**Figure S1**

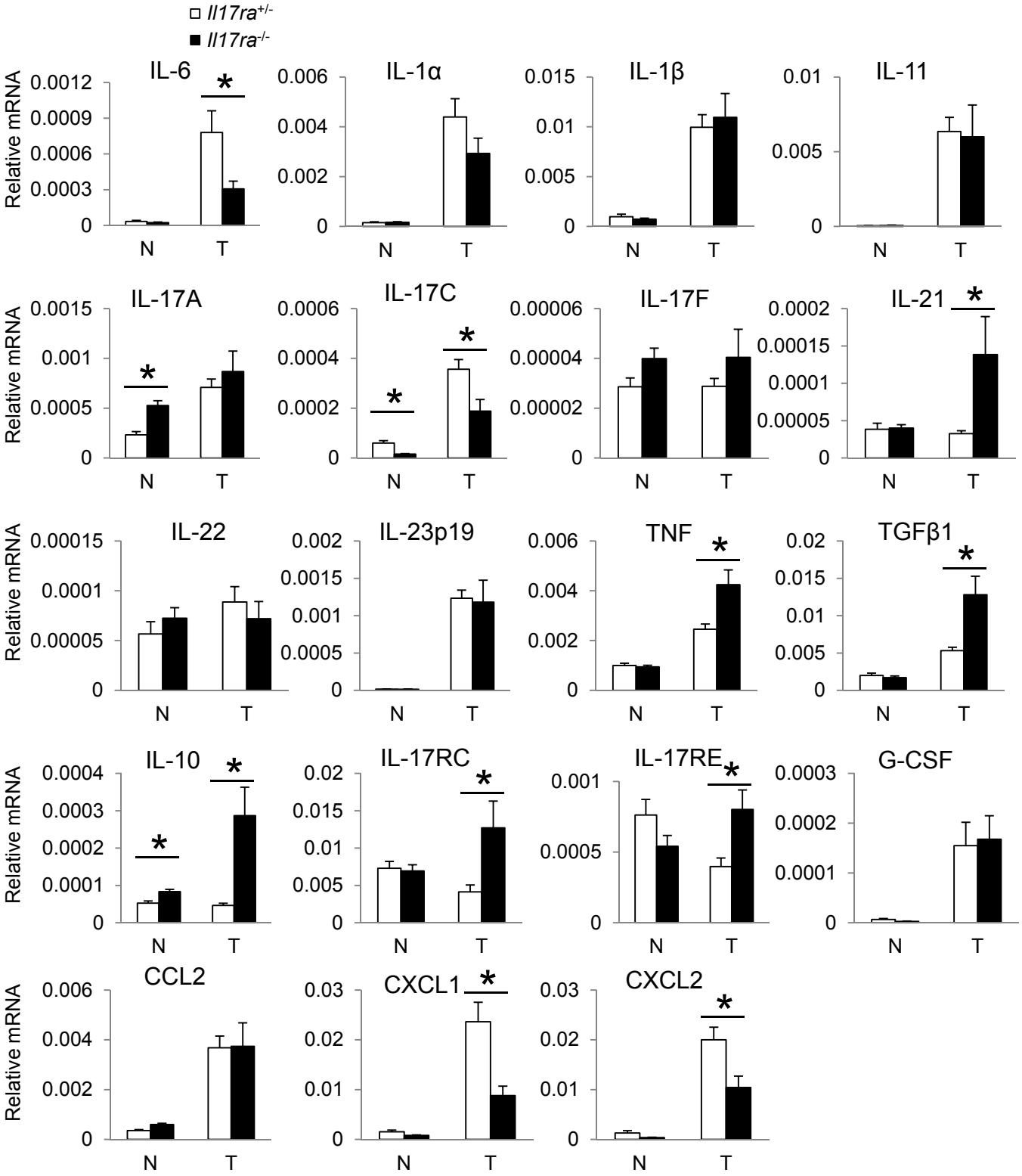


**Figure S1. Regulation of cytokine expression by IL-17RA signaling, related to Figure 1.** Five-month old tumor-bearing CPC-APC mice harboring heterozygous (+/-) or knockout (-/-) *Il17ra* gene were sacrificed for Q-RT-PCR analysis of the indicated cytokine mRNAs in normal (N) and tumor (T) tissues. N=11. Data represent averages ± S.E.M. * $p < 0.05$.

