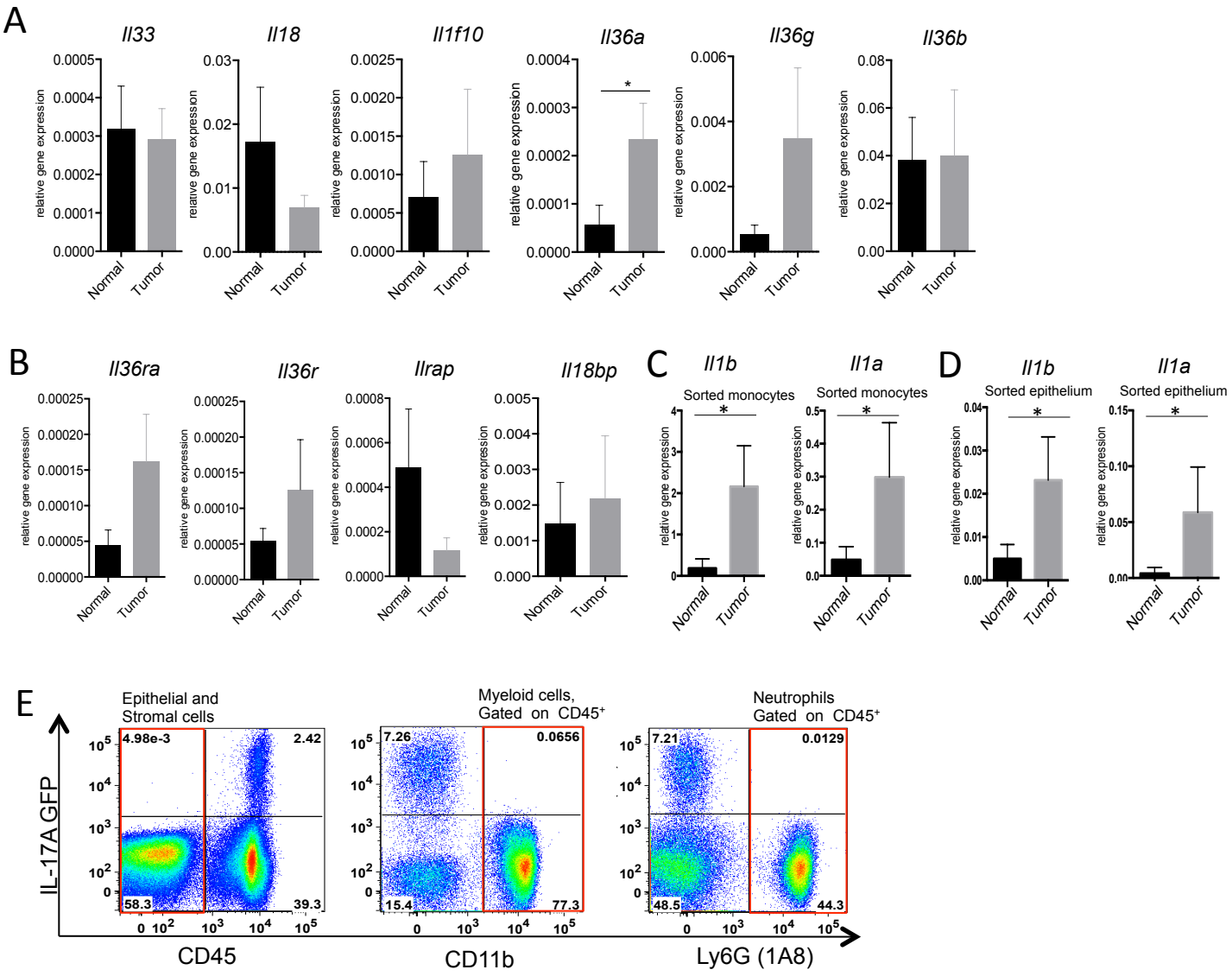

Figure S1. (Related to Figure 1) Expression of IL-1 cytokine members and their receptors in mouse CRC.

(A) Q-RT-PCR analysis of mRNA expression of ligands and (B) receptors of IL-1/IL-1R family members in CRC tumors and matching normal colon tissue from CPC-APC mice; normalized to *RpL32* housekeeping gene, N=5. (C, D) Various cell populations from LPL fractions of CRC tumors from CPC-APC mice were FACS sorted and analyzed for *Il1a* and *Il1b* mRNA expression by Q-RT-PCR; monocytes (Live/Dead$^-$CD45$^+$CD11b$^+$Ly6C$^+$Ly6G$^-$); enriched cancer/epithelial cells (Live/Dead$^-$CD45$^-$), N=4 (E) FACS analysis for IL-17A-GFP reporter expression in LPL tumor cell fraction isolated from *Il17a*^{GFP}-CPC-APC mice, representative of N=5. Data are mean ± SEM. Representative of three independent experiments.

