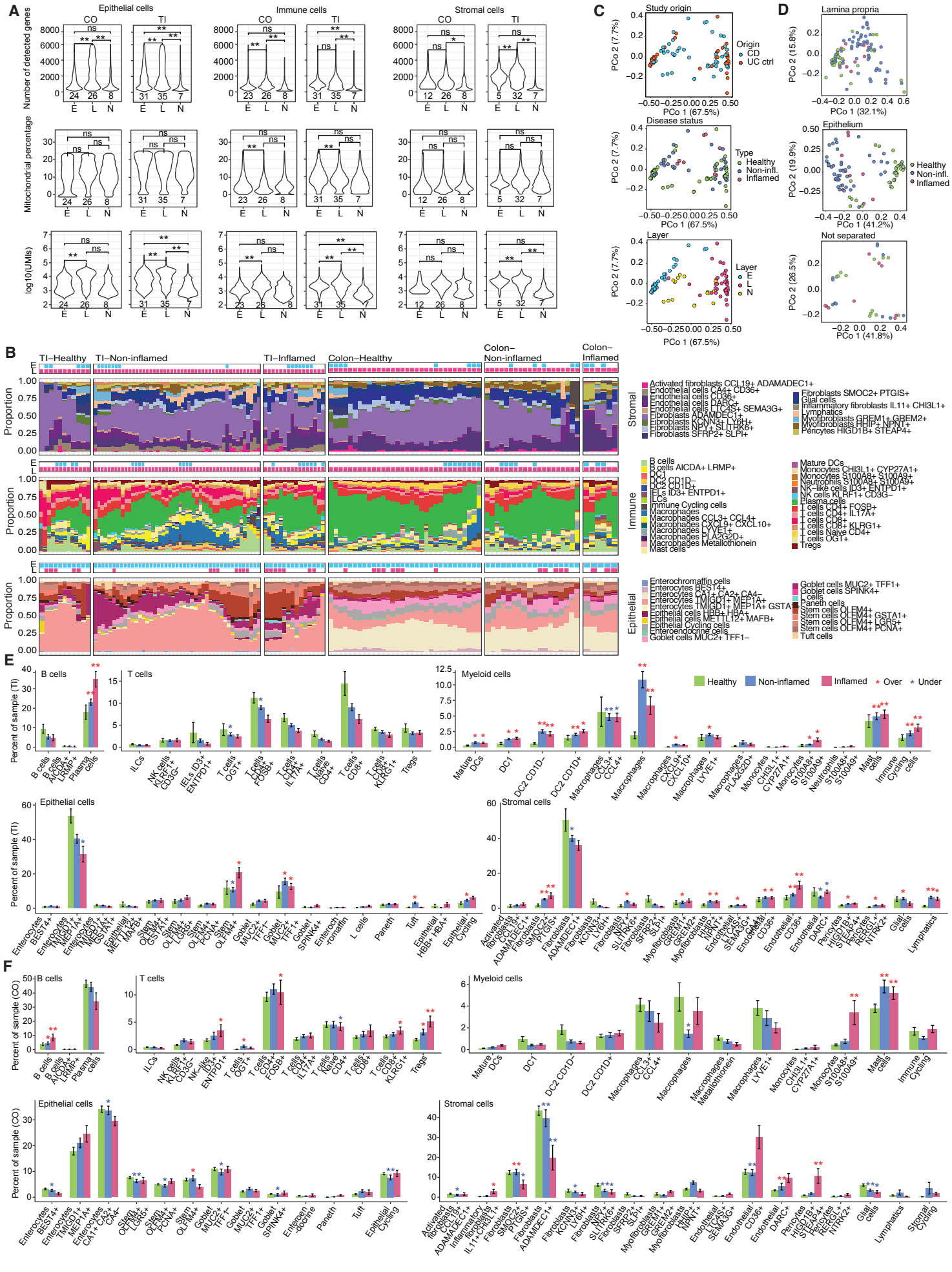
A
Epithelial cells
Immune cells
Stromal cells
CO
TI
Number of detected genes
Mitochondrial percentage
log10(UMIs)
E
L
N
B
TI–Healthy
TI–Non-inflamed
TI–Inflamed
Colon–Healthy
Colon–Non-inflamed
Colon–Inflamed
Proportion
Stromal
Immune
Epithelial
C
Study origin
Origin
CD
UC ctrl
Disease status
Type
Healthy
Non-infl.
Inflamed
Layer
PCo 1 (67.5%)
PCo 2 (7.7%)
D
Lamina propria
Epithelium
Not separated
PCo 1 (32.1%)
PCo 1 (41.2%)
PCo 1 (41.8%)
PCo 2 (15.8%)
PCo 2 (19.9%)
PCo 2 (26.5%)
E
Percent of sample (TI)
B cells
T cells
Myeloid cells
Epithelial cells
Stromal cells
Healthy
Non-inflamed
Inflamed
Over
Under
F
Percent of sample (CO)

Figure S1, related to Figure 1. QC Metrics and cell type distribution by disease and inflammation status. (**A**) Violin plots of layer preparation effects on (top to bottom): Number of detected genes in cells, mitochondrial percentages, and total number of UMIs, from all three cell compartments (left to right), and between colon and TI locations. P-values: **<0.01, *<0.05. P-values are from the *anova* function of the *lmerTest* package in R with formula y ~ Layer + (1 | Donor) + (1 | Channel)). The number of donors contributing to each violin plot is shown below. Violin plots were weighted by the inverse of the number of cells per donor to reduce the weight of donors that contributed many cells. (**B**) Fraction of the cells from each sample belonging to each cell type, broken down by cell compartment, in TI (left) and CO (right). For epithelial cell types, only samples from the epithelial layer or non-separated samples were used, while for stromal and immune cell types, lamina propria and non-separated samples were used. Top bars: E: epithelium, L: lamina propria. Non-separated samples are represented with both E and L. (**C**) Principal coordinates analysis of Bray-Curtis dissimilarities from cell type composition using data only from colon. Left to right: Study origin (CD: from this study UC Control: from Smillie, et al and Jasso, et al[16,20]; Disease status (Healthy, Non-inflamed or Inflamed); Layer (E: epithelium, L: lamina propria, N: not separated). (**D**) Principal coordinates analysis of Bray-Curtis dissimilarities from sample-level cell type composition profiles as **Fig. 1D**, split by layer and colored by disease status. (**E-F**) Barplots show significant differences in cell type frequency for non-inflamed (blue) and inflamed (red) samples relative to healthy (green) samples in immune, stromal and epithelial compartments in TI and CO. (*adjusted p<0.05, **adjusted p<0.01, red asterisks means overrepresented in inflamed or non-inflamed samples vs. healthy, blue asterisks means underrepresented).

