Efficacy of Keratinocyte Growth Factor-2 in Dextran Sulfate Sodium-Induced Murine Colitis

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ABSTRACT
The purpose of this study was to determine the efficacy of a novel human protein, keratinocyte growth factor-2 (KGF-2), in a model of murine colitis induced by ad libitum exposure to a 4% solution of dextran sulfate sodium (DSS) in the drinking water. Initial evaluation of KGF-2 was based on its ability to reduce weight loss, stool score, and histological score in mice exposed to DSS for 7 days. When KGF-2 (0.1–10.0 mg/kg i.p. or s.c.) was injected daily into DSS-treated mice from day 0 to 7, it significantly reduced all three parameters in a dose-response fashion, with a minimum effective dose of between 1 and 3 mg/kg. When KGF-2 was given therapeutically, starting 4 days after initiation of the 7-day DSS treatment, the 3- but not the 0.5-mg/kg dose significantly enhanced weight recovery after discontinuation of DSS treatment. When DSS treatment was prolonged beyond the normal 7 days, therapeutic intervention on day 2 or 4 also significantly reduced mortality, weight loss, and stool score at the 1- and 3-mg/kg dose. Therapeutic treatment also resulted in reduction of colon myloperoxidase levels by more than 50%. These experiments suggest that KGF-2 may be clinically useful in the treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease.

Keratinocyte growth factor-2 (KGF-2) is a novel therapeutic protein described and claimed in the patent literature by Human Genome Sciences Inc. It is a member of the fibroblast growth factor (FGF) family, comprised of at least 16 homologous proteins, associated with soft tissue growth and repair (Basilico and Moscatelli, 1992). Within the general FGF superfamily is the smaller keratinocyte growth factor (KGF) family, consisting of two members, KGF-1 or FGF-7 and KGF-2, also known as FGF-10 (Yamasaki et al., 1996).

Although KGF-2 shares many of the attributes of its KGF-1 family member, it possesses some dissimilarities as well. Whereas KGF-2 is 96 and 92% homologous to rat and mouse FGF-10 protein, respectively, it bears a 57% homology to the human KGF-1 protein (Jimenez et al., 1999). Both KGF-1 and -2 bind to the FGFR-2iiib receptor (Igarashi et al., 1998), but in our hands, using BaF3 cells transfected with various FGF receptors, KGF-1 bound to the FGFR-2iiib receptor with a Ki of 0.1 nM, whereas the affinity of KGF-2 was 10-fold lower. In addition, KGF-2, in this assay, also bound to the FGFR-1iiib receptor, whereas KGF-1 exhibited no such binding (Jimenez et al., 1999). Perhaps the differences in their receptor affinity and specificity account for differences in the phenotype of their respective knockouts. The KGF-2 knockout is a perinatally lethal mutant, stemming from the absence of lung or limb development (Min et al., 1998). The KGF-1 knockout, on the other hand, survives to maturity, although its response to DSS-induced colitis is more severe (R. Boismenu, personal communication).

Despite some biological differences, both proteins induced proliferation of epidermal cells in vitro (Rubin et al., 1995; Emoto et al., 1997) and were up-regulated in vivo during the wound-healing process (Tagashira et al., 1997; Werner, 1998). Because of its positive effect on epithelial repair in the skin (Jimenez and Rampy, 1999), KGF-2 was tested in a preclinical model of inflammatory bowel disease (IBD) to determine whether it could effect colonic epithelial tissue repair.

KGF-2 was evaluated in the trinitrobenzene sulfonic acid-induced model of colitis (Peterson and Davey, 1997), because KGF-1 had been reported to exhibit some efficacy in this model (Zeeh et al., 1996). KGF-2, however, was inactive in this assay (data not shown), possibly because of the lack of immunoregulatory activity usually associated with successful treatment in a Th1 cell-mediated model like trinitrobenzene sulfonic acid colitis. In contrast, KGF-1, with its association with γδ-T lymphocytes (Boismenu and Havran, 1994), may have an underlying immunological component associated with its in vivo activity.

