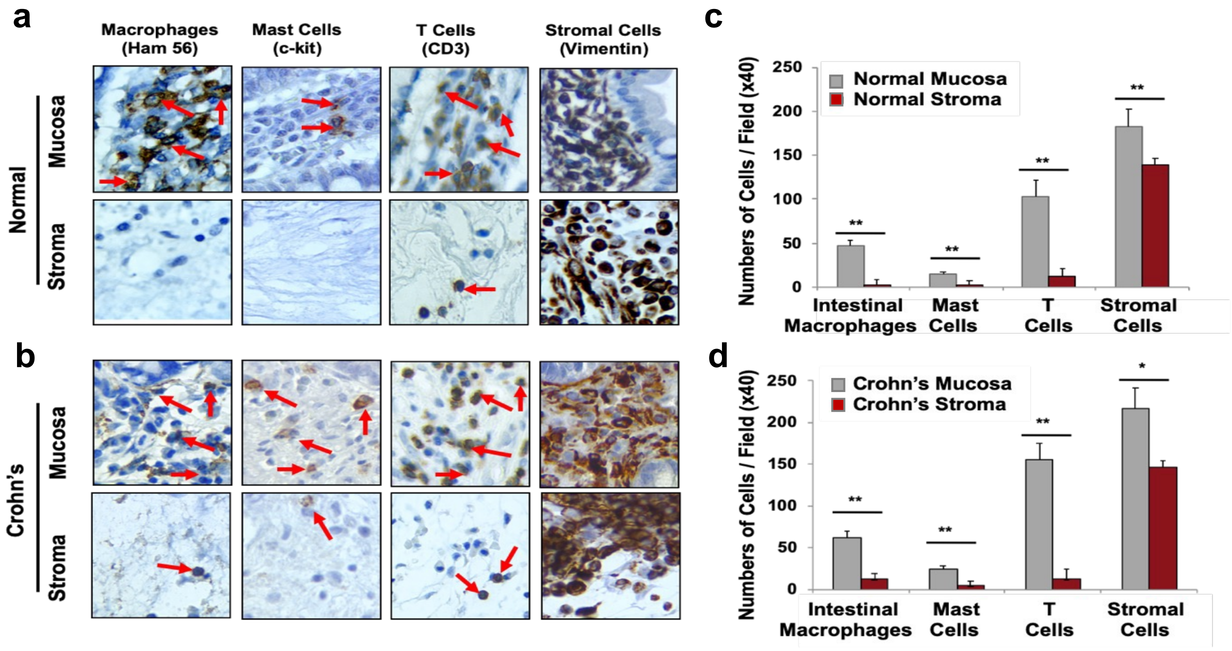
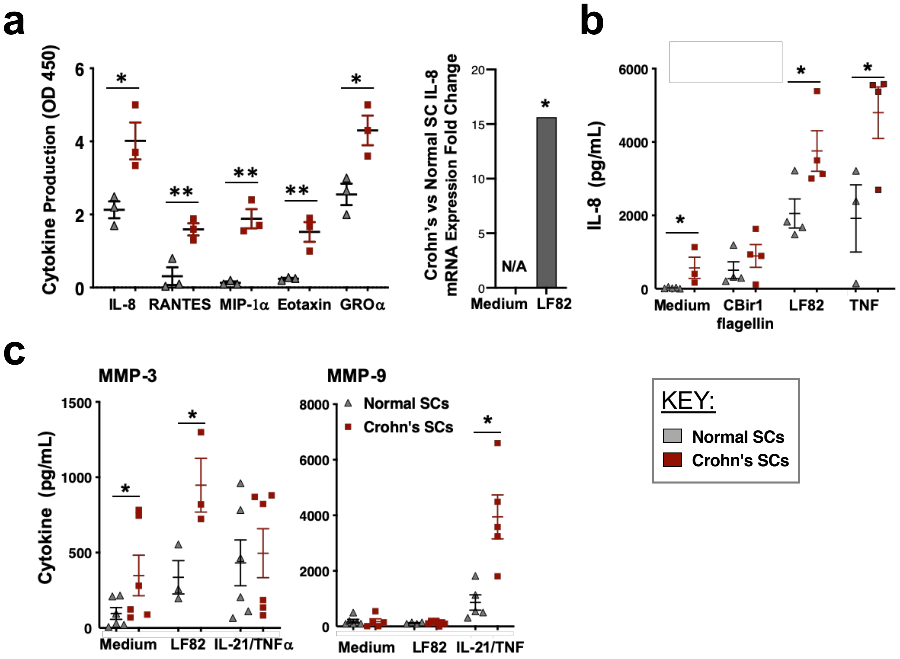


