Molecular Subtypes of Colorectal Cancer and Their Clinicopathologic Features, With an Emphasis on the Serrated Neoplasia Pathway

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Context.—Colorectal cancer is a heterogeneous disease entity with 3 molecular carcinogenesis pathways and 2 morphologic multistep pathways. Right-sided colon cancers and left-sided colon and rectal cancers exhibit differences in their incidence rates according to geographic region, age, and sex. A linear tendency toward increasing frequencies of microsatellite instability–high or CpG island methylator phenotype–high cancers in subsites along the bowel from the rectum to the cecum or the ascending colon accounts for the differences in tumor phenotypes associated with these subsites. The molecular subtypes of colorectal cancers exhibit different responses to adjuvant therapy, which might be responsible for differences in subtype-specific survival.

Objectives.—To review the clinicopathologic and molecular features of the molecular subtypes of colorectal cancer generated by combined CpG island methylator phenotype and microsatellite statuses, to integrate these features with the most recent findings in the context of the prognostic implications of molecular subtypes, and to emphasize the necessity of developing molecular markers that enable the identification of adenocarcinomas involving the serrated neoplasia pathway.

Data Sources.—Based on the authors’ own experimental data and a review of the pertinent literature.

Conclusions.—Because colorectal cancers arise from 2 different morphologic multistep carcinogenesis pathways with varying contributions from 3 different molecular carcinogenesis pathways, colorectal cancer is a heterogeneous and complex disease. Thus, molecular subtyping of colorectal cancers is an important approach to characterizing their heterogeneity with respect to not only prognosis and therapeutic response but also biology and natural history.


Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer–related death in the United States, regardless of sex. The incidence of CRC has decreased in both men and women in the United States since the mid 1980s.1–3 In South Korea, there was a rapid increase in the incidence of CRC between 1999 and 2012, and CRC became the second and third most common cancer in males and females, respectively (www.cancer.go.kr; accessed May 1, 2015). The incidence of CRC varies markedly worldwide, with the highest incidence in Oceania and Europe and the lowest incidence in Africa and South-Central Asia (globocan.iarc.fr; accessed May 1, 2015). Recently, high rates of CRC have been reported in newly developed countries in which the risk was once low, including South Korea, Slovakia, and Hungary.4 In areas with lower incidences of CRC, the proportion of right-sided cancers (cancer arising proximal to the splenic flexure) is lower than the proportion of right-sided cancers in areas with higher incidences of CRC.5 Within the same geographic area, the incidence of CRC and the proportion of right-sided cancers show age- and sex-related differences.3,6 Men and older people are at higher risk of CRC than women and younger people, respectively.7 Women and older people have a higher percentage of right-sided cancers than men and younger people, respectively. The proportion of women with CRC increases as the cancer location becomes more right-sided, and the proportion of right-sided cancers increases with age, a characteristic observed in women more than in men.5,8 These sex- and age-related differences in the incidence of CRC and the proportion of right-sided cancers are found in both high- and low-incidence areas.3,4,5,10 Furthermore, within the same geographic area, race and ethnicity influence both the incidence of CRC and the proportion of right-sided cancers.11,12 In the United States, the incidence is lower in Asian American individuals than in the white population and other races. African American individuals have the highest incidence of right-sided and left-sided colon cancer, compared with the white population and other races, and the reverse is true for rectal cancer.13 In Southern Asia, the Chinese population has a significantly higher incidence of CRC than the Indian and Malay populations.2 In addition to differences in the sex and age of onset between right-sided and left-sided colon or...
rectal cancers, the gross or histologic appearance of cancers can vary. The gross appearance of right-sided cancers is often exophytic, whereas that of the left-sided colon or rectal cancers is usually endophytic. Histologic variants, including medullary carcinoma, serrated adenocarcinoma, and cribriform comedo-type adenocarcinoma, are more common in the right-sided colon than in the left-sided colon or rectum. What causes such subsite-related differences in terms of age, sex, race, geography, or morphologic findings? The reasons for these variations may be related not only to genetic or behavioral factors, including diet and lifestyle, but also to differences in the proportions of molecular carcinogenesis pathways that are active in right-sided colon, left-sided colon, and rectal cancers. In this review, we examined (1) the association between molecular carcinogenesis pathways and sex, race, or age of onset; (2) the clinicopathologic and molecular features of CRCs according to molecular subtypes; (3) the prognostic implications of molecular subtypes; and (4) adenocarcinomas arising from the serrated neoplasia pathway and their phenotypic features.

