Proposal of a New Hypothesis on the Development of Colorectal Epithelial Neoplasia: Nonspecific Inflammation – Colorectal Paneth Cell Metaplasia – Colorectal Epithelial Neoplasia

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Key Words

Paneth cell metaplasia • Colorectal cancer • Colorectal adenoma • Colorectal epithelial neoplasia • Paneth cell • K-ras • Microsatellite • DNA • Replication error

Abstract

Colorectal epithelial neoplasia (CR-EN), both adenoma and adenocarcinoma, may develop from the essential tubules of the colorectum. In order to conclude the carcinogenesis of the colorectal cancer more clearly, the biological features including the genetic abnormality of the nonneoplastic mucosal epithelium of colon and rectum, which coexist in connection with CR-EN, should be investigated. In this review, the importance of Paneth cell metaplasia of colorectum as one of the original mucosal regions of the development of CR-EN, and the new hypothesis on the development of CR-EN (nonspecific inflammation – colorectal Paneth cell metaplasia – colorectal epithelial neoplasia) are examined.

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Introduction

For a long time, 2 hypotheses of the development of the colorectal cancer (the adenoma-carcinoma sequence and the de novo theory) have been discussed. However, it is more important to notice that the initial neoplastic cells, such as in colorectal epithelial neoplasia (CR-EN; adenoma or adenocarcinoma), may derive from the essential tubules of the colorectum, even if these cells originate from the bone marrow. That is to say, in CR-EN, the adenoma or the adenocarcinoma may develop from the essential tubules of the colorectum, and in order to conclude the carcinogenesis of the colorectal cancer more clearly, the biological features including the genetic abnormality of the nonneoplastic mucosal epithelium of the colon and rectum, which coexist in connection with CR-EN, should be investigated.

Although these abnormal morphological findings connected with CR-EN, aberrant crypt foci and hyperplastic polyp have been well known, I will show the importance of Paneth cell metaplasia (PaM) of the colorectum as one of the original mucosal regions of the development of CR-EN, for the reason described below.

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Fig. 1. Paneth cell in the colorectal adenoma. Some neoplastic cells in the colorectal adenoma resemble Paneth cells. Hematoxylin-eosin. $\times 200$.

Fig. 2. PaM in the adjacent mucosa to the colorectal adenocarcinoma lesion. Hematoxylin-eosin. $\times 100$.

Fig. 3. CR-PaM (light microscope). Paneth cells were seen at the base of the glands of the large intestine. Hematoxylin-eosin. $\times 200$.

Fig. 4. CR-PaM (electron microscope). Granules were seen in the cytoplasm of the CR-PaM, like small intestine.

The Coexistence of Colorectal PaM and CR-EN

Up to date, many investigators have reported that neoplastic Paneth cells seen in CR-EN and/or colorectal PaM (CR-PaM) are seen in the nonneoplastic mucosa adjacent to CR-EN (fig. 1, 2) [1–3].

Paneth cells, which are usually situated at the base of the glands of the small intestine, were first identified by Schwalbe [4] in 1872 and studied in detail morphologically by Paneth [5] in 1888.

In the case of the gastrointestinal tract, Paneth cells are normally seen as one type of the epithelial cells in the glands of the small intestine, and they should be referred to as ‘metaplasia’ when they appear as the large intestinal epithelium.

CR-PaM are commonly seen in the cecum of elderly individuals [6], frequently in the mucosal epithelium of the large intestine in special inflammatory diseases like ulcerative colitis [7] and sometimes in CR-EN and the adjacent mucosa to CR-EN, as described above. Morphologically, no differences have been detected between the Paneth cells in the CR-PaM and those in the small intestine (fig. 3, 4).

Although the cause of CR-PaM is unclear, regeneration and destruction by inflammation as well as abnormalities of bloody microcirculation and/or immunodefense abnormalities may be thought to induce CR-PaM, considering the functions of Paneth cells [4, 5]. Anyway, it should be assumed that some nonspecific inflammation induces CR-PaM.

