# SUPPLEMENTAL INFORMATION

# Hepatic cytochrome P450 8B1 and cholic acid potentiate intestinal epithelial injury in colitis by suppressing intestinal stem cell renewal

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**Figure S1.** The synthesis of cholic acid is altered in colitic mice with different treatments. Related to Figure 2 and Figure 3.

**Figure S2.** Hepatic CYP8B1-CA metabolic pathway exacerbates colitis. Related to Figure 2 and Figure 3.

**Figure S3.** Supplementation of CA and hepatic specific overexpression of CYP8B1 does not directly influence inflammatory and immune responses. Related to Figure 2 and Figure 3.

**Figure S4.** Hepatic CYP8B1-CA axis impairs intestinal epithelial barrier function in colitic mice. Related to Figure 4.

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**Table S1.** Clinical characteristics of UC patients and healthy controls. Related to Figure 1 and STAR Methods.

**Table S2.** Clinical characteristics of UC patients for correlation analysis. Related to STAR Methods and Figure S3.

**Table S3.** Sequences of primers used for quantitative real-time PCR. Related to Figure 1-Figure 7, Figure S2, Figure S4-S7 and STAR Methods.

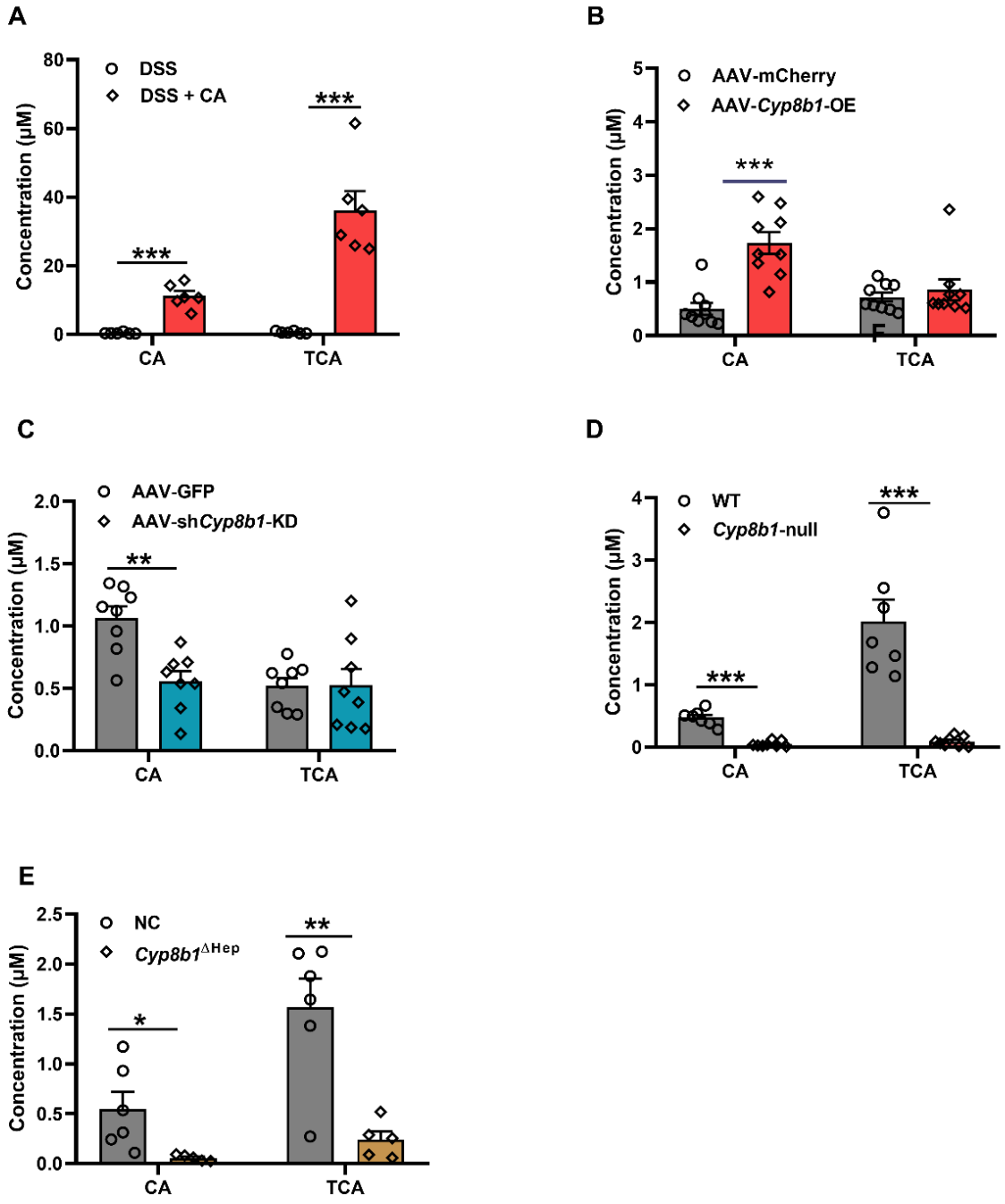


**Figure S1. The synthesis of cholic acid is altered in colitic mice with different treatments. Related to Figure 2 and Figure 3.**

(A) The concentration of CA and TCA in serum of CA-treated colitic mice without recovery period (n = 6 mice/group).

(B) The concentration of CA and TCA in serum of colitic *Cyp8b1*-overexpressing mice without recovery period (n = 9 mice/group).

(C) The concentration of CA and TCA in serum of colitic *Cyp8b1*-knockdown mice without recovery period (n = 8 mice/group).

(D) The concentration of CA and TCA in serum of *Cyp8b1*-null mice (n = 7-8 mice/group).

(E) The concentration of CA and TCA in serum of *Cyp8b1*$^{\Delta Hep}$ mice (n = 5-6 mice/group).