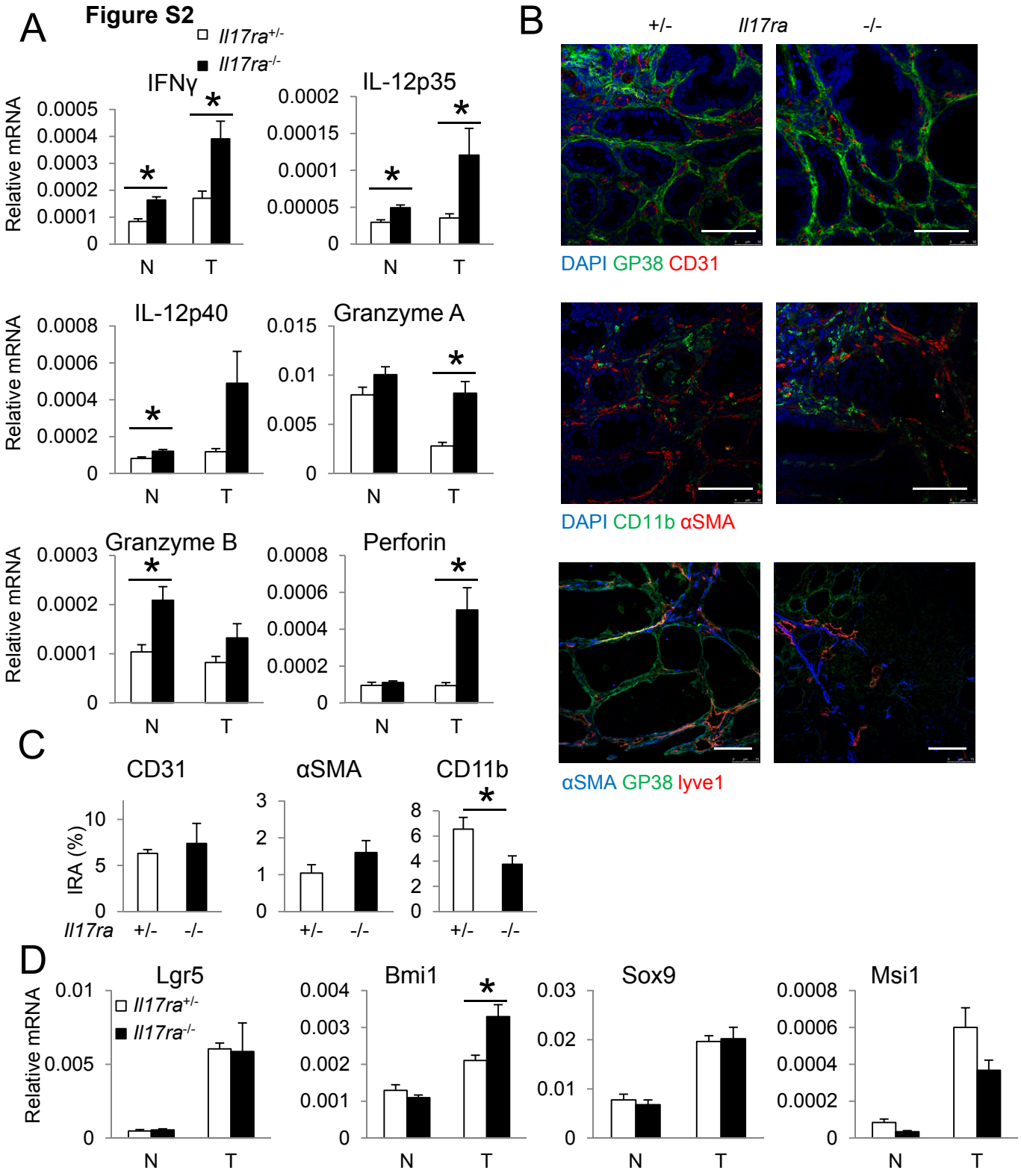


**Figure S2. Regulation of cytotoxicity by IL-17 signaling, related to Figure 1.**
(**A, D**) Q-RT-PCR analysis of the indicated mRNAs in normal (N) and tumor (T) tissues of 5-month old CPC-APC mice. N=11. (**B, C**) Immunostaining of colon tumors that are heterozygous or null for *Il17ra*. Six HMF images taken on tumor sections from four mice on each side were used for quantification by measuring immuno-reactive areas (IRA, **C**). Data represent averages ± S.E.M. * $p < 0.05$. Scale bar = 100 μm.

