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〈症例〉

自然軽快したcap polyposisの1例

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〔Key Words〕cap polyposis

和文要旨

患者：55歳，女性。過敏性腸症候群として加療されていたが，2001年2月頃より粘血便が頻回となり，左下腹部痛が出現したため当科に入院。大腸内視鏡検査にて直腸には平盤状隆起，S状結腸にはタコいぼ状隆起や強い発赤斑を認めた。平盤状隆起の生検で，cap部の化膿性滲出物，炎症性肉芽組織，軽度の線維筋症を認め特異な内視鏡像とあわせcap polyposis(CP)と診断した。排便習慣の是正により症状が軽快したCPの1例を経験したので報告する。

症　例

患者：55歳，女性。

主訴：下痢，粘血便，左下腹部痛。

既往歴：骨髄炎，肺炎。

家族歴：父・母，糖尿病。

生活歴：喫煙歴・飲酒歴なし。

現病歴：元来緊張すると便秘や下痢をきたす傾向があった。1995年，粘血便を認めたため近医で注腸を受けるが異常所見を認めず過敏性腸症候群と診断された。2001年2月頃より粘血便が頻回となり，ポリカルボフィル製剤，整腸剤等の投与を受けるも改善なく，9月頃より左下腹部痛も認めるようになった。近医での大腸内視鏡検査で潰瘍性大腸炎を疑われたため，同年10月に当科を受診，入院となった。

入院時現症：身長157cm，体重53kg，血圧100/60 mmHg，脈拍66回/分・整，体温36.2度，腹部平坦・軟，腸音低下，左下腹部に圧痛あり，反跳痛なし，筋性防御なし，他異常所見認めず。

検査所見：赤沈12mm/1st hr，WBC $6.2\times10^3/\mu l$，Hb 13.6g/dl，Plt $25.7\times104/\mu l$，TP 6.2g/dl，Alb 3.7 g/dl，TC 196mg/dl，TB 0.4mg/dl，BUN 8.6mg/dl，Cr 0.6mg/dl，CRP 0.01mg/dl，LDH 177IU/l，AST 24IU/l，ALT 19IU/l。

便潜血反応陽性，軽度の低蛋白血症を認めた。糞便の培養検査は陰性，血清アメーバ抗体も陰性，尿素呼気試験陰性であった。

大腸内視鏡検査所見(**Color 1**)：Rb第一ヒューストン弁上に約半周にわたって横走する平盤状隆起を認め，頂部には黄白色の粘液の付着を伴っていた。Ra, Rsには小型の平盤状隆起，S状結腸には頂部の陥凹が強い発赤を呈するタコいぼ状隆起が多発し，隆起の周囲には小白斑を認めた。口側のS状結腸では隆起は目立たず，強い発赤斑の多発を認めた。なお，下行結腸より口側の結腸には異常所見を認めなかった。

大腸生検病理組織像(**Fig. 1**)：平坦発赤部の生検では炎症性細胞浸潤，腺窩上皮の過形成性変化を認めた。平盤状隆起の頂部からの生検では，いわゆるcap部の化膿性滲出物，炎症性肉芽組織を認め，周囲の隆起部では軽度の炎症細胞浸潤と腺管の延長を認めた。強拡大，およびActin染色(**Color 2**)で，粘膜深層を中心に軽度の線維筋症が確認できた。以上より，特異な内視鏡像とあわせcap polyposis(CP)と診断した。

入院後経過：入院時，排便時のいきみ習慣がみられたため，腸管安静(維持輸液1,000mlと腸炎食)と乳酸菌製剤に加え，排便習慣の改善の指導をしたところ，徐々に症状は改善し，第19病日には腹痛・粘血便ともに消失した。また，低アルブミン血症も改善した。その後，症状の再燃は無く，約1年後に施行した注腸造影，3年後の大腸内視鏡像においても異常所見を認めなかった。

考　察

CPは膿性粘液におおわれた隆起の頂部が帽子様の形態を示す，特異な炎症性疾患として，1985年Williamsら，続いて1993年Campbellらによって報告された比較的新しい疾患概念である。CP提唱前のeroded polypoid hyperplasia(6例)，分類不能腸炎(3例)，直腸腺腫(1例)，多発性炎症性過形成結節(1例)として報告されていた症例をあわせ，Medline，医中誌による検索では自験例を含め68例が該当した。従来より，CPは，病理学的に線維筋症を伴うことや，排便習慣の異常を高率に伴うことから，直腸粘膜脱症候群(以下，MPS)との異同が問題になっており**Table 1**に比較検討の表を示す。年齢・性比に明らかな差は認めなかった。MPSでは排便時のいきみ習慣がほぼ必発であるが，CPでも60%に認めた。MPSでは血液検査所見に異常を認めることはほとんどないがCPでは低蛋白血症を82%と高率に認めた。MPSの好発部位は直腸前壁，歯状線より2cm以内が多く後壁側の発生は稀であるのに対しCPはほとんどがS状結腸や深部結腸

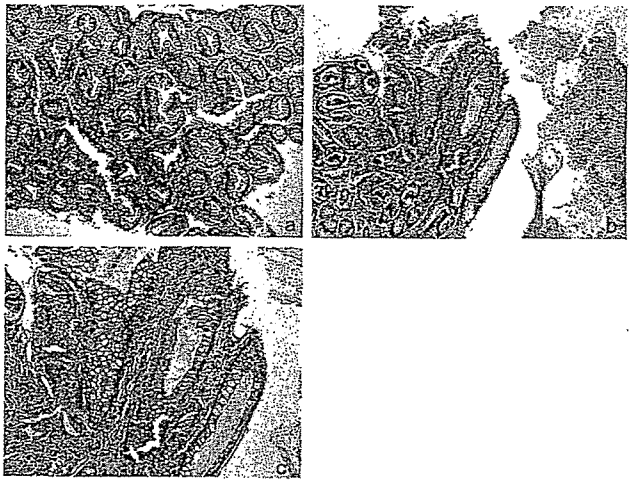

Fig. 1 Microscopic picture of cap polyposis obtained by endoscopic biopsy. a) Early phase of cap polyposis, a small flat lesion with dense superficial and localized inflammation, accompanied by crypt dilatation. b) The surface of sessile polyp which is covered by granulation tissue and fibrinopurulent exudates (arrow head), the so-called "cap". c) Mild fibromuscular obliteration is recognized in the deep lamina propria (hematoxylin & eosin).

にも分布し，腸管の前後左右壁に好発部位はない。CPの個々の病変は大きさ0.5～2 cmで，平盤状，たこいぼ状，芋虫状隆起で，表面は発赤調，易出血性で粘液や白苔付着，びらん形成を伴う。病変の境界は比較的明瞭で介在粘膜は正常ないしは浮腫状で白斑を伴う。病理組織上，MPSでは粘膜表層部の毛細血管の増生と拡張，粘膜固有層にみられる線維筋症および幼若上皮からなる腺管の過形成が特徴的である。一方CPではcapの部分は膿性の線維素性浸潤物と炎症性肉芽組織からなり，隆起部分は腺管の延長，過形成性変化がみられる。線維筋症も高頻度に見られるのが，MPSと異なり隆起深層を中心に軽度のものがほとんどである。

MPSの治療が排便習慣の改善にあるのに対し，CPに対する治療法は多岐にわたるものが報告されている。メトロニダゾールが22例に使用され，約3分の1で有効と報告されていた。ステロイド注腸が有効であった症例は散見されるが，ステロイド内服やサラゾピリンは無効であった。最近では*H. pylori*除菌が行われ6例中5例に有効であり，感染の関与を示唆するもので注目される。本例のように，排便習慣の改善によって軽快したとする報告も11例中6例あった。さらに低蛋白血症の進行や症状により手術を余儀なくされた症例が16例報告されているが，手術が有効とされた症例でも約半数に術後再燃がみられた。その他ポリカルボフィル，EMR，エカベトナトリウム+PSL内服，Infliximab

Table 1 Clinical features-MPS and cap polyposis.

	MPS	cap polyposis (n=68)
年齢・性比	9歳～83歳，やや男性に多い	10歳～77歳で平均50.7歳，男女比1:2.79
臨床症状	肛門痛，排便時出血，排便障害 いきみ習慣あり	粘液下痢(75%)，粘血便(45.6%)，腹痛(36.8%) いきみ習慣あり(60.5%)
血液検査	特になし	低蛋白血症(82.2%)
病変部位	下部直腸前壁，歯状線より 2cm以内が多い	直腸－S状結腸(58.8%)，直腸(13.2%)， 直腸－下行結腸(5.9%)，直腸－上行結腸(5.9%)
内視鏡像	平坦型，隆起型，潰瘍型	平盤状隆起(83.6%)，粗大結節状隆起(38.8%)， 表面は発赤調，易出血性で粘液や白苔付着， びらん形成を伴う。
病理組織	粘膜表層部の毛細血管の増生 拡張，線維筋症，腺管過形成。	隆起頂部の肉芽組織，線維筋症の程度は軽い。
治療法	排便習慣の改善。	メトロニダゾール，PSL注腸，*H.Pylori*除菌，手術， 排便習慣の改善。
病　因	直腸粘膜脱説	感染説，免疫説，腸管運動機能異常説， 直腸粘膜脱説。

1970年から2005年にかけての医中誌，Medlineによる検索で自験例を含めたcap polyposisと考えられた68例を対象にした

などの報告もある。

我々は排便習慣の是正により症状が軽快し，内視鏡的にも正常化したCPの1例を経験した。CPとMPSとの異同は議論のあるところであり，本例においてもその病態に粘膜脱という要因が存在すると考えられた。しかし，文献的検討では，CPはMPSにはみられない，感染・免疫異常・腸管運動機能異常などの様々な要因が発症に関与しており，独立したclinical entityとすべきと考えられた。

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〈カラーは7頁に掲載〉

A case report of cap polyposis with spontaneous remission.

