Table S1. **Primers for real-time PCR**

Name	Sequences of primers
VDR Fw	5- ATGCGGCAATCTCCATTGAAG -3
VDR Rv	5- GAATGTGCCTCGGATCTGTGG -3
Atg16L1 Fw	5- CAGAGCAGCTACTAAGCGACT -3
Atg16L1 Rv	5- AAAAGGGGAGATTCGGACAGA- 3
LYZ Fw	5- GAGACCGAAGCACCGACTATG -3
LYZ Rv	5- CGGTTTTGACATTGTGTTCGC-3
IFNγ Fw	5-GCCACGGCACAGTCATTGA-3
IFNγ Rv	5-TGCTGATGGCCTGATTGTCTT-3
IL1β Fw	5-GAAATGCCACCTTTTGACAGTG-3
IL1β Rv	5-TGGATGCTCTCATCAGGACAG-3
TNFα Fw	5-CAGGCGGTGCCTATGTCTC-3
TNFα Rv	5-CGATCACCCCGAAGTTCAGTAG-3
β-actin Fw	5- TGTTACCAACTGGGACGACA -3
β-actin Rv	5- CTGGGTCATCTTTTCACGGT -3

Table S2. Bacterial 16S rDNA Real-time PCR primers.

Primers name	Sequence
Bacteroidales fragilis 16s F	5′- GGCGCACGGGTGAGTAACA -3′
Bacteroidales fragilis 16s R	5′- CAATATTCCTCACTGCTGC -3′
Lactobacillus 16s F	5′- AGCAGTAGGGAATCTTCCA-3′
Lactobacillus 16s R	5′- CACCGCTACACATGGAG-3′
E.Coli 16s F	5′- CCTACGGGAGGCAGCAGT -3′
E.Coli 16s R	5′- CGTTTACGGCGTGGACTAC -3′
Univ bacteria 16s F	5′- TCCTACGGGAGGCAGCAGT -3′
Univ bacteria 16s R	5′- GGACTACCAGGGTATCTAATCCTGTT -3′

STAR*METHODS KEY RESOURCES TABLE

REAGENT or RESOURCE	**SOURCE**	**IDENTIFIER**
Bacterial and Virus Strains		
S. Typhimurium ATCC 14028s	Zhang et al., 2012	N/A
GFP-*Salmonella*	Zhang et al., 2012	N/A
Experimental Models: Organisms/Strains		
VDR^{loxp}mice	Van Cromphaut et al., 2001	NA
Defα6-cre mice	Adolph et al., 2013	NA
REAGENT or RESOURCE		
Antibodies		
ATG16L1	Abcam	Cat # ab188642
LYZ	Santa cruz	Cat # sc-518058
VDR	Santa cruz	Cat # sc-13133
β-actin	Sigma-Aldrich	Cat # A5316
CD24	Invitrogen	Cat #12-0241-82
Alexa Fluor 594 donkey anti-rabbit IgG	Invitrogen	Cat # A32740
Alexa Fluor 488 donkey anti-mouse IgG	Invitrogen	Cat # A32766
Chemicals, Peptides, and Recombinant Proteins		
Fetal bovine serum	GIBCO	Cat # 16000044
DMEM	GIBCO	Cat # 11965084
Penicillin-streptomycin	GIBCO	Cat # 15140122
TRIzol	Thermo Fisher Scientific	Cat # 15596026
Pierce™ BCA protein assay kit	Thermo Fisher Scientific	Cat # 23225
iScript cDNA synthesis kit	BioRad	Cat # 1708840
SYBR Green PCR kit	BioRad	Cat # 1708880
Phosphate-Buffered Saline	Corning	Cat#21-040-CV
Triton X-100	Fisher BioReagents	BP151-100
16% Formaldehyde	Fisher BioReagents	Cat#28908
sucrose	Fisher BioReagents	Cat#15503022
LB Broth, Miller	Fisher BioReagents	Cat#BP1426
LB Agar, Miller	Fisher BioReagents	Cat#BP1425
TNF alpha Mouse ELISA Kit	Thermo Fisher Scientific	Cat # BMS607-3
LAL Chromogenic Endpoint Assay	Hycult Biotech	Cat# HIT302
Lcn-2 ELISA kit	R&D Systems	Cat# DY1857
ProcartaPlexTM Multiplex kit	Thermo Fisher Scientific	Cat# 26088-901
RNAqueous-Micro Kit	Thermo Fisher Scientific	Cat#AM1931
TrypLE	GIBCO	Cat#12605-010
Cyto ID® autophagy detection kit	ENZO	Cat# 031-K200

