Molecular differences in colon cancer according to location: A literature review

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ABSTRACT

Differences in clinical presentation, epidemiology, prognosis, and molecular mechanisms between left-sided colon cancer (LCC) and right-sided colon cancer (RCC) have been widely studied in recent years. Indeed, mutations seen in LCC differ in nature and frequency compared to LCC. Furthermore, the differences in the biological environment, including histopathological, microbiological, and biochemical differences of the two regions promote different gene expressions in carcinomas. These molecular differences distinguish the nature of colorectal cancer according to the primary site of formation. In this narrative review, all such differences have been explored in detail with the aim of providing further insights into the topic, since in the era of individualised treatment, sidedness is a major factor in the treatment of colorectal cancer.

Key Words: *Colorectal cancer; primary tumour location; sidedness; molecular differences*

INTRODUCTION

Colon cancer, otherwise known as colorectal cancer (CRC), is the third most common cancer (after lung and breast cancers) and the second most common cause of death associated with cancer worldwide, regardless of gender [1]. The number of deaths caused by CRC has been decreasing in the last decade, possibly due to early diagnosis with screening programs and novel therapeutics [2,3]. Nevertheless, the disease continues to be of paramount significance in the field of oncology. Colorectal cancer can be caused by both genetic disorders (as in hereditary colon cancer), or environmental factors (as in sporadic colon cancer) [4]. Sporadic colon cancer, consisting of approximately 95% of all CRC cases, is associated both with genetic predisposition or gene mutations, as well as other risk factors, including some related to lifestyle such as obesity, lack of exercise, diet, smoking and alcohol

ABBREVIATIONS: *ALK: Anaplastic lymphoma kinase, APC: Adenomatous Polyposis Coli, BA: Bile Acids, BMPR1A: bone morphogenetic protein receptor type 1A, BRAF: v-raf murine sarcoma viral oncogene homolog B1, BRCA1: BReast CAncer gene 1, CDH1: Cadherin-1 or Epithelial cadherin (E-cadherin), CMS1: Consensus Molecular Subgroup 1, CMS2: Consensus Molecular Subgroup 2, CMS3: Consensus Molecular Subgroup 3, CMS4: Consensus Molecular Subgroup 4, CRC: Colorectal Cancer, DCA: Deoxycholic acid, EGFR: Epidermal Growth Factor Receptor, KRAS: Kirsten rat sarcoma virus, LCA: Lithocholic acid, LCC: Left-sided Colon Cancer, mCRC: metastatic colorectal cancer, MLH1: MutL homolog 1, MRE11: meiotic recombination 11, MSH6: MutS homolog 6, MSH2: MutS homolog 2, MSI: MicroSatellite instability, NOTCH1: Neurogenic locus notch homolog protein 1, NRAS: Neuroblastoma RAS viral oncogene homolog, NTRK: Neurotrophic tyrosine receptor kinase, PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase, POLE: DNA Polymerase Epsilon, Catalytic Subunit, PTEN: Phosphatase and TENsin homolog deleted on chromosome 10, RCC: Right-sided Colon Cancer, RNF43: Ring Finger Protein 43, SMAD2: Mothers against decapentaplegic homolog 2, TP53: Tumor protein P53*

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consumption [5,6]. It is therefore necessary to study the molecular mechanisms of CRC carcinogenesis, as it can lead to the discovery of novel screening and therapeutic methods, which can assist the diagnosis and prognosis clinically.

