**ABSTRACT**

AMP-activated protein kinase (AMPK) is an important cellular energy sensor that is responsible for maintaining systemic and cellular energy balance. Its role in intestinal inflammation remains unclear. Recent studies indicate that AMPK activation initiated by 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) participates in modulating inflammatory responses. Inflammatory bowel disease (IBD) has been characterized by dysregulated immune responses, play an important role in the development of IBD (Xavier and Podolsky, 2007; Fiocchi, 2009). A dysregulation of intestinal mucosal immunity causes an overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-12, and IL-23, which are produced mainly by macrophages (Kamada et al., 2005). Immune cells such as macrophages and T cells, together with these proinflammatory cytokines, take part in maintaining the uncontrolled inflammatory response, eventually leading to the intestinal tissue damage seen in IBD (Mahida, 2000). Recently, T helper type 1 (Th1) cells and IL-17-producing T helper (Th17) cells have been shown to play an important role in IBD (Ahern et al., 2008). The dysregulated T-cell response leads to alterations in mucosal cytokine expression. Th1-type cytokines such as interferon (IFN)-γ and Th17-type cytokines such as IL-17 are important for the development of intestinal inflammation because both IFN-γ and IL-17 are highly expressed in the inflamed mucosa of IBD patients (Kobayashi et al., 2008). Inhibiting the production of these cytokines leads to the improvement of...
man IBD and murine colitis (Fuss et al., 2006; Bai et al., 2009b). For this reason, IBD is also known as a Th1 and Th17 disease. Down-regulating the established inflammatory response, which normally includes extraordinary activation of macrophage and Th1 and Th17 responses, can successfully ameliorate IBD, as indicated by clinical and experimental research (Mannon et al., 2004; Andou et al., 2009).

5-Aminoimidazole-4-carboxamide ribonucleoside (AICAR) is a chemical compound with a molecular mass of 258.2 Da. As an activator of AMP-activated protein kinase (AMPK), it has been extensively studied in various experimental research and clinical treatments (Nath et al., 2005; Kim et al., 2007). Whether the activator of AMPK influences inflammatory responses during the development of IBD, however, has not been explored.

In the present study, for the first time, we examined the role of AICAR, the activator of AMPK, in the down-regulation of immune responses during the development of acute and chronic murine colitis induced by dextran sulfate sodium (DSS). As we have found, AICAR-initiated AMPK activation could act as a central inhibitor of the immune response by suppressing Th1 and Th17 cell responses and subsequently attenuating experimental acute and chronic colitis.

Materials and Methods

Animals. Seven- to 8-week-old female C57BL/6 mice were purchased from Charles River Laboratories (St. Constant, QC, Canada). The mice were maintained in standard animal cages under specific pathogen-free conditions in the animal facility at the Central Animal Care Services, University of Manitoba, Canada. All of the protocols used were approved by the University of Manitoba Animal Ethics Committee.

Evaluation of AICAR in DSS-Induced Acute Colitis. Five percent of DSS (molecular mass, 36–50 kDa; MP Biomedicals, Solon, OH) was added to the drinking water of C57BL/6 mice to induce acute colitis, with modification to a previously described method (Fina et al., 2008; Bai et al., 2009a). The drinking water was changed daily, according to the water volume the mice had consumed during the previous day. Mice were intraperitoneally injected on day 3 with 100 μl of either AICAR (500 mg/kg, dissolved in 0.9% saline; Toronto Research Chemicals Inc., North York, ON, Canada) (DSS + AICAR group) or 0.9% saline (DSS group) because symptoms such as diarrhea appeared. The treatment was repeated daily until day 7. Normal control mice received distilled water only. The disease activity index (DAI) was recorded according to the change of body weight and clinical symptoms such as fecal bleeding and diarrhea (Bai et al., 2009a). The mice were sacrificed on day 8, and colonic tissues were harvested for analysis. Serial paraffin sections of the colons were stained with hematoxylin and eosin, and histological disease scores were evaluated based on the presence of crypt loss and inflammatory cell infiltration as described previously (Murano et al., 2000) by two persons blinded to the source of treatment.