**Figure S3**

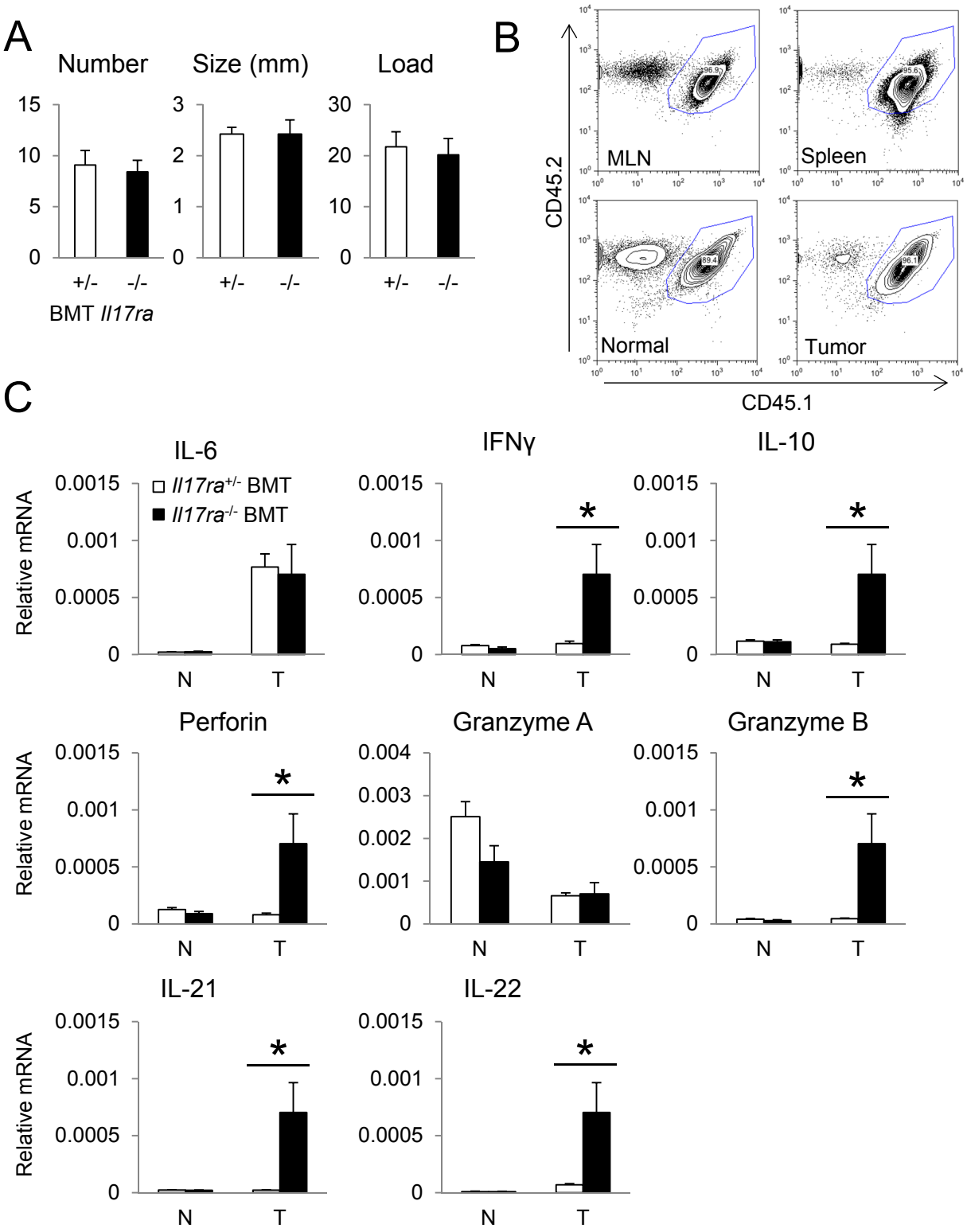
A
Number
Size (mm)
Load
15
10
5
0
3
2
1
0
30
20
10
0
+/-
-/-
BMT Il17ra
B
MLN
Spleen
Normal
Tumor
CD45.2
CD45.1
C
IL-6
IFNγ
IL-10
Perforin
Granzyme A
Granzyme B
IL-21
IL-22
Il17ra+/- BMT
Il17ra-/- BMT
Relative mRNA
0.0015
0.001
0.0005
0
0.004
0.003
0.002
N
T
*