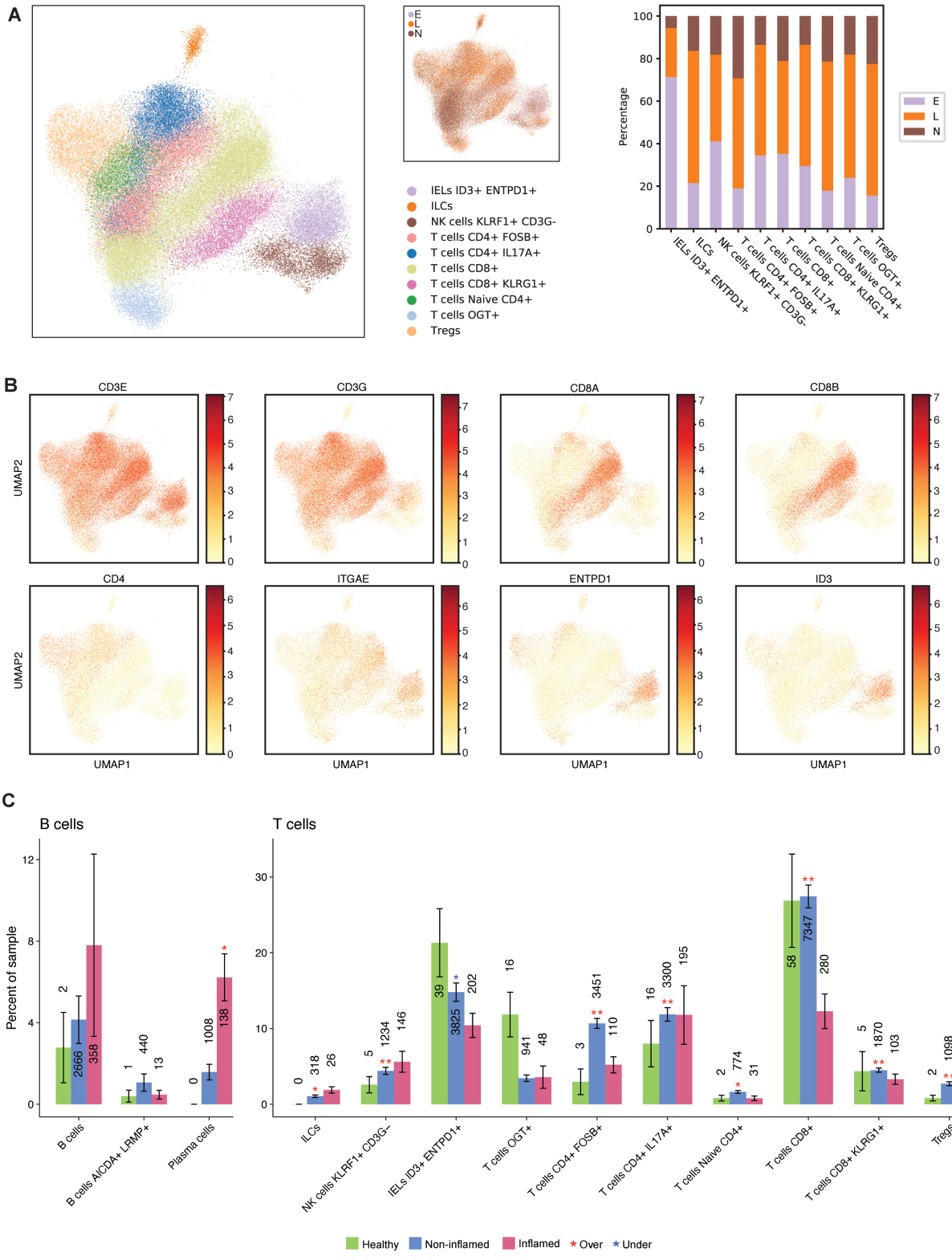
A
E
L
N
IELs ID3+ ENTPD1+
ILCs
NK cells KLRF1+ CD3G-
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells CD8+
T cells CD8+ KLRG1+
T cells Naive CD4+
T cells OGT+
Tregs
Percentage
B
CD3E
CD3G
CD8A
CD8B
CD4
ITGAE
ENTPD1
ID3
UMAP1
UMAP2
C
B cells
T cells
Percent of sample
B cells
B cells AICDA+ LRMP+
Plasma cells
ILCs
NK cells KLRF1+ CD3G-
IELs ID3+ ENTPD1+
T cells OGT+
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells Naive CD4+
T cells CD8+
T cells CD8+ KLRG1+
Tregs
Healthy
Non-inflamed
Inflamed
* Over
* Under

Figure S2, related to Figure 1. Intraepithelial lymphocytes (IELs) in TI. (**A**) UMAP visualization of T cells in TI colored by cell type (left) and layer preparation (middle). Right: Fraction of cells from each layer for each T cell type. (**B**) Expression profiles of selected marker genes for the IELs ID3+ ENTPD1+ population in TI. (**C**) Significant differences in cell type frequency for non-inflamed (blue) and inflamed (red) samples relative to healthy (green) samples in the immune compartment in TI, among epithelial layer samples. (*adjusted $p<0.05$, **adjusted $p<0.01$, red* means overrepresented in inflamed or non-inflamed samples vs. healthy, blue* means underrepresented). The total number of cells contributing to each bar is also shown.

