Supplementary Materials

Figure S1. Single-cell data in UMAP space from **Fig. 1B** (biopsy) and **Fig. 1C** (blood), separately displayed by immunosuppression for biopsies **(A)**, and for blood data, by disease **(B)**, CPI **(C)**, and immunosuppression **(D)**.

Figure S2. Marker genes for conserved blood and colon biopsy fine subpopulations.
(A) Dot plots showing marker genes for scRNAseq immune (B, plasma, myeloid, and cycling cell) subpopulations in biopsy samples.
(B) Dot plots showing marker genes for scRNAseq nonimmune (epithelial, endothelial, and stromal cell) subpopulations in biopsy samples.
(C) Dot plots showing marker genes for scRNAseq blood subpopulations (B and myeloid cells).

Figure S3: Cell frequencies of select immune and non-immune subpopulations in blood and biopsies of CPI colitis patients and controls.
Cell frequencies of scRNAseq annotated populations, stratified by disease state (mean + standard deviation; each dot represents one patient; * $p < 0.05$ and $q < 0.1$).
(A) Immune fine subpopulations in biopsies (cycling, B, and plasma cells).
(B) Nonimmune fine subpopulations in biopsies (epithelial, endothelial, and stromal cells).
(C) Coarse populations in blood.
(D) Immune fine subpopulations in blood (T, B, and myeloid cells).

Figure S4. Upregulated pathways in CPI colitis. For coarse immune **(A)**, coarse non-immune **(B)**, and fine populations **(C)**, the top 10 significantly upregulated pathways in CPI colitis over healthy controls are shown, with Reactome annotation. Corresponding pathway information, including p values, combined scores, and contributing genes are in **Table S6**.

Figure S5. Downregulated pathways in CPI colitis. For coarse immune **(A)**, coarse non-immune **(B)**, and fine populations **(C)**, the top 10 significantly downregulated pathways in CPI colitis over healthy controls are shown, with Reactome annotation. Corresponding pathway information, including p values, combined scores, and contributing genes are in **Table S7**.

Figure S6. DE genes in CPI colitis across individual patients. For significantly DE genes highlighted in figures for each population, the z-score is shown as a heatmap across individual patients (columns) for immune (top) and non-immune (bottom) populations.

Figure S7. **Statistical testing of TCR data from CPI colitis and controls. (A)** Comparisons of the number of expanded clusters (node size >1), normalized to the total number of cells per sample, across disease states in biopsies (top) and blood (bottom).
(B) Gini coefficient for all T cells per sample in blood and biopsies across disease states. **(C)** Descriptive statistics of the number of individual expanded TCR$\alpha\beta$ clusters shared by combinations of CD4T RM, CD8T RM, and CD8T GZMB cells in blood and biopsies. **(D)** Descriptive statistics of the number of individual expanded clusters shared by combinations of CD4T RM, CD8T RM, and CD8T GZMB cells in biopsies across disease states.

Figure S8. Interferon signaling and antigen presentation across cell populations in CPI colitis. DE genes ($p < 0.05$ and $\log_2(FC) > 1$ or < -1) between healthy and CPI colitis biopsies are shown for individual coarse cell types. DE genes related to **(A)** IFNγ signaling or **(B)** antigen presentation are labeled.

Figure S9. Co-regulation of genes by CPI treatment, and in CPI colitis, in external data from the steroid-naive state (ref. 2).

(A) Overlapping DE genes in both healthy vs CPI colitis (x axis) and CPI only vs CPI colitis (y axis) in select T cell subpopulations, with genes of interest labeled focusing on IFN signaling and antigen presentation.
(B-C) DE genes between HC and CPI only in coarse immune populations **(B)** and specific T cell subpopulations **(C)**.

Table S1. Baseline demographic and clinical data for study participants.

Table S2. Antibody panels for CITEseq (TotalSeq-C, top), and mass cytometry (CyTOF, bottom).

Table S3. Marker features used to identify coarse and fine cell annotations in blood and biopsies from CPI colitis. Lists are provided for this predominantly steroid-experienced data set, and external steroid-naïve data set (Luoma et al. Cell 2020). Features are transcripts, with the exception of CITEseq features which are specifically noted.

Table S4. DE gene lists for coarse biopsy populations by disease in predominantly steroid-experienced disease (healthy vs CPI colitis, healthy vs UC, UC vs CPI colitis).

Table S5. DE gene lists for fine blood subpopulations by disease in predominantly steroid-experienced disease (healthy vs CPI colitis, healthy vs UC, UC vs CPI colitis).

Table S6. GSEA upregulated pathways in CPI colitis. For individually listed coarse and fine populations, significantly upregulated pathways in CPI colitis versus healthy controls, associated Reactome annotation, p values, combined scores, and contributing genes are shown.

Table S7. GSEA downregulated pathways in CPI colitis. For individually listed coarse and fine populations, significantly downregulated pathways in CPI colitis versus healthy controls, associated Reactome annotation, p values, combined scores, and contributing genes are shown.

Table S8. DE gene lists for fine biopsy subpopulations by disease in predominantly steroid-experienced disease (healthy vs CPI colitis, healthy vs UC, UC vs CPI colitis).

Table S9. DE gene lists for coarse biopsy populations by suppression in predominantly steroid-experienced disease (healthy vs steroid only, healthy vs anti-TNF, steroid only vs anti-TNF).

Table S10. DE gene lists for coarse biopsy populations by checkpoint inhibitor in predominantly steroid-experienced disease (healthy vs combo anti-PD-1+anti-CTLA-4, healthy vs anti-PD-1, anti-PD-1 vs combo). As noted in Results, this analysis is restricted to patients who received steroids only but not anti-TNF.

Table S11. DE gene lists for CD45-sorted biopsy populations by disease in steroid-naïve external CPI colitis data set (ref. 2; healthy vs CPI colitis, CPI only no colitis vs CPI colitis, healthy vs CPI only).

Table S12. DE gene lists for CD3-sorted biopsy populations by disease in steroid-naïve external CPI colitis data set (ref. 2; healthy vs CPI colitis, CPI only no colitis vs CPI colitis, healthy vs CPI only).