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Mucosal Remodeling and Alteration of Stromal Microenvironment in Ulcerative Colitis as Related to Colorectal Tumorigenesis

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1. Introduction

As an organ-specific, chronic inflammation-carcinoma sequence, it is well known that colorectal neoplasia is prone to appear in long-standing ulcerative colitis (UC) (Lennard-Jones et al., 1983). It has been shown that the tumor suppressor gene, *p53* mutation, which results from chromosomal instability due to inflammation-driven DNA damage plays an important role in the early stage of tumorigenesis (Hussain et al., 2000; Yoshida et al., 2003; 2006). However, the incidence of *p53* mutation is approximately up to 50% in dysplasia and carcinoma lesions in UC, according to our examination with our novel combined method of microdissection and polymerase chain reaction (PCR)-direct sequencing of the full-length *p53* gene from single crypts in long-standing UC (Yoshida et al., 2004). Instead, we have shown that mucosal remodeling and stromal genomic instability can be raised as another factor for carcinoma development. In this chapter, we describe the mucosal remodeling and genomic instability of stromal cells as well as epithelial cells, suggesting insufficient cross-talk between epithelium and stroma in long-standing UC.

2. Mucosal remodeling, correlative to the duration of ulcerative colitis (UC)

2.1 Colorectal mucosal remodeling in long-standing UC

Regarding the structural alterations of colorectal mucosa formerly, there were no systemic analyses but there were sporadic descriptions such as distortion and atrophy of crypts, and Paneth cell metaplasia in UC (Floren et al., 1987; Day et al., 2003). For a general image of mucosal remodeling in long-standing UC, we reconstituted 3-dimensional features after taking serial histological sections of UC cases. Representative three-dimensional reconstructed images are shown in Fig. 1.

In order to find risk factors for cancer development in long-standing UC, according to these general features, we tried to assess mucosal remodeling of rectal mucosa, including

decreased number (/cm), height (μm) and angle (degree) of crypts and increased fused crypts (/100 crypts), metaplastic Paneth cells (/100 crypts) and thickening of muscularis mucosa (μm) quantitatively, and found most of items correlated significantly with the duration of illness in UC (Fig. 2).

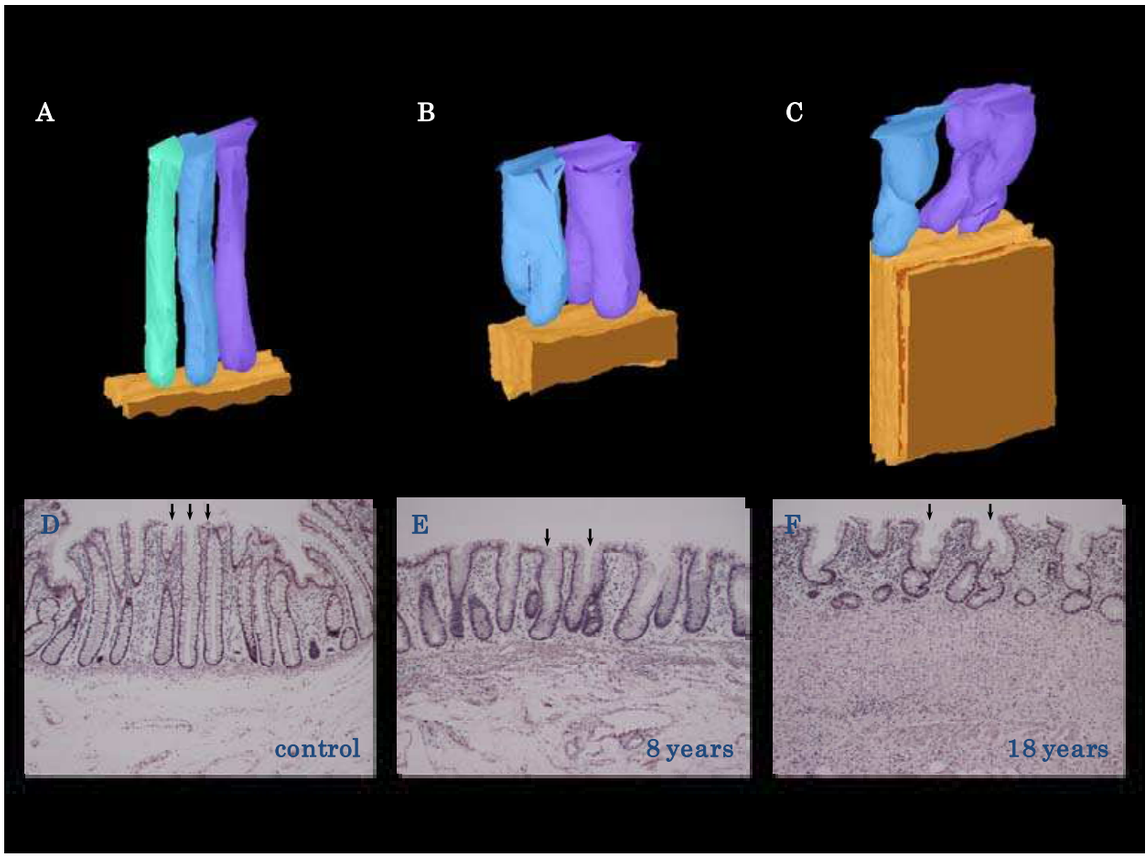

Fig. 1. A three-dimensional, reconstructed figure of rectal mucosa in UC (Control and UC cases for 8 and 18 years) (Mitsuhashi et al., *Pathol Int*, 2005)

However, there were no significant differences of increased or decreased correlation lines of each marker between the two groups, UC, inactive, without neoplasia and with neoplasia, or between the two groups, UC, active without neoplasia and with neoplasia. For immunohistochemical markers, Ki-67 (for cellular proliferative activity), p53, p21 and ssDNA (for apoptosis) labeling indices (LI) (%) were significantly correlated with the duration of illness (Fig. 3). The period-dependent increase of epithelial p53 and p21 LI is clearly shown. Furthermore, epithelial p53 and p21 LI were significantly higher in the non-neoplastic rectal mucosa of long-standing UC patients with colorectal neoplasia compared with those without neoplasia (Mitsuhashi et al., 2005).

Epithelial p53 and p21 overexpression means acceleration of G1 check point due to inflammatory oxidative stress, indicating accumulation of DNA damage in line with pathway for tumorigenesis (Yoshida et al., 2003; 2006). Canonical discriminative analysis using duration of UC illness, number of crypts, angles of crypts and thickness of muscularis mucosa gave no clear difference between UC with neoplasia and without neoplasia (Fig. 4-

1). However, in particular, Ki-67LI, p53LI and p21LI can give reliable canonical discriminative values to estimate the risk of cancer development as compared with UC without neoplasia (Fig. 4-2).