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〈症例〉

大腸全摘術後の回腸嚢炎・多発関節炎に白血球除去療法が奏功した潰瘍性大腸炎の1例

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〔Key Words〕回腸嚢炎，潰瘍性大腸炎関連関節炎

要旨

大腸全摘術後に出現した回腸嚢炎，多発関節炎に対し白血球除去療法(leukocytapheresis：LCAP)が奏功した潰瘍性大腸炎を経験した。また，6-MPによる緩解維持効果もみられ，今後これらが術後の回腸嚢炎や腸管外合併症の緩解導入および維持療法の選択肢のひとつになることが期待された。

症　例

患者：40歳，女性。

主訴：関節痛，腹痛，血便。

既往歴：大腿骨頭壊死(32歳時)。

家族歴：特記すべきことなし。

生活歴：喫煙，アルコールともなし。

現病歴：1999年(34歳)発症の全大腸炎型潰瘍性大腸炎(Ulcerative colitis：UC)で再燃緩解を繰り返し，2000年6月入院時にはステロイド動注療法で緩解導入がえられた。しかし，徐々にステロイド抵抗性となり，難治性と判断され2003年4月大腸全摘・回腸嚢肛門管吻合術を受けた。術後症状は安定していたが，2005年4月より両上下肢などの多発関節炎が出現しエトドラク400mg/日の内服とともにジクロフェナクナトリウムの坐薬を頓用していた。さらに，8月下旬より腹痛，血便の増悪もみられ入院となった。

身体所見：体格中等，体温37.1℃，貧血/黄疸なし。口腔内，表在リンパ節著変なし。腹部右下腹部に圧痛みとめるが反跳痛や筋性防御なし。両側手，足，左顎関節の腫脹あり。

検査成績：血液検査では血沈88mm/1h，白血球数9,180/μl，CRP8.59mg/dlと炎症所見を呈した。Hb11.0 g/dlと軽度貧血がみられたが，TP 7.1g/dl，Alb 3.9g/dl，TC167mg/dl，Ch-E3.76IU/lと栄養状態はよく，肝腎機能も正常であった。RF，ANAとも陰性であった。入院時の内視鏡では回腸嚢粘膜は顆粒状で血管透見性は消失し，膿性粘液を伴った潰瘍がみられ，吻合部でも線状潰瘍がみられた(**Fig. 1-a, b**)。生検組織ではびらんを伴うリンパ球，形質細胞や好中球の著明な浸潤がみられた(**Fig. 2**)。以上よりPDAI score 11点で中等症の回腸嚢炎と診断した[1]。

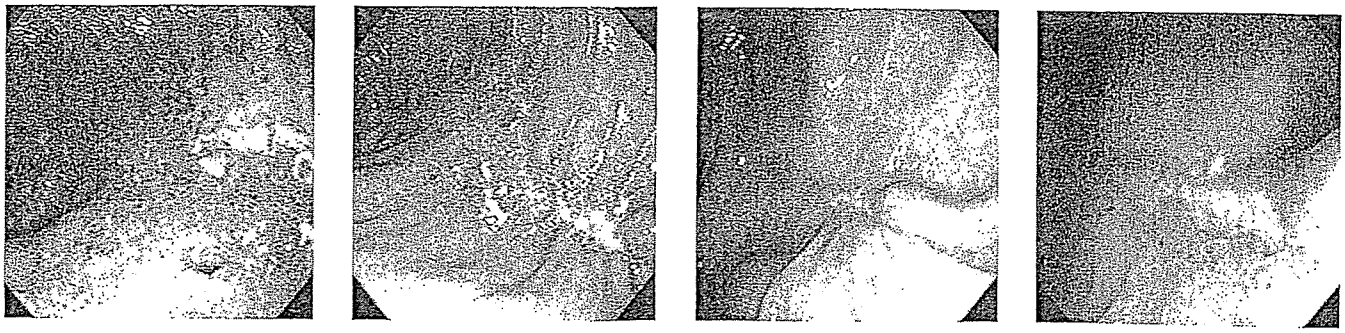
経過：非ステロイド系抗炎症薬の効果不十分な関節炎に対し，ステロイドの使用も考慮したが，大腿骨頭壊死既往のため不適応と判断した。また回腸嚢炎についてはメシル酸パズフロキサシン1,000mg/日点滴(2週間)を行った。さらにこれらの症状とUCとの関連性を考え第3病日より5-ASA製剤内服2,250mg/日とLCAPを開始しCRPは徐々に低下した。関節痛はLCAP翌日には著明な改善がみられたが施行直後の改善と数日後の増悪を繰り返した。LCAP 5回終了時にはPDAI score 7点となり，第40病日の内視鏡で回腸嚢および吻合線上の潰瘍の縮小，粘膜の炎症の改善が確認された(**Fig. 1-c, d**)。緩解維持目的に9月29日より6-MP 30mg/日内服を開始し2006年7月現在まで再燃をみとめていない。

考　察

潰瘍性大腸炎関連関節症はUCの発症前または経過中に発症する非感染性関節炎である[2]。強直性脊椎炎やReiter症候群などとともにリウマチ因子陰性のseronegative spondyloarthropathyで，発症様式は腸炎先行型，末梢型の関節炎が多い。治療は非ステロイド系抗炎症薬が主で，末梢型では原疾患の治療で軽快することが多いが，大腸摘出術に至る重症例も報告されている。術後に関節炎が消失した例が4例，逆に本例のように術後に関節炎が出現した例も6例みられ原疾患の活動性とは必ずしも一致しない。

最近UC関連関節炎でのLCAPの有用性が報告されているが[3]，術後関節炎を生じた例も含めいずれも本症例と同様腸炎先行型，ステロイド抵抗性症例であった。

一方UCでの回腸嚢炎の発生頻度は20%前後で，診断基準にはMayo Clinicから提唱されたPouchitis disease activity index(PDAI)などがある。臨床症状，内視鏡および組織学的所見から点数化しPDAIでは7点以上が回腸嚢炎と診断される。治療はメトロニダゾールの他，ステロイドの坐薬や注腸，メサラジン注腸の有用性が報告されているが[1]，本症例では大腿骨頭壊死の既往からステロイド不適応と判断した。関節炎症状が主体であったため全身療法としてLCAPをおこな



a　　b　　c　　d

Fig. 1 Colonoscopy on admission. Mucosal inflammation with ulcers in J-pouch (a) and along the staple line (b) were seen. On 40th day remarkable improvement of ulcers and mucosal inflammation was seen both in J-pouch (c) and along the staple line (d).

Fig. 2 Histological finding of biopsy specimen from J-pouch on admission. Remarkable infiltraion of neutrophils, plasma cells and eosinophils with erosive change were seen.

い，局所療法は行わなかったが，抗菌剤終了後も臨床症状，内視鏡所見の改善が維持され回腸嚢炎に対しての有用性も示唆された。

さらに，6-MPはUCの緩解維持に有効とされているが，本症例で術後に発症した回腸嚢炎や多発関節炎の緩解維持にも有用であったことは，免疫異常を主体とするUCにおいては粘膜病変形成のみならず術後発症の合併症の病態を考える上でも興味深い。

本症例は今後術後発症の回腸嚢炎や腸管外合併症にLCAPおよび6-MPが治療法のひとつになることを示唆するものと考えられた。

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A case report of pouchitis and polyarthritis after total colectomy for ulcerative colitis which showed the effect of leukocytapheresis

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Journal of Gastroenterology

Inhibition of neutrophil elastase prevents the development of murine dextran sulfate sodium-induced colitis

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Background. Neutrophil elastase (NE) is a major secretory product from activated neutrophils and a major contributor to tissue destruction. However, little is known about the pathogenic contribution of NE to ulcerative colitis (UC). This study was designed to investigate the contribution of NE by measuring NE activity in plasma and colonic mucosal tissue from UC patients and a murine acute colitis model, and to elucidate the therapeutic effect of the NE-specific inhibitor ONO-5046. ***Methods.*** The NE enzyme activities in plasma and colonic mucosal tissue from UC patients were directly measured using an enzyme–substrate reaction. Acute colitis was induced in mice by administration of 1.5% dextran sulfate sodium (DSS) for 5 days. DSS-induced colitis mice were then treated with ONO-5046 (50 mg/kg body weight) intraperitoneally twice a day. ***Results.*** In UC patients, the NE enzyme activity was significantly elevated in both the plasma and colonic mucosal tissue compared with healthy controls. In DSS-induced colitis mice, the NE enzyme activity increased in parallel with the disease development. ONO-5046 showed therapeutic effects in DSS-treated mice by significantly reducing weight loss and histological score. ONO-5046 suppressed the NE enzyme activities in both plasma and culture supernatant of colonic mucosa from DSS-induced colitis mice. ***Conclusions.*** ONO-5046, a specific NE inhibitor, prevented the development of DSS-induced colitis in mice. NE therefore represents a promising target for the treatment of UC patients.