Although the coexistence of neoplastic/nonneoplastic Paneth cells and CR-EN has been well known, there are few studies on the reason of this coexistence.

We have previously pointed out that CR-PaM were seen very frequently in the adjacent mucosa to the minute-sized (within 5 mm in the maximum dimensions) CR-EN as well as within these neoplasias [7, 8]. As the tiny-sized neoplasias and their adjacent regions may include the initial conditions for the development of the neoplasias, it is more important to study these tiny-sized neoplasias and their adjacent regions to clarify the histogenesis of neoplasias. Furthermore, our report in the 1980s, when the incidence of colorectal cancer in native Japanese was lower than in Japanese descendants and Caucasian residents in Hawaii or the USA, revealed that the incidences of these coexistences are higher in Japanese descendants and Caucasian residents in Hawaii than in native Japanese [9]. Thus, the investigation of CR-PaM is very important to clarify the histogenesis of CR-EN.

Gene Abnormalities in CR-PaM

Vogelstein et al. [10] have reported the involvement of multistage genetic abnormalities in the development of colorectal cancers and pointed out that K-ras mutation is the initial genetic abnormality in the adenoma-carcinoma sequence [11, 12] of the development of colorectal cancer. Recently, some reports have pointed out that the replication errors and loss of heterozygosity of the microsatellite markers show the development of colorectal cancer [13, 14].

Molecular biological investigations for Paneth cells are rare [15, 16], and there are only few reports about the genetic abnormalities of CR-PaM using human materials [17, 18]. Recently, we have reported the frequencies of the K-ras codon 12 mutations (K-ras) and the loss of heterozygosity of dinucleotide microsatellite markers (LOH-MS) in the propria mucosa with PaM of the right colon [19]. This report revealed that K-ras mutation was detected in 15 regions among 52 PaM (28.9%). All mutations were a single mutation. For K-ras mutation patterns, 11 showed GGT to AGT and 4 showed GGT to GAT. The

report also showed that LOH-MS was detected in 21 regions among 52 PaM (40.4%; D2S123: 35.4%, 17/48 regions; D17S250: 13.7%, 7/51 regions; D5S346: 0%, 0/52 regions). No K-ras mutations and LOH-MS were detected in the controls (colorectal mucosa with no PaM, no neoplastic lesion, no aberrant crypt foci and no hyperplastic polyp). Thus, the frequency of both K-ras mutation and LOH-MS in the colonic mucosa with PaM were significantly higher than those of the controls ($p < 0.01$, χ^2 test).

K-ras mutation has been pointed out to be the initial genetic abnormality in the development of colorectal cancers [10]. Recently, it has been hypothesized that the replication errors of the gene are important in the development of colorectal cancer. Also, the loss of heterozygosity of the microsatellite markers, which are often used as the targets in the investigation for the replication errors of the gene, is also considered to be important in the development of colorectal cancer [13, 14]. That is to say, some PaM have gene abnormalities connected with the development of colorectal cancer.

Is CR-PaM a Preneoplastic Condition of Colonic Cancer or Not?

Although many riddles about Paneth cells still remain, many reports have shown the coexistence of CR-PaM and CR-EN and few reports have revealed that CR-PaM had gene abnormalities connected with CR-EN. Furthermore, the gene abnormalities of colonic mucosa with PaM in our recent study may not be equal to those of a single Paneth cell in the colonic mucosa, because it is difficult to obtain only single Paneth cells in the colonic mucosa, even if microdissection is used.

However, it is indeed very interesting that some PaM, which coexist in the adjacent mucosa to CR-EN, have K-ras mutation and LOH-MS. At present, CR-PaM may be one of the preneoplastic mucosa in the development of CR-EN, although further molecular studies concerning CR-PaM should be warranted. As a conclusion, I will propose a new hypothesis on the development of the CR-EN: nonspecific inflammation – CR-PaM – CR-EN.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

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