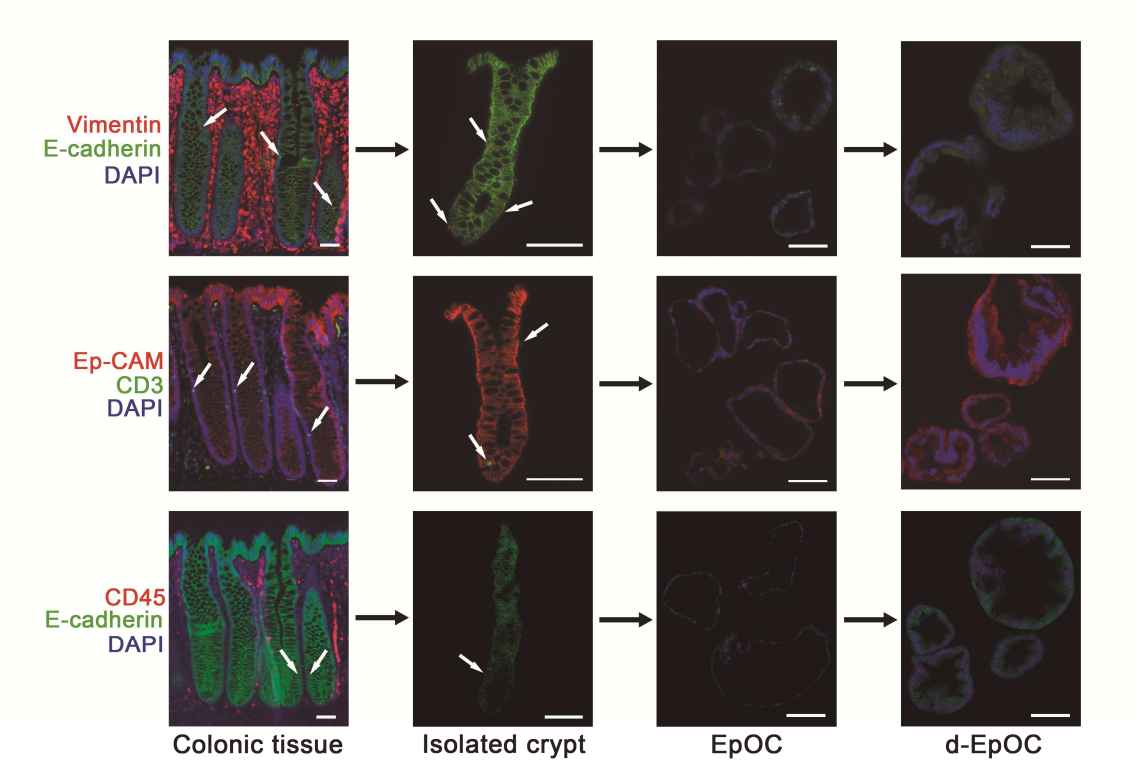
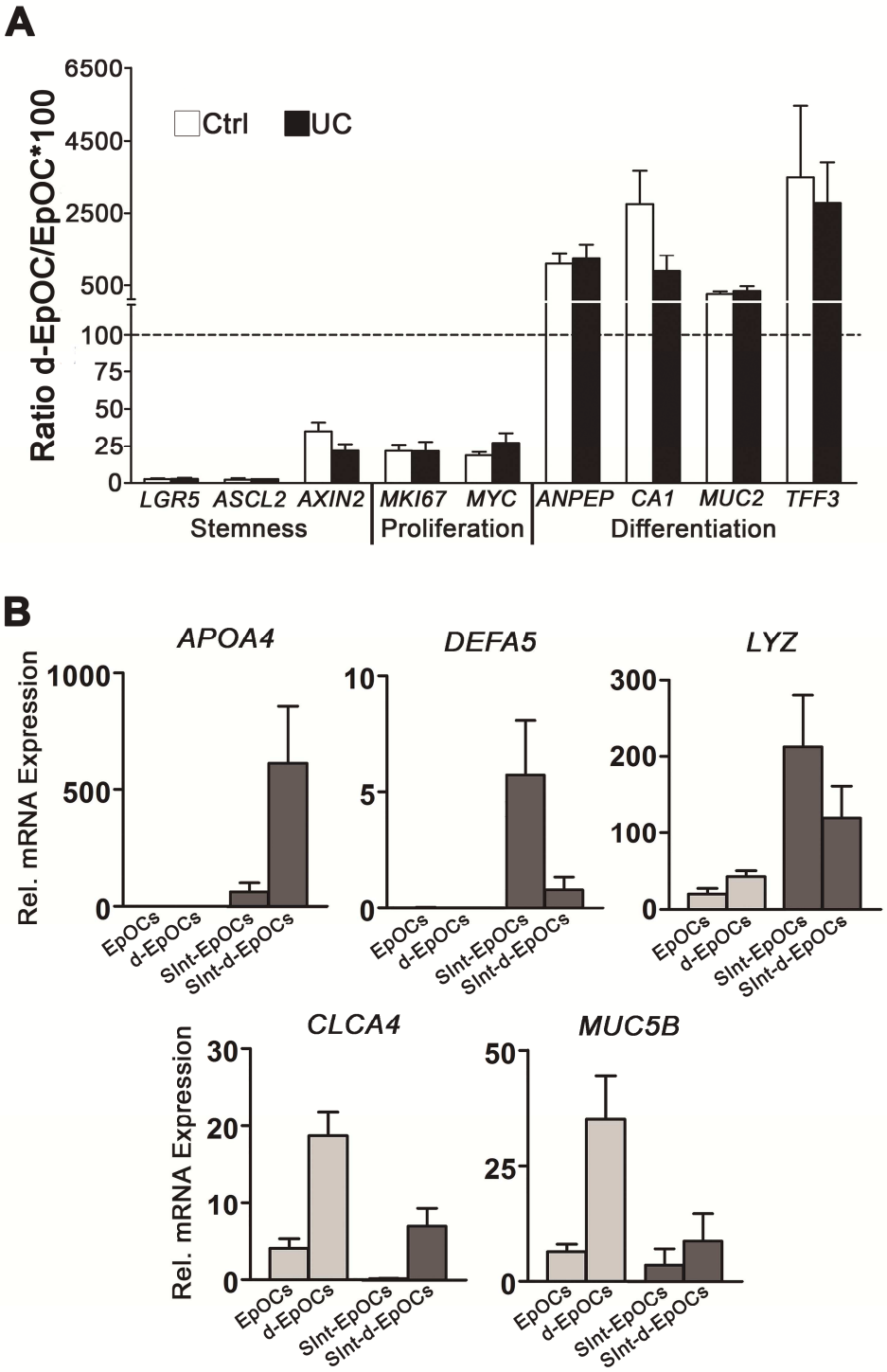
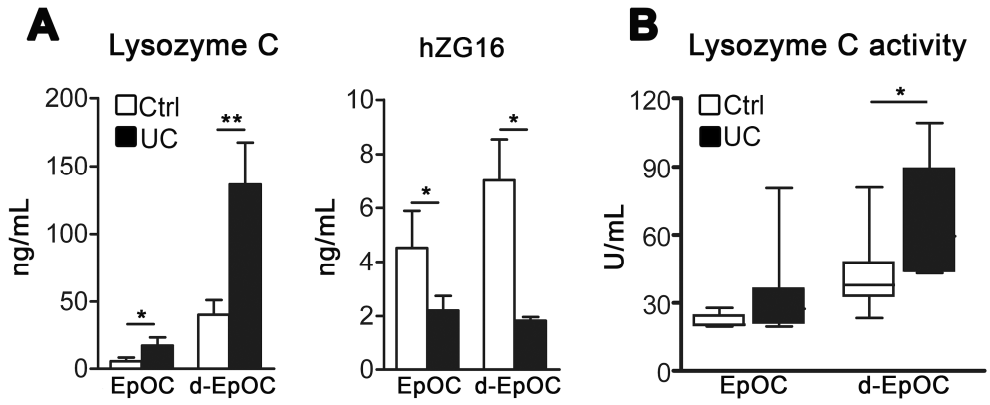
SUPPLEMENTARY FIGURES



