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Proteomics, Genomics, and Molecular Biology in the Personalized Treatment of Colorectal Cancer

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Abstract

Colorectal cancer develops and progresses from genetic and genomic changes that occur within and transforms the growth behavior of a normal colonic cell. Molecular tools have advanced enough to allow the scientific community to probe deeper into risk alleles within a population as well as into individual patient genetic data that can ascribe such a risk. Detected genetic and genomic changes from colorectal cancer can help determine a patient's prognosis, predict response to chemotherapy, and determine the approach to care with biological therapies. Utilizing stool, blood/plasma, and tumor tissue to obtain genetic, genomic, and pharmacokinetic information contribute to a person's profile to direct specific cancer care.

Keywords

Colorectal cancer; Personalized medicine; Genetics; Genomics; DNA mismatch repair; *KRAS*; EGFR; Cancer staging

Ever since Bert Vogelstein's laboratory published its initial observations on colorectal cancer highlighting genetic material gains and losses within the cancer,^{1,2} the scientific community has pushed to understand what it takes to transform a normal colonic epithelial cell into a malignant cell with metastatic potential. The ability to control the processes of tumor cell initiation, progression, and metastasis indeed could impact patient survival. Evidence suggests that a person's genetic makeup accounts for 35 % of the risk of developing colorectal cancer. Despite this, the local environment of the colon plays an even larger role in the genetic development of colonic neoplasms.³ Many elements of the metastatic process are yet to be understood. Some elements of genetic contribution for colorectal cancer are gleaned from conditions with extreme phenotypic expression. Inherited mutated genes that contribute the high risk for colon cancer development in patients with polyposis syndromes are often the same ones somatically affected in sporadic colon cancers to drive its development.⁴

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Molecular tools have advanced enough to allow the scientific community to probe deeper into risk alleles within a population as well as into individual patient genetic data that can ascribe such risk. Hereditary colon cancer syndromes, for instance, can be tested in at-risk individuals by analysis of a single gene that is found mutated in the family. When found, proactive screening to minimize the individual's chances for subsequent cancer development may be adopted. Even in patients with a hereditary predisposition who succumb to cancer, the genetic and metabolic makeup of the patient and the unique aspects of that patient's tumor beyond the mutated inherited gene can define and afford a more personalized approach to optimize the patient's longevity and quality of life.

The treatment of patients with sporadic colorectal cancer is primarily surgical.⁵ Most precursor lesions (adenomatous polyps) can be removed by polypectomy at colonoscopy, whereas larger, more complex polyps, and early cancers require a surgical approach for cure. Cancers that extend into the muscularis propria (Astler–Coller–Dukes stage IIB) and cancers that have spread to regional lymph nodes (stage III) also are treated with curative intent by surgery, but some stage II and all stage III patients may have a survival benefit with adjuvant chemotherapy.^{5–7} The approach for widely metastatic disease (stage IV) can also be surgical for palliation or intent to cure if metastases are isolated, and patients are often offered chemotherapy or biological therapy with small improvements in survival.⁷ Although stage of disease dictates care in patients with colon cancer, biological, and genetic information are increasingly incorporated into clinical decision making to allow a more precise, specific, and individualized treatment plan. For instance, some patients with stage II colon cancer may benefit from adjuvant chemotherapy like their stage III counterparts, but it is difficult to know which stage II patients will benefit. A panel of seven cancer-related genes associated with colon cancer recurrence (*Ki-67*, *c-MYC*, *MYBL2*, *FAP*, *BGN*, *INHBA*, and *GADD45B*) analyzed from the tumor specimen via real-time RT-PCR has been validated as a tool to help predict stage II patients whose tumors behave like stage III disease.^{8,9} This assay translates tumor biology into individual treatment planning for stage II patients.

Approximately, 15–20 % of patients with sporadic colon cancer have tumors manifesting microsatellite instability, a marker for loss of DNA mismatch repair (MMR) function.⁴ Functional DNA MMR repairs DNA polymerase mistakes to maintain the fidelity of replicating DNA. Additionally, the MMR system can recognize certain chemotherapeutic agents that intercalate or get incorporated into DNA, and may be an important trigger to execute cell death.^{8–11} With MMR deficiency, repair of polymerase mistakes are lacking and affected cells accumulate mutations that may drive tumorigenesis.⁴ Importantly, MMR deficiency may prevent the recognition of DNA-damaging chemotherapy to initiate cell killing by that agent,^{10,12,13} including the core agent for treating advanced colon cancer, 5-fluorouracil. In multiple published retrospective and prospective studies, sporadic colorectal cancer patients with DNA MMR-deficient tumors do not derive any survival benefit from 5-fluorouracil-based adjuvant chemotherapy.^{6,14–16} This is in contrast to patients with retained MMR function in their tumors where a significant survival advantage was observed.^{6,14–16} Collectively, these data suggest that 5-FU-based chemotherapy does not prolong survival in patients with MMR-deficient colorectal cancers. Thus, biological information (e.g., tumor DNA MMR status) in addition to stage, should be considered in the approach to treatment of patients with advanced colorectal cancer.

The proto-oncogene *KRAS*, a GDP/GTP binding protein facilitating ligand-dependent tyrosine kinase growth factor signaling, is found mutated in >40 % of colon cancers,^{17–20} and its mutational activation drives constitutive signaling for proliferation through BRAF to activate the MAPK pathway.¹⁸ The upstream regulator of *KRAS* is the epidermal growth factor receptor (EGFR) which is expressed or overexpressed in the majority of colon cancers

and predicts a poor prognosis.^{18–20} While tumor mutant *KRAS* appears to have no influence on clinical response to 5-fluorouracil-based chemotherapy, its presence has a profound effect on the use of EGFR-targeted therapy. Evidence from clinical trials indicate that EGFR antibody therapy with cetuximab or panitumumab is ineffective in patients whose tumors harbor-mutant *KRAS*.^{18–20} This is likely because mutant *KRAS* signals independently of EGFR activation. Current recommendations are to test tumors for mutant *KRAS* in patients who are candidates for anti-EGFR therapy prior to initiating therapy.^{18–21} There is growing evidence that anti-EGFR therapy may likewise be ineffective in patients whose tumors possess mutant *BRAF*.²⁰ Since an individual's tumor genetic profile may predict response and outcome to targeted therapies, this should be considered in the approach to treatment of patients with colorectal cancer.

Biologically-driven decision making for optimal care and outcome for patients with advanced colon cancer is becoming increasingly adopted as diagnostics and treatments become more advanced, going beyond stage.²² By assessing tumors for genetic and proteomic profiles,^{23,24} and understanding the pharmacogenomics of an individual patient,²⁴ we can identify and treat high risk individuals by optimizing therapy to their personal profiles, and thus maximize their longevity and quality of life. Utilizing stool, blood/plasma, and tumor tissue, genetic and genomic (gene copy number, methylation, mRNA expression, miRNA profiles, sequencing, etc.) and pharmacogenomic information,²³ the use of high throughput bioinformatics and systems biology approaches, including analysis of the gut microbiome²⁵ may all contribute to a person's profile to direct specific cancer care.

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