Key words: ulcerative colitis, neutrophil elastase, dextran sulfate sodium-induced colitis, ONO-5046

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Introduction

Although the etiology of ulcerative colitis (UC) has not been clarified, increasing evidence indicates that abnormal immune responses are involved in its pathogenesis.[1,2] While recent studies have focused mainly on lymphocytes or antigen-presenting cells such as dendritic cells, little is known about the pathogenic role of neutrophils in UC. Indeed, dense neutrophil infiltration and crypt abscess formation are characteristic pathological findings in the inflamed mucosa of UC patients.[3,4] Moreover, in Japan, granulocyte adsorption apheresis therapy has been reported to show a remarkable therapeutic effect in active UC patients.[5] Taken together, neutrophils almost certainly play an important role in the pathogenesis of UC.

Neutrophil elastase (NE) is a major secretory product from activated neutrophils and a major contributor to tissue destruction in inflammatory diseases such as acute respiratory distress syndrome (ARDS), lung emphysema, glomerulonephritis, and rheumatoid arthritis.[6,7] Ninety percent of the NE circulating in the blood is bound to α_1-anti-trypsin (α_1-AT), an endogenous NE inhibitor, resulting in the formation of NE-α_1-AT complexes. The remaining 10% of the NE is bound to α_2-macroglobulin, another endogenous NE inhibitor. Therefore, NE is systemically and tightly inactivated by endogenous protease inhibitors. However, at inflammatory sites, these protease inhibitors are inactivated by neutrophil-derived reactive oxygen species (ROS).[8] Thus, NE might become capable of displaying its strong protease activity and degradeing the main structural elements of connective tissue, such as elastin, collagen, and proteoglycans, at inflammatory sites.

It has previously been reported that NE is elevated in the plasma, colonic mucosal tissues, and feces of active UC patients.[9–11] It has also been demonstrated that the plasma NE level is correlated with the clinical activity of UC.[9,12] However, a definitive conclusion cannot be

drawn regarding the pathological contribution of NE to UC, since the NE levels measured by using an enzyme-linked immunosorbent assay in the previous studies included NE–α_1-AT complexes, an inactive form of NE. Since only free NE shows protease activity, it is critical to measure the NE enzyme activity directly to clarify the pathogenic contribution of NE to UC.

ONO-5046 is a specific synthetic inhibitor of NE. In contrast to endogenous protease inhibitors, ONO-5046 can even effectively inhibit NE at inflammatory sites, since it is not structurally inactivated by ROS.[8] In Japan, ONO-5046 has already been used clinically in the treatment of patients with ARDS, which is characterized by the accumulation of numerous neutrophils in the lungs. Furthermore, ONO-5046 has shown a protective effect against neutrophil-mediated tissue injury in some animal models, including lung injury, neurologic damage after spinal cord injury, and collagen-induced arthritis.[13–16]

In this study, we first measured NE enzyme activity in plasma and colonic mucosal tissues from UC patients using an enzyme–substrate reaction. We next measured NE enzyme activity in a dextran sulfate sodium (DSS)-induced colitis model. Furthermore, we evaluated the therapeutic effect of ONO-5046 in colonic inflammation.

Materials and methods

Reagent

ONO-5046 was purchased from Ono Pharmaceutical (Osaka, Japan). It was dissolved in phosphate-buffered saline (PBS) and administered intraperitoneally twice a day at a dose of 50 mg/kg. The administration of ONO 5046 began 1 day prior to DSS administration and continued until the end of the experiment. Nontreated control mice were administered the same amount of PBS without ONO-5046.

Patients and samples

UC was diagnosed on the basis of clinical, endoscopic, and histological findings using established criteria.[17,18] Plasma samples were obtained from UC patients with moderate to severe activity (Table 1), defined by a clinical activity index (CAI) >8 points.[19] Patients treated with steroids or immunosuppressants were excluded from the study. Colonic mucosal samples were obtained from biopsy specimens of the inflamed mucosa of UC patients. Control samples of noninflamed colonic mucosa were obtained from macroscopically unaffected areas of patients with colon polyps. The tissues were weighed, gently homogenized in 500 µl of PBS, and then centrifuged (1500*g*, 15 min, 4°C). The supernatants were collected and immediately stored at –80°C until use. The study using human material was approved by the ethical committee of Keio University and written informed consent was obtained from all patients.

Table 1. Clinical profiles of the ulcerative colitis patients

Number of patients	10
Sex (female/male)	4/6
Age (years), mean (range)	28.7 (21–38)
Clinical Activity Index, mean (range)	11.3 (9–15)
Disease location, pan/left-sided colitis (no.)	9/1
Disease duration (years), mean (range)	4.2 (0.1–11.5)

Murine DSS-induced colitis model

Female 8-week-old C57BL/6 mice weighing around 20 g were used. The mice were housed under specific pathogen-free conditions. Colitis was induced by giving 1.5% DSS (molecular weight 50 kDa; BioResearch, Yokohama, Japan) dissolved in sterile distilled water ad libitum for 5 days followed by regular drinking water for the rest of the experimental period. Body weight was measured every day during the experiments. All experiments were performed in accordance with the institutional animal care guidelines of Keio University.

Histological score

Histological evaluation was performed on day 4. The total colon was fixed in 20% formalin and sectioned with a sagittal aspect. Tissues were embedded in paraffin and stained with hematoxylin-eosin. Histological analysis was performed in a blinded fashion. The histological score was estimated by the combined score of inflammatory cell infiltration (score, 0–3) and tissue damage (score, 0–3) as previously reported.[20,21] Briefly, the infiltration scoring was as follows: 0, no infiltration; 1, presence of occasional inflammatory cells in the lamina propria; 2, increased numbers of inflammatory cells in the lamina propria; and 3, confluent inflammatory cells extending into the submucosa. The tissue damage scoring was as follows: 0, no mucosal damage; 1, discrete lymphoepithelial lesions; 2, surface mucosal erosion or focal ulceration; and 3, extensive mucosal damage and extension into deeper structures of the bowel wall. The combined histological score therefore ranged from 0 to 6.

Colon organ culture

After the induction of colitis, each murine colon sample was weighed, cut into 2–3 pieces, and then cultured in a 6-well dish (Falcon, Franklin Lakes, NJ, USA) in serum-free RPMI-1640 medium supplemented with 100 U/ml penicillin G and 100 µg/ml streptomycin (Invitrogen,

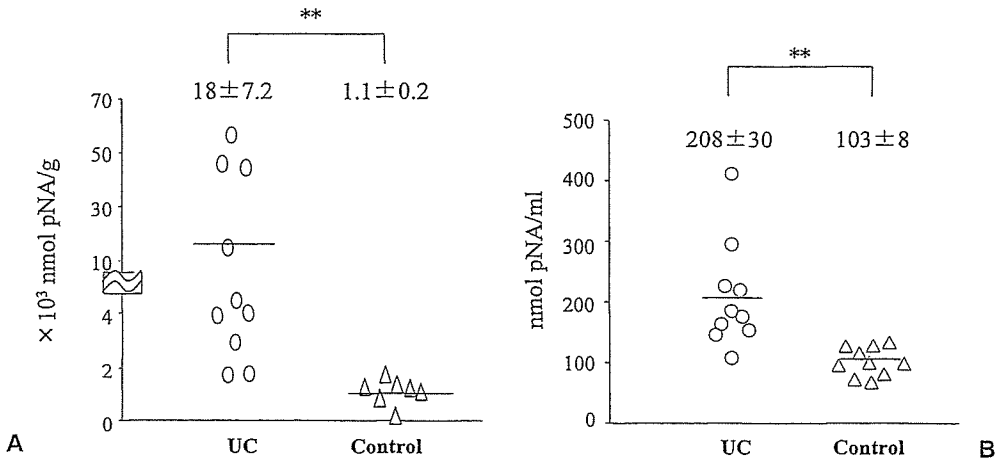


Fig. 1A,B. Neutrophil elastase (NE) enzyme activity is increased in UC patients. NE enzyme activity was directly measured using a NE-specific substrate as described in Materials and methods. The NE enzyme activities in colonic mucosal tissues (**A**) and plasma (**B**) from patients with active ulcerative colitis (*UC*) (*circles*) or controls (*triangles*) are shown (UC, $n = 10$; controls, $n = 7$). The means ± SEM are shown at the top. *pNA*, *p*-nitroanilide; $^{**}P < 0.01$

Grand Island, NY, USA) in a 5% CO_2 incubator for 24 h. The tissues were carefully positioned so that the mucosal surface was uppermost on the insert.[10] The culture supernatant was collected from the well, filter-sterilized (0.22 μm), and stored at –80°C until use.