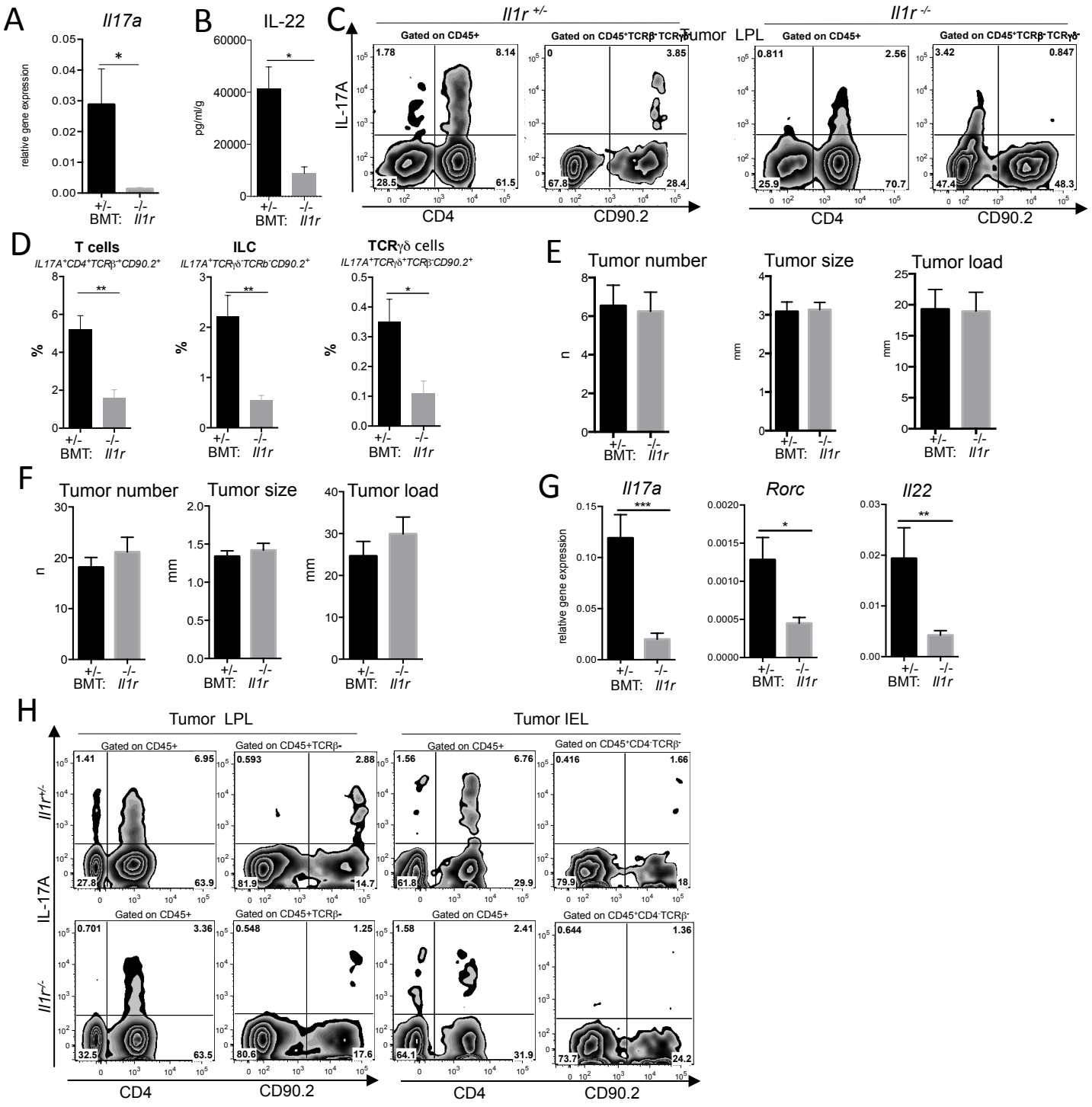

Figure S2.(Related to Figure 1) IL-1R signaling in hematopoietic cells controls IL-17A/IL-22 TEI but not CRC tumorigenicity. (A-E) 6-8-week-old CPC-APC mice were irradiated and reconstituted with BM from *Il1r*$^{-/-}$ or *Il1r*$^{+/-}$ mice and allowed to develop CRC for 4 months. (A) Q-RT-PCR analysis for *Il17a* normalized to *RpL32* expression. (B) ELISA measurement of IL-22 in tumor culture supernatants. Data are mean ± SEM. N=10, *p < 0.05.(C) Intracellular cytokine staining and (D) quantification for IL-17A in LPL fraction of CRC tumors, representative of N=5 (E) Tumor multiplicity, load and size in BM chimeric CPC-APC mice harboring *Il1r*$^{-/-}$ or *Il1r*$^{+/-}$ BM, N≥6, NS, (p=0.8). (F-H) *CDX2ERT-Apc*$^{f/f}$ mice were irradiated and transplanted with BM of *Il1r*$^{-/-}$ or *Il1r*$^{+/-}$, allowed for reconstitution for 2 months, injected with tamoxifen and allowed to develop CRC for 6 weeks. (F) Analysis of tumor multiplicity, size and load upon necropsy 5-6 weeks after last Tamoxifen injection. N≥8, NS p=0.4. (G) Q-RT-PCR analysis of *Il17a, Rorc,* and *Il22* mRNA expression in CRC tumor lysates, N=14, p*<0.04, p**<0.001, p***<0.001. (H) Intracellular cytokine staining for IL-17A in LPL and IEL cells isolated from CRC tumors of indicated genotypes, representative of N≥5. Data are mean ± SEM. Representative of three independent experiments.