Data are mean ± SEM. Unpaired Student's t test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

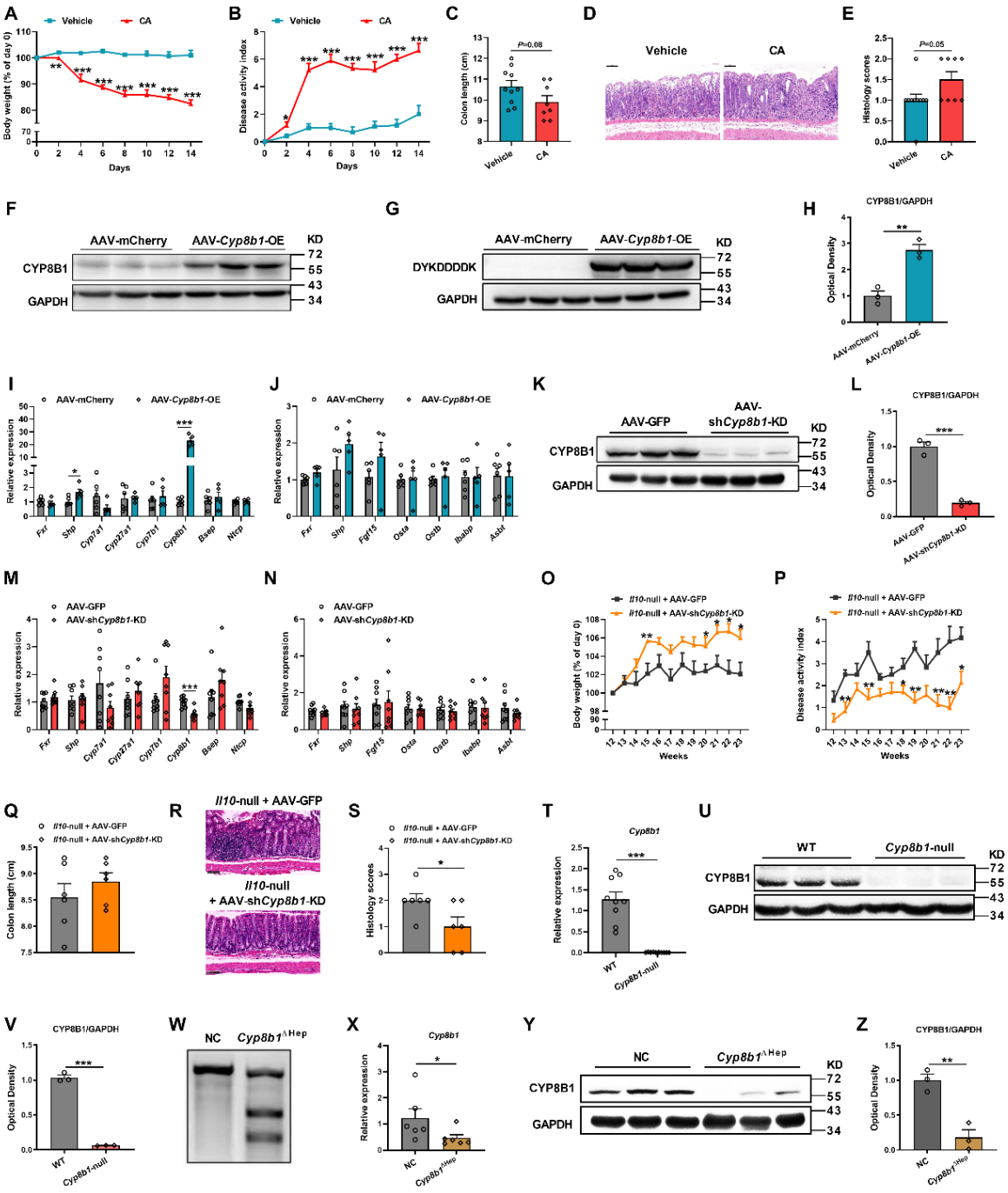


**Figure S2. Hepatic CYP8B1-CA metabolic pathway exacerbates colitis. Related to Figure 2 and Figure 3.**

(A-E) Mice from T cell transfer colitis model were treated with vehicle or CA for 15 days (n = 8-10 mice/group). Body-weight loss (A), DAI (B), colon length (C), representative H&E staining of intestine sections (D), histology score (E).

(F-H) Representative immunoblots of CYP8B1 and DYKDDDK, and quantitation of CYP8B1 in liver of colitic AAV-*Cyp8b1*-OE and AAV-mCherry mice.

(I and J) mRNAs of indicated genes in liver (I) and intestine (J) of colitic AAV-*Cyp8b1*-OE and AAV-mCherry mice (n = 5-6 mice/group).

(K and L) Representative immunoblots and quantitation of CYP8B1 in liver of colitic AAV-

sh*Cyp8b1*-KD and AAV-GFP mice.
(M and N) mRNAs of indicated genes in liver (M) and intestine (N) of colitic AAV-sh*Cyp8b1*-KD and AAV-GFP mice (n = 8 mice/group).
(O-S) *Il10*-null mice were injected with recombinant AAV-sh*Cyp8b1*-KD and AAV-GFP via tail vein at the age of 8 weeks and the development colitis was evaluated from the age of 12 weeks (n = 6 mice/group). Body-weight loss (O), DAI (P), colon length (Q), representative H&E staining of intestine sections (R), histology score (S).
(T) mRNA expression of *Cyp8b1* in liver of *Cyp8b1*-null mice (n = 9-10 mice/group).
(U and V) Representative immunoblots and quantitation of CYP8B1 in liver of *Cyp8b1*-null mice.
(W) Surveyor assay of *Cyp8b1* in liver of *Cyp8b1*$^{\Delta Hep}$ mice.
(X) mRNA expression of *Cyp8b1* in liver of *Cyp8b1*$^{\Delta Hep}$ mice (n = 6 mice/group).
(Y and Z) Representative immunoblots and quantitation of CYP8B1 in liver of *Cyp8b1*$^{\Delta Hep}$ mice.
Scale bars, 100 μm (D and R). Data are mean ± SEM. Unpaired Student's t test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

