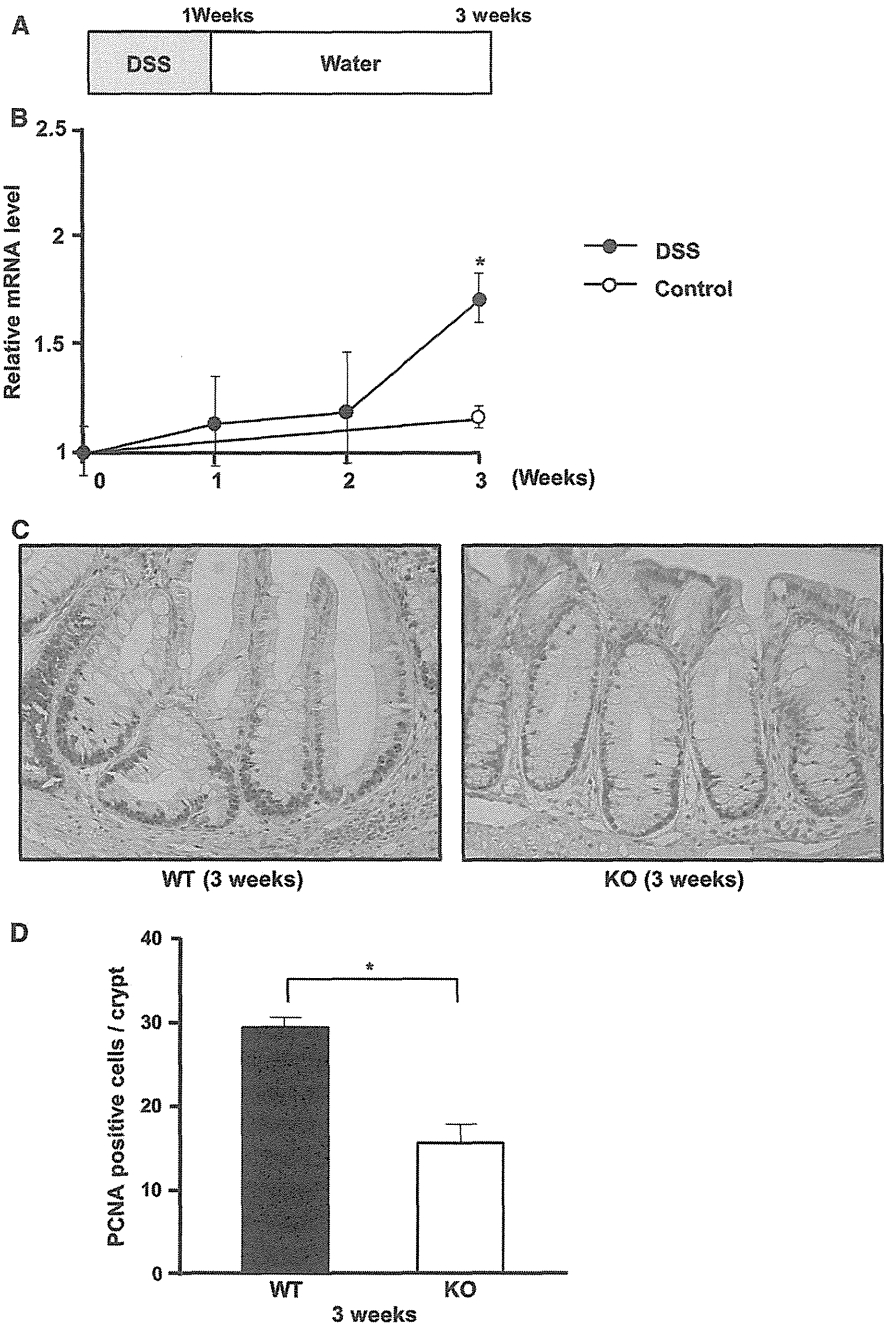

Fig. 4 MFG-E8 was up-regulated during colonic inflammation, while the proliferation of colon epithelial cells was lower in MFG-E8 KO mice as compared to the WT mice. **a** Schematic overview of chronic DSS colitis model. Mice were given 2.5 % DSS in drinking water for 7 days, followed by 14 days of regular water. **b** Time-course change of MFG-E8 mRNA expression in colon tissues ($n = 4$/group), $^*p < 0.05$ vs. control. **c** Representative images showing PCNA staining in the histological sections during the recovery phase of DSS colitis (3 weeks). **d** Average PCNA-positive cells per colon crypt (3 weeks, *blank bar* WT, *black bar* KO), $n = 4$; KO, $n = 4$, $^*p < 0.05$ vs. WT

integrin significantly reduced the proliferation of Colon-26 cells stimulated with rMFG-E8.

Discussion

In the present study, a deficiency of MFG-E8 reduced the incidence and size of colon tumors in a murine CAC model, though the severity of colonic inflammation became severe in MFG-E8 KO mice. On the other hand, experiments using a sporadic colon cancer model showed that MFG-E8 expression influenced tumor growth but not the incidence of tumor development. These findings indicate that MFG-E8 promotes tumor growth regardless of the presence or absence of colonic inflammation, whereas the development of colon tumors is initiated by MFG-E8 under inflammatory conditions.

In the present study, MFG-E8 deficiency exacerbated DSS-induced colitis, which supports our previous report showing the protective effects of rMFG-E8 in mice colitis

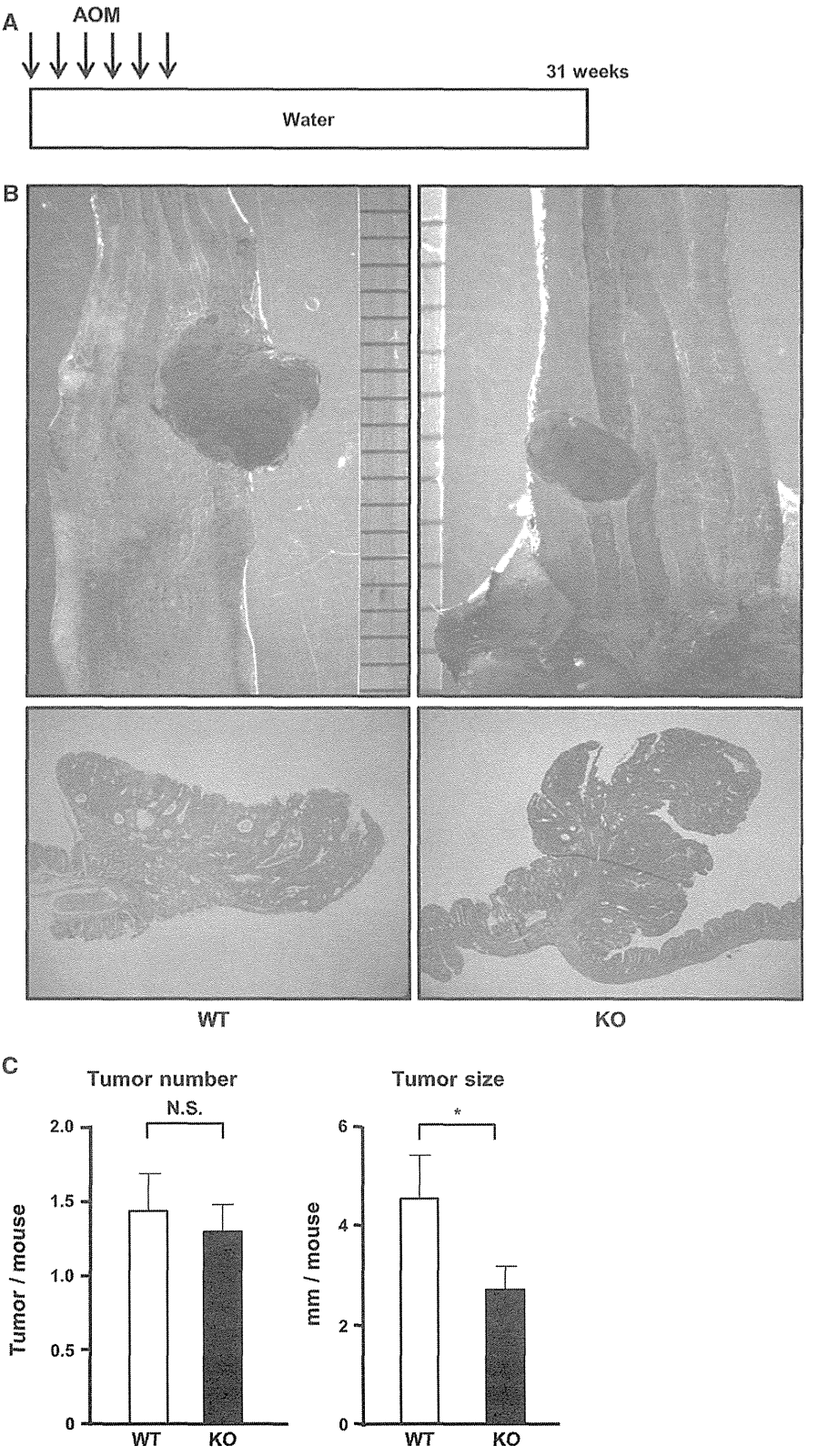

Fig. 5 In the sporadic cancer model, tumors developed in MFG-E8 KO mice were smaller than those in WT mice. **a** Schematic overview of sporadic cancer model. Mice were injected with AOM (10 mg/kg) in an intraperitoneal manner weekly for 6 weeks and euthanized at 31 weeks. **b** Tumor morphology shown by stereoscopic microscopy (*upper* 0.2 % methylene blue staining) and histology (*lower* hematoxylin and eosin (H&E) staining). **c** Average number and size of tumors in WT ($n = 26$) and MFG-E8 KO ($n = 21$) mice. $*p < 0.05$ vs. WT

