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Expanding Role of Bio Markers in Colo-Rectal Cancer (CRC)

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Abstract

Colorectal cancer (CRC) is the second most common cancer among females and third among males globally. It has significant cancer-related mortality, despite substantial progress achieved in diagnosis and management strategies. Tumor biomarkers are assuming an increasingly important role in the detection and treatment of patients with colorectal cancer. New biomarkers alone or as a complement of existing diagnostic tests in high risk population might recognize the predisposition or early stage disease. The biomarkers have also the potential to change diagnostic approaches and treatment algorithms by selecting the proper chemotherapeutic drugs across a broad divergent spectrum of CRC patients. In future we are set to see personalized chemotherapy and or treatment based on presence or absence of some of these specific biomarkers [1,2].

Patients diagnosed with early stage I–III CRC have a good prognosis with a 5-year survival over 50%. Patients with metastatic stage IV disease have a less than 12% five years survival. Better understanding of the patho-biology, effective combinations of cytotoxic chemotherapy and biologic agents have significantly improved overall survival (OS) and progression free survival (PFS). CRC is a heterogeneous disease at molecular level that harbors many distinct genetic characteristics. Molecular testing is performed to identify patients who are candidates for targeted biologic agents or immunotherapy. Colorectal cancer (CRC) is a heterogeneous disease for which the treatment backbone has primarily been cytotoxic chemotherapy. CRC biomarkers evaluated include KRAS, NRAS, and BRAF mutation (MT), DNA mismatch repair (MMR) status, microsatellite instability (MSI), and CpG island methylation. With better understanding of the involved molecular mechanisms, it is now known that there are a number of epigenetic and genetic events, which are involved in CRC pathogenesis. Specific biomarkers have been identified which can be used to determine the clinical outcome of patients beyond tumor staging and predict for treatment efficacy. Molecular testing is now routinely performed to select for patients that will benefit the most from targeted agents and immunotherapy. In addition to KRAS, NRAS, and BRAF mutation (MT), analysis of DNA mismatch repair (MMR) status, tumor infiltrating lymphocytes, and checkpoint protein expression may be helpful to determine whether patients are eligible for certain therapies. The focus of this commentary is to discuss present and upcoming biomarkers in CRC [2]. The commonly used biomarkers are CEA, RAS, BRAF, and MSI. The potential markers in future are TIL, check point proteins, neo antigens, gene MTs, CpG island methylation.

Carcinoembryonic Antigen

Carcino embryonic antigen (CEA) both in the fetal colon and in the blood of patients with adeno carcinoma of the colon first identified in 1965 [3,4]. As this is the protein detected in only cancer and embryonic tissue, it is called carcino embryonic antigen [5] CEA gene is part of the immunoglobulin super family and codes for a different number of glycoproteins which differs both in amino acid composition and function. The gene is attached to the cell membrane by glycosyl phosphatidylinositol anchor and released in soluble form by phospholipase C or D, and has two parts the CEA-related cell adhesion molecules (CEACAMs) and the pregnancy-specific glycol proteins [6]. In humans, the gene is clustered on the long arm of chromosome 19 and consists of 29 genes of which 18 expressed, 7 belonging to the CEA subgroup and 11 to the pregnancy-specific glycoprotein subgroup [6,7]. CEA is the serum tumor recommended for determining prognosis, surveillance after CRC curative surgery, and also used for monitoring the response of metastatic disease to systemic therapy [8,9]. CEA has no role in screening and detecting early CRC because of the low sensitivity rate (18-69%) [10]. A high level of is a strong predictor of decreased overall survival [11]. In the postoperative setting is associated with early recurrence [12].

RAS

RAS proteins are Small GTPases. They are essential components of signaling pathways responsible for cell growth, migration, adhesion, survival, and differentiation. RAS can activate several downstream effectors, including the PI3K-AKT-mTOR pathway, which is involved in cell survival; and the RAS-

RAF-MEK-ERK pathway, which is involved in cell proliferation [13]. Oncogenic activation and mutations of RAS proteins frequently detected in many types of cancer. Three different human RAS genes are identified: KRAS (Kirsten rat sarcoma virus Oncogene Homolog), HRAS (Harvey rat sarcoma virus oncogene), and NRAS (neuroblastoma RAS viral oncogene homolog) [14]. RAS proteins cycle between inactive guanosine diphosphate (GDP)-bound and active guanosine triphosphate (GTP)-bound forms [15]. Activating RAS mutations occur in 30% of human cancers and specific RAS genes are mutated in different types of cancer.

