Supplementary figure 1. Increased FBXW7 level in human samples with intestinal inflammation. (A) Comparison of FBXW7 mRNA expression level between colonic mucosa tissues from ulcerative colitis (UC) patients with active and inactive disease status, the data were collected from GEO database (GCS3119) (n=20), **p<0.01. Statistical analysis of FBXW7 mRNA expression in peripheral blood monocytes from ulcerative colitis (UC) patients (B) with different severity of colitis: mild (n=8), moderate (n=8) or severe (n=8), and from Crohn’s disease (CD) patients (C) with different severity of colitis: mild (n=12), moderate (n=19) or severe (n=14). Statistical significance was assessed by one-way ANOVA with Tukey’s multiple comparisons test; *p<0.05, **p<0.01, ***p<0.001. Data are presented as mean ± SEM.
Supplementary figure 2. Myeloid \textit{Fbxw7} deficiency maintains intestinal barrier integrity in DSS-induced colitis model. (A) Histopathological scores of colonic cross-sections by H&E staining were assessed at day 9 of DSS colitis mice (n=10), as described in the section ‘methods’. (B) Quantitative assessment for mRNA expression of tight junction proteins in intestinal epithelial cells (n\geq6). (C) The immunofluorescence staining of cell tight junction proteins TJP1 (red) and Cytokeratin (green) in colonic sections from the mice treated with DSS for 5 days. Scale bars, 50 \textmu m. Data are presented as mean \pm SEM and representative of at least three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; \(*p<0.05, \ ***p<0.001\).
Supplementary figure 3. Myeloid Fbxw7 deficiency protects the mice from the trinitro-benzene-sulfonic acid (TNBS)-induced experimental colitis. LysM*Fbxw7^f/f mice and Fbxw7^f/f littermates were injected 50% ethanol (Control, Con) or 2.5% TNBS at day 1 to induce acute colitis for disease analysis, mice were sacrificed after 5 days. (A) Colon length, (B) body weight change and (C) disease activity index (DAI) were assessed daily as described in the ‘methods’ section (n≥5). (D) H&E staining of colonic tissues from TNBS induced colitis mice of Fbxw7^f/f and LysM^Fbxw7^f/f. Scale bars, 200 µm (whole colon section) and 50 µm (detail). Data are presented as mean ± SEM and representative of at least three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; *p<0.05, **p<0.01, ***p<0.001.
Supplementary figure 4. Decreased susceptibility to DSS-induced colitis in 
*LysM*/*Fbxw7*<sup>−/−</sup> mice was not due to the role of microbiota. (A) The relative 
abundances of the top 10 bacteria at the phylum level in *Fbxw7*<sup>−/−</sup> (WT) and 
*LysM*/*Fbxw7*<sup>−/−</sup> (KO) mice were assessed using 16S rDNA amplicon sequencing (n=3). (B) The analysis 
of beta-diversity (Principal Co-ordinates Analysis: PCoA, based on unweighted UniFrac) 
in WT and KO groups. KO mice and WT littermates were either housed alone or cohoused 
for 7 weeks before DSS treatment. After DSS treatment, changes in body weight (C), 
disease activity index (DAI) (D), and survival rate (E) were assessed daily (n=5), Log-rank 
test, **p<0.01. Colon length (F) and H&E staining (G) of co-housed *Fbxw7*<sup>−/−</sup> (WT) and 
*LysM*/*Fbxw7*<sup>−/−</sup> (KO) colonic tissues. Scale bars, 200 µm (whole colon section) and 50 µm (detail). (C-G) Data are presented as mean ± SEM and representative of three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; **p<0.01.
Supplementary figure 5

Supplementary figure 5. Comparable accumulation of dendritic cells (DCs) in CLP of LysM*Fbxw7ff mice and Fbxw7ff littermates. (A) Dynamics of CD11b+Ly6G+ neutrophils infiltration in CLP after DSS treatment (n=5 for any time point). (B) Graphical summary of percentage of DC subsets out of CD45+ cells at day 9 (n≥5) in Fbxw7ff mice (black) and LysM*Fbxw7ff mice (red). Data are presented as mean ± SEM and representative of three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test. *p<0.05.
Supplemental figure 6