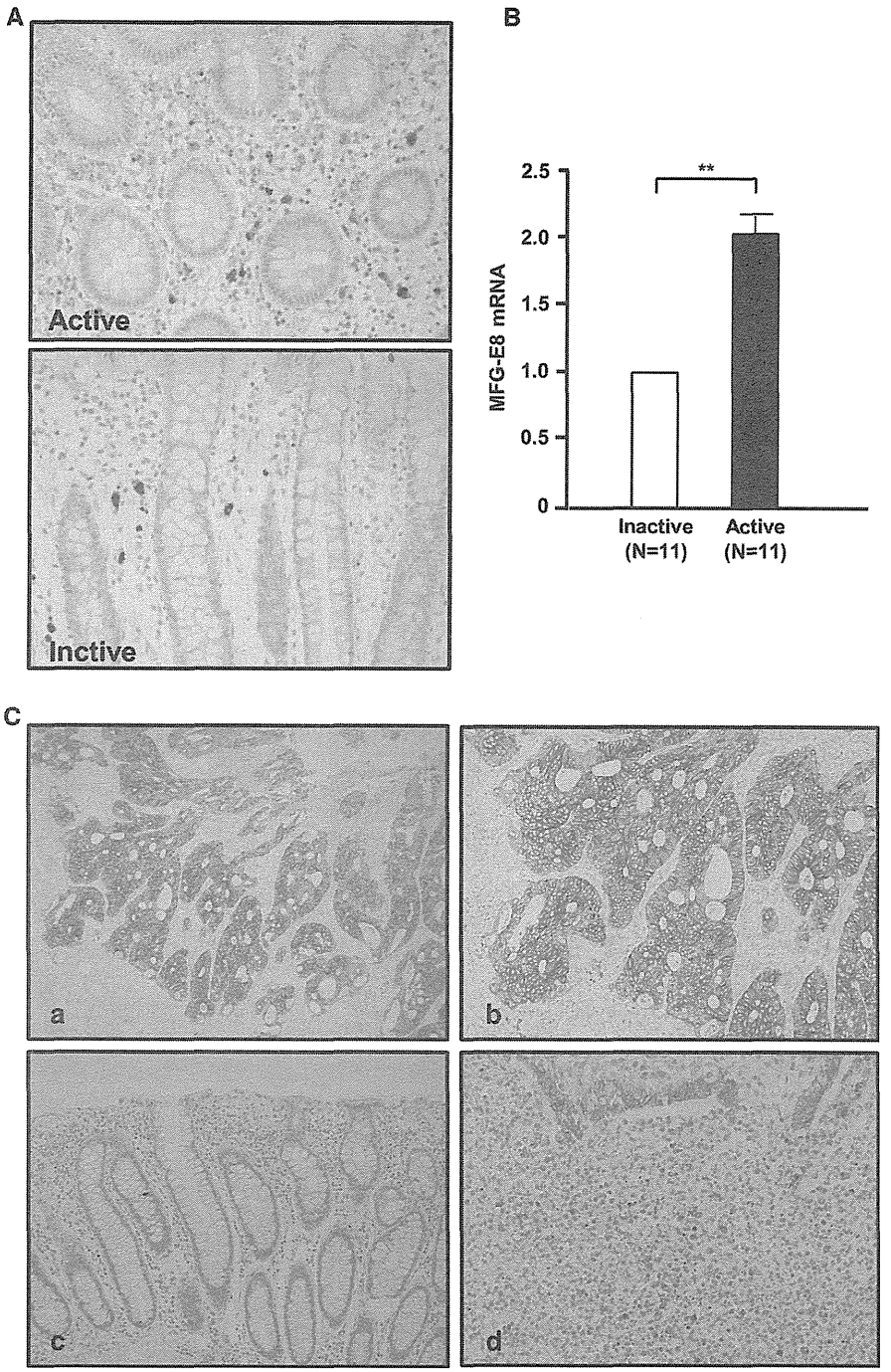

Fig. 6 **A** Increased expression of MFG-E8 in mononuclear cells infiltrating the active mucosa of UC patients. Representative immunohistochemical images of MFG-E8 expression. **B** MFG-E8 mRNA levels in active and inactive colonic tissues, $p < 0.01$ vs. inactive. **C** Abundant expression of MFG-E8 in human colon cancer. Surgically resected human colon cancer tissues were obtained and MFG-E8 expression was examined by immunohistochemistry. Representative images of MFG-E8 expression in colon cancer cells (**a**, **b**), a non-tumorous lesion (**c**), and infiltrating mononuclear cells (**d**)

models. The anti-inflammatory effects of MFG-E8 were also confirmed in I/R- and sepsis-induced intestinal injury models, and mainly dependent on the prompt clearance of apoptotic cells as well as an inhibition of inflammatory cytokines produced by macrophages [17–22]. Apart from the anti-inflammatory effect, MFG-E8 directly regulates epithelial functions including proliferation and apoptosis. Chogle et al. [17] reported that DSS administration induced more severe crypt-epithelial injury with delayed regeneration of colonic epithelium in MFG-E8 KO mice as compared to WT mice. In addition, Ajakaiye et al. found that rMFG-E8 treatment reduced radiation-induced intestinal mucosal damage with improved survival.

Enhancement of the proliferation and anti-apoptotic characteristics of epithelial cells contributes to decrease inflammation and induces repair of inflamed tissues. On the

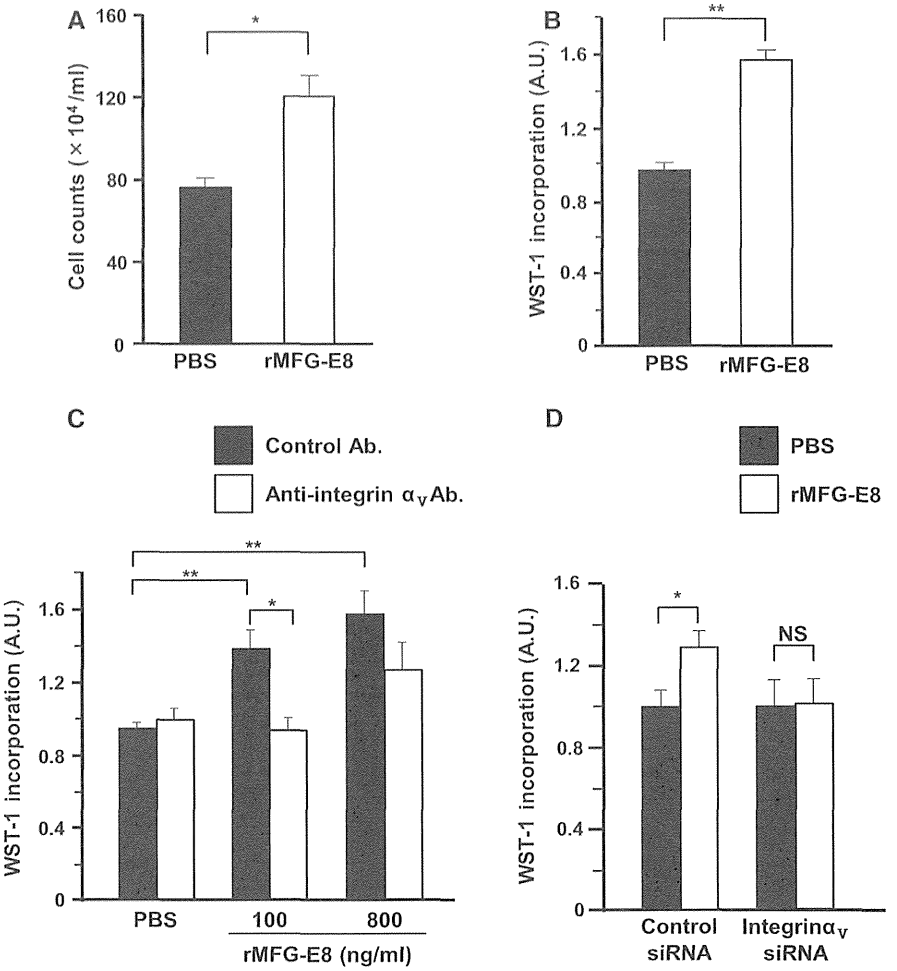

Fig. 7 MFG-E8 was found to promote epithelial cell proliferation via $\alpha_v\beta_3$-integrin. **a**, **b** Colon-26 cells (2×10^5/well) were seeded and treated with rMFG-E8 (400 ng/ml) for 24 h. Cells were counted and a WST-1 assay was assessed, $*p < 0.05$ vs. PBS. *Error bars* indicate SEM values obtained from three independent experiments. **c**, **d** Colon-26 cells (2×10^5/well) were seeded and pre-treated with the neutralizing antibody for α_v-integrin (400 ng/ml) for 3 h or siRNA targeting α_v-integrin for 24 h and then treated with rMFG-E8 (100 or 800 ng/ml) for 24 h. The effect of rMFG-E8 (100 ng/ml) was assessed by a WST-1 assay. $*p < 0.05$, $**p < 0.01$ vs. PBS or control antibody. *Error bars* indicate SEM values obtained from three independent experiments