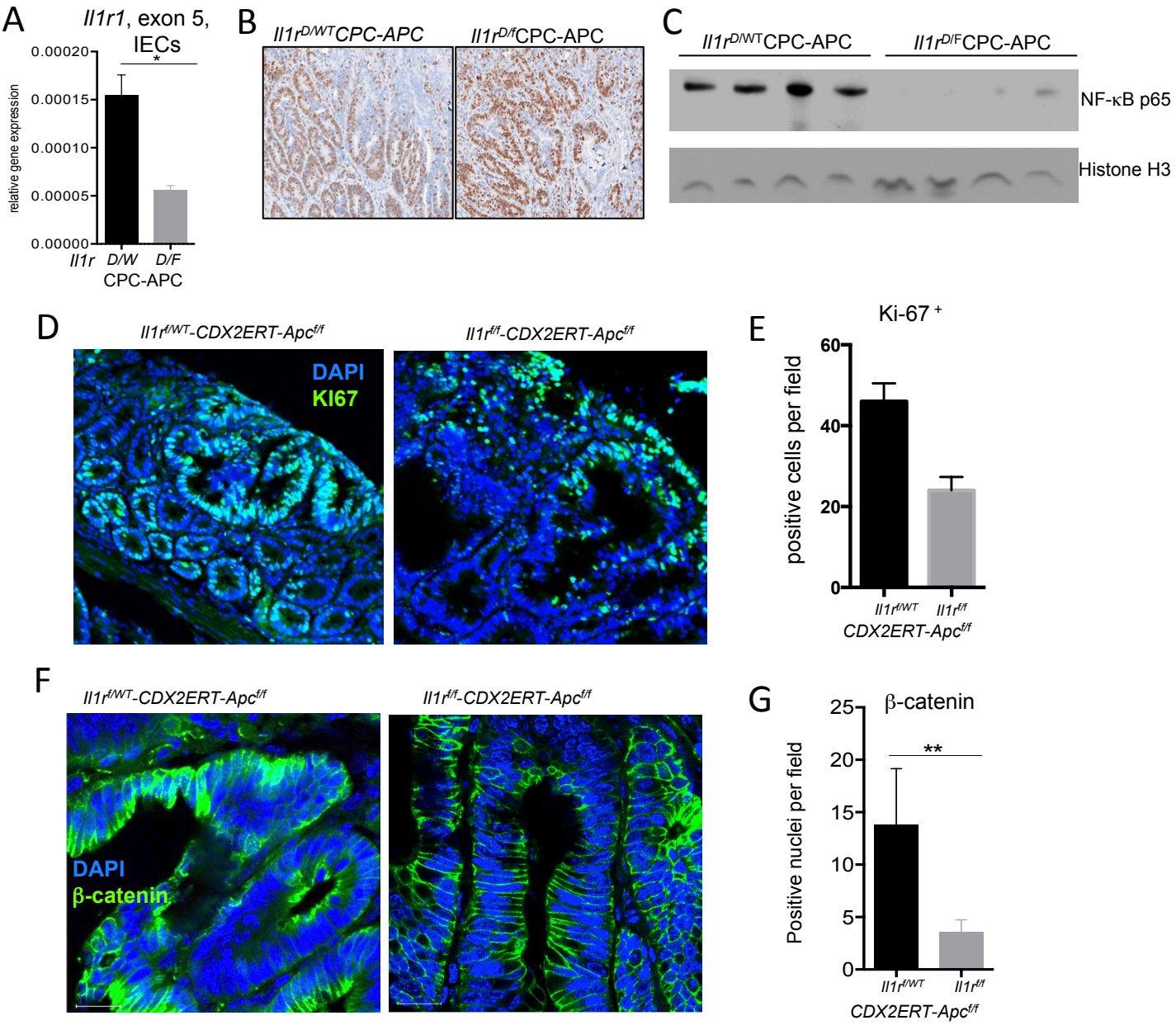

Figure S3. (Related to Figure 2) IL-1R in epithelial and cancer cells controls early CRC tumorigenesis, NF-κB and β-catenin activation.

Q-RT-PCR analysis for exon 5 of *Il1r1* gene expression/deletion efficiency in intestinal epithelial cell (IEC) isolated by mechanical shaking/dissociation and centrifugation. N=5 (B) Representative (N≥5) images of IHC staining for Ki-67 proliferation marker of IL-1R epithelial-deficient and IL-1R control tumors (C) Nuclear extracts of tumor IEC from indicated mice were prepared and analyzed for NF-κB p65 by western blot analysis; Histone H3 as loading control. Every lane represents tumors from individual mice. (D, E) Representative IF images of Ki-67 staining on frozen sections of CRC bearing colons from *Il1r$^{f/f}$-CDX2ERT-Apc$^{f/f}$* and *Il1r$^{f/WT}$-CDX2ERT-Apc$^{f/f}$* control mice after 2 weeks after last tamoxifen injection and quantification (E), N=5. (F, G) Representative IF images of β-catenin staining on frozen sections of CRC bearing colons from *Il1r$^{f/f}$-CDX2ERT-Apc$^{f/f}$* and *Il1r$^{f/WT}$-CDX2ERT-Apc$^{f/f}$* control mice 2 weeks after last tamoxifen injection, and quantification (G), N=5. Data are mean ± SEM. Representative of two independent experiments.

