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Involvement of IL-17A in the pathogenesis of DSS-induced colitis in mice

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ABSTRACT

To investigate the etiological implication of IL-17A in inflammatory bowel disease (IBD), dextran sodium sulfate (DSS) was administered to the mice deficient for the IL-17A gene. They showed only faint manifestations of colitis, as revealed by body weight loss, shrinkage in the colon length, serum haptoglobin concentration, and disease activity index. Although the mortality rate of WT mice reached approximately 60%, more than 90% of the IL-17A KO mice survived the DSS treatment. Histological change was also marginal in the IL-17A KO intestine, in which epithelial damage and inflammatory infiltrates were not obvious and the myeloperoxidase activity elevated only slightly. G-CSF and MCP-1 were abundantly produced in WT mouse intestine, whereas the production of these chemokines was drastically hampered in IL-17A-null intestine. The present results show that IL-17A plays a pivotal role in the pathogenesis of DSS-induced colitis, while MCP-1 and G-CSF may be crucially involved in the IL-17A-induced inflammation.

Inflammatory bowel diseases (IBD) are chronic disorders of the intestine. A number of cytokines and chemokines are produced in the inflammatory lesions and believed to play important roles in the progression of the diseases. Anti-TNF-α antibody was recently shown to be extremely effective in alleviating IBD in patients [1].

Mice with acute DSS-induced colitis exhibit similar expression profiles of cytokines as well as histological changes to those observed in human IBD, particularly UC [2]. In DSS-induced acute colitis, massive infiltrates appear in the inflammatory lesions, mainly consisting of T and B lymphocytes, macrophages, as well as neutrophils, which produce a variety of proinflammatory cytokines including TNF-α, IFN-γ, IL-6, IL-8, IL-12, and IL-17 [2–4].

IL-17A is an important proinflammatory cytokine that is secreted by a particular subset of T lymphocytes, namely Th17 [5], while the monocyte/macrophage lineage also produces this cytokine [6]. In mice, IL-17A is furthermore secreted by NKT-like cells as well as γδ T cells. The IL-17 receptor A (IL-17RA) is ubiquitously expressed on a variety of cell types and essentially involved in the IL-17A and IL-17F signaling [5].

IL-17A stimulates a wide range of stromal cells to express various inflammatory mediators [7]. These include some CXC chemokines, CC chemokines such as MCP-1 [8,9], and hematopoietic cytokines such as G-CSF [7]. IL-17A also enhances TNF-α-mediated induction of MCP-1 in intestinal myofibroblasts [10]. Moreover, a series of proinflammatory cytokines are induced by IL-17A. It has been demonstrated that IL-17A fulfills crucial roles in various inflammatory disorders. They include airway infiltration, bronchial asthma, rheumatoid arthritis (RA), multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, psoriasis, *Helicobacter pylori*-associated gastritis, and renal allograft rejection [5].

However, a causative relationship between IBD and IL-17A remains controversial. It has been reported that IL-17A was produced from T cells or $CD68^+$ macrophages in colonic mucosa of IBD patients, leading to significant elevation of the serum IL-17A titer, while the cytokine was not detected in colorectal tissue of normal individuals [6]. Also expression of IL-17A mRNA was seen in severe, active UC patients as well as in CD patients of various degrees of activity [11]. More recently, when 2,4,6-trinitrobenzen sulfonic acid (TNBS) was administered to IL-17RA KO mice, it was found that the TNBS-induced colitis was attenuated in the receptor gene KO animals [12]. In contrast, after administration of a neutralizing anti-IL-17A antibody, the DSS-induced colitis in mice aggravated, suggesting that IL-17A may play an inhibitory, rather than enhancing, role in the development of experimental colitis [13].

Abbreviations: CD, crohn's disease; DSS, dextran sodium sulfate; IBD, inflammatory bowel diseases; TNBS, 2,4,6-trinitrobenzen sulfonic acid; UC, ulcerative colitis.

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In the present study, we administered DSS to IL-17A gene-deficient mice and examined acute intestinal inflammation in the animals. We also estimated the expression levels of some chemokines in the colon in an attempt to investigate the mechanisms of IL-17A-mediated IBD pathogenesis.

Materials and methods

Animals and DSS treatment. All the animal experiments were performed according to the approved guidelines of the Kyoto Prefectural University of Medicine. Male IL-17A KO mice (backcrossed onto C57BL/6) [14] and age-matched WT C57BL/6 mice were fed a standard diet, and housed under specific pathogen free conditions. Acute colitis was induced by administering 2.5% (w/v) DSS (mol. wt. 5000; Lot No. CEN0649, Wako, Osaka, Japan) in drinking water for 7 days. Healthy control animals received tap water only.

