Molecular Markers for Colorectal Cancer

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KEYWORDS

• Colorectal neoplasm • Drug therapy • Antineoplastic combined chemotherapy
• Biomarkers • Tumor/genetics • Antibodies • Monoclonal/therapeutic use

KEY POINTS

- Colorectal carcinoma develops through 3 main pathways, including chromosomal instability, mismatch repair, and methylator phenotype.
- Microsatellite instability (MSI) is a marker of mismatch repair, which occurs from MLH1 gene mutation as in Lynch syndrome or from sporadic silencing of a normal MLH1 gene via promoter hypermethylation.
- Anti–vascular endothelial growth factor therapy is preferred over anti–epidermal growth factor receptor therapy for metastatic colorectal cancers with KRAS gene mutation.
- High MSI colorectal cancer with BRAF gene mutation is most likely associated with sporadic nature rather than with Lynch syndrome.
- Programmed cell death protein 1 receptors in T cells are used by colorectal cancer cells to downregulate the antitumor effects of the immune system.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world. There has been abundant research on its pathophysiology and treatment. CRC has variable genetic signatures, which can be as unique as the individual host. CRC develops through at least 3 major pathways, which include chromosomal instability, mismatch repair, and methylator phenotype. These pathways can coexist in a single CRC and result in neoplasms with distinct genotype and phenotype. These major pathways of tumorigenesis can be present in both sporadic and inherited CRC. In spite of the unique molecular and genetic signatures of individual CRCs, nonspecific chemotherapy based on the antineoplastic effects of 5-fluorouracil (5-FU) is the cornerstone of therapy for stage III and some stage II disease. More recently, 5-FU-leucovorin-oxaliplatin

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(FOLFOX) has become the standard of care for CRC adjuvant therapy. Additional therapies have emerged to treat CRC based on the specific molecular markers present. Techniques to recognize CRC at the molecular and genetic levels have facilitated the development of new signature drugs designed to inhibit the unique pathways of CRC growth and immunity. This article focuses on the new developments in molecular markers associated with CRC with emphasis on the clinical implications and relevance for the practicing physician.

DEVELOPMENT OF CARCINOMA PATHWAYS

Chromosomal Instability

Fearon and Vogelstein[1] first described the well-known adenoma-to-carcinoma sequence for CRC in 1990. This pathway details the multiple mutations required to progress from normal colonic mucosa to carcinoma. At the time of original introduction of the adenoma-to-carcinoma sequence, it was understood that the accumulation of genetic mutations is what actually leads to carcinogenesis, rather than the specific order of mutations. Therefore, this pathway for colorectal neoplasia was coined the chromosomal instability (CIN) pathway.[2] The adenoma-to-carcinoma sequence is generally described as a stepwise process starting with mutation of the adenomatous polyposis coli (APC) gene, a tumor suppressor gene, which regulates neoplasia prevention in its wild state. APC mutations are also the most common mutation in this CIN pathway, affecting up to 85% of patients with sporadic CRC.[3] APC mutations are generally followed by mutations in KRAS, deleted in CRC, and p53 genes on the path to carcinoma.[1] The accumulation of genetic mutations by the natural tendency of chromosomal instability, with loss of complementary chromosomal pairs known as loss of heterozygosity, leads to inherent risk of neoplasia. These deleterious genetic mutations can interfere with downstream cellular function pathways such as those associated with programmed cell death (apoptosis). Interference with apoptosis can result in immortal cells and neoplasms.

Adenomatous polyposis coli

APC gene mutations are present in most CRCs, giving rise to the APC gene tumor suppressor role as a gatekeeper mutation in CRC.[3] APC is part of the Wnt signaling pathway that regulates cytoplasmic levels of B-catenin, which is involved in cytoskeletal integrity.[3] The Wnt pathway is important in organ development, cellular proliferation, morphology, motility, and fate of embryonic stem cells.[4] Increased levels of B-catenin that result from APC mutation or enhanced expression can lead to increased levels of c-myc, a known factor in cell proliferation.[4] The relationship between APC, B-catenin, c-myc, and cytoskeleton integrity results in APC becoming part of the cell-cell adhesion complex. Therefore, mutations in APC may result in poor cell-cell adhesion and cell migration.[4]

When functioning appropriately, the APC gene is responsible for maintaining the normal direction of upward movement of specialized colonic epithelial cells toward the gut lumen.[4] Cells with mutations in APC tend to migrate aberrantly or less efficiently toward the crypt base where they accumulate and form neoplastic polyps.[4] APC gene mutations are, therefore, associated with the tendency to form adenomatous polyps in the gastrointestinal (GI) tract, which carry a risk of carcinoma.

KRAS

The next most common mutation in the traditional CIN pathway to neoplasia is KRAS, which is part of a mitogen-activated protein kinase (MAPK) pathway. Alterations in this pathway are generally found in both the tumor and its metastases, indicating that