Supplementary Figure 1. Stromal cells are the predominant cell in the ileal mucosa. Tissue sections of **a** normal and **b** Crohn's disease ileal mucosa and (donor-matched) stroma (n=5) stained for intestinal macrophages (HAM56$^+$/DAB$^+$), mast cells (Ckit$^+$/DAB$^+$), CD4$^+$ T cells (CD4$^+$/DAB$^+$) and SCs (vimentin$^+$/DAB$^+$) and analyzed by IHC (40X). Numbers of intestinal macrophages, mast cells, CD4$^+$ T cells and SCs present in 10 randomly selected fields/section of **c** normal mucosa and stroma and **d** Crohn's disease mucosa and stroma (n=4).



d

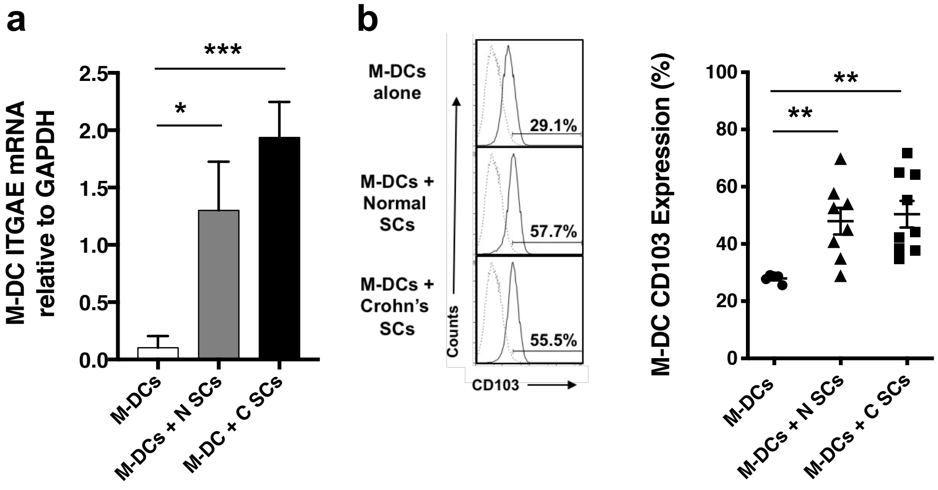
INFLAMMATORY RESPONSE		UNSTIMULATED CROHN'S SCS *vs* NORMAL SCS			STIMULATED CROHN'S SCS *vs* NORMAL SCS	
Symbol	Gene	Fold Change	*P* value		Fold Change	*P* value
TREM1	triggering receptor expressed on myeloid cells 1	1.355	0.904		458723.462	0.000
IL1RN	interleukin 1 receptor antagonist	15.977	0.049		1331.891	0.000
CSF3	colony stimulating factor 3	58.026	0.016		819.796	0.001
CCL3L1	C-C motif chemokine ligand 3 like 1	1.280	0.834		375.948	0.000
IL1B	interleukin 1 beta	23.453	0.001		234.135	0.000
CCL20	C-C motif chemokine ligand 20	1.542	0.775		80.658	0.032
CXCL11	C-X-C motif chemokine ligand 11	-13.153	0.024		69.363	0.006
IL1A	interleukin 1 alpha	25.799	0.001		64.123	0.001
TLR2	toll like receptor 2	5.084	0.067		53.203	0.001
TLR4	toll like receptor 4	2.035	0.368		42.512	0.001
IDO1	indoleamine 2,3-dioxygenase 1	-18.875	0.052		42.349	0.068
IL6	interleukin 6	12.504	0.007		40.710	0.003
IL11	interleukin 11	5.421	0.052		15.806	0.020
CSF2	colony stimulating factor 2	1.613	0.694		13.965	0.107
NFKBIZ	NFKB inhibitor zeta	1.915	0.187		6.630	0.005
ICAM1	intercellular adhesion molecule 1	3.476	0.039		5.701	0.034
NFKB1	NFKB-p105	-1.078	0.777		3.779	0.000
NFKBIA	IKBA	1.037	0.923		3.634	0.013
RELA	NF-kappa B (p65)	1.145	0.426		1.948	0.004
IL1R1	interleukin 1 receptor type 1	-1.295	0.649		1.640	0.522
IL6R	interleukin 6 receptor	-1.725	0.185		-3.111	0.042