General assessment of colitis. Occult bleeding was detected based on the peroxidase activity of heme in stool (Occult blood Slide 5 Shionogi; Shionogi, Osaka, Japan). DAI was determined by scoring change in body weight, occult blood and gross bleeding as described [4].

To measure colon length, the animals were anesthetized with sevoflurane and killed by bleeding. The colon was excised between the ileocaecal junction and the proximal rectum, close to its passage under the pelvisternum. The colon was placed on a nonabsorbent surface and its length was measured with a ruler, in such a manner that the organ was not stretched.

Cytokine and chemokine concentrations in colonic tissue. To examine IL-17A concentration in colonic tissues, colons were rinsed with chilled PBS. After being weighed, the specimen was homogenized in PBS supplemented with Complete Miniproteinase Inhibitor Cocktails (Roche Molecular Biochemicals, Mannheim, Germany) (1 ml per 100 mg of tissue). After centrifugation, the concentration of IL-17A in the supernatant was evaluated using mouse IL-17A Quantikine ELISA kits (R&D System, Minneapolis, MN, USA). To examine chemokine concentrations, colon was rinsed with chilled PBS and homogenized (1 ml per 50 mg of tissue). After centrifugation, the supernatant was assayed for G-CSF and MCP-1 (Quantikine ELISA kits; R&D System). The haptoglobin concentrations in sera were determined as described [4].

Histological observation and scoring. The colons were divided into three parts (distal, middle, and proximal parts) of equal lengths. The specimens were fixed in 4% paraformaldehyde, embedded in paraffin and sliced into sections of 3 μm thickness. After H&E staining, histological analysis was performed in a blind fashion. The histological score of individual mouse represented the mean of the scores of the three parts as described [4,15,16]. Myeloperoxidase (MPO) activity in the colinic homogenate was determined as described [4].

Statistical analysis. Survival curves for the treatment groups were compared using the Log-rank test, while DAI and histological scores were analyzed by the Mann–Whitney *U*-test. For other comparisons, Student's *t-test* was used.

Results and discussion

WT and IL-17A KO mice were orally administered with 2.5% DSS to induce acute colitis, while untreated mice were used as controls. ELISA analysis revealed that IL-17A was produced at significant levels in the WT colon after daily administration with DSS for 7 days, while induction of IL-17A was not evident in KO mice (data not shown).

When WT mice were administered with DSS for 7 days, they drastically lost weight from the 5th day after initiation of the medication, and on day 10 their body weight was reduced approximately 37% compared with that of untreated WT animals (Fig. 1A). Kaplan–Meyer analysis demonstrated that approximately 60% of the mice had died by day 17 (Fig. 1B). Although the IL-17A KO mice also lost weight after treatment with DSS, the degree of their body weight change was significantly smaller compared to WT mice. The survival rate of DSS-treated IL-17A KO mice was approximately 92%, which was not significantly lower than that of untreated KO mice, while a statistically significant difference was seen between the mortality rates of WT and KO mice administered with the drug.

After DSS treatment, WT mice showed occult and rectal bleeding as well as diarrhea, which were less remarkable in IL-17A KO mice given the same medication. The severity of colitis was expressed as the disease activity index (DAI) based on three parameters, i.e., the magnitudes of body weight loss, diarrhea, and hemorrhage. The DAI was markedly higher in DSS-treated WT mice compared to non-treated WT animals (Fig. 1C). Although the IL-17A KO mice given administrations with DSS showed significantly higher DAI than untreated KO mice, the DAI for DSS-treated IL-17A KO mice was significantly lower in comparison with that for DSS-treated WT mice, indicating that the IBD-like symptoms were only marginally induced in the absence of the IL-17A gene (Fig. 1C).

As another index to assess the severity of colitis, we evaluated the concentration of serum haptoglobin that is a typical acute-phase protein produced in accordance with the progression of systemic inflammation [3]. As shown in Fig. 1D, haptoglobin was almost undetectable in sera of untreated WT mice, while the serum concentration of the protein was remarkably elevated after DSS administrations. The serum titer of this inflammatory marker was not as much increased in DSS-treated IL-17A KO mice as that in WT mice. These results are compatible with the colitis symptoms described above, strongly suggesting that the IL-17A KO mice were relatively resistant to the intestinal inflammation triggered by DSS.