Oligonucleotides		
Primers for VDR, see Table S1	IDT	N/A
Primers for ATG16L1, see Table S1	IDT	N/A
Primers for LYZ, see Table S1	IDT	N/A
Primers for IFNγ, see Table S1	IDT	N/A
Primers for IL1β, see Table S1	IDT	N/A
Primers for TNFα, see Table S1	IDT	N/A
Bacteroidales fragilis 16s F Table S2	IDT	N/A
Bacteroidales fragilis 16s R Table S2	IDT	N/A
Lactobacillus 16s F Table S2	IDT	N/A
Lactobacillus 16s R Table S2	IDT	N/A
E.Coli 16s F Table S2	IDT	N/A
E.Coli 16s R Table S2	IDT	N/A
Univ bacteria 16s F Table S2	IDT	N/A
Univ bacteria 16s R Table S2	IDT	N/A
Software and Algorithms		
FlowJo Version 10.3	Treestar	www.flowjo.com/
Microsoft Excel Version 16.24	Office 365	www.office.com/
Prism Version 8.1.1	GraphPad	www.graphpad.com/
Zeiss LSM710 confocal microscope	Carl Zeiss	N/A
Nanodrop 2000	Thermo Fisher Scientific	N/A
PALM RoboSoftware	Carl Zeiss	N/A

Figure S1: Proliferation marker PCNA and β-catenin (p-Ser552) are downregulated in the $VDR^{\Delta PC}$ mice, compared with the VDR^{Lox} mice.

(A) The expression of PCNA in the ileum tissue in the $VDR^{\Delta PC}$ mice was lower than that in the VDR^{lox} mice, as determined by IHC staining. Images are representative of experiments in triplicate; Data are expressed as mean ± SD, n=6; Welch's t test; *P < 0.05.