Because KGF-2 is a wound-healing agent and not an immunoregulatory molecule, demonstration of its in vivo effi-
cacy was divided into two phases: 1) testing it in a non-T cell-dependent model of intestinal injury and 2) developing a T cell-dependent model of IBD [e.g., interleukin (IL)-10 knockout mice] and testing KGF-2 with and without ancillary immunomodulatory therapy (e.g., anti-IL-12 antibody). Dextran sulfate sodium (DSS)-induced colitis was chosen as an appropriate model of colonic injury, based on the rapidity and regularity of onset and easily quantifiable parameters of weight loss, stool score, mortality, and histological evaluation (Savendahl et al., 1997). A 4% solution of DSS causes clinical symptoms of ulcerative colitis within 4 days. Histological examination after 1 week of DSS treatment revealed erosions of the descending and sigmoid colon, crypt shortening and abscesses, and lymphocyte, macrophage, and neutrophil infiltration of the colonic wall (Kim and Berstad, 1992). Prolonged exposure to DSS resulted in perforation of the gut and death.

In this series of experiments, we showed that human KGF-2 did have a positive effect on DSS-induced colitis, as measured by weight change, stool score, histology, mortality, and tissue myeloperoxidase (MPO) level. The mechanism behind its efficacy in vivo is still speculative, although the presumption is that it induces proliferation and migration of gastrointestinal epithelial cells, resulting in accelerated healing.

Materials and Methods

Animals. Female Swiss-Webster mice (weighing 20–25 g) were obtained from Charles River Laboratories (Raleigh, NC), housed five per cage, and kept under standard conditions for 1 week before being used in experiments. The animals were maintained according to National Research Council standards for the care and use of laboratory animals. Mice were housed in micro-isolator units with recycled paper bedding (Harlan Sprague Dawley, Inc., Indianapolis, IN) and provided with pelleted rodent diet (Harlan Sprague Dawley, Inc.) and bottled drinking water on an ad libitum basis. The animal protocols used in this study were reviewed and approved by the Human Genome Sciences, Inc., Institutional Animal Care and Use Committee.

Chemicals and Reagents. DSS (36,000–44,000 $M_w$) was purchased from American International Chemistry (Natick, MA). It was made up fresh as a 4% solution in distilled water twice a week. Human KGF-2 was purchased from Calbiochem Corp. (San Diego, CA). All other chemical reagents used in MPO measurement (hexadecyltrimethylammonium bromide, o-dianisidine, and hydrogen peroxide) were purchased from Sigma Chemical Co. (St. Louis, MO).

DSS-Induced Colitis. Mice were divided into groups of 10 to 15 animals. All experiments consisted of a normal control group, a DSS control group, and several groups receiving KGF-2 and DSS. Normal controls received regular drinking water throughout the experiment. All other groups were given a 4% solution of DSS ad libitum for at least 7 days, starting on day 0. The volume of water consumed was monitored to ensure that any KGF-2 efficacy observed was not an artifact of reduced consumption of the DSS solution. In survival studies, DSS was given for an additional 1 to 2 weeks. KGF-2 was made up daily from a stock concentration (2.2 mg/ml) stored at 4°C. Mice were given daily injections either i.p. or s.c. starting on day 0 or at some later time point, if a therapeutic time course was being evaluated. Both normal and DSS controls were injected with vehicle instead of KGF-2. At the end of the experiment, on day 7 or later, animals were euthanized with carbon dioxide and necropsied, if colon samples were to be taken. The colon was flushed with saline, divided into three sections, and preserved in formalin for histological analysis. Alternatively, the cleaned distal colon section was frozen in liquid nitrogen and stored at −70°C in preparation for measurement of MPO.

Clinical Parameters. Total body weight was measured 5 days a week. The data are expressed as mean percent change from starting body weight. The following formula was used: [(test day wt − day 0 wt)/day 0 wt] × 100. Weight changes were reported until the number of animals per group dropped to three or fewer.

Mortality rate was tracked daily. For humane reasons, when mice lost more than 25% of their body weight, they were euthanized, included in the mortality column, and excluded from that day's calculation of weight loss.

The stool score, based on a modification of the system outlined by Cooper et al. (1993), was comprised of two parts, totaling a maximum score of 4. Stool consistency was graded as: 0 = firm, 1 = loose, 2 = diarrhea. Blood in the stool was also evaluated on a 0- to 2-point scale. Occult blood kits were used as directed to detect occult blood: 0 = no blood, 1 = occult blood, 2 = gross rectal bleeding. Stool scores were taken at several points throughout the course of the disease.