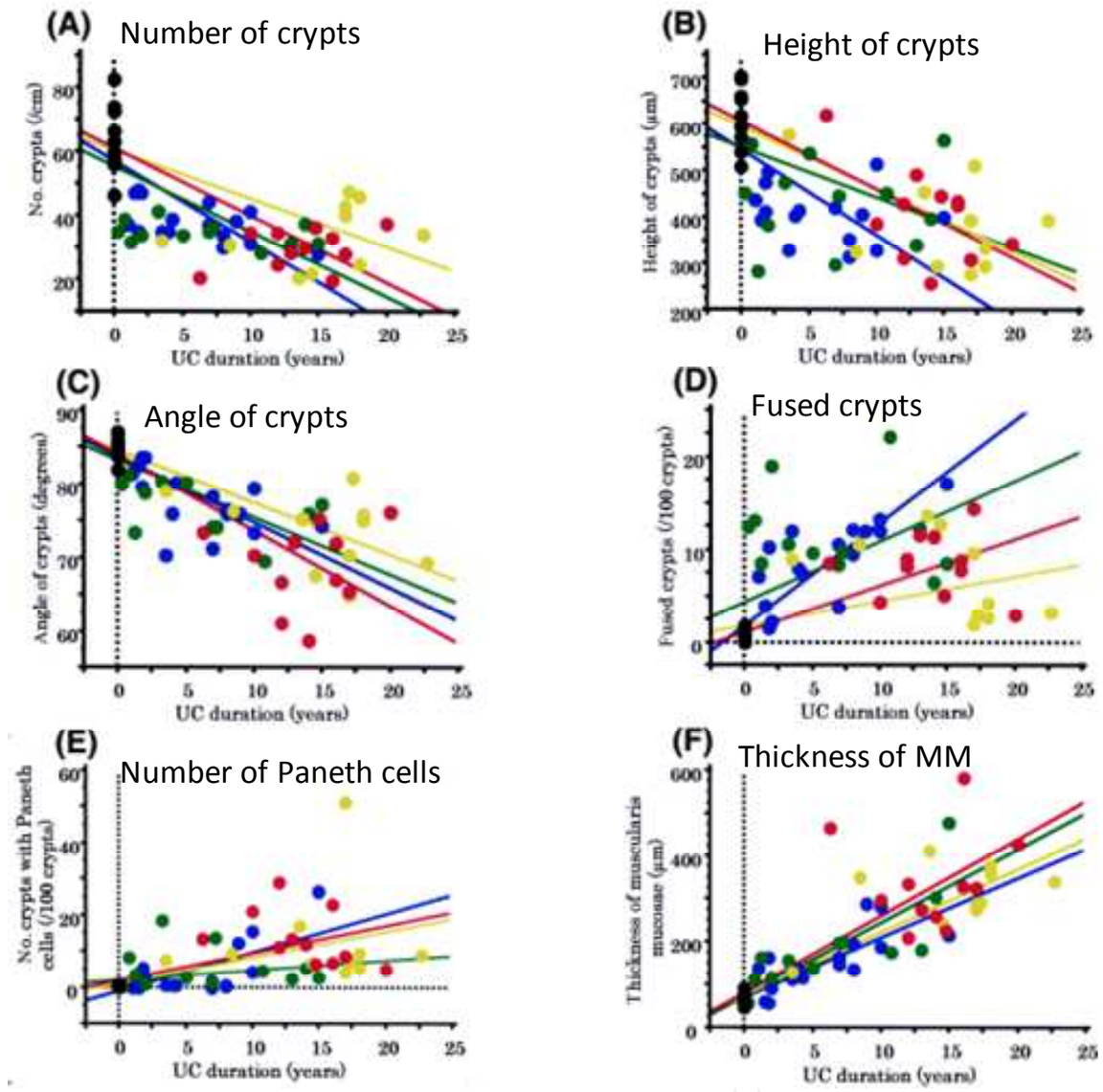

Fig. 2. Morphometrical assessment of mucosal remodeling of rectum in UC
(A) Number, (B) height and (C) angle of crypts, (D) fused crypts , (E) crypts with Paneth cells and (F) thickness of muscularis mucosa (MM) with relation to the duration of UC illness and cancer development (○ UC, active with neoplasia; ○ UC, active without neoplasia; ○ UC, inactive with neoplasia; ○ UC, inactive without neoplasia) (Mitsuhashi et al., *Pathol Int*, 2005)

Thus, the above described markers in rectal biopsy specimens can be useful to predict the risk of colorectal tumor development in long-standing UC, using canonical discriminative analysis.

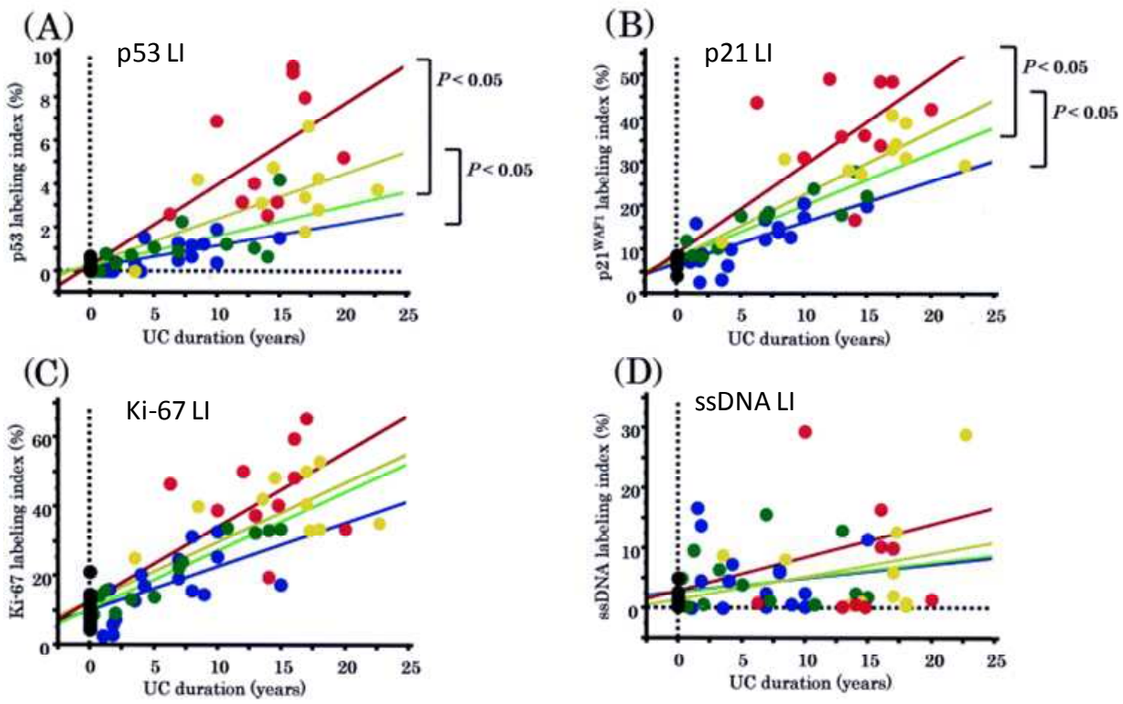

Fig. 3. (A) p53, (B) p21, (C) Ki-67 and (D) ssDNA labeling indices (LI) with relation to the duration of UC illness and cancer development (○ UC, active with neoplasia; ○ UC, active without neoplasia; ○ UC, inactive with neoplasia; ○ UC, inactive without neoplasia) (Mitsuhashi et al., *Pathol Int*, 2005)

2.2 The increase of stem-cell mutated crypts as related to the duration of UC illness

O-acetylation of epithelial sialoglycoprotein identified by mild PAS staining can show N-acetyl neuraminic acid phenotypes (Fig. 5). Mutated crypts in UC patients of heterozygous *O*-acetylation (oat^a/oat^b), which show a positive reaction with mild periodic acid-Schiff (PAS) staining in negative background mucosa (Fig. 5), were counted per 10,000 crypts. With this method, mutated crypts increased correlatively with the UC duration. Furthermore, clusters of crypts, positive with mild PAS staining, indicating regenerated crypts covered by a single tissue stem cell after erosion, also increased correlatively with the duration of the UC illness (Fig. 6). Moreover, non-neoplastic mucosal crypts in cases of sporadic colorectal carcinoma also showed significant increase of mutated crypts with mild PAS staining, although angles of their correlation lines were extremely low compared with those in UC cases. Elongated lines of the correlation between two factors showed 0 crypts at 0 years old, indicating gradual appearance of mutated crypts after birth. Thus, mutated crypts appear extremely higher in UC patients than non-UC patients (Fig. 6).
These results indicate the base of a chronic inflammation- carcinoma sequence (Okayasu et al., 2002; 2006).