**THREE MOLECULAR CARCINOGENESIS PATHWAYS AND 2 MORPHOLOGIC MULTISTEP PATHWAYS**

Colorectal cancer is a heterogeneous disease entity in terms of both molecular carcinogenesis and morphologic multistep pathways. Three molecular carcinogenesis pathways have been identified: (1) chromosomal instability (CIN), (2) microsatellite instability (MSI), and (3) CpG island methylator phenotype (CIMP) or epigenetic instability pathways. The 2 morphologic multistep pathways are the classical pathway (the so-called adenoma-carcinoma sequence) and the serrated neoplasia pathway. The CIN pathway is characterized by alterations in the number and structure of chromosomes and accompanying genetic mutations of proto-oncogenes and tumor suppressor genes. The MSI pathway features alterations in the number of nucleotide repeats located in the exons and subsequent frameshift mutations in tumor suppressor genes or tumor-related genes. The epigenetic instability (or CIMP) pathway is characterized by widespread hypermethylation of numerous promoter CpG island loci and consequent inactivation of tumor suppressor genes or tumor-related genes. The classical pathway (so-called adenoma-carcinoma sequence) begins with premalignant lesions comprising conventional adenomas, including tubular or tubulovillous adenomas, whereas the serrated neoplasia pathway begins with hyperplastic polypos or sessile or traditional serrated adenomas. These 2 morphologic pathways are driven by different molecular pathways: the classical pathway is driven by either CIN or MSI, whereas the serrated neoplasia pathway has epigenetic instability as its initial driving force and MSI as an optional secondary force. Although Lynch syndrome CRCs and sporadic MSI-high (MSI-H) CRCs both have a high level of MSI, their premalignant lesions are different because they develop through different morphologic multistep pathways: Lynch syndrome tumors follow the classical pathway and manifest their premalignant lesions as tubular or tubulovillous adenoma, whereas the premalignant lesions of sporadic MSI-H CRCs are sessile serrated adenomas that arise through the serrated neoplasia pathway and undergo further hypermethylation-associated inactivation of MLH1 and subsequent acquisition of high level MSI. The Cancer Genome Atlas study results demonstrate that the CIN and MSI pathways are mutually exclusive. Whereas the CIMP pathway overlaps with the MSI pathway because of the presence of sporadic MSI-H CRCs, which are also usually CIMP-high (CIMP-H), the CIMP pathway does not appear to be in an exclusive relationship with the CIN pathway. CIMP-H/non–MSI-H CRCs show some copy number variations across the genome, although the degree of CIN is less pronounced than that of CIMP-negative or -low (CIMP-0,L)/non–MSI-H CRCs. This finding suggests that the CIMP pathway itself may not be sufficient for the malignant transformation of serrated polyps and requires collaboration with either the CIN or MSI pathway to promote successful malignant transformation.

**GEOGRAPHY-, AGE-, AND SEX-DEPENDENT DIFFERENCES IN THE PROPORTIONS OF MOLECULAR CARCINOGENESIS PATHWAYS**

The frequency of MSI in CRCs differs between Western and Eastern populations. MSI-H CRCs comprise approximately 15% of all CRCs in the United States but less than 10% of all CRCs in South Korea or Taiwan. Because the prevalence of Lynch syndrome is approximately 3% and is similar in Eastern and Western patients with CRC, sporadic MSI-H CRCs account for the difference in the proportion of MSI-H CRCs in all CRCs between populations in South Korea and the United States. Most sporadic MSI-H CRCs develop from sessile serrated adenomas through CIMP-associated inactivation of MLH1. The reason why the proportion of sporadic MSI-H CRCs is lower in South Korea is because the proportion of CIMP-H CRCs is lower in all CRCs in South Korea than in all CRCs in the United States. The proportion of CIMP-H CRCs defined by at least 5 of 8 methylated CIMP panel markers is lower in South Korea than in the United States (6%–7% versus 17–18%, respectively). Accordingly, the mutation rate of BRAF is lower in CRCs in the Korean population than in CRCs in the American population (4%–5% versus 13%–15%, respectively). Most Chinese studies have reported a relatively low frequency of BRAF mutation in CRCs (<7%). Within the same geographic area, white individuals have a higher rate of CIMP-H in CRCs than do African American or Asian American individuals (14%–18% versus 8%–11% versus 7%, respectively). Thus, the lower rate of MSI-H in African American than in white individuals reported in a population-based study (14% versus 7%, respectively) might be attributed to the lower rate of CIMP-H in African American than in white persons.