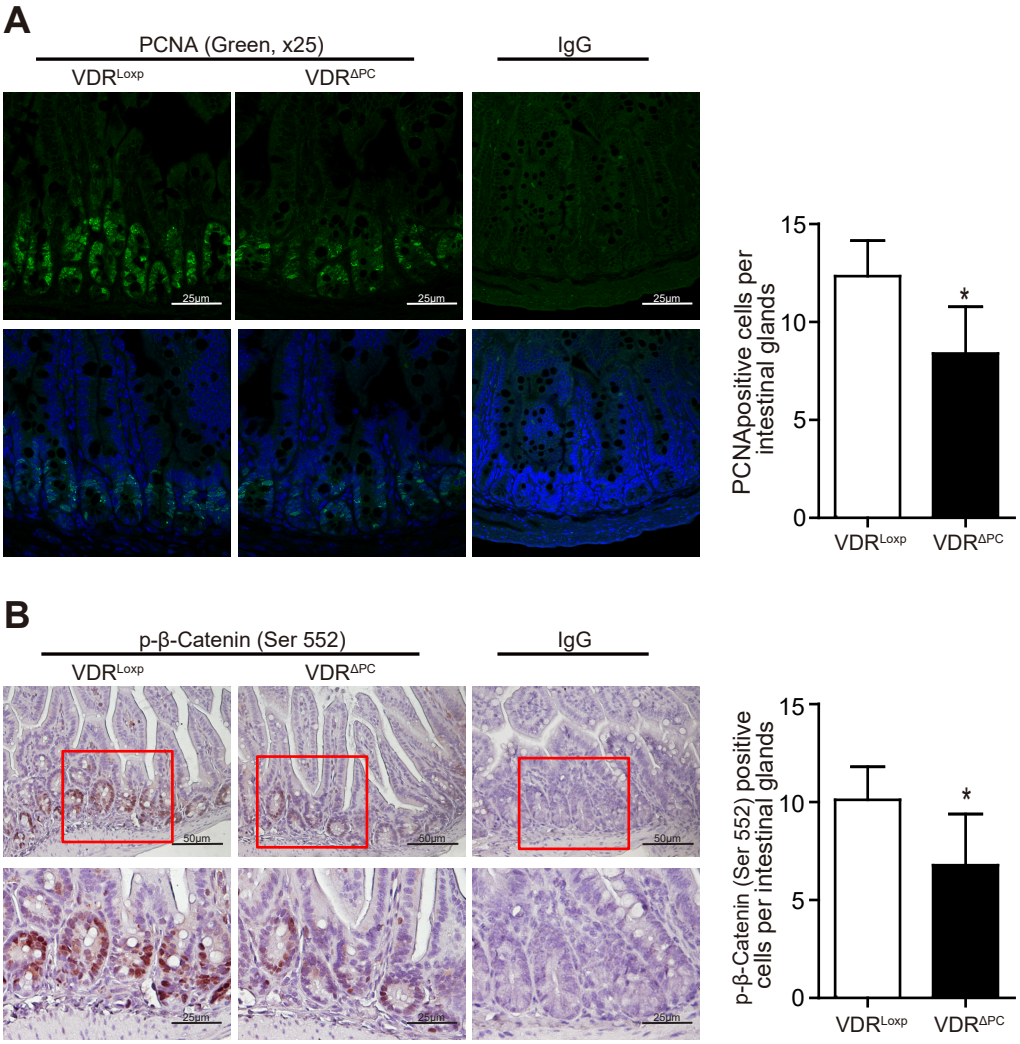
(B) The expression of p-β-catenin (Ser552) in the ileum tissue in the $VDR^{\Delta PC}$ mice was lower than that in the VDR^{lox} mice, as determined by IHC staining. Images were representative of experiments in triplicate; Data were expressed as mean ± SD, n=6; Welch's t test; *P < 0.05).

Figure S2. Lack of VDR in intestinal Paneth cells affected gut microbiota and sensitivity to DSS damage.

(A) H&E of colon tissues from $VDR^{\Delta PC}$ mice and VDR^{LoxP} mice with or without co-housing in DSS-colitis. Images were representative of experiments in triplicate.

(B) Inflammation scores in the colon tissues of the $VDR^{\Delta PC}$ mice were reduced after co-housing with VDR^{LoxP} mice. Data were expressed as mean ± SD, n = 5-6; one way ANOVA test; **P < 0.01).

(C) The numbers of Paneth cells per crypt in the $VDR^{\Delta PC}$ mice were restored after co-housing with VDR^{LoxP} mice. Data were expressed as mean ± SD, n = 5-6; one way ANOVA test; *P < 0.05, ***P < 0.001.