2.3 Shortening of telomere length of colonic epithelial cells in UC

In addition to chromosomal alterations due to chronic inflammation-driven DNA damage through the generation and effects of reactive oxygen species, telomere shortening in mucosal epithelia is an important factor in tumorigenesis. The telomere shortening in colonic

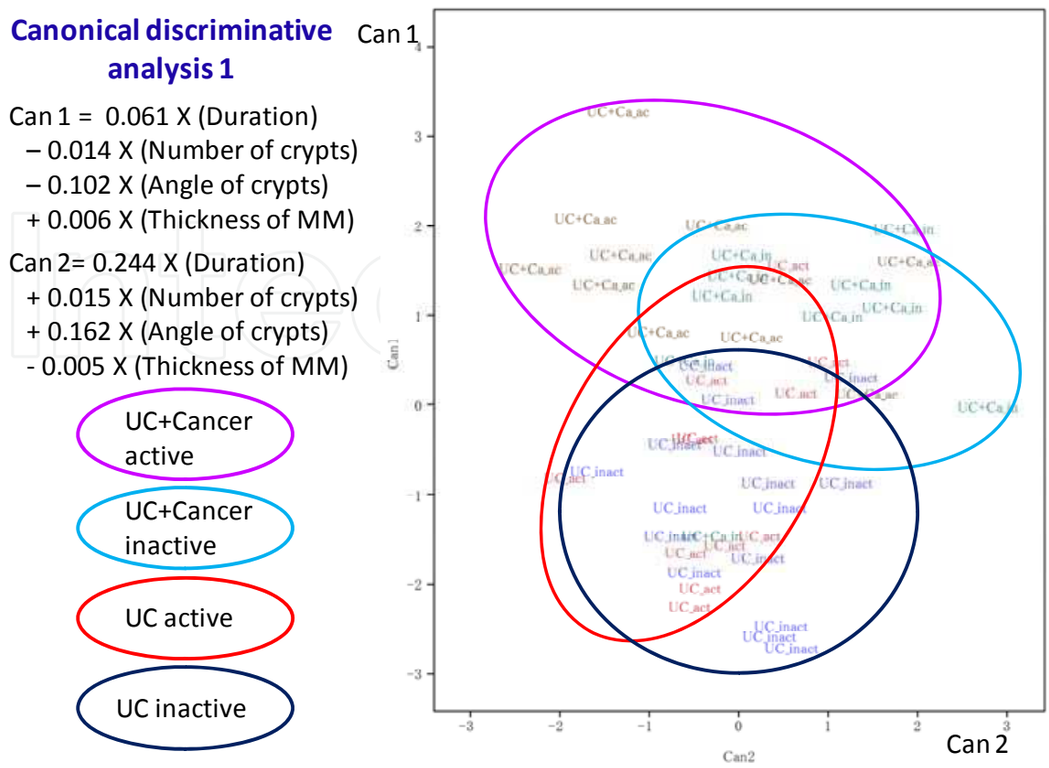

Fig. 4-1. Canonical discriminative analysis with number and angle of crypts and thickness of muscularis mucosa (MM) among UC active or inactive and with or without neoplasia

epithelia is reported in long-standing UC, particularly in patients with colorectal cancers, suggesting an unstable state of chromosomes in which cells can easily mutate (Risques et al., 2008; 2011, Bronner et al., 2008). In addition to UC, telomere shortening is detected in esophageal Barrett's mucosa-Barrett's adenocarcinoma sequence by our group (Shiraishi et al., 2009). This phenomenon suggests an accelerated aging in inflamed lesions (Risques et al., 2008; 2011).

3. Alteration of subepithelial (pericryptal) myofibroblasts and interstitial fibrosis in UC

We have clearly shown that subepithelial myofibroblasts forming crypt niches have various phenotypic expressions of α-smooth muscle actin (αSMA), NCAM, PGP9.5, HSP47 and cytoglobin (Cygb) by immunohistochemistry (Fig. 7) or immunofluorescence (Fig. 8) and immunoelectron microscope (Fig.9). Therefore, we first identified these subepithelial myofibroblasts as colonic stellate cells (also known as perisinusoidal cells or Ito cells, fat storing cells in perisinusoidal spaces of the liver). Subepithelial myofibroblasts are localized between mucosal epithelia and capillaries, similar to hepatic stellate cells between liver cells and sinusoids. Further, subepithelial myofibroblasts occasionally have small lipid droplets indicating vitamin A storage. Subepithelial myofibroblasts are localized more at the crypt base than they are at the crypt surface, similar to the dense localization of hepatic stellate cells at the periportal area in hepatic lobules. These features indicate that subepithelial myofibroblasts correspond to colonic stellate cells (Okayasu et al., 2009; 2011).

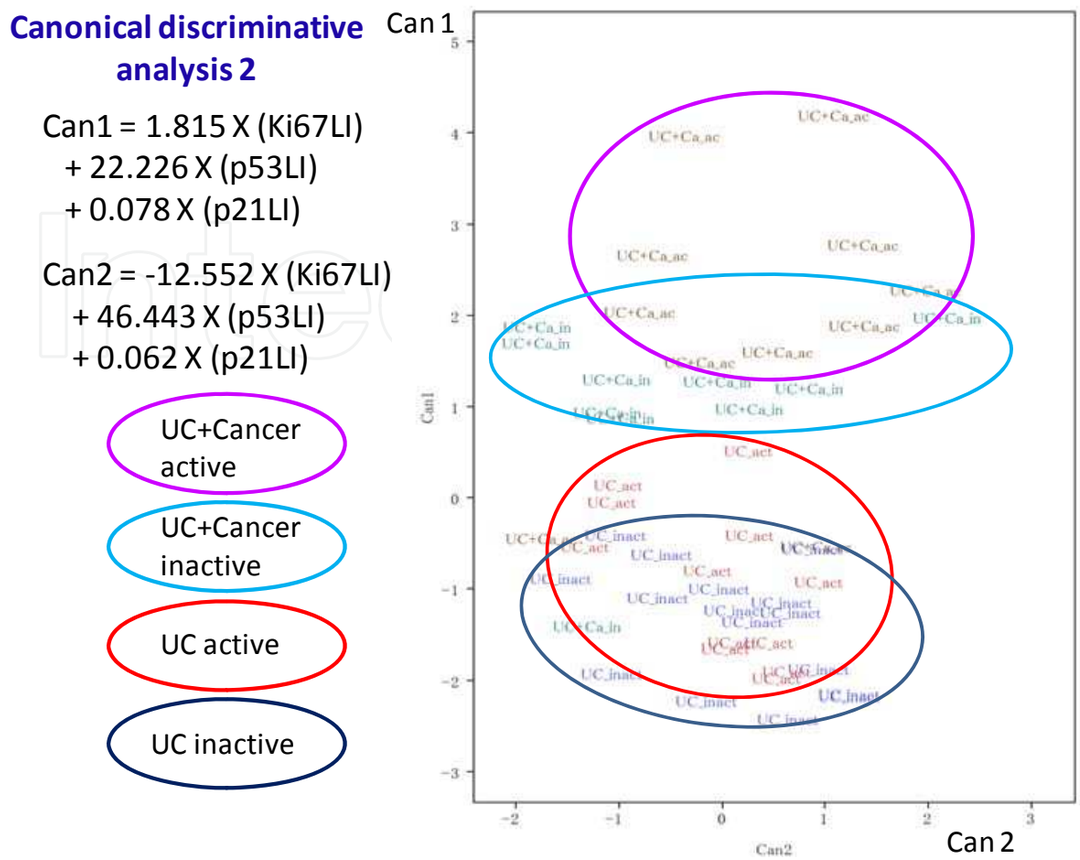

Fig. 4-2. Canonical discriminative analysis with Ki-67, p53 and p21LI among UC active or inactive and with or without neoplasia. There is no overlap between UC+Cancer and UC groups.