other hand, those functions also accelerate the development of cancers under chronic inflammatory conditions [32, 34, 36–42]. In the present study, we found that severe colitis developed in DSS-treated KO mice due to the lack of an anti-inflammatory effect of MFG-E8. It is known that CAC development occurs more readily with severe colonic inflammation. However, the number of colon tumors that developed in the present KO mice was lower than that of those in the WT mice, indicating that MFG-E8 deficiency suppressed the potential of inflammation-induced cancer development even under severe colitis condition. PCNA has been identified as an antigen expressed in cell nuclei during the DNA synthesis phase of the cell cycle (G1 to S phase). To further confirm the influence of MFG-E8 on colonic epithelial proliferation, we determined the frequency of PCNA-positive epithelial cells in our DSS-induced colitis model and found that the number of those cells was significantly greater in WT mice as compared to KO mice, which was associated with colonic expression of MFG-E8. Ki67, a nuclear protein expressed from the G1 to M phase, is known as a cellular marker of proliferation. We also examined Ki67 expression in colonic tissues and found it to be increased in WT mice. A recent study showed that MFG-E8 regulates expression of cyclin-dependent kinase (CDK)-3 and enhances proliferation of mammary epithelial cells [25]. On the other hand, p27 and p57 are CDK inhibitors that down-regulate the cell cycle and inhibit excess cell proliferation. We speculate that expression of those CDK inhibitors is accelerated in a homeostatic manner in response to increased epithelial cell proliferation, which may regulate initiation of the process of MFG-E8-related CAC development. We previously reported that MFG-E8 expression is upregulated in mononuclear cells infiltrating the lamina propria during the regeneration phase of DSS-induced colitis [14]. A similar expression pattern was also found in human inflammatory colonic mucosa of UC patients (Fig. 6A). In addition, our present in vitro results clearly showed that MFG-E8 stimulates proliferation of colonic epithelial cells. Taken together, these findings suggest that MFG-E8 secreted by infiltrating inflammatory cells may stimulate epithelial proliferation by regulating several cell cycle-related molecules in a

paracrine manner during colitis, which might enhance the turnover of epithelial cells and initiate CAC development.

In the present study, it is possible that small latent cancer not found macroscopically or by stereoscopic microscopy did not grow to become overt cancer due to reduced cell proliferation in the CAC model KO mice. To examine this issue, sections with tumors (areas around the tumors) as well as serial sections were examined using a histological method. However, no small latent cancer areas or dysplastic epithelial lesions were found, suggesting that MFG-E8 contributes to initiation of CAC development. There are few reports regarding the correlation between MFG-E8 and cancer initiation markers. Ajakaiye et al. [23] reported that treatment with rMFG-E8 increased the expression of p53, bcl-2, and p21 in intestinal epithelial cells, and also enhanced the anti-apoptotic function of those cells. Okuyama et al. [43] revealed that p63, a member of the p53 family, stimulates MFG-E8 expression via p53-binding consensus sequences and/or related sites, which regulates various biological functions including cell proliferation. Although those findings suggest that the expression and function of MFG-E8 associated with p53 or p63 might initiate cancer development, further studies are necessary to clearly explain the role of MFG-E8 in initiation of CAC development.

A few studies that examined the role of MFG-E8 in cancer development without inflammatory stimuli have been presented. Sugano et al. [26] investigated development of carcinogen-induced bladder cancer in MFG-E8 KO mice and found that the extent of tumors, but not their incidence, was significantly lower in KO mice as compared to WT mice. Neutzner et al. [28] used Rip1-Tag2 transgenic mice, a model of pancreas cancer, and established MFG-E8-deficient Rip1-Tag2 mice to examine the role of MFG-E8 in development and growth of pancreas cancer. Tumor growth in their model was lower as compared to the control (Rip1-Tag2 mice), though the incidence of tumors was similar between those strains. We also examined the influence of genetic MFG-E8 ablation on tumor incidence and growth in a sporadic colon cancer model without colitis induction in the present study. Similarly, though the average tumor size was lower in KO mice, we did not find any differences regarding tumor incidence between KO and WT mice. We also found that a deficiency of MFG-E8 significantly decreased tumor growth in the CAC model. Thus, MFG-E8 contributes to the promotion of tumor growth regardless of the presence or absence of inflammation.

Previous studies reported the overexpression of MFG-E8 in advanced tumor cells including breast, bladder, and pancreas cancers, which was associated with tumor growth, invasion, and metastasis [25–30]. Tumor cells overexpressing MFG-E8 show a high growth potential as well as resistance to apoptosis induction in an autocrine manner, and silencing the MFG-E8 gene in those cells inhibits their growth [25, 27, 29]. Although we examined MFG-E8 expression in colon tumors of experimental mice by immunohistochemistry, immunoreactive signals were not detected due to the low affinity of commercially available anti-mouse antibodies to the tissue samples. In this regard, we used surgically resected human colon cancer tissues for immunohistochemistry and found abundant expression of MFG-E8 in tumor and infiltrating mononuclear cells, suggesting that MFG-E8 may promote tumor growth mainly in autocrine as well as paracrine manners. On the other hand, other mechanisms regarding MFG-E8-mediated tumor growth have been reported. Increased expression of MFG-E8 in tumor cells also down-regulates E-cadherin expression, which promotes metastasis by controlling epithelial–mesenchymal transition (EMT) [27]. In addition to the direct effects of MFG-E8 on tumor cells, that secreted from tumor tissues induces angiogenesis by accelerating production of vascular endothelial growth factor (VEGF) [24, 28]. Moreover, MFG-E8 induces the infiltration of Foxp3-positive regulatory T cells (Tregs) in tumor tissues, which increases the extent of tumor proliferation by down-regulating host tumor immunity [26, 27, 29, 30].

$\alpha_v\beta_3$-Integrin is expressed in a variety of cells including macrophages, epithelial cells, and endothelial cells [44]. MFG-E8 binds to $\alpha_v\beta_3$-integrin and contributes to various MFG-E8-induced biological events [6, 7]. Bu et al. [20] observed that treatment with rMFG-E8 enhanced migration of intestinal epithelial cells by activating intracellular protein kinase C (PKC), as well as reorganizing F-actin and Arp2/3 on the cells via $\alpha_v\beta_3$-integrin. Silvestre et al. [24] reported that MFG-E8 induces $\alpha_v\beta_3$-integrin-dependent phosphorylation in endothelial cells and promotes VEGF-mediated neovascularization. In the present study, we clearly demonstrated that MFG-E8-induced proliferation of colonic epithelial cells was dependent on $\alpha_v\beta_3$-integrin expression in those cells. However, further investigations are necessary to clarify the precise mechanisms regarding $\alpha_v\beta_3$-integrin-dependent intracellular signaling in epithelial cells and its association with cancer development.

MFG-E8-blocking therapy may be a double-edged sword, as it may reduce carcinogenesis but enhance colonic inflammation. In this regard, MFG-E8 treatment should be performed to reduce colonic inflammation only in severe phases of UC, as long-term maintenance with this therapy may accelerate CAC development. On the other hand, after development of CAC or sporadic cancers, blocking MFG-E8 function contributes to reduce tumor growth and metastasis by inhibiting cell proliferation and angiogenesis. Further investigations regarding effectiveness and safety are necessary prior to clinical use of the therapy targeting MFG-E8.

In summary, we investigated the role of MFG-E8 in intestinal inflammation and its relationship to tumor development in a murine CAC model. The present results show that MFG-E8 expression is up-regulated in inflamed colonic tissues and initiates CAC development, which may be dependent on increased proliferation of epithelial cells via $\alpha_v\beta_3$-integrin. Furthermore, MFG-E8 promoted tumor growth in both our CAC and sporadic colon cancer models. These results are the first to show the role of MFG-E8 in the pathogenesis of colon cancer. For development of a novel therapy targeting MFG-E8, additional findings regarding the various physiological, immunological, and clinical aspects must be evaluated in the future.

Conflict of interest Kinoshita Y, Kusunoki R, Ishihara S, Oka A, Sonoyama H, Tada Y, Fukuba N, Oshima N, Moriyama I, Yuki T, and Kawashima K received research grants from Daiichi-Sankyo Pharm, Takeda Pharm, Astellas Pharm, AstraZeneca KK, Mitsubishi Tanabe Pharm and Eisai Pharm. Kinoshita Y received honoraria for lecture fees from Daiichi-Sankyo Pharm, Takeda Pharm, Astellas Pharm, AstraZeneca KK, and Eisai Pharm.