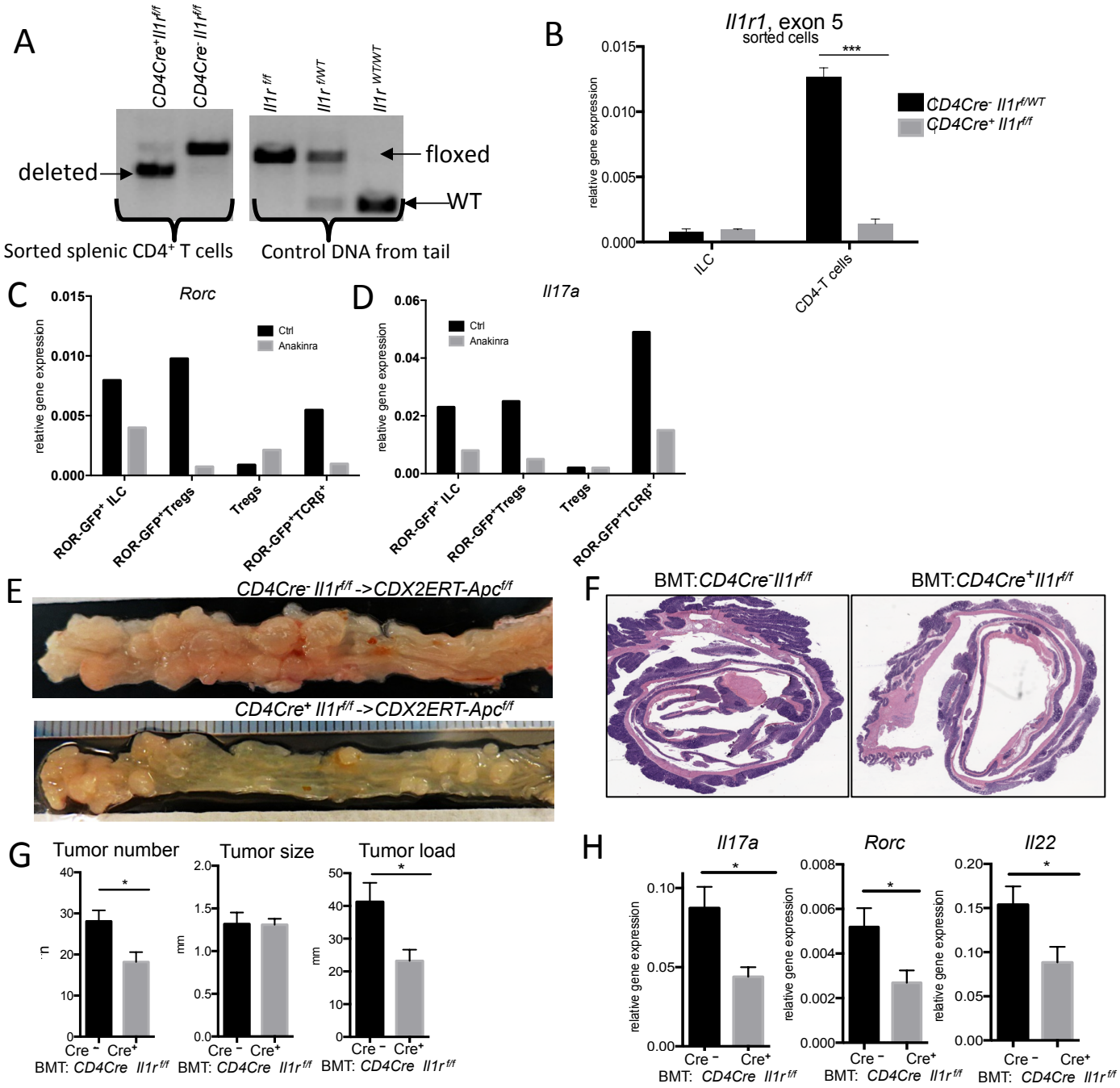

Figure S4. (Related to Figure 3) IL-1R signaling in T cells controls IL-17A and IL-22 expression and CRC development.

CDX2ERT-Apc$^{f/f}$ mice were transplanted with BM from *CD4Cre*$^{+}$*Il1r*$^{f/f}$ or control mice. After 8-10 weeks of BM reconstitution mice were injected with tamoxifen and allowed to develop CRC for 6 weeks. (A) PCR analysis for the efficiency of *Il1r1* gene deletion in sorted cells from indicated mice. (B) Q-RT-PCR analysis for the *Il1r1* gene deletion in sorted ILC and T cells from CRC tumors of BM-chimeric mice, demonstrating efficient repopulation, recruitment and gene deletion in T cells. (C, D) Q-RT-PCR analysis for *Il17a* and *Rorc* mRNA expression in sorted LPL cells from tumors from *Rorc*^{GFP}-CPC-APC mice, treated or untreated with Anakinra, each graph represents multiple tumors pooled from at least 7 mice per group. ILC (CD90.2^{+}TCRβ^{-}TCRγδ^{-}RORγt-GFP^{+}); Tregs (CD90.2^{+}TCRβ^{-}CD4^{+}CD25^{+}FR4^{+})- either RORγt-GFP^{+} or RORγt-GFP^{-}; RORγt-GFP^{+}TCRβ^{+} (CD90.2^{+}TCRβ^{+}CD4^{+}FR4^{-}CD25^{-}RORγt-GFP^{+}). Technical replications were performed 3 times. (E-H) Analysis of CRC-bearing bone marrow chimeric *CDX2ERT-Apc*$^{f/f}$ mice transplanted with *CD4Cre*$^{+}$*Il1r*$^{f/f}$ or control *CD4cre*$^{-}$*Il1r*$^{f/f}$ BM. (E) Representative images of tumor bearing colons and H&E staining of colonic paraffin sections (F). (G) Tumor multiplicity, size, and load in 5-6 weeks after the last tamoxifen injection, N≥11. (F) Q-RT-PCR analysis for *Il17a*, *Rorc* and *Il22* mRNA expression in tumor tissue. N≥7. Data are mean ± SEM. Representative of three independent experiments.