Evaluation of AICAR in DSS-Induced Chronic Colitis. Chronic colitis was induced by three-cycle administrations of DSS drinking water with a modification to a previously described method (Takedatsu et al., 2008). Female C57BL/6 mice received 4% (w/v) DSS drinking water for 7 days, followed by 3 days of regular drinking water. These mice continued to receive 3% DSS drinking water during days 11 to 15 and 19 to 23 (DSS group). In the treatment group (DSS + AICAR), mice with chronic DSS-induced colitis were intraperitoneally injected with AICAR (500 mg/kg b.wt.) daily on days 5 to 7, 13 to 15, and 19 to 23 (Fig. 8A). Normal control mice received the same amount of drinking water without DSS and without AICAR treatment. Mice were sacrificed on day 24, and histological inflammation scores were evaluated based on the presence of crypt loss and inflammatory cell infiltration (Murano et al., 2000) by two persons blinded to the source of treatment.

Culture of Mesenteric Lymph Node Cells and Lamina Propria Mononuclear Cells. Mesenteric lymph node (MLN) cells were removed aseptically and gently crushed to prepare single-cell suspensions in Hank’s balanced salt solution (HBSS; Sigma-Aldrich, St. Louis, MO). The suspensions were washed and resuspended in complete RPMI 1640 medium. Lamina propria mononuclear cells (LPMCs) were isolated from freshly obtained colonic specimens using a modified method, described previously (Bai et al., 2007). In brief, the colonic specimens were washed in HBSS-calcium-magnesium free solution and then were incubated in HBSS containing 0.75 mM EDTA (Sigma-Aldrich) and 1 mM dithiothreitol (Sigma-Aldrich) at 37°C for 30 min to remove the epithelium. The tissues were digested further in RPMI 1640 medium (HyClone Laboratories, Logan, UT) containing 400 U/ml collagenase IV (Sigma-Aldrich) and 0.01 mg/ml DNase I (Sigma-Aldrich) in a shaking incubator at 37°C. This step was repeated two or three times. The cells released from the tissues were purified by a 40 to 100% Percoll (GE Healthcare, Little Chalfont, Buckinghamshire, UK) gradient. LPMCs were enriched in T cells by incubating LPMCs in Petri dishes for 3 h at 37°C to remove adherent cells. MLNs and T cell-enriched LPMCs were cultured in 96-well round-bottom plates at 1.0 × 106 cells/ml complete medium (RPMI 1640 medium containing 10% fetal bovine serum, 2 mM glutamine, 25 mM HEPES buffer, 100 U/ml penicillin, and 100 μg/ml streptomycin), with or without plate coated murine anti-CD3 antibody (8 μg/ml; R&D Systems, Minneapolis, MN) and soluble anti-CD28 antibody (1 μg/ml; R&D Systems) for 48 h.

Intracellular Cytokine Staining and Flow Cytometry Analysis. A total of 1.0 × 106 T cell-enriched MLCs or MLNs were stained with phorbol myristate acetate (Sigma-Aldrich) and ionomycin (Sigma-Aldrich) for 5 h at 37°C. Brefeldin A (10 μg/ml; Sigma-Aldrich) was added during the final 4 h of stimulation. The cells were harvested, preincubated with an Fc receptor blocking monoclonal antibody (mAb; CD16/32, 2.4G2) for 15 min, and incubated with fluorescein isothiocyanate-anti-CD4 mAbs for surface staining for 30 min. The cells were then subjected to intracellular cytokine staining using PE-anti-IFN-γ, PE-anti-IL-17, PE-anti-IL-21, PE-anti-TNF, and PE-anti-CD127 mAbs for 30 min. The cells were then subjected to intracellular cytokine staining using PE-anti-IFN-γ, PE-anti-IL-17, PE-anti-IL-21, PE-anti-TNF, and PE-anti-CD127 mAbs for 30 min. The cells were then subjected to intracellular cytokine staining using PE-anti-IFN-γ, PE-anti-IL-17, PE-anti-IL-21, PE-anti-TNF, and PE-anti-CD127 mAbs for 30 min.
fluorescence-activated cell sorting Calibur flow cytometer (BD, Franklin Lakes, NJ).

**Cytokines Measured by Enzyme-Linked Immunosorbent Assays.** Cytokine levels in culture supernatants or colonic homogenates were assayed by enzyme-linked immunosorbent assay (ELISA) following manufacturer’s instructions (BD Biosciences Pharmingen, San Diego, CA). In short, polyclonal rat anti-mouse cytokine antibodies were used as capturing antibodies, and biotinylated polyclonal rat anti-mouse cytokine antibodies were used for detection. Streptavidin-horseradish peroxidase and tetramethylbenzidine sulfonate were added as color indicators, and plates were read at 405 nm.