A
PCNA (Green, x25)
IgG
VDRLoxp
VDRΔPC
25μm
PCNApositive cells per intestinal glands
15
10
5
0
*
VDRLoxp
VDRΔPC
B
p-β-Catenin (Ser 552)
IgG
VDRLoxp
VDRΔPC
50μm
25μm
p-β-Catenin (Ser 552) positive cells per intestinal glands
15
10
5
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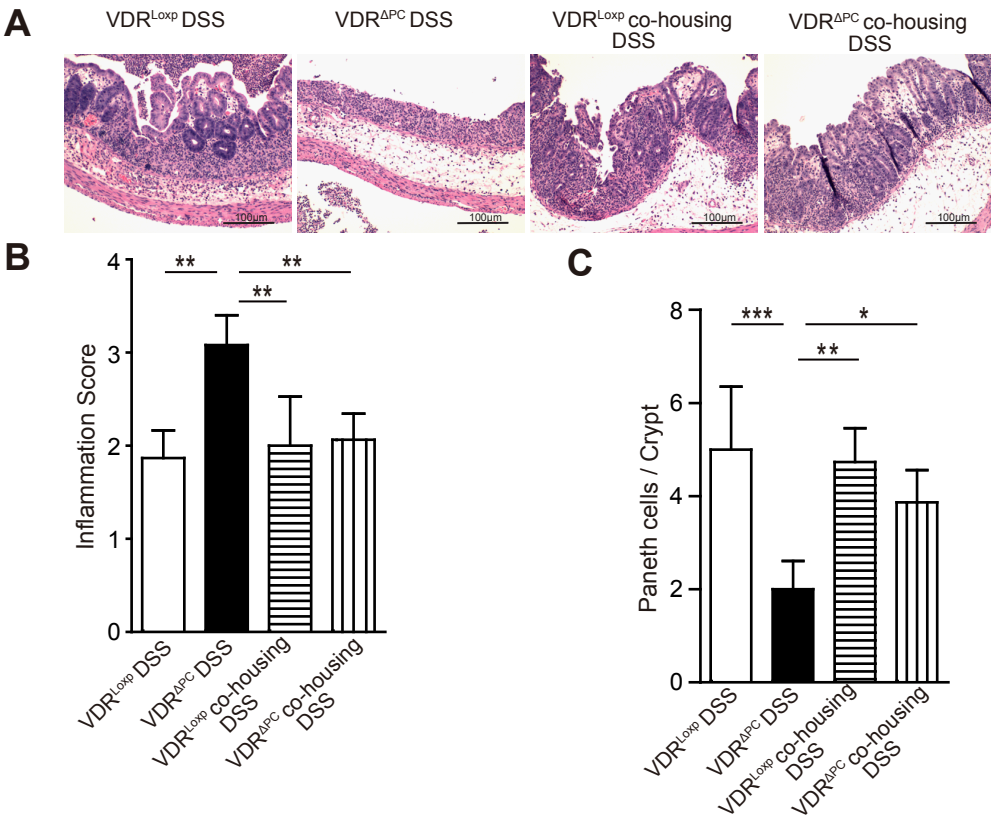
*
VDRLoxp
VDRΔPC


A
VDR^Loxp DSS
VDR^ΔPC DSS
VDR^Loxp co-housing DSS
VDR^ΔPC co-housing DSS
100μm
B
Inflammation Score
0
1
2
3
4
**
**
**
VDR^Loxp DSS
VDR^ΔPC DSS
VDR^Loxp co-housing DSS
VDR^ΔPC co-housing DSS
C
Paneth cells / Crypt
0
2
4
6
8
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*
**
VDR^Loxp DSS
VDR^ΔPC DSS
VDR^Loxp co-housing DSS
VDR^ΔPC co-housing DSS

METHOD DETAILS

LEAD CONTACT AND MATERIALS AVAILABILITY

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Jun Sun (Junsun7@uic.edu).

Human intestinal biopsies

Slides containing paraffin-embedded small intestinal biopsy samples of patients with CD and healthy controls were obtained from Dr. Arthur Kaser, University of Cambridge, Cambridge, U.K. After obtaining written informed consent, human intestinal biopsies from the terminal ileum of CD patients and healthy controls were collected upon colonoscopy and stored in optimal cutting temperature compound. All protocols were approved by Cambridgeshire 4 Research Ethics Committee (reference 03/5/012). Patient characteristics are outlined in previous publication [1].

Gene expression datasets

For expression analyses, we took advantage of microarray data reported in the Gene Expression Omnibus [2] repository (https://www.ncbi.nlm.nih.gov/geo/). In particularly, gene expression data in biopsy of human intestinal tissues were obtained from the dataset (GEO accession number GSE102134) reported on ileum of patients with Crohn's Disease and normal ileum from control individuals [3]. Gene expression data for VDR and ATG16L1 from CD patients (n=51) and normal (n=11) were extracted and further analyzed in our study.