Measurement of NE enzyme activity

The NE enzyme activity of each material (plasma, supernatant of colon organ culture, and homogenized tissue) was determined by an enzyme–substrate reaction method using *N*-methoxysuccinyl-Ala-Ala-Pro-Val-*p*-nitroanilide (Sigma, St. Louis, MO), a specific synthetic substrate of NE.[22] This substrate was specifically cleaved to *p*-nitroanilide (pNA) by NE, and the NE enzyme activity was quantified by measuring the quantity of pNA spectrophotometrically. Each sample was incubated with 0.2 M Tris-HCl buffer (pH 8.0) containing 2.5 M NaCl and 50 mM substrate at 37°C for 24 h, and the amount of pNA was measured by the absorbance at 405 nm.

Statistical analysis

The data were expressed as means ± SEM. Comparisons of the data were performed using a nonparametric Mann-Whitney *U* test. A *P* value below 0.05 was accepted as statistically significant.

Results

NE enzyme activity is elevated not only locally but also systemically patients with active UC

First, we measured the NE enzyme activity in colonic mucosal tissues from UC patients ($n = 10$) to investigate the local production of NE enzyme activity. As shown in Fig. 1A, NE enzyme activity in colonic mucosal tissues from UC patients ($n = 10$) was approximately 16 times that in controls ($n = 7$) (UC, 18 ± 7.2 vs. control, 1.1 ± 0.2 × 10^3 nmol pNA/g, $P < 0.01$). Furthermore, the NE enzyme activity in plasma samples from UC patients ($n = 10$) was approximately twice that in controls ($n = 10$) (Fig. 1B; UC, 208 ± 30.2 vs. control, 103 ± 8.0 nmol pNA/ml, $P < 0.01$). Thus, the NE enzyme activity was elevated not only locally but also systemically in UC patients. These results prompted us to evaluate the therapeutic effect of a NE-specific inhibitor, ONO-5046, in a murine DSS-induced colitis model, which resembles UC in many pathological features, such as dense neutrophil infiltration and crypt abscess formation.

NE increases in DSS-induced colitis in parallel with disease development

Before evaluating the therapeutic effect of the NE inhibitor, we confirmed that the NE enzyme activity was elevated in the murine DSS-induced colitis model. We first examined three concentrations of DSS, because the severity of DSS colitis depends on its molecular weight. In our preliminary results, administration of 1% DSS caused mild inflammation. In contrast, one-third of mice died by administration of 2% DSS. With administration of 1.5% DSS, body weight loss reached about 20% and severe inflammation was histologically confirmed without any mortality. Therefore, we chose 1.5% DSS in the following experiments. Colitis was induced by giving 1.5% DSS for 5 days followed by regular drinking water for the rest of the experimental period. The body weight began to decrease from day 4 and reached its minimum, 23% weight loss on days 8–9 (Fig. 2A). In colon culture supernatants, NE enzyme activity was elevated on day 4, when the body weight loss had just begun (Fig. 2A, B; culture supernatant, 360 ± 16 nmol pNA/ml on day 4). In contrast, the plasma NE enzyme activity was elevated on day 8 (300 ± 100 nmol pNA/ml), when the body weight loss reached its peak (Fig. 2D).

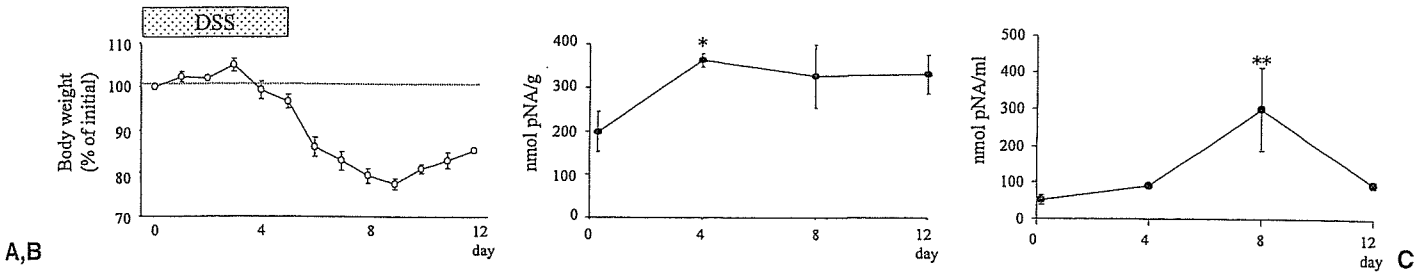


Fig. 2A–C. NE enzyme activity is elevated in a dextran sulfate sodium (*DSS*)-induced colitis model. **A** Body weight loss of DSS-induced colitis mice. The NE enzyme activities in supernatants from colon cultures (**B**) and plasma (**C**) from DSS-induced colitis mice ($n = 6$) are shown. The data represent an means ± SEM. $^{**}P < 0.01$; $^{*}P < 0.05$

ONO-5046 ameliorates DSS-induced colitis

We next assessed the therapeutic effect of ONO-5046. To determine an adequate dose of ONO-5046, we first administered four different doses of ONO-5046 (1, 5, 25, and 50 mg/kg) in DSS-induced colitis. The therapeutic effects were seen in a dose-dependent manner (data not shown), and the administration of 50 mg/kg showed the strongest effect. Therefore, we decided to use this dose through all of our experiments. ONO-5046 was administered intraperitoneally twice a day at the dose of 50 mg/kg in 200 µl PBS. Control mice were given the same dose of PBS without ONO-5046. ONO-5046 was administered 1 day prior to DSS administration and continued until the end of the experiment (Fig. 3A). Figure 3B shows that the body weight loss of mice treated with ONO-5046 was significantly reduced compared with control mice (control, 98.6 ± 0.9% vs. ONO-5046, 101.8 ± 0.9% on day 4, $P < 0.01$; control, 90.6 ± 1.8% vs. ONO-5046, 96.2 ± 1.5% on day 5, $P < 0.05$; control, 81.6 ± 1.6% vs. ONO-5046, 86.6 ± 1.1% on day 6, $P < 0.05$). The macroscopic findings on day 4 are shown in Fig. 3C. Colon length in the control group had a tendency to be shorter than that in the ONO-5046 treated group. However, the difference was not statistically significant (control, 61.3 ± 1.8 vs. ONO-5046, 66.3 ± 2.9 mm, $P = 0.11$). Histologically, the colons from control mice revealed severe ulceration and inflammatory cell infiltration (Fig. 3D, E). In contrast, the colons from DSS-induced colitis mice treated with ONO-5046 showed reduced ulceration and inflammation (Fig. 3F, G). The histological scores on day 4 were significantly reduced in the ONO-5046-treated group compared with the control group (Fig. 3H, control, 2.9 ± 1.2 vs. ONO-5046, 4.0 ± 1.6, $P < 0.05$).

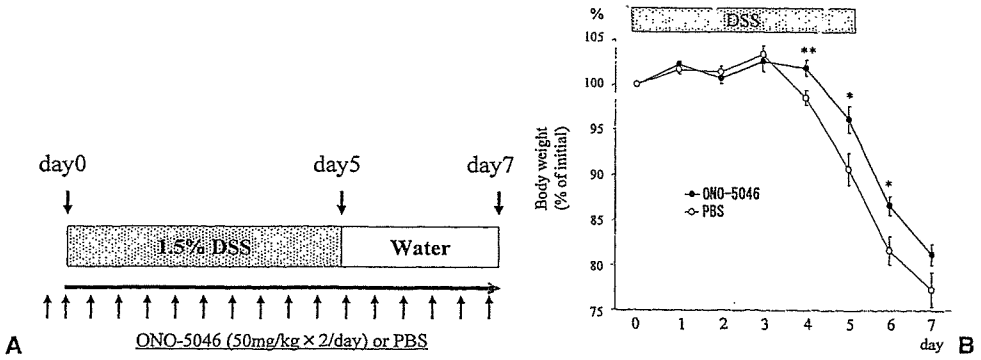
ONO-5046 reduces NE enzyme activity in DSS-induced colitis

To confirm that NE enzyme activity was inhibited by ONO-5046 in the DSS-induced colitis model, the effect of ONO-5046 on the plasma enzyme activity was measured on day 8, when the activity was found to be at its highest level (Fig. 2C). As shown in Fig. 4A, ONO-5046 completely suppressed the increase in NE enzyme activity (DSS-induced colitis mice treated with PBS, 340 ± 270 vs. DSS-induced colitis mice treated with ONO-5046, 93 ± 3 nmol pNA/ml, $P < 0.01$). Furthermore, to investigate the inhibition of local NE enzyme activity, colons from DSS-treated mice were cultured, and then ONO-5046 (1 mg/ml) was added to the culture medium 2 h before the end of the culture. As shown in Fig. 4B, the NE enzyme activity was inhibited in the supernatants from ONO-5046-treated specimens (PBS, 690 ± 110 vs. ONO-5046, 430 ± 57 nmol pNA/ml, $P < 0.05$). These results confirmed that NE enzyme activity was inhibited by ONO-5046 in the DSS-induced colitis model.

Discussion

The most important finding in the present study is that a specific NE inhibitor could prevent the development of DSS-induced colitis in mice. Given that murine DSS-induced colitis possesses certain pathophysiological features of UC, the data indicate that NE may represent a new target for the treatment of UC patients.

