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Recent Advances in Colon/Colorectal Cancer Biomarker Developments

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Abstract

Cancers of the colon and rectum known as colorectal cancer. Colorectal cancer is one of the leading causes of cancer-related deaths worldwide. Colorectal cancer usually begins as a slow-growing, non-cancerous polyp, which can progress over time to aggressive cancer. If a cancerous polyp is not removed, it can enter the lining of the large intestine, causing the cancer to spread to other organs through the blood or lymphatic vessels. With screening, it is possible to detect and remove polyps before they become cancerous. The increase in colorectal cancer awareness and screening has contributed to an overall decrease in the incidence of colorectal cancer over the past 30 years. Scientist have learned a lot about colorectal cancer, but it needs more research to find ways to prevent and detect the disease earlier. It is difficult to detect in the early stages. However, secretory proteins have been used as an ideal biomarker to detect the progression of colon cancer in cancer patients. Colorectal cancer detection techniques at the molecular level have facilitated the development of new signature drugs designed to inhibit unique pathways of colorectal cancer development and immunity.Serum/tissue protein expression may help general practitioners to identify colon cancer in earlier stages. Recently, the discovery of biomarkers is important in cancer biology and disease management. DNA, RNA, metabolites, enzymes, mRNAs, aptamers, and proteins biomolecules may help an early prediction of disease. This review explains recent advances on new developments in molecular markers associated with colorectal cancer.

Keywords: colon, colorectal, cancer, biomarker, mutation.

1. Introduction

Colon (large intestine) is a long, coiled, tube like organ that extracts water from digested food. The remaining material, solid waste called feces, moves from the colon to the rectum and leaves the body through the anus. The colon is only 6 feet (1.8 m) long. This 6 feet dense muscle is divided into four parts: the ascending colon, the transverse colon, the descending colon and the sigmoid colon. Each part represents a location in a broken rectangle shape that forms the colon in the body (Bradford, 2016). Colorectal carcinoma is one of the most common cancers and leading causes of cancer-related death in the United States (Fleming et al., 2012) with a low reported incidence in India (Patil et al., 2017). Colon cancer is a malignancy that arises from the inner lining of the colon. Colon cancer is a malignancy that arises from the inner lining of the colon. Most of these cancers develop from colonic polyps. Early colon cancer and colon polyps mostly have no sign and symptom of illness. Full-blown colon cancer can cause occult blood in the stool, overt rectal bleeding, bowel obstruction, and weight loss. Colon cancer risk factors include a family history of it or colonic polyps and prolonged ulcerative colitis (Melissa).

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2. Results

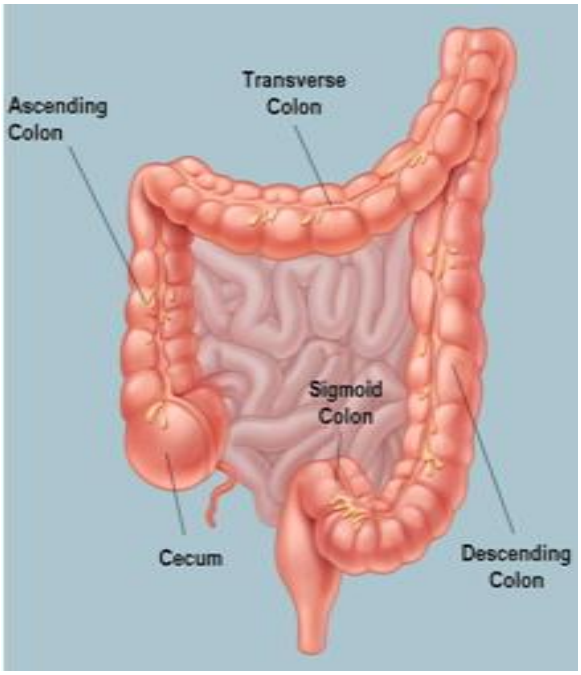

Fig. 1. Typical picture of colon anatomy (Hoffman)

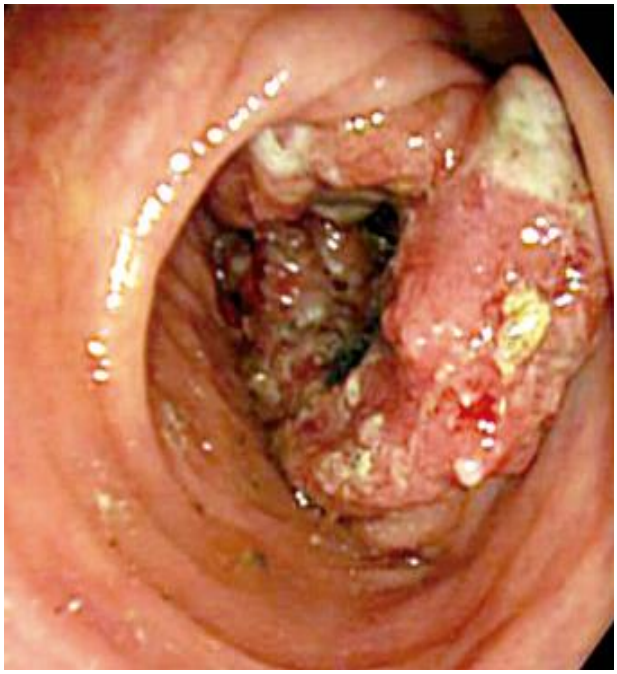

Fig. 2. Colon cancer in the cecum (Akihiro Kobayashi et al., 2006)