Experimental Animals

$VDR^{loxP/loxP}$ mice were originally developed by Dr. Geert Carmeliet [4]. DEFA6-cre mice were from Dr. Richard Blumberg [5]. Paneth cell VDR specific knockouts ($VDR^{\Delta PC}$) were obtained by crossing $VDR^{loxP/loxP}$ mice with DEFA6-cre mice. The mice were provided with water ad libitum and maintained in a room with a 12 h dark/light cycle. Multiple breeding pairs were set up within a specific vivarium room where environment, cage changes, and dietary schedules are more uniform**.** All animal work adhere to the ARRIVE guidelines and was approved by the University of Illinois at Chicago Committee on Animal Resources and ethical guidelines were followed with the treatment.

Bacterial strains and growth conditions

The *Salmonella* strain used in this study was *S*. Typhimurium 14028 [6]**.** Bacterial cultures were prepared by inoculating 10 ml of Luria–Bertani broth with 0.01 ml of a stationary-phase culture, followed by overnight incubation (> 18 h) at 37 ℃, as previously described [7, 8].

***Salmonella*-infected mouse model**

Animal experiments were performed using $VDR^{loxP/loxP}$ and $VDR^{\Delta PC}$ mice (male and female, 2–3-month-old). Water and food were withdrawn 4 h before oral gavage, with 7.5 mg/ mouse of streptomycin. Afterwards, the animals were supplied with water and food ad libitum. Twenty hours after the streptomycin treatment, the water and food were withdrawn again for 4 h, before the mice were infected with $1*10^6$ colony-forming units of *Salmonella* (100-ml suspension in HBSS by gavage, as previously described [7, 8].

Co-housing of VDR^{lox} and $VDR^{\Delta PC}$ mice

Two-to-three-month-old female VDR^{lox} and $VDR^{\Delta PC}$ mice were co-housed in new cages according to previously published methods[9]. One cage contained three VDR^{lox} and two $VDR^{\Delta PC}$, another one contained two mice each. The mice were fed with the same food and water. After 4 weeks of co-housing, 5% DSS dissolved in filter-purified water was administered to the mice. Animals were weighed daily. At day 7 after DSS administration, mice were sacrificed under anesthesia.

Induction of DSS-colitis

Mice were administered 5% DSS (MW = 40–50 kDa; USB Corp. Cleveland, OH) dissolved in filter-purified and sterilized water ad libitum for the experimental period. Animals were weighed daily. At day 7 after DSS administration, mice were sacrificed under anesthesia. Severity of colitis was quantified by a disease activity index, determined by weight loss, fecal blood and diarrhea.

Induction of small-intestinal lesions

To induce small-intestinal injury, 10 mg/kg indomethacin (Sigma Chemical, St. Louis, MO, USA) was subcutaneously given to non-fasted animals. The animals were killed 24 h after anesthetization. The jejunum and ileum were then removed, opened along the anti-mesenteric attachment, and examined for lesions under a dissecting microscope with square grids. The area (mm^2) of visible lesions was macroscopically measured, summed per small intestine and expressed as an ulcers core[10].

EXPERIMENTAL DETAILS

***Salmonella*-infected mouse model**

Animal experiments were performed using $VDR^{loxP/loxP}$ and $VDR^{\Delta PC}$ mice (male and female, 2–3-month-old). Water and food were withdrawn 4 h before oral gavage, with 7.5

mg/ mouse of streptomycin (100 ml of sterile solution). Afterwards, the animals were supplied with water and food ad libitum. Twenty hours after the streptomycin treatment, the water and food were withdrawn again for 4 h, before the mice were infected with $1*10^6$ colony-forming units of *Salmonella* (100-ml suspension in HBSS (Hank's Balanced Salt Solution) or treated with sterile HBSS (control) by oral gavage, as previously described [7, 8]. After the *Salmonella* gavage, the tissue samples were collected after 8 hours and 4 days. The mice were sacrificed under anesthesia. The severity of the colitis was quantified by a disease activity index, determined by weight loss, fecal blood, and diarrhea. The intestines were harvested, fixed in 10 % formalin (pH 7.4), processed, and embedded in paraffin. Sections (5 µm) were stained with H&E. Blinded histological inflammatory scores were performed by a validated scoring system by a trained pathologist [9].