Since neutrophil infiltration and crypt abscess are histological features common to both UC and the murine DSS-induced colitis model, neutrophils may play a critical role in the pathogenesis of both UC and the DSS-induced colitis model. NE is a major secretory product from neutrophils and is capable of hydrolyzing most connective tissue components, leading to tissue injury at inflammatory sites. To clarify the pathological role of NE in intestinal inflammation, we first determined the levels of NE enzyme activity in UC patients. We showed that NE enzyme activity was increased in UC patients, while previous reports have measured total NE, including NE–α1-AT, complexes.[9,11,12] We directly measured the NE enzyme activity by an enzyme–substrate reaction using a specific synthetic substrate of NE. As blood contains abundant physiological NE inhibitors such as


day0
day5
day7
1.5% DSS
Water
ONO-5046 (50mg/kg × 2/day) or PBS
A
%
DSS
105
100
95
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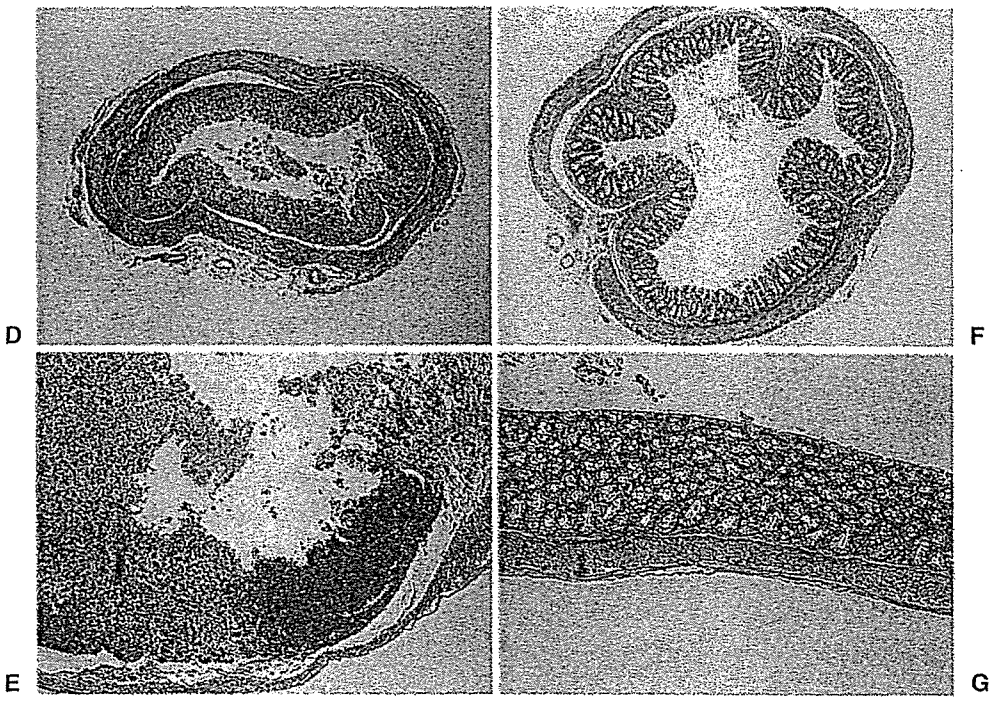
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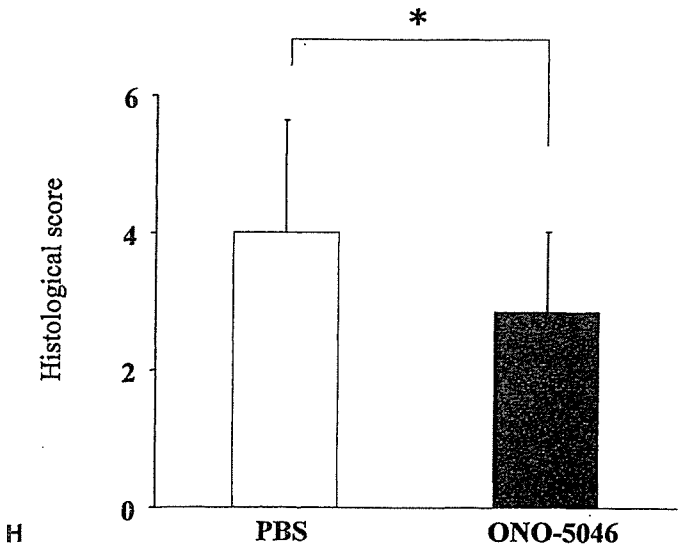

Fig. 3A–H. A NE-specific inhibitor, ONO-5046, suppresses the development of murine DSS-induced colitis. **A** The experimental protocol. ONO-5046 was administered intraperitoneally twice a day at the dose of 50 mg/kg. Nontreated mice were administered the same amount of phosphate-buffered saline (*PBS*) without ONO-5046. **B** Body weight loss of DSS-induced colitis mice treated with ONO-5046 (*closed circles*, $n = 12$) or PBS (*open circles*, $n = 12$). The data were collected from three independent experiments. **C** Macroscopic findings of colons from DSS-induced colitis mice treated with PBS (*left*) or ONO-5046 (*right*). Hematoxylin-eosin staining of colons from DSS-induced colitis mice treated with PBS (**D, E**) or ONO-5046 (**F, G**) on day 4. **H** Histological scores of DSS-induced colitis mice treated with ONO-5046 (*black bar*) or PBS (*white bar*) on day 4. The data represent means ± SEM. $^{**}P < 0.01$; $^{*}P < 0.05$

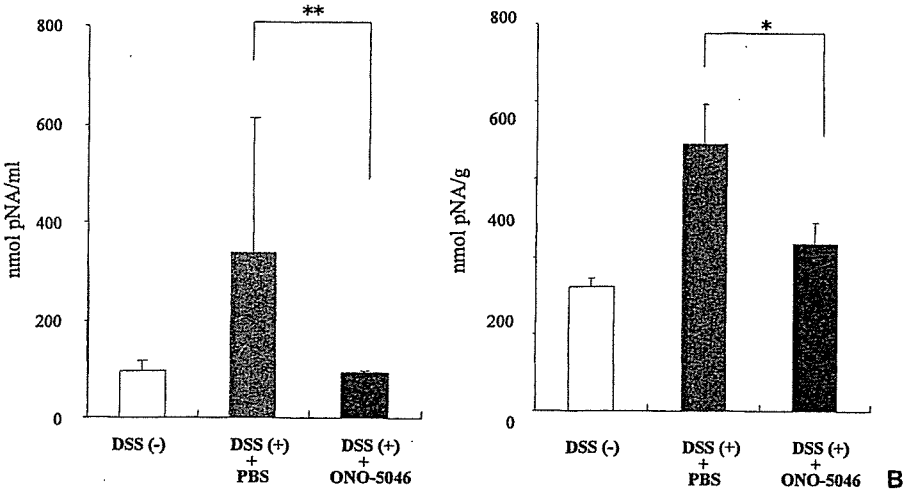

Fig. 4A,B. ONO-5046 reduces NE enzyme activity in DSS-induced colitis. **A** NE enzyme activities in plasma from mice without DSS (*white bar*, $n = 6$) and DSS-induced colitis mice treated with ONO-5046 (*black bar*, $n = 6$) or PBS (*hatched bar*, $n = 6$). Plasma samples were obtained on day 8. **B** Colons were obtained from mice without DSS (*white bar*, $n = 6$) and DSS-induced colitis mice on day 4. ONO-5046 (1 mg/ml, *black bar*, $n = 6$) or PBS (*hatched bar*, $n = 6$) was added into the medium of the colon culture, and the NE enzyme activities of the culture supernatants were measured. The data represent means ± SEM. $^{**}P < 0.01$; $^{*}P < 0.05$

α1-AT, little plasma NE enzyme activity can normally be detected. However, it has been reported that plasma NE enzyme activity can be detected in an ARDS hamster model,[13] possibly because local NE production is so huge that it overcomes the capacity of physiological NE inhibitors. In the same way, we were successful in detecting NE enzyme activity in not only colonic mucosal tissues but also plasma samples of UC patients. These results suggest that a considerable amount of NE is produced in colons of UC patients, which overcomes physiological NE inhibitors in blood. Next, we measured NE enzyme activity in a murine DSS colitis model. We found that local NE enzyme activity was increased from an early stage of the disease and elevated throughout the experimental period and that systemic NE cold be measured following local NE production at the maximal stage of the disease. These results suggest that NE may contribute to both the induction and perpetuation of colitis.

Furthermore, we assessed the therapeutic effect of a specific NE inhibitor. We demonstrated that ONO-5046 could prevent the development of murine DSS-induced colitis. While the results further support the pathophysiological contribution of NE to intestinal inflammation, the precise mechanisms of how the decreased NE enzyme activity led to the amelioration of colitis could

not be determined in this study. NE is considered to be involved in tissue destruction through its protease activity. Moreover, recent studies have revealed some new functions of NE in inflammatin. (1) NE enhances the migration and adhesion of neutrophils;[23] (2) NE stimulates the production of proinflammatory cytokines such as cytokine-induced neutrophil chemoattractant, macrophage inflammatory protein-1, and interleukin-1β;[24] and (3) NE cleaves phosphatidylserine receptors on macrophages and disrupts the phagocytosis of neutrophils, thus enhancing the scattering of NE.[25] Since NE seems to have such various biological activities, further studies are required to identify the exact mechanism of how NE inhibition ameliorates colitis.