**Western Blot.** Proteins were extracted from colonic tissues or cultured cells by using a lysis buffer (0.1 M phosphate-buffered saline, pH 7.4, containing 1% deoxycholic acid sodium, 0.2% SDS, and protease inhibitors). The proteins of the samples were separated by SDS-polyacrylamide gel electrophoresis and then electrophoretically transferred to polyvinylidene difluoride membranes. The membranes were incubated with primary antibodies, which included rabbit antibodies against phospho-NF-κB (Ser276), inducible nitric oxide synthase (iNOS), B P65 (Ser276), and phospho-AMPKα (Thr172) (Cell Signaling Technology Inc., Danvers, MA), respectively. After incubating with secondary antibodies, the immunoreactive bands were visualized using an enhanced chemiluminescence method (GE Healthcare). Rabbit anti-β-actin was used as an inner control.

**Real-Time Polymerase Chain Reaction.** Total RNA was extracted from colonic tissues or from cultured cells by TRIzol reagent (Invitrogen, Milan, Italy) and retrotranscribed into cDNA. Polymerase chain reaction (PCR) was performed using a SYBR green-based PCR using iQ SYBR mix (Bio-Rad Laboratories, Hercules, CA). Real-time PCR was performed, and the primer sequences were as follows: RA orphan receptor γ (ROrγ) forward, 5′-ACA CGG AGG GCT TAA CAA GAC ACT-3′; reverse, 5′-TGT GTG GTT GGT GCC ATT GTA GGC-3′; IL-23 P19 forward, 5′-TGC ACC AGG ACA TAT GAA TCT-3′; reverse, 5′-TGT TGT CCT TCA GTC CTT GTG GTT-3′; IL-12 P35 forward, 5′-AAG TCT GCC GGC TAT CCA GAC AAT-3′; reverse, 5′-AAC TGA GGT TTA GGA GGG CAA-3′; T-box forward, 5′-CTG CGC TAG AGG TGA AAT TC-3′; reverse, 5′-ATG TCA TGA GCA AAG GCG CAC AAG-3′; IL-12 P35 forward, 5′-GC CCG TAG AGG TGA AAT TC-3′; and reverse, 5′-TTG GCA AAT GCT TTC GCT C-3′. The expression of the genes was analyzed using TaqMan-based assays (Applied Biosystems, Darmstadt, Germany) and calculated relative to the housekeeping gene 18S ribosomal RNA using the ΔΔCt algorithm.

**Statistical Analysis.** Differences between experimental groups were assessed by one-way analysis of variance, the Tukey-Kramer multiple comparisons test (for multiple groups), or Student’s t test (for comparisons between two groups). \( P < 0.05 \) was considered to be statistically significant.

**Results**

**AICAR Attenuates DSS-Induced Acute Colitis.** Untreated mice (DSS group) exhibited body weight loss beginning on day 4 of the DSS administration, whereas treated mice (DSS + AICAR) showed body weight loss beginning on day 6 (Fig. 1A). By day 7, untreated mice exhibited a weight...
loss of more than 10% of their initial body weights and showed watery or bloody diarrhea. By contrast, AICAR-treated mice had significantly less body weight loss from day 4 to day 8 and fewer signs of severe colitis compared with the DSS group (P < 0.05) (Fig. 1, A and B). Macroscopically, the colon length was markedly shorter in the untreated mice than in those with AICAR treatment (Fig. 1D). Histopathologically, untreated mice showed marked infiltration of inflammatory cells, loss of crypts, reduction of goblet cells, focal ulcerations and/or extensive destruction of mucosal layer, and lymphoid aggregates, whereas AICAR-treated mice showed mild infiltration of inflammatory cells in the mucosa, minimal loss of crypts, and reduction of goblet cells (Fig. 1C). Furthermore, TNF levels in colon tissue were significantly reduced (Fig. 1E). The results suggest that AICAR significantly inhibits the inflammatory process of DSS-induced acute colitis.

**AICAR Inhibits Macrophage Activation in DSS-Induced Acute Colitis.** Transcription factors of the NF-κB family play an important role in the regulation of genes involved in inflammation. In IBD, NF-κB activation is mainly found in monocytes/macrophages of inflamed intestinal mucosa (Rogler et al., 1998) and induces the expression of iNOS and heavy production of proinflammatory cytokines such as TNF. As shown in Fig. 2, in untreated mice, phosphorylated-AMPK (p-AMPK) is undetectable, but p-NF-κB, iNOS expression, and production of proinflammatory cytokines such as TNF in colon tissues are significantly increased. AICAR treatment induces, to a high degree, the expression of p-AMPK in the colon tissues of AICAR-treated mice (Fig. 2A). This is accompanied by significantly inhibited NF-κB activation and thus down-regulated iNOS expression and TNF production in colon tissues of mice compared with mice without AICAR treatment (Fig. 2, B–D). These results collectively suggest that AICAR has a broad inhibitory effect on the inflammatory properties of monocytes/macrophages.