Immunoblotting

Mouse intestine tissues were lysed in lysis buffer (1 % Triton X-100, 150 mM NaCl, 10 mM Tris (pH 7.4), 1 mM EDTA, 1 mM EGTA (pH 8.0), 0.2 mM sodium orthovanadate, and protease inhibitor cocktail), and the protein concentrations were measured. Equal amounts of protein were separated by SDS-polyacrylamide gel electrophoresis, transferred onto nitrocellulose membranes, and immunoblotted with anti-ATG16L1 (Abcam, Cambridge, MA, USA), anti-Lysozyme (Cell Signal, Beverly, MA), and anti-VDR antibodies (Santa Cruz Biotechnology Inc., CA) as previously described [11, 12].

Real-time quantitative PCR analysis

Total mRNA was extracted from the scraped mouse colonic epithelial cells using TRIzol reagent (Invitrogen, Carlsbad, CA), and reverse transcribed using the iScript cDNA synthesis kit (BioRad, Hercules, CA). cDNA was then subjected to real-time PCR (SYBR

Green PCR kit, BioRad) with primers (**Table S1**). The percent expression was calculated as the ratio of the normalized value of each sample relative to that of the corresponding untreated control samples. All real-time PCR reactions were performed in triplicate.

Immunohistochemistry

Intestinal tissues were fixed in 10 % buffered formalin and processed the next day with standard techniques as previously described [7, 12-14]. The slides were stained with anti-VDR (Santa Cruz Biotechnology Inc., CA) and anti-ATG16L1 (Abcam, Cambridge, MA, USA). Immunohistochemistry of VDR and ATG16L1 staining was initially assessed as a product of staining intensity (0, no staining; 1, minimal; 2, slight; 3, moderate; 4, marked intensity). We randomly took 3 scores derived from each samples. The final analytical sample consisted of 18 normal and 24 CD samples.

Immunofluorescence

Ileum tissues were freshly isolated and embedded in paraffin wax after fixation with 10 % neutral buffered formalin. Immunofluorescence was performed on paraffin-embedded sections (4 μm), after preparations of the slides, as described previously [15], followed by incubation for 1 hour in a blocking solution (2 % bovine serum albumin, 1 % goat serum in HBSS) to reduce the non-specific background of staining. The tissue samples were incubated overnight with primary antibodies at 4 °C. The following antibodies were used: anti-ATG16L1 (Abcam, Cambridge, MA, USA), anti-Lysozyme (Cell Signal, Beverly, MA), anti-Defensin 4, and anti-VDR antibodies (Santa Cruz Biotechnology Inc., CA). Slides were washed 3 times for 5 minutes each at room temperature in the wash buffer. The samples were then incubated with secondary antibodies (goat anti-rabbit Alexa Fluor 488, Molecular Probes, CA; 1:200) for 1 hour at room temperature. Tissues were mounted with SlowFade Antifade Kit (Life technologies, s2828, Grand Island, NY, USA),

followed by a coverslip, and the edges were sealed to prevent drying. Specimens were examined with a Zeiss laser scanning microscope (LSM 710, Carl Zeiss Inc., Oberkochen, Germany).

Laser capture microdissection of Paneth cells

Laser capture microdissection (LCM) of individual Paneth cells was performed with the PixCell I LCM System (Arcturus Engineering, Mountain View, CA), as previously described [16]. The LCM was performed on a Zeiss Axiovert 200M microscope equipped with PALM RoboSoftware (Carl Zeiss, Thornwood, NY), and the total area of the tissue collected per slide was tracked and recorded. The RNA was isolated from the dissected tissue by following the protocol provided by the RNA queous-Micro kit (Ambion, Austin, TX) via column purification [17].