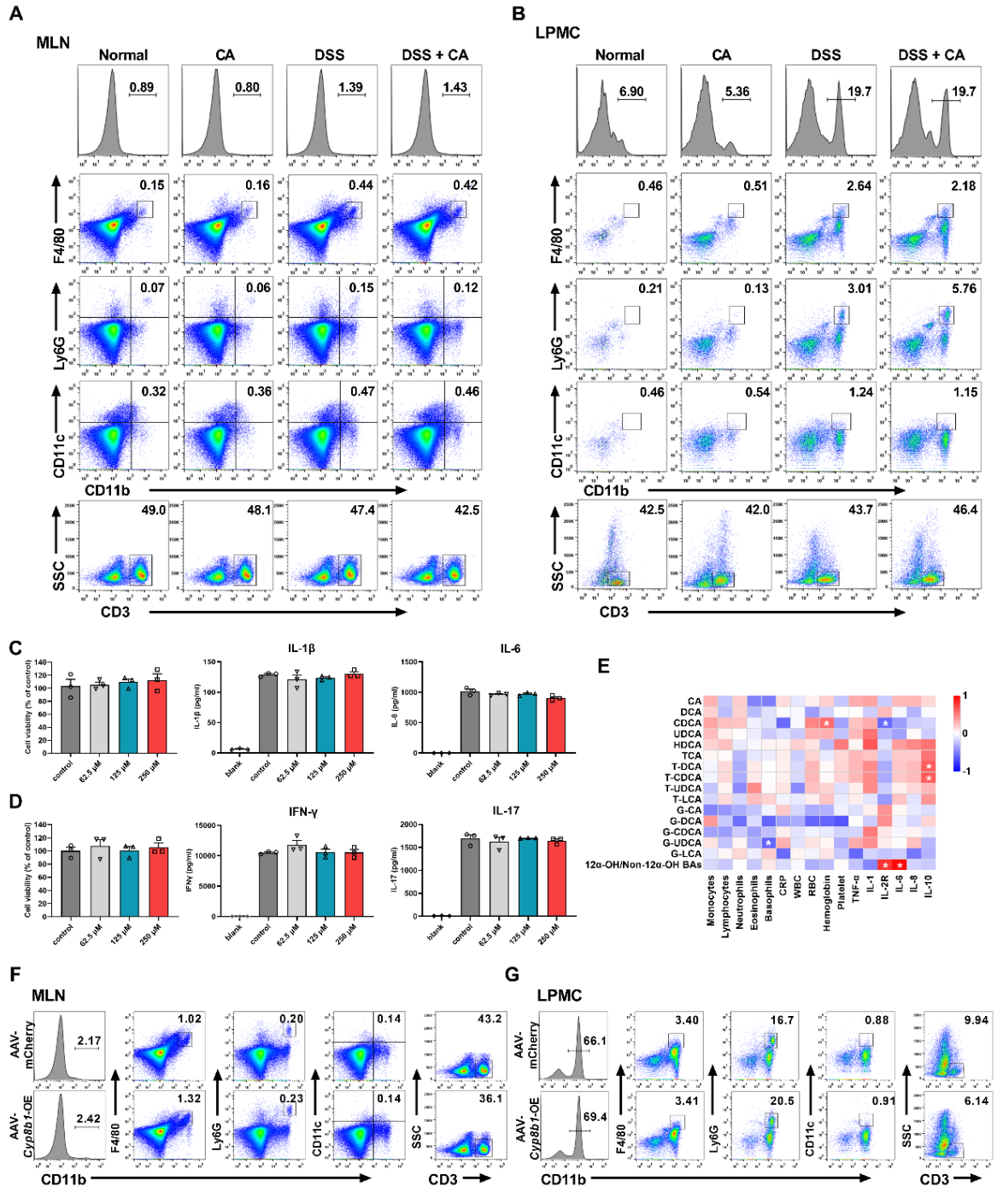


**Figure S3. Supplementation of CA and hepatic specific overexpression of CYP8B1 does not directly influence inflammatory and immune responses. Related to Figure 2 and Figure 3.**

(A and B) Representative results of flow cytometric analysis for $CD11b^+$ monocytes, $CD11b^+F4/80^+$ macrophages, $CD11b^+Ly6G^+$ inflammatory neutrophils, $CD11b^+CD11c^+$ dendritic cells and $CD3^+$ T cells in MLN (A) and LPMC (B) of CA-treated colitic mice.

(C and D) The expression of cytokines in LPS-induced BMDMs (C) and CD3/CD28-stimulated purified T cells (D). n = 3 biological replicates/group.

(E) Correlation analysis among individual BAs and IBD-related indicators in the serum of UC

patients (n = 15) by nonparametric Spearman's test. * $P < 0.05$.
(F and G) Representative results of flow cytometric analysis for $CD11b^+$ monocytes, $CD11b^+F4/80^+$ macrophages, $CD11b^+Ly6G^+$ inflammatory neutrophils, $CD11b^+CD11c^+$ dendritic cells and $CD3^+$ T cells in MLN (F) and LPMC (G) of *Cyp8b1*-overexpressing colitic mice.
Data are mean ± SEM. One-way ANOVA with Dunnet's multiple comparisons test. CRP: C-reactive protein. WBC: white blood cell. RBC: red blood cell.