ONO-5046 has already been clinically used for the treatment of ARDS associated with systemic inflammatory response syndrome in Japan. It has a few side effects, such as mild liver dysfunction (8.4%) and mild leukopenia (1.6%), but no serious side effects have been reported. Therefore, ONO-5046 might actually have the potential to be a new therapeutic approach for patients with active UC.

In summary, we demonstrated that NE enzyme activity is increased in both UC and a murine DSS-induced colitis model. Furthermore, we showed that ONO-5046, a NE-specific inhibitor, could ameliorate murine DSS-induced colitis. These findings provide evidence that NE contributes to the pathophysiology of mucosal inflammation. NE therefore represents a promising target for the treatment of UC patients.

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Review

Novel pathophysiological concepts of inflammatory bowel disease

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Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis

Introduction

Gut-associated lymphoid tissue (GALT) harbors more than 80% of the total lymphoid tissue in the body, and intestinal inflammation is caused and/or maintained by abnormal immune responses to foods or microbes in GALT (Fig. 1). Although the pathogenesis of inflammatory bowel disease (IBD) is still unknown, significant progress and new insights have been gained through a wide variety of analyses consisting of genetic factors, environmental factors, and immunological abnormalities (Fig. 2). The unraveling of immunopathogenic mechanisms has been critical to the discovery of new therapeutic targets, which has, in turn, driven the development of new biological therapies. Recently, several excellent reviews have focused on IBD pathophysiology. Bouma and Strober[1] discussed recent advances in understanding the induction and regulation of mucosal inflammation, highlighting the role of mucosal T cells. Recent advances in understanding the function of mucosal T cells were also the focus of an article by Watanabe et al.,[2] and Gordon et al.[3] contributed a very detailed chapter on cytokines, chemokines, and growth factors in the pathogenesis of IBD to a book on cytokines and chemokines in autoimmune disease. Innate immunity and the role of intestinal bacteria were excellently reviewed by Macdonald and Montelone[4] and Elson et al.[5] The genetics of IBD have been reviewed by Annese et al.[6] A good general overview has been published by Rogler.[7] Herein, the updated pathophysiological concepts of IBD are reviewed.

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Genetic factors

It is very clear that genetic factors play an important role in the pathogenesis of IBD and in both Crohn's disease (CD) and ulcerative colitis (UC). Epidemiological studies in monozygotic and dizygotic twins, as well as family studies, have indicated that genetic factors may be more important in CD than in UC.

The search for susceptibility genes had its first success in 1996, when the first susceptibility locus for CD was identified in the pericentromeric region of chromosome 16, which was called IBD1. In 2001 a caspase recruitment domain-containing protein, CARD15/NOD2, was found to be mutated in 20%–30% of CD patients, establishing a proof of principle for the "genetic concept" of IBD pathophysiology. Multiple mutations in the CARD15/NOD2 gene have been identified (Fig. 3), three of which have been shown to be independently associated with CD (arg702trp, gly908arg, and leu1007fsinsC).[8] These three variants confer a 15%–20% attributable population risk among cases of familial CD. The relevance of CARD15/NOD2 for the etiology of CD was confirmed in a number of subsequent studies.[9,10] CARD15/NOD2 mutations are associated with ileal disease, earlier age of disease onset, and stricturing disease.[11] In contrast, a few articles support data that CARD15/NOD2 mutations do not play a role in the etiology of CD in Asia[12] (see Fig. 3). However, there are several abnormalities in genetic factors of Japanese IBD patients, including the HLA-DR regions.[13,14] Interestingly, most of these abnormalities are not found in Western countries. In addition, healthy homozygous carriers of the 3020insC frameshift mutation have been described,[15] indicating that CARD15/NOD2 mutations are not the sole determinant of CD and that environmental factors also play an important role. Although epidemiological data concerning CARD15/NOD2 are rather clear and have been con-

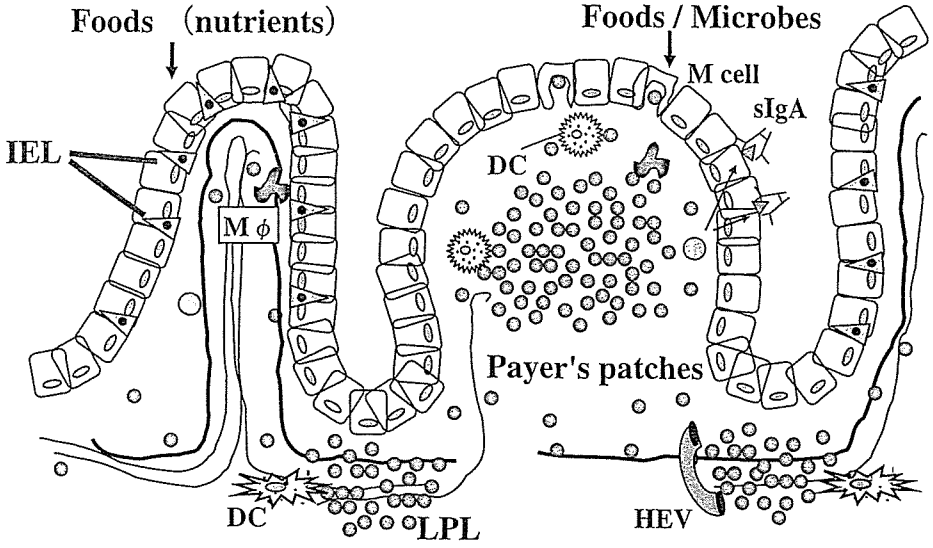


Fig. 1. Mechanism of gut-associated lymphoid tissue (GALT). Intestinal mucosa has a specific immunological apparatus, GALT, and plays a role in the defense system against microorganisms or food antigens from the luminal side

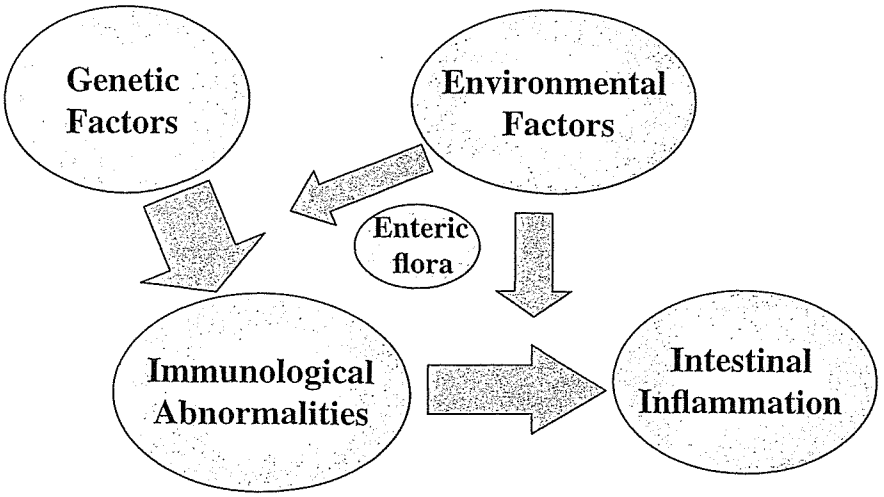


Fig. 2. General background of inflammatory bowel disease (IBD)

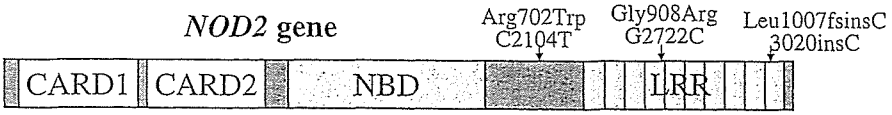
firmed, the pathway of how these mutations cause CD is less clear.

By immunohistochemistry, in situ hybridization, and reverse transcription-polymerase chain reaction, Berrebi et al.[16] showed that CARD15/NOD2 was present only in the cytoplasm of macrophages in the normal colon. Increased CARD15 expression was detected in intestinal epithelial cells (IECs) and macrophages in CD lesions. A role for Paneth cells in CARD15/NOD2-induced pathophysiology is supported by data showing CARD15/NOD2 mRNA-enriched Paneth cells in CD mucosa.[17] Expression of CARD15/NOD2 by IEC has also been shown by Hisamatsu et al.[18] They provide evidence that CARD15/NOD2 mRNA and protein were upregulated by tumor necrosis factor (TNF)-α in SW480 cells.[18]

Environmental factors

Among the environmental factors, food intake seems to be one of the most important factors that affects the pathophysiology of IBD (Fig. 4). Sakamoto et al.[19] analyzed what kind of foods were risk factors for IBD, comparing food habits of the patients with those of healthy controls at the same age. They found that intake of fast foods containing large amounts of fat and sugar-rich foods may accelerate the development of CD. Another study demonstrated that long-chain fatty acids are more irritable for intestinal inflammation than medium-chain fatty acids.[20] In most Western countries, sugar-rich foods have also been recognized as one of the risk factors for CD.