Supplemental figure 6. Depletion of neutrophils did not reduce the differences between colitis of LysM\(^{Fbxw7\text{fl}}\) mice and Fbxw7\(^{fl}\) littermates. Fbxw7 mRNA expression in peripheral blood neutrophils (A) and in CLP neutrophils (B) from colitis mice and healthy littermates (n=6). (C) Flow cytometry analysis of the efficiency of neutrophils depletion in steady-state and colitis colon by Ly6G monoclonal antibody (Ly6G-Ab) treatment. After DSS treatment, changes in body weight (D), disease activity index (DAI) (E) and colon length (F-G) were assessed (n=5). Data are presented as mean ± SEM and representative of three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; *p<0.05, **p<0.01, ***p<0.001.
Supplementary figure 7. The protection from DSS colitis by myeloid Fbxw7 deficiency is dependent on macrophage population. (A-B) Flow cytometry analysis of the efficiency of macrophage depletion in steady-state peritoneal cavity and spleen by clodronate treatment. P-Mφ, peritoneal macrophage. S-Mφ, spleen macrophage. Colitis mice were sacrificed at day 9. (C) Quantitative assessment of mRNA expression of tight junction proteins in colon epithelial cells was shown (n≥6). (D) Colonic tissues were cultured overnight, the supernatants were harvested and cytokines were measured by ELISA (n=6). (E) CD11b+CX3CR1hi macrophages and CD11b+CX3CR1int MPh were sorted from the CLP of healthy (H2O) and colitis (DSS) C57BL/6 mice. Fbxw7 mRNA level in those cells was analyzed by RT-PCR (n=7). The expression level in control mice was set as 1. CLs: clodronate-containing liposomes; Mφ: macrophages. Data are presented as mean ± SEM and representative of at least three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; *p<0.05, **p<0.01. ns, not statistically significant.
Supplementary figure 8. *Fbxw7* deficiency has no effect on phagocytic function of macrophages. (A) Bone marrow-derived macrophages (BMDMs) of *Fbxw7* 

\[ \text{f/f} \] (WT) and LysM*Fbxw7* 

\[ \text{f/f} \] (KO) mice were incubated with E. coli-FITC for 60 minutes and analyzed by flow cytometry. (B) Expression of phagocytosis related genes in macrophages from peritoneal cavity and colon tissues (n=5). Primary peritoneal macrophages were stimulated for indicated hours with 100 ng/ml LPS. CLP CD11b\(^+\)CX3CR1\(^+\) macrophages (colon) were sorted from healthy and DSS-induced colitis mice. (C) Survival of BMDMs cultured in normal or starvation media after 48 hours (n=5), FVD (Zombie Violet™ Fixable Viability Dye) were used for gating living cells. Data are presented as mean ± SD and representative of at least three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s *t* test.
Supplementary figure 9. Fbxw7 deficiency downregulated Ccl2 and Ccl7 production in resident macrophages. (A) 5 days after DSS challenge, colonic tissue was cultured overnight, IL-10 in supernatant was measured by ELISA (n=5). (B) Relative mRNA levels for the indicated genes in Fbxw7^−/− (WT) and LysM^+Fbxw7^−/− (KO) BMDMs stimulated with LPS for 3 hours. (C) CD11b^+CX3CR1^hi resident macrophages, CD11b^+CX3CR1^int pro-inflammatory MPPh and Ly6C^hi monocytes populations were sorted from mice, the heat map shows the expression of selected cytokine and chemokine genes in cells sorted from CLP of WT and KO mice in response to 5-day DSS or H2O administration, gene expressions were quantified by gene specific amplification and qRT-PCR, the expression profile is accompanied by a colored bar (n=5/group). Graphical summary of qRT-PCR analysis showing the mRNA level of Ccl2 and Ccl7 in the inflamed colon of both groups of WT and KO mice after DSS (D) or TNBS (E) onset (n=5). (F) Colonic tissues of WT and KO mice treated with TNBS for 5 days were cultured overnight, supernatant was harvested and CCL2, CCL7 production were measured by ELISA (n=5). (G) Correlation of Fbxw7 mRNA levels with Ccl2 mRNA levels in colonic mucosa samples with signs of inflammation from patients with ulcerative colitis (UC) collected from GEO database (GDS3119, n=20). Statistical significance was assessed by unpaired two-tailed Student’s t test; *p<0.05, **p<0.01, ***p<0.001. Data are presented as mean ± SD and representative of at least three independent experiments. Con: Control.
Supplementary figure 10. Attenuated CCL2/7 in CX3CR1\textsuperscript{hi} macrophages contributes to the decreased migration of Ly6C\textsuperscript{hi} monocytes in vitro.