**Figure S3. IL-17RA signaling in hematopoietic cells does not affect CRC tumor development, related to Figure 1.**

(**A**) Six weeks old CPC-APC mice underwent adoptive transfer of bone marrow from *Il17ra* heterozygous (+/-) or null (-/-) donors. Mice were sacrificed at 5 months of age and tumor parameters were determined (n=12). (**B**) Six weeks old CPC-APC mice (C57BL/6 background) were irradiated and transplanted with bone marrow from CD45.1/CD45.2 C57BL/6 mice. Recipient mice were sacrificed at 5 months of age and cells from spleen, mesenteric lymph nodes (MLN), normal colon tissue (Normal) and colonic tumors (Tumor) were collected and stained for CD45.1 and CD45.2 and analyzed by flow-cytometry. Live $CD45^+$ cells were gated on in the graphs. Percentages of donor-originated CD45.1/CD45.2 double positive cells indicate the rate of reconstitution. (**C**) Q-RT-PCR analysis of mRNAs corresponding to the indicated genes in normal colon (N) and tumor (T) tissues from CPC-APC mice that received heterozygous or *Il17ra*-null bone marrow (n=18). Data represent averages ± S.E.M. * $p < 0.05$.

**Figure S4**

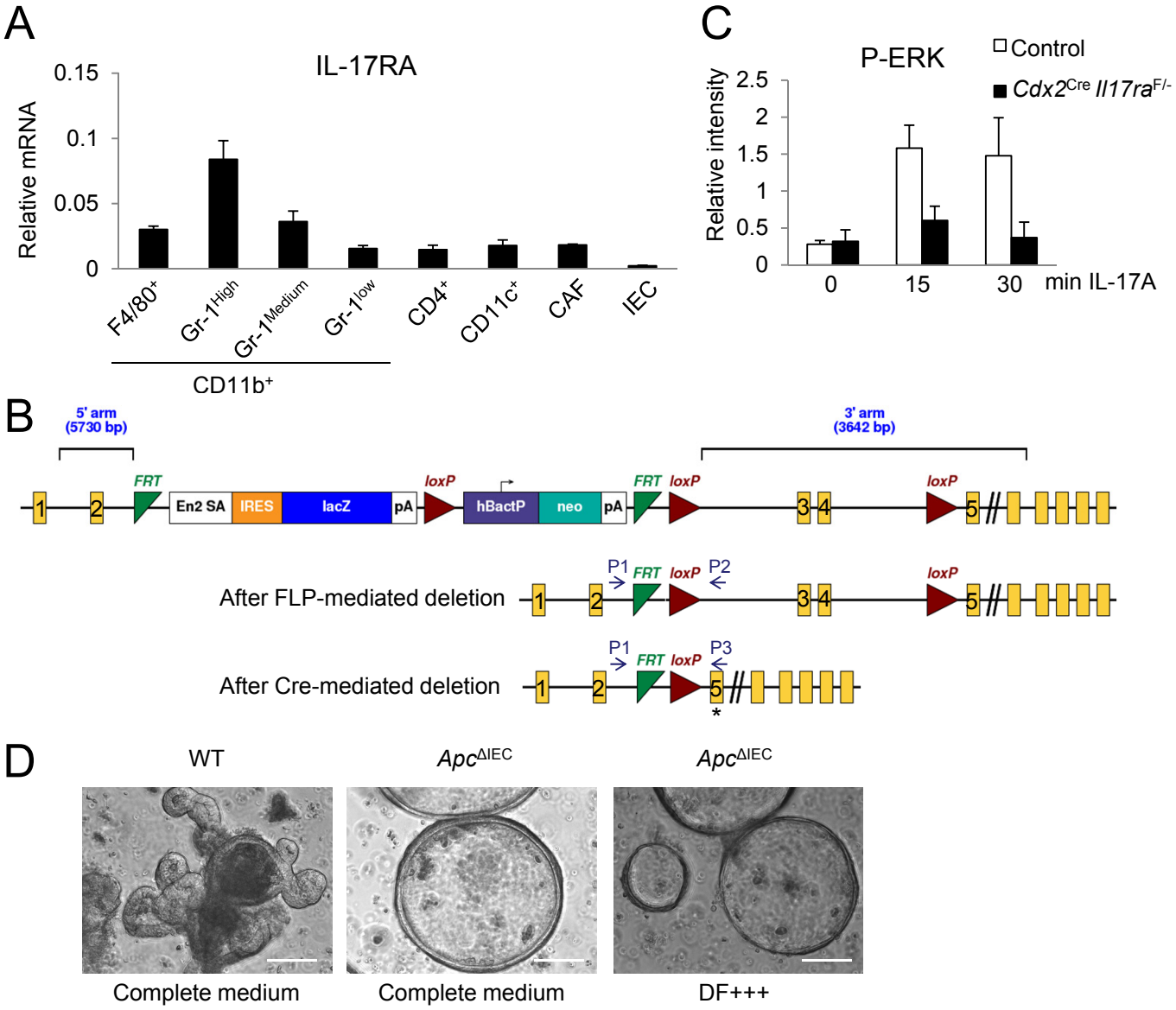


