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IL-17F deficiency inhibits small intestinal tumorigenesis in *Apc*$^{Min/+}$ mice

Wook-Jin Chae, Alfred L.M. Bothwell *

Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520, USA

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ABSTRACT

IL-17 plays an important role in gut homeostasis. However, the role of IL-17F in intestinal tumorigenesis has not been addressed. Here we demonstrate that ablation of IL-17F significantly inhibits spontaneous intestinal tumorigenesis in the small intestine of *Apc*$^{Min/+}$ mice. IL-17F ablation decreased IL-1β and Cox-2 expression as well as IL-17 receptor C (IL-17RC) expression, which were increased in tumors from *Apc*$^{Min/+}$ mice. Lack of IL-17F did not reverse the splenomegaly but partially restored thymic atrophy, suggesting a local effect of IL-17F in the intestine. IL-17F deficient *Apc*$^{Min/+}$ mice showed a significant decrease in immune cell infiltration in the lamina propria. Interestingly, the expression of IL-17A from CD4 T cells in the lamina propria remains unchanged in the absence of IL-17F. Collectively, our results suggest the proinflammatory and essential role of IL-17F to develop spontaneous intestinal tumorigenesis in *Apc*$^{Min/+}$ mice in the presence of IL-17A.

1. Introduction

IL-17F and IL-17A are highly homologous cytokine members in the IL-17 family and closely genetically linked in both humans and mice. Both IL-17A and IL-17F bind to IL-17RA and IL-17RC receptor complexes. The binding affinity of IL-17F to IL-17RA is much lower than that of IL-17A and only IL-17F binds to IL-17RC in the mouse [1]. Several lines of evidence have demonstrated that IL-17A is responsible for the development of various autoimmune diseases [2]. Unlike IL-17A, IL-17F plays only marginal roles in these models [3]. It has been suggested that the role of IL-17A and IL-17F may be differential and dependent on microenvironmental context [3]. In colitis models using Dextran Sulfate Sodium (DSS), the role of IL-17A and IL-17F differed, while another DSS model showed that the role of these two cytokines in intestinal inflammation might be similar [4,5].

The *Apc*$^{Min/+}$ mouse strain has been extensively utilized as a model to study intestinal tumorigenesis as it showed a very similar phenotype to human FAP (Familial Adenomatous Polyposis). The mutated truncated forms of APC are often lacking the β-catenin binding domains [6]. The complete loss of heterozygosity (LOH) of the *Apc* gene facilitates nuclear localization of β-catenin in intestinal epithelial cells [6]. This binding serves as a central role to negatively regulate Wnt signaling which drives intestinal tumorigenesis.

The relationship between IL-17 and tumor immunopathology has been controversial in both human and mice while most of the studies have addressed the role of IL-17A [7]. Recent studies suggest that the presence of Th17 cells is an indicator of poor prognosis in CRC (colorectal cancer) [8,9]. It has been suggested that polymorphisms especially in IL-17F are associated with increased gastric cancer in patients [10]. Previously we showed the role of IL-17A in spontaneous intestinal tumorigenesis is proinflammatory and very potent at a relatively early stage of tumor development [11]. However, it has been emphasized that the role of IL-17F in intestinal tumorigenesis and cancer in general is still elusive [12]. To address this issue, we investigated the role of IL-17F in spontaneous intestinal tumorigenesis.

2. Materials and methods

2.1. Mice

Apc$^{Min/+}$ mice were purchased from Jackson. Mice were bred and maintained under specific pathogen-free conditions at the animal facility of the Yale University School of Medicine. In all experiments, WT littermates of *Apc*$^{Min/+}$ mice on the C57BL/6 background were used. IL-17F-deficient (IL-17F KO) mice on the C57BL/6 background were provided by Chen Dong (MD Anderson Cancer Center). Each strain has been bred more than six generations in our facility. *Apc*$^{Min/+}$ mice on were bred to IL-17F-deficient C57BL/6 mice and used in our mouse facility. For all experiments, C57BL/6 mice were obtained as littermate controls of *Apc*$^{Min/+}$ mice. The intestinal tract was removed, washed with PBS, opened longitudinally for counting tumors. For histopathology, the ileum was dissected, fixed in 10% formalin, washed in PBS solution, paraffin-embedded, sectioned at 5 μm, and stained. All mouse protocols were approved by the Yale University Institutional Animal Care and Use Committee in

* Corresponding author. Address: Yale University School of Medicine, TAC S640, 300 Cedar Street, New Haven, CT, USA. Fax: +1 203 785 4263.
E-mail address: Alfred.bothwell@yale.edu (A.L.M. Bothwell).