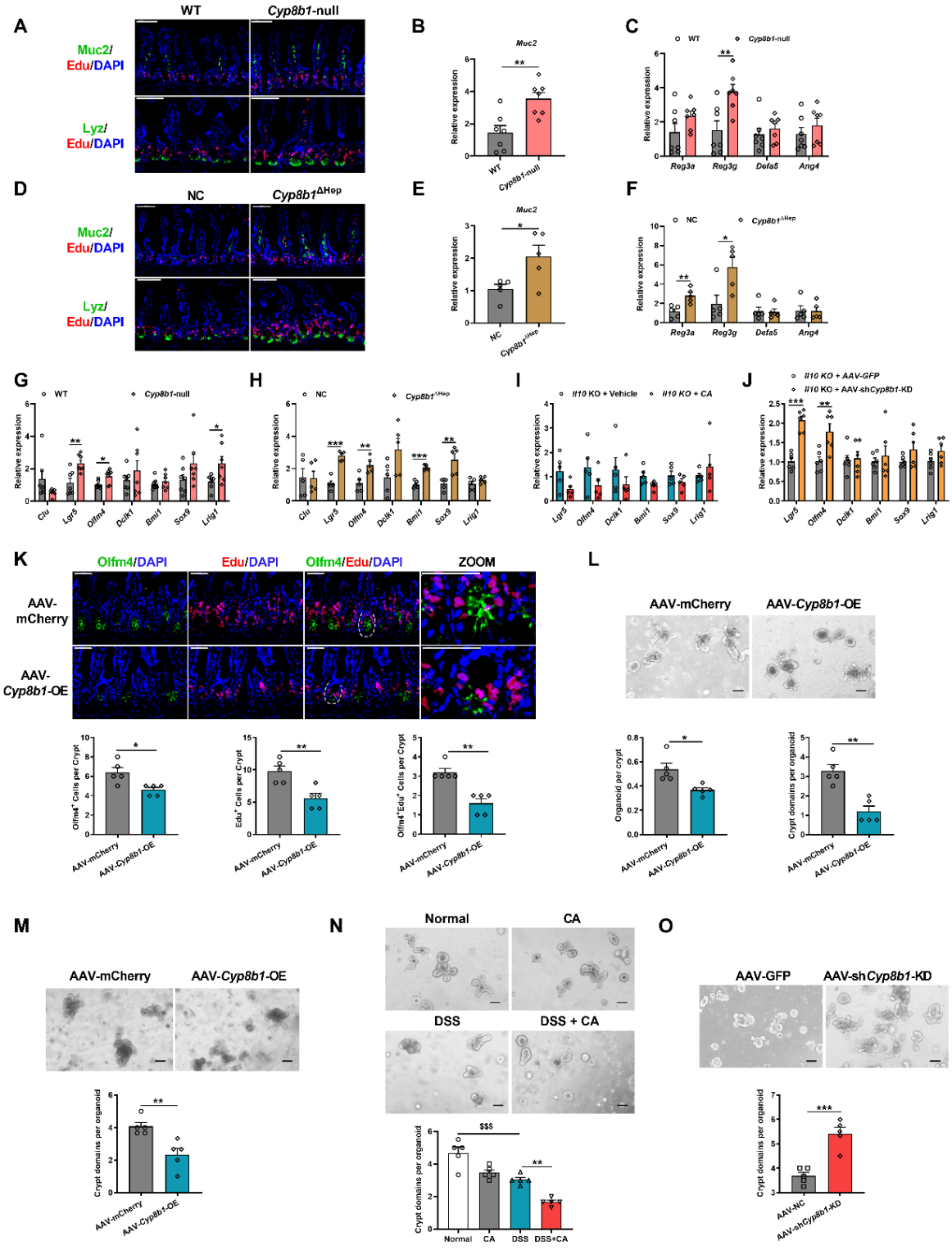


**Figure S4. Hepatic CYP8B1-CA axis impairs intestinal epithelial barrier function in colitic mice. Related to Figure 4.**

(A) Representative Muc2 or Lyz combined with Edu staining of intestine sections from colitic *Cyp8b1*-null mice.

(B, C, G) mRNAs of indicated genes in intestine of colitic *Cyp8b1*-null mice (n = 7 mice/group).

(D) Representative Muc2 or Lyz combined with Edu staining of intestine sections from colitic

*Cyp8b1*$^{\Delta Hep}$ mice.
(E, F, H) mRNAs of indicated genes in intestine of colitic *Cyp8b1*$^{\Delta Hep}$ mice (n = 5 mice/group).
(I and J) mRNAs of indicated genes in intestine of *Il10*-null mice treated with CA (I, n= 5 mice/group) or with AAV-sh*Cyp8b1*-KD (J, n = 6 mice/group).
(K) Representative Edu and Olfm4 staining and quantitation in intestine of colitic AAV-*Cyp8b1*-OE mice (n = 5 mice/group).
(L and M) Representative images and quantitation of the intestinal crypts isolated from colitic AAV-*Cyp8b1*-OE mice in primary (L) and secondary (M) cultures (n = 5 mice/group).
(N) Representative images and quantitation of the intestinal crypts isolated from CA-treated colitic mice in secondary cultures (n = 5 mice/group).
(O) Representative images and quantitation of the intestinal crypts isolated from colitic AAV-sh*Cyp8b1*-KD mice in secondary cultures (n = 5 mice/group).
Scale bars, 100 μm (A, D, L-O), 50 μm (K). Data are mean ± SEM. (B, C, E-M, O) Unpaired Student's t test. (N) One-way ANOVA with Dunnet's multiple comparisons test. * $P < 0.05$; ** $P < 0.01$; ***/$$$ $P < 0.001$.