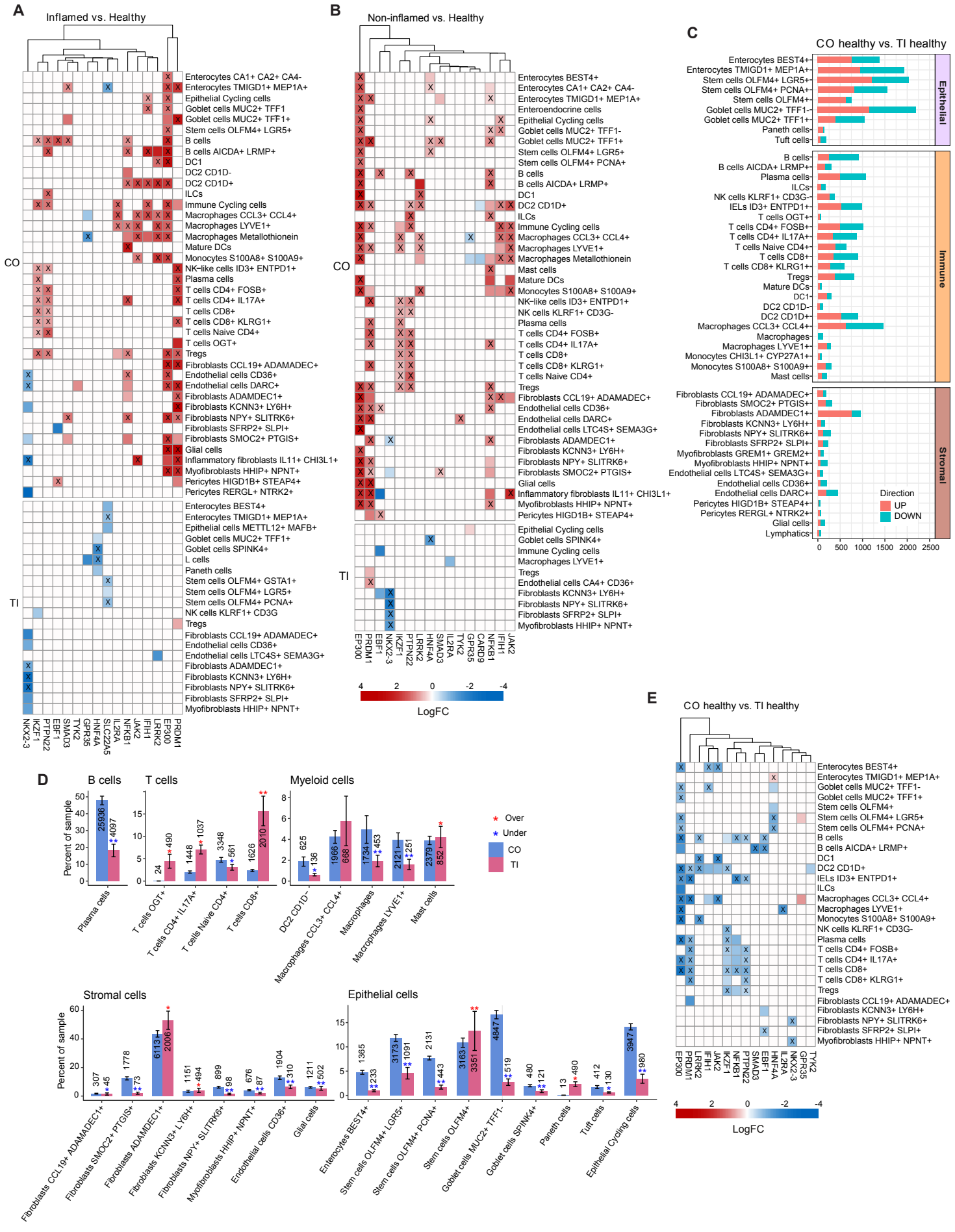
A
Inflamed vs. Healthy
CO
TI
Enterocytes CA1+ CA2+ CA4-
Enterocytes TMIGD1+ MEP1A+
Epithelial Cycling cells
Goblet cells MUC2+ TFF1
Goblet cells MUC2+ TFF1+
Stem cells OLFM4+ LGR5+
B cells
B cells AICDA+ LRMP+
DC1
DC2 CD1D-
DC2 CD1D+
ILCs
Immune Cycling cells
Macrophages CCL3+ CCL4+
Macrophages LYVE1+
Macrophages Metallothionein
Mature DCs
Monocytes S100A8+ S100A9+
NK−like cells ID3+ ENTPD1+
Plasma cells
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells CD8+
T cells CD8+ KLRG1+
T cells Naive CD4+
T cells OGT+
Tregs
Fibroblasts CCL19+ ADAMADEC+
Endothelial cells CD36+
Endothelial cells DARC+
Fibroblasts ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SFRP2+ SLPI+
Fibroblasts SMOC2+ PTGIS+
Glial cells
Inflammatory fibroblasts IL11+ CHI3L1+
Myofibroblasts HHIP+ NPNT+
Pericytes HIGD1B+ STEAP4+
Pericytes RERGL+ NTRK2+
Enterocytes BEST4+
Enterocytes TMIGD1+ MEP1A+
Epithelial cells METTL12+ MAFB+
Goblet cells MUC2+ TFF1+
Goblet cells SPINK4+
L cells
Paneth cells
Stem cells OLFM4+ GSTA1+
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+ PCNA+
NK cells KLRF1+ CD3G
Tregs
Fibroblasts CCL19+ ADAMADEC+
Endothelial cells CD36+
Endothelial cells LTC4S+ SEMA3G+
Fibroblasts ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SFRP2+ SLPI+
Myofibroblasts HHIP+ NPNT+
NKX2-3
IKZF1
PTPN22
EBF1
SMAD3
TYK2
GPR35
HNF4A
SLC22A5
IL2RA
NFKB1
JAK2
IFIH1
LRRK2
EP300
PRDM1
B
Non-inflamed vs. Healthy
CO
TI
Enterocytes BEST4+
Enterocytes CA1+ CA2+ CA4-
Enterocytes TMIGD1+ MEP1A+
Enteroendocrine cells
Epithelial Cycling cells
Goblet cells MUC2+ TFF1-
Goblet cells MUC2+ TFF1+
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+ PCNA+
B cells
B cells AICDA+ LRMP+
DC1
DC2 CD1D+
ILCs
Immune Cycling cells
Macrophages CCL3+ CCL4+
Macrophages LYVE1+
Macrophages Metallothionein
Mast cells
Mature DCs
Monocytes S100A8+ S100A9+
NK−like cells ID3+ ENTPD1+
NK cells KLRF1+ CD3G-
Plasma cells
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells CD8+
T cells CD8+ KLRG1+
T cells Naive CD4+
Tregs
Fibroblasts CCL19+ ADAMADEC+
Endothelial cells CD36+
Endothelial cells DARC+
Endothelial cells LTC4S+ SEMA3G+
Fibroblasts ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SMOC2+ PTGIS+
Glial cells
Inflammatory fibroblasts IL11+ CHI3L1+
Myofibroblasts HHIP+ NPNT+
Pericytes HIGD1B+ STEAP4+
Epithelial Cycling cells
Goblet cells SPINK4+
Immune Cycling cells
Macrophages LYVE1+
Tregs
Endothelial cells CA4+ CD36+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SFRP2+ SLPI+
Myofibroblasts HHIP+ NPNT+
EP300
PRDM1
EBF1
NKX2-3
IKZF1
PTPN22
LRRK2
HNF4A
SMAD3
IL2RA
TYK2
GPR35
CARD9
NFKB1
IFIH1
JAK2
4
2
0
-2
-4
LogFC
C
CO healthy vs. TI healthy
Enterocytes BEST4+
Enterocytes TMIGD1+ MEP1A+
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+ PCNA+
Stem cells OLFM4+
Goblet cells MUC2+ TFF1-
Goblet cells MUC2+ TFF1+
Paneth cells
Tuft cells
Epithelial
B cells
B cells AICDA+ LRMP+
Plasma cells
ILCs
NK cells KLRF1+ CD3G-
IELs ID3+ ENTPD1+
T cells OGT+