It is known that subepithelial myofibroblasts secrete pericryptin, a specific extracellular matrix protein, which recruits activated fibroblasts and forms collagen fibrils, supporting the growth of epithelial components after mechanical stress in tissue repair processes (Shimazaki et al., 2008).

Cytoglobin (Cygb), a novel member of the globin family is also expressed in splanchnic fibroblasts-like cells, including hepatic stellate cells and colonic subepithelial myofibroblasts. A recent study demonstrated that Cygb served as a defensive mechanism against oxidative stress under hypoxic conditions in a kidney ischemia-reperfusion experimental system (Nishi et al., 2011). Thus, subepithelial myofibroblasts at the crypt base play important roles to protect and support crypt stem cells and their differentiation and maturation as stem cell niches.

Furthermore, we reported the decrease of subepithelial myofibroblasts, along with the inversely correlated increase of interstitial myofibroblasts and fibrosis, in relation to the duration of UC illness (Okayasu et al., 2009) (Table 1). Loss of subepithelial myofibroblasts means dysregulation of colonic crypt stem cell protection and differentiation. Interstitial fibrosis with the increase of stromal myofibroblasts in colonic mucosa, may also accelerate erroneous interactions between epithelial and stromal cells. These alterations might be major components of a microenvironment conductive to tumorigenesis (Fig. 11).

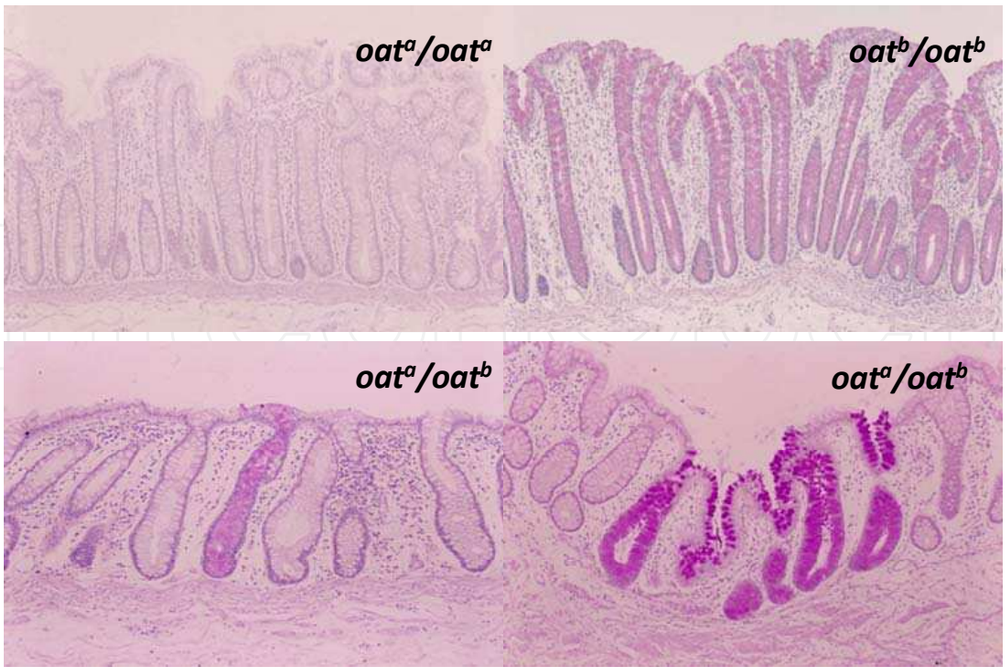

Fig. 5. *O*-acetylation phenotypes (*o*-acetyl transferase) in colonic mucosa with mild PAS staining. Single mutated crypt and a cluster of mutated crypts in UC patients of heterozyogous *O*-acetylation (oat^a/oat^b) are shown in the lower left and right figures, respectively. (Okayasu et al., *Cancer Res*, 2002)

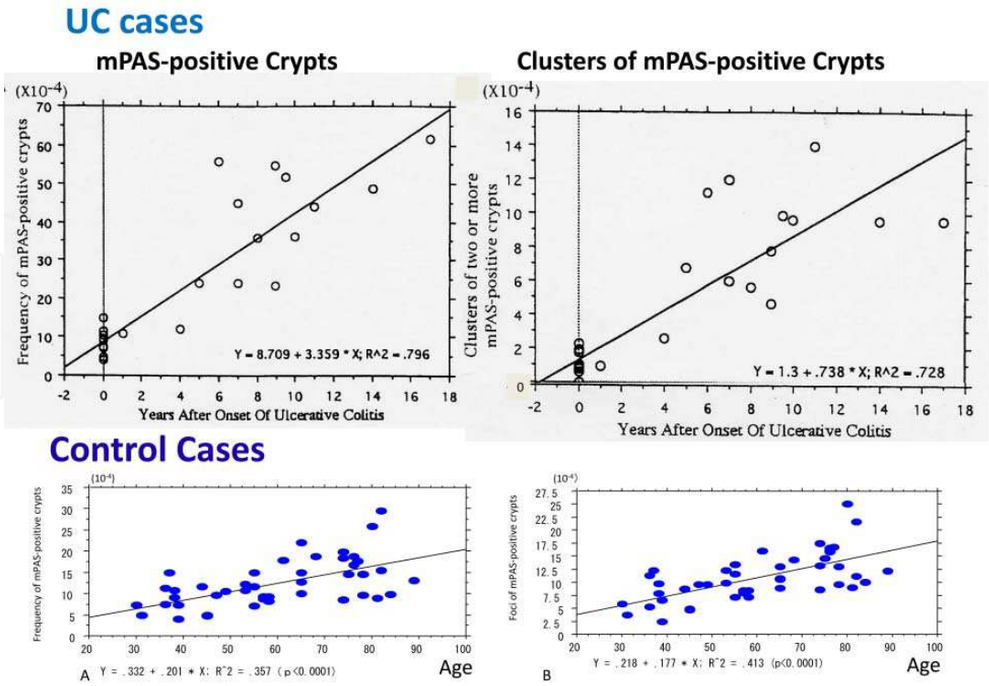

Fig. 6. Correlative increase of mild PAS$^+$ crypts with the duration of illness in UC, and with the age in control cases (/1x10^5 crypts) (Okayasu et al., *Cancer Res*, 2002; *Cancer Sci*, 2006)