Traditionally, the large bowel has been categorised into three main groups, the proximal or right colon, the distal or left colon and the rectum. The border of the right and left colon is the point between the proximal two thirds and the distal third of the transverse colon [7]. This reflects the differences in embryologic development [8]. From the midgut arise the superior mesenteric artery and vein, which vascularize the cecum, the ascending colon and the proximal two thirds of the transverse colon, while the distal transverse, the descending colon and the sigmoid colon are irrigated by the inferior mesenteric artery and vein, which derive from the hindgut [7]. Colon cancers are considered right sided or proximal if they are located before the splenic flexure. Left-sided colorectal cancers or distal carcinomas are cancers found distal to the splenic flexure. Tumours found in the splenic flexure are considered left-sided colon cancers [9]. Due to their embryologic origin, cancers of the right colon resemble gastric carcinomas and small bowel tumours [10,11]. It is of interest that neoplasms of the appendix and distal small bowel, although of shared embryologic descent and vascularisation with the right colon, are not included in the right sided colon cancer group [10]. They have differences in carcinogenesis and therefore are not in this group. Additionally, rectal carcinomas share similar molecular pathways with the distal large bowel and are considered left-sided cancers [11,12].

MOLECULAR BIOLOGY OF COLORECTAL CANCER

Multiple mutations of oncogenes and tumour suppressor genes occur in the oncogenesis process of colon cancer. Two main pathogenic pathways are involved in this sequence [13]. The first pathway involves the APC and β-catenin genes and features chromosomal instability. Normally, the APC tumour suppressor gene promotes β-catenin degradation [14]. The APC tumour suppressor gene is lost in this pathway, an event which promotes the development of an adenoma and occurs early in this process. The accumulation of β-catenin forces it to translocate to the nucleus. This activates the transcription of MYC and cyclin D1 genes. Mutations of the K-RAS gene begin to occur and subsequently mutations of the 18q21 and TP53 genes occur [13,15]. The second pathway consists of damage to DNA mismatch repair genes and accounts for approximately 10-15% of all cases of

sporadic cancer [16,17]. The most common of these DNA mismatch repair genes to have genetic lesions is MLH1, resulting in a hypermutable state where repetitive DNA sequences, called microsatellites, become unstable during DNA replication [18]. This phenomenon, called microsatellite instability (MSI), characterises defective DNA mismatch repair, which results in the accumulation of mutations of growth-regulating genes and further development of colorectal cancer. In addition to these two main pathways, the CpG island methylator phenotype (CIMP) pathway is also involved in the CRC carcinogenesis [19].

Colorectal cancer is a heterogeneous disease which develops through various genetic and epigenetic mutations, with three distinct molecular pathways. These are chromosomal instability (CIN), microsatellite instability (MSI) and epigenetic methylation (Serated/CIMP) [19,20]. Chromosomal instability refers to many structural and numerical changes in chromosomes. This means whole chromosomes or parts of them are duplicated, inserted, or deleted, leading to aneuploidy [21].

Microsatellites, also known as Short Tandem Repeats (STR), are repeated sequences of DNA, with 1-4 bases per unit that are repeated and scattered throughout the genome, in areas that are coding or non-coding regions and account for about 3% of the entire genome [22]. Due to their repeated structure, they are susceptible to multiple errors and mutations during DNA replication. The system that corrects these errors is called DNA mismatch repair (MMR) [23]. Microsatellite instability is defined as the result of impaired MMR, which is phenotypically evident when there is a change in length of microsatellites. MSI occurs in genetically inherited mutations of MMR genes, such as Lynch syndrome, or in an epigenetic inactivation of these genes during methylation of MLH1 [18]. Carcinomas with high microsatellite instability are called MSI deficient, or MSI-d, whereas carcinomas with stable microsatellites are called MSI-proficient or MSI-p. Microsatellites that are unstable are highly immunogenic. This has an excellent effect with treatments of unstable tumours that activates the immune system [24,25].

GENES AND COLORECTAL TUMOR POSITION

Gene expression and tumor position

Gene expression in the normal colon varies between right and left side. For example, cytochrome p450 genes are expressed more in the right colon compared to the left colon in normal subjects. This may be due to differences in exposure of materials consumed in the colon [11]. Furthermore, methylation of genes is different on each side of the large bowel. The mismatch repair gene hMLH1 and

the O-6-methylguanine-DNA methyltransferase MGMT is found predominantly in the normal right colon of older females [11,26]. This may reflect epigenetic abnormalities that may lead to dysplasia and further development of adenocarcinomas of the right colon.