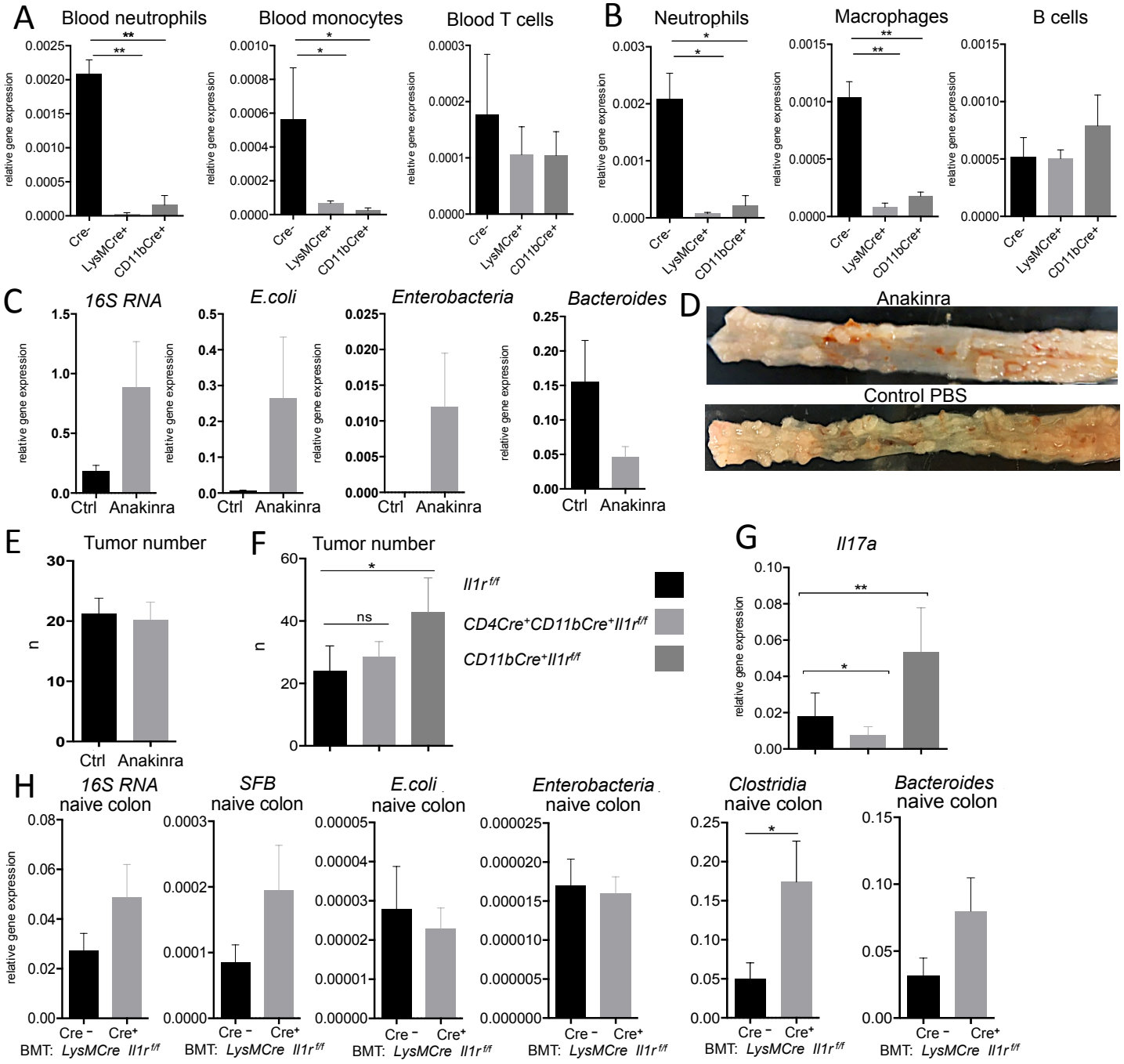

Figure S5. (Related to Figures 4 and 5) Inactivation of IL-1R signaling in myeloid cells leads to dysbiosis and increased CRC tumorigenesis. (A, B) Q-RT-PCR for exon 5 of *Il1r1* gene in FACS sorted cell population from blood (A) or peritoneal cavities of mice injected with thyoglycollate for 4-5 h (B) from *Il1r*$^{f/f}$ mice with indicated Cre transgene. Neutrophils (CD11b^{+}Ly6G^{+}), Monocytes (CD11b^{+}Ly6G^{-}Ly6C^{+}), T cells (TCRβ^{+}), B cells (B220^{+}CD19^{+}), N=4. (C-E) *CDX2ERT-Apc*$^{f/f}$ mice were injected with tamoxifen and treated with Anakinra for the last 12 days of 4 week CRC experiment (C) Q-RT-PCR for bacteria in tumors; normalized to *RpL32* expression, N=5. (D) Representative images of CRC bearing colons (E) Tumor multiplicity, N=5, not significant (p=0.2). (F,G) *CDX2ERT-Apc*$^{f/f}$ mice were reconstituted with BM from *CD11bCre*$^{+}$*-Il1r*$^{f/f}$, *Il1r*$^{f/f}$ (control) or with BM from *CD11bCre*$^{+}$*CD4Cre*$^{+}$*-Il1r*$^{f/f}$ (double deletion in myeloid and T cells) mice, reconstituted BM for 2 months, injected with tamoxifen and analyzed for CRC in 6 weeks. (F) Tumor multiplicity, N=4 per group. (G) Q-RT-PCR analysis for *Il17a* mRNA in tumors. (H) *CDX2ERT-Apc*$^{f/f}$ mice were reconstituted with BM from *LysMCre*$^{+}$*Il1r*$^{f/f}$ (removes *Il1r1* in macrophages and neutrophils) or Cre^{-} mice and injected with tamoxifen. Q-RT-PCR analysis of naive normal colon lysates for bacterial content, normalized to *RpL32* expression; N=5, p*<0.05, others- not significant. Data are mean ± SEM. Representative of three independent experiments.