KRAS is a proto-oncogene, a kind of guanine nucleotide (GTP/GDP) binding protein with intrinsic GTPase activity, attached to internal aspect of the plasma membrane by a lipid anchor. The Size of KRAS IS 189 amino acids, 21656 Da. Localized to the inner surface of cell membrane, it interacts with more than 20 effector proteins located at 12p12 consisting of six exons, spread over 35kb of genomic DN [15]. Mutations in KRAS gene results in activation of signaling pathway of the Epidermal Growth Factor Receptor (EGFR). Activation of EGFR triggers the signaling cascade through RAS/RAF/MEK/MAPK and PI3K/AKT pathways resulting in increased tumor cell proliferation, protection against apoptosis, stimulating angiogenesis and metastasis [16].

Table 1: Frequency of Significant KRAS Mutations.

Codon	Amino Acid Substitution	Amino Acid Change	Incidence, %
12	Gly12Asp	Aspartate	32.5
12	Gly12Val	Valine	22.5
12	Gly12Cys	Cysteine	8.8
12	Gly12Ser	Serine	7.6
12	Gly12Ala	Alanine	6.4
12	Gly12Arg	Arginine	0.9
13	Gly13Asp	Aspartate	19.5
Others			1.8

KRAS mutations occur early in CRC carcinogenesis and occur in 30-50% of all CRC cases with 95% concordance between primary cancers and metastasis [17,18]. About 90% of the Single nucleotide point mutations occurs in codons 12 and 13 of exon 2 [19]. (Table 1) Specific mutations in KRAS can result in the KRAS protein being inherently activated independently of upstream growth factor receptor activation. The use of KRAS mutations as a prognostic marker in CRC is controversial. There are studies found KRAS mutations associated with poor prognosis and reduced survival [20-22]. Few studies associate KRAS mutation with shorter survival rate to the stage of the disease mainly with early stage disease [23], and specific mutation site within KRAS gene alone or in combination with mutations in p53 [24].

KRAS mutation is a predictive marker in metastatic CRC with anti-EGFR target therapy [25]. KRAS gene mutation in codon 12 or codon 13 associated with a no response to anti-EGFR target therapy such asCetuximab or Panitumumab [26-28]. Testing for KRAS and NRAS mutation in patients with metastatic CRC before initiation of anti-EGFR therapy is now a standard of care in clinical practice [29]. NRAS mutations occur in 1–6% of CRC. The NRAS oncogenes when mutated, can cause normal cells to become cancerous. The NRAS gene provides instructions for making NRAS protein which plays important roles in cell division, cell differentiation, and apoptosis through signal transduction. To transmit the signals, the N-Ras protein needs to be activated by binding to a molecule of GTP when the protein is bound to GDP; it does not transmit signals to the cell's nucleus. Wild-type NRAS, together with wild-type BRAF and KRAS, is associated with good response to EGFR antibody therapy [30], while patients with NRAS-mutated tumors are unlikely to respond to Cetuximab or Panitumumab [31].

BRAF is an oncogene, discovered in the 1980's, a member of the RAS family, and a mediator of the EGFR pathway. BRAF is a protein kinase downstream of RAS in the RAS/RAF/MEK/ERK pathway and has been a target in several malignancies. The dominant V600E mutation is similar to one seen in melanoma. More than 90% of all BRAF mutations involve V600E, by a substitution of valine-to-glutamic acid amino acid, resulting in abnormal activation of MEK-ERK pathway [32-34]. The BRAF mutant genotype influences the molecular and phenotypic characteristics of CRC. The mutation occurs at the early stage of colorectal carcinogenesis through activation and de-regulation of the downstream signaling pathways [33-34]. It leads to serrated adenoma-type tissue that has defective mismatch repair, and a tumor that is diploid and microsatellite-unstable. BRAF mutations are found in 5-15% of CRC cases [35], of which 34-70% seen in MSI-H tumors by epigenetic inactivation of the MMR system, by promoter hypermethylation of MLH1.Only 1.4% of patient with Lynch syndrome carry a BRAF mutation. BRAF mutations are found in the high-grade tumors, and right-sided colonic tumors [36,37]. Mutations in BRAF are associated with poor clinical outcome [38]. The patients with MSS tumors and BRAF mutations have a poor prognosis with low progression-free survival (PFS) and low overall survival [39-40]. Patients with BRAF V600E mutations does not benefit from anti EGFR-target monoclonal antibody therapies [41].