**Figure S4. APC-deficient organoids are resistant to growth factor withdrawal, related to Figure 2.**

(**A**) Q-RT-PCR analysis of IL-17RA mRNA in purified cells from colon tumors. CAF: cancer associated fibroblasts; IEC: intestinal epithelial cells. N=4. (**B**) Scheme for conditional knockout of the *Il17ra* locus. *Il17ra*$^{\text{LacZ-Flox}}$ mice were generated by conventional ES cell targeting and blastocyst injection. Transgene positive mice were crossed to a *FLP*$^{+}$ strain for deletion of the *FRT*-flanked *LacZ* cassette to generate the *Il17ra*$^{\text{F/+}}$ strain. (**C**) Quantification on the amount of activated ERK assayed by Western blotting in IL-17A stimulated IEC isolated from control or *Cdx2*$^{\text{Cre}}$ *Il17ra*$^{\text{F/-}}$ mice. α-tubulin was used as loading control. N=2 for control, 3 for *Il17ra* conditional knockout. (**D**) Bright-field images of WT and *Apc*-deleted (*Apc*$^{\Delta\text{IEC}}$) small intestinal organoids in 3-D culture, supplied with complete culture medium (left and middle panels). Right panel: *Apc*-deleted (*Apc*$^{\Delta\text{IEC}}$) small intestinal organoids maintained and propagated in medium without serum and growth factors (DF+++) for more than one month. Scale bar = 100 μm.