An association between MSI-H CRCs and female sex has been recognized but the association is valid only when MSI-H CRCs are sporadic. In Lynch syndrome, CRC risk is higher in male mutation carriers than in female mutation carriers. In other words, an association between MSI-H CRCs and female sex is provided by CIMP-H because MSI-H CRCs are generated by CIMP-associated inactivation of MLH1, and CIMP-H is closely associated with female sex. The relationship between female sex and CIMP-H is persistent regardless of geographic location, race, or age. Although CIMP-H is associated with increased patient age, the proportion of CIMP-H is higher in females than in males regardless of age.
MOLECULAR SUBTYPES BASED ON COMBINED CIMP AND MSI STATUSES

Jass\(^4\) classified CRCs into 5 molecular subtypes primarily by underlying types of genetic instability and the presence of DNA methylation: (1) CIMP-H/MSI-H, (2) CIMP-H/non–MSI-H, (3) CIMP-L/non–MSI-H, (4) CIMP-0/non–MSI-H, and (5) CIMP-0/MSI-H. Jass’ subtypes 1 and 2 and subtype 4 reflect CRCs arising from the serrated neoplasia pathway and the classical pathway, respectively. Jass’ subtype 5 was suggested to be indicative of possible Lynch syndrome. However, with regard to Jass’ subtype 3, it is unclear whether CRCs arise from the classical pathway or the serrated neoplasia pathway. Furthermore, there are no consensus diagnostic criteria for CIMP-L. Conceptually, the term *CpG island methylator phenotype–L* (CIMP-L) was coined to describe a group of tumors that show intermediate amounts of aberrant DNA methylation.\(^48\) CIMP-L is defined when the number of methylated CIMP panel markers exceeds 0 but does not reach the cutoff value for CIMP-H. In the 8-marker panel, CIMP-L tumors have methylation at 1 to 4 or 5 markers, whereas in the 5-marker panel, CIMP-L has methylation at 1 to 2 or 3 markers.\(^45, 48\) Because conventional adenomas or CRCs contiguous with conventional adenomas often harbor methylation of 1 or more of the 8-panel markers or of 1 or 2 of the 5-panel markers,\(^49\) CIMP-L/non–MSI-H CRCs are thought to arise from the classical pathway as well as the serrated neoplasia pathway.\(^15\) Thus, the clinicopathologic and molecular features overlap substantially between subtypes 3 and 4.\(^15\)

CLINICOPATHOLOGIC OR MOLECULAR FEATURES OF 4 MOLECULAR SUBTYPES OF CRCs

In our previous study,\(^31\) we analyzed the CIMP and MSI statuses of surgically resected CRCs (n = 734). Of the 5 molecular subtypes according to Jass’ classification, the CIMP-0/non–MSI-H subtype was the most common, comprising 63% (n = 464) of the CRCs, whereas the CIMP-H/MSI-H subtype was the least common, comprising 3% (n = 19) of the CRCs (Table 1). The age of onset was the highest for the CIMP-H/MSI-H subtype and the lowest for the CIMP-0/L/MSI-H subtype. The 5 molecular subtypes showed distinct clinicopathologic and molecular features. Compared with the CIMP-0/non–MSI-H subtype, which is the most common subtype, the CIMP-H/non–MSI-H subtype was associated with a more common right-sided colon location, poor differentiation, luminal serration, nodal metastasis, distant metastasis, and BRAF mutation. Compared with the other 3 molecular subtypes, the CIMP-0/L/MSI-H subtype was associated with the youngest age of onset, less frequent nodal metastasis, less frequent distant metastasis, and near absence of BRAF mutation.

