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Inflammation Research

Effect of rectal administration of rebamipide on dextran sulfate sodium-induced colitis: Role of hepatocyte growth factor

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Abstract. *Objective and design:* Since rebamipide is effective for the treatment of ulcerative colitis (UC), we examined the involvement of hepatocyte growth factor (HGF) in the action of rebamipide.
Materials: Fifty-five and forty female Balb/c mice, respectively, were used in Exp. 1 and 2. *Treatment:* 50 mg/kg/day rebamipide (Exp. 1) and 1×10^7 pfu pAxCAHGF (the CAG promoter-driving HGF gene in adenovirus vector) (Exp. 2) were intrarectally introduced after induction of colitis by 4 % dextran sulfate sodium (DSS).
Methods: Therapeutic effects were assessed by cell proliferation and apoptosis.
Results: Rebamipide caused proliferation of epithelial cells at 10 days after treatment, and decreased apoptosis at 10, 14 and 21 days, compared with controls. Expression of HGF was greatly increased in rebamipide-treated mice. pAxCAHGF caused cell proliferation and apoptosis, which showed the same pattern as with rebamipide treatment.
Conclusions: Rectal administration of rebamipide is effective for DSS-induced colitis in association with induction of HGF.

Key words: Rebamipide – Hepatocyte growth factor – Rectal administration – Experimental colitis

Introduction

Ulcerative colitis (UC) is a chronic disease of unknown cause, which is characterized by relapsing and refractory to the therapy. 5-Aminosalicylic acid (5-ASA) and corticosteroids have been used for the chronic phase as well as acute phase. Although these agents are effective in many patients, these drugs become ineffective in some patients and surgery is often be required in these patients [1]. Since the current medical treatment with corticosteroids and anti-inflammatory drugs is often associated with undesired side effects and cannot completely cure inflammatory bowel disease (IBD), these current advances in our understanding of intestinal pathology may allow the development of new treatment strategies.

Rebamipide, 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolion-4-yl] propionic acid, CAS11911-87-6, is used clinically as a potent anti-ulcer agent, especially in Japan and Korea. Rebamipide increases gastric mucosal prostaglandins by stimulating the biosynthesis of prostaglandin E2-like substances [2, 3]. On the other hand, rebamipide inhibits lipid peroxidation, acting as an antioxidant in the gastric mucosa [4]. Recently, it has been reported that rectal administration of rebamipide suppresses colonic lesions induced by dextran sulfate sodium phosphate (DSS), and its mechanisms include radical scavenging action and increased production of mucus [5]. Furthermore, rebamipide enema is effective in patients with UC who are corticosteroid-resistant [6, 7]. Experimental data suggest that rebamipide is useful for DSS-induced colitis [8, 9, 10], however, its precise mechanisms remain to be clarified.

Regulatory peptides have been demonstrated to be expressed in the intestine and modulate several functional properties such as proliferation, differentiation, migration, extracellular deposition and degradation. HGF, a factor which is expressed in a broad range of organs, is an important regulator of cell proliferation and tissue repair in the gastrointestinal tract [11, 12]. Induction of HGF mRNA expression was observed in human gastric ulcer and murine experimental colitis [13, 14]. Expression of HGF and its receptor, c-Met, were high in a rat model and patients with UC [14, 15]. Administration of HGF ameliorates diarrhea and bowel inflammation in a rat model of IBD [16]. Furthermore, HGF gene

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therapy is effective for experimental colitis in mice [17, 18]. These data suggest that intestinal mucosal healing is stimulated by the HGF/c-Met signaling system.

Recently, several important reports focusing on the relationship between prostaglandins and HGF have been published; prostaglandins and HGF induce each other [19, 20]. These studies suggest that prostaglandin-inducers also stimulate expression of HGF. Indeed, our previous study reported that rebamipide strongly induced HGF mRNA in gastric mucosa, affecting the outcome of acetic acid-induced gastric ulcer [21]. In the present study, we examined the effect of rectal administration of rebamipide on DSS-induced colitis, and clarified the involvement of HGF in this effect.