The CIMP phenotype consists of hypermethylation of CpG islands. These are clusters of cytosine-guanine complexes. CIMP is an epigenetic control aberration that is important for inactivation of onco-suppressor genes in cancer cells. Under normal circumstances, these areas are not methylated [20]. When hypermethylation occurs and onco-suppressor genes are inactivated, carcinogenesis may develop. According to the proportion of CpG islands methylated, tumours are divided into CIMP-high, CIMP low and CIMP-normal groups. CIMP-high tumours are often associated with microsatellite instability due to hypermethylation of MMR genes, and with BRAF mutations but are usually wild type for p53 mutations [27].

In 2015, in order to resolve inconsistencies in classifications of CRC based on gene expression, an international consensus decision was made on the molecular subtypes of colorectal cancer [28]. Four consensuses of molecular subtypes with distinguishing features were defined (CMSs). The CMS1 (microsatellite instability immune) subtype, consisting of 14% of CRCs, has the best prognosis but worse survival after recurrence. They are hypermutated and microsatellite unstable and are immunogenic; CMS1 samples were hypermutated and had low prevalence of somatic copy number alterations, and they had overexpression of proteins involved in DNA damage repair. As expected, the analysis of methylation profiles in TCGA showed that CMS1 tumours display a widespread hypermethylation status; The CMS2 subtype or canonical subtype is epithelial and occur in 37% of CRCs and have the highest overall survival. They detected more frequent copy number gains in oncogenes and copy number losses in tumor suppressor genes in CMS2 than in the other subtypes; the CMS3 subtype or the metabolic subtype occurs in 13% of cases and are also epithelial [29]. They also have an evident metabolic cancer phenotype; the CMS4 subtype, or the mesenchymal subtype occurs in 23 % of cases is prominent transforming growth factor-β activation, stromal invasion, and angiogenesis [30].

Molecular differences in colon cancer according to location can be seen using the molecular subtypes. In right colon cancer, CMS1 and CMS3 are more common, while CMS2 and CMS4 are more common in left colon cancer [11]. All subtypes are found on both sides, but the proportion is different according to location. CMS has been proved to be a significant clinical prognostic factor in overall survival (OR) and progression-free survival (PFS). In CMS1 groups,

patients treated with bevacizumab had significantly better overall OS than those treated with cetuximab. In the CMS2 group, patients treated with cetuximab had significantly longer OS than patients treated with bevacizumab [31,32].

Carcinomas of the right colon are usually CIMP-high; they are also MSI high, hypermutated, and have a high affinity for BRAF mutations, especially the V600E mutation. Several other gene mutations such as KRAS, PIK3CA and RNF43 are found more frequently in RCC. Some gene mutations are exclusive to the right side. These genes are CDH1, MRE11, SMAD2 and NOTCH1 [11,33,34]. BRAF mutations and CIMP-high status have poor prognosis, giving right-sided colon cancer generally a worse prognosis than LCC [35,36]. Adversely, left sided colon cancers are microsatellite stable, they present chromosomal instability and APC and p53 mutations and genes that have Tyrosine Kinase Receptors are augmented, causing the upregulation of HER2 and EGFR genes [25,36,37].

Genes whose mutations are associated with cancer predisposing syndromes like Lynch syndrome, juvenile polyposis syndrome, PTEN hamartoma tumour syndrome, neurofibromatosis type 2 and hereditary breast ovarian cancer syndrome have slightly higher prevalence in RCC, which are namely the MSH6, MLH1, MSH2, POLE, PTEN, BMPR1A, BRCA1, BAP1, BRIP1, NF2, and MEN1 genes [11,26,37-39].

