenocarcinoma cell lines were obtained from ATCC.
 Primary organoids cultures were cultured in our lab using different mouse lines or wild type mice (C57BL/6J)

Authentication

The cell lines were not authenticated

Mycoplasma contamination

All cell lines tested negative for mycoplasma contamination

Commonly misidentified lines
(See [ICLAC](#) register)

No such cell lines were used

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

Female C57BL/6 mice were obtained from Charles River (Germany). Osmrfl/fl mice (B6;129-Osrmrtm1.1Nat/J; Jax Strain #:011081) were obtained from The Jackson Laboratory and genotyped via PCR to confirm the targeted allele deletion. VillinCreERT2, Col1a2creERT2, or Cdh5cre were crossed with Osmrfl/fl to establish cell type-specific OSMR-deficient mouse lines including VillinCreERT2 Osmrfl/fl (IECs-Osmr), Col1a2creERT2 Osmrfl/fl (Stroma-Osmr), or Cdh5cre Osmrfl/fl (Endo-Osmr); or with B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J (Ai9) to generate VillinCreERT2 Ai9, Col1a2creERT2 Ai9, or Cdh5cre Ai9; and with Stat3fl/fl to generate VillinCreERT2 Stat3fl/fl. VillinCre were crossed with Stat3fl/fl. Rag2-/- Rorc-/- mice were provided by Chiara Romagnani, VillinCre Stat3fl/fl were obtained from Stefan Wirtz, and VillinCre Il22ra1fl/fl, Il22-/-, and Stat1-/- mouse lines were provided by Andreas Diefenbach and Max Löhning, respectively.

Wild animals

No wild animals were used in this study

Reporting on sex

Only female mice were used in this study, as it is not practical to randomize male mice into co-housed treatment groups due to aggressive behavior between non-littermate males. Additionally, mice were co-housed with wild-type mice from Charles River to ensure a diverse gut microbiota and to minimize microbiota drift associated with specific breeding facilities.

Field-collected samples

No field collected samples in this study

Ethics oversight

All mice were bred under specific pathogen-free (SPF) conditions at the animal facilities of the Federal Institute for Risk Assessment (Berlin, Germany), the Research Institute for Experimental Medicine (FEM) of Charité (Berlin, Germany), Genentech (Dixon, California, USA), or the Jackson Laboratory. Animal experiments conducted in Germany were approved by the responsible governmental authority (Landesamt für Gesundheit und Soziales) under application G 0291/18 and were performed in accordance with German animal protection laws. Studies performed at Genentech were approved by Genentech's Institutional Animal Care and Use Committee and adhered to the NRC Guidelines for the Care and Use of Laboratory Animals.

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

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	The colons were processed to isolate lamina propria mononuclear cells (LPMCs) and stroma cells through sequential EDTA washes, collagenase digestion, and Percoll gradient separation. The EDTA washes were also collected for intestinal epithelial cell isolation. the cells were filtered and prepared as needed for further downstream analyses.
Instrument	Data acquisition was performed using a BD FACSymphony or BD LSR Fortessa flow cytometer, and for cell sorting the LPMCs were sorted using a FACS Aria I (BD Biosciences) equipped with a 70-µm nozzle, while stromal and epithelial cells were sorted using an SH800S cell sorter (Sony Biotechnology) with a 100-µm nozzle.
Software	The data were analyzed using FlowJo v10.6.01
Cell population abundance	The purity of the sorted epithelial, stromal, and immune cells was assessed immediately after cell sorting, and the purity was above 95%. Examples of the cell purity are shown in Fig. S7.
Gating strategy	A detailed gating strategy for FACS analysis is provided in Fig. 5c, Fig. S5a, b, Fig. S6b, Fig. S7a-c, ED Fig2e, ED Fig. 8a, d. The gating strategy is also clearly explained in the figure legends.
<input checked="" type="checkbox"/> Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.	