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells Naive CD4+
T cells CD8+
T cells CD8+ KLRG1+
Tregs
Mature DCs
DC1
DC2 CD1D-
DC2 CD1D+
Macrophages CCL3+ CCL4+
Macrophages
Macrophages LYVE1+
Monocytes CHI3L1+ CYP27A1+
Monocytes S100A8+ S100A9+
Mast cells
Immune
Fibroblasts CCL19+ ADAMADEC+
Fibroblasts SMOC2+ PTGIS+
Fibroblasts ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SFRP2+ SLPI+
Myofibroblasts GREM1+ GREM2+
Myofibroblasts HHIP+ NPNT+
Endothelial cells LTC4S+ SEMA3G+
Endothelial cells CD36+
Endothelial cells DARC+
Pericytes HIGD1B+ STEAP4+
Pericytes RERGL+ NTRK2+
Glial cells
Lymphatics
Direction
UP
DOWN
Stromal
0
500
1000
1500
2000
2500
D
B cells
T cells
Myeloid cells
Percent of sample
Over
Under
CO
TI
Plasma cells
T cells OGT+
T cells CD4+ IL17A+
T cells Naive CD4+
T cells CD8+
DC2 CD1D-
Macrophages CCL3+ CCL4+
Macrophages
Macrophages LYVE1+
Mast cells
Stromal cells
Epithelial cells
Fibroblasts CCL19+ ADAMADEC1+
Fibroblasts SMOC2+ PTGIS+
Fibroblasts ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Myofibroblasts HHIP+ NPNT+
Endothelial cells CD36+
Glial cells
Enterocytes BEST4+
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+ PCNA+
Stem cells OLFM4+
Goblet cells MUC2+ TFF1-
Goblet cells SPINK4+
Paneth cells
Tuft cells
Epithelial Cycling cells
E
CO healthy vs. TI healthy
Enterocytes BEST4+
Enterocytes TMIGD1+ MEP1A+
Goblet cells MUC2+ TFF1-
Goblet cells MUC2+ TFF1+
Stem cells OLFM4+
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+ PCNA+
B cells
B cells AICDA+ LRMP+
DC1
DC2 CD1D+
IELs ID3+ ENTPD1+
ILCs
Macrophages CCL3+ CCL4+
Macrophages LYVE1+
Monocytes S100A8+ S100A9+
NK cells KLRF1+ CD3G-
Plasma cells
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells CD8+
T cells CD8+ KLRG1+
Tregs
Fibroblasts CCL19+ ADAMADEC+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SFRP2+ SLPI+
Myofibroblasts HHIP+ NPNT+
EP300
PRDM1
LRRK2
IFIH1
JAK2
IKZF1
NFKB1
PTPN22
SMAD3
EBF1
HNF4A
IL2RA
NKX2-3
GPR35
TYK2
4
2
0
-2
-4
LogFC

Figure S3, related to Figure 2. Expression of IBD-related genes in disease in TI and CO. (**A**) DE coefficients of core IBD risk genes from inflamed vs. healthy samples. Genes that have FDR<0.1 in at least one cell type were shown. X in the heatmap indicates FDR < 0.05. (**B**) Same as (**A**), but in non-inflamed vs. healthy samples. (**C**) Number of differentially-expressed genes between healthy colon and healthy TI samples, broken down by cell type (discrete component of a MAST model; FDR < 0.05). (**D**) Significant differences in cell type frequency for colon (blue) healthy samples relative to TI (red) healthy samples in immune, stromal and epithelial compartments in TI, among epithelial layer samples. (*adjusted p<0.05, **adjusted p<0.01, red* means overrepresented in inflamed or non-inflamed samples vs. healthy, blue* means underrepresented). (**E**) DE coefficients of core IBD risk genes from healthy colon and healthy TI samples. Genes that have FDR<0.1 in at least one cell type were shown. X in the heatmap indicates FDR < 0.05.