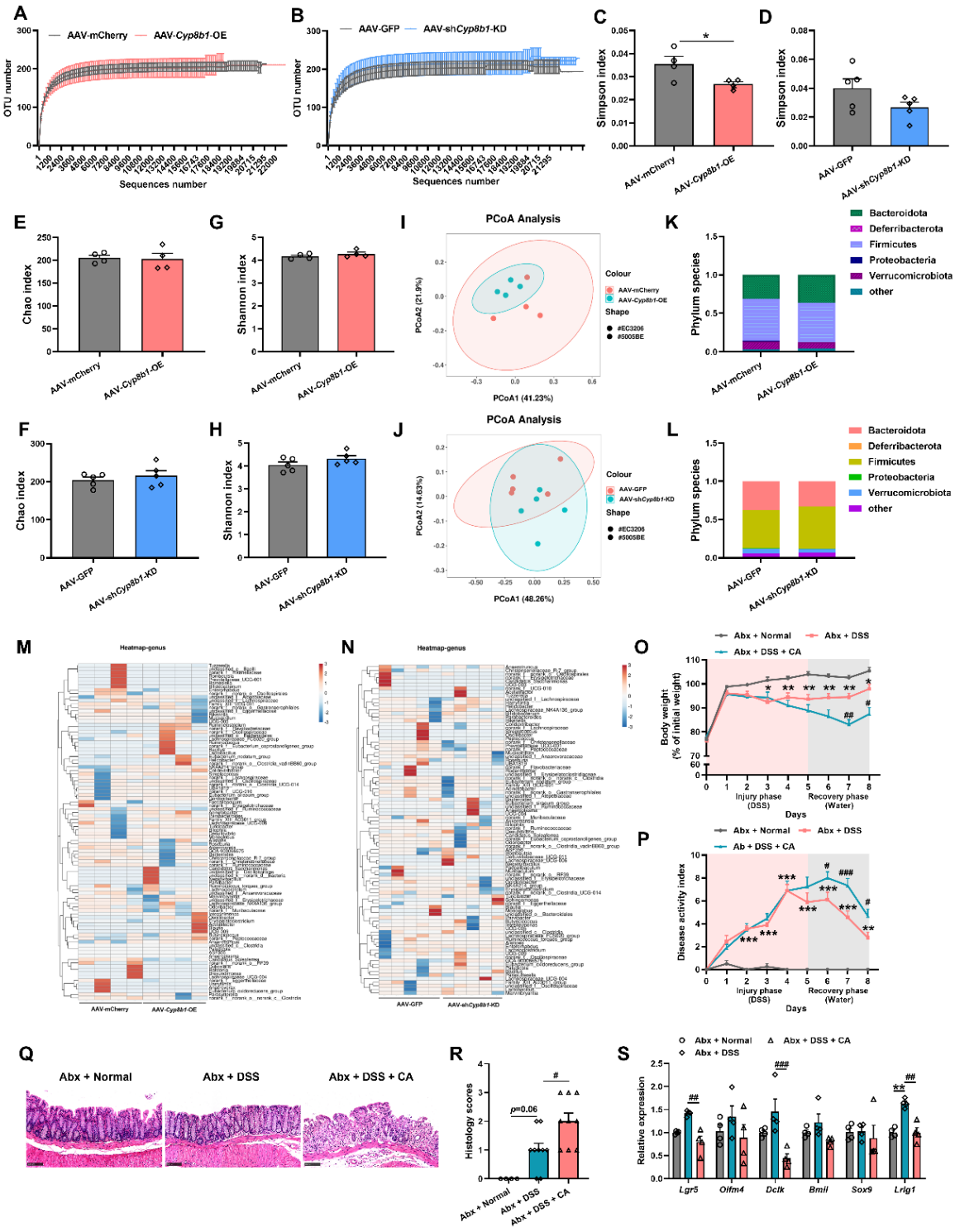


**Figure S5. Hepatic CYP8B1-CA axis aggravates colitis independently of intestinal microbiota. Related to Figure 3.**

(A-N) 16S rRNA sequencing analysis of cecum contents from colitic AAV-*Cyp8b1*-OE mice (n = 4 mice/group) or AAV-*Cyp8b1*-KD mice (n = 5 mice/group). OTU number (A and B), Simpson index (C and D), Chao index (E and F), Shannon index (G and H), PCoA analysis (I and J), relative abundance of phylum species (K and L), heatmaps displaying genus distribution patterns (M and N).

(O-S) Mice were treated with the antibiotic cocktail for 3 days and replaced by DSS for 5 days followed with a 3-day recovery, and then were administrated with vehicle or CA (n = 4-9 mice/group). Body-weight loss (the initial weight of the mice was the weight before antibiotic administration) (O), DAI (P), representative H&E staining of intestine sections (Q), histology score (R), mRNAs of indicate genes in intestine (S).
Scale bars, 100 μm (Q). Data are mean ± SEM. (C-H) Unpaired Student's t test. (O, P, R, S) One-way ANOVA with Dunnet's multiple comparisons test. *, Abx + DSS vs Abx + Normal; #, ABX + DSS + CA vs ABX + DSS. */$^{\#}$ $P < 0.05$; **/$^{\#\#}$ $P < 0.01$; ***/$^{\#\#\#}$ $P < 0.001$.

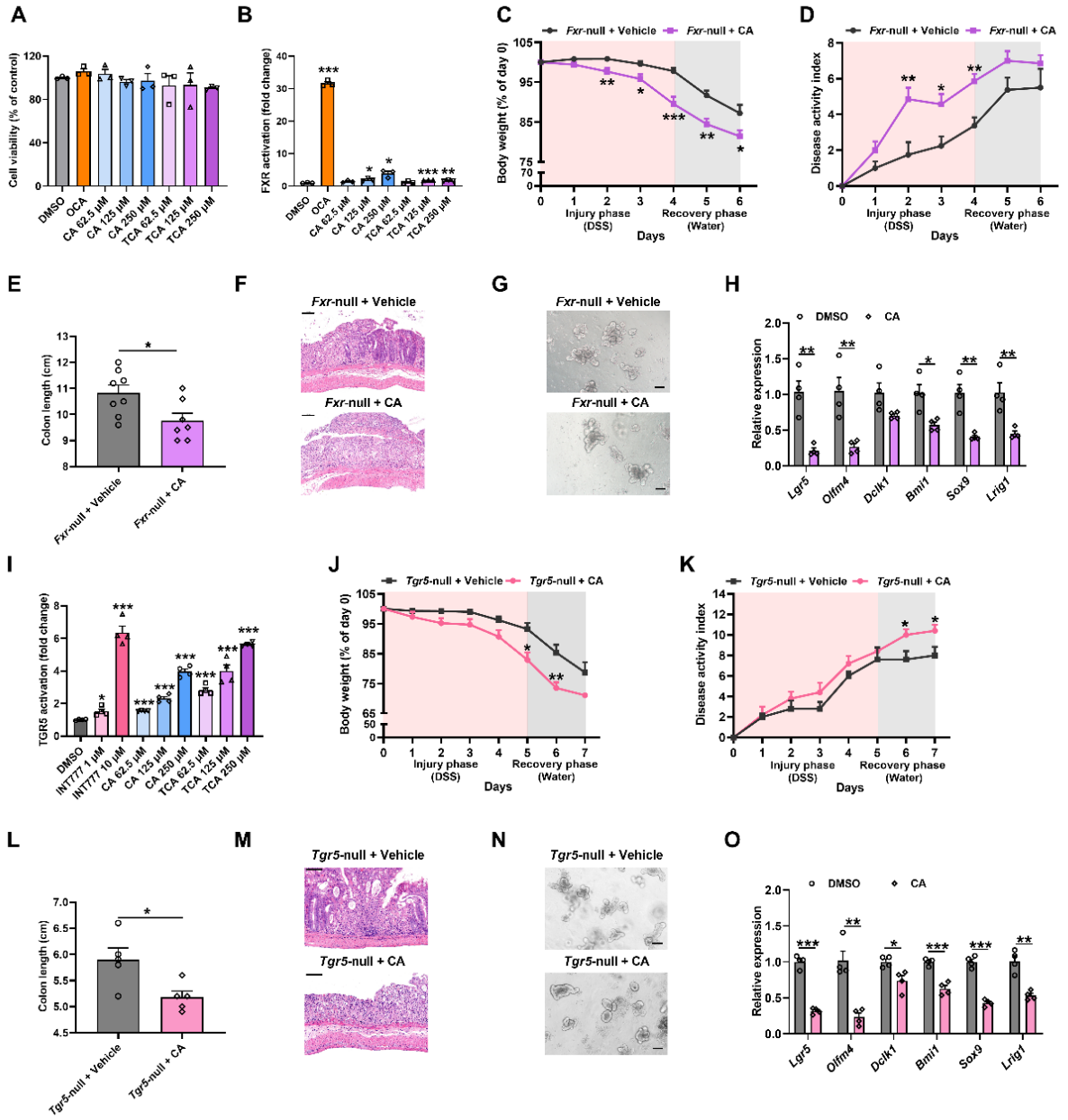


**Figure S6. The impairment that CA has on intestinal barrier function is independent of FXR and TGR5. Related to Figure 5.**

(A-B) Cytotoxicity (A) and FXR reporter assay (B). n = 3 biological replicates/group.

