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EDITORIAL

Microsatellite instability and MLH1 promoter hypermethylation in colorectal cancer

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Abstract

Colorectal cancer (CRC) is caused by a series of genetic or epigenetic changes, and in the last decade there has been an increased awareness that there are multiple forms of colorectal cancer that develop through different pathways. Microsatellite instability is involved in the genesis of about 15% of sporadic colorectal cancers and most of hereditary nonpolyposis cancers. Tumors with a high frequency of microsatellite instability tend to be diploid, to possess a mucinous histology, and to have a surrounding lymphoid reaction. They are more prevalent in the proximal colon and have a fast pass from polyp to cancer. Nevertheless, they are associated with longer survival than stage-matched tumors with microsatellite stability. Resistance of colorectal cancers with a high frequency of microsatellite instability to 5-fluorouracil-based chemotherapy is well established. Silencing the MLH1 gene expression by its promoter methylation stops the formation of MLH1 protein, and prevents the normal activation of the DNA repair gene. This is an important cause for genomic instability and cell proliferation to the point of colorectal cancer formation. Better knowledge of this process will have a huge impact on colorectal cancer management, prevention, treatment and prognosis.

Key words: MLH1; Methylation; Colorectal cancer; Microsatellite instability; CpG island methylator phenotype; Chromosomal instability

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Colorectal cancer (CRC) is caused by a series of genetic or epigenetic changes, and in the last decade there has been an increased awareness that there are multiple forms of CRC that develop through different pathways. The common mechanism (more than 50% of sporadic CRCs) is that of chromosomal instability (CIN)[1-3]. The second pathway (35% of sporadic CRCs) is caused by epigenetic inactivation of tumor suppressor genes. Because of the mechanism involved in this, it is called the CpG island methylator phenotype (CIMP). A third pathway is caused by failure of the DNA mismatch repair system, and these tumors have a characteristic signature mutation called microsatellite instability (MSI), MSI-high (MSI-H), MSI-low (MSI-L) or MSI-stable (MSS). Recently, Jass classified CRCs according to CpG island methylator phenotype and MSI status into 5 new types: (1) CIMP-high, MSI-H, BRAF mutation; (2) CIMP-high, MSI-L or MSS, BRAF mutation; (3) CIMP-low, MSS or MSI-L, KRAS mutation; (4) CIMP-negative, MSS; (5) CIMP-negative, MSI-H (Lynch Syndrome)[4]. There were clinical, morphological and prognostic factors characteristic of every type, thus Jess concluded that this approach will have a tremendous impact on management, prevention and treatment of CRC.

Microsatellite instability is involved in the genesis of about 15% of sporadic CRCs and most of hereditary nonpolyposis CRCs (HNPCC)[5-7]. The multiple errors in repetitive DNA sequences (microsatellites) result from a failure of the DNA mismatch repair (MMR) system to edit errors made during DNA replication[8]. The DNA MMR system is inactivated either by hypermethylation of the promoter, which silences gene transcription of hMLH1 (epigenetic phenomenon; sporadic CRC), or because of germ-like mutations in MMR genes MLH1, MSH2, MSH6 and others (genetic phenomenon, HNPCC)[9,10]. Recently, Hitchins and colleagues described an inheritance of a cancer-associated MLH1 germ-line epimutation[11]. They found evidence that MLH1 promoter hypermethylation of one allele was transmitted from a mother to her son but was erased in his spermatozoa, thus the allele had reverted to the normal active state.

Tumors with a high frequency of MSI-H tend to be diploid, to possess a mucinous histology, and to have a surrounding lymphoid reaction. They are more prevalent in the proximal colon and have a fast pass from polyp to cancer. Nevertheless, they are associated with longer survival than stage-matched MSI-L tumors or MSS tumors[12-18]. It is still unclear if this favorable prognosis is attributable to the inherently lower aggressiveness of MSI-H tumors or their greater sensitivity to chemotherapy

other than 5-fluorouracil (5-FU).

Resistance of MSI-H CRC to 5-FU based chemotherapy is well established[19]. A significant overall survival benefit was noted in patients with CRC who were treated with 5-FU based chemotherapy compared with those who were not. However, within the MSI-H group, there was no difference in survival by 5-FU treatment, whereas in the MSS group, the authors noted a significant difference in survival between patients given 5-FU and untreated patients. These findings indicate that the type of genomic instability within a colorectal tumor might dictate patient response to 5-FU based chemotherapy[20]. Ribic and co-investigators[21] used specimens from patients with stage Ⅱ or Ⅲ CRC who were previously enrolled in prospective, randomized trials of 5-FU based chemotherapy. Among the patients who had not received adjuvant chemotherapy, those with MSI-H tumors had longer overall survival and higher rates of 5-year disease-free survival than patients with MSI-L or MSS tumors. MSI-H status in patients who did not receive 5-FU based adjuvant chemotherapy was significantly associated with a better survival. However, among the group with MSI-H tumors, treatment was associated with a worse outcome for both stage Ⅱ and Ⅲ cancers.

Recently, an association between JC virus and CRC has been reported[22]. The virus may act by stabilizing β-catenin, facilitating its entrance to the cell nucleus and triggering proliferation and cancer formation. Another possibility is initiation of hMLH1 methylation, since association between methylation and exposure to carcinogens such as viruses has been observed[23].

In summary, MLH1 promoter hypermethylation is an important event, silencing the MLH1 gene expression and preventing the formation of MLH1 protein and normal activation of the DNA repair gene. This induces genomic instability and cell proliferation to the point of CRC formation. Better knowledge of this process will have a significant impact on CRC management, prevention, treatment and prognosis.

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