**AICAR Inhibits Th1 and Th17 Levels and Polarization in DSS-Induced Acute Colitis.** DSS-induced acute colitis is characterized as having predominant Th1 and Th17 cytokine responses (Fina et al., 2008). To determine the role that AICAR might play in both IFN-γ and IL-17 production in the mucosa of mice with DSS-induced acute colitis, we examined the expressions of the IL-12/IFN-γ pathway and the IL-23/IL-17 pathway in the colon. High levels of Th1 and Th17 cytokines and the transcriptional factors of IFN-γ and IL-17, such as T-bet and RORγt, were detected in the colon of untreated mice. In contrast, treatment with AICAR inhibited the production of IFN-γ and IL-17, as well as the expression of T-bet and RORγt in colon tissues (Fig. 3).

Next, we isolated MLNs and LPMCs from the mice and stimulated those cells with anti-CD3/CD28 antibodies. IFN-γ and IL-17 production of MLNs and LPMCs from AICAR-treated mice was significantly decreased compared with that of untreated mice (Fig. 4, B and D). Thus, in addition to a significant attenuation of DSS-induced colitis, AICAR treatment suppressed the production of IFN-γ and IL-17 cytokines from mucosal T cells.

MLNs from the mice with DSS-induced acute colitis were also stimulated with anti-CD3/CD28 antibodies. The cells were incubated with AICAR directly from the beginning of culture. Compared with the cells where AICAR was not added into the culture medium, the production of IFN-γ and IL-17 from MLNs with AICAR treatment was significantly inhibited. This provides direct evidence that AICAR has the potential to sufficiently inhibit IFN-γ and IL-17 production (Fig. 5). To confirm the in vivo effects of AICAR treatment on CD4+ T-cell differentiation, we performed intracellular staining of LPMCs and MLNs by membrane CD4 and intracellular IFN-γ or IL-17 double staining to detect Th1 or Th17 cell population. The administration of AICAR decreased the numbers of both IFN-γ-producing cells and IL-17-producing cells in LPMCs and MLNs (P < 0.05; Fig. 4, A and C), in agreement with the result of inhibited production of IFN-γ and IL-17 by LPMCs and MLNs. This result indicates that AICAR may inhibit Th1 and Th17 cell responses and thus down-regulate IFN-γ and IL-17 production.

**AICAR Attenuates DSS-Induced Chronic Colitis.** During the process of chronic DSS-induced colitis, the loss of body weight in untreated mice was first observed on day 6, and a maximum weight loss was seen on day 11. In contrast, the mice receiving AICAR treatment showed less body weight loss during days 6 to 11, 14, 15, and 21 to 24 (P < 0.05) (Fig. 6A). Moreover, AICAR treatment improved the macro-

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**Fig. 2.** AICAR treatment inhibits the inflammatory responses of DSS-induced acute colitis. Mice were sacrificed at day 8, and colon tissue protein and RNA were extracted. The expressions of p-AMPK/AMPK, p-NF-κB P65, iNOS, and β-actin were identified by Western blot analysis (A and B), and the expressions of iNOS and TNF were identified by real-time PCR (C and D, n = 5/group).
scopic and histological appearance of the colon wall, with longer colon length (Fig. 6B) and lower histological scores (Fig. 6C), compared with those of untreated mice.

In the chronic DSS-induced colitis experiment, similar to those results found in the acute colitis experiment, while inducing AMPK activation in colon cells, AICAR treatment also inhibited NF-κB activation and thus down-regulated iNOS expression (Fig. 7, A and B) and TNF production (Fig. 6D) in colon tissues. In addition, AICAR treatment decreased Th1 and Th17 cytokine levels such as IFN-γ and IL-17 in colon tissues (Fig. 6D) and also inhibited IFN-γ and IL-17 production of anti-CD3/CD28-stimulated MLNs (Fig. 7C).