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accordance with the Association for Assessment and Accreditation of Laboratory Animal Care International.

2.2. Flow cytometry

Spleens and thymi of 16-week-old *Apc*$^{Min/+}$ mice and their littermate controls, and IL-17F deficient (KO) *Apc*$^{Min/+}$ mice were harvested. After RBC lysis, cells were stained with CD16/CD32 antibody and then subsequently stained with anti-CD4 (clone RM4-5), anti-CD8α (clone 53-6.7), and anti-B220 (clone RA3-6B2) antibodies. For the stimulation of LP cells, PMA (100 ng/mL) and ionomycin (1 μM) were used. Brefeldin A (1 μg/mL) was added for the last 4 h of culture. For LP preparation, each group of 16-week-old mice *Apc*$^{Min/+}$ mice and their littermate control mice as well as IL-17F deficient *Apc*$^{Min/+}$ mice were sacrificed, and the individual small intestines were processed as described [11]. After Percoll gradient separation, lymphocytes were collected, washed with PBS twice, and counted. FACSCalibur (BD Biosciences) was used for flow cytometry and data were analyzed by FlowJo software (Treestar).

2.3. Real-time PCR

Tumors (>2.0 mm) from *Apc*$^{Min/+}$ and IL-17F deficient *Apc*$^{Min/+}$ mice were isolated from both small and large intestines and homogenized using homogenizing beads (MP Bio) with Trizol solution. cDNA was synthesized with a BDsprint cDNA synthesis kit (Clontech). Real-time PCR was performed with Real time bioanalyzer (BioRad). Primers were synthesized by the Keck Biotechnology Institute (Yale University). Relative gene expression was calculated by the ΔC_T method and the mRNA expression was normalized against HPRT.

3. Results

3.1. Ablation of IL-17F inhibits spontaneous intestinal tumorigenesis

To address the role of IL-17F in intestinal tumorigenesis, IL-17F-deficient (KO) *Apc*$^{Min/+}$ mice were generated. A very significant decrease in total tumor numbers in the small intestine was observed after 16 weeks (Fig. 1A, left panel). Tumor numbers in the large intestine were not decreased (Fig. 1A, right panel). The effect of IL-17F ablation in the small intestine was more notable in large tumors (>2.0 mm, 70% reduction) than small tumors (<2.0 mm, 47% reduction) (Fig. 1B). Next, we examined whether IL-17F ablation abrogated tumorigenesis in different regions of the small intestine. Consistent with previous reports, most tumors were found in the ileum in *Apc*$^{Min/+}$ mice (Fig. 1C). Seventy-five percent of small intestinal tumors were found in ileum, and overall approximately a 50% reduction in tumor numbers was observed in animals deficient in IL-17F. This 50% reduction was observed in the entire small intestinal tumor numbers, suggesting that the role of IL-17F is proinflammatory in the entire small intestine. We examined small and large tumor numbers in each region of small intestine. We found that the large tumors were mostly found in the ileum, and also the inhibition of large tumor formation was the most obvious in