The bowels were resected from WT and IL-17A KO mice and subjected to macroscopic and histopathological examinations. The gross appearance of the organs from DSS-treated WT mice showed apparent reddening and shortening of the colon, which are typical signs of acute intestinal inflammation (Fig. 2B), while the DSS-treated IL-17A KO mice showed milder pathological changes of the organ (Fig. 2D). Statistical analysis confirmed that the colon of WT mice drastically shrank in length in response to DSS administration, while the mean length of the colon of IL-17A KO mice was significantly, but less remarkably, shortened after induction of the disease (Fig. 3A).

Consistent with these findings are the results obtained by microscopic survey of the bowel, which demonstrated that the WT animals administered with DSS showed obvious manifestations of inflammatory colitis, including loss of crypts, mucosal erosions, ulcers, and infiltration of inflammatory cells (Fig. 2F). In contrast, the specimens from the DSS-administered IL-17A KO mice showed much less severe inflammation, with marginal infiltrates in the mucosa (Fig. 2H).

To statistically evaluate the morphological changes, the histological sores were calculated. The mean histological scores were significantly elevated in both DSS-treated WT and IL-17A KO mice, but the former showed considerably higher values than the latter (Fig. 3B). The data demonstrated that toxicity of DSS was attenuated in the mice with an IL-17A null phenotype.

Because MPO is a useful indicator of the extent of neutrophil infiltration, the colon was homogenized and activity of MPO in the lysate was estimated. As shown in Fig. 3C, WT mice treated with DSS showed drastically higher MPO activity compared with untreated WT mice, in consistent with severe intestinal inflammation in these animals. In contrast, the increase in the enzyme activity was much less evident in DSS-treated IL-17A KO mice compared with DSS-treated WT mice, confirming that the infiltra-

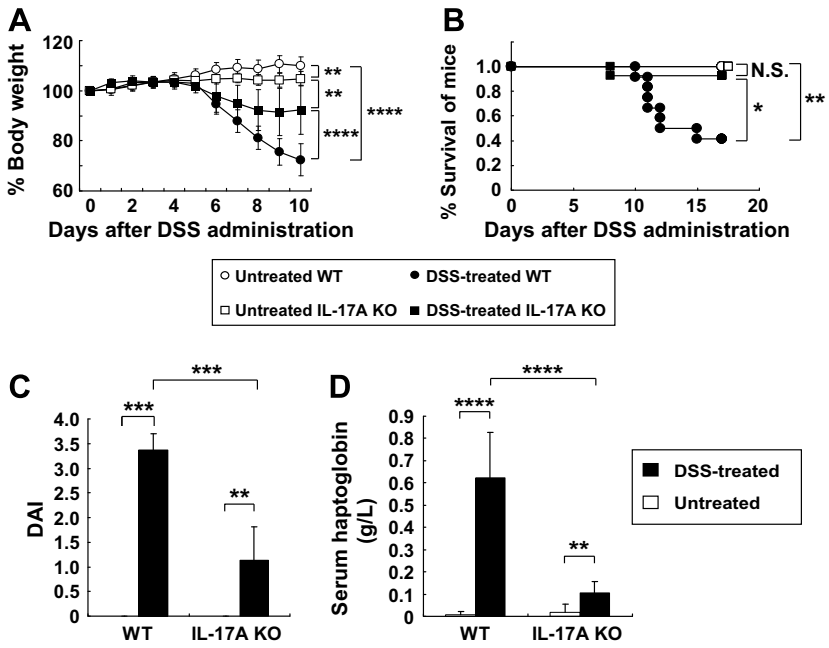

Fig. 1. Inflammatory colitis was significantly attenuated in IL-17A KO mice given DSS administration. WT and IL-17A gene KO mice were treated with DSS for 7 days or left untreated. (A) Body weight (BW) was measured daily and means ± SD of percent BW are plotted. *P* values on day 10 are: $^{**}P < 0.005$, $^{****}P < 0.00005$ ($n = 10$ mice for untreated WT group, $n = 12$ mice for DSS-treated WT group, and $n = 10$ mice for KO groups). (B) Survival rates of the mice are shown. *P* values on day 17 are: $^{*}P < 0.05$, $^{**}P < 0.005$, N.S., Not significant. ($n = 12$ mice for WT groups, $n = 10$ mice for untreated KO group, and $n = 14$ mice for DSS-treated KO group). (C, D) The DAI (C) and serum haptoglobin levels (D) were determined on day 7. Data represent the means ± SD. $^{**}P < 0.005$, $^{***}P < 0.0005$, $^{****}P < 0.00005$ (In (C), $n = 10$ mice for each group; in (D), $n = 9$ mice for WT groups, $n = 8$ mice for untreated KO group and $n = 10$ mice for DSS-treated KO group).