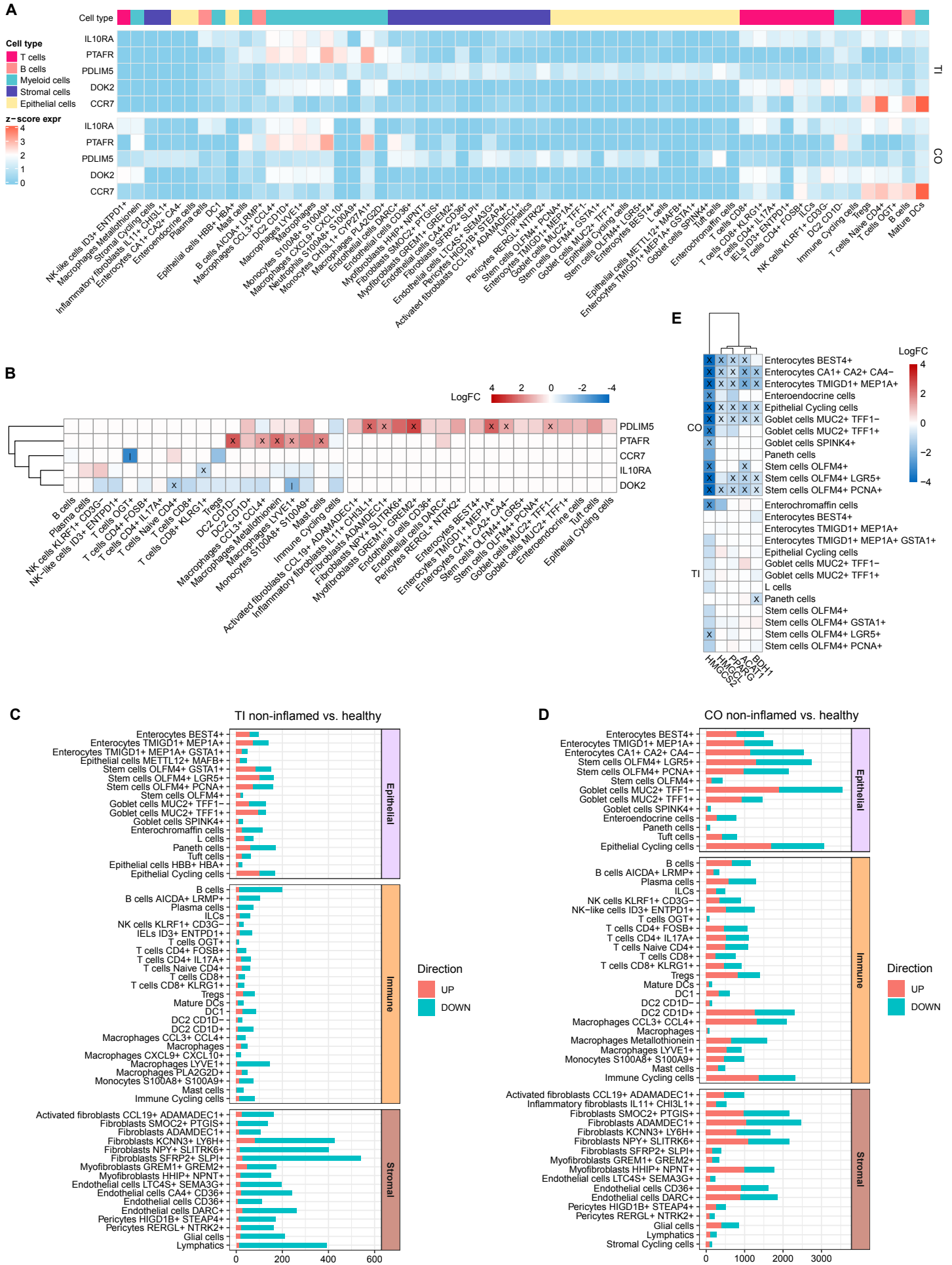
A
Cell type
T cells
B cells
Myeloid cells
Stromal cells
Epithelial cells
z−score expr
IL10RA
PTAFR
PDLIM5
DOK2
CCR7
TI
CO
B
LogFC
C
TI non-inflamed vs. healthy
Epithelial
Immune
Stromal
Direction
UP
DOWN
D
CO non-inflamed vs. healthy
E
LogFC

Figure S4, related to Figure 3. Expression of five IBD-associated loci, non-inflamed vs healthy differential expression, and the Ketogenesis and *PPAR* signaling pathways in CD. (**A**) Scaled mean expression (**Methods**) of five new IBD-associated loci in both TI and colon. (**B**) Heatmap of DE coefficients for five new IBD-associated loci in CO. “X” in the heatmap indicates FDR<0.05 and “|” indicates FDR<0.1. Results in TI showed less significance; full results in **Table S3**. (**C**) Number of differentially-expressed genes between non-inflamed CD and healthy samples in TI and colon (**D**), broken down by cell type. (**E**) Heatmap of key genes involved in Ketogenesis and *PPAR* signaling pathway in Inflamed-Healthy in TI and CO. X in the heatmap indicates FDR < 0.05.

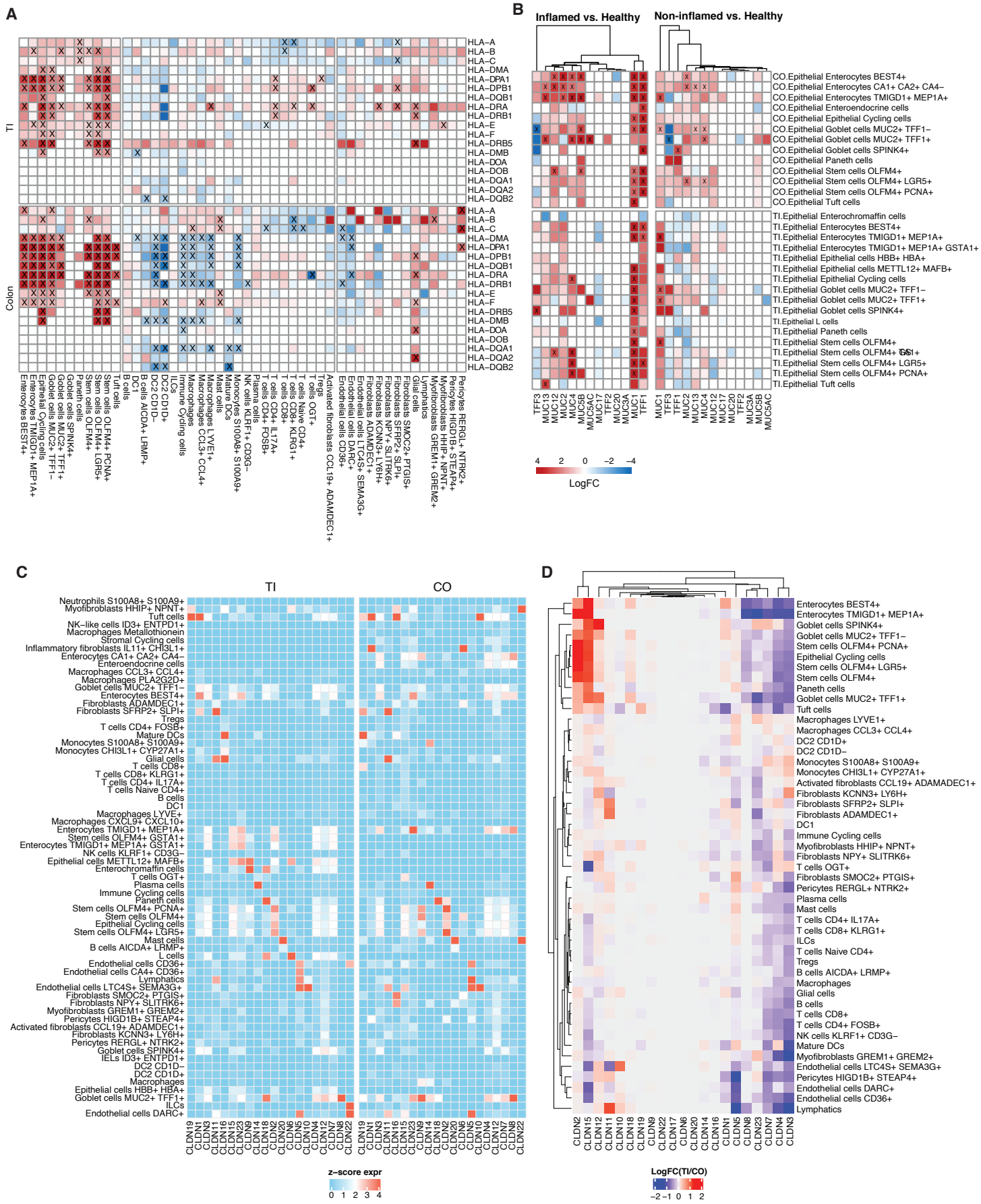
A
TI
Colon
HLA–A
HLA–B
HLA–C
HLA–DMA
HLA–DPA1
HLA–DPB1
HLA–DQB1
HLA–DRA
HLA–DRB1
HLA–E
HLA–F
HLA–DRB5
HLA–DMB
HLA–DOA
HLA–DOB
HLA–DQA1
HLA–DQA2
HLA–DQB2
Enterocytes BEST4+
Enterocytes TMIGD1+ MEP1A+
Epithelial Cycling cells
Goblet cells MUC2+ TFF1–
Goblet cells MUC2+ TFF1+
Goblet cells SPINK4+
Paneth cells
Stem cells OLFM4+
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+ PCNA+
Tuft cells
B cells
DC1
B cells AICDA+ LRMP+
DC2 CD1D+
DC2 CD1D–
ILCs
Immune Cycling cells
Macrophages
Macrophages LYVE1+
Macrophages CCL3+ CCL4+
Mast cells
Mature DCs
Monocytes S100A8+ S100A9+
NK cells KLRF1+ CD3G–
Plasma cells
T cells CD4+ FOSB+
T cells CD4+ IL17A+
T cells CD8+
T cells CD8+ KLRG1+
T cells Naive CD4+
T cells OGT+
Tregs
Activated fibroblasts CCL19+ ADAMDEC1+
Endothelial cells CD36+
Endothelial cells DARC+
Endothelial cells LTC4S+ SEMA3G+
Fibroblasts ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Fibroblasts SFRP2+ SLPI+
Fibroblasts SMOC2+ PTGIS+
Glial cells
Lymphatics
Myofibroblasts GREM1+ GREM2+
Myofibroblasts HHIP+ NPNT+
Pericytes HIGD1B+ STEAP4+
Pericytes RERGL+ NTRK2+
B
Inflamed vs. Healthy