Discussion

In this study, we have shown that AICAR, the activator of AMPK, has beneficial effects in treating murine colitis. Treatment with AICAR as a novel immunomodulatory agent during the course of the murine models of IBD induced significant attenuation in the clinical symptoms, as well as attenuation in the overall pathology of the disease. By analyzing the mechanisms involved in its anti-inflammatory effects, we found that AICAR reduced the proinflammatory immune response through the inhibition of the overactivation of macrophages and the down-regulation of excessive Th1- and Th17-type immune responses. These results indicate that AICAR, as well as other AMPK activators, may be a potential therapeutic approach for IBD and other inflammatory diseases.

Recently, it has been reported that AMPK activation induced by AICAR can inhibit NF-κB activation and thus down-regulate TNF production of macrophages (Sag et al., 2008). The effectiveness of AICAR for certain inflammatory diseases was shown in murine models such as LPS-induced lung injury (Zhao et al., 2008) and autoimmune encephalomyelitis (Nath et al., 2005). In IBD, intestinal macrophages localized in the subepithelial region and intestinal lamina propria are the main source for proinflammatory cytokines, including TNF and IL-1β (Kamada et al., 2005). Because macrophages represent the principal inflammatory cells in the mucosal microenvironment and contribute significantly to the tissue damage involved in IBD (Mahida, 2000), we studied the inhibitory effect of AICAR on macrophages during the process of murine colitis. In the experiments, we found that AICAR administration inhibited NF-κB activation, which subsequently resulted in a down-regulation of iNOS expression in macrophages and an inhibition of TNF production, a key proinflammatory cytokine for the pathogenesis of IBD. Overall, AICAR administration resulted in an amelioration of experimental colitis, indicating that the mechanism for the anti-inflammatory effect of AICAR is through the inhibition of macrophage-driven proinflammatory processes of colitis.

IBD has been characterized by excessive Th1 and Th17 cell
responses (Nielsen et al., 2003). The dysregulated Th1 and Th17 cell responses lead to alterations in mucosal cytokine expression, including increased IFN-γ and IL-17 expression, two key mediators in IBD. Promotion of Th1 and Th17 cell responses induced by IL-21 (Fina et al., 2008), IL-23 (Kobayashi et al., 2008), and TNF-like ligand 1A (Takedatsu et al., 2008) leads to the exacerbation of colitis, whereas inhibition of Th1 and Th17 cell responses by mAbs or an IgG fusion protein to the p40 subunit of IL-12 and IL-23 improves IBD and murine colitis (Stallmach et al., 2004; Fuss et al., 2006). Because these cytokines presented at the time of activation may alter the pathogenicity of effector T cells, blocking them...
AICAR treatment reduces inflammatory responses of DSS-induced chronic colitis. Mice were sacrificed at day 24, and colon tissue protein was extracted. The expressions of p-AMPK/AMPK (A), p-NF-κB P65, iNOS, and β-actin (B) were identified by Western blot analysis. C, AICAR treatment decreases IFN-γ and IL-17 productions of MLNs from DSS-induced chronic colitis. MLNs were isolated, cultured, and stimulated with anti-CD3/CD28 for 48 h. The concentrations of IFN-γ and IL-17 in the supernatants were measured by ELISA (n = 5/group).

**Fig. 6.** AICAR treatment significantly improves DSS-induced chronic colitis. Chronic colitis is induced by three repeats of the administration of DSS water, and AICAR is given intraperitoneally daily at the indicated days as shown in A. Control mice drank only distilled water. Mice were sacrificed at day 24. A, body weight changes (n = 10). B, colon length. C, colon inflammation. Colon sections stained with hematoxylin and eosin from three groups of mice were at the same magnification (40×). Inflammation scores were evaluated (C, right). D, the levels of TNF, IFN-γ, and IL-17 in colonic homogenates determined by ELISA (n = 5/group).
has been investigated as a potential therapy for Th1- and Th17-mediated autoimmune diseases. Thus, another possible mechanism for the therapeutic effect of AICAR on colitis is the down-regulation of Th1 and Th17 responses. To confirm this and analyze the immune responses in the mice with colitis, we induced three murine colitis models that were shown with possible characterization of Th1 and Th17 cell responses (Fina et al., 2008; Takedatsu et al., 2008) and found that AICAR inhibited adaptive immune responses during the process of colitis, with reduced Th1 and Th17 cell populations in the lamina propria and MLNs. This coincided with the inhibition of Th1-type cytokines IFN-γ and IL-12, the Th1-associated transcription factor T-bet, the Th17-type cytokines IL-17 and IL-23, and the transcription factor RORγt.