Regardless of CIMP status, the 2 MSI-H subtypes showed a more frequent right-sided colon location, less frequent dysplasia, more frequent Crohn-like lymphoid reaction, more frequent mucinous histology, and less frequent KRAS mutation than the CIMP-0/L/MSI-H subtype. Despite these shared clinicopathologic and molecular features, the CIMP-H/MSI-H and CIMP-0/L/MSI-H subtypes differ in several clinicopathologic features, including age of onset, tumor multiplicity in the large bowel, cancer stage, and frequency of BRAF mutation. These differences were corroborated in a large-scale study of MSI-H CRCs.\(^30\) Although extensive exonal microsatellite alterations and increased point mutations caused by mismatch repair defects bestow very considerable overlap on the altered gene expression signatures between the 2 MSI-H subtypes, the serrated neoplasia pathway–associated gene signature can be found in the CIMP-H/MSI-H subtype.\(^51\) Because serrated polyps, including hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas, are associated with aberrant gastrin-type differentiation, the
CIMP-H/MSI-H subtype is characterized by a gain of gastric differentiation (ANXA10, TFF2, and MUC5AC expression) and loss of intestinal expression (CDX2 and KRT20 loss). Furthermore, histologic features that differ between the 2 MSI-H subtypes include sheeting appearance, eosinophilic cytoplasm, acinar appearance, signet ring cell formation, and stratified nuclei. The first 4 of these features are more frequent in the CIMP-H/MSI-H subtype, whereas the last feature is more frequent in the CIMP-0/L/MSI-H subtype.

Right-sided and left-sided colon cancers and rectal cancers differ in various clinicopathologic and molecular features. These differential clinicopathologic and molecular features do not change abruptly at the borders between the right-sided colon and the left-sided colon or between the left-sided colon and the rectum, but change gradually along the large bowel. Yamauchi et al examined the clinicopathologic and molecular features of CRCs at 9 bowel subsites from the rectum to the cecum and found that the frequencies of female sex, poor differentiation, mucinous histology, CIMP-H, MSI-H, and BRAF mutation increased linearly along the bowel from the rectum to the ascending colon. Our previous study also found a linear trend toward increasing female occurrence, advanced T category, N category, overall stage, poor differentiation, absence of luminal necrosis, luminal serration, mucinous histology, Crohn-like lymphoid reaction, CIMP-H, and MSI-H from the rectum to the cecum. These findings support the concept of the large bowel as a continuum rather than a segmented structure in terms of molecular and clinicopathologic features.

The association between molecular subtypes and survival of colon cancers or CRCs was first explored by Ward et al who showed that, of the 4 molecular subtypes generated by combinations of CIMP (CIMP-H versus CIMP-L,0) and MSI (MSI-H versus non–MSI-H) statuses, the CIMP-H/non–MSI-H subtype was associated with the shortest overall survival and disease-free survival time (Table 2). Ward et al analyzed the CIMP panel markers CDKN2A (p16), MINT1, MINT2, MINT12, and MINT31 for their methylation statuses by using bisulfite or methylation-specific polymerase chain reaction in study subjects who included adjuvant-treated or untreated patients with stage I to IV CRC. Our previous studies, which analyzed stage I to IV CRC cases with or without adjuvant treatment, also found that the CIMP-H/non–MSI-H subtype was associated with the shortest overall survival time. In contrast, in a study by Ogino et al, the CIMP-0/L/non–MSI-H subtype showed the worst cancer-specific survival in the cohort of study patients with stage I to IV colon cancer. A recent study assessed the association between molecular subtypes and survival of patients with stage III colon cancer who were randomly assigned to treatment with adjuvant fluorouracil and leucovorin (FU/LV) alone or with irinotecan (IFL) (a phase III intergroup trial [C89803]) and found that the CIMP-H/non–MSI-H subtype was associated with the worst overall survival or disease-free survival in patients treated with adjuvant FU/LV but not in patients treated with adjuvant IFL. In adjuvant IFL–treated patients, no survival difference was identified among the 4 molecular subtypes. This finding suggests that differences in the response to adjuvant therapies contribute to subtype-specific survival.
In a study of patients with stage III or high-risk stage II CRC who were treated with adjuvant FU/LV plus oxaliplatin (FOLFOX), the 4 molecular subtypes did not show significant differences in disease-free survival. In lieu of the CIMP-H/non–MSI-H subtype, concurrent methylation of 2 CIMP panel markers, CDKN2A (p16) and NEUROG1, was associated with recurrence after adjuvant FOLFOX treatment in stage II/III CRCs. In a recent population-based study that evaluated differences in survival across CRC subtypes defined by CIMP, MSI, BRAF mutation, and KRAS mutation status at stages I to IV, Phipps et al suggested that the CIMP-H/non–MSI-H subtype with BRAF mutation had the highest disease-specific mortality. However, this study was not stratified according to the difference in adjuvant therapy regimens. Additional studies are needed to test whether the CIMP-H/non–MSI-H subtype with BRAF mutation has the highest disease-specific mortality in adjuvant FOLFOX–treated patients with stage II or III CRC. In a recent study of a large number of patients with stage III colon cancer who were treated with adjuvant FOLFOX or adjuvant FOLFOX plus cetuximab, Sinicrope et al reported that non–MSI-H colon cancers with KRAS mutations or BRAF mutations were associated with poorer disease-free survival than non–MSI-H colon cancers with wild-type KRAS and BRAF. Additionally, MSI-H colon cancers did not differ from non–MSI-H colon cancers with wild-type KRAS and BRAF in terms of disease-free survival. Overall, the findings suggest that the CIMP-H/non–MSI-H subtype is associated with the shortest survival time in adjuvant FU–treated patients with stage III CRC but not in adjuvant IFL– or FOLFOX–treated patients with stage III CRC. In adjuvant FOLFOX–treated patients with stage III CRC, non–MSI-H CRCs with mutations in either KRAS or BRAF appear to have the worst outcomes.