Materials and methods

Experimental procedures

Experiment 1. Eight weeks-old female Balb/c mice were kept under pathogen-free conditions and were maintained in a temperature-controlled room with a 12 h light/dark illumination cycle. Colitis was induced in mice by administration of 4 % dextran sulphate sodium (DSS, molecular weight 36,000–50,000, Wako Pure Chemical Industctries, Ltd, Osaka, Japan) in distilled water ad libitum for 7 days. Seven days after induction of colitis, the mice were divided into three groups, Group C, Group R and Group S (Fig. 1). The mice of Group R received daily rectal administration of 50 mg/kg/day rebamipide in dissolved in 100 µl of 0.5 % CMC (carboxymethylcellulose, Wako Pure Chemical Industries, Ltd.), and the mice of Group C daily received rectal administration of 100 µl of 0.5 % CMC. Treament of 1 % DSS in the mice of Group C and R was performed from 7 days to 21 days. The mice of Group S did not receive DSS treatment, rebamipide or CMC. These mice were sacrificed at 10, 14 and 21 days after starting DSS treatment. The number of mice of each group at each time point was 5. Rebamipide was kindly provided by the Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan.

Experiment 2. Seven days after induction of colitis, the mice were divided into two groups, pAxCAHGF-administered group and pAxCALacZ-administered group (Fig. 1). The mice received 1×10^7 pfu/mouse of pAxCAHGF and 1×10^7 pfu/mouse of pAxCALacZ, respectively, since in our preliminary experiments 1×10^7 pfu/mouse of pAxCALacX was almost as effective as 1×10^8 pfu/mouse and 1×10^9 pfu/mouse in staining intensity. pAxCAHGF was constructed as follows. Rat HGF cDNA was inserted in CAG promoter driving adenovirus vector lacking E1A, E1B and E3. In case of pAxCALacZ, LacZ cDNA was inserted instead of HGF cDNA [22]. The number of mice of each group at each time point was 5. Animals received humane care in accordance with study guidelines established by the Tottori University Subcommittee on Laboratory Animal Care.

Grading of histologic changes

Segments from the distal colon taken from the first to fourth centimeter from the anus of each animal were removed at indicated time points and embedded in paraffin. Paraffin sections were made and stained with hematoxylin and eosin. The degree of inflammation on microscopic cross-sections of the colon was graded semiquantitatively from 0 to 9. The scoring was done by epithelial damage, cellular infiltration, and damage or alteration of smooth muscle architecture [23]. Five sections from each animal were selected and grading was done in a blinded fashion by RM and KT.

Immunohistochemistry

The tissues were fixed in 4 % PFA overnight and embedded in paraffin. After deparaffinization and rehydration, sections were pretreated with 0.3 % hydrogen peroxidase and incubated with horse serum blocking solution for 20 min. The sections were incubated with mouse anti-PCNA monoclonal antibody (Novacastra Laboratories, Newcastle, UK), and then stained with the avidin-biotin-peroxidase complex (Vector Laboratories, Burlingame, CA). The PCNA-positive cells were determined by analyzing 1,000 epithelial cells in the crypts randomly selected. Positive controls and negative controls were selected from colonic tissues at 7 days and 0 day in this experiment, respectively.

TUNEL staining

Terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) was performed by using ApoTag Plus Peroxidase in situ Apoptosis Detection kit (Intergen Co., Purchase, NY, USA) according to the manufacture's instruction. In brief, paraffin-sections were dewaxed, rehydrated through a graded alcohol series and washed in distilled water. After digestion in 20 µg/ml proteinase K (Boehringer Mannheim/Yamanouchi, Tokyo, Japan) for 10–20 min at room temperature, the sections were washed in tap water. The sections were treated with 2 % H2O2/methanol and washed in distilled water. Then, terminal deoxynucleotidyl transferase (TdT) buffer (100 mM potassium cacodylate, 2 mM cobalt chloride, 0.2 mM dithiothreitol, pH 7.2) containing 0.3 U/l TdT (Gibco BRL, MD, USA) and 0.04 nmol/l bitinylated dUTP (Boehringer Mannheim/Yamanouchi) were added to cover the sections, which were incubated in a humidified atmosphere for 90 min at 37 °C. The sections were washed in TB buffer (300 mM sodium chloride, 300 mM sodium citrate) for 15 min at room temperature. After washing with phosphate buffer, they were subsequently incubated with peroxidase-labeled streptavidin-H2O2. The sections were counterstained with methyl green. The TUNEL-posi-