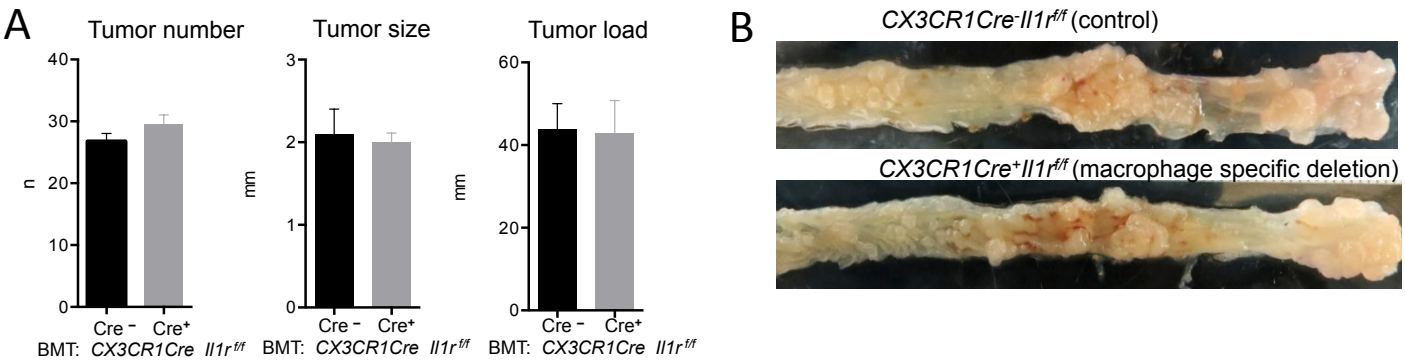

Figure S6. (**Related to Figures 5 and 6)**
IL-1R signaling in intestinal macrophages is dispensable for CRC development
CDX2ERT-Apc$^{f/f}$ mice were reconstituted with BM from *CX3CR1Cre^{+}Il1r$^{f/f}$* (IL-1R1 deletion in monocytes/macrophages) or *CX3CR1Cre^{-}Il1r$^{f/f}$* (control) mice and tumors were induced with 2 injections of Tamoxifen (2mg and 1.5mg /mouse). (A) Macroscopic tumor multiplicity, size, and load analysis upon necropsy 1 month after last Tamoxifen injection. N=5, NS (p=0.726). (B) Representative images of CRC bearing colons of BM transplanted mice with indicated genotypes, N=5. Representative of two independent experiments.