Transmission electron microscopy

For transmission electron microscopy (TEM), small intestines were fixed in 4 % paraformaldehyde / 3 % glutaraldehyde, in 10 mM sodium phosphate buffer (pH 7.4) for 48 h. All samples were post-fixed with 1 % osmium tetroxide in 100 mM cacodylate buffer (pH 7.4) on ice for 1 h. Samples were then treated with 0.5 % aqueous uranyl acetate, dehydrated in graded alcohol, treated with propylene oxide, and embedded in Embed 812 (Electron Microscopy Sciences). The resin was polymerized in a 60 °C oven for 2–3 d. The samples were sliced into 1 × 2 × 2 mm pieces and examined with a Philips CM 100 electron microscope (Philips, Eindhoven, The Netherlands) at an accelerating voltage of 80 KV for images.

Lipopolysaccharides (LPS) detection

LPS in serum samples was measured with Limulus amebocyte lysate (LAL) chromogenic endpoint assays (HIT302, Hycult Biotech, Plymouth Meeting, PA, USA), according to the manufacturer's indications. The samples were diluted 1:4 with endotoxin-free water and then heated at 75 °C for 5 min, in a warm plate to denature the protein before the reaction. A standard curve was generated and used to calculate the concentrations, which were expressed as EU/ml, in the serum samples.

Quantification of serum 1,25-dihydroxyvitamin D3 by ELISA

Mouse blood samples were collected by cardiac puncture and placed in tube containing EDTA (10mg/ml). The serum was collected after centrifugation. The level of serum 1,25-dihydroxyvitamin was detected by a mouse 1, 25-dihydroxyvitamin D3 (DVD/DHVD3) ELISA Kit (Biomatik, Delaware, USA).

Quantification of fecal lipocalin 2 (Lcn-2) by ELISA

Freshly collected fecal samples were reconstituted in PBS containing 0.1 % Tween 20 (100 mg/ml) and vortexed for 20 min to get a homogenous fecal suspension. These samples were then centrifuged for 10 min at 12 000 rpm and 4 ^{o}C. The clear supernatants were collected. The fecal Lcn-2 level was estimated using Duoset murine Lcn-2 ELISA kit (R&D Systems, Minneapolis, MN).

Quantification of fecal defensin-6 by ELISA

Ileum tissue samples were collected from VDR^{lox} and $VDR^{\Delta PC}$ mice. 100mg tissue was rinsed with 1X PBS, the homogenates were centrifuged for 5 minutes at 5000 x g, 2 - 8°C. The supernatant was collected and assayed immediately. The defensin-6 level was estimated using Mouse defensin-6 (DEFA6) ELISA Kit (MyBioSource, San Diego, CA).

Autophagy activity

Autophagy activity were quantified using the commercial Cyto ID® autophagy detection kit (ENZO Life Sciences, ENZ-51,031-K200), in accordance with the manufacturer's protocol. The kit contained a 488 nm excitable green fluorescent detection reagent that became brightly fluorescent when incorporated into the vesicles produced during autophagy. Then the specimens were examined with a Zeiss laser scanning microscope (LSM 710 (Carl Zeiss Inc., Oberkochen, Germany).

Isolation of Paneth cell

The small intestines were harvested. The intestines were flushed with cold PBS to remove the large debris and then cut lengthwise to open the intestinal segment. They were then placed in ice-cold PBS and rocked for 5 min in a cold room. The PBS was carefully removed and Buffer #1 added (2mM EDTA in PBS). They were then rocked for 30 min in a cold room, Buffer #1 was then carefully removed and Buffer #2 added (54.9 mM D-sorbitol and 43.4 mM sucrose in PBS) in 15 ml conical tubes. They were shaken for 2~3 min vigorously by hand to dissociate the crypts from the intestine as much as possible. They were then put in a 100 μm cell strainer on top of a 50 ml conical tube on ice and Buffer #2 was pouted on top of the contents. The tubes were then centrifuged at 150 g for 10 min at 4 ℃ and the supernatant removed as much as possible without disturbing the pellet. The crypts were resuspended with TrypLE Express supplement with DNAse I (200 U/ml), and incubated at 37 ℃, with gentle shaking every 5 min. The solution was filtered through a 70 μm filter and centrifuged at 200 g for 10 min at 4 ℃. The pellet was resuspended with a flow washing buffer (2 mM EDTA and 1 % FBS in PBS), incubated with CD24-PE Ab in the dark at 4 ℃ for 15 min. It was then centrifuged

at 150 g for 5 min, then the cells were washed 2 times with the washing buffer. The pellet was then resuspended with the washing buffer for flow sorting.