### SERRATED PATHWAY ADENOCARCINOMAS

The associations of reduced survival with (1) the CIMP-H/non–MSI-H subtype in patients with CRC who are treated with FU-based adjuvant therapy and (2) non–MSI-H CRCs with BRAF or KRAS mutations in patients with CRC who are treated with adjuvant FOLFOX suggest that CRCs arising from the serrated neoplasia pathway may be more aggressive or more resistant to adjuvant therapy than those arising from the classical adenoma–carcinoma pathway. Serrated pathway adenocarcinomas refer to CRCs resulting from the serrated neoplasia pathway. Serrated adenocarcinoma is a newly introduced disease entity that defines a subset of colorectal adenocarcinomas characterized by epithelial serrations, eosinophilic or clear cytoplasm, abundant cytoplasm, vesicular nuclei, distinct nucleoli, absence of necrosis, extracellular mucin production, and cell balls and papillary fronds in mucinous areas. Given that 20% to 30% of CRCs are attributed to the serrated neoplasia pathway and that 7% to 12% of CRCs are serrated adenocarcinomas, it is known regarding the proportions of CIMP-L and CIMP-H in serrated adenocarcinomas and regarding the proportion of serrated adenocarcinomas in CIMP-H CRCs. In other

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Patients</th>
<th>Adjuvant</th>
<th>Molecular Markers</th>
<th>No. of Subtypes: Subtype With the Worst Outcome</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward et al, 2003</td>
<td>612 stage I–IV CRCs</td>
<td>Surgery only or FU-based regimen or radiotherapy</td>
<td>CIMP (5 markers) and MSI</td>
<td>4 subtypes: CIMP-H/non–MSI-H</td>
<td>OS and DFS</td>
</tr>
<tr>
<td>Lee et al, 2008</td>
<td>134 stage I–IV CRCs</td>
<td>Surgery only or FU-based regimen</td>
<td>CIMP (5 markers) and MSI</td>
<td>4 subtypes: CIMP-H/non–MSI-H</td>
<td>OS</td>
</tr>
<tr>
<td>Kim et al, 2009</td>
<td>318 stage I–IV CRCs</td>
<td>Surgery only or FU-based regimen</td>
<td>CIMP (5 markers) and MSI</td>
<td>4 subtypes: CIMP-H/non–MSI-H</td>
<td>OS</td>
</tr>
<tr>
<td>Ogino et al, 2009</td>
<td>649 stage I–IV colon cancers</td>
<td>Not informed</td>
<td>CIMP (8 markers) and MSI</td>
<td>4 subtypes: CIMP-0/L, non–MSI-H</td>
<td>OS</td>
</tr>
<tr>
<td>Sanchez et al, 2009</td>
<td>391 stage I–IV CRCs</td>
<td>Not informed</td>
<td>CIMP (5 markers) and MSI</td>
<td>6 subtypes: CIMP-H/non–MSI-H</td>
<td>CSS</td>
</tr>
<tr>
<td>Dahlin et al, 2010</td>
<td>574 stage I–IV CRCs</td>
<td>Surgery only or FU-based regimen or radiotherapy</td>
<td>CIMP (8 markers) and MSI</td>
<td>4 subtypes: CIMP-H/non–MSI-H</td>
<td>OS</td>
</tr>
<tr>
<td>Han et al, 2013</td>
<td>322 stage II–III CRCs</td>
<td>FOLFOX</td>
<td>CIMP (8 markers) and MSI</td>
<td>5 subtypes: CIMP-H/non–MSI-H/BRAF mutation</td>
<td>CSS and OS</td>
</tr>
<tr>
<td>Shiozawa et al, 2014</td>
<td>615 stage III colon cancers</td>
<td>FU/LV or IFL</td>
<td>CIMP (5 markers) and MSI</td>
<td>4 subtypes: CIMP-H/non–MSI-H in FU/LV setting</td>
<td>OS and DFS</td>
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<tr>
<td>Phipps et al, 2015</td>
<td>2080 stage I–IV CRCs</td>
<td>Surgery only or variable treatment</td>
<td>CIMP (5 markers), KRAS, BRAF, MSI</td>
<td>5 subtypes: CIMP-H/non–MSI-H/BRAF mutation</td>
<td>CSS and OS</td>
</tr>
<tr>
<td>Sinicrope et al, 2015</td>
<td>2720 stage III colon cancers</td>
<td>FOLFOX or FOLFOX + cetuximab</td>
<td>KRAS, BRAF, MSI</td>
<td>5 subtypes: non–MSI-H and mutations of either KRAS or BRAF</td>
<td>DFS</td>
</tr>
</tbody>
</table>