**Figure S5**

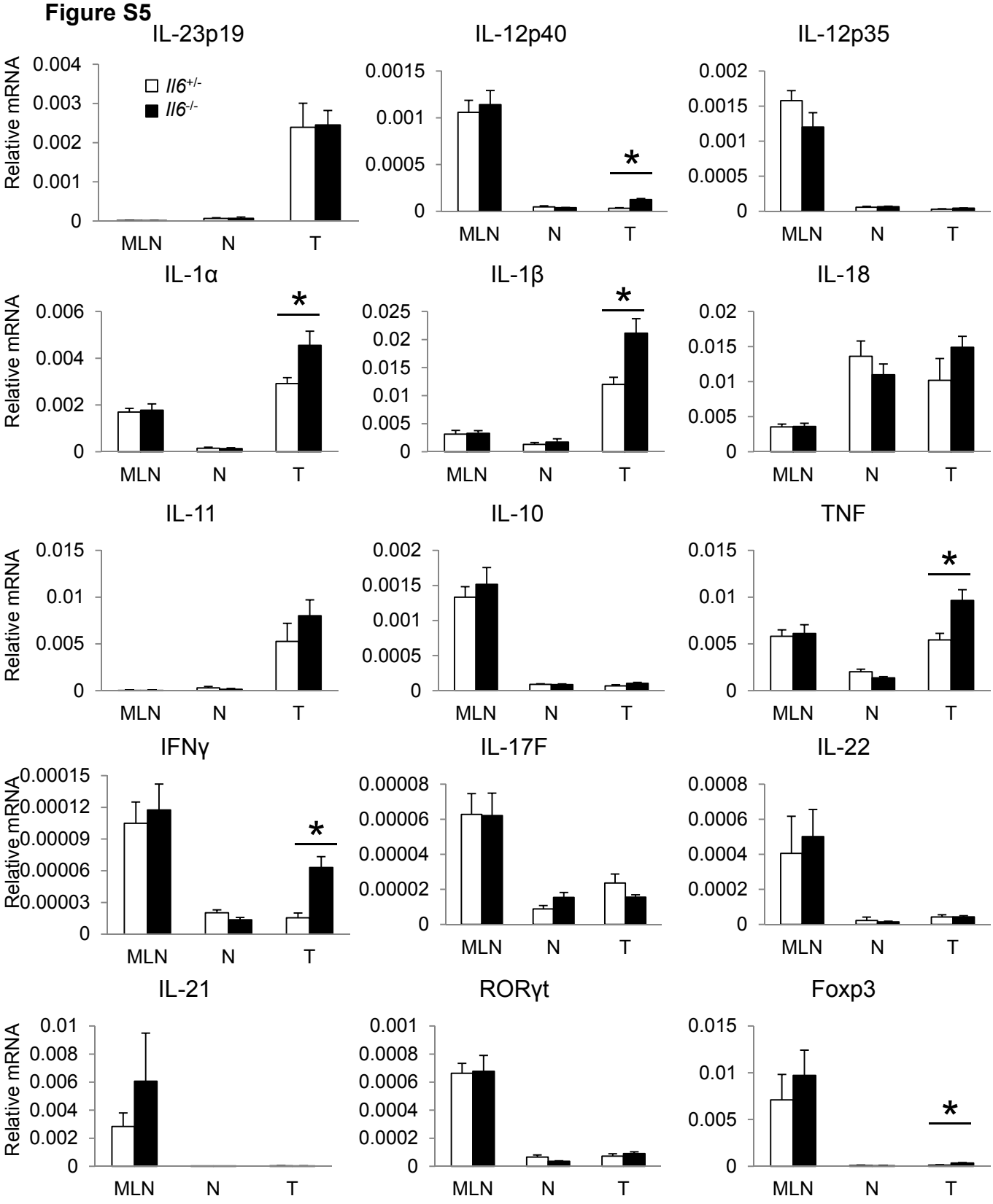


**Figure S5. IL-6 signaling affects the expression of cytokines and immune markers in colonic tumors, related to Figure 3.**

CPC-APC mice that are heterozygous (+/-) or null (-/-) for the *Il6* gene were sacrificed at 5 months of age for Q-RT-PCR analysis of the indicated genes in mesenteric lymph nodes (MLN), normal (N) colon and tumor (T) tissues. n=9. Data represent averages ± S.E.M. * $p < 0.05$.