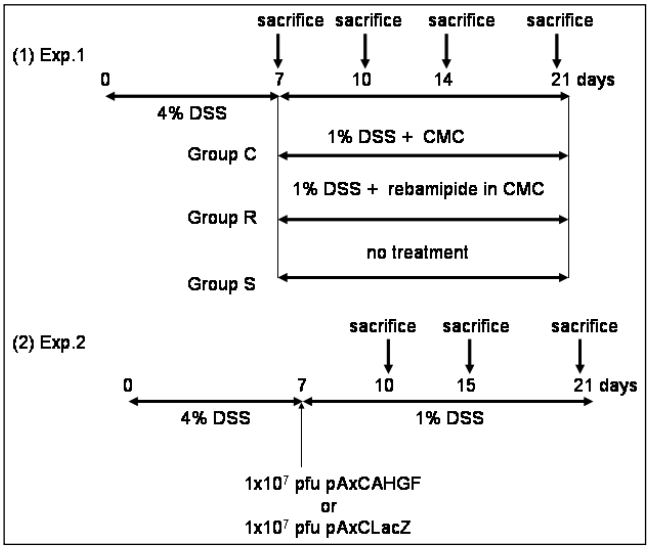

Fig. 1. Time course of experimental schedules. (1) Experiment 1. Colitis was induced in mice by administration of 4 % DSS for 7 days. Seven days after induction of colitis, the mice were divided into three groups, Group C, Group R and Group S. The mice of Group R received rectal administration of 50 mg/kg/day rebamipide in 0.5 % CMC, and those of Group C did 0.5 % CMC. Treament of 1 % DSS in the mice of Group C and R was performed from 7 days to 21 days. The mice of Group S did not receive DSS treatment, rebamipide or CMC. All the mice were sacrificed at 10, 14 and 21 days after starting DSS treatment. (2) Experiment 2. Colitis was induced in mice by administration of 4 % DSS for 7 days. Seven days after induction of colitis, the mice were divided into two groups. The mice of one group received rectal administration of 1×10^7 pfu pAxCAHGF, and those of the other group did 1×10^7 pfu pAxCALacZ. All the mice were sacrificed at 10, 15 and 21 days after starting DSS treatment.

tive cells were determined by analyzing 1,000 cells in the fields randomly selected. Positive controls and negative controls were selected from colonic tissues at 7 days and 0 day in this experiment, respectively.

Western blot and immunoprecipitation analysis

To examine the effect of rebamipide administration expression of HGF, colonic samples were obtained on 10, 14 and 21 days after starting DSS treatment. Equal amounts of protein homogenates (50 μg), obtained after centrifugation of homogenates with PBS from mice colonic tissues, were separated by SDS-PAGE, and proteins were transferred to polyvinylidene difluoride membrane followed by immunoblot analysis with anti-c-met (Santa Cruz Biotechnologies) and anti-β-actin (Santa Cruz Biotechnologies) antibodies.

For analysis of c-met phosphorylation, 500 μg of protein was immunoprecipitated with anti-c-met (Santa Cruz Biotechnologies) overnight, and then analyzed by western blot with phospho-c-met (Santa Cruz Biotechnologies). Membranes were incubated with horseradish peroxidase-conjugated secondary antibodies followed by detection with enhanced chemiluminescence (ECL, Amersham Bioscience Corp., Piscataway, NJ).

Statistics

Differences between groups were compared using the Mann-Whitney U-test. A P value less than 0.05 was considered to be significant.

Results

Effect of rebamipide on mucosal damage, cell proliferation and apoptosis

The histologic findings of DSS-induced colitis were composed of epithelial destruction, remarkable infiltration of inflammatory cells, and submucosal edema [18]. In the present study, we especially focused on ongoing inflammation, and grading system was performed previously described [23]. Massive infiltration of inflammatory cells was observed in the colonic mucosa at 14 days of the mouse of Group C (Fig. 2A). The crypt regeneration and restoration of colonic mucosa were observed in the mouse of Group R at the same day (Fig. 2B). Histological score showed that mucosal damage of the colon in Groups R was similar to that in Group C at 10 days, however, it was significantly improved at 14 and 21days ($P < 0.05$, $P < 0.01$, respectively, Fig. 3A). No DSS treatment resulted in around 3 of grading score at 14 and 21 days in the mice of Group S.