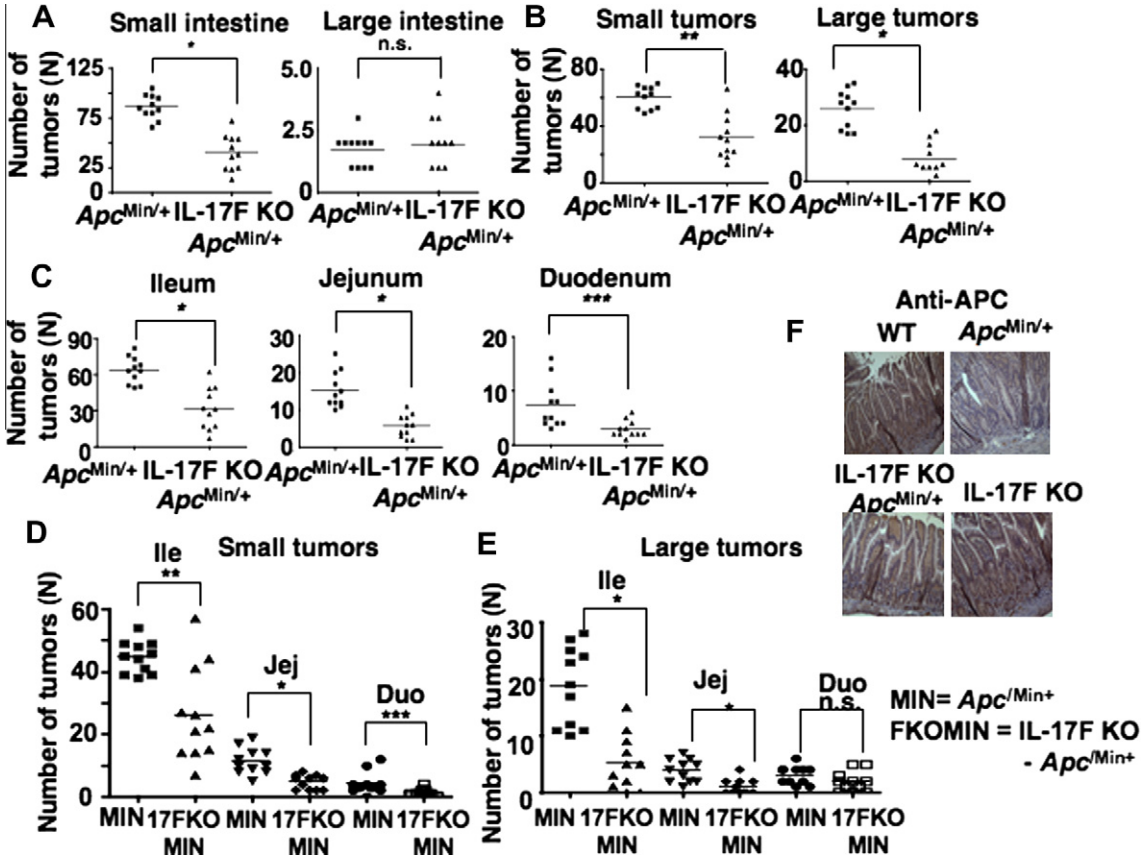

Fig. 1. Ablation of IL-17F inhibits spontaneous intestinal tumorigenesis. (A) Total tumor numbers of small and large intestine were counted in 16-week-old Apc$^{Min/+}$ mice and IL-17F KO-*Apc*$^{Min/+}$ mice (n = 11). (B) Tumors smaller than 2 mm and larger than 2 mm were counted separately. (C) Small intestines (ileum) of 16-week-old C57BL/6 (WT) (n = 5), *Apc*$^{Min/+}$ (n = 5), IL-17F KO (n = 4), and IL-17F KO *Apc*$^{Min/+}$ (n = 6) mice were harvested and stained with anti-APC monoclonal antibody in paraffin-embedded sections. Original magnification is X20. (D) Tumor numbers from each part of small intestine (duodenum, jejunum, and ileum) were counted in 16-week-old *Apc*$^{Min/+}$ mice and IL-17F KO-*Apc*$^{Min/+}$ mice (n = 11). Student's t test was used. $^{*}P < 0.0005$, $^{**}P < 0.005$, $^{***}P < 0.03$, n.s. = not significant. (E) Small and (F) large tumors of each group of mice were counted for each region. Student's t test was used. Ile = Ileum, Jej = Jejunum, Duo = Duodenum. $^{*}P < 0.0005$, $^{**}P < 0.005$, $^{***}P < 0.03$, n.s. = not significant.