Biomarkers for early detection

Tumor endothelial markers (TEMs): Tumors and normal endothelium can be easily identified on the basis of TEMs. The most promising TEM1, TEM5, TEM7 and TEM8 appeared to be promising for oncogenic signaling in colorectal cancer. Over expression of TEMs, especially TEM1, TEM7, and TEM8 in colorectal tumor tissues, compared to healthy tissues, suggest their role in the formation of tumor blood vessels. These TEMs appear to be candidates for perspective for early detection, monitoring, and treatment of CRC patients (Aukasz et al., 2016).

Carcinoembryonic antigen (CEA)**:** CEA is a cell-surface high molecular weight glycoprotein important for cell adhesion (Shiromizu et al., 2017) CEA is usually produced at birth and is present in very small amounts in healthy patients. However, it may be elevated in CRC, other types of cancer and non-fatal conditions (Shively et al., 1980).

Annexins: In humans there are subfamilies in the annexin family; A1-A11 and A13 (Nicholson et al., 2014). The sensitivity of annexin A3, A4 and A11 peptides to early stage CRC detection is reported to be higher than CEA and as such these peptides are promising biomarkers for CRC detection (Rescher et al., 2004).

Complement component C3: Complement component C3 (C3), and its fragments C3 anaphylatoxin (C3a), have been demonstrated to have over expression in fecal, serum, and histological samples from CRC patients. C3 over expression in CRC stool samples was performed in two separate studies (Bosch et al., 2017; Bosch et al., 2012).

S100 proteins: S100 is a family calcium-binding protein, consisting of 24 members divided into three groups; only intracellular regulatory functions, only extracellular functions and those with both intracellular and extracellular functions (Donato et al., 2013). The same study identified chitinase 3-like 1 (CHI3L1) protein over expression in adenomas and advanced adenomas and CRC, with over expression confirmed to be present in the serum of patient subtypes compared to controls (Fijneman et al., 2012).

Angiogenesis biomarkers: Angiogenesis, an important step in the progression of cancer, is a new blood vessel generation from the endothelial precursor, which is mediated through a group of ligands and receptors that work together (Kerbel, 2008). A group of glycoproteins, including placental growth factor (PIGF) and the VEGF family (VEGF-A, VEGF-B, VEGF-C, and VEGF-D),

act as effectors of angiogenesis (Kerbel, 2008; Ebos et al., 2008). VEGF has been reported to have a potential value as a predictor or prognosis biomarker for metastatic CRC (Gabay et al., 1999).

Inflammatory biomarkers: In patients with inflammatory bowel diseases, chronic inflammation was suggested as an important factor for CRC and increases the risk of developing CRC with prolonged duration of colitis. Another inflammatory biomarker, macrophage inhibitory cytokine 1, has been reported to be positively associated with CRC risk (Mehta et al., 2014).

Circulating tumor cells (CTCs): CTCs are primarily tumor cells derived from primary tumors or metastases circulating in peripheral blood. CTCs in colorectal cancer have epithelial origin with a defined immunophenotyping signature (CD45-, EpCAM) (Akagi et al., 2013). This promises to develop more efficient personalized therapies to eliminate cancer stem cells in CRC patients.

Circulating cell-free DNA: The discovery of circulating cell-free DNA (ccf-DNA) may open a new possibility for non-invasive analysis of tumor-derived genetic material, as it can be isolated from human body fluids (Utting et al., 2002). MSI or LOH within CCF-DNA have been investigated from plasma/sera of CRC patients as a very valuable biomarker (Lazarev et al., 2014). Various studies have reported the diagnostic / symptomatic value of mutated genes within ccf-DNA (Diehl et al., 2008).

Circulating microRNAs: miR-21 is one of the most expressed miRNAs in CRC; and miR-21 is highly secreted by cancer cells which can be measured as exosomes or free miRNAs in plasma or serum (Schetter et al., 2008). As another potential circulating microRNA, elevated serum levels of miR-92a have been reported for adenomas and CRCs (Liu et al., 2013). Significantly higher expression of miR-17-92 cluster and miR-135 was found in CRC patients compared to healthy controls (Perilli et al., 2014).