Histological Evaluation. Histological evaluation of the colon was made via an index devised by Murthy et al. (1993). The colon was flushed with saline and divided into three sections (ascending, transverse, and descending colon) before being preserved in formalin. Four cross-sections from each tissue were prepared, stained with H&E, and evaluated in a blinded fashion for inflammation score and crypt score. Each area of interest was given a raw inflammation score of 0 to 3 and a raw crypt score of 0 to 4. These changes were also scored as to the percent area of involvement according to the scale 1 = 25%, 2 = 50%, 3 = 75%, and 4 = 100%. Raw scores were multiplied by a percent involvement score to get a final inflammation or crypt score totaling 100%. To arrive at the total inflammation or crypt score for a given mouse, final scores for the ascending, transverse, and descending colon were added together. The histological index is as follows: Raw inflammation score—focal infiltrate including polymorphonuclear neutrophils with no disruption of crypt epithelium = 1; mononuclear cell and polymorphonuclear neutrophil infiltrate with crypt epithelium disruption = 2; mucosal ulceration = 3. Raw crypt score—loss of the bottom third of crypt = 1; loss of bottom two-thirds of crypt = 2; loss of entire crypt with surface epithelium remaining intact = 3; loss of entire crypt and surface epithelium (erosion) = 4. Final score = raw score × percent involvement score. Total inflammation/crypt score = final score of ascending + transverse + descending.

MPO Measurement. The distal third of the mouse colon was flushed with saline, frozen in liquid nitrogen, and stored at −70°C until assayed. At that time, it was weighed and added to a tube containing 1 ml of 50 mM potassium phosphate buffer, pH 6.0, plus 0.5% hexadecyltrimethylammonium bromide. The tissue was homogenized for 10 s on ice, sonicated for 30 s, and freeze thawed three times to lyse granules. The tissue homogenate was centrifuged at 1200g for 5 min, and the supernatant was assayed for MPO activity. Substrate for the MPO assay was made by adding 1 µl of hydrogen peroxide and 6.7 µg of o-dianisidine dihydrochloride to 40 ml of the potassium phosphate buffer. Substrate was dispensed in 200-µl aliquots into the wells of a 96-well plate. Five microliters of test supernatant or MPO standard (Calbiochem) was added to the wells containing the substrate. The plate was incubated at room temperature for 15 min and read at 490 nm. Test samples were calibrated against the standard and expressed as nanograms of MPO per milligram of tissue.

Statistics. Student’s unpaired $t$ test was used to analyze MPO levels and to determine significant weight-change differences between the KGF-treated group and the DSS controls. Error bars represent S.E.M. The Mann-Whitney nonparametric test was used to determine significant differences in stool and histological scores. Wilcoxon’s ranked statistical analysis coupled with the SAS Analysis
of Survival Function was used to determine significant differences in survival rates.

Results

Prophylactic Efficacy of KGF-2 on Weight Change in DSS-Treated Mice. DSS exposure and KGF-2 injections were both begun on day 0 and ended on day 7. Weight loss normally occurred 3 to 4 days after initiation of DSS. KGF-2 did not usually eliminate this weight loss but did significantly reduce it. Figure 1 represents the mean weight change from several experiments where DSS and KGF-2 were started on day 0 and continued for 1 week. In all experiments, each group contained 10 animals. The DSS controls averaged an 11% weight loss, whereas the normal controls had a mean weight gain of 3%. Treatment with 0.1 or 0.5 mg/kg of KGF-2 did not reduce the DSS-associated weight loss. The 1-mg/kg dose of KGF-2 reduced weight loss to 9%, which was not significantly different from the DSS controls. However, a KGF-2 dose of 3, 5, or 10 mg/kg significantly reduced weight loss to 5% percent in the case of the 3-mg/kg dose and 3% with the 5- or 10-mg/kg dose.

Prophylactic Efficacy of KGF-2 on Stool Score of DSS-Treated Mice. When mice were exposed to a 4% solution of DSS on day 0, the stool score gradually rose over 1 week to an average score of 3 on a 4-point scale (Fig. 2). Occult blood in the stool was noted by day 4 and diarrhea by day 6. DSS-treated mice that received daily injections of 1, 5, or 10 mg/kg of KGF-2 i.p. from day 0 all had significantly reduced stool scores compared with DSS controls. The separation between scores of the KGF-2-treated and untreated groups was apparent by day 4. Significant improvement was evident by day 6 (Mann-Whitney nonparametric analysis). On day 7, the 10-mg/kg group had a stool score 50% lower than that of the untreated controls, with the 1- and 5-mg/kg groups exhibiting a 30 to 35% reduction in stool score compared with untreated DSS controls. In an additional experiment, a KGF-2 dose of 0.5 mg/kg also significantly reduced stool score, whereas a 0.1-mg/kg dose had no effect (data not shown).