CYTOKINES		UNSTIMULATED CROHN'S SCS *vs* NORMAL SCS			STIMULATED CROHN'S SCS *vs* NORMAL SCS	
Symbol	Gene	Fold Change	*P* value		Fold Change	*P* value
IFNA1/IFNA13	interferon alpha 1, interferon alpha 13	25.213	0.007		116.987	0.004
IL-10	CSIF, interleukin 10, TGIF	-4.167	0.181		65.155	0.003
IFN-β1	IFN-β, IFN-β1, interferon beta 1	-2.872	0.482		59.696	0.026
IL-8	C-X-C motif chemokine ligand 8, IL8	3.748	0.390		15.642	0.189
IL-23	IL-23, IL23P19, interleukin 23	-1.165	0.747		14.913	0.000
IL-4	BCGF, BCGF-1, BSF-1, Il4e12, interleukin 4	2.692	0.322		-1.787	0.672
IL-5	EDF, interleukin 5, TRF	6.883	0.465		-15.148	0.442

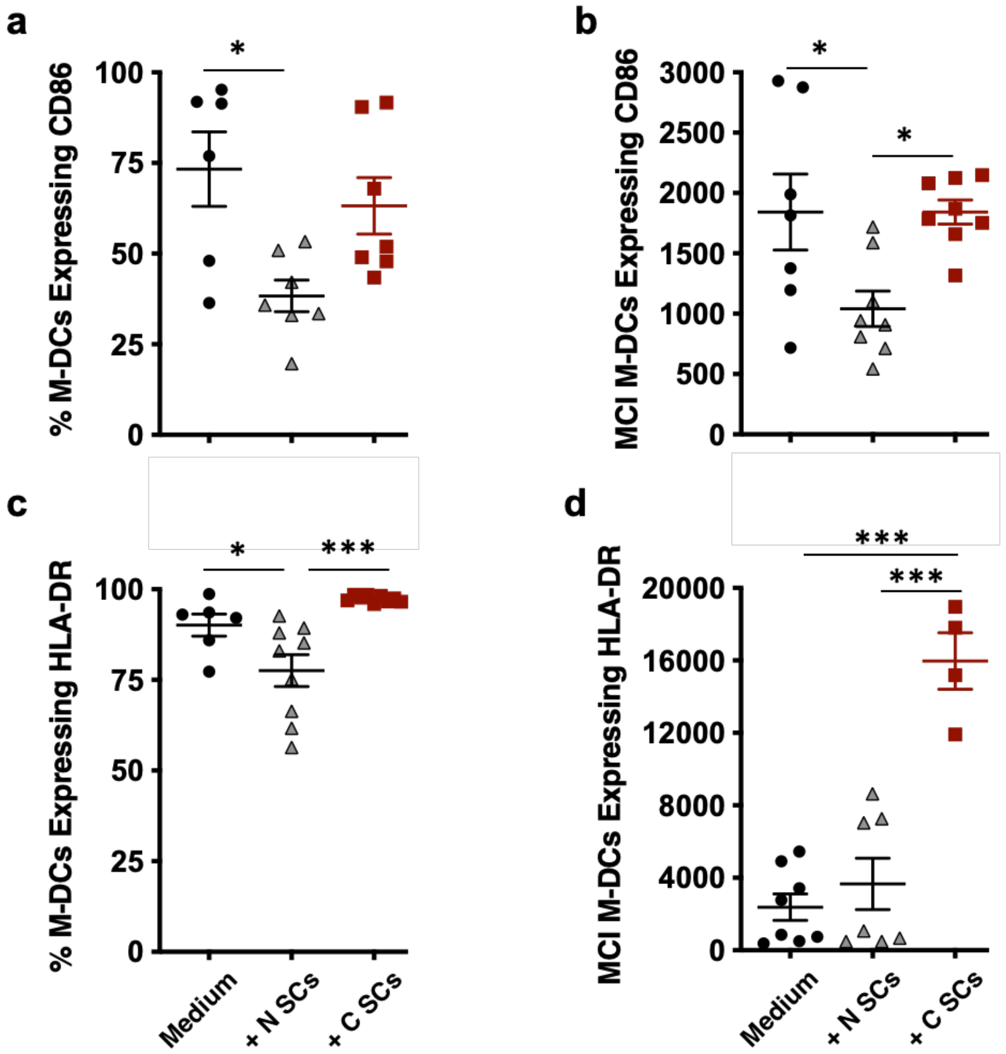
Supplementary Figure 2. Crohn's SCs are more inflammatory than Normal SCs.
a Cytokine levels in unstimulated 7-day culture supernatants from 2-4x10^5 Normal SCs and Crohn's SCs/mL (n>4). **b,c** mRNA or protein expression of IL-8, MMP-3 and MMP-9 before and after 18h exposure to CBir1 flagellin (5 µg/mL), LF82 (MOI 1), IL-21 (25 ng/mL) plus TNF (7.5 ng/mL) (n>6). (Mean +/- SEM; $*P < 0.05$, $**P < 0.01$). **d** Transcriptomic analysis of key inflammatory response and cytokine genes in the indicated SC populations. Identification of genes up- (red) and down- (green) regulated was based on RNA-Seq data for Ingenuity Pathway Analysis Canonical Pathways and Biological Function/Disease categories in unstimulated and LF82-stimulated Normal and Crohn's disease SCs. For genes to be considered up- or down-regulated, an absolute fold change cutoff of 2.0 was required.