Real-Time PCR Measurement of Bacterial DNA

Mice feces sample DNA was extracted using the stool DNA Kit (Omega Bio-tek, Norcross, GA) according to the manufacturer's instructions. 16S ribosomal DNA PCR reactions used the MyiQ single-color real-time PCR detection system (Bio-Rad Laboratories) and iTaq Universal SYBR green supermix (1725121; Bio-Rad Laboratories) according to the manufacturer's directions. Primers specific to 16S ribosomal RNA were used as an endogenous control to normalize loading between samples. The relative amount of 16S ribosomal DNA in each sample was estimated using the ΔΔCT. Primer sequences were designed using Primer-BLAST or were obtained from the Primer Bank primer pairs listed in Table S2.

Shotgun metagenomic sequencing

We used whole-genome shotgun sequencing to sequence fecal samples. Genomic DNA was fragmented into relatively small pieces prior to sequencing. Sequencing was performed using a recent Illumina HiSeq system[18]. Basic processing of the raw data for all samples were performed including the quality checking, filtering the reads, removing noisy sequences, metagenomic assembly, gene calling and binning[19]. We filtered the resulting assemblies to exclude contigs shorter than 1,000 nucleotides or *base pairs* (*bp*) and classified all remaining contigs with Centrifuge [20], an efficient metagenomic classifier capable of indexing the entirety of nucleotide (nt), searching for the comprehensive NCBI Genbank non-redundant nucleotide database to obtain a taxonomic classification

of each contig(genes) (as described in https://merenlab.org/2016/06/18/importing-taxonomy). Identical sequences with ≥99% identity of each other have been removed to make it nonredundant, but even after this reduction, in a total of 10 samples, this data set contains over 70 million reads, with an average of 7,025,354 reads per sample. Of which, total 24,739,969 reads are taxonomic alignments, with an average of 2,473,997 reads per sample.

Statistical Analysis

The results are presented as the mean value ± SD or SEM (the standard error of the mean). All the tests were two-tailed and the differences were considered statistically significant when P-value < 0.05. The normality distribution test of each variable was performed using Shapiro-Wilk's test. The differences between the two samples were analyzed by a Student's *t* test or Welch-*t*-test based on whether the two samples have unequal variances and/or unequal sample sizes.

The differences among three or more groups were analyzed using parametric one-way ANOVA or non-parametric Kruskal–Wallis test, depending on whether the variable is normally distributed or not. For two factors of samples, a two-way ANOVA test was used. For the human data in CD and control patients, we performed a regression of VDR against ATG16L1 and conducted a scatter plot with a regression line. For microbiome data, we first performed PCoA to visualize the Bray-Curtis dissimilarities between groups; then we performed the permutational multivariate ANOVA (PERMANOVA) to detect the statistical differences of Bray-Curtis dissimilarities between groups, followed by a variance homogeneity assumption testing to ensure the reliability of the PERMANOVA results. Next, a nonparametric procedure analysis of similarity

(ANOSIM) based on a permutation test was used for analyzing between- and within-group similarities. To correct multiple comparisons, a Tukey method was used to adjust for p-values for experimental data. The statistical analyses of experimental data were performed with GraphPad Prism 5 (GraphPad Software, La Jolla, CA**)**. The regression and scatter plot of VDR against ATG16L1 were performed using SAS version 9.4 (Cary, NC: SAS Institute Inc.). The microbiome data were analyzed by using R packages of ampvis2, microbiome, phyloseq, and vegan, which were implemented with the latest version of R, as did in our book on statistical analysis of microbiome data [19].

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