Prophylactic Efficacy of KGF-2 on Histological Score of DSS-Treated Mice. DSS was given from day 0 to day 7, as were daily injections of KGF-2 at 1, 5, or 10 mg/kg i.p., resulting in a dose-dependent reduction in histological score on H&E-stained colon sections. Normal colon sections (Fig. 3, A and B) showed the characteristic intact surface epithelium, well-defined crypt length, and lack of edema and cellular infiltrate in the mucosa and submucosa.

In contrast to the appearance of normal control tissue, the colon tissue from the DSS control group showed a severe mucositis with lesions extensively distributed throughout the mucosa (Fig. 3, C and D). The inflammatory damage was largely restricted to the mucosa layer, although there was some submucosal edema and inflammatory infiltration. Characteristic of DSS-induced pathology was the epithelial destruction, with both surface and crypt epithelial cells detaching or becoming necrotic. In many cases, the mucosa layer was replaced by inflammatory granulation tissue comprised of diffusely proliferating fibroblasts and capillary vessels. Lymphocytes and, to a lesser extent, macrophages comprised the bulk of the inflammatory infiltrate in the granulation tissue, whereas the necrotic epithelial surface tissue contained a high percentage of neutrophils. Vascular dilatation and blood congestion was widely disseminated throughout the lamina propria. In the most severe pathology, diffusely distributed microthrombi were prominent in the lamina propria, with the lumen filled with fibrinoid exudate and necrotic tissue. In such cases, mucosal erosion and superficial ulceration were evident.

The pathology of the colons from mice treated with 5 mg/kg of KGF-2 was mild (Fig. 3, E and F) and similar to the results...
with 10 mg/kg. There was a limited amount of cellular infiltrate and edema in the lamina propria mucosae and submucosa.

Figure 4 depicts inflammation, crypt, and total (inflammation + crypt) score for the full-length colon derived by adding together the scores of the ascending, transverse, and descending colon. In terms of inflammation, the DSS control scored 27 out of 36 because of the massive influx of mononuclear cells and neutrophils. KGF-2 significantly reduced the inflammation score at all doses. At the two upper doses, the score was almost 50% less than that of the controls. In the low-dose group, inflammation was more pronounced and characterized by vessel dilation, edema, and scattered inflammatory infiltrate. In the crypt evaluation, the DSS controls had a score of 28 out of 48, based on the reduction in crypt depth and loss of surface epithelium. Again, at the 5- and 10-mg/kg doses, the scores were reduced by 50%. At the 1-mg/kg dose, crypt score was lower, but not significantly, and localized erosions were evident.

Several investigators have noted that DSS-induced damage is largely confined to the descending and transverse colon, with the ascending colon spared from extensive injury (Okayasu et al., 1990). Our histological evaluation confirms this report. When ascending, transverse, and descending colons were evaluated for inflammation, crypt, and total score, the DSS controls in all of the transverse and descending sections had a similar level of pathology (data not shown). However, the pathology from the ascending colon of the DSS controls was much less severe.

**Lack of Effect of KGF-2 on Weight Change and Gastrointestinal Parameters in Normal Mice.** Despite its activity in DSS-treated mice, KGF-2 (10 mg/kg s.c.) had no
effect on weight change, stool score, or histology score when injected into normal female Swiss-Webster mice for 7 days (data not shown). At the end of the experiment, the weight of the vehicle-treated normal controls remained the same, whereas the KGF-2-treated group had a 1% weight gain. On a scale of 0 to 4, the stool score for both groups was 0.1. On a scale of 0 to 72, the histology score for both groups was less than 2.

**Efficacy of KGF-2 Given in Therapeutic Regimen.**
KGF-2 in all previous studies had been given on day 0, the same time as the DSS treatment. It would be more clinically relevant if drug treatment could be started at some point after disease onset. In the following experiment, KGF-2 was given therapeutically, starting 4 days after initiation of DSS treatment and continued daily over the course of the experiment. DSS treatment was discontinued after 7 days, so that recovery from the DSS-induced colitis could be measured.