the ileum (Fig. 1D). Consistent with total tumor number reduction in the small intestine of IL-17F KO *Apc*$^{Min/+}$ mice, small tumor numbers were less affected by IL-17F deficiency (Fig. 1E). This suggests that IL-17F significantly promotes tumor growth. As loss of heterozygosity (LOH) in the *Apc* gene is the critical event in spontaneous intestinal tumorigenesis, we examined whether the ablation of IL-17F can affect LOH in the *Apc* gene and protect normal intestinal architecture. Small intestine tissues from wildtype littermate control, *Apc*$^{Min/+}$ mice, and IL-17F KO *Apc*$^{Min/+}$ mice were stained with anti-APC antibody, which recognizes the C-terminal region of the APC protein. The level of APC protein was decreased in *Apc*$^{Min/+}$ mice compared to wildtype or IL-17F KO *Apc*$^{Min/+}$ mice (Fig. 1F). These results demonstrate that IL-17F deficiency inhibits intestinal tumorigenesis with decreased LOH of the *Apc* gene. This suggests that the main inhibitory effect of IL-17F-deficiency in spontaneous intestinal tumorigenesis does occur in the ileum of *Apc*$^{Min/+}$ mice.

3.2. IL-1β and Cox-2 as well as IL-17RC are significantly decreased in the tumors of IL-17F KO *Apc*$^{Min/+}$ mice

To investigate whether the ablation of IL-17F can down-regulate inflammation in the intestinal tract, we isolated tumors (2.0 mm in size) from the ileum of *Apc*$^{Min/+}$ and IL-17F KO *Apc*$^{Min/+}$ mice and quantitated the expression of proinflammatory cytokines and mediators. There was a marked decrease in IL-1β and Cox-2, but not in IL-6 in IL-17F KO *Apc*$^{Min/+}$ mice (Fig. 2A). The unchanged IL-6 expression in tumors from IL-17F KO *Apc*$^{Min/+}$ mice coincides with relatively reduced inhibition of small tumor numbers and also large intestinal tumors. The decrease of IL-1β and Cox-2 expression may contribute to form large tumors, as there were more marked changes in tumor size than tumor incidence (Fig. 1A). Our results show that IL-17F deficiency primarily inhibits key proinflammatory mediators such as IL-1β and Cox-2 expression in the tumor microenvironment. Next, we quantitated IL-17RA and IL-17RC mRNA expression from excised tumors from small intestine and large intestine, respectively. IL-17RC was increased in tumors from *Apc*$^{Min/+}$ mice compared to tumors from IL-17F KO *Apc*$^{Min/+}$ mice in the small intestine (Fig. 2B, right panel). We examined IL-17RA in the ileum but there was no significant change (Fig. 2B, left panel). In the large intestine, we observed that IL-17RC expression is significantly downregulated in IL-17F-deficient mice (Fig. 2C, right panel). Furthermore, IL-17RC expression in *Apc*$^{Min/+}$ mice was also markedly reduced (Fig. 2C right panel). This suggests that the responsiveness to IL-17F may be substantially reduced. We also examined IL-17RA in large intestinal tissues and tumors. *Apc*$^{Min/+}$ and IL-17F KO *Apc*$^{Min/+}$ tumors expressed about 50% less IL-17RA than wildtype and IL-17F-deficient mice. Taken together this result demonstrates that IL-17F ablation reduces the expression of proinflammatory mediators as well as IL-17RC expression in the small intestine, contributing intestinal tumorigenesis.

3.3. Ablation of IL-17F does not affect splenomegaly but partially restores thymic atrophy

Apc$^{Min/+}$ mice undergo lymphodepletion in spleen and thymus. In contrast, more immune cells infiltrate the LP during spontaneous intestinal tumorigenesis. It has been demonstrated that APC is involved in hematopoiesis and these two events have been suggested to coincide with the severe onset of tumorigenesis in *Apc*$^{Min/+}$ mice [13]. Indeed it has been demonstrated that vigorous hematopoiesis including subsets of erythroblasts and megakaryocytes occurs in *Apc*$^{Min/+}$ mice at 3–4 months after birth [14]. We previously have shown that the ablation of IL-17A largely corrects splenomegaly and thymic atrophy, preventing active lymphodepletion [11]. IL-17F ablation did not significantly reverse splenomegaly, while thymic atrophy was partially reversed (Fig. 3A and B). We further observed that the loss of CD4 and CD8 T cells as well as B cells from the spleen in *Apc*$^{Min/+}$ mice was not reversed (Fig. 3B). As a control we examined IL-17F-deficient mice but we did not observe any significant changes in thymus and spleen (Fig. 3A–C). Our results indicate that the effect of IL-17F ablation is somewhat limited to intestinal tumorigenesis rather than having systemic effects on primary immune organs such as spleen or thymus.