INFLAMMATORY RESPONSE		UNSTIMULATED CROHN'S SCS *vs* NORMAL SCS			STIMULATED CROHN'S SCS *vs* NORMAL SCS	
Symbol	**Gene**	**Fold Change**	***P* Value**		**Fold Change**	***P* Value**
ALDH1A2	aldehyde dehydrogenase 1 family member A2	23.216	0.00102		17.763	0.0243
DHRS3	retinaldehyde reductase	2.31	0.142		7.02	0.012
CYP2E1	cytochrome P450 family 2 subfamily E member 1	1.488	0.179		1.803	0.144
RARA	retinoic acid receptor alpha	1.351	0.125		1.368	0.24
RARG	retinoic acid receptor gamma	1.337	0.0865		1.52	0.0689
FOXO1	forkhead box O1	1.184	0.499		1.459	0.264
CYP2S1	cytochrome P450 family 2 subfamily S member 1	1.153	0.863		1.991	0.54
APC	APC regulator of WNT signaling pathway	1.114	0.556		-1.253	0.368
ALDH1A3	aldehyde dehydrogenase 1 family member A3	1.016	0.986		17.763	0.0243
ADH5	alcohol dehydrogenase 5 (class III)	-1.11	0.53		-1.111	0.64
ALDH1A1	aldehyde dehydrogenase 1 family member A1	-1.141	0.811		-2.632	0.197
RDH10	retinol dehydrogenase 10	-1.16	0.759		3.418	0.0617
CYP3A5	cytochrome P450 family 3 subfamily A member 5	-1.165	0.407		1.19	0.486
RDH5	retinol dehydrogenase 5	-1.205	0.796		-1.584	0.639
CYP27C1	cytochrome P450 family 27 subfamily C member 1	-1.216	0.8		-1.88	0.548
CYP1A1	cytochrome P450 family 1 subfamily A member 1	-1.267	0.793		-2.062	0.558
RDH16	retinol dehydrogenase 16	-1.305	0.44		-1.024	0.962
AHR	aryl hydrocarbon receptor	-1.352	0.339		1.052	0.906
ALDH8A1	aldehyde dehydrogenase 8 family member A1	-1.685	0.251		1.694	0.402
ADH1C	alcohol dehydrogenase 1C (class I)	-1.797	0.675		21.181	0.157
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	-2.693	0.21		2.844	0.382
RBP1	retinol binding protein 1	-3.323	0.187		2.187	0.528
CYP26B1	cytochrome P450 family 26 subfamily B member 1	-6.226	9.92E-12		-1.996	0.0572