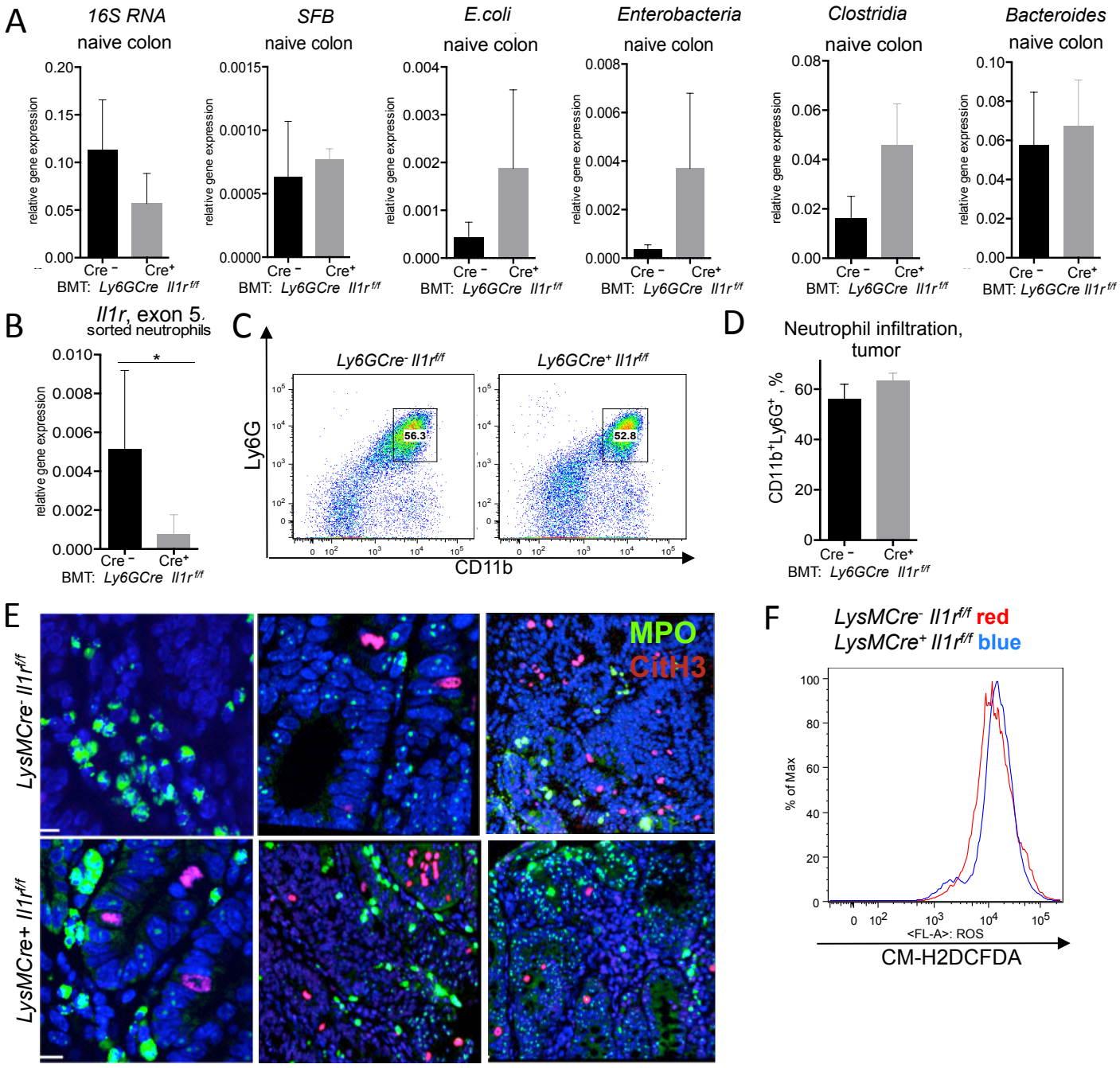

Figure S7. (**Related to Figures 6 and 7) IL-1R signaling in neutrophils in CRC tumors is not required for neutrophil recruitment, NET formation and ROS prodcution.** (A)*CDX2ERT-Apc$^{f/f}$* mice were reconstituted with BM from *Ly6GCre^{+}Il1r$^{f/f}$* or *Ly6GCre^{-}Il1r$^{f/f}$* (control) mice, injected with tamoxifen, and allowed to develop CRC for 6 weeks. Analysis of bacteria by specific Q-RT-PCR primers for bacterial 16S rRNA in naïve colon tissue results are normalized to mouse housekeeping gene (*RpL32*) expression; N=4. (B) Q-RT-PCR analysis for the efficiency of *Il1r* gene deletion in sorted neutrophils (CD45^{+}CD11b^{+}Ly6G^{+}), N=5, each sorting included multiple pooled tumors from at least 3 mice. Data are mean ± SEM. (C, D). Analysis of tumor-infiltrating neutrophils from CRC tumors of BM transplanted mice with indicated genotypes. (C) Representative FACS plots, (D) quantification, N=6. (E, F) *CDX2ERT-Apc$^{f/f}$* mice were transplanted with *LysMCre^{+}Il1r$^{f/f}$* or control BM, allowed to reconstitute and injected with tamoxifen to induce CRC tumors. (E) Representative images (N≥4) of confocal microscopy analysis of sections of paraffin-embedded CRC-bearing colonic rolls (MPO-"green"; CitH3-"red" and DAPI-"blue") (F) Representative FACS plots (N≥3) of IEL tumor fraction stained *ex vivo* with CM-H2DCFDA for ROS levels, gated on neutrophils (CD45^{+}CD11b^{+}Ly6G^{+}). Representative of three independent experiments.