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REVIEW

Clinical features of eosinophilic esophagitis: Differences between Asian and Western populations

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Key words
Asian populations, endoscopic findings, eosinophilic esophagitis, epidemiology, esophageal eosinophilia.

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Abstract

The prevalence and incidence of eosinophilic esophagitis (EoE) have been rapidly increasing in Western countries. It is thought to be more common among Caucasians than other racial or ethnic groups, but epidemiological studies have not been fully evaluated in Asian populations, and its clinical manifestation is rarely documented. In this review, recent reports regarding EoE in Asian countries have been collected, and differences in the clinical features, including symptoms and endoscopic findings, between Asian and Western populations have been evaluated. In Asia, EoE is still much less prevalent than in Western countries. Baseline values for average age, male/female ratio, and personal history of allergic disease were comparable to those in Western populations. Predominant symptoms were dysphagia, and food impaction was extremely rare among Asian patients. Although the frequency of abnormal endoscopic findings varies among studies, over 90% of patients with EoE have shown abnormal findings such as linear furrow, which is the most common findings, in recent prospective studies in Asia. There are few reports regarding the treatment of EoE and no prospective studies evaluating drugs or elimination diet in patient with EoE have been reported in Asia. Overall, EoE had similar clinical characteristics in Asian populations. Because the incidence of EoE could increase in the future with the increase in allergic disorders in Asian countries, large-scale, nationwide prospective studies should be performed to more fully understand the epidemiology and pathophysiology of EoE in Asian populations.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder characterized by dense eosinophilic infiltration of the esophageal epithelium without infiltration of other parts of the gastrointestinal tract.[1,2] It is a relatively new disease entity first described by Landres *et al.* in 1978,[3] and increasingly recognized over the past decade. The incidence and prevalence of EoE have been rapidly increasing, especially in Western countries,[4,5] and it has become a major cause of gastrointestinal morbidity among children and adults. Cases of EoE have been reported from all continents except Africa. The clinical characteristics of EoE have been extensively investigated in Western countries, but not other countries.[2,6] The first case of a Japanese patient with EoE was reported in 2006.[7] Since then, it appears that cases of EoE are increasingly reported from other Asian countries, including South Korea,[8] China,[9] Thailand,[10] India,[11] Turkey,[12] and Saudi Arabia.[13] However, the disease is recognized as a rare condition and its epidemiology has not been fully estimated in Asia.

EoE is clinicopathological disease that is diagnosed by symptoms related to esophageal dysfunction accompanied by more than 15 intraepithelial eosinophils/high-power field (HPF) in at least one biopsy specimen without pathogenesis of gastroesophageal reflux disease (GERD) as shown by lack of response to high-dose proton-pump inhibitor (PPI) medication.[14,15] The presenting symptoms in patients with EoE can differ between children and adults.[16] Children often have symptoms of feeding intolerance, vomiting, and failure to thrive, while adults usually have symptoms of dysphagia, food impaction, heartburn, and chest pain. Moreover, a variety of clinical features by racial and ethnic differences have been reported. Solid food dysphagia is reported to be more common among white patients, whereas reflux symptoms are more common in black/Hispanic patients.[17] On the other hand, Sperry *et al.* reported that the majority of symptoms, endoscopic findings, and histological features were not different between Caucasians and African American subjects.[18] It remains to be elucidated if there is a difference between Asian and non-Asian populations because most current knowledge about EoE in Asian population is based on case reports and small case series. However, it is of importance to identify the clinical features, including presenting symptoms and endoscopic findings, in Asian populations in the context of growing recognition of EoE widely in Asia.

We review the present status of EoE in Asia and discusses the differences in the clinical features of Asian and Western populations.

Epidemiology

Prevalence. The prevalence of EoE varies on the basis of study design and setting, and most of the studies have reported from Western countries. In the general population, case estimates have ranged from 0.2 to 4/1000 in asymptomatic patients,[5,19,20] but in those undergoing endoscopy for upper gastrointestinal (UGI) symptoms, EoE is found in 5–16%.[4,21,22] Current estimates suggest that the overall prevalence of EoE in Western population is between 43 and 56.7/100 000.[23–25] In Japan, the first EoE case was reported by Furuta *et al.*[7] in 2006, and since then the cases have been reported increasingly.[26,27] Likewise, the number of case reports regarding EoE in other Asian countries has been gradually increasing from 2009.[8,10,11,13] To date, nine epidemiological studies have been conducted in Asian countries (Table 1). The first prospective study carried out in 23 346 patients who had underwent routine esophagogastroduodenoscopy (EGD) in Japan estimated 0.02% (17.1/100 000),[28] which was much lower than the reports from Western countries. These data indicate that EoE could be found in approximately 1 in 5000 endoscopy-investigated cases. Consistently, studies have reported that the prevalence of EoE ranges from 0.01% to 0.13% in patients who undergo EGD.[32–34] There have been a few studies evaluating the presence of EoE in patients with UGI symptoms, such as dysphagia and heartburn. A prospective Korean study reported a prevalence of EoE among patients with esophageal or UGI symptoms as 6.6% (8/122).[30] In a Turkish study, the frequency of EoE in patients with esophageal symptoms was 2.6% (8/311).[31] We recently evaluated the prevalence of esophageal eosinophilia (EE), which is a pathological hallmark of EoE, among esophageal symptoms and found eight patients (2.5%) among 319 with esophageal symptoms.[35] These data indicate that the prevalence of EoE with UGI symptoms may not be so low as compared with Western countries. The mean age at diagnosis of EoE in adults ranges from 40 to 63 years, so it is frequently observed in middle-aged persons (Table 2). The difference is a somewhat older age of Asian patients with EoE as compared with Western patients.[38] Similar to Western reports, EoE is more common in males (50–100%). Only one study of the prevalence of EoE in children has been reported, from Saudi Arabia in 2012.[29] That study found 18 patients among 2127 EGD cases for UGI symptoms who were diagnosed as EoE, constituting 0.85% of the total number of patients. The prevalence of EoE in children has never been reported in East Asian countries. Collectively, EoE and EE are still rare in the general Asian population, but clinicians should be aware of EoE in patients with UGI symptoms.

Allergic status. EoE is considered to be an allergy-associated inflammatory disorder, possibly caused by antigens in the air and food. Indeed, cases of EoE are frequently associated with atopic disorders, as affected individuals often have coexistent bronchial asthma, allergic rhinitis, atopic dermatitis, and various food or drug allergies.[39,40] The frequency of allergic diseases in patients with EoE as a comorbidity in Asian populations

Table 1 Prevalence of EoE and EE in Asian countries

Study (published year)	Study period	Country	Study method (adults/children)	Sample size	No. of patients (M/F)	Prevalence
Fujishiro *et al.*[28†] (2011)	2010	Japan	Multicenter, prospective (adults)	23 346 (endoscopy cases)	4 (2/2)	0.02%(17.1/100 000)
Saadah *et al.*[29] (2012)	2002–2011	Saudi Arabia	Multicenter, retrospective (children; < 18 years)	2 127 (endoscopy cases)	18 (13/5)	0.85%
Joo *et al.*[30] (2012)	2009	South Korea	Single center, prospective (adults)	122 (UGI symptoms)	8 (5/3)	6.6%
Shi *et al.*[9†] (2012)	2006–2010	China	Single center, retrospective (adults)	3 490 (esophageal biopsy cases)	12 (7/5)	0.34%
Altun *et al.*[31] (2013)	2010–2011	Turkey	Single center, prospective (adults)	311 (UGI symptoms)	8 (4/4)	2.6%
Fujiwara *et al.*[32†] (2012)	2010–2011	Japan	Multicenter, prospective (adults)	13 634 (endoscopy cases)	7 (7/0)	0.05% (EE) 0.01% (EoE)
Tomomatsu *et al.*[33†] (2013)	2010–2011	Japan	Single center, retrospective (adults)	7 557 (endoscopy cases)	10 (7/3)	0.13%(132.3/100 000)
Hori *et al.*[34] (2014)	2010–2012	Japan	Single center, prospective (adults)	2 545 (endoscopy cases)	2	0.08%
Shimura *et al.*[35†] (2014)	2011–2012	Japan	Multicenter, prospective (adults)	319 (UGI symptoms)	8 (4/4)	2.5%

†Including cases of PPI-responsive esophageal eosinophilia.
EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; PPI, proton-pump inhibitor; UGI, upper gastrointestinal.