(C-G) *Fxr*-null mice were treated with DSS and administrated with vehicle or CA (n = 7-8 mice/group). Body-weight loss (C), DAI (D), colon length (E), representative H&E staining of intestine sections (F), representative images of organoids of crypts isolated from colitic *Fxr*-null mice in primary culture for 5 days (G).

(H) mRNAs of indicated genes of crypts isolated from *Fxr*-null mice treated with DMSO or CA for 6 days *in vitro* (n = 4 biological replicates/group).

(I) TGR5 activation assay (n = 4 biological replicates/group).

(J-N) *Tgr5*-null mice were treated with DSS and administrated with vehicle or CA (n = 5 mice/group). Body-weight loss (J), DAI (K), colon length (L), representative H&E staining of intestine sections (M), representative images of organoids of crypts isolated from colitic *Tgr5*-

null mice in primary culture for 5 days (N).
(O) mRNAs of indicated genes of crypts isolated from *Tgr5*-null mice treated with DMSO or CA for 6 days *in vitro* (n = 4 biological replicates/group).
Scale bars, 100 μm (F, G, M, N). Data are mean ± SEM. (A, B, I) One-way ANOVA with Dunnet's multiple comparisons test. (C-E, H, J-L, O) Unpaired Student's t test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

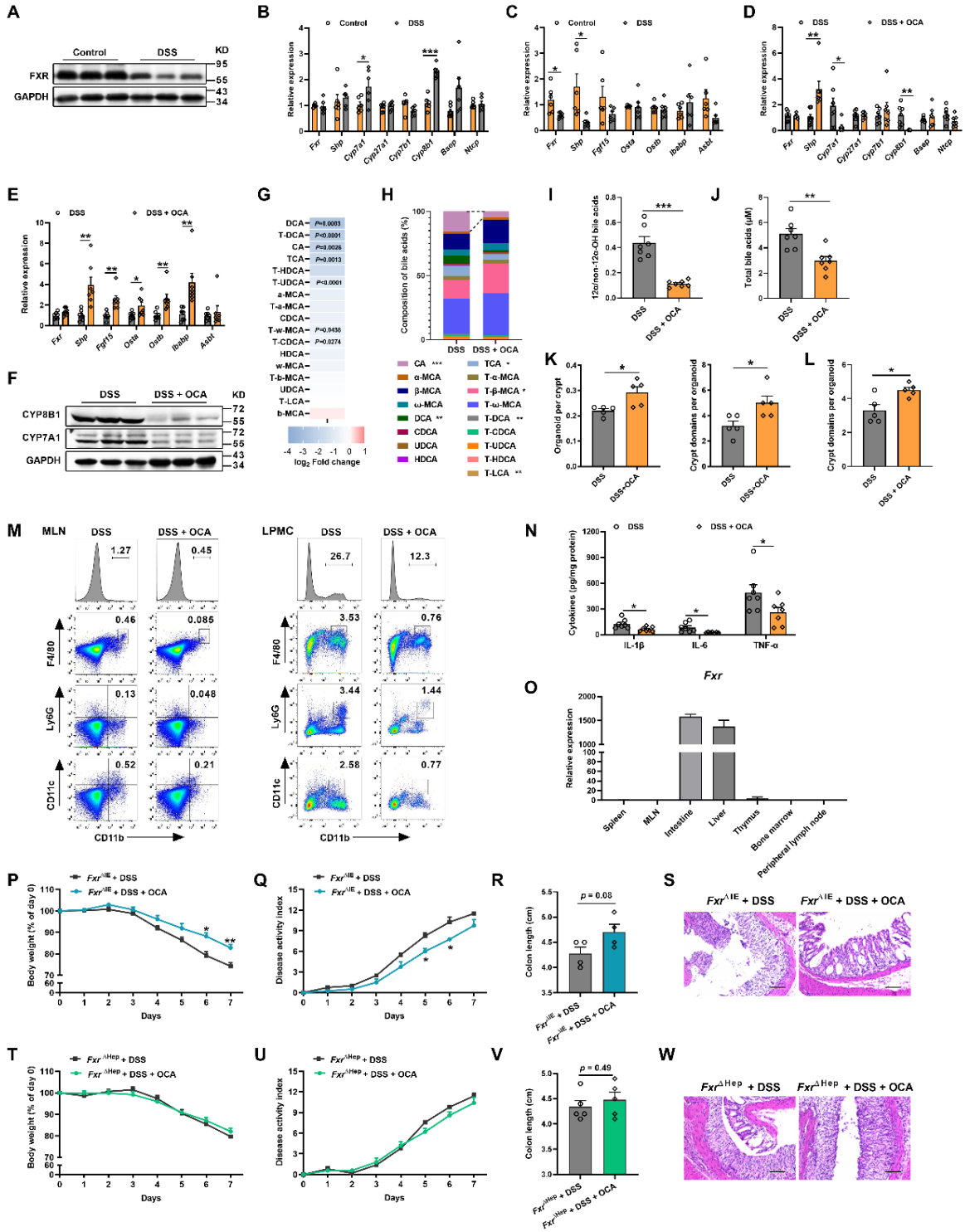

**Figure S7. OCA ameliorates colitis through hepatic FXR. Related to Figure 7.**

(A-C) Representative immunoblots of FXR (A), mRNAs of indicated genes in liver (B) and intestine (C) of mice treated with DSS for 7 days (n = 6 mice/group).

(D-N) Mice were treated with DSS for 7 days followed by 3 days of water, together with vehicle or OCA. mRNAs of indicated genes in liver (D) and intestine (E), representative immunoblots of indicated proteins (F), fold change (G) and proportion (H) of individual BAs in serum, 12α-OH/non-12α-OH BAs (I) and total BAs (J) in serum, quantitation of the intestinal crypts

isolated from OCA-treated mice in primary (K) and secondary (L) culture, representative results of flow cytometric analysis for $CD11b^+$ monocytes, $CD11b^+F4/80^+$ macrophages, $CD11b^+Ly6G^+$ inflammatory neutrophils and $CD11b^+CD11c^+$ dendritic cells in MLNs and LPMCs (M), expression of cytokines in intestines (N). (D, E, G-J, N) n = 7 mice/group. (K and L) n = 5 mice/group.

(O) mRNA expression of *Fxr* in different tissues of mice (n = 4 mice/group).

(P-S) Intestinal *Fxr*-null ($Fxr^{\Delta IE}$) mice were treated with DSS together with vehicle or OCA for 7 days (n = 4 mice/group). Body-weight loss (P), DAI (Q), colon length (R), representative H&E staining of intestine sections (S).