To examine the effect of rebamipide on colonic cell proliferation and apoptosis, the mucosa was examined with PCNA staining and TUNEL analysis. For PCNA staining, more PCNA-positive cells were observed in the mice in Group R than in Group C (Fig. 2C, 2D). Especially, many PCNA-positive cells were present near the base of the crypt. Serial analysis showed that the numbers of PCNA-positive cells in Groups R were greater than those in Group C at 10 days ($P < 0.01$, Fig. 3B). The PCNA-positive cells gradually decreased with time in the mice of Group S.

On the other hand, the TUNEL-positive cells were seen randomly in the epithelial cells in the mice in Group C (Fig. 2E). However, the TUNEL-positive cells were decreased in the mice treated with rebamipide (Fig. 2F). The numbers of apoptotic cells in Group R were smaller than those in Group C at 10, 14 and 21 days ($P < 0.01$, each, Fig. 3C). The serial numbers of the TUNEL-positive cells in Group S were similar to those to those of Group R. These data suggest that the effect of rebamipide cancelled ongoing damage of 1 % DSS.

Analysis of HGF expression

The expression of HGF protein in Group C was very low, however, dramatic increase by rebamipide is effective for colonic cell damage. A dramatic increase in HGF expression was observed at 10, 14 and 21 days in Group R (Fig. 4).

Histological changes, cell proliferation and apoptosis by HGF gene transduction

To test whether HGF induction by rebamipide is effective for colonic cell damage, cell proliferation and apoptosis, the

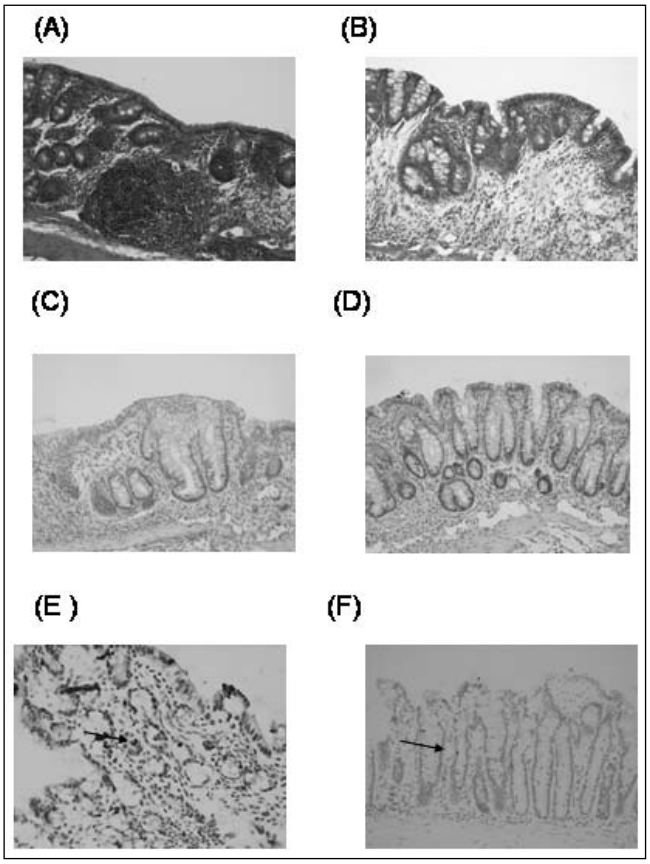

Fig. 2. Morphological examinations. The colonic tissues were histologically examined, and the proliferation and apoptosis of colonic cells were examined by PCNA expression and TUNEL staining on 10 or 14 days of the experiment. (A) H&E staining at 14 days in the mouse of Group C (magnification: ×200). (B) H&E staining at 14 days in the mouse of Group R (magnification: ×200). (C) PCNA staining at 10 days in the mouse of Group C (magnification: ×200). (D) PCNA staining at 10 days in the mouse of Group R (magnification: ×200). (E) TUNEL staining at 14 days in the mouse of Group R (magnification: ×200). The arrow showed the TUNEL-positive cells. (F) TUNEL staining at 14 days in the mouse of Group C (magnification: ×200). The arrow showed the TUNEL-positive cells.

