Molecular Diagnostics in Colorectal Carcinoma

Advances and Applications for 2018

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KEYWORDS

• Colorectal carcinoma • Serrated polyp pathway • KRAS • BRAF
• CpG island methylator phenotype

KEY POINTS

- The molecular pathogenesis and classification of colorectal carcinoma are based on the traditional adenoma–carcinoma sequence in the Vogelstein model, serrated polyp pathway, and MSI.
- The genetic basis for hereditary nonpolyposis colorectal cancer is based on detection of mutations in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes.
- Genetic testing for the Lynch syndrome includes MSI testing, methylator phenotype testing, BRAF mutation testing, and molecular testing for germline mutations in mismatch repair genes.
- Molecular makers with predictive and prognostic implications include quantitative multigene reverse transcriptase polymerase chain reaction assay and KRAS and BRAF mutation analysis.
- Mismatch repair-deficient tumors have higher rates of programmed death-ligand 1 expression.

INTRODUCTION

The pathogenesis of colorectal carcinoma is heterogeneous and involves complex multistep molecular pathways initiated by genetic and epigenetic events. The molecular classification of colorectal carcinoma provides the basis for evaluation of prognostic, predictive, and theranostic markers. The goal is precise, efficient, and accurate application of molecular tests for patient management.[1–3]

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EPIDEMIOLOGY

Constitutional (endogenous) as well as environmental (exogenous) factors are associated with the development of colorectal carcinoma. Multiple risk factors have been linked to colorectal carcinoma. Colorectal carcinoma is more common in late-middle-aged and elderly individuals. Men are at a higher risk for developing this malignancy. There is a strong association with a Western type of diet consisting of high-calorie food, rich in animal fat.[4]

Clinical Features

Clinical presentation includes change in bowel habit, constipation, abdominal distension, hematochezia, tenesmus, weight loss, malaise, fever, and anemia. Regarding screening, the American Gastroenterological Association, American Medical Association, and American Cancer Society recommend endoscopy with biopsy as the standard screening approach. Radiologic evaluation by computed tomography scan and MRI are used to assess locoregional spread and distant metastases.[4–9]

PATHOPHYSIOLOGY AND MOLECULAR GENETICS

The various molecular alterations described in colorectal carcinoma are enlisted in **Box 1**.[10] The diagrams depict the adenoma–carcinoma sequence and serrated polyp pathway arising from a complex interplay of genetic alterations (**Figs. 1–4**).[1]

TRADITIONAL VOGELSTEIN MODEL AND APC GENE PATHWAY

The traditional model of Vogelstein describes the classic adenoma–carcinoma sequence and accounts for approximately 80% of sporadic colon tumors. The pathogenesis involves mutation of the APC gene early in the neoplastic process.[2]

APC Gene

A tumor suppressor gene located on the long (q) arm of chromosome 5 between positions 21 and 22 plays a key role in regulating cell division cycle and regulates the WNT/β-catenin signaling pathway. With loss of APC function, β-catenin accumulates and activates the transcription of MYC and cyclin D1 genes, resulting in enhanced proliferation of cells. More than 700 mutations in the APC gene have been identified in familial adenomatous polyposis (FAP), both classic and attenuated types. In this regard,

Box 1
Common genetic and epigenetic alterations in colorectal cancer

Tumor Suppressor Genes	Proto-Oncogenes	Other Molecular Alterations
• APC	• BRAF	• Chromosome instability
• ARID1A	• ERBB2	• CpG island methylator phenotype
• CTNNB1	• GNAS	• Microsatellite instability
• DCC	• IGF2	• Mismatch-repair genes
• FAM123B	• KRAS	• SEPT9
• FBXW7	• MYC	• VIM, NDRG4, BMP3
• PTEN	• NRAS	• POLE/POLD1
• RET	• PIK3CA	
• SMAD4	• RSPO2/RSPO3	
• TGFBR2	• SOX9	
• TP53	• TCF7L2	