Figure 5 shows the weight change in DSS-treated mice, with and without KGF-2. Just as weight loss trailed initiation of DSS treatment by several days, weight loss continued for several days after DSS had been removed. However, animals injected with KGF-2 (3 mg/kg s.c.) on day 4 gained weight at a faster rate than the DSS controls. By day 10, 6 days after the start of drug treatment, KGF-2-injected mice had gained significantly more weight than the DSS controls. This trend continued on day 11, and by day 15, mice treated with 3 mg/kg of KGF-2 had regained all the weight lost in the DSS treatment, whereas the control group still retained a 9% weight loss compared with their starting weight. Low-dose treatment with 0.5 mg/kg of KGF-2 resulted in some weight gain over DSS controls, but this was not significant.

Up to this point, exposure to DSS was terminated after 7 days. Continued treatment with DSS is lethal, and animals begin to die during the 2nd week of exposure. In the following experiment, DSS exposure was begun on day 0 and continued for 15 days to determine whether KGF-2 treatment, started 2 to 4 days after DSS, could protect from the morbidity and mortality associated with prolonged exposure to DSS. Therapeutic treatment with KGF-2 did significantly prolong survival in mice continuously treated with DSS (Fig. 6). Only 1 of the 15 DSS control animals (6%) survived through day 15. Groups treated with KGF-2 (1 or 3 mg/kg) starting on day 2 or 4 all had a significantly better survival rate of 30 to 50%, as measured by the SAS Analysis of Survival Function. All groups treated with KGF-2 also had significantly less weight loss than the DSS controls (Fig. 7). Because of the attrition of the DSS controls, the last comparable time point was on day 11, when the controls showed a weight loss of 20%, whereas all four of the KGF-2-treated groups had significantly less weight loss of 12 to 13%. In addition, the stool scores of mice treated therapeutically with KGF-2 were all significantly lower than those of DSS controls (Fig. 8) by 25 to 50%.

Although KGF-2 at 1 and 3 mg/kg exhibited therapeutic activity when dosing was started on day 2 or 4, there was no effect on DSS-induced weight loss or mortality when dosing was delayed until day 7 (data not shown). There was also no efficacy when prophylactic KGF-2 treatment was administered on the 3 days before initiation of DSS exposure (data not shown). Likewise, no matter when treatment was initiated, a low, 0.5-mg/kg dose of KGF-2 was ineffective in reducing weight loss or mortality (data not shown).

**Effect of KGF-2 on Colon Tissue MPO Levels.** Therapeutic treatment with KGF-2 also was effective in reducing tissue levels of MPO, a marker enzyme for neutrophil presence. In the following experiment, DSS-treated mice were injected daily with KGF-2 (1 and 3 mg/kg s.c.) starting on day 2. DSS was given ad libitum from day 0 to day 10, after which...
1-week model and saw no effect (data not shown). With the Pentney and Bubenik (1995), we tested melatonin in our article reporting on the efficacy of melatonin over 7 weeks two of the drugs of choice in the clinic. In response to a recent dexamethasone or 5-aminosalicylic acid (data not shown), inhibit a characteristic refractory response to treatment. In our 1995).

Results represent mean of at least four animals animals. As the experiment progressed, group size fell as animals died. Injection of KGF-2 was started on day 2 [1 mg/kg s.c. (c) or 3 mg/kg s.c.(●)] or day 4 [1 mg/kg s.c. (●) or 3 mg/kg s.c.(▲)] and continued daily until the end of the experiment. All groups initially started with 15 animals. As the experiment progressed, group size fell as animals died. Results represent mean of at least four animals ± S.E. Statistical significance versus DSS control was calculated with Student’s t test. *P < .05, ***P < .001. , normal; ■, DSS control.

the groups were euthanized. The descending colon was remoted, rinsed in saline, and frozen. The procedure for measuring tissue levels of MPO was followed as described in Materials and Methods. Colons from the DSS controls had an MPO level of 10 ng/mg of tissue, 2-fold higher that of the normal controls (Fig. 9). Colons from the groups treated with 1 and 3 mg/kg of KGF-2 had a significant reduction in MPO activity of 58 to 84%.

Discussion

IBD is a chronic condition characterized by acute flare-ups of the bowel accompanied by an influx of inflammatory cells and the release of inflammatory mediators. The etiology of the disease is unknown, and the treatment is relatively ineffective, based largely on administration of steroids or sulfasalazine (Murthy et al., 1993), although cytokine-related therapy, spurred by the success of anti-tumor necrosis factor (TNF) α treatment, is gaining support (van Dullemen et al., 1995).