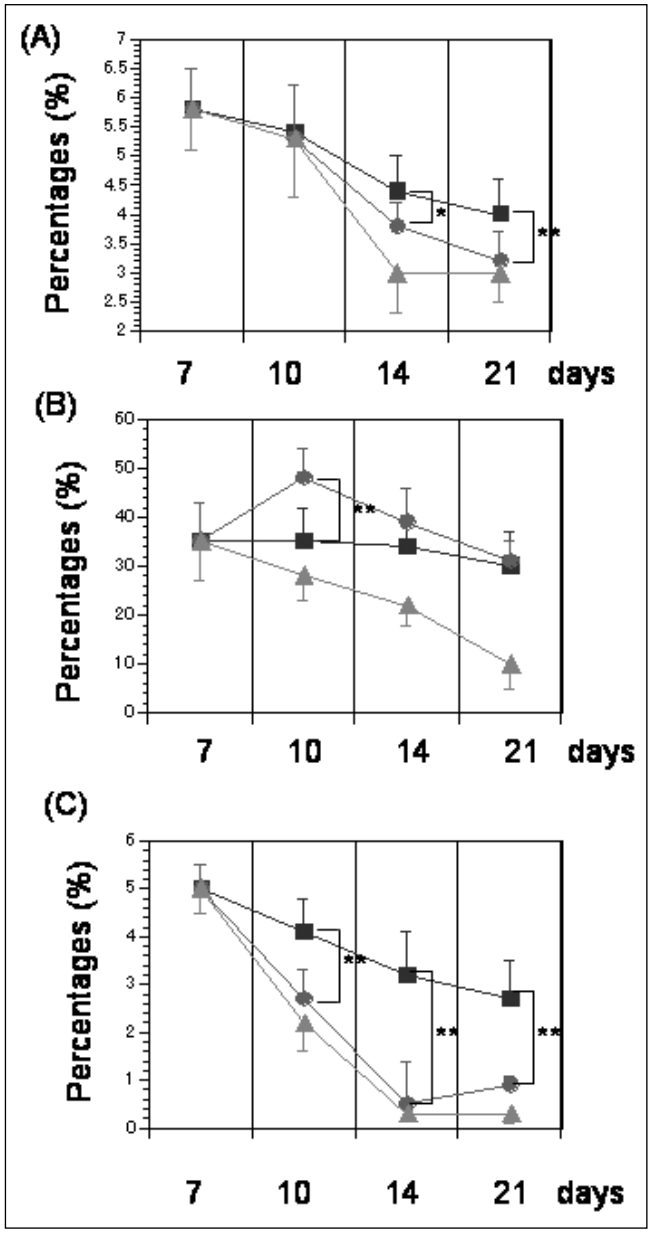

Fig. 3. Effect of rebamipide on histological score, cell proliferation and apoptosis. (A) Histological score, (B) Cell proliferation, (C) Apoptosis, □ C Group; ○, R Group, △, S Group. * $P < 0.05$; ** $P < 0.01$.

histological score, labeling index by PCNA, and TUNEL-positive cells were examined. The histological score was not changed at 10 days, however, it was significantly improved at 15 days and 21 days ($P < 0.01$, each, Fig. 5A). Cell proliferation by pAxCAHGF was enhanced at 10 and 15 days ($P < 0.01$, each, Fig. 5B), however, it was decreased to that by pAxCALacZ. The number of apoptotic cells was greater at 15 and 21 days in pAxCAHGF than that in pAxCALacZ (Fig. 5C). Thus, serial changes of histological score, cell proliferation and apoptosis in pAxCAHGF-treated mice was similar to that in rebamipide-treated mice. These data suggest that effect of rebamipide is mediated by HGF.