Abbreviations: CIMP, CpG island methylator phenotype; CIMP-H, CIMP-high; CIMP-0/L, CIMP-negative or -low; CSS, cancer-specific survival; DFS, disease-free survival; FOLFOX, FU plus LV plus oxaliplatin; FU, fluorouracil; IFL, FU plus LV plus irinotecan; LV, leucovorin; MSI-H, MSI-high; OS, overall survival.
words, whether all CIMP-H CRCs show histologic features of serrated adenocarcinomas remains to be determined. Because conventional adenomas can harbor aberrant hypermethylation of CIMP panel markers,39 CIMP-L CRCs can arise from either the serrated neoplasia pathway or the classical pathway. At present, methylation assays of CIMP panel markers cannot differentiate between CIMP-L serrated pathway adenocarcinomas and CIMP-L CRCs arising from the classical pathway. There is a need to develop auxiliary markers to identify serrated pathway adenocarcinomas. Immunohistochemical markers associated with the serrated neoplasia pathway include ANXA10, CLDN18, CTSE, MUC5AC, MUC6, TFF2, and VSIG2, which are overexpressed in hyperplastic polyps, sessile serrated adenoma/polyps, and traditional serrated adenomas, compared with conventional adenomas.51,52,65–67 Little information is available regarding the expression statuses of these markers in CIMP-L CRCs and the differential clinicopathologic features of CIMP-L CRCs associated with the expression of these markers.

In summary, although the factors triggering the CIMP pathway are unknown, the CIMP pathway is associated with the right-sided colon, female sex, older age, and white patients. Familiarity with the differential clinicopathologic features of CRCs associated with molecular carcinogenesis pathways is a requisite for a better understanding of the mechanisms that lead CRCs to exhibit bowel subsite–associated differences with regard to age of onset, sex, race, and geographic area. Different responses of the molecular subtypes of CRCs to adjuvant therapy underlie the survival differences between sexes or between right-sided colon cancers and left-sided colon or rectal cancers. Clinical trials of adjuvant chemotherapies or targeted therapies should be conducted taking into account the molecular subtypes of CRCs. It is recognized that a considerable portion of CIMP-L colorectal cancers or CIMP-L serrated adenocarcinomas do not exhibit any of CIMP-H, CIMP-C, or conventional adenocarcinomas. Because CIMP-L CRCs can arise from both the classical pathway and the serrated neoplasia pathway, it is necessary to develop molecular or immunohistochemical markers to identify CIMP-L serrated pathway adenocarcinomas. With the help of these biomarkers, a better understanding of the clinicopathologic and molecular features of CIMP-L serrated adenocarcinomas will be reached.

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