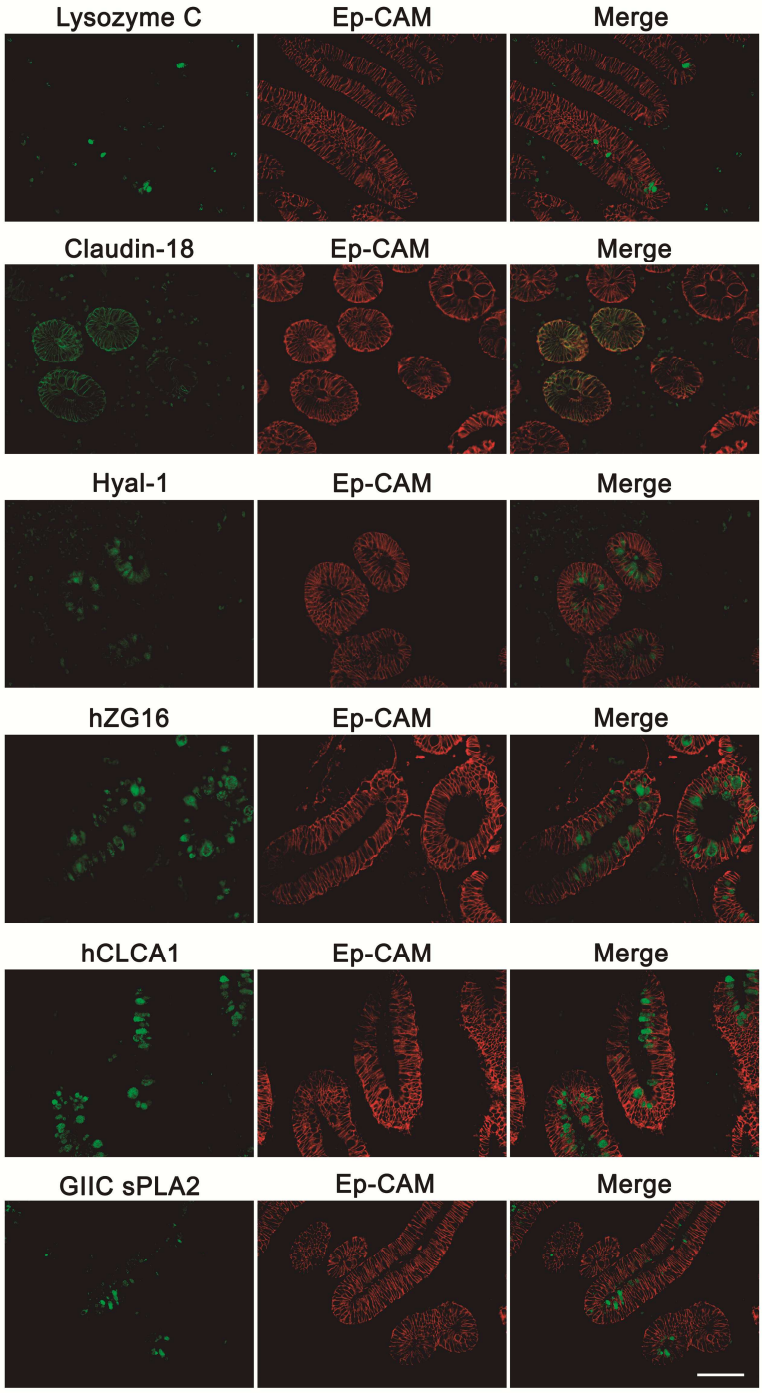
Supplementary Figure 1. No contamination by non-epithelial cells is detected in expanded EpOCs and d-EpOCs. From left to right, images show representative immunofluorescent staining of sections of the normal sigmoid colon, isolated intestinal crypt units, and EpOCs and d- EpOCs. Samples were stained for expression of vimentin, CD3 and CD45 in combination with the epithelial markers Ep-CAM or E-cadherin. Sections were counterstained with DAPI (blue). White arrows indicate vimentin, CD3 or CD45 positive intraepithelial cells. DAPI, 4',6-diamidino-2-phenylindole. Scale bars: 100 μm.