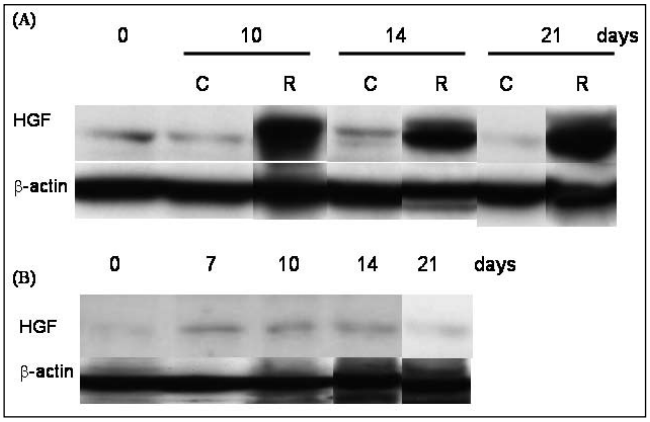

Fig. 4. Expression of HGF protein. (A) HGF expression at 0, 10, 14 and 21 days in Group C and Group R. C, Group C; R, Group R. Great induction of HGF was observed at 10, 14 and 21 days of Group R. (B) HGF expression at 0, 7, 10, 14 and 21 days in Group S. HGF expression was low throughout the experiment, however, it was the highest at 7 days. (C) Group C; R, Group R. β-actin was used as an internal control.

Phosphorylation of c-Met by pAxCAHGF

Phosporylation of c-Met receptor was increased in the mice into which pAxCAHGF was administered at 10, 15 and 21 days. Phospho-c-Met is not so evident at 10 and 15 days, but became stronger at 21 days in mice into which pAxCALacZ was administered (Fig. 6). These data suggest that HGF gene transfer really activates c-Met receptor.

Discussion

Rebamipide has been reported to be effective for IBD in experimental models and human. Rebamipide prevented DSS-colitis through suppressing inflammatory cytokines [8] and myeloperoxidase activity in leukocytes [9]. Recently, intrarectal administration has been to be an effective route of rebamipide [5, 10]. Indeed, the efficacy of rebamipide enemas have been reported [6, 7]. However, the efficacy of precise mechanism of intrarectal administration of rebamipide remains to be clarified. In the present study, rectal administration of rebamipide ameliorated experimental murine colitis, and this effect is closely associated with strong induction of HGF. This is the first paper demonstrating that rebamipide up-regulates HGF and HGF/c-Met signal in colonic mucosa. Previously, we reported that rebamipide up-regulates HGF in gastric mucosa [21]. In that report, expression of Cox-2 and EP2 were also increased. This induction of Cox-2 and EP2 may be associated with the action of rebamipide, which was originally described [2, 3]. Prostaglandins have been shown to be strong transcriptional inducers of HGF gene in skin fibroblast [19]. The administration of anti-prostaglandin E2 antibody abolished the cytoprotective effect of HGF, and proliferation of gastric mucosal cells by prostaglandins was mediated by HGF [24]. In addition, prostaglandin E2 induced by interleukin 1β was to activate cAMP, resulting