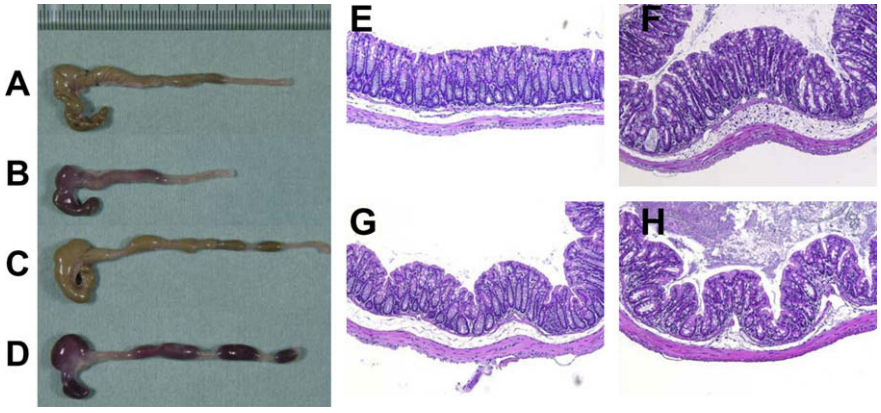

Fig. 2. Macroscopic and microscopic appearance of the intestinal tissues. WT(A, B, E, and F) and IL-17A gene KO (C, D, G, and H) mice were administered with DSS for 7 days (B, D, F, and H) or left untreated (A, C, E, and G). Shown are the representative gross appearance (A–D) and microscopic views of HE-stained sections (E–H) of the colons. Original magnification in (E–H) was 100×.

tion of neutrophils into colonic tissue was only marginal in the genetically modified animals (Fig. 3C).

We hypothesized that the decrease of intestinal infiltrates in IL-17A KO mice may be due to reduction of some cytokine and/or chemoattractant, which otherwise facilitate(s) infiltration of the inflammatory cells. Therefore we investigated the expression profiles of G-CSF and MCP-1. The former leads to the survival, expansion and activation of polymorphonuclear cells, while the latter attracts neutrophils and monocytes into the colonic mucosa in UC patients [17,18]. It has been reported that these factors are induced by IL-17A stimulation [7,8,19,20].

As shown in Fig. 4, ELISA analysis showed massive production of both G-CSF and MCP-1 in WT mouse colon that was damaged by DSS. Interestingly, in the intestinal tissue of DSS-treated IL-17A KO mice, MCP-1 was produced at a low titer, while G-CSF was not detected at a statistically significant level. These findings strongly suggest that G-CSF and MCP-1 may contribute to the development of intestinal inflammation, and IL-17A may be critically responsible for the induction of these soluble mediators.

IL-17A is the prototype of a family of cytokines that contains five other members, i.e., IL-17B-F [5,21]. IL-17F possesses the highest degree of homology with IL-17A, sharing similar functions through binding to the common cell surface receptor complex that is consisted of IL-17RA and IL-17RC [22,23]. In contrast, biological roles of other IL-17 family members have not been fully characterized [5,21]. The present data indicate that, with regard to DSS-induced colitis, IL-17A essentially contributes to the development of bowel inflammation, and other IL-17 isoforms including IL-17F are incapable of compensating for IL-17A. The functional discrepancy among these homologous cytokines is quite intriguing and may have a profound impact on the implication of redundancy and multiplicity of the IL-17 family member cytokines.