MSI

Microsatellite instability (MSI) reflects the presence of defective mismatch repair genes caused by the loss of DNA mismatch repair activity. MSI is detected in 15% of all CRC. About 3% are of these are associated with Lynch syndrome and 12% are caused by sporadic, acquired hypermethylation of the promoter of the MLH1 gene, which occurs in tumors with the CpG island methylator phenotype [40]. MSI is not only a key component for the pathogenesis of CRC but can also be

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a biomarker for improved prognosis and predict efficacy of chemotherapy and immunotherapy.

Tumors that have cells with high MSI (MSI-H) are associated with good prognosis and favorable outcome compared to microsatellite stable (MSS) disuses [42]. Mutations in TGF-RII, BAX or EGFR; are often seen in tumors exhibiting MSI-H [43]. Mutations in these genes have not shown a significant impact on the favorable prognosis characterizing MSI colon tumors [44]. Mutation in BRAF V600E gene commonly occurs in sporadic MSI tumors [45]. The BRAF mutation in CRC that is MSS showed a poor patient prognosis, whereas BRAF mutant microsatellite unstable (MSI) colorectal cancers have an excellent prognosis [46]. Regarding the MSI and the responsiveness to 5-FU chemotherapy, some studies have shown that MSI-H tumor cells are resistant to 5-FU [47]. Patients with MSI-H colon cancer stage II and III do not have the same survival benefit from adjuvant 5-FU chemotherapy as patients with MSS and MSI-L tumors [48], this resistance may be due to MLH1hypermethylation, as the cells regain their sensitivity towards 5-FU upon MLH1 demethylation [49].

Colorectal tumors with MSI have distinctive features, including a tendency to arise in the proximal colon, lymphocytic infiltrate, and a poorly differentiated, mucinous or signet ring appearance. patients who have MSI-H tumors did better than MSS in general, and patients with stage II and III MSI-H tumors did not benefit from adjuvant 5-fluorouracil (5-FU) chemotherapy (HR =1.07, P=0.80) [24]. Conversely, patients with MSS tumors did benefit from 5FU therapy (HR =0.72, P=0.04) [25]. However, patients with stage III MSI-H cancers, like MSS cancers, do benefit from adjuvant FOLFOX chemotherapy. A pooled analysis of adjuvant chemotherapy trials evaluated patients with stage III who received FOLFOX alone or in combination with cetuximab, and showed that patients with MSI-H tumors did as well as patients with MSS tumors (BRAF and KRAS WT) and there was no difference in the 3-year disease free survival [28]. A large retrospective study evaluating 433 patients with MSI-H tumors who had stage II or III CRC, reported that patients with stage III MSI-H tumors still benefited from adjuvant 5FU and oxaliplatin (FOLFOX) chemotherapy [29]. There is preclinical data suggesting that MSI-H tumor cells are resistant to fluoropyrimidines possibly due to higher levels of thymidylate synthase but more sensitive to irinotecan and mitomycin C [14,15,21]. Further studies are needed to confirm this in the clinical setting [2].

Continous and rapid advances in CRC tumor characterization have enabled us to personalize the treatment for CRC patients. Currently KRAS, NRAS, and BRAF MT testing are of importance to determine eligibility for anti-EGFR antibody therapy. In addition, DNA MMR and MSI status is emerging as clinically significant to determine whether patients may be eligible and benefit from immunotherapy. Better understanding of pathological and genomic features seen in MSI-H CRC will enable us to look for other biomarkers, such as TILs, checkpoint proteins, or other genomic MTs so that we may be better able to include eligible patients even with MSS tumors in future for immunotherapy. In CRC, analyses of immune reaction and TILs have already been explored as a means for tumor classification and as a prognostic biomarker. There has been characterization of TILs with tumor invasion, spread to lymph node, and tumor (TNM) staging system. The extent of immune reaction at the tumor site is correlated with improved clinical outcome [2]. The authors concluded that while PD-L1 expression is a reasonable predictive biomarker there is no universal consensus, as there is substantial heterogeneity in the methodology of evaluation and the expression is possibly a dynamic process which changes according to the tumor microenvironment [2]. The association of the MSI-H phenotype with the presence of TILs is explained by the accumulation of frame shift MTs and synthesis of neo antigens thus triggering the host immune system [49]. Neo antigens are mutated peptides that arise in the tumor and are not present in the normal genome. With the use of whole-exome RNA sequencing, it has become possible to identify novel neo antigens [50]. Patients who had a high number of neo antigens were more likely to respond to anti-CTLA-4 therapy (b). More importantly, understanding why MSI-H tumors are responsive to immunotherapy will help us develop better treatment combinations to improve efficacy for all CRC patients.

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