Experimental models such as DSS-induced colitis also exhibit a characteristic refractory response to treatment. In our model of DSS, we saw no positive effect after treatment with dexamethasone or 5-aminoalicylic acid (data not shown), two of the drugs of choice in the clinic. In response to a recent article reporting on the efficacy of melatonin over 7 weeks (Pentney and Bubenik, 1995), we tested melatonin in our 1-week model and saw no effect (data not shown). With the exception of a recent report on the activity of the antisense oligo intercellular adhesion molecule (Bennett et al., 1997) and a report on the activity of cyclosporin A (Murthy et al., 1993), there has been little success in identifying positive standards in this model.

However, there are several pieces of evidence that support use of an epithelial growth factor such as KGF-2 in a disease such as IBD, with its inflamed and necrotic gastrointestinal epithelium. One preclinical study demonstrated that the entire length of the gastrointestinal tract is positive for one of the KGF-2 receptors, FGFR-2iiib (Housley et al., 1994). In several clinical studies, KGF-1 tissue levels in IBD patients were found to be elevated over those of normal controls (Finch et al., 1996; Bajaj-Elliott et al., 1997) and were found to correlate with the degree of intestinal inflammation (Brauchle et al., 1996).

In our DSS-induced colitis model, KGF-2 significantly and dose-responsively decreased weight loss, stool score, and histological score when given at the initiation of a 7-day DSS treatment regimen. When DSS exposure was prolonged so that mortality occurred, KGF-2 significantly enhanced survival. KGF-2 also possessed therapeutic activity, significantly reducing mortality, weight loss, stool score, and tissue MPO levels when started 2 to 4 days after initiation of DSS treatment. This therapeutic, as opposed to prophylactic, activity of KGF-2 differentiates it somewhat from KGF-1, which had to be given in a pretreatment regimen to demonstrate efficacy in various models of lung injury induced by hyperoxia (Panos et al., 1995), acid (Yano et al., 1996), bleomycin (Deterding et al., 1996; Yi et al., 1996), and α-naphthylthioare (Mason et al., 1996). The prophylactic activity of KGF-1 has also been reported in models of chemotherapy (Ulich et al., 1997; Farrell et al., 1998) and radiation treatment (Khan et al., 1997).

The exact mechanism of action of KGF-2 is unknown. By histological analysis, it causes proliferation of epithelial tissue in murine wound-healing studies (Jimenez et al., 1997). We have also observed the ability of KGF-2 to induce in vitro proliferation and migration in human Caco-2 cells (D. S. Han, F. Li, L. Holt, and R. B. Sartor, manuscript in preparation), in keeping with the mitogenic activity of KGF-1 reported by others (Housley et al., 1994; Dignass et al., 1994). The presumption is that a wound-healing agent stimulates colonic epithelial cell proliferation and hastens wound closure. As shown in Fig. 3, by maintaining or rapidly reestablishing the integrity of the epithelial mucosa, KGF-2 helped reinforce the barrier function of that tissue, thereby effectively reducing the degree of inflammatory infiltrate. It has been difficult to verify intestinal cell proliferation in vivo, because the background level of colonic proliferation is so high, even in the DSS-treated group. However, in rat studies, KGF-2 enhanced in vivo proliferation of other gastrointestinal tissue, specifically epithelial cells from the salivary glands (S. Strawn, R. Daoud, R. Williams and D. L. Mendrick et al., manuscript in preparation). There is also some preliminary evidence that KGF-2, like KGF-1 (Zeeh et al., 1996), may accelerate goblet cell proliferation, causing an increase in the protective capacity of the mucosal lining of the intestine (D. Mendrick, personal communication).

Despite the efficacy of TNF antibody against Crohn’s disease (van Dullemen et al., 1994, 1995), DSS-induced colitis was not ameliorated by injection of antiserum to TNF (Olson.
et al., 1995). Because the pathology in DSS-induced colitis is not immunologically based, it is not surprising that the model responds to a wound-healing agent like KGF-2 but not to an immunological agent like TNF antibody (Olson et al., 1995). Conversely, a wound-healing agent such as KGF-2, when administered alone, might not be expected to exhibit impressive efficacy in an immunologically driven model of IBD. However, in combination therapy, where different disease targets are simultaneously attacked, KGF-2 and an immunoregulatory compound may have synergistic activity in the treatment of IBD. Future in vitro and in vivo work will focus on a better understanding of the mechanism of action behind the activity of KGF-2 in additional T-lymphocyte-dependent and -independent models of IBD.

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References


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