Differences in immunohistochemistry amongst right and left side cancers have also been identified. The expression of programmed cell death (PD-1) and PD-1 ligand-1 (PDL-1) is expressed approximately two times more in RCC rather than LCC [11,40,41]. The molecular differences mentioned are presented in Figure 1, Table 1.

THE ROLE OF THE MICROENVIRONMENT IN GENETIC DIFFERENCES

The microenvironment of the large bowel lumen plays an important role in the development of colorectal cancer. Environmental factors such as distinct microbiota, bile acid levels and chronic inflammation may contribute to carcinogenesis of the intestinal epithelial cells [44]. The microenvironment in the right side of the colon differs from the left side, which also affects the expression of genes between the regions.

Differences in the microbiota

The large bowel hosts a large number of different bacteria, including *E.coli*, and *F.nucleatum* and the percentage of these bacterial species is quite similar in the left side and the right side of the colon, accounting the microbe population of the colon as uniform [45]. Nevertheless,
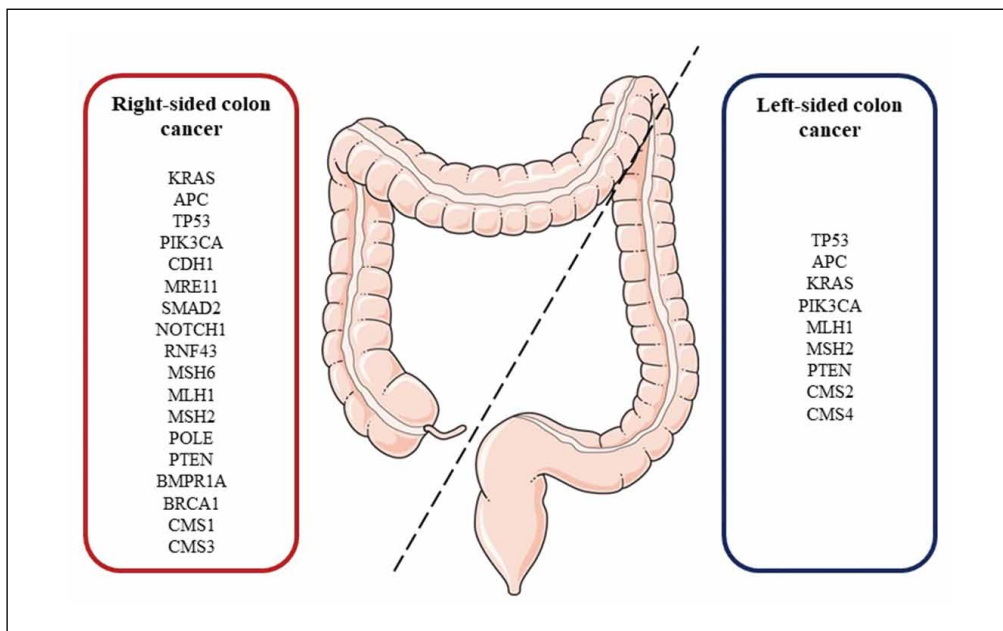
FIGURE 1. Main significant gene mutations in colon cancer per location.

this balance changes when colon cancer develops and differences in bacterial flora exist between patients with left and right sided colon cancer [46] .

Carcinogenesis related to bacterial exposure occurs via two different pathways. The first pathway has to do with chronic inflammation related to colitis and the bacteria responsible for this situation are usually *E. coli*, *B.fragilis, B.dorei, B.vulgatus* and *B.massiliensis* [47]. The second pathway consists of the creation of a microenvironment by different bacterial strains, which promotes immunological response and inflammation not related to colitis and bacterial strains involved in this second pathway are usually *F.nucleatum,* Pophyromonas, Parvimonas and Leptotrichiae [40].