(T-W) Hepatic *Fxr*-null ($Fxr^{\Delta Hep}$) mice were treated with DSS together with vehicle or OCA for 7 days (n = 5 mice/group). Body-weight loss (T), DAI (U), colon length (V), representative H&E staining of intestine sections (W).

Scale bars, 100 μm (S and W). Data are mean ± SEM. (B-E, G-L, N, P-R, T-V) Unpaired Student's t test. (O) One-way ANOVA with Dunnet's multiple comparisons test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

**Table S1. Clinical characteristics of UC patients and healthy controls. Related to Figure 1 and STAR Methods.**

| Characteristic | UC patients (n = 35) | Healthy controls (n = 35) |
|---|---|---|
| Age (years) | | |
| Mean ± SD | 43.2 ± 16.7 | 45.5 ±16.0 |
| Range | 23.0 - 76.0 | 19.0 - 72.0 |
| Gender, n (%) | | |
| Male | 19 (54.3%) | 19 (54.3%) |
| Female | 16 (45.7%) | 16 (45.7%) |
| Duration of disease (years) | 5.4 ± 5.4 | n/a |
| Location of the disease | | |
| Pancolitis | 28 | n/a |
| Left-sided colitis | 6 | n/a |
| Proctitis | 1 | n/a |
| C-reactive protein (mg/mL) | 18.5 ± 25.4 | n/a |
| Hemoglobin (g/L) | 112 ± 21.4 | n/a |
| Lymphocytes (10^9/L) | 1.8 ± 0.89 | n/a |

Data are presented as mean ± SD.

**Table S2. Clinical characteristics of UC patients for correlation analysis. Related to STAR Methods and Figure S3.**

| Characteristic | UC patients (n = 15) |
|---|---|
| Age (years) | |
| Mean ± SD | 40.7 ± 13.3 |
| Range | 23.0-72.0 |
| Gender, n (%) | |
| Male | 8 (53.3%) |
| Female | 7 (46.7%) |
| Duration of disease (years) | 6.2 ± 5.7 |
| Location of the disease | |
| Pancolitis | 13 |
| Left-sided colitis | 1 |
| Proctitis | 1 |
| C-reactive protein (mg/mL) | 20.7 ± 28.1 |
| Hemoglobin (g/L) | 98.3 ± 35.2 |
| Lymphocytes (10^9/L) | 1.49 ± 0.78 |

Data are presented as mean ± SD.

**Table S3. Sequences of primers used for quantitative real-time PCR. Related to Figure 1-Figure 7, Figure S2, Figure S4-S7 and STAR Methods.**

| Mouse primers | Primer sequence |
|---|---|
| *Eef2* | F:5'-TGTCAGTCATCGCCCATGTG-3' |
| | R:5'-CATCCTTGCGAGTGTCAGTGA-3' |
| *Gapdh* | F:5'-TTGATGGCAACAATCTCCAC-3' |
| | R:5'-CGTCCCGTAGACAAAATGGT-3' |
| *Fxr* | F:5'-TGGGCTCCGAATCCTCTTAGA-3' |
| | R:5'-TGGTCCTCAAATAAGATCCTTGG-3' |
| *Shp* | F:5'-TCTGCAGGTCGTCCGACTATTC-3' |
| | R:5'-AGGCAGTGGCTGTGAGATGC-3' |
| *Cyp7a1* | F:5'-AACAACCTGCCAGTACTAGATAGC-3' |
| | R:5'-GTGTAGAGTGAAGTCCTCCTTAGC-3' |
| *Cyp8b1* | F:5'-CTAGGGCCTAAAGGTTCGAGT-3' |
| | R:5'-GTAGCCGAATAAGCTCAGGAAG-3' |
| *Cyp27a1* | F:5'-CCAGGCACAGGAGAGTACG-3' |
| | R:5'-GGGCAAGTGCAGCACATAG-3' |
| *Cyp7b1* | F:5'-GGAGCCACGACCCTAGATG-3' |
| | R:5'-TGCCAAGATAAGGAAGCCAAC-3' |
| *Bsep* | F:5'-TCTGACTCAGTGATTCTTCGCA-3' |
| | R:5'-GTGTAGAGTGAAGTCCTCCTTAGC-3' |
| *Ntcp* | F:5'-CAAACCTCAGAAGGACCAAACA-3' |
| | R:5'-GTAGGAGGATTATTCCCGTTGTG-3' |
| *Fgf15* | F:5'-GCCATCAAGGACGTCAGCA-3' |
| | R:5'-CTTCCTCCGAGTAGCGAATCAG-3' |
| *Osta* | F:5'-AATTACAGCATCTCCCCTGC-3' |
| | R:5'-GGTCAAGATGATGGTGAGGG-3' |
| *Ostb* | F:5'-AGAGAAAGCTGCAGCCAATG-3' |
| | R:5'-CCAGGACCAGGATGGAATAA-3' |
| *Ibabp* | F:5'-CTTCCAGGAGACGTGATTGAAA-3' |
| | R:5'-CCTCCGAAGTCTGGTGATAGTTG-3' |
| *Asbt* | F:5'-GTCTGTCCCCCAAATGCAACT-3' |
| | R:5'-CACCCCATAGAAAACATCACCA-3' |
| *Ocln* | F:5'-TTGAAAGTCCACCTCCTTACAGA-3' |
| | R:5'-CCGGATAAAAAGAGTACGCTGG-3' |
| *Cldn2* | F:5'-CAACTGGTGGGCTACATCCTA-3' |
| | R:5'-CCCTTGGAAAAGCCAACCG-3' |
| *Cdh1* | F:5'-CAGGTCTCCTCATGGCTTTGC-3' |
| | R:5'-CTTCCGAAAAGAAGGCTGTCC-3' |
| *Tjp1* | F:5'-GCCGCTAAGAGCACAGCAA-3' |
| | R:5'-GCCCTCCTTTTAACACATCAGA-3' |
| *Muc2* | F:5'-AGGGCTCGGAACTCCAGAAA-3' |
| | R:5'-CCAGGGAATCGGTAGACATCG-3' |
| *Reg3a* | F:5'-TCACCTGGTCCTCAACAGTATT-3' |
| | R:5'-GGAGCGATAAGCCTTGTAACC-3' |
| *Reg3g* | F:5'-ATGCTTCCCCGTATAACCATCA-3' |
| | R:5'-GGCCATATCTGCATCATACCAG-3' |
| *Defa5* | F:5'-CTAATACTGAGGAGCAGCCAGG-3' |
| | R:5'-GCAGCCTCTTATTCTACAATAGCA-3' |