**Figure S6**

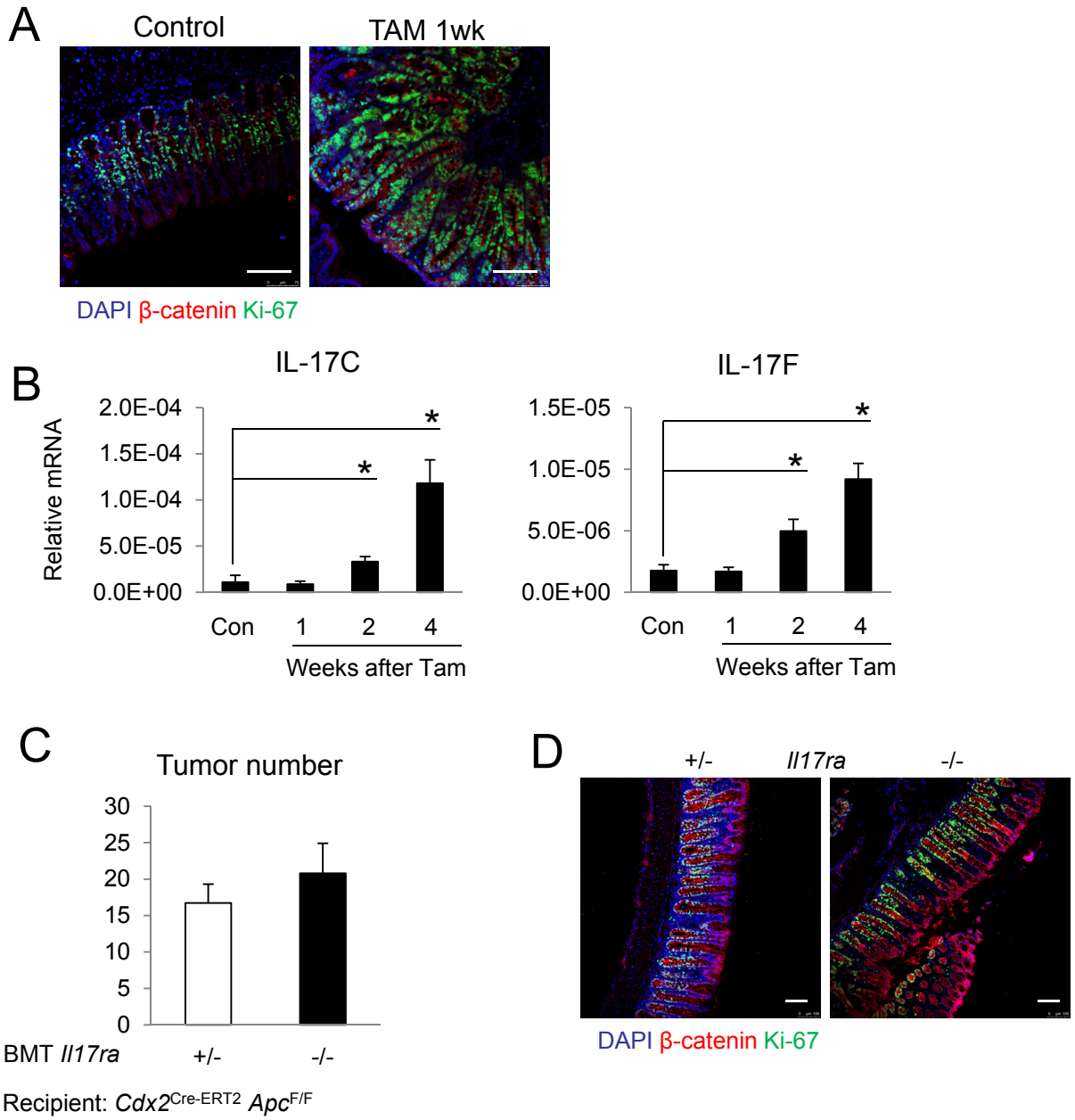


**Figure S6. IL-17 does not affect normal crypt proliferation, related to Figure 4.**
(**A**) Immunostaining of colon cryosections from *Apc*$^{F/F}$ (Control) or *Cdx2*$^{Cre\text{-}ERT2}$ *Apc*$^{F/F}$ (TAM 1wk) mice 1 week after tamoxifen injection. (**B**) Q-RT-PCR analysis of IL-17A and IL-17C mRNAs in colon tissues following tamoxifen injection (n=8). (**C**) *Cdx2*$^{Cre\text{-}ERT2}$ *Apc*$^{F/F}$ mice underwent adoptive transfer of bone marrow cells from control (*Il17ra*$^{+/-}$) or *Il17ra*$^{-/-}$ donors. At 5 months of age, the recipient mice were i.p. injected with tamoxifen and sacrificed one month later for analysis of colon tumor parameters (n=5). (**D**) Immunostaining of cryosections of colons from *Apc*$^{F/F}$ mice that are heterozygous (+/-) or null (-/-) for *Il17ra* 1 week after tamoxifen injection. Data represent averages ± S.E.M. * $p < 0.05$. Scale bar = 100 μm.