E.coli are very common microorganisms and are part of the normal gut and the majority of group B2 *E.coli* can

harbour genomic pks islands, which are responsible for the production of polyketide synthase [48]. In turn, polyketide synthase can cause double strand breaks in DNA which in turn causes an increase in γH2AX histones. These histones create polyploidy due to incomplete DNA repair, which can also create anaphasic bridges leading essentially to multiple mutations [49]. It is worth mentioning that the incidence of group B2 *E.coli* in biopsies of patients with right-sided colon cancer has been found to be higher in comparison to patients with left sided colon cancer [50].

F.nucleatum is the most studied of all oncogenic bacteria and has been found to have the most malignant potential and is found in a vast number of colorectal cancer patients, bound to mucin-producing cells of the intestinal lumen [51]. It binds to intestinal mucosa in two ways, with FadA and Fap 2 receptors. It promotes an

TABLE 1. Differences in characteristics of colon cancer according to location.

Right-sided colon cancer		Left-sided colon cancer	
Dominant characteristics	**References**	**Dominant characteristics**	**References**
More frequent mutations associated with cancer predisposing syndromes	[12,37,55]	Better prognosis and response to treatment	[31,32,53]
Higher incidence of group B2 E. coli	[50]	Microsatellite stability	[25,27]
Invasive biofilm	[47,57]	Chromosomal instability	[11,26]
Higher concentration of conjugated primary bile acids	[55]	Upregulation of Tyrosine Kinase Receptors	[36]

inflammatory microenvironment without colitis (NF-κB, IL-6,IL-8, IL-10, IL-18, and TNF) and via other pathways it creates an immune-deficient environment (by recruiting myeloid-derived suppressor cells or MDSC's with short chain fatty acids and polypeptides) by reducing CD3+ T-lymphocytes and promoting the beta-catenin pathway [52,53]. The result is cellular dysplasia and carcinogenesis. Interestingly, levels of *F.nucleatum* increase from rectum to cecum and accumulate gradually on normal colonic tissue in the adenoma-carcinoma sequence [53].

A layer of mucin containing bacteria on the luminal surface of the colonic epithelium is defined as bacterial biofilm [54]. This biofilm has been found to be invasive in approximately 90% of patients with colon cancer on the right side, while this has only been seen in about 10% of patients with cancer on the left side and subsequently, correlation between carcinogenesis and biofilms has been found in right colon cancer but not in left-sided cancer [55]. Epithelial E-cadherin has been found to be significantly decreased, whereas interleukin-6 is found increased and Stat-3 is activated when a biofilm is present, resulting in increased proliferation [56]. Association between high levels of pro-proliferative polyamine metabolite N, N-diacetylspermine, and biofilm in the lumen of the large bowel has been found, suggesting a relation between bacterial biofilms and host cancer [57]. Therefore, the formation of colonic bacterial biofilms with synchronous procarcinogenic epithelial responses has been suspected in the process of carcinogenesis in right-sided colon cancer [47].

Differences in bile acid levels

Bile acids (Bas) are produced in the liver by hepatocytes and only approximately 5%-10% of Bas pass the terminal ileum without getting absorbed and are deconjugated by bacterial bile salt hydrolases in the colon to secondary Bas [58]. Most of these molecules are absorbed by colon cells and returned to the liver to be reused. Bile acids, as well as their metabolites, have been associated with the development of colon cancer through different mechanisms such as angiogenesis, enhancing cancer cell proliferation, inhibiting apoptosis and assisting invasion [59]. The levels of these substances in the colonic lumen vary and are regulated by the normal colonic bacterial flora. Primary bile acids in the right colon interact with biofilms and microbiomes and are converted to secondary bile acids by means of deconjugation [60]. Deoxycholic acid (DCA) is the most found secondary bile acid and Lithocholic acid (LCA) is the second most common secondary bile acid. These acids are reabsorbed by the intestinal epithelial and subsequently alter DNA causing permanent damage through reactive oxygen and nitrogen species [59,60].

Conjugated primary bile acids are more commonly found in the right colon versus the left colon, almost 10 times more on the right [55]. Aspirates from the cecum and rectal fecal samples have been compared and have shown high levels of enzymatic activity, converting primary bile acids to DCA, in the cecal samples [61]. These findings suggest a possible role of differential bile acid levels according to location in colon cancer development.