Table 2 Characteristics and clinical presentation of adult patients with EoE and EE in Asia

Study	Year	Country	No. of patients	Age, years		Male sex		Heartburn	Dysphagia	Food impaction	Allergy
				Mean	Range	*n*	%	*n*	*n*	*n*	*n*
Abe *et al.*[26†]	2011	Japan	12	47.7	32–68	9	75	1 (8.3%)	7 (58.3%)	0	3 (25%)
Fujishiro *et al.*[28†]	2011	Japan	4	63.3	51–83	2	50	2 (50%)	1 (25%)	1 (25%)	NR
Joo *et al.*[30]	2012	South Korea	8	41.1	25–61	5	62.5	4 (50%)	3 (37.5%)	2 (25%)	NR
Shi *et al.*[9†]	2012	China	12	51.4	29–71	7	58.3	2 (16.7%)	4 (33.3%)	0	NR
Altun *et al.*[31]	2013	Turkey	8	40.2	27–52	4	50	7 (87.5%)	1 (12.5%)	0	3 (37.5%)
Fujiwara *et al.*[32†]	2012	Japan	7	50.3	37–70	7	100	3 (42.9%)	(3)[‡]	(3)[‡]	4 (57.1%)
Tomomatsu *et al.*[33†]	2013	Japan	10	47.5	26–73	7	70	3 (30%)	4 (40%)	2 (20%)	9 (90%)
Kinoshita *et al.*[36†]	2013	Japan	26	49	25–70	20	76.9	2 (7.7%)	12 (46.2%)	0	13 (50%)
Lee *et al.*[37†]	2013	South Korea	8	40.0	19–60	6	75	1 (12.5%)	6 (75%)	0	5 (62.5%)
Shimura *et al.*[35†]	2014	Japan	12	49.3	24–82	7	58.3	4 (33.3%)	5 (41.7%)	0	3 (25.0%)

[†]Including cases of PPI-responsive esophageal eosinophilia.

[‡]Cases of dysphagia or food impaction.

EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; NR, not reported; PPI, proton-pump inhibitor.

is shown in Table 2. Although the association of a history of allergic diseases and EoE varies among studies because of small sample sizes, approximately half of the Asian patients have a history of allergic disease that is similar to reports from Western populations.

Foods have been shown to be an important cause of EoE through the use of elimination diets or elemental formulas in both pediatric and adult patients.[41,42] On the other hand, seasonal variation in esophageal mucosal eosinophilia and incidence is described, suggesting a correlation with seasons of more intense allergen exposure.[43–45] Although patients with EoE are frequently positive for allergy testing such as skin prick test and serum antigen-specific IgE antibody, the clinical significance of these tests for management of EoE remains controversial. Both laboratory-based research and clinical studies have indicated a strong role for the non-IgE-mediated T-helper 2 (Th2)-delayed hypertensive response in EoE.[46,47] Therefore, the usefulness of allergy testing for EoE may be limited. Indeed, Gonsalves *et al.* recently demonstrated that skin prick testing predicted only 13% of food-associated cases of EoE.[41] Because there are no reports evaluating the efficacy of food elimination diets for patients with EoE in Asian countries, it remains unclear how food and/or aeroallergens affect patients with EoE in Asia. We have recently evaluated the possible involvement of food and/or aeroallergen factors in EoE using serum antigen-specific IgE antibodies in a Japanese population.[48] Consistent with the higher levels of serum total IgE antibodies, patients with EoE were frequently sensitized to multiple antigens. However, no particular antigen causing EoE was detected by measuring serum antigen-specific IgE antibodies.

Helicobacter pylori *infection.* Reduced exposure to microorganisms during childhood may result in failure to activate the Th1 immune response, leading to an imbalance between the Th1 and Th2 immune responses and a predisposition to develop allergic disorders that are triggered by altered or missing innate immune cell activation. This concept is termed the "hygiene hypothesis"[49] and provides a general explanation for the increase in allergic diseases, including EoE, parallel to the decrease in infectious diseases. Of note, early life exposure to *H. pylori* infection has been inversely associated with conditions such as asthma and allergic rhinitis,[50–52] and a decrease in *H. pylori* infections may predispose individuals to various allergic diseases. Recent study has suggested that *H. pylori* infection is inversely associated with EE.[53] However, there are few reports of the relationship between EoE and *H. pylori* infection in either Western or Asian populations.[54] Furuta *et al.* recently investigated the possible influence of *H. pylori* infection on EoE in Japanese patients by case–control study.[55] In that study, 22.3% of the patients with EoE were infected with *H. pylori*, as compared with 55.5% of their age- and sex-matched healthy controls. The odds ratio for EoE patients to have *H. pylori* infection was 0.22, which was significantly lower in EoE and consistent with reports regarding other allergic diseases. Because the recent increase in EoE might be related not only to *H. pylori* infection, but also to changes in the social environment,[25] large-scale and multicenter studies should be carried out to further determine the relation between *H. pylori* and allergic disorders.

Diagnosis

Symptoms. EoE is one of most the common causes of intermittent solid-food dysphagia or food impaction in adults in Western countries. In 10 studies evaluating the symptoms of patients with EoE in Asia, the most common presenting symptom was dysphagia (Table 2). Interestingly, food impaction was very rare in contrast to Western reports. Moreover, most of the Asian reports show no severe progressive cases, such as complete obstruction or long segment obstruction. We recently demonstrated that none of the presenting symptoms, including dysphagia, heartburn, and chest pain, was useful for diagnosis of EoE by logistic regression analysis.[35] Consistently, Mackenzie *et al.* prospectively assessed the risk factors and prevalence of EoE in an adult population with dysphagia.[21] Of 261 patients enrolled, 31 (12%) met the pathological criteria for EE, but EE was found only in five cases (1.9%) with normal endoscopic findings, suggesting that endoscopic abnormal findings suspicious of EoE are more important and effective for predicting EoE than esophageal symptoms.

Table 3 Endoscopic findings of adult patients with EoE and EE in Asia

Study	Year	Country	No. of patients	Abnormal EGD findings	Type of findings			Normal EGD findings
					Linear furrows	Rings	Whitish exudate	
Abe *et al.*[26†]	2011	Japan	12	11 (91.7%)	10 (83.3%)	10 (83.3%)	9 (75%)	1 (8.3%)
Fujishiro *et al.*[28†]	2011	Japan	4	4 (100%)	2 (50%)	1 (25%)	3 (75%)	0
Joo *et al.*[30]	2012	South Korea	8	6 (75%)	2 (25%)	2 (25%)	3 (37.5%)	2 (25%)
Shi *et al.*[9†]	2012	China	12	9 (75%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	3 (37.5%)
Altun *et al.*[31]	2013	Turkey	8	4 (50%)	0	2 (25%)	2 (25%)	4 (50%)
Fujiwara *et al.*[32†]	2012	Japan	7	7 (100%)	6 (85.7%)	3 (42.9%)	3 (42.9%)	0
Tomomatsu *et al.*[33†]	2013	Japan	10	10 (100%)	10 (100%)	3 (30%)	6 (60%)	0
Kinoshita *et al.*[36†]	2013	Japan	26	15 (57.7%)	9 (34.6%)	5 (19.2%)	6 (23.1%)	11 (42.3%)
Lee *et al.*[37†]	2013	South Korea	8	7 (87.5%)	6 (75%)	4 (50%)	0	1 (12.5%)
Hori *et al.*[34†]	2014	Japan	5	5 (100%)	3 (60%)	3 (60%)	2 (40%)	0
Shimura *et al.*[35†]	2014	Japan	12	11 (91.7%)	10 (83.3%)	3 (25.0%)	4 (33.3%)	1 (8.3%)

†Including cases of PPI-responsive esophageal eosinophilia.
EE, esophageal eosinophilia; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; PPI, proton-pump inhibitor.

Endoscopic findings. There are a number of reports of the endoscopic features of EoE in Western patients, which include esophageal rings, linear furrows, whitish exudates, and stenosis.[56,57] Endoscopic findings may differ by race. Bohm *et al.* reported that normal endoscopy and reflux changes were more common in black/Hispanic patients, whereas linear furrows and rings were more common in white patients.[17] Eleven studies have evaluated the endoscopic features of patients with EoE in Asia (Table 3). In most of them, > 75% of patients with EoE had abnormal endoscopic findings. In contrast, according to the report with the largest number of EoE cases in Asia, 11 (42.3%) of 26 patients had a normal-appearing esophagus.[36] The study was based on a questionnaire administered to patients with EoE who had been diagnosed from 2004 to 2009. Thus, the results may reflect a lack of awareness of the disease because most of the Asian studies have been published since 2011. According to a recent meta-analysis, in prospective studies, at least one abnormality was detected by endoscopy in 93% of EoE patients.[58] Consistent with that, more recent prospective studies conducted in Japan have shown endoscopic abnormalities in 91.7% to 100% of the patients with EoE.[32–35] In those studies, linear furrows were the most frequently found endoscopic abnormality in patients with EoE and/or EE, suggesting that endoscopic abnormal findings suspicious of EoE, especially linear furrows, can be detected in most of the patients with EoE by experienced endoscopists with careful observation using a high-resolution endoscope or narrow band imaging endoscopy[59] (Fig. 1). Miller *et al.* reported that upper endoscopy with biopsy for EoE appears to be a cost-effective approach in patients when the prevalence of EoE is 8% or greater.[60] Thus, a biopsy may not be recommended for the evaluation of patients with esophageal symptoms but no endoscopic abnormalities.

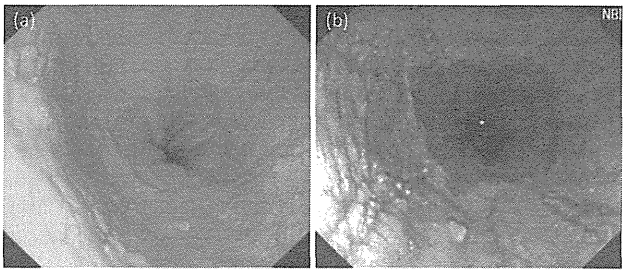

Figure 1 Endoscopic finding of linear furrows in patients with eosinophilic esophagitis. (a) Conventional endoscopy and (b) narrow-band imaging endoscopy.