**Supplemental Table 1: List of primers used in Q-RT-PCR analysis, related to Experimental Procedures.**

| Gene | Forward (5' – 3') | Reverse (5' – 3') |
|---|---|---|
| Bmi1 | GTTCGATGCATTTCTGCTTG | TGGCTCGCATTCATTTTATG |
| CCL2 | TCTCCAGCCTACTCATTGGG | AGGTCCCTGTCATGCTTCTG |
| CXCL1 | TCTCCGTTACTTGGGGACAC | CCACACTCAAGAATGGTCGC |
| CXCL2 | CTTTGGTTCTTCCGTTGAGG | CAAAAAGTTTGCCTTGACCC |
| FOXP3 | ACTGGGGTCTTCTCCCTCAA | CGTGGGAAGGTGCAGAGTAG |
| G-CSF | TGACACAGCTTGTAGGTGGC | TCCTGCTTAAGTCCCTGGAG |
| Granzyme A | AACCGTGTCTCCTCCAATGA | GATGAGGAACGCCTCTGGT |
| Granzyme B | CTCTCGAATAAGGAAGCCCC | CTGACCTTGTCTCTGGCCTC |
| IFNγ | TGAACGCTACACACTGCATCT | GACTCCTTTTCCGCTTCCTGA |
| IL-10 | GGTTGCCAAGCCTTATCGGA | ACCTGCTCCACTGCCTTGCT |
| IL-11 | GCAGGTGGTCCTTCCCTAA | AGGCGAGACATCAAGAGCTG |
| IL-12p35 | GAGGACTTGAAGATGTACCAG | CTATCTGTGTGAGGAGGGC |
| IL-12p40 | GACCCTGCCCATTGAACTGGC | CAACGTTGCATCCTAGGATCG |
| IL-17A | GCCCTCAGACTACCTCAACC | ACACCCACCAGCATCTTCTC |
| IL-17C | ACACAAGCATTCTGCCACC | CTGGAAGCTGACACTCACGA |
| IL-17F | AATTCCAGAACCGCTCCAGT | TTGATGCAGCCTGAGTGTCT |
| IL-18 | CTTCTGCAACCTCCAGCATC | TCCTTGAAGTTGACGCAAGA |
| IL-1α | ATGTATGCCTACTCGTCGGG | TGAGTTTTGGTGTTTCTGGC |
| IL-1β | TGTGAAATGCCACCTTTTGA | TTGTTGATGTGCTGCTGTGA |
| IL-21 | CCCTTGTCTGTCTGGTAGTCATCTT | GGAGGCGATCTGGCCC |
| IL-22 | CAGGAGGTGGTACCTTTCCTG | TCTGGTCGTCACCGCTGAT |
| IL-23p19 | CCAGCGGGACATATGAATCT | AGGCTCCCCTTTGAAGATGT |
| IL-6 | ACCAGAGGAAATTTTCAATAGGC | TGATGCACTTGCAGAAAACA |
| IL-17RA | AGTGGACCCTGCAGACAGAT | CAGCATGGACAGAAACTGGA |
| IL-17RC | CCTGCTCCTCAGAGACATCC | ATCTGGTCCTACACGAAGCC |
| IL-17RE | CTCTGGAAGGATGCTGGTGT | GCCTACCGTGTGGATAAACG |
| Msi1 | AATTCGGGGAACTGGTAGGT | GATGCCTTCATGCTGGGTAT |
| Lgr5 | CAACCTCAGCGTCTTCACCT | TCTTCTAGGAAGCAGAGGCG |
| Perforin | TAGCCAATTTTGCAGCTGAG | TGGAGGTTTTTGTACCAGGC |
| RORγt | CCGCTGAGAGGGCTTCAC | TGCAGGAGTAGGCCACATTAC |
| RPL32 | GGGAGCAACAAGAAAACCAA | TTGTGAGCAATCTCAGCACA |
| Sox9 | TCCACGAAGGGTCTCTTCTC | AGGAAGCTGGCAGACCAGTA |
| TGFβ1 | GGAGAGCCCTGGATACCAAC | AAGTTGGCATGGTAGCCCTT |
| TNF | CAGCCTCTTCTCATTCCTGC | GGTCTGGGCCATAGAACTGA |