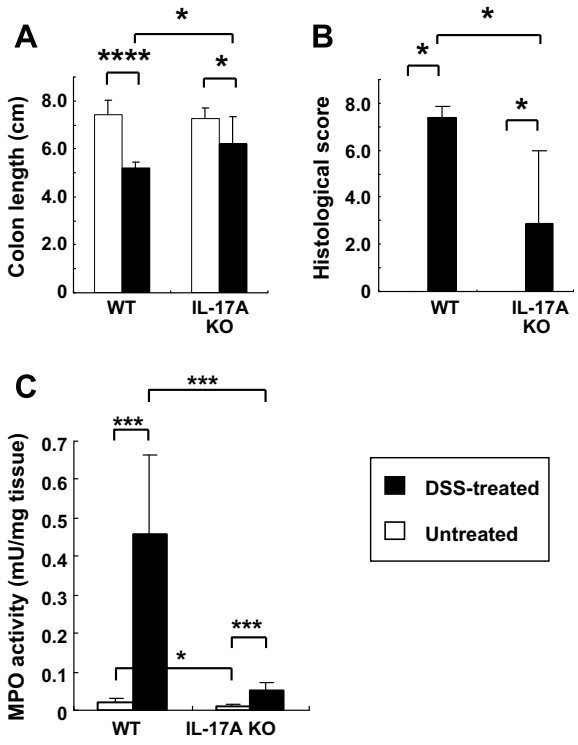

Fig. 3. Evaluation of morphological changes associated with intestinal inflammation. (A, B) Macroscopic as well as microscopic observation was performed as in Fig. 2, and the colon lengths (A), and histological scores (B) are plotted. Data represent means ± SD. $^{*}P < 0.05$, $^{****}P < 0.00005$. (In (A), $n = 9$ mice for each group; in (B) $n = 4$ mice in each group, and three sections were examined for each mouse). (C) The colons were homogenized and MPO activities in the lysates were measured. Data represent means ± SD. $^{*}P < 0.05$, $^{***}P < 0.0005$ ($n = 7$ mice in each group).

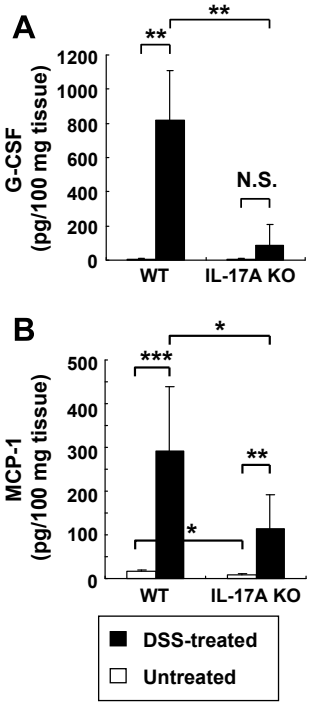

Fig. 4. DSS treatment failed to induce G-CSF in the absence of IL-17A, while MCP-1 was only faintly elevated in the DSS-irritated IL-17A KO intestine. The colons were homogenized and the concentrations of G-CSF and MCP-1 levels in the lysates were measured by ELISA. Data represent the means ± SD. $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$, N.S., Not significant. ($n = 4$ mice in each group).

In a previous report, DSS-induced colitis was deteriorated by an anti-IL-17A neutralizing antibody [13], suggesting that a trace amount of IL-17A could aggravate IBD, whereas complete lack of this cytokine may alleviate the disease. Alternatively, genetic background of mice may affect immunopathogenesis of IBD.

Although CD and UC are collectively referred to as IBD, it is considered that the two diseases develop through different immunopathological mechanisms. DSS-induced colitis is a murine model resembling human UC rather than CD, while the TNBS-induced colitis, which is another widely-used murine model of IBD, is more like CD. T cell-mediated acquired immune responses fulfill central roles in the pathogenesis of CD and TNBS-induced colitis [24]. Recent reports strongly suggested that the IL-23/IL-17 axis that is associated with Th17 is required for the development of TNBS-colitis as well as bacterially induced intestinal inflammation [12,25,26]. In sharp contrast, T cell responses may not play indispensable roles in the initiation of DSS-induced colitis, because the disease is inducible in T cell-deficient mice [27], while neutrophils and macrophages are important mediators in the cause of UC and DSS-induced colitis [3]. The present results clearly demonstrated that IL-17A signaling is also etiologically important for this category of IBD of which pathogenesis is predominantly based on innate immunity. It has previously been shown that IL-17A was produced by monocyte/macrophage lineage cells in inflamed colonic tissue [6]. In this regard, IL-17A may be the key molecule to explain the mechanism by which common features as IBD are shared by the two groups of diseases that develop via different (T cell-dependent and T cell-independent) etiologies.

The present study suggests IL-17A to be an appropriate target molecule to control IBD. Anti-IL-17A therapy may provide a promising strategy for therapeutic molecular targeting for the distressful, disabling, and currently incurable illness.

Conflict of interests

There is no financial/commercial conflict of interests.

Acknowledgments

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