Cytokine expression. The results of genome-wide association study (GWAS) have implicated the 5q22 locus in the pathogenesis of EoE and identify thymic stromal lymphopoietin (*TSLP*) as the most likely candidate gene in the region.[61] TSLP is an interleukin (IL)-7-like cytokine that is a critical factor linking responses at interfaces between the body and environment (skin, airway, gut, ocular tissues, etc.) to Th2 responses. Stimulated Th2 lymphocytes produce IL-5 and IL-13, and dendritic cells produce IL-15. Then, IL-13 and IL-15 increase eotaxin-3 production by esophageal epithelial cells. Eotaxin-3 is a potent chemokine that facilitates the trafficking of eosinophils from peripheral blood to the esophageal epithelium. Moreover, genetic polymorphism in the human gene *CCL26* (eotaxin-3) has been found to be associated with increased susceptibility for EoE.[62] Indeed, patients with EoE have been reported to have higher concentrations of these cytokines in peripheral blood than normal individuals.[46,63,64] However, the expression of these cytokines in patients with EoE in Asian populations has not been fully evaluated. Kinoshita *et al.* investigated plasma concentrations of these cytokines (TSLP, IL-5, IL-13, IL-15, eotaxin-3) in 18 Japanese EoE patients.[65] Consistent with previous reports, they found that plasma concentrations of IL-5 and IL-15 were significantly higher in EoE patients as compared with healthy controls. Although the diagnostic value of cytokine measurement is limited because of the large overlap between patients and controls, the similar responses suggest a similar role for these cytokines in EoE in both Asian and Western populations. Likewise, a single nucleotide polymorphism in the TSLP locus has been reported to be associated with adult asthma in populations of both Japanese and non-Hispanic individuals of European ancestry.[66] GWAS of EoE in Asian populations is needed for future research.

Table 4 Treatment of adult patients with EoE and EE in Asia

Study	Year	Country	No. of patients	PPI responsive	PPI non-responsive			No treatment
					Topical steroid	Oral steroid	Others	
Abe *et al.*[26†]	2011	Japan	12[‡]	5	2	0	0	3
Fujishiro *et al.*[28†]	2011	Japan	4	2	1	0	0	1
Shi *et al.*[9†]	2012	China	12[‡]	7	—	—	—	3
Fujiwara *et al.*[32†]	2012	Japan	7	3	1	0	1	2
Tomomatsu *et al.*[33†]	2013	Japan	10	2	0	3	1	4
Kinoshita *et al.*[36†]	2013	Japan	26	4	(16)[§]	(16)[§]	—	4
Lee *et al.*[37†]	2013	South Korea	8	4	0	3	0	1

[†]Including cases of PPI-responsive esophageal eosinophilia.

[‡]Two cases not treated by PPI.

[§]Sixteen cases treated either by topical or oral steroid.

—, data not shown; EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; PPI, proton-pump inhibitor.

Treatment

At present, there is no standardized treatment for EoE, and different therapeutic regimens have been used for patients with EoE in Asia. Treatment for EoE has been described in seven case series studies (Table 4). Importantly, all these studies included PPI-responsive symptomatic patients with esophageal eosinophilic infiltration greater than 15–20 eosinophils/HPF, possibly because of the small sample sizes. This condition is referred to as "PPI-responsive esophageal eosinophilia" (PPI-REE),[14,15] and is diagnosed when a trial of PPI improves symptoms and eosinophilic infiltration in patients with clinical characteristics similar to EoE.[67,68] Initially, PPI-REE was considered to be a separate entity from EoE. To distinguish EoE from other causes of EE, including GERD and PPI-REE, the guideline strongly recommends that patients with suspected EoE should be given a 2-month course of a PPI followed by endoscopy with biopsies. However, as EoE has become more widely recognized, it has also become increasingly evident that the distinction between EoE and GERD is not always clear.[69,70] Moreover, the pathogenesis of PPI-REE remains unclear.[71] Because of the potential mechanism that gastric acid plays a role in the pathogenesis of EoE and that PPIs have anti-inflammatory actions independent of their effects on gastric acid secretion,[72–74] EoE patients might benefit from PPI therapy whether or not they have coexisting GERD. More studies are sorely needed to recognize, define, and mechanistically understand PPI-REE.

As for PPI non-responsive patients diagnosed as having typical EoE, topical or oral steroids have been used as treatment in several cases. Because of the rareness of EoE patients with food impaction or other severe complications in Asia, intensive treatment such as esophageal dilatation or surgical operation has not been reported. Administration of steroid has been effective for most of the patients with EoE regarding symptoms and endoscopic findings; however, prognosis remains obscure. Although oral topical steroids can be effective in limiting EoE-associated inflammation, there are concerns regarding the long-term use of steroids, particularly in children. Adherence to an elemental diet that eliminates exposure to foods that trigger EoE results in resolution of symptoms in many patients; however, this approach requires disruptive changes in lifestyle and eating habits. The effect of elimination diet therapy remains to be elucidated in Asia. Thus, there is a need to identify the effect of diet therapies for Asian patients, who have different dietary habits from those in Western countries.

Conclusion

The findings of a thorough review of the medical literature reported in Asian countries suggest that EoE affects middle-aged men who have an allergic predisposition that is similar to the clinical features of patients in Western populations. Dysphagia is a more common symptom than food impaction, and the complication of food bolus obstruction has not been reported, suggesting that the clinical presentation of EoE in Asian patients is milder than in Western patients. Typical endoscopic findings include linear furrows, rings, and whitish exudates. Most of the recent studies have shown endoscopic abnormalities in over 90% of patients with EoE in Asia. Although case series have been reported increasingly, larger scale, nationwide studies should be performed in Asian populations.

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臨床各科
差分解説

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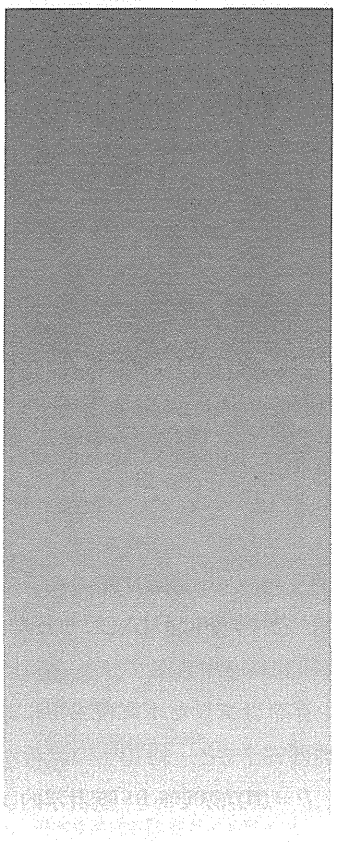

差分【さぶん・patch】
一旦完成したプログラムの一部を修正すること。また，修正を行うために変更点（差分情報）のみを抜き出して列挙したファイル。「パッチファイル」「差分ファイル」などとも呼ばれる。バグ（不具合）の修正や，小規模なバージョンアップなどを行う際に，ソフトウェア全体を入れ替えるのは効率的でないため，修正点だけを抜き出してパッチ作成し，これを既存のソフトに組み込むことで修正を行う。
（IT用語事典 e-Wordsより引用）

■内科：消化器

好酸球性食道炎

日本でも胃食道逆流症（GERD）が増加し，人口の約20％にGERDがみられると報告されている。胸焼け，胸がつまった感じ，食べ物のつかえ感などはGERDの代表的な症状であるため，これらの症状があるとGERDを疑い，内視鏡検査で食道びらんがあれば逆流性食道炎，なければ非びらん性胃食道逆流症（NERD）と診断される。

最近，食物抗原を主なアレルゲンとして食道粘膜に起こる遅発性のアレルギー疾患として，好酸球性食道炎の増加が注目されている。数年前までわが国では1例ずつの症例報告が主であったが，最近では数例まとめた報告が多数みられるようになった。花粉症，喘息などのアレルギー疾患同様，急速に増加しているようである。

患者は何らかのアレルギー疾患を有する中年男性が多く，GERD例と区別が難しい症状を訴えるが，食べ物が胸につまると訴える頻度が高い。内視鏡検査で発見される最も特徴的な異常は食道の縦走溝と呼ばれる細く長い縦長の陥凹である。この陥凹を逆流性食道炎のびらんと見間違えないようにしないといけない。食道粘膜を生検すると上皮内に多数の好酸球の浸潤がみられるため診断がつく。ただし，好酸球の組織内分布は均一ではないため，数個採取することが必要である[1]。

治療はGERDと同様，プロトンポンプ阻害薬（PPI）を投与することで症状と異常所見が改善する例もあるが，喘息の吸入治療で用いられる局所作用型ステロイドが必要となることも多い。

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1) Kinoshita Y, et al:J Gastroenterol. 2013;48(3):333-9.