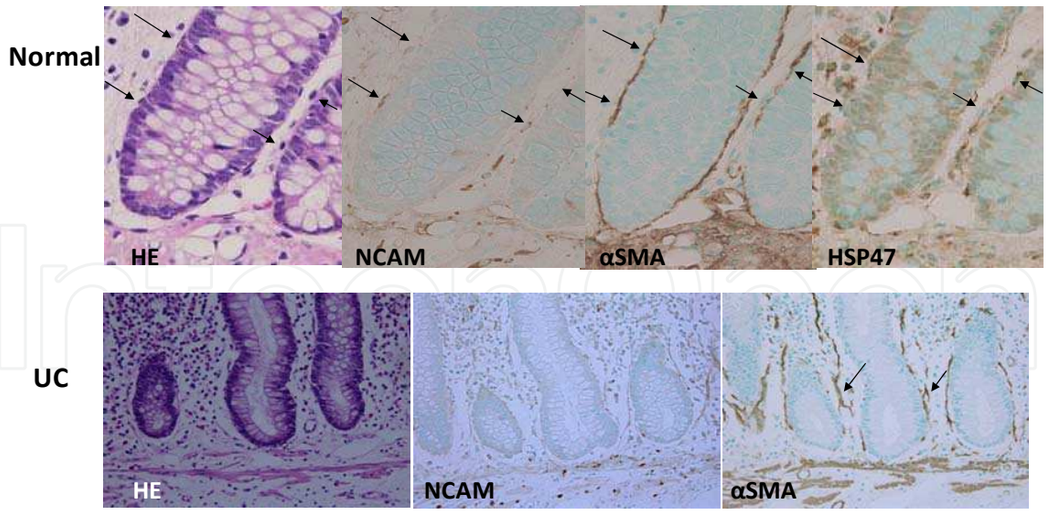

Fig. 7. Immunohistochemical phenotypes of subepithelial myofibroblasts (arrows) in UC. Subepithelial myofibroblasts (arrows) are located around the crypts. Identification of subepithelial myofibroblasts as colonic stellate cells (Ito cells, fat-storing cells) by findings of αSMA$^+$, NCAM$^+$, HSP47$^+$, Cytoglobin$^+$ and lipid droplets. (Okayasu et al., *Pathol Int*, 2009; *Histol Histopathol*, 2011)

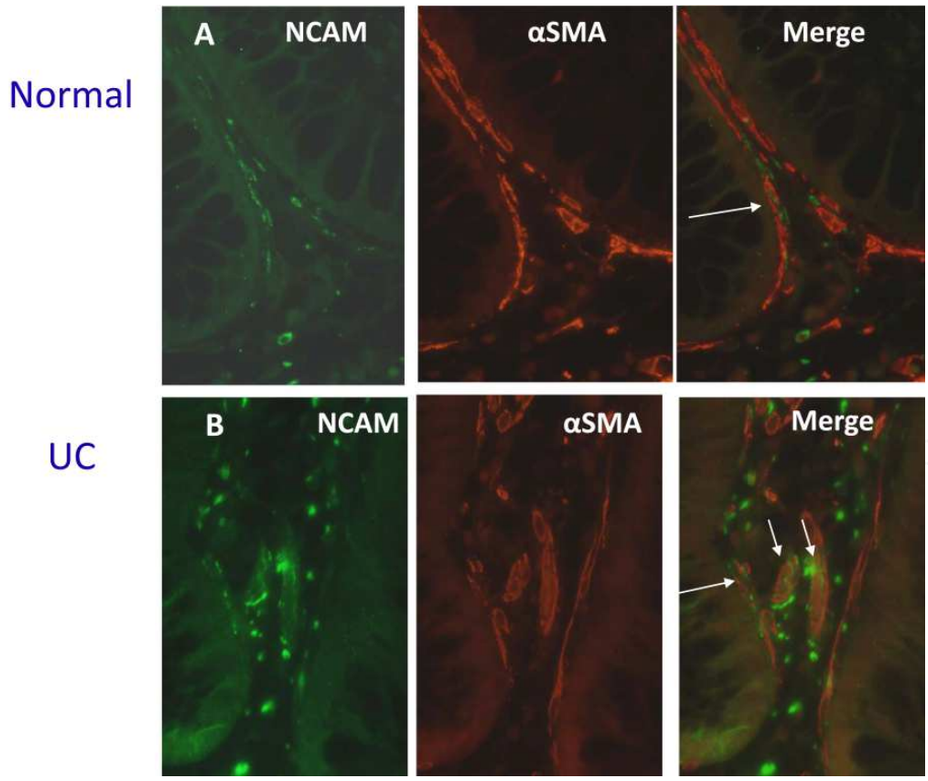

Fig. 8. Double immunofluorescences of subepithelial myofibroblasts (arrows) in UC. Double positive reactions are shown in subepithelial myofibroblasts (large arrows) of normal mucosa and in both subepithelial myofibroblasts (large arrow) and interstitial myofibroblasts (small arrows) of UC-mucosa. (Okayasu et al., *Pathol Int*, 2009)

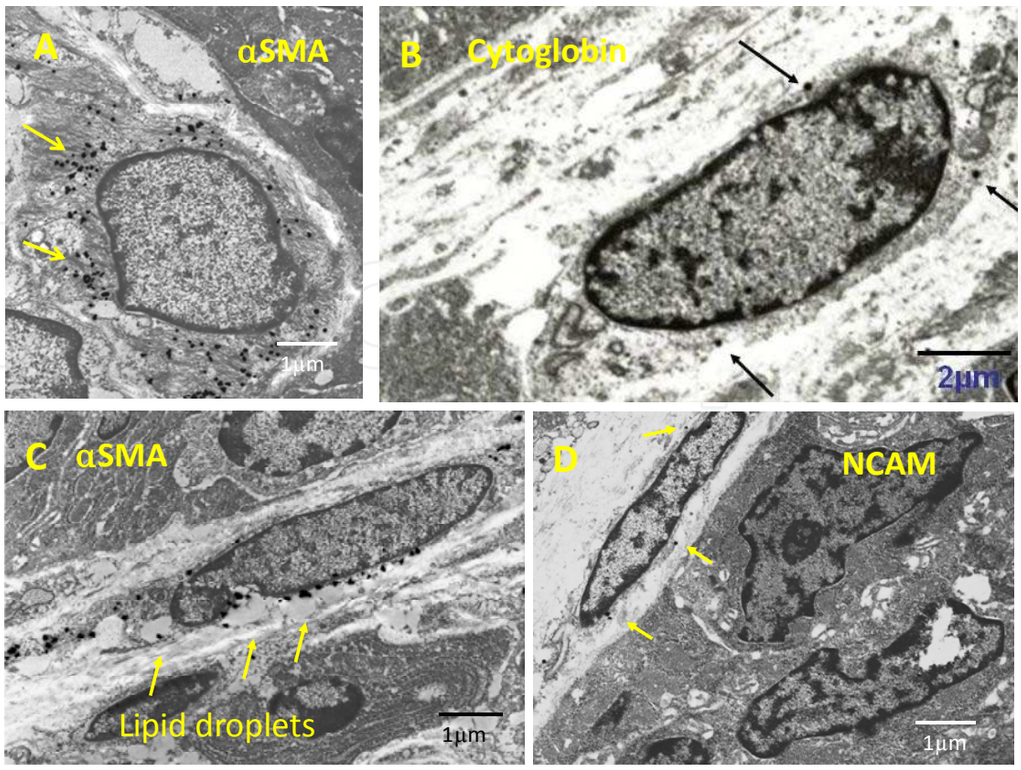

Fig. 9. Immunoelectron microscopic features of subepithelial myofibroblasts (arrows, immunogold deposits). A, Smooth muscle actin (αSMA); B, Cytoglobin; C, αSMA. Lipid droplets (arrows) in a subepithelial myofibroblast, indicating a vitamin A storage cell; D, NCAM. (Okayasu et al., *Pathol Int*, 2009; *Histol Histopathol*, 2011)