A
Ratio d-EpOC/EpOC*100
6500
4500
2500
500
100
75
50
25
0
Ctrl
UC
LGR5
ASCL2
AXIN2
MKI67
MYC
ANPEP
CA1
MUC2
TFF3
Stemness
Proliferation
Differentiation
B
APOA4
DEFA5
LYZ
CLCA4
MUC5B
Rel. mRNA Expression
EpOCs
d-EpOCs
SInt-EpOCs
SInt-d-EpOCs

Supplementary Figure 2. Transcriptional characterization of EpOCs and d-EpOCs from non-IBD controls and patients with UC. (*A*) Epithelial organoid cultures from Ctrl and patients with UC show similar expression levels of intestinal epithelial stem, proliferation and differentiation markers. The bar chart represents the relative mRNA expression ratio of these markers between d-EpOCs and EpOCs. The line intersecting the ratio of 100 refers to the basal mRNA expression in EpOCs. (*B*) Region-specific identity is maintained in colon versus small intestinal organoid cultures. Expression analysis of small intestinal (i.e., *APOA4*, *DEFA5*, *LYZ*) and colonic (i.e., *CLCA4*, *MUC5B*) epithelial markers was performed in a cohort of sigmoid EpOCs (n=23) and d-EpOCs (n=20), small intestinal EpOCs (SInt-EpOCs, n=9) and small intestinal differentiated EpOCs (SInt-d-EpOCs, n=7). The organoid cultures derived from biopsy samples of pediatric and adult subjects. SInt-EpOCs have been generated, differentiated and analyzed following the procedures described in the Method section for colonic organoid cultures. Gene expression is relative to *ACTB* gene.