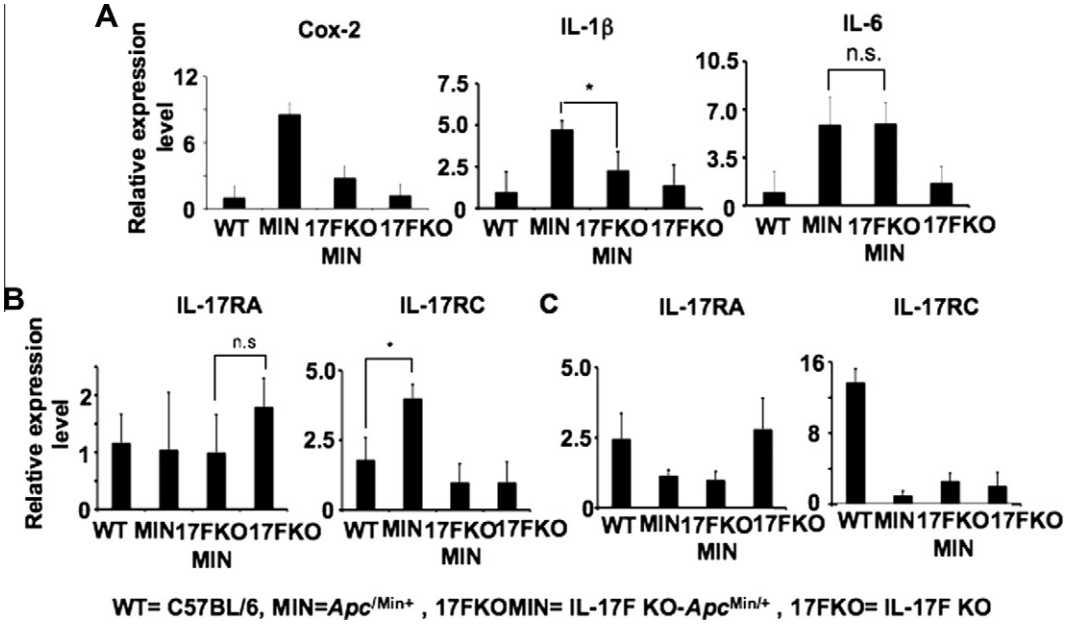

Fig. 2. IL-17F ablation reduced proinflammatory cytokines and mediators in tumors. (A) Tumors (2 mm; one from each mouse) were dissected from 16-week-old *Apc*$^{Min/+}$ mice ($n = 6$) and IL-17F KO *Apc*$^{Min/+}$ mice ($n = 6$). mRNA expression level for each gene was normalized against HPRT. For WT C57BL/6 mice and IL-17F KO mice, 5 mm of ileum was used ($n = 5$). (B) and (C) Tumors (2 mm; one from each mouse) from small intestines (B) and large intestines (C) were dissected from 16-week-old *Apc*$^{Min/+}$ mice ($n = 6$) and IL-17F KO-*Apc*$^{Min/+}$ mice ($n = 6$). mRNA expression level for each gene was normalized against HPRT. For WT C57BL/6 mice and IL-17F KO mice, 5 mm of ileum (B) and large intestine (C) piece was used ($n = 5$). Values are means ± SD for all experiments.