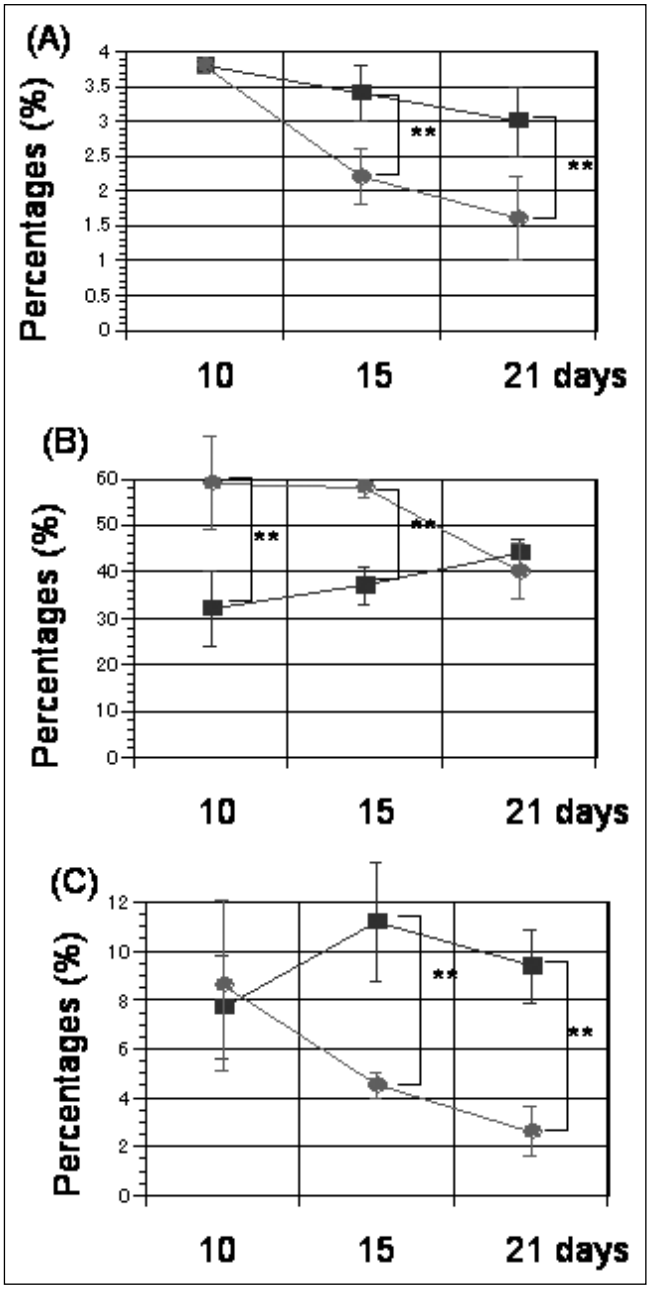

Fig. 5. Effect of adenovirus-mediated HGF gene transfer on serial changes of histological score, cell proliferation and apoptosis. (A) Histological score, (B) Cell proliferation, (C) Apoptosis

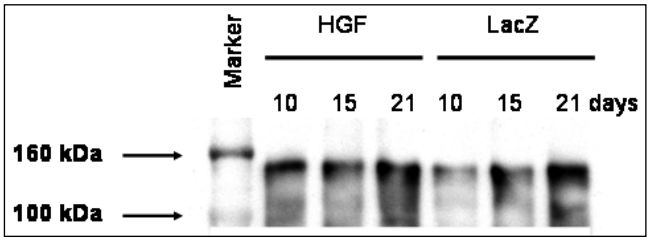

Fig. 6. Phospho-c-Met protein expression. HGF, pAxCAHGF-administered mice; LacZ, pAxCALacZ-administered mice

in production of HGF, and then the prostaglandin E2-interleukin1β-cAMP-HGF pathway may play a role in the repair process of the gastric mucosa [25]. The mechanism of action of rebamipide on colonic cells includes the radical scavenging action and increase in the production of mucus [5]. In the present study, the state of oxidative stress and the amount of mucous production were not examined. However, HGF produced in response to rebamipide may be the major cause of the rebamipide action, since the time course of histological score, cell proliferation and apoptosis in rebamipide-treated mice were similar to those in pAxCAHGF-administered mice. Since how HGF is induced by rebamipide in colonic cells and how rebamipide acts on DSS-induced colitis are of great interest, experiments using knockdown HGF action using siRNA against HGF, etc may be required in the future.

Recently, analysis of the gene expression profiles has provided helpful insights into the mechanisms of inflammatory bowel disease (IBD). In our recent work, the regulated genes by HGF in DSS-induced colitis were examined [18]. The genes which were increased over 5-fold by HGF were 284 genes in experiment 1 and 205 genes in experiment 2, respectively [18]. In that work, we identified two genes whose overexpression was very intriguing. The one gene was Max, a transcription factor working as a heterodimer with c-Myc, and the other gene was Musashi2, a RNA-binding protein associated with stem cells. These findings were very intriguing since recent studies have reported that c-Myc has unexpected functions during both self-renewal and the differentiation of stem and early progenitor cells [26].

In IBD, especially UC, the repeated injury and repair may lead to an increase in the risk of colorectal cancer [27]. Recently, HGF and c-Met was demonstrated to be highly expressed in the mucosa of UC and c-Met was increased in UC-associated colorectal cancer [15]. These observations suggest that local expression of HGF may enhance the risk of colorectal cancer in the colonic mucosa of IBD via a cycle of repeated injury and repair. However, the blockade of this cycle by repair of colonic mucosa by rebamipide should reduce the genetic damage instead.

In conclusion, the results of the present study suggest that rectal administration of rebamipide is effective for DSS-colitis in mice.

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