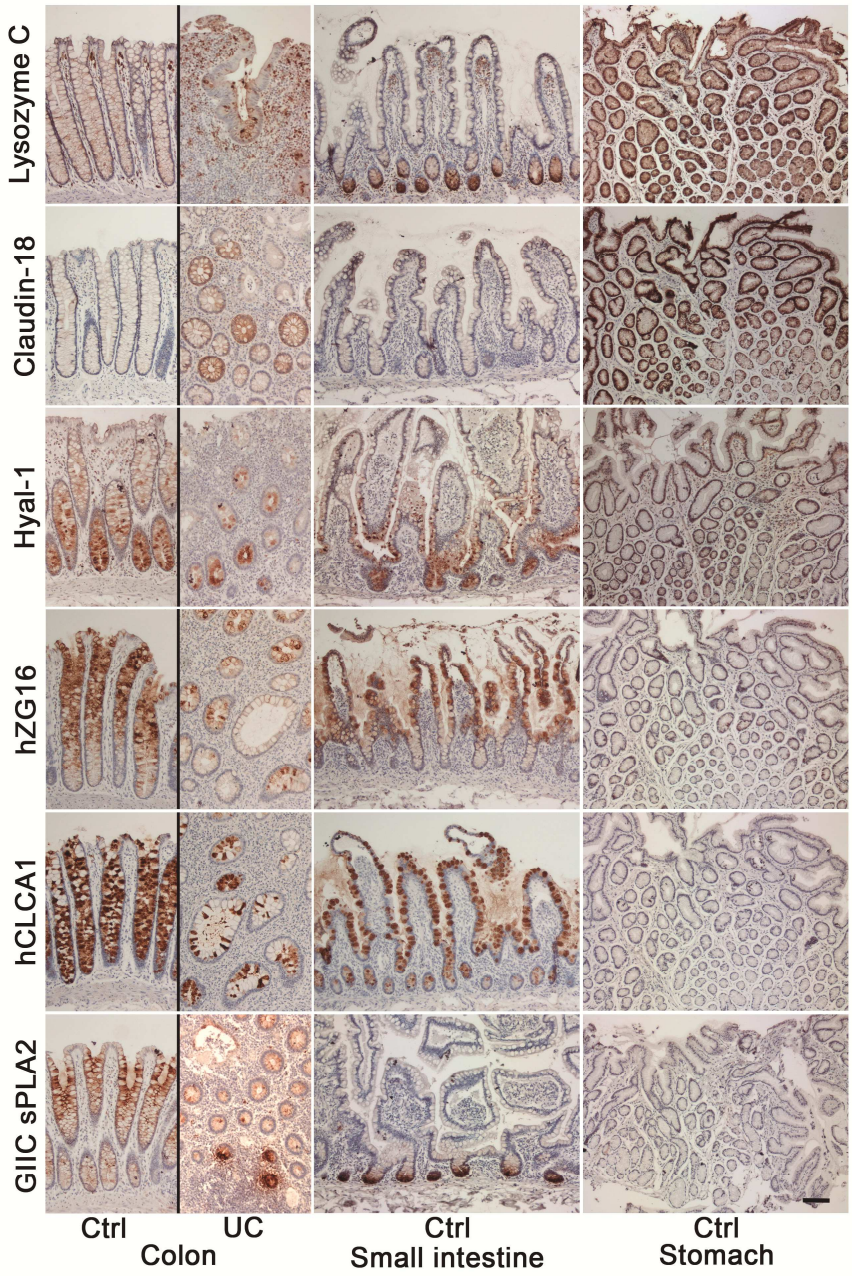


Supplementary Figure 3. Differential protein secretion in EpOCs and d-EpOCs derived from patients with UC compared to non-IBD controls. (*A*) Bar chart representation of lysozyme C and hZG16 protein secretion (ng/mL) in the supernatant of EpOCs and d-EpOCs from non-IBD controls and UC patients. Mean±SEM. **P* < .05, ***P* < .01 by one-tailed Wilcoxon test. (*B*) Box plot representation of lysozyme C activity (U/mL) in EpOCs and d-EpOCs from non-IBD controls and UC patients. Mean±SEM. **P* < .05 by one-tailed Wilcoxon test.



Supplementary Figure 4. Co-localization of lysozyme C, claudin-18, hyal-1, hZG16, hCLCA1 and GIIC sPLA2 proteins with the epithelial marker Ep-CAM. These images show representative immunofluorescent co-staining of fixed paraffin-embedded sections of colon samples from patients with active UC (lysozyme, claudin-18, hyal-1, hZG16,

hCLCA1 staining) and non-IBD controls (GIIC sPLA2 staining). Samples were counterstained with DAPI. DAPI, 4',6-diamidino-2-phenylindole. Scale bar: 100 μm.



Supplementary Figure 5. Immunohistochemical analysis of lysozyme C, claudin-18, hyal-1, hZG16, hCLCA1 and GIIC sPLA2 in control and UC sigmoid colon, compared to healthy small intestine (ileum) and stomach (antrum). Pictures of Ctrl and UC sigmoid colon refer to the samples used for Figures 5 and 6. Scale bar: 100 μm.