| Mouse primers | Primer sequence |
|---|---|
| *Ang4* | F:5'-GGTTGTGATTCCTCCAACTCTG-3' |
| | R:5'-CTGAAGTTTTCTCCATAAGGGCT-3' |
| *Lgr5* | F:5'-CCTACTCGAAGACTTACCCAGT-3' |
| | R:5'-GCATTGGGGTGAATGATAGCA-3' |
| *Olfm4* | F:5'-AAAGTGACCTTGTGCCTGCC-3' |
| | R:5'-AGGGTTCTCTCTGGATGCTGA -3' |
| *Dclk1* | F:5'-ATGTGGACCAGAGAAGTTCCG-3' |
| | R:5'-CCGCCATGCTGAGAGATCC-3' |
| *Bmi1* | F:5'-ATCCCCACTTAATGTGTGTCCT-3' |
| | R:5'-CTTGCTGGTCTCCAAGTAACG-3' |
| *Sox9* | F:5'-GCCAGATGGACCCACCAGTAT-3' |
| | R:5'-TCCAAACAGGCAGGGAGATTC-3' |
| *Lrig1* | F:5'-TTGAGGACTTGACGAATCTGC-3' |
| | R:5'-CTTGTTGTGCTGCAAAAAGAGAG-3' |
| *Clu* | F:5'-AGCAGGAGGTCTCTGACAATG-3' |
| | R:5'-GGCTTCCTCTAAACTGTTGAGC-3' |
| *Cdk4* | F:5'-GTCAGTTTCTAAGCGGCCTG-3' |
| | R:5'-CACGGGTGTTGCGTATGTAG-3' |
| *Cdk5* | F:5'-CCCTGAGATTGTGAAGTCATTCC-3' |
| | R:5'-CCAATTTCAACTCCCCATTCCT-3' |
| *Cdkn1c* | F:5'-CGAGGAGCAGGACGAGAATC-3' |
| | R:5'-GAAGAAGTCGTTCGCATTGGC-3' |
| *Cdc25b* | F:5'-TCCGATCCTTACCAGTGAGG-3' |
| | R:5'-GGTCTCTGGAAGCGCACATT-3' |
| *Cdc25c* | F:5'-AAAATGCAGCGTTCCTGCTTC-3' |
| | R:5'-CTTGGGGTCCTAGTGCCTC-3' |
| *Cdkn3* | F:5'-ACCCTGATACATTGTTACGGAGG-3' |
| | R:5'-CTCGAAGGCTGTCTATGGCTT-3' |
| *Foxa2* | F:5'-CCCTACGCCAACATGAACTCG-3' |
| | R:5'-GTTCTGCCGGTAGAAAGGGA-3' |
| *Fgfr3* | F:5'-GCCTGCGTGCTAGTGTTCT-3' |
| | R:5'-TACCATCCTTAGCCCAGACCG-3' |
| *Pax6* | F:5'-GAATCAGAGAA-GACAGGCCA-3' |
| | R:5'-GTGTAGGTATCATAACTCCG-3' |
| *Neurog3* | F:5'-CGCCGGTAGAAAGGATGAC-3' |
| | R:5'-GACGTGGGGCAGGTCACTT-3' |
| *Nkx2.2* | F:5'-AAGCATTTCAAAACCGACGGA-3' |
| | R:5'-CCTCAAATCCACAGATGACCAGA-3' |
| *Crept* | F:5'-AAGATTGCTGAACATCTGGCA-3' |
| | R:5'-GTAGTCATCATCTTCCTCCTCTTGT-3' |
| *Cd44* | F:5'-GGCAGAAGAAAAAGCTGGTG-3' |
| | R:5'-TCTGGGGTCTCTGATGGTTC-3' |
| *c-Myc* | F:5'-GCTGTTTGAAGGCTGGATTTC-3' |
| | R:5'-GATGAAATAGGGCTGTACGGAG-3' |
| *Ccnd1* | F:5'-GCCATCCAAACTGAGGAAAA-3' |
| | R:5'-AGGTAAGGGCCATCTGAAAACT-3' |
| *Ephb2* | F:5'-AGAATGGTGCCATCTTCCAG-3' |
| | R:5'-GCACATCCACTTCTTCAGCA-3' |

| Mouse primers | Primer sequence |
|---|---|
| *Ephb3* | F:5'-CATGGACACGAAATGGGTGAC-3' |
| | R:5'-GCGGATAGGATTCATGGCTTCA-3' |
| *Axin2* | F:5'-GCTCCAGAAGATCACAAAGAGC-3' |
| | R:5'-AGCTTTGAGCCTTCAGCATC-3' |
| *Ascl2* | F:5'-GCCTGACCAAATGCCAAGTG-3' |
| | R:5'-ATTTCCAAGTCCTGATGCTGC-3' |
| *Hpox1* | F:5'-AGGAGCAGACGCAGAAATG-3' |
| | R:5'-GAAACATCAAAACAGCCTGGG-3' |
| *Fzd3* | F:5'-ATGGCTGTGAGCTGGATTGTC-3' |
| | R:5'-GGCACATCCTCAAGGTTATAGGT-3' |
| *Fzd4* | F:5'-TGCCAGAACCTCGGCTACA-3' |
| | R:5'-ATGAGCGGCGTGAAAGTTGT-3' |
| *Fzd9* | F:5'-GCGTAGAGCGAGCAGAAGAA-3' |
| | R:5'-GAAACATCAAAACAGCCTGGG-3' |
| *Ppara* | F:5'-AGAGCCCCATCTGTCCTCTC-3' |
| | R:5'-ACTGGTAGTCTGCAAAACCAAA-3' |
| *Acox1* | F:5'-GGGCACGGCTATTCTCACAG-3' |
| | R:5'-CATCAAGAACCTGGCCGTCT-3' |
| *Cpt1a* | F:5'-CTCCGCCTGAGCCATGAAG-3' |
| | R:5'-CACCAGTGATGATGCCATTCT-3' |
| *Acot1* | F:5'-ATACCCCCTGTGACTATCCTGA-3' |
| | R:5'-CAAACACTCACTACCCAACTGT-3' |
| *Cyp4a10* | F:5'-TTCCCTGATGGACGCTCTTTA-3' |
| | R:5'-GCAAACCTGGAAGGGTCAAAC-3' |