Non-inflamed vs. Healthy
CO.Epithelial Enterocytes BEST4+
CO.Epithelial Enterocytes CA1+ CA2+ CA4–
CO.Epithelial Enterocytes TMIGD1+ MEP1A+
CO.Epithelial Enteroendocrine cells
CO.Epithelial Epithelial Cycling cells
CO.Epithelial Goblet cells MUC2+ TFF1–
CO.Epithelial Goblet cells MUC2+ TFF1+
CO.Epithelial Goblet cells SPINK4+
CO.Epithelial Paneth cells
CO.Epithelial Stem cells OLFM4+
CO.Epithelial Stem cells OLFM4+ LGR5+
CO.Epithelial Stem cells OLFM4+ PCNA+
CO.Epithelial Tuft cells
TI.Epithelial Enterochromaffin cells
TI.Epithelial Enterocytes BEST4+
TI.Epithelial Enterocytes TMIGD1+ MEP1A+
TI.Epithelial Enterocytes TMIGD1+ MEP1A+ GSTA1+
TI.Epithelial Epithelial cells HBB+ HBA+
TI.Epithelial Epithelial cells METTL12+ MAFB+
TI.Epithelial Epithelial Cycling cells
TI.Epithelial Goblet cells MUC2+ TFF1–
TI.Epithelial Goblet cells MUC2+ TFF1+
TI.Epithelial Goblet cells SPINK4+
TI.Epithelial L cells
TI.Epithelial Paneth cells
TI.Epithelial Stem cells OLFM4+
TI.Epithelial Stem cells OLFM4+ LGR5+
TI.Epithelial Stem cells OLFM4+ PCNA+
TI.Epithelial Tuft cells
TFF3
MUC13
MUC12
MUC22
MUC4
MUC5B
MUC5AC
MUC17
TFF2
MUC20
MUC3A
MUC1
TFF1
MUC1
TFF3
TFF1
MUC22
MUC13
MUC4
MUC12
MUC17
MUC20
TFF2
MUC3A
MUC5B
MUC5AC
4 2 0 –2 –4
LogFC
C
TI
CO
Neutrophils S100A8+ S100A9+
Myofibroblasts HHIP+ NPNT+
Tuft cells
NK–like cells ID3+ ENTPD1+
Macrophages Metallothionein
Stromal Cycling cells
Inflammatory fibroblasts IL11+ CHI3L1+
Enterocytes CA1+ CA2+ CA4–
Enteroendocrine cells
Macrophages CCL3+ CCL4+
Macrophages PLA2G2D+
Goblet cells MUC2+ TFF1–
Enterocytes BEST4+
Fibroblasts ADAMDEC1+
Fibroblasts SFRP2+ SLPI+
Tregs
T cells CD4+ FOSB+
Mature DCs
Monocytes S100A8+ S100A9+
Monocytes CHI3L1+ CYP27A1+
Glial cells
T cells CD8+
T cells CD8+ KLRG1+
T cells CD4+ IL17A+
T cells Naive CD4+
B cells
DC1
Macrophages LYVE+
Macrophages CXCL9+ CXCL10+
Enterocytes TMIGD1+ MEP1A+
Stem cells OLFM4+ GSTA1+
Enterocytes TMIGD1+ MEP1A+ GSTA1+
NK cells KLRF1+ CD3G–
Epithelial cells METTL12+ MAFB+
Enterochromaffin cells
T cells OGT+
Plasma cells
Immune Cycling cells
Paneth cells
Stem cells OLFM4+ PCNA+
Stem cells OLFM4+
Epithelial Cycling cells
Stem cells OLFM4+ LGR5+
Mast cells
B cells AICDA+ LRMP+
L cells
Endothelial cells CD36+