Bas, when found in high concentrations in the large bowel, may cause cell membrane destruction, via their detergent properties, resulting in damage to intestinal epithelium. This situation promotes repair mechanisms that involve inflammatory cells and the proliferation and accumulation of undifferentiated cells [26,59]. This is a pre-cancerous state which leads to formal carcinogenesis and CRC development. Furthermore, BAs have an oncogenic effect by making cells resistant to apoptosis [60]. This is possible by the degradation of tumor suppressor p53 by BAs which is responsible for cell processing of DNA repair and initiates apoptosis if DNA repair is not possible [62].

POLYPS IN COLORECTAL CANCER

Polyps are commonly found in the colon and are considered precursors of colonic adenocarcinomas. Tubular and tubulovillous polyps are seen both on the right as well as the left side of the colon but they may present high-grade dysplasia and evolve into cancer more often on the right side of the colon, especially when found in smaller sizes [27]. Sessile serrated adenomas are also predominantly found in the cecum, ascending and transverse colon [27,42]. Comparatively, sessile serrated adenomas, found in right-sided colon cancer, present CIMP high levels, MSI high levels, MLH1 methylation and BRAF mutation while this is not seen in conventional adenomas found on both right and left sided colon cancer, whereas the opposite is seen for CIN where this is present in conventional polyps and not in sessile serrated polyps [43].

CLINICAL IMPLICATIONS AND POTENTIAL THERAPEUTIC TARGETS

Colorectal cancer is a heterogeneous disease and is treated today based on the presence of MSI or driver mutations such as KRAS, NRAS and BRAF. Recent trials showed progress in the development of personalised treatments which use alternative genes. These alternative genes are possibly responsible for progression of disease. Alternative receptors tyrosine kinases beyond EGFR and HER2 and additional fusions beyond ALK and NTRK should be examined before initiation of treatment and can further improve outcomes in mCRC. Studies have

found the presence of certain mutations that may indicate contraindications for some treatments, such as ARHGEF33. This gene is similar to KRAS/NRAS activating mutations and has a negative impact in anti-EGFR treatment [63].

In addition, some targeted therapies that are already in use in other cancers with very good results, namely Sotorasib, harbouring the KRAS pG12C mutation in non-small-cell lung cancer, should be further investigated for potential use in CRC.

Presently several types of immunotherapies are applied in the treatment of CRC. These include monoclonal antibodies, ICB to reinvigorate T-cell immunity, CAR-T cell therapy, oncolytic viruses and cancer vaccines. Furthermore, the activation of the immune system with therapeutic DNA cancer vaccines is a very promising approach. Pre-clinical trials have shown that monotherapy with these vaccines have not changed the outcomes of cancer, but the combination with other personalized treatments based on the patient's genetic profile and biomarkers should be used. This way, effective treatments can be ensured and side-effects can be minimised [64].

CONCLUSIONS

As seen in this narrative, colorectal cancer presents major differences according to location regarding molecular characteristics which in turn, affects its histopathology, prognosis, and response to treatment. Overall, colorectal cancer cannot be considered a single disease but should be treated as 2 different diseases in the same organ [9,12]. The underlying causes of the reported molecular differences between colorectal tumor locations may be multifactorial. Environmental, genetic and immunological factors all play roles in the development and overall survival of colorectal cancer patients [26,32,40,53]. The clinical significance of these findings requires replication and additional studies need to be undertaken in larger populations. Indeed, nowadays, in the era of personalised medicine, sidedness is a major factor in the treatment of colorectal cancer and the biology and genetic pathways of this disease need to be studied further to determine potential targets for individualised treatment [63]. Therefore, there is a need for further research and broader genomic profiling for a better understanding of tumour biology, hopefully leading to new discoveries in diagnostics and therapeutics.

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