【解説】
木下芳一　島根大学第二内科教授

序　文

疾患の頻度は時代とともに移り変わっていく．日本においても，その頻度が急速に増加していた動脈硬化を原因とした心筋梗塞や脳梗塞・出血は減少の兆しがみえている．また，胃がんや肝臓がんは少なくなり，悪性腫瘍全体をみても頭打ちとなってきたように思える．一方で気管支喘息，アトピー性皮膚炎，アレルギー性鼻炎，食物アレルギーなどのアレルギー疾患が増加している．アレルギー疾患は動脈硬化性疾患や悪性腫瘍と違って，社会的に活動性の高い若年者に発症しやすいことが大きな問題である．アレルギー疾患の増加は，先進国から始まり徐々に発展途上国にまで広がりつつある．好酸球性消化管疾患は以前からその存在が知られていたが，頻度は高いものではなかった．ところが1990年代の初めから，欧米を中心に好酸球性消化管疾患の中でも特に，好酸球性食道炎の急激な増加が報告されるようになってきた．現在欧米では，上部消化管の内視鏡検査受検例のうち200人に1人が好酸球性食道炎と診断される時代になっている．日本では従来，好酸球性胃腸炎の報告は比較的多かったが，最近では好酸球性食道炎の報告も珍しくなくなってきている．すなわち，日本においても欧米の現状を追いかけるように，消化管疾患の中で腫瘍，感染症，機能性疾患とともにアレルギー疾患を含む炎症性疾患の重要性がますます大きくなってきている．

好酸球性食道炎，好酸球性胃腸炎を含む好酸球性消化管疾患は主に食物がアレルゲンとなって発症する遅延型のアレルギー疾患であると考えられているが　その病態の解析は始まったばかりであり，診断方法も治療方法もやっとコンセンサスが得られつつある状況である．診断と治療の方法は確立，統一の途上ではあるが，患者数は増加しており診療の現場では最新情報の普及と早急な診療指針の確立が必要となっている．そこで本書は，厚生労働省の好酸球性消化管疾患の研究班で様々な検討を行っておられる専門の先生方を中心に，好酸球性消化管疾患の疫学，病態，診断，治療，予後，鑑別すべき類縁疾患に関する最新情報を診療の現場で役立つように，わかりやすくまとめていただいた．

本書を通読していただくと，好酸球性消化管疾患の全体像がつかめるとともに，好酸球性食道炎の診断は内視鏡像に精通し生検を積極的に行えば難しくないこと，好酸球性食道炎と比べて好酸球性胃腸炎の診断は難しいこと，組織所見で胃腸の粘膜に浸潤好酸球が多いというだけでは好酸球性胃腸炎の診断をつけることができないこと，好酸球性胃腸炎の診断のためには綿密な鑑別診断とそれに加えて詳細な経過観察が必要であること，治療は好酸球性食道炎も好酸球性胃腸炎も確立していないこと，などを理解していただける構成となっている．

好酸球性消化管疾患に関する研究は急速に進行しており，日本においても疾患の本態を把握して発症リスクを判定することを目指したgenome-wide association study（GWAS），簡便な診断のための血液バイオマーカーを同定するための多施設研究，根本治療を目指した6食材除去食を用いた治療の試みなど多数の研究が行われている．本書を読破して好酸球性消化管疾患の基本知識を得たのちに原著論文にあたっていただき，診療の現場に最新の研究成果を反映させるように努力していただければ幸いです．

2014年6月

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木下芳一

【講　座】　好酸球性食道炎・胃腸炎の診断と治療

木下（きのした）　芳一（よしかず）
（島根大学医学部第二内科学講座）

はじめに

食物やカビ，花粉などがアレルゲンとなってTh2タイプの免疫反応がおこり消化管に好酸球が浸潤してアレルギー反応を起こす疾患を好酸球性消化管疾患と総称している。最近，喘息，アレルギー性鼻炎，アトピー性皮膚炎などのアレルギー疾患が増加しているがこれらと共に好酸球性消化管疾患も増加していると考えられている。好酸球性消化管疾患は傷害される消化管の部位によって好酸球性食道炎と好酸球性胃腸炎に分類されている。好酸球性食道炎は健常者では好酸球が存在しない食道の上皮層内に多数の好酸球浸潤がみとめられるアレルギー性疾患で，どのような機序で上皮細胞間に好酸球が浸潤するのか注目されている。好酸球性食道炎と診断するためには胃や腸管などの他の消化管に好酸球の異常な浸潤がないことを証明することが必要であると考えられている。一方，好酸球性胃腸炎は健常者でも好酸球が少数浸潤している消化管粘膜の粘膜固有層を中心に消化管粘膜に好酸球が多数浸潤する疾患で胃や腸管に病変が発生する。胃や腸管に加えて食道に病変が発生することもありこのような例も好酸球性胃腸炎に分類されている。

好酸球性食道炎と一部の食道病変を有する好酸球性胃腸炎は食道粘膜に起こる慢性の炎症のために嚥下障害を主とする様々な症状を起こし特徴的な内視鏡像も呈する。そこで本稿では好酸球性消化管疾患のうち好酸球性食道炎を中心にその診断と治療について解説する。

好酸球性食道炎の病態

好酸球性食道炎はおもに食物がアレルゲンとなっておこるTh2タイプの免疫反応のために食道粘膜が傷害をうけ，さらに粘膜下層の線維化が原因となって食道の狭窄が発症する疾患である。好酸球とマスト細胞が本疾患の発症に大きく関与しIL-5, 13, eotaxin 3, thymic stromal lymphopoietin（TSLP）などのサイトカインが重要な役割をもっている。さらに食道扁平上皮の透過性を低く保つために重要な役割をもつfilaggrinやinvolcrinの発現低下も重要な要因であろうと考えられている（図1）[1-3]。また，ヘリコバクター・ピロリの感染頻度の低下が好酸球性食道炎の増加の一因となっている可能性も指摘されている[4]。

アレルゲンとしては欧米での検討ではミルク，小麦，大豆，卵，ピーナツなどのナッツ類，海産魚類の6種の抗原が重要であると報告されているが日本での詳細な検討は行われていない[5,6]。

好酸球性食道炎の診断

厚生労働省の好酸球性消化管疾患の研究班が作成した診断の指針案が発表されているのでこれを参考として診断を行うのが望ましいと考えられる（表1）。好酸球性食道炎の好発年齢は40-50歳前後で男性が約80%を占めている。また半数に何らかのアレルギー疾患を合併しておりその半数は気管支喘息であることが分かっている[7]。日本での検討では家族歴は明らかでないことがほとんどである。すなわち好酸球性食道炎の好発グループはアレルギー疾患の病歴を有する中年男性ということになる。

症状は日本人患者の60%が食事の嚥下障害や胸のつまり感を訴える。嚥下障害に次いで多い症状は胸焼けや胸痛である。欧米の報告では食道の狭窄や蠕動運動障害に起因する食物の食道内での停滞のために救急外来を受診し内視鏡による食物塊の除去が必要な例が少なくないと報告されているが日本においてはこのような例は

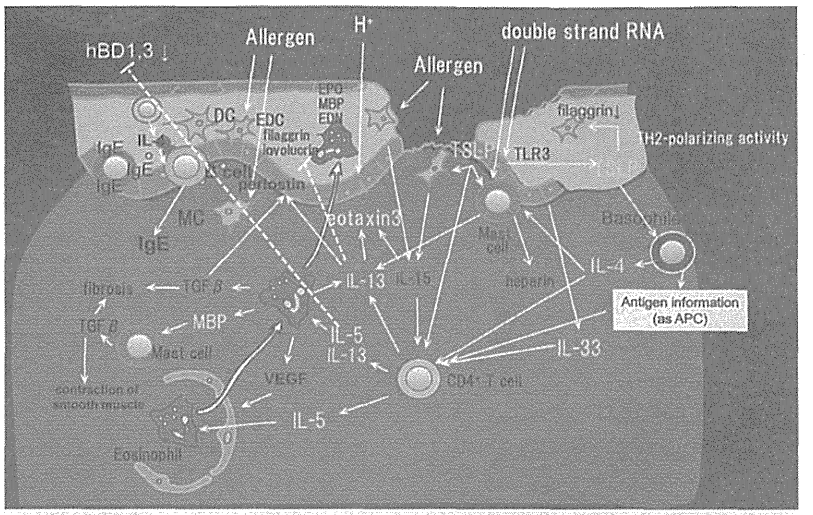

図1　想定される好酸球性食道炎の病態

表1　好酸球性食道炎の診断指針（案）

1. 症状（嚥下障害、つかえ感等）を有する。
2. 食道粘膜の生検で上皮内に20／HPF以上の好酸球が存在している。
（生検は食道内の数ヶ所を行うことが望ましい）
3. 内視鏡検査で食道内に白斑、縦走溝、気管様狭窄を認める。
4. CTスキャンまたは超音波内視鏡検査で食道壁の肥厚を認める。
5. 末梢血中に好酸球増多を認める。
6. 男性
7. プロトンポンプ阻害薬は無効でグルココルチコイド製剤が有効である。

