Supplemental figure legends

Supplemental Figure 1: *Villin-promoter-dependent claudin-2 overexpression is specific to the intestinal tract*. **A.** Cartoon depicting the claudin-2 transgene expression construct used to generate Cl-2TG mice; **B.** Immunoflourescent analysis of claudin-2 expression in the colon of Cl-2TG mice and WT-littermates; **C.** Immunoblot analysis to detect claudin-2 expression in organs known to express (small intestine and kidney) or not express (lung and heart) the Villin protein; **D.** Immunofluorescent analysis of claudin-2 expression in the intestine of Cl-2TG mice and WT-littermates; **E.** Intestine length increases in Cl-2TG mice *versus* WT-mice; **F.** Paracellular Na+ flux (N# 5, *p<0.05); **G.** Immunofluorescent imaging demonstrating higher retention of rectally administered FITC-dextran in the colonic epithelium of Cl-2TG mice; and **H.** Representative electron microscopic images demonstrating tight junction ultrastructure in Cl-2TG mice and WT littermates (N# 6).

Supplemental Figure 2: *Details of the histopathological analysis from DSS-treated Cl-2TG mice and WT littermates*. Values are presented as mean} sem (n = 12). *p<0.05, ***p<0.001 *versus* DSS-treated WT mice.

Supplemental Figure 3: *Protection of Cl-2TG mice against DSS-colitis is not strain dependent.* Cl-2TG mice backcrossed (more than 10 generations) to the C57BL/6 strain were used. To induce colitis, mice were provided with DSS (3% w/v) in the drinking water for 7 days. **(A).** Weight loss during the course of DSS administration; **(B).** Disease activity index; **C (***i-ii***).** Colon length (cm) in control and DSS-treated mice; and **C (***iii***).** Colon weight/cm ratio; **(D).** Cumulative injury scores from the colons of DSS-treated mice; **(E).** Representative H&E staining of colonic tissues from control and DSS-treated mice. Values are presented as mean} sem. **p<0.01, ***p<0.001. Scale bars=500 or 50 µm.

Supplemental Figure 4: *Details of the histopathological analysis from WT and Cl-2TG mice subjected to DSS-dependent chronic colitis*. Values are presented as mean} sem (*N*#12). *p<0.05, ***p<0.001 *versus* DSS-treated WT mice.

Supplemental Figure 5: *Representative tables depicting the downregulation of genes associated with epithelial integrity and survival, and upregulation of genes associated with mucosal inflammation*. The DSS-treated WT-mice were compared with the control WT-mice that received regular drinking water and DSS-treated Cl-2TG mice were compared with DSS-treated WT-mice**. (A).** Genes associated with proliferation/survival and epithelial integrity; and **(B).** Genes associated with mucosal inflammation. Fold change in expression and associated P-value is provided.

Supplemental Figure 6: *FACS analysis data demonstrating the % enrichment of F480+-cells is presented to demonstrate purity of the macrophages used in our in-vitro activation analysis.*