Endothelial cells CA4+ CD36+
Lymphatics
Endothelial cells LTC4S+ SEMA3G+
Fibroblasts SMOC2+ PTGIS+
Fibroblasts NPY+ SLITRK6+
Myofibroblasts GREM1+ GREM2+
Pericytes HIGD1B+ STEAP4+
Activated fibroblasts CCL19+ ADAMDEC1+
Fibroblasts KCNN3+ LY6H+
Pericytes RERGL+ NTRK2+
Goblet cells SPINK4+
IELs ID3+ ENTPD1+
DC2 CD1D–
DC2 CD1D+
Macrophages
Epithelial cells HBB+ HBA+
Goblet cells MUC2+ TFF1+
ILCs
Endothelial cells DARC+
CLDN19
CLDN1
CLDN3
CLDN11
CLDN16
CLDN15
CLDN23
CLDN9
CLDN14
CLDN18
CLDN2
CLDN20
CLDN6
CLDN5
CLDN10
CLDN4
CLDN12
CLDN7
CLDN8
CLDN22
z–score expr
0 1 2 3 4
D
Enterocytes BEST4+
Enterocytes TMIGD1+ MEP1A+
Goblet cells SPINK4+
Goblet cells MUC2+ TFF1–
Stem cells OLFM4+ PCNA+
Epithelial Cycling cells
Stem cells OLFM4+ LGR5+
Stem cells OLFM4+
Paneth cells
Goblet cells MUC2+ TFF1+
Tuft cells
Macrophages LYVE1+
Macrophages CCL3+ CCL4+
DC2 CD1D+
DC2 CD1D–
Monocytes S100A8+ S100A9+
Monocytes CHI3L1+ CYP27A1+
Activated fibroblasts CCL19+ ADAMADEC1+
Fibroblasts KCNN3+ LY6H+
Fibroblasts SFRP2+ SLPI+
Fibroblasts ADAMDEC1+
DC1
Immune Cycling cells
Myofibroblasts HHIP+ NPNT+
Fibroblasts NPY+ SLITRK6+
T cells OGT+
Fibroblasts SMOC2+ PTGIS+
Pericytes RERGL+ NTRK2+
Plasma cells
Mast cells
T cells CD4+ IL17A+
T cells CD8+ KLRG1+
ILCs
T cells Naive CD4+
Tregs
B cells AICDA+ LRMP+
Macrophages
Glial cells
B cells
T cells CD8+
T cells CD4+ FOSB+
NK cells KLRF1+ CD3G–
Mature DCs
Myofibroblasts GREM1+ GREM2+
Endothelial cells LTC4S+ SEMA3G+
Pericytes HIGD1B+ STEAP4+
Endothelial cells DARC+
Endothelial cells CD36+
Lymphatics
CLDN2
CLDN15
CLDN12
CLDN11
CLDN10
CLDN18
CLDN19
CLDN9
CLDN22
CLDN17
CLDN6
CLDN20
CLDN14
CLDN16
CLDN1
CLDN5
CLDN8
CLDN23
CLDN7
CLDN4
CLDN3
LogFC(TI/CO)
–2 –1 0 1 2

Figure S5, related to Figure 2-3. Differential expression in HLA, mucin and TFF genes in TI and CO. (**A**) Heatmaps of DE coefficients between inflamed vs. healthy samples in HLA- genes. X in the heatmap indicates FDR < 0.05. (**B**) Heatmaps of DE coefficients among 14 mucin and TFF genes. Left: inflamed vs. healthy; Right: noninflamed vs. healthy. X in the heatmap indicates FDR < 0.05. (**C**) Scaled mean expression (**Methods**) of claudin genes in both TI and colon. (**D**) logFC of TI/CO in mean expression among claudins.