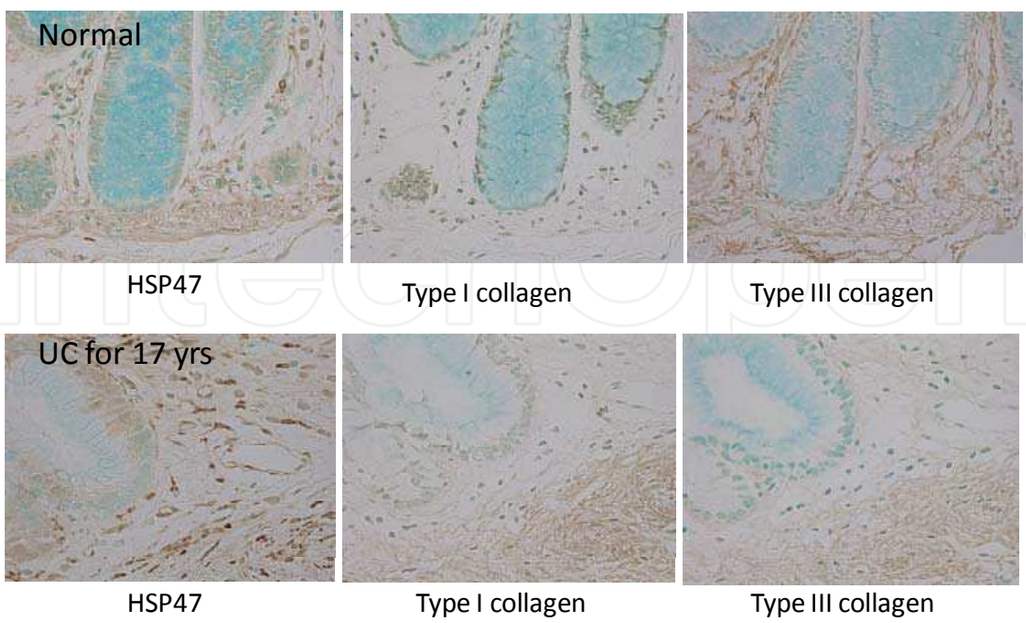

Fig. 10. Immunohistochemical features of the stroma in the rectal mucosa in UC for 17 years and control. (Okayasu et al., *Pathol Int*, 2009)

4. Epithelial and stromal genomic instability in UC and its relation to tumorigenesis

We have analyzed genomic instability, microsatellite instability (MSI) and loss of heterozygosity (LOH) in stromal cells, as well as epithelial cells, in order to see the role of stromal cell alterations in UC-associated tumorigenesis, using a combination of laser-captured microdissection and the Gene-scan approach (Fig. 12). Stromal genomic instability kept the same incidences in dysplasia and invasive carcinoma lesions as those of regenerative mucosa. The frequency of LOH or MSI for 5 tumor suppressor gene (TSG) markers, D9S161 (close to $p16^{INK4A}$), D7S486 (close to ST-7), D13S268 (close to Rb), D18S474 (close to Smad 4 and DCC) and D3S1300 (close to the FHIT [fragile histidine triad]) was almost constantly found to be increased in stromal components of all lesion types (regenerative mucosa, dysplasia and carcinoma). In contrast, the epithelial cells showed a step-up increase of MSI in tumor progression and a constant increase of LOH for TSG markers. In epithelium, LOH for 4 chromosome17 markers, D17S796 (17p13 close to the *p53* gene, TP53 (17p13, the *p53* gene locus), D17S786 (17p13, close to the *p53* gene) and D17S579 (p17q21, close to *BRCA1*) increased along with histological progression. In stroma, LOH was relatively low, but there was a constant incidence in all types of lesions. When data were combined for TSG and chromosome 17 markers, the tendency was prominent that stromal cells showed a constantly increased incidence of both MSI and LOH in all types of lesions, including regenerative mucosa, dysplasia and carcinoma, compared with the step-up increase in epithelium along with histological progression (Matsumoto et al., 2003a; 2003b; Yagishita et al., 2008). On the other hand, genomic instability for NCI-recommended standard microsatellite markers for colorectal cancers, BAT25, BAT26, D2S123, D3S346 and D17S250 (Boland et al., 1998) was not remarkable, indicating that chromosome 17 and tumor suppressor gene markers are more sensitive in UC-associated mucosal lesions (Matsumoto et al., 2003a).

	Mucosa propria			Muscularis mucosae		
	Without neoplasia		With neoplasia	Without neoplasia		With neoplasia
Total duration	<5 years	≥5 years	≥5 years	<5 years	≥5 years	≥5 years
Thickness†	↓	↓▽	↓▽	↑	↑△	T△▲
Subepithelial myofibroblasts						
α-SMA+ cells	↓	↓▽	↓▽			
NCAM+ cells	↓	↓	↓▽▼			
HSP47+ cells	↑	↑	↓▽▼			
Interstitium in lamina propria						
NCAM+ interstitial cells	→	→	↓▼			
α-SMA+ interstitial cells	↑	↑	↑△▲			
CD68+ macrophages	↑	→	▲			
Collagen type I	↑	↑	↑	↑	↑△	↑△
Collagen type III	↑	↑	↑	↑	↑△	↑△

‡Inactive phase according to the Seo clinical activity index at surgical operation. †Partly from Ref 19.
↓or ↑ significantly decreased or increased, compared to the normal control group.
▽ or △ significantly decreased or increased, compared to the group (<5 years).
▼ or ▲ significantly decreased or increased, compared to the group (≥5 years, without neoplasia).
→ not significant, compared to the normal control group.

Table 1. Summary of stromal cell alterations in the rectal mucosa in UC (Okayasu et al., *Pathol Int*, 2009)

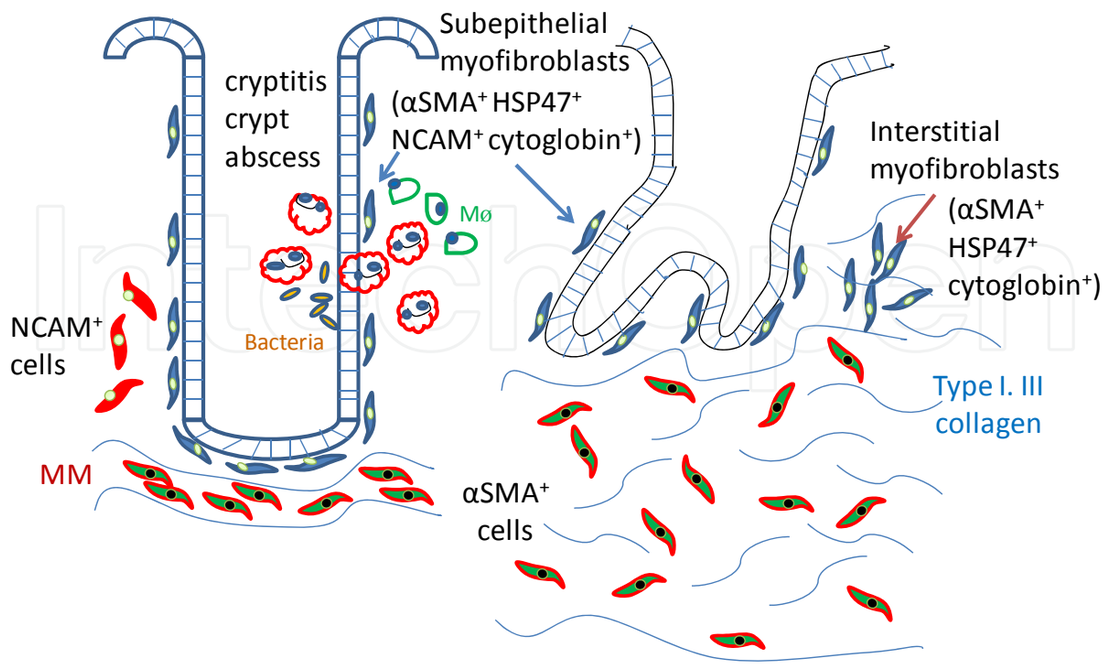

Fig. 11. Schema of mucosal remodeling in UC (Lt, early active lesion; Rt, long-standing UC)
MM, muscularis mucosa