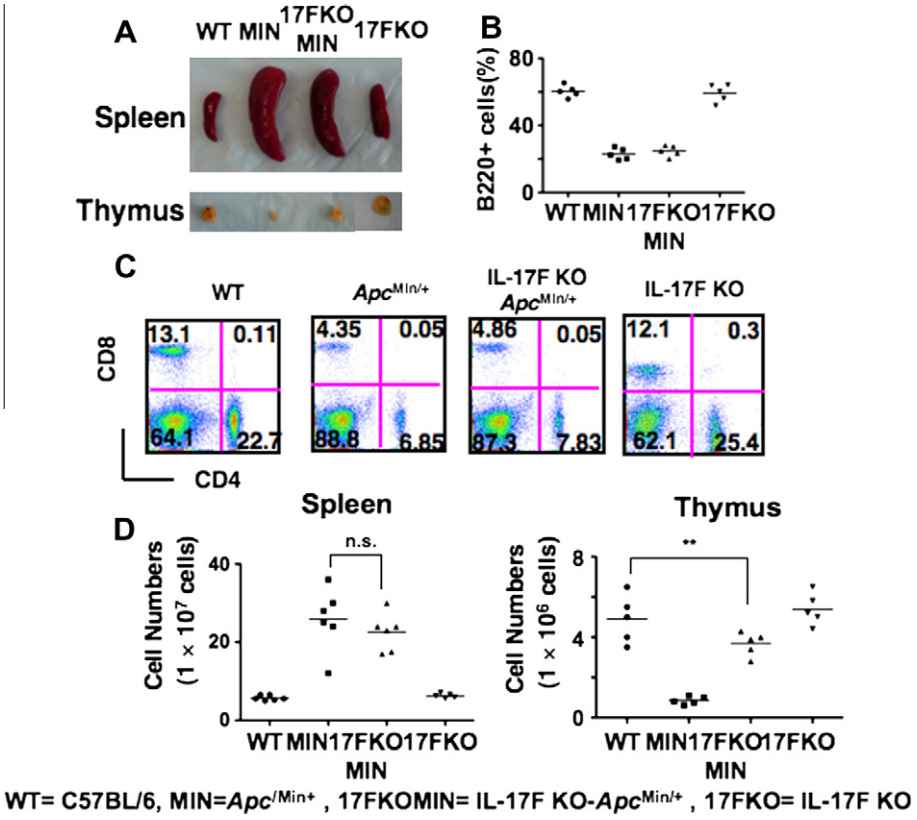

Fig. 3. IL-17F ablation does not reverse splenomegaly and partially reverses thymic atrophy. (A) Spleens and thymi from 16-week-old $Apc^{Min/+}$ and IL-17F KO $Apc^{Min/+}$ mice and littermate controls of $Apc^{Min/+}$ were dissected. (B) and (C) Spleens were analyzed by flow cytometry. The flow cytometry is representative of five mice per group. B220 was used for quantitating B cells. (D) Spleens and thymi from 16-week-old $Apc^{Min/+}$ and IL-17F KO-$Apc^{Min/+}$ mice and littermate controls of $Apc^{Min/+}$ were dissected and counted for cell numbers. Student's *t* test was used. $^{**}P < 0.005$, n.s. = not significant.

3.4. The ablation of IL-17F reduces intestinal tumorigenesis in the presence of IL-17A

To investigate whether the ablation of IL-17F alters lymphocyte infiltration, we quantitated the total cell numbers from the LP. We showed that the number of cells in the LP was increased in $Apc^{Min/+}$ mice, and the ablation of IL-17F decreased cell numbers in the LP (Fig. 4A). This suggests that IL-17F contributes to lymphocyte infiltration in the small intestine. As IL-17A and IL-17F are physically linked and tend to be co-expressed in CD4 T cells, we questioned whether IL-17A expression is affected in IL-17F KO $Apc^{Min/+}$ mice. Interestingly, the CD4+ IL-17A+ T cell population in the LP was unchanged in IL-17F KO $Apc^{Min/+}$ mice, indicating that IL-17F ablation did not affect IL-17A expression from CD4 T cells (Fig. 4B). In $Apc^{Min/+}$ mice, it has been demonstrated that CD4+ Foxp3+ cells are highly enriched in the LP, and IL-17F ablation decreased these cells in the LP. However, CD4+ Foxp3+ T cells did not express significant levels of IL-17F (Fig. 4C). Further examination of $Apc^{Min/+}$ mice in LP CD4 T cells showed that IL-17F was expressed in CD4 T cells but only marginally expressed in other immune cells (Fig. 4D). The marked effect of IL-17F ablation in intestinal tumor growth in the presence of IL-17A suggests that both isoforms are needed to achieve maximal intestinal tumorigenesis observed in $Apc^{Min/+}$ mice. Taken together, our results suggest that IL-17F is an important proinflammatory cytokine that can drive intestinal tumorigenesis in $Apc^{Min/+}$ mice.