1と2は必須　これら以外の他の項目も満たせば可能性が高くなる。

ほとんどみられない。一方，日本では健診受診者に対して内視鏡検査を行うことが多いため内視鏡検査でたまたま発見され，症状がほとんどない好酸球性食道炎患者も少なくない。

理学的所見では特徴的な異常は認められないがアトピー性皮膚炎などのアレルギー疾患の合併がみられることがある。

血液検査等の検体検査を行うと，一部の例で末梢血中の白血球増加，好酸球増加，CRP などの炎症反応の上昇，IgE の増加などを見ることができるが診断の決め手にはなりにくい。また末梢血中の Th2 免疫にかかわるサイトカインの測定を行って診断の補助や重症度の判定に用いようとする試みも行われているが現状では有用とは言えない[5,8]。

このため診断には上部消化管の内視鏡検査が行われることが多い。内視鏡検査では縦走溝，輪状収縮輪，輪状狭窄，白斑，発赤，浮腫，クレープピールサインなどの異常が認められると報告されている（図2）。これらの異常像の中で内視鏡医間の診断一致率が高くて診断のブレが少なくかつ診断感度と特異度が他の所見に比べて高い内視鏡所見は縦走溝である。縦走溝は食道の縦軸方向に数条みられる溝状の陥凹で食道内の空気量を少なくして観察すると発見しやすい。ただし内視鏡検査で異常を発見すること

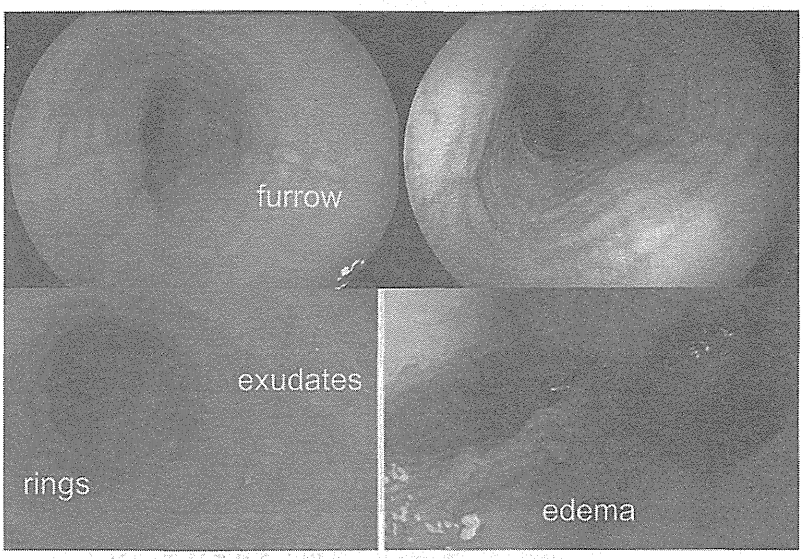

図2　好酸球性食道炎の内視鏡像

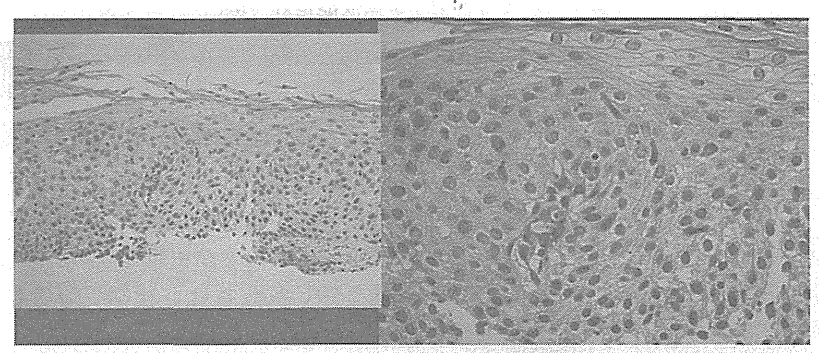

図3　好酸球性食道炎の病理組織像

ができない好酸球性食道炎も10–30％ぐらいは存在すると考えられており内視鏡検査で異常がなくても好酸球性食道炎を否定しないことが重要である。

内視鏡検査で好酸球性食道炎の存在を疑わせる異常が発見された場合や症状から好酸球性食道炎が疑われる場合には食道の生検を行って粘膜上皮層内に好酸球の浸潤があるか否かを確認する必要がある。400倍の高倍率視野で食道上皮層内に１視野あたり15–20個以上の好酸球が存在している部位が一か所でもあれば好酸球性食道炎の疑いが強くなる（図３）。ただし生検を一か所だけ行った場合には診断感度は50％程度であり感度を100％近くとするためには５個以上の食道粘膜の生検が必要であると報告されている。

鑑別診断

好酸球性食道炎との鑑別診断上最も重要な疾患は胃食道逆流症（GERD：gastro-esophageal reflux disease）である。GERD 例は胸焼け症状を訴え好発年齢の一つは中年の男性である。すなわち GERD と好酸球性食道炎は好発グループも症状も類似していることになる。発症頻度は GERD の方が圧倒的に多いため中年男性が胸焼け症状を訴えるときには GERD と臨床診断をしてプロトンポンプ阻害薬（PPI：proton pump inhibitor）を用いた治療が行われる事が多い。臨床的に GERD と診断した例に PPI 治療を行っても30％程度の例は症状が軽快しな

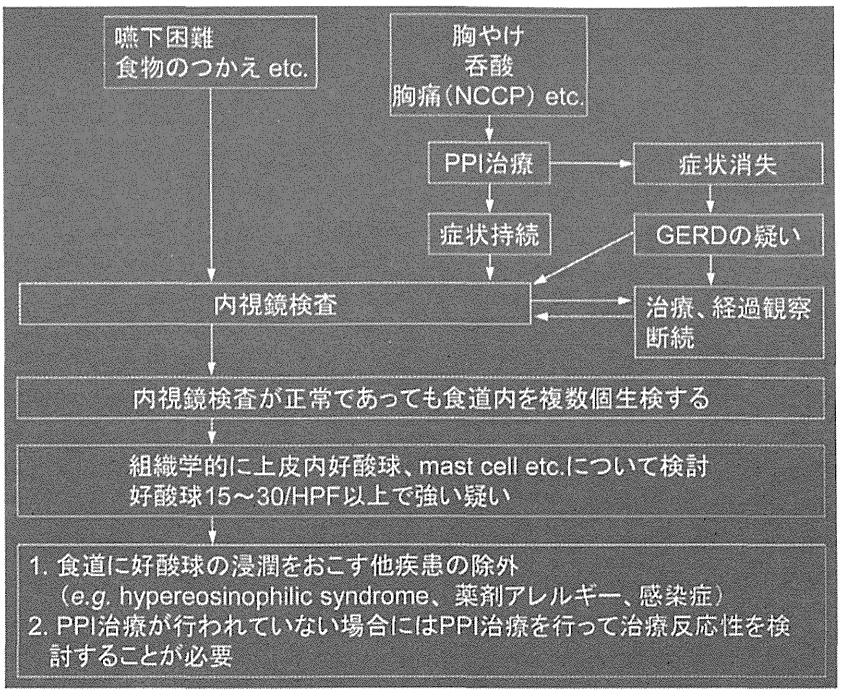

図4　好酸球性食道炎の診断のプロセス

い。このようなPPI抵抗性GERD例の中に4％程度の頻度で好酸球性食道炎が混入していることが分かっている。このためGERDと考えられる例がPPI治療に抵抗する場合には一度は好酸球性食道炎の可能性を考えてみることが重要であると考えられる。

一方反対に，症状，内視鏡所見，生検組織診断から好酸球性食道炎と診断される特徴を有しながらPPI治療によって症状や内視鏡所見，組織学的な好酸球浸潤が改善する例が少なからずあることが明らかとなり，このような例を好酸球性食道炎とするべきか，それともGERDとするべきかについて議論が交わされている。現状ではこのようなPPIに反応する例はPPI-responsive esophageal eosinophiliaとして好酸球性食道炎とは区別して扱うべきであるとする意見が強い[6]。ただし，今後さらなる検討の結果に基づいて定義や概念が変えられる可能性があると考えられる。

好酸球性食道炎の治療

好酸球性食道炎の治療に関して治療フローを提案してきたので参照していただきたい（図4）。治療はまずPPIに反応するか否かを検討するところから始める。臨床的に好酸球性食道炎と診断される例の一部はPPIに反応して自覚症状と内視鏡所見が改善する。このような例に対してはPPIの投薬を行うことが望ましいと考えられる。PPIは有効性が高く副作用も少ないため本薬剤に反応するPPI-responsive esophageal eosinophiliaの治療は薬剤の副作用をあまり心配することなく行うことができる。

次いで好酸球性食道炎例のアレルゲンがミルク，小麦，大豆，卵，ピーナツなどのナッツ類，海産魚類の6種であることが多いためこれらの食材を除いた除去食を指導することがある。これは現状では各種検査で原因アレルゲンを同定することが困難であるためリスクの高い6種の食材を除こうとする治療方法である。本治療の有効性は高いことが報告されているがコンプライアンスが悪いため6種の食品除去食で病状の改善がみられた後に長期にわたって除去することが必要な食材を同定するために除去した食材を1種類ずつ摂取させ病状の再燃の有無