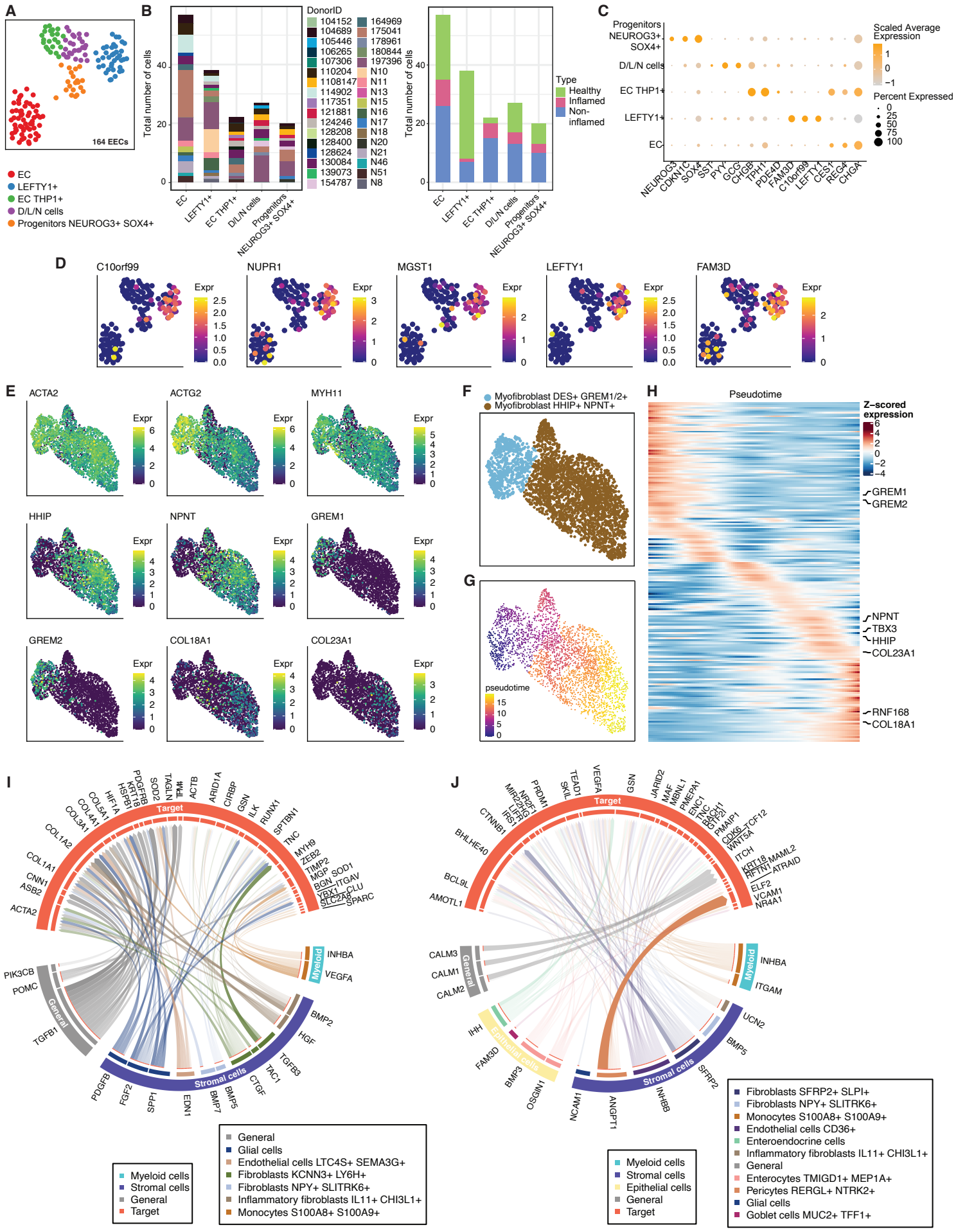
A
164 EECs
EC
LEFTY1+
EC THP1+
D/L/N cells
Progenitors NEUROG3+ SOX4+
B
Total number of cells
DonorID
104152
104689
105446
106265
107306
110204
1108147
114902
117351
121881
124246
128208
128400
128624
130084
139073
154787
164969
175041
178961
180844
197396
N10
N11
N13
N15
N16
N17
N18
N20
N21
N46
N51
N8
Type
Healthy
Inflamed
Non-inflamed
C
Progenitors
NEUROG3+ SOX4+
D/L/N cells
EC THP1+
LEFTY1+
EC
Scaled Average Expression
Percent Expressed
NEUROG3
CDKN1C
SOX4
SST
PYY
GCG
CHGB
TPH1
PDE4D
FAM3D
C10orf99
LEFTY1
CES1
REG4
CHGA
D
C10orf99
NUPR1
MGST1
LEFTY1
FAM3D
Expr
E
ACTA2
ACTG2
MYH11
HHIP
NPNT
GREM1
GREM2
COL18A1
COL23A1
F
Myofibroblast DES+ GREM1/2+
Myofibroblast HHIP+ NPNT+
G
pseudotime
H
Pseudotime
Z–scored expression
GREM1
GREM2
NPNT
TBX3
HHIP
COL23A1
RNF168
COL18A1
I
Target
Myeloid
General
Stromal cells
Myeloid cells
Stromal cells
General
Target
General
Glial cells
Endothelial cells LTC4S+ SEMA3G+
Fibroblasts KCNN3+ LY6H+
Fibroblasts NPY+ SLITRK6+
Inflammatory fibroblasts IL11+ CHI3L1+
Monocytes S100A8+ S100A9+
J
Target
Myeloid
General
Epithelial cells
Stromal cells
Myeloid cells
Stromal cells
Epithelial cells
General
Target
Fibroblasts SFRP2+ SLPI+
Fibroblasts NPY+ SLITRK6+
Monocytes S100A8+ S100A9+
Endothelial cells CD36+
Enteroendocrine cells
Inflammatory fibroblasts IL11+ CHI3L1+
General
Enterocytes TMIGD1+ MEP1A+
Pericytes RERGL+ NTRK2+
Glial cells
Goblet cells MUC2+ TFF1+

Figure S6, related to Figure 4-5. Enteroendocrine Cells (EEC) and Myofibroblasts in the colon. (**A**) UMAP of 164 EECs in colon, colored by subset. (**B**) Donor and disease composition among EEC subsets. (**C**) Expression of markers for major EEC subsets. (**D**) Expression profiles of select top genes expressed in the LEFTY1+ cluster. (**E**) UMAP of the myofibroblast sub-groups in colon (HHIP+ NPNT+ and GREM1+ GREM2+), overlaid with expression of myofibroblast markers and sub-group markers. (**F**) Myofibroblast sub-groups clustered into two distinct clusters. (**G**) Pseudotime trajectory UMAP in TI myofibroblasts. **(H)** Expression profiles of 200 selected genes with significant expression changes with respect to pseudotime (**Methods**). Expression was first smoothed with a cubic spline and standardized to highlight expression differences (**Methods**). (**I**) Circos plot summarizes the predicted upstream ligands (bottom half genes) based on the DEGs in Myofibroblasts GREM1+ GREM2+ (Target, top half genes) by NicheNet. Predicted ligands were assigned to the cell type with maximum expression if Gini>0.5, otherwise the ligand is “General”. Cell types were further grouped into cell categories (overall and detailed cell type legends were shown next to the circo plot). (**J**) Heatmap (left, orange) showed the predicted ligand activity driving DEGs in myofibroblasts GREM1+ GREM2+ in inflamed samples, ranked by Pearson correlation coefficient (**Methods**). The potential of each ligand for inducing differential expression of myofibroblast target genes was shown by regulatory potential (right, purple heatmap).