Intestinal flora and mucosal defense systems are also playing major key roles. The evidence that bacteria play



	Population	Disease	Allele frequencies of the mutations (%) C2104T	G2772C	3020insC
Ogura et al (Nature 2001)	American	NL	4.0	1.7	4.0
		CD	10.8	4.3	8.4
Hugot et al (Nature 2001)	European	NL	4	1	2
		UC	3	0	1
		CD	11	6	12
Hampe et al (Lancet 2001)	German and British	NL	N.D.	N.D.	4.8
		UC	N.D.	N.D.	3.1
		CD	N.D.	N.D.	16.0
Inoue、Hibi et al (Gastroenterology 2002)	Japanese	NL(n=272)	0	0	0
		UC(n=292)	0	0	0
		CD(n=350)	0	0	0
Leong et al (Aliment Pharma-Col Ther 2003)	Chinese	NL(n=70)	0	0	0
		UC(n=63)	0	0	0
		CD(n=65)	0	0	0
Croucher et al (Eur J Hum Genet 2003)	Korean	NL(n=232)	0	0	0
		CD(n=252)	0	0	0

Fig. 3. Crohn's disease (CD) and *NOD2* gene. Three variants in the coding region of the *NOD2* gene, located on chromosome 16q12, are associated with CD

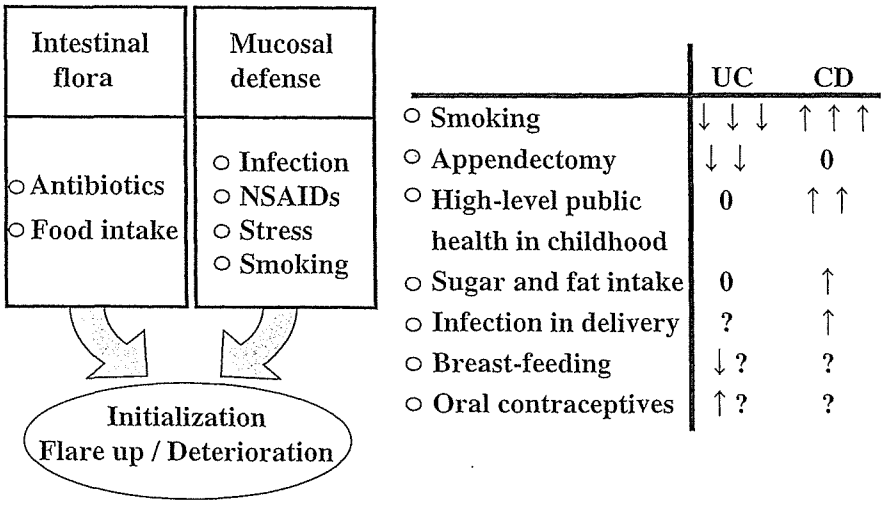


Fig. 4. Environmental factors that affect the initialization/flare-up and deterioration of IBD

a major role in the initiation and perpetuation of intestinal inflammation comes from studies with germfree animal models, a condition under which these animals do not develop intestinal inflammation, in contrast to specific pathogen-free rodents.[21] In colonic lesions of CD patients, adherent-invasive *Escherichia coli* have been found. In addition, an increased bacterial translocation into deeper layers of the mucosa has been described in CD patients, which could be of pathophysiological relevance. *E. coli* Nissle has been proved to have therapeutic potential in IBD. The mechanism could be an inhibition of the adherence and invasion of pathogenic *E. coli*,[22] which further supports a role of bacterial translocation into the mucosa in the pathogenesis of CD. In fact, fecal bacterial composition is altered in CD patients compared with healthy control subjects.[23] A role for certain bacteria in the pathogenesis of IBD is further supported by the positive effects of probiotic bacteria on intestinal inflammation and secretion of proinflammatory cytokines.[24] A lysate of *E. coli* ameliorates disease in a colitis model.[25] An increased bacterial invasion into the mucosa could be caused by ineffective innate responses such as mutated and defective CARD15/NOD2 or NF-κB protein. On the other hand, impaired or defective protection mechanisms of the mucosa could be involved. Direct mucosal protection is mediated by molecules such as mucins, trefoil peptides, or defensins. A deficiency in these molecules could cause a breakdown of mucosal protection.[26]

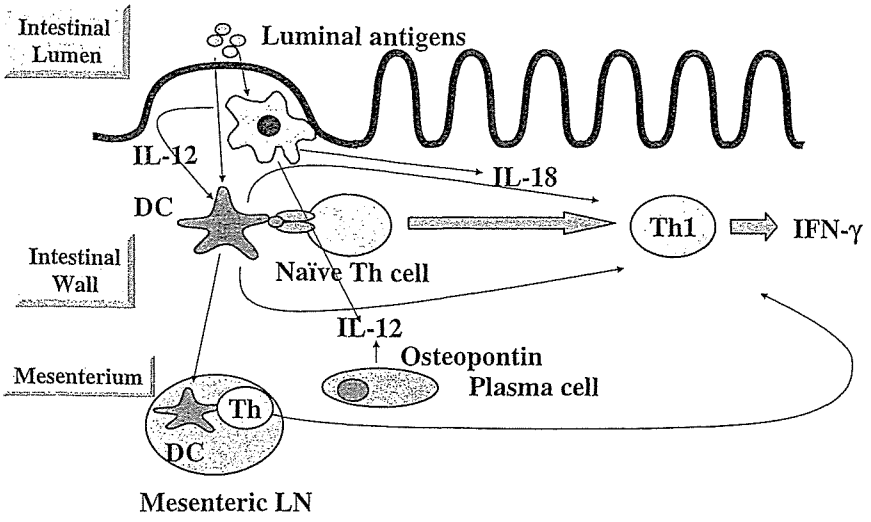


Fig. 5. Pathophysiology of Crohn's disease (CD)

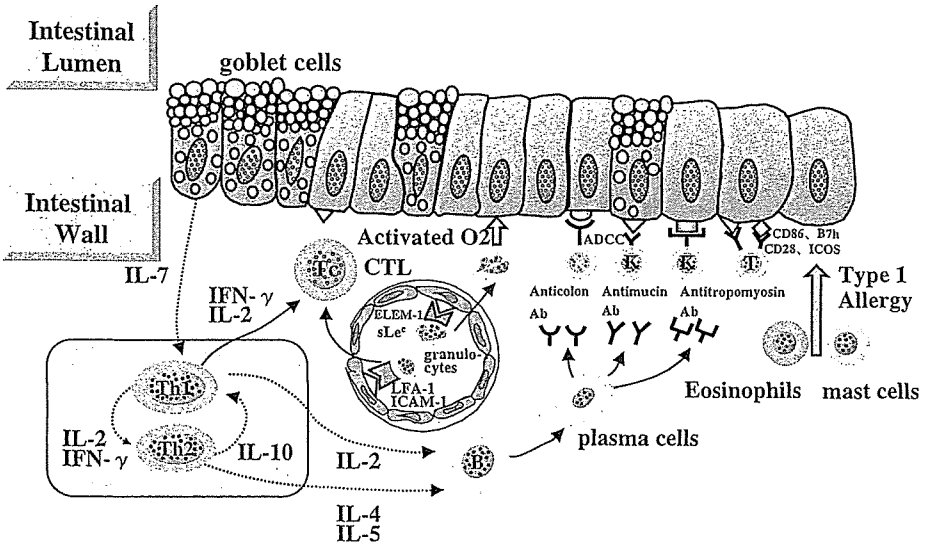


Fig. 6. Pathophysiology of ulcerative colitis (UC)

Prebiotics are nondigestible food constituents that benefit the host by selectively stimulating the growth or activity of one or a limited number of bacterial species already resident in the colon. Some examples of prebiotics are dietary fiber and some types of oligosaccharides. Intake of prebiotics can significantly alter the colonic microflora by increasing the populations of certain bacteria and thereby quantitatively changing the composition of the microflora. These alterations may act beneficially, in part, by causing a luminal increase in short-chain fatty acids (SCFAs), which are important nutrients for the intestine and inducers of an acidic environment. Butyrate, the most important SCFA, is a potent antiinflammatory factor in local chemokine secretion.[27] Clinical usefulness of prebiotics for treatment of IBD patients has been reported.[28,29]

Several studies have addressed the impact of family history of smoking in Asia as well as in Western countries. In Japanese patients, smoking showed a protective effect against UC,[30] while no relationship between smoking and severity of UC was detected in a large population of Chinese patients.[31] Among Chinese patients, exsmokers, but not current smokers or previous and current smokers combined, were at greater risk of developing CD.[32]

The protective effect of appendectomy in UC was also evaluated in a large multicenter case-control study of Japanese patients.[33] As found in European and American studies, the results showed that appendectomy had a negative association with development of UC, particularly when performed in younger patients. In a Korean study, appendectomy was also found to be protective against UC. These studies suggest that changes in environmental factors may be one of the important causes for the gradual increase of IBD patients in Asia.