AMPK is well known as an important cellular energy sensor that plays a role in maintaining systemic and cellular energy balance (Kemp et al., 2003). As an energy-sensing/signaling intracellular protein, AMPK remains inactive unless it has been phosphorylated by upstream kinases at a threonine residue (Thr172) in response to cellular stresses that deplete cellular energy levels and increase the AMP/ATP ratio (Shaw et al., 2004). Once activated, AMPK restores cellular energy levels by stimulating catabolic pathways, such as glucose uptake and/or glycolysis and fatty acid oxidation, and curtails ATP-consuming cellular events, including synthesis of fatty acids, cholesterol, and protein (Hadad et al., 2008). The unique ability of AMPK places it in an ideal position to mediate high cellular energy-consuming processes and to regulate cell division and proliferation, processes that occur in tumor tissues (Rattan et al., 2005; Zhou et al., 2009). Activation of immune cells requires high metabolic demands and is associated with increased glycolysis and energy consumption (Frauwirth and Thompson, 2004; Maciver et al., 2008). AMPK activation is largely superfluous for immune cell function. Using AMPKα1-knockout mice, Mayer et al. (2008) studied AMPK activity in response to metabolic stress and to initiating an immune response. They found that AMPKα1-knockout mice were fully immunocompetent and displayed normal cell proliferation and humoral and delayed-type hypersensitivity responses after antigen injection. They then concluded that lymphocytes do not rely on AMPK to adjust their metabolism in anticipation of an immune response. This may be true under regular conditions or even under some inflammatory conditions where AMPK activation is at a very low level, such as in wide-type immune cells and colons of normal mice. AMPK activation under these conditions is almost undetectable compared with those cells and mice treated by AICAR, as shown by our data. Because AMPK activation is relatively low during normal conditions, it may not be applicable to use AMPKα1-knockout mice as a model for studying the biological activity of AMPK activation. By introducing AICAR, the potent activator of AMPK, to cultured cells and mice with colitis, we have discovered that AICAR-induced AMPK activation in immune cells and tissues successfully inhibits LPS-induced macrophage activation and Th1 and Th17 cell differentiation in vitro and impaired immune responses in inflamed colons of mice with acute and chronic colitis. Although lymphocytes do not require AMPK to adjust their metabolism in the anticipation of an immune response (Mayer et al., 2008), we conclude that when it is activated thoroughly by a variator such as AICAR, AMPK may have the ability to down-regulate an immune response.

AICAR has been studied extensively as an activator of AMPK (Nath et al., 2005; Kim et al., 2007; Su et al., 2007; Boon et al., 2008; Zhao et al., 2008). In the intracellular milieu, AICAR is phosphorylated by adenosine kinase to AICA ribose monophosphate, which mimics AMP and activates AMPK without altering the cellular levels of ATP, ADP, or AMP (Hardie, 2007b). Binding of AICA ribose monophosphate to AMPK produces allosteric alterations in AMPK, making the enzyme a better substrate for the upstream serine/threonine kinase 11 (also called LKB1) (Hardie, 2007a). This may be one reason that AICAR has been widely used in many studies.

Current treatments of IBD include corticosteroids, azathioprine, and mAbs targeting cytokines such as infliximab (the mAb against TNF). However, only 60 to 80% of patients show remission under the management of these drugs (Sandborn, 2008), and the treatment may cause many side effects, including bone marrow suppression induced by corticosteroids, neutropenia by azathioprine, and infusion reactions and the development of antibodies to the infused mAb by infliximab therapy (Makins and Ballinger, 2003). Administration of AICAR may avoid the side effects of these existing drugs. Up to now, no side effects of AICAR have been reported. In addition, AICAR has been clinically used in the treatment of type 2 diabetic patients for reduction of blood glucose concentrations (Boon et al., 2008), in obese females for stimulating fatty acid oxidation (Steinberg et al., 2004), and in healthy men to determine whether AICAR stimulates muscle glucose uptake in humans (Cuthbertson et al., 2007). Thus, as shown by our data, the successful introduction of AICAR into experimental acute and chronic colitis not only provides a treatment for the exacerbated inflammatory response during the process of murine colitis, but it may also provide a new strategy and choice for the treatment of human IBD in the near future.

Acknowledgments

We thank Terry Enno for providing histological examination and Xiaoling Gao for providing flow cytometry analysis.

References