Supplemental Table 1

Antibody	Company	Address
Anti-Claudin-2	Invitrogen Corp.	San Francisco, CA, USA
Anti-Claudin-3	-do-	-do-
Anti-Claudin-4	-do-	-do-
Anti-Occludin	-do-	-do-
Anti-Zo-1	-do-	-do-
Anti-Phospho-P65	Cell Signaling Technology, Inc.	Danvers, MA, USA
Anti-P65	-do-	-do-
Anti-Phospho-P38	-do-	-do-
Anti-P38	-do-	-do-
Anti-Phospho-AKT	-do-	-do-
Anti-AKT	-do-	-do-
Anti-Phospho-ERK1/2	-do-	-do-
Anti-ERK1/2	-do-	-do-
Anti-Phospho-P65	-do-	-do-
Anti-Phospho-STAT3	-do-	-do-
Anti-STAT3	-do-	-do-
Anti-Cleaved Caspase-3	-do-	-do-
Anti-E-cadherin	BD Biosciences	San Jose, CA, USA
Anti-β Catenin	BD Biosciences	San Jose, CA, USA
Anti-P-27	Santa Cruz biotechnology Inc.	Santa Cruz, CA, USA
Anti-c-myc	-do-	-do-
Anti-Cyclin D1	-do-	-do-
Anti-Brdu	BD Biosciences	San Jose, CA, USA
Anti-Active Caspase-3	BD Biosciences	San Jose, CA, USA
Brdu	Sigma-Aldrich	St. Louis, MO, USA
Anti-β Actin	Sigma-Aldrich	St. Louis, MO, USA
RNeasy Kit	Qiagen	Valencia, Santa Clarita, CA, USA
Dextran Sodium Sulfate	MP Biomedicals	Solon, OH, USA
iScript cDNA synthesis kit	Bio-Rad	Hercules, California, USA
2× iQ™ SYBR Green Supermix	Bio-Rad	Hercules, California, USA
MILLIPLEX MAP Mouse Cytokine/Chemokine Panel Kit	Millipore Corp.	Billerica, Massachusetts, USA
FITC-labeled dextran	Sigma-Aldrich	St. Louis, MO, USA
anti-mouse F4/80	Invitrogen Corp.	San Francisco, CA, USA).
Streptavidin magnetic beads	BD Biosciences	San Jose, CA, USA
Collagenase	Sigma-Aldrich	St. Louis, MO, USA
Dispase II	Sigma-Aldrich	St. Louis, MO, USA
70-µm cell strainer	BD Biosciences	San Jose, CA, USA
Zeocin	Invitrogen	Carlsbad, CA, USA
Chemiluminescence	Amersham Biosciences	Piscataway, NJ, USA

Supplemental Table 2

Injury score Criteria:

Inflammation (A)	% involved by inflammation (B)	Depth of inflammation (C)	Crypt damage (D)	% involved by crypt damage (E)	Injury score
0-3 0 (None) 1 (Mild) 2 (Moderate) 3 (Severe)	1-4 1 (1 to 25%) 2 (26 to 50%) 3 (51 to 75%) 4 (>75%)	0-3 0 (None) 1 (Mucosa) 2 (Submucosa) 3 (Transmural)	1-4 1 (Basal 1/3 damaged) 2 (Basal 2/3 damaged) 3 (Only surface intact) 4 (Entire crypt and surface lost)	1-4 1 (1 to 25%) 2 (26 to 50%) 3 (51 to 75%) 4 (>75%)	=(A+C)*B+(D*E)

Supplemental Table 3 (Real-time PCR primers)

Gene	Sense Primer	Antisense Primer
Actin	5’-CCAGAGCAAGAGAGGTATCC-3’	5’-CTGTGGTGGTGAAGCTGTAG-3’
KC	5’-GCTGGGATTCACCTCAAGAA-3’	5’-CTTGGGGACACCTTTTAGCA-3’
TNF	5’-CTGTGAAGGGAATGGGTGTT-3’	5’-GGTCACTGTCCCAGCATCTT-3’
IFN	5’-GCCACGGCACAGTCATTGAA-3’	5’-CGCCTTGCTGTTGCTGAAGA-3’
IL-6	5’-AGAGACTTCCATCCAGTTGC-3’	5’-TCCTTAGCCACTCCTTCTGT-3’
IL-10	5’-TAGAGCTGCGGACTGCCTTC-3’	5’-CTTCACCTGCTCCACTGCCT-3’
TLR-2	5’-GCTGGAGGACTCCTAAGGCT-3’	5’-GTCAGAAGGAAACAGTCCGC-3’
TLR-4	5’-ACCAGGAAGCTTGAATCCCT-3’	5’-TCCAGCCACTGAAGTTCTGA-3’
MyD 88	5’-GAGCGTTTCGATGCCTTCAT-3’	5’-CGGATCATCTCCTGCACAAA-3’
Ki67	5’-AGAAGACCTGCTACTCCAAAGA-3’	5’-AGTTTGCGTGGCCTGTACTAA-3’
P21	5’-TGTCCGTCAGAACCCATGC-3’	5’-AAAGTCGAAGTTCCATCGCTC-3’