4. Discussion

In this study, we showed a significant inhibitory effect of IL-17F ablation on spontaneous intestinal tumorigenesis. Most studies have considered IL-17A as a proinflammatory cytokine in autoimmune diseases and in cancer models. We showed that intestinal tumorigenesis is largely inhibited in the small intestine by IL-17F ablation. The increased expression of IL-17RC in $Apc^{Min/+}$ mice and the decreased expression of IL-17RC expression in IL-17F deficient $Apc^{Min/+}$ mice suggests that IL-17R-mediated signaling can be facilitated by the increased IL-17RC expression. A previous study showed that IL-17RC is highly expressed in colonic epithelial cells, whereas IL-17RA is preferentially expressed in immune cells such as macrophages and T cells [15]. Other studies with samples from human cancer patients suggested that the decrease in tumor-infiltrating Th17 cells is a poor prognosis of cancer progression in ovarian cancer and gastrointestinal adenocarcinoma [16,17]. In other types of cancer such as hepatocellular carcinoma (HCC), increased intratumoral IL-17-positive cells also correlate with poor survival. However, studies in a B16 melanoma mouse model showed that IL-17 could enhance anti-tumor immunity of CD8 T cells in TILs (Tumor Infiltrating Lymphocytes) [18]. These controversial data regarding IL-17 in tumor development suggests the tumor microenvironment is complicated and there are significant differences in different tissues and stages. The presence of IL-17A producing CD4 T cells in the small intestinal LP suggest that IL-17RC expression is needed to fully achieve intestinal tumorigenesis. Hence, the differential IL-17R expression in the small and large intestine as well as the presence of IL-17A and IL-17F need to be considered.

IL-17F KO $Apc^{Min/+}$ mice had significant splenomegaly and only a partial reversion of thymic atrophy indicating that these two tissues are mainly affected by IL-17A because IL-17A KO $Apc^{Min/+}$ mice completely restored these immune abnormalities [11]. The substantial decrease of IL-1β and Cox-2 suggests that the induction