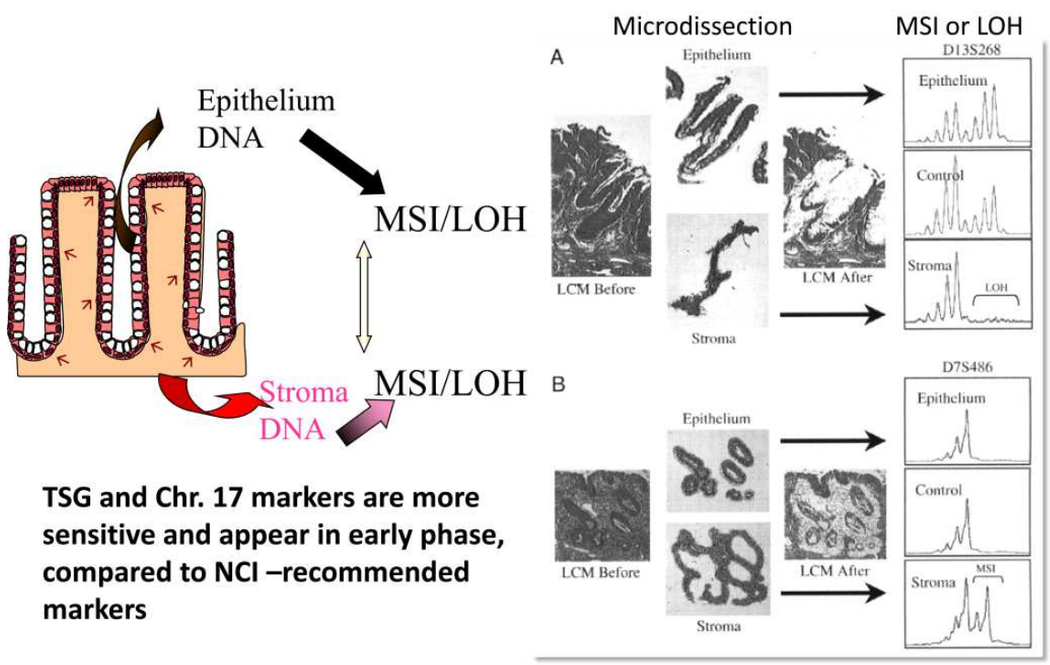

Fig. 12. Analysis method of genomic instability in both epithelial and stromal cells by a combination of microdissection and PCR-gene scan
MSI, microsatellite instability; LOH, loss of heterozygosity; LCM, laser-captured microdissection (Yagishita et al, *Scand J Gastroenterol*, 2008)

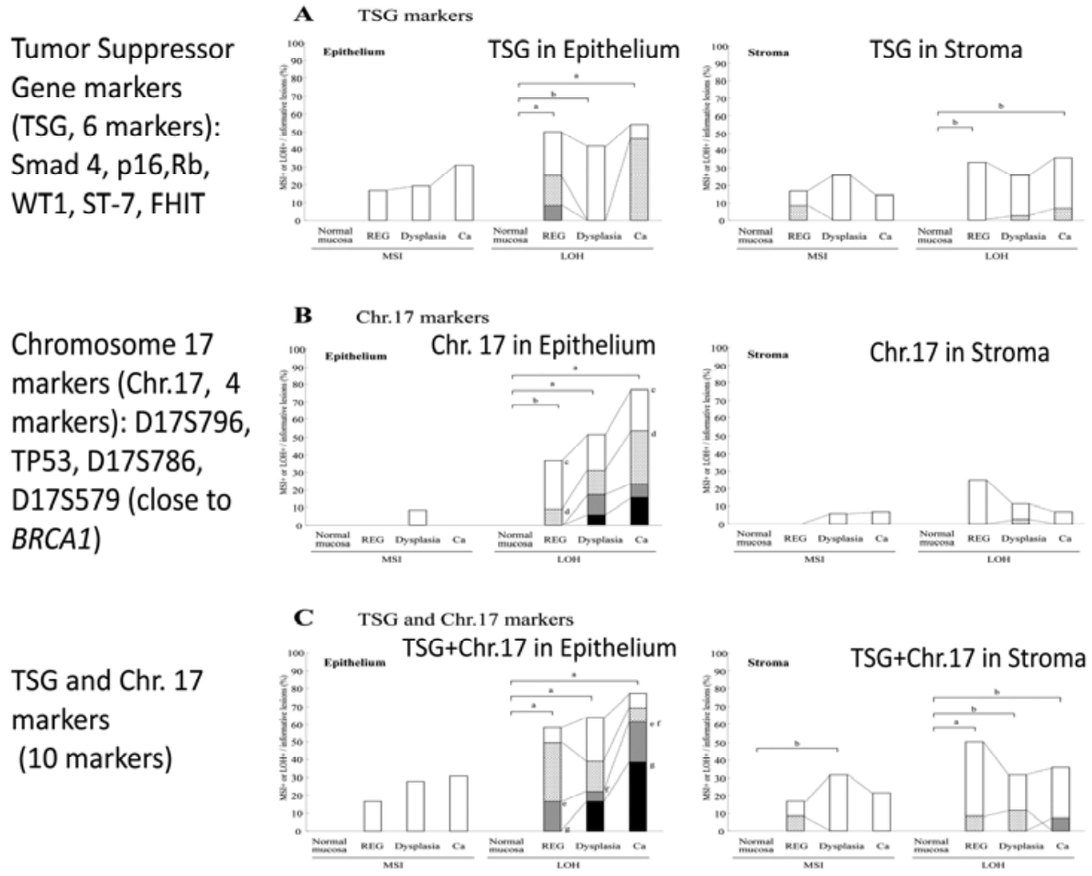

Fig. 13. MSI and LOH incidences in mucosal epithelial and stromal cells in UC
MSI, microsatellite instability; LOH, loss of heterozygosity. Bars on horizontal axis show normal mucosa, regenerative mucosa, dysplasia and carcinoma, respectively. Open bars, positive for 1 marker; dotted bars, for 2 markers; gray bars, for 3 markers; black bars for 4 or more markers. Horizontal lines indicate significant difference ($p<0.05$~0.01) between two bars (lesion groups). Left part shows MSI, and right part shows LOH in each figure.
(Yagishita et al., *Scand J Gastroenterol*, 2008)

Genomic instability in sporadic colorectal tumorigenesis, including *de novo* carcinogenesis and the adenoma-carcinoma sequence, was prominent in epithelium compared with a low incidence in stroma (Ishiguro et al., 2006; Ogawa et al., 2006). We also demonstrated that genomic instability was accelerated in stromal cells in Barrett's mucosa and Barrett's adenocarcinoma sequence in the esophagus similarly to UC tumorigenesis (Shiraishi et al., 2006).