Fecal biomarkers: Because stool markers are derived directly from tumor cells, which is considered a highly specific biomarker for CRC. These fecal biomarkers include stool DNA (sDNA), which can be used for specific cancer-related genes, miRNAs, protein biomarkers as well as secreted molecules and biochemical substances for MSI, aberrant DNA methylation, or somatic mutations. Several panels of methylated genes within sDNA have been reported for different stages of CRC, *including BMP3, CDH1, CDH13, CRBP1, CXCL12, ESR1, HLTF, ID4, IRF8, ITGA4, MINT1, MINT31, NDRG4, P14, RX3. , SFRP2, SLC5A8, a*nd *TIMP3* (Coppedè et al., 2014).

***KRAS* gene mutations:** KRAS, a GTPase protein, is encoded by the KRAS protoonco gene, which is an early player in many biological pathways. Differential point mutations in codons 12 and 13 of exon 2, or mutations in codon 61 of exon 3, lead to constitutive activation of the RAS signaling pathway. Therefore genetic disruption of the KRAS gene is one of the essential steps in the development of many cancers, including CRC (Santini et al., 2008).

***BRAF* gene mutations:** BRAF is a direct downstream effect or KRAS within the Ras/Raf/MAPK signaling pathway. BRAF gene mutation has been reported to be associated with CRC development and poor prognosis of patients (Fransén et al., 2004; Davies et al., 2002). Based on previous studies, BRAF gene mutation is associated with aging, female gender, proximal colon location, poor differentiation, mucous histology, infiltrating lymphocytes and advanced stage of the disease (Li et al., 2006). BRAF mutations occur more frequently in MSI-H cases of CRC (de la Chapelle, 2002).

***TP53* gene mutations:** The TP53 gene is a very important tumor suppressor, which plays a role as a central regulator of various cellular processes, including growth arrest and apoptosis, DNA damage, stress response, oxidative stress and prolific signals (Vogelstein et al., 2000). TP53 protein dysfunction is a common hallmark of human solid tumors, reported in more than 25 % of adenomas and CRC in 50-70 % of patients (Leslie et al., 2002).

***APC/b*-Catenin Mutation:** Genetic disruption of APC leading to the activation of Wnt pathway, is one of the important early genetic event in genetic disruption of APC leads to activation of the Wnt pathway, an important early genetic event in colorectal tumorigenesis (Powell et al., 1992). The *APC* gene product is a large protein that regulates development, chromosomal segregation, cellular differentiation, polarity, adhesion, migration, and also apoptosis. APC promoter hypermethylation is also reported in more than 18 % of primary colorectal carcinomas and adenomas (Esteller et al., 2000).

Aberrant DNA hypermethylation in CRC: Recently a third class of CRCs characterized by a high frequency of DNA hypermethylation has been reported and defined as having a “CpG

island methylator phenotype(CIMP). A study report CIMP in CRC, based on the methylation status of five genes (*CACNA1G, IGF2, NEUROG1, RUNX3, and SOCS1*) (Weisenberger et al., 2006). These hypermethylation of various genes, i.e. *SLC5A8, ITGA4, SFRP2, PTCH1, CDKN2A, HLTF,* and *MGMT* play a role in the initiation and progression of adenomas to CRC (Qi et al., 2006; Li et al., 2003). To date, a large number of hypermethylated genes including *APC*, *ATM*, *BMP3*, *CDKN2A*, *SFRP2*, *GATA4*, *GSTP1*, *HLTF*, *MLH1*, *MGMT*, *NDRG4*, *RASSF2A*, *SFRP2*, *TFPI2*, *VIM*, and *WIF1,* have been found in stool DNA assays for the early detection of CRC (Chen et al., 2005).

Telomere length dynamics: In mammals the ends of chromosomes are composed of telomeres, a 6-bp variable repeat sequence (TTAGGG), which is added by elomerase and plays an important role in the maintenance of chromosomal stability (Chen et., 2005; Blackburn et al., 1991). Since tumors in the sporadic form of CRC appear relatively later than hereditary nonpoliposis colorectal cancer (HNPCC), the number of splits between initiation and clinical presentation in sporadic may be higher than HNPCC, hence their baseline likely to occur upon initiation of telomere. Shortened to sporadic form of CRC (Muraki et al., 2012; Bisoffi et al., 2006). Well-differentiated tumors, suggesting a shortening of telomere length as an early event in colorectal cancer, directly reflecting pathologic cell proliferation (O'Sullivan et al., 2006; Raynaud et al., 2008).

3. Conclusion

Several biomarkers of colon/colorectal cancer have been proposed and understanding the behavior of CRC at the molecular level has been encouraged. Even if further validation studies are required, assessing the role of a biomarker in experimental models and in patients may open new perspectives regarding the patient-tailored approach. Biomarker development can target therapies for cancer and improve the selection of adjuvants for drug development. The use of protein biomarkers may also reduce economic burden in the treatment of cancer. In addition, an automated and inexpensive standardized protein marker is required for colon cancer detection. Existing colon cancer biomarker screening assays with high accuracy need to be improved. The discovery of more specific serum and tissue proteins is required in colorectal cancer patients and may enhance the development of new drugs.

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