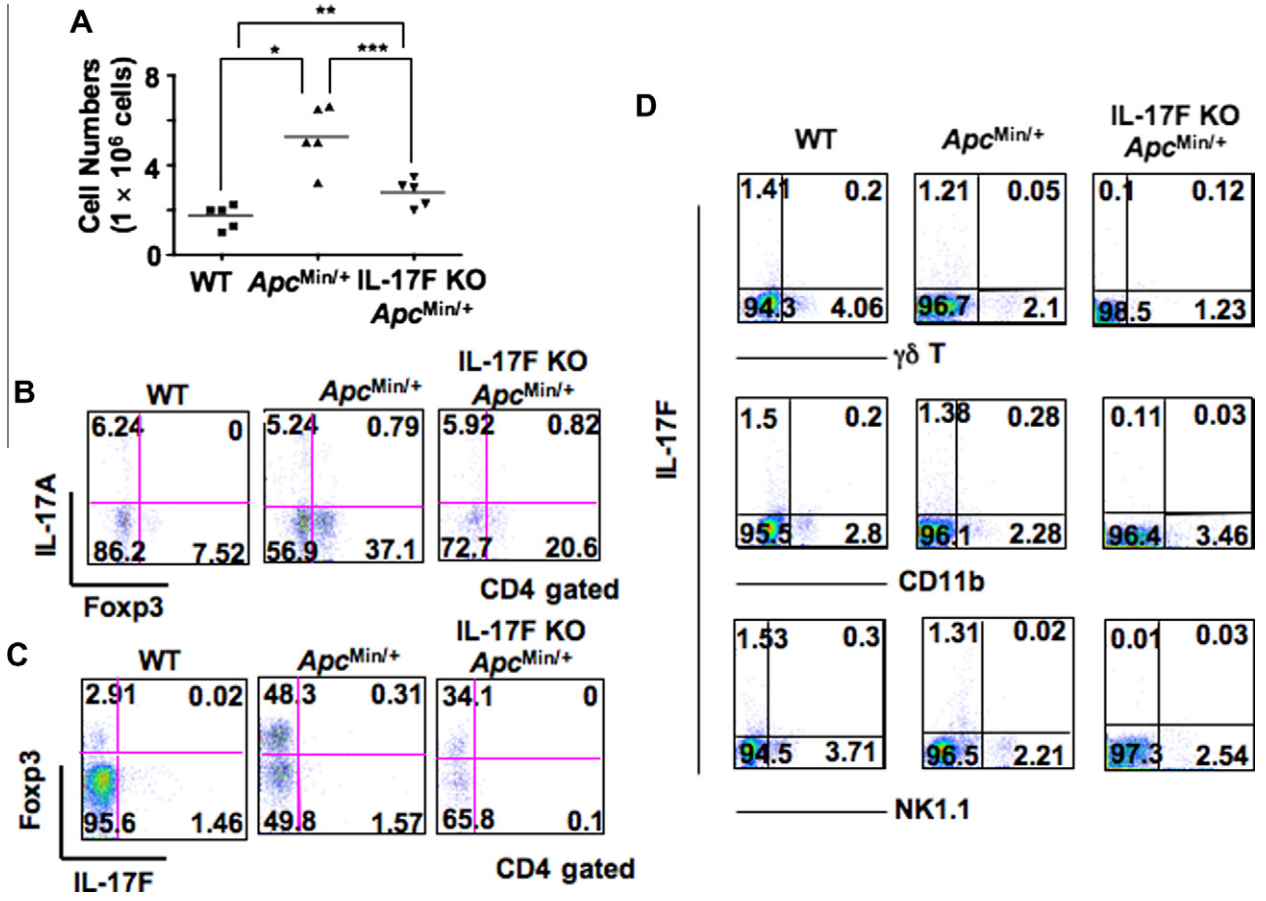

Fig. 4. IL-17F contributes to intestinal tumorigenesis in the presence of IL-17A. (A) LP cells from small intestine were counted. Student's *t* tests were used. $^{*}P < 0.0005$, $^{**}P < 0.005$, $^{***}P < 0.03$, n.s. = not significant. (B–D) Purified LP cells from 16-week-old littermate controls (WT), $Apc^{Min/+}$ mice and IL-17F KO-$Apc^{Min/+}$ mice were stained with antibodies after 6 h of stimulation with PMA and Ionomycin. One of three independent experiments is shown.

of these two genes is critical to initiate intestinal tumorigenesis in the small intestine of $Apc^{Min/+}$ mice. It has been demonstrated that Cox-2 deficient $Apc^{Min/+}$ mice showed a substantial decrease in intestinal tumorigenesis in previous studies [19–21]. The unchanged IL-6 expression upon IL-17F ablation suggests that the proinflammatory effect of IL-6 in Th17 cell development and IL-17F production is limited. Indeed, IL-6 deficient $Apc^{Min/+}$ mice showed only marginal effects (30%) on tumor reduction [22]. IL-17A and IL-17F can be functional in homodimeric or heterodimeric form. The less potent effect of IL-17F compared to IL-17A in intestinal tumorigenesis may be due to relatively weak biological activity of IL-17F. Given that the biological activity of IL-17F homodimers are known to be weaker than the other two isoforms [4,23], it is possible that IL-17F deficiency might have contributed to the depletion of IL-17A/F heterodimers as well as IL-17F homodimers. Collectively, the inhibition of intestinal tumorigenesis in IL-17F KO $Apc^{Min/+}$ mice and IL-17A KO $Apc^{Min/+}$ mice [11] suggests that both IL-17A and IL-17F are required to develop maximal levels of intestinal tumorigenesis. Taken together, our results suggest that IL-17F is an important proinflammatory cytokine that can drive intestinal tumorigenesis in $Apc^{Min/+}$ mice.

Conflict of interest

The authors have declared that no conflict of interest exists.

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