Immunological abnormalities

Crohn's disease (CD) results from an excessive and persistent CD4 T-helper cell type 1 (Th1) in the gut mucosa[34] (Fig. 5). Tissue from the gut of patients with CD contains abundant transcripts for interferon (IFN)-γ, and isolated mucosal T-cells secrete large amounts of INF-γ.[35] Production of interleukin (IL)-12, one of the key cytokines involved in Th1 polarization and differentiation, is markedly increased in patients with CD.[36] The increased expression of Th1 cytokines in CD is associated with T-bet, an IFN-γ-inducible novel member of the T-box family of transcription factors.[37] IL-18 also drives Th1 cell differentiation, activates the transcription factors AP-1 and nuclear factor-κB (NF-κB) in T cells, and acts synergistically with IL-12. It is markedly upregulated in CD.[38] There are several mechanisms that induce macrophages to the production of IL-12 and IL-18. NOD2 and Toll-like receptor must be important for bacterial products to induce IL-12 production. Further, IL-12 production is accelerated by osteopontin derived from intestinal plasma cells in CD.[39] The IL-12 p40 chain can form a heterodimer with p19 protein to form a recently described cytokine, IL-23.[40] In an IL-12p40 transgenic mouse model, constitutive p40 promoter activity is seen in the terminal ileum with high expression of IL-23 p19/p40 proteins in dendritic cells.[41] There are no publications on IL-23 in CD. L-21 is another newly described T-cell cytokine, with homology to IL-3, IL-4, and IL-15, which enhances Th1 signaling and IFN-γ production. It is increased in CD in comparison with UC and controls.[42] IL-17 is a cytokine with strong proinflammatory activity.[43,44] T-cell and macrophage production of IL-17 is significantly increased in both CD and UC but not in infective or ischemic colitis.[45]

The immunological basis for ulcerative colitis (UC) is much less clearly understood. Despite the evidence of a role for Th1 in CD, support for a Th2 pathogenesis in UC is much weaker. The presence of autoantibodies such as anticolon antibody, antimucin antibody, or antitropomyosin antibody is suggestive of a Th2 pathogenesis. Although there are several conflicting immunological findings, several immunological abnormalities exist and may induce colonic inflammation (Fig. 6). Mucosal T-cell production of IFN-γ is no higher than in controls, and although isolated T cells from UC patients make considerably more IL-5 than CD or control subjects, IL-4 production is reduced.[46] In mouse colitis induced by intracolonic injection of oxazolone, another Th2 cytokine, IL-13, produced by natural killer (NK) T cells, seems to be important.[47] Nonclassical NK T cells isolated from UC mucosa also produce markedly increased levels of IL-13 and are cytotoxic to epithelial cell targets.[48] IL-13 also increases epithelial permeability.[49]

STAT3 is involved in a wide variety of sometimes opposing signaling pathways. It is the major signaling molecule for the IL-6 family of cytokines but is also activated by IL-10, granulocyte colony-stimulating factor (G-CSF), and hepatocyte growth factor.[50] STAT3, activated phospho-STAT3, and the endogenous inhibitor of STAT3 signaling, SOCS3, are markedly increased in IBD patients compared with controls.[51] Myeloid cell-specific STAT3 deletion in a mouse model makes neutrophils and macrophages unresponsive to IL-10, and produces a slow-onset chronic Th1-mediated colitis, similar to that seen in IL-10 knockout mice.[52] IFN-γ-induced somatic inactivation of STAT3 in myeloid cells also triggers an aggressive and fatal colitis.[53] Deletion of STAT3 in the bone marrow during hematopoiesis leads to the development of a rapidly fatal, CD-like enteropathy.[54]

Intestinal macrophages in normal mice showed a bone marrow-derived macrophage phenotype, and thus act as antiinflammatory macrophages, producing a high amount of IL-10 in response to enteric bacteria. By using an IL-10 knockout mouse model, intestinal macrophages in colitis showed an inflammatory phenotype in response to enteric bacteria, and whole bacteria could induce IL-12 from tissue macrophages. Further, IL-10 supplementation could attenuate abnormal IL-12 production from macrophages, and this abnormal differentiation of macrophages is also found in some CD patients.[55]

The IL-6 cytokine family signals through the gp130-like receptor, activating both STAT3 and SHP-2/ras/Erk pathways. IL-6 when complexed with soluble IL-6 receptor can bind to cells lacking the IL-6R (trans-signaling). IL-6 trans-signaling is elevated in patients with IBD and enhances T-cell resistance to apoptosis. A neutralizing antibody to IL-6R induces T-cell apoptosis and prevents trinitrobenzene sulfonic acid (TNBS) colitis, and anti-IL-6 receptor antibody shows some promise for the treatment of CD.[56] The spontaneous IBD that occurs in mice with targeted disruption of STAT3 in immune cells is probably caused by a failure of IL-10 downregulation. At the same time, in models of immune-mediated gut inflammation in normal mice, IL-6 is overexpressed in the mucosa (as it is in IBD), and signaling through gp130 helps prevent mucosal T-cell apoptosis to drive inflammation.

Epithelial repair

The chronic inflammatory process leads to the disruption of the epithelial barrier and formation of epithelial ulceration. Resolution of inflammatory activity is associated with repair processes that facilitate tissue remodeling, which restores normal intestinal architecture.

Repair processes in UC patients are often effective in restoring a normal mucosal architecture, but stricture formation associated with excess fibrosis frequently occurs in CD patients.[57] Mesenchymal cells derived from bone marrow stem cells play a crucial role in the process of intestinal repair and fibrosis.[58,59]

Bone marrow (BM)-derived cells substantially repopulate the epithelia of the human gastrointestinal tract during regeneration.[60,61] BM-derived epithelial cells reside as progenitor cells residing in the crypt and also as terminally differentiated epithelial cells. Moreover, the proliferation and the differentiation of BM-derived cells toward secretory lineage epithelial cells are accelerated when epithelial regeneration is required, thereby contributing to the epithelial regeneration following severe inflammation of the human gastrointestinal tract.[62] In IBD patients, this epithelial repair process may be disturbed.

Conclusion

Important new insights have been gained recently into the pathophysiology of IBD, particularly in regard to CD. There is strong evidence for Th1-mediated response in the pathogenesis. Microbes or food antigens may directly stimulate macrophages and dendritic cells to produce Th1 cytokines and to activate T cells. In contrast, invasion of intestinal antigens or activation of immune cells is not easily induced under normal conditions. In IBD, this vicious circle is thought to accelerate the intestinal inflammation. Thus, more precise analyses regarding some genetic or environmental factors, immunological abnormalities, and epithelial repair disorder appear to be converging to explain the pathophysiology of IBD.

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Psychological aspects of inflammatory bowel disease

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Introduction

Psychological stress has been described as "a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease."[1]

Psychological stress is widely believed to play a major role in functional gastrointestinal disorders, especially irritable bowel syndrome. There is a long history of observations suggesting that psychological stress contributes to the course of inflammatory bowel disease (IBD). The chronic medical conditions characterizing IBD, chronic diarrhea, bloody stools, abdominal pain, weight loss, malnutrition, and weakness, seem to be exacerbated by physiological and psychological stress. From this viewpoint, we often see an overlap of pathophysiology between IBD and irritable bowel syndrome (IBS). Furthermore, recent studies on IBS have demonstrated that dysregulation of the immune system and its interaction with bacteria/flora may contribute to IBS pathophysiology, just as with IBD. Here, we review the role of psychological stress in IBD, including our current preliminary observations of patients with ulcerative colitis (UC), and the possibility of an overlap in pathophysiology between IBD and IBS.

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The influence of psychological stress on gastrointestinal tract homeostasis through corticotrophin-releasing factor, a key player in the brain–gut axis

Stress can be defined as any threat to an organism's homeostasis.[2] The function of the stress response is to maintain both psychological and physiological homeostasis. Stress stimulates the release of corticotrophin-releasing factor (CRF) from the hypothalamus, causing the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. Stress finally stimulates secretion of cortisol from the adrenal cortex, and it also directly activates the autonomic nervous system. Stimulation of the sympathetic nervous system in response to stress causes the release of adrenaline and noradrenaline from the adrenal medulla. The autonomic nervous system also directly affects all nerves of the gut, that is, the enteric nervous system (ENS). The ENS contains around 100 million neurons and provides a highly systematic neural network in the gut. Thus, brain and ENS together make up a network termed the brain–gut axis[3,4] (Fig. 1). While central CRF regulates the ACTH-cortisol system, peripheral CRF directly induces alteration of gastrointestinal (GI) motility. Endogenous CRF mediates the stress-induced inhibition of the upper GI tract and the stimulation of colonic motility. The inhibition of gastric emptying by CRF may be through CRF-2 receptor signaling, while CRF-1 receptors are involved in colonic motility in response to stress.[5] Consistent with this is that peripheral administration of CRF antagonist affects colonic and gastric motility.[6] Endogenous serotonin (5-hydroxytryptamine, 5-HT) released in response to stress seems to be involved the alteration of colonic motility by stress-induced CRF through 5HT-3 receptors. Further, CRF is thought to have the potential to change the production of several cytokines[7,8] and the function of immune cells, including lymphocytes and NK cells.[9] Interestingly, it has been reported that CRF contributes to the