Diagrammatic illustration for the transwell assay procedure: Ly6C\textsuperscript{hi} Monocytes were sorted from spleen, CX3CR1\textsuperscript{hi} macrophages or CX3CR1\textsuperscript{int} MPh were sorted from CLP on day 5 after DSS challenge, Upper: 1\times10^4 of Fbxw7\textsuperscript{f/f} (WT) or LysM\textsuperscript{+} Fbxw7\textsuperscript{f/f} (KO) splenic monocytes were cultured in serum-free medium. Lower: culture supernatant of CX3CR1\textsuperscript{hi} macrophages or CX3CR1\textsuperscript{int} MPh from WT or KO mice (A), or culture supernatant of CX3CR1\textsuperscript{hi} macrophages from WT or KO mice with or without CCL2 and CCL7 antibodies (CCL2/7 antibodies) (B). (C-D) DAPI staining of monocytes that cling to the bottom side of upper chamber according to the transwell assay procedure shown in A. Scale bars: 400 \mu m. (D) The lower chamber contains culture supernatant of resident macrophages with or without CCL2/7 antibodies according to the procedure shown in B. DAPI was used to stain the monocytes that cling to the bottom side of polycarbonate membrane. Scale bars: 400 \mu m. (C-D) All data were from three independent experiments.
Supplementary figure 11

Supplementary figure 11. Attenuated CCL2/7 in vivo relieves colitis and contributes to the decreased migration of Ly6C<sup>hi</sup> monocytes. CCL2 and CCL7 were blocked in vivo with anti-CCL2/7 antibodies (Abs) in Fbxw7<sup>fl/fl</sup> (WT) and LysM<sup>−/−</sup>Fbxw7<sup>fl/fl</sup> (KO) mice and subjected to 3% DSS treatment for 7 days, mice were sacrificed on day 9. (A) Representative flow cytometric analysis of CD11b<sup>+</sup>CX3CR1<sup>int</sup> Mph in CLP of mice after anti-isotype or anti-CCL2/7 Ab treatment at inflammation status. (B) Graphical summary of percentage of CX3CR1<sup>int</sup> Mph subsets out of CD45<sup>+</sup> cells at day 9 (n=5). (C) Disease activity index (DAI) were assessed daily (n=5). (D) Colon sections from colitis mice with or without anti-CCL2/7 Abs treatment were analyzed by H&E staining. Scale bars, 200 µm (whole colon section) and 50 µm (detail). Data are presented as mean ± SEM and representative of at least three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; **p<0.01. (E) Experimental outline for transfer experiment using WT and KO mixed monocytes in vivo.
Supplementary figure 12

Supplementary figure 12. The protein level of EZH2 is decreased in macrophages after LPS stimulation. (A) Immunoblot analysis of EZH2 proteins in BMDMs from C57BL/6 mice after stimulated for indicated times with LPS (100 ng/ml). (B) Representative flow cytometric plots of EZH2 expression in CD45⁺CD11b⁺ cells from CLP of DSS-induced colitis and control C57BL/6 mice. (C) qRT-PCR analysis of Ezh2 mRNA expression in BMDMs from Fbxw7flo/flo and LysM⁺Fbxw7flo/flo mice after LPS (100 ng/ml) stimulation (n=5). Data are presented as mean ± SD and representative of at least three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test.
Supplementary figure 13. Treatment with pAAV-shFbxw7 (Fbxw7 knockdown) relieved mice colitis. (A) Microscopic examination of EGFP fluorescence. Fixed frozen sections of colon from healthy and colitis C57BL/6 mice treated with AAV-shFbxw7-EGFP were mounted in DAPI and examined by confocal microscopy. Scale bars: 100 µm. (B) Silencing of Fbxw7 in inflamed colonic tissue and lamina propria cells (CLP) were confirmed by qRT-PCR (n=6). Data are presented as mean ± SD and representative of three independent experiments. Statistical significance was assessed by unpaired two-tailed Student’s t test; ***p<0.001.
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**Supplementary Table 1. Basic information of non-IBD normal control, UC and CD patients from Sir Run Run Shaw Hospital.**

Human samples were obtained from Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Hangzhou, P. R. China), including peripheral blood sample of 50 non-IBD normal control, 22 non-IBD inflammation control (IC, acute diarrhea), 44 Crohn’s disease (CD) and 24 ulcerative colitis (UC) cases. The diagnosis of CD and UC was based on a standard combination of clinical, endoscopic, histological and radiological criteria.
**Supplementary Table 2. Primers for RT-PCR analysis**

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