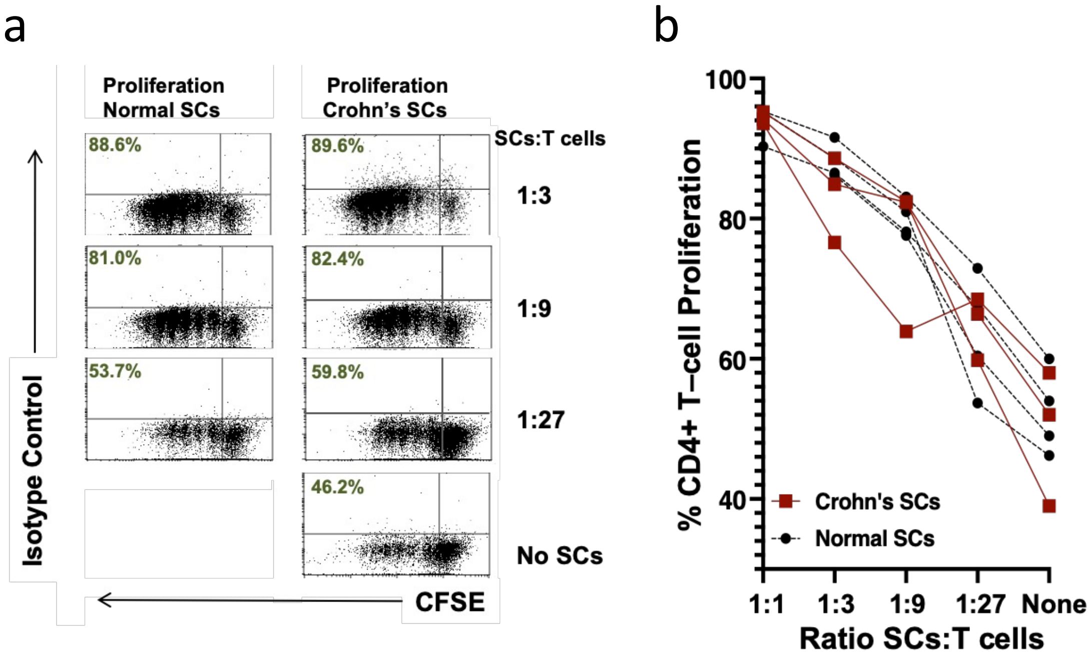
Supplementary Figure 3. Normal SCs and Crohn's SCs impact RA metabolic pathway gene expression. Transcriptomic analysis of key inflammatory transcripts involved in the RA metabolic pathway in the indicated SC populations. Identification of up (red)- and down (green)- regulated genes was based on RNA-seq data for Ingenuity Pathway Analysis Metabolic Pathway category in unstimulated and LF82 bacteria-stimulated Normal SCs and Crohn's SCs (n=16). For genes to be considered up- or down-regulated, an absolute fold change cutoff of 2.0 was required.



Supplementary Figure 4. Human intestinal SCs induce expression of CD103 on differentiating mucosal DCs. CD103 **a** gene (ITGAE) and **b** protein expression profiles and % CD103 expression by M-DCs generated in the presence of GM-CSF and IL-4 in the absence of SCs and the presence of Normal SCs (N SCs) or Crohn's SCs (C SCs) ($n \geq 7$).



Supplementary Figure 5. Crohn's SCs drive higher M-DC expression of CD86 and HLA-DR than Normal SCs. M-DCs generated in the presence of GM-CSF and IL-4 plus media or Normal SCs (N SCs) or Crohn's SCs (C SCs) in the absence of antigen (4 days) and analyzed for % cells that express **a** CD86 and **b** HLA-DR and for mean channel intensity (MCI) of **c** CD86 and **d** HLA-DR (n=4-8).



Supplementary Figure 6. T-cell proliferation is equivalent in Normal SC– and Crohn's SC–T-cell co-cultures. **a** Proliferation (CFSE) and **b** % proliferation of anti-CD3/CD28 antibody-stimulated CD4$^+$ T cells co-cultured with medium alone or increasing numbers of Normal SCs or Crohn's SCs from a representative donor or three donors, respectively.