Contribution of genomic instability in stromal cells to carcinogenesis is variable in the tumorigenesis of various organs. It has been demonstrated that stromal genomic instability due to hormonal dysfunction precedes in tumorigenesis of the breast (Moinfar et al., 2000; Shekhar et al., 2001). Thus, enhanced genomic instability in stromal cells is important in the chronic inflammation-carcinoma sequence.

5. Stochastic pathways in a chronic inflammation-carcinoma sequence

Various kinds of inflammatory cytokines, cell cycle regulators and other cell signal molecules are repeatedly cycle regulators are repeatedly or continuously activated in chronic

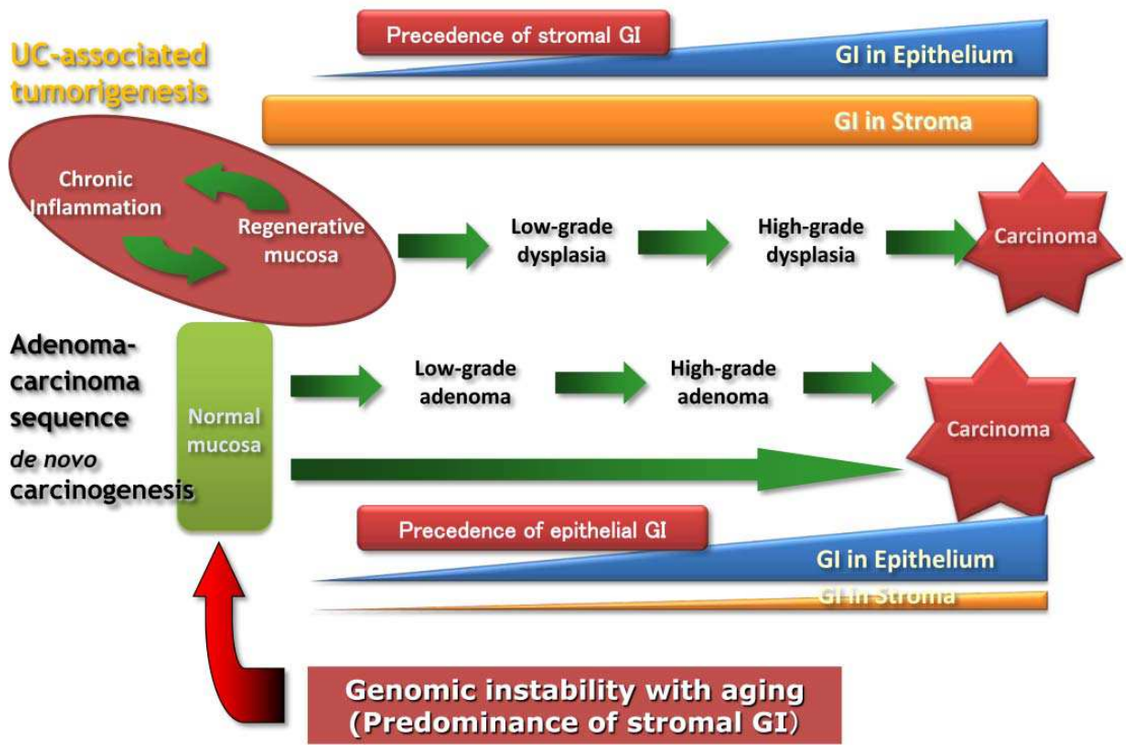

Fig. 14. Summary of genomic instability patterns in epithelium and stroma in various carcinogenesis of the colorectum. GI, genomic instability

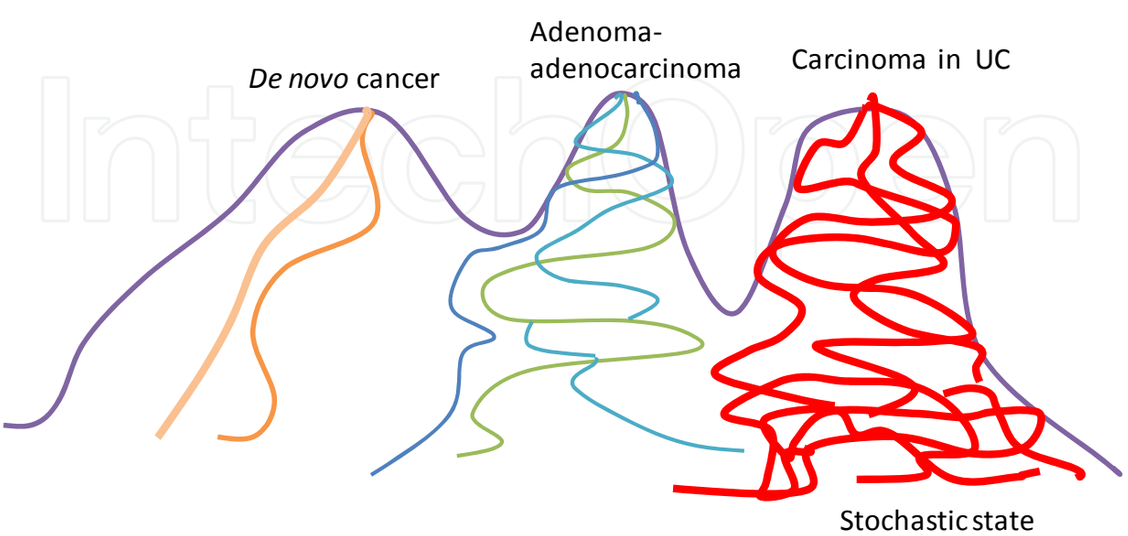

Fig. 15. Schema of tumorigenesis in colorectal cancers

inflammation, such as TNF-α, IL-8, IL-6, toll-like receptors, cell cycle G1-check point and NF-kB (Yoshida et al., 2003, 2004; Ohkusa et al., 2009). Compared to de novo cancer development and the adenoma-carcinoma sequence, stochastic pathways to tumor development can be proposed in a chronic inflammation-carcinoma sequence. In a mountain climbing analogy, it is obvious that various climbing pathways connecting with that various climbing pathways connecting with each other showing stochasticity at the mountain-base are reduced to several paths and then even fewer paths as one approaches closer to the top of the mountain. The analogy in the body is that stochastic (probabilistic) pathways to tumor development over time gain commonalty through chronic inflammatory stimulation (Kobayashi and Inoue, 2008; Inoue and Kobayashi, 2011).

6. Conclusions

Not only chromosomal instability, telomere shortening and genomic instability of epithelial cells due to chronic inflammation-driven DNA damage, we also stressed the important role of mucosal remodeling, including morphological alterations and genomic instability of stromal cells, suggesting insufficient crosstalk between epithelial and stromal cells, as it relates to UC-associated tumorigenesis.

7. References

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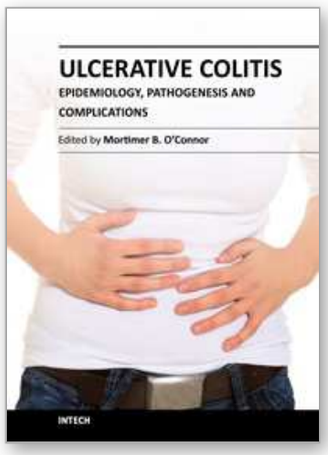

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This book is intended to act as an up-to-date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular, Ulcerative Colitis. All authors of the chapters are experts in their fields of publication, and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating, and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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