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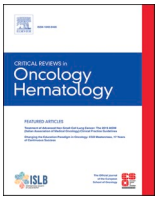

Dichotomous colorectal cancer behaviour

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ABSTRACT

Colorectal cancer (CRC) is the third most common malignant tumor and one of the deadliest cancers. At molecular level, CRC is a heterogeneous disease that could be divided in four Consensus Molecular Subtypes. Given the differences in the disease due to its anatomical location (proximal and distal colon), another classification should be considered. Here, we review the current knowledge on CRC dichotomics behaviour based on two different entities; right and left-sided tumors, their impact on clinical trial data, microbiota spatial composition and the interaction with the nervous system. We discuss recent advances in understanding how the spatial tumor heterogeneity influences the tumor growth, progression, and responses to current therapies.

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths worldwide, with an incidence of 1.9 millions of patients and almost 1 million of deaths in 2020 (Sung et al., 2021). Median age of diagnosis of CRC in the USA is 66 years in men and 69 years in women (Katsaounou et al., 2022).

Clinical management of CRC is based on a multidisciplinary approach tailored to the stage of the disease. In general, patients with invasive nonmetastatic tumors are candidates to surgical resection, with or without adjuvant chemotherapy. On the other hand, systemic therapy is the cornerstone of advanced CRC treatment. In selected cases, surgical resection, radiotherapy or local ablation techniques could be indicated to achieve a better control or even a radical approach. However, relapse occurs in 40% of local disease and more than 85% of metastatic disease treated with curative intent.

Systemic treatment for metastatic disease is mainly based on fluoropyrimidines like 5-fluorouracyl (5-FU), oxaliplatin and irinotecan (Argilés et al., 2020). Additionally, other treatment approaches include the addition of molecular therapies directed against specific targets involved in the angiogenesis process or the epidermal growth factor receptor (*EGFR*) pathway. In recent years new molecular therapies have been developed to treat specific molecular subtypes of CRC patients, such as immune checkpoint inhibitors in mismatch repair deficient/microsatellite instability (dMMR/MSI-H) or RAF and MET-inhibitors in *v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E* mutated CRC patients. These therapies have demonstrated successful improvement in overall survival (OS) in some CRC (Xie et al., 2020).

Various endogenous and environmental factors have the potential to influence the likelihood of developing CRC (Table 1). It is widely proven that age is one of the main risk factors in CRC. Additionally, being male is associated with higher incidence and mortality rates compared to females (American Cancer Society, 2020). Another well-known risk factor is body mass index (BMI) and obesity, which also play a key role in CRC development. While the association between these factors and CRC is clear, the exact figures may vary depending on whether it is considered as a continuous variable or based on defined thresholds for specific age groups. It is important to note than in certain subgroups, such as individuals with a family history of Hereditary Non-Polyposis CRC (HNPCC), the association with BMI/obesity may not be as significant despite the existing evidence. Other factors that contribute to CRC risk include ethnicity, with Non-Hispanic Black having the highest risk. Habits and diet also play a role, where smoking is an unquestionable risk factor for cancer, including CRC. However, the association between alcohol consumption and CRC can vary depending on the population group. Consumption of dairy products, fiber and fruits has been known to protect against CRC, while high intake of fat and red meat has been linked to an increased risk. Furthermore, diabetes has been found to be associated with an increased risk of CRC development, although it is yet

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to be determined whether this association is due to the disease itself or other conditions associated with it, such as drug intake. Non-steroidal anti-inflammatory drugs (NSAIDs) are suggested to have a protective effect against CRC development, but further research is needed to confirm this relationship (Lewandowska et al., 2022; American Cancer Society, 2020; Sawicki et al., 2021; Diergaarde et al., 2007; Betés et al., 2003).

Despite CRCs high heterogeneity, the omics development has refined tumoral classification, and this tumoral entity can be stratified, based on its gene expression features, into four Consensus Molecular Subtypes (CMS) (Guinney et al., 2015). CMS1 is characterized by microsatellite instability and an hypermethylation status. These tumors normally have an increase in immune activation and infiltration. DNA damage repair proteins impairment are another typical attribute of the CMS1 subtype, also known as MSI immune. Additionally, *BRAF* mutations are enriched in CMS1. The CMS2 (canonical) subtype displays somatic copy number variations, with gain in oncogenes and loss in tumor suppressor genes. Hepatocyte Nuclear Factor 4 Alpha (HNF4A) and WNT/MYC pathways are upregulated in this subgroup. Although KRAS mutations appear in all subtypes, those are enriched in the "metabolic subtype" (CMS3), whereas CMS4 has a mesenchymal phenotype with high stromal infiltration and TGF-β activation (Parmar and Easwaran, 2022).

Herein, we comprehensively examine the impact of sidedness on clinical and molecular features of CRC characteristics. This review focuses on two emerging areas: the role of the microbiome in CRC carcinogenesis and nervous system involvement. We tried to summarize clinical trials which mentioned sidedness effects.

2. Dichotomic behaviour

Besides molecular classification, CRC is no longer considered a unique disease and could be distinguished, by its anatomical location and embryological origins, into right-sided colon cancer (RCC) and left-sided colorectal cancer (LCRC). Although some authors believe in a continuum model (Yamauchi et al., 2012), side differences have a great impact in all aspects of the disease, from anatomopathological features to treatment response. Epidemiology of CRC is indeed affected as well by this dichotomous behaviour, LCRC has a higher incidence (68%) and is more characteristic of men, whereas RCC is more common in women and has and incidence of 32% (Mangone et al., 2021). This tendency is also observed when cohorts are spit up into colon and rectum, analogue to RCC and LCRC respectively (Table 1) (American Cancer Society, 2020). When taking into account risk factors there are also differences between CC and RC, for instance smoking has a higher Hazard Ratio (HR) in rectum than in colon cancer (Murphy et al., 2019). Interestingly, these differences are also observed regarding familial CRC risk (Johns and Houlston, 2001). RCC is proximal to the splenic flexure and is considered a tumor of the cecum and the ascending colon up, arising from the midgut. Its histology consists of mucinous adenocarcinomas with flat morphology and less frequently sessile serrated adenomas, which sometimes makes it difficult to distinguish from normal colon tissue (Baran et al., 2018). Moreover, the excrements on the right side are liquid and delay the appearance of symptoms, which can be held accountable for the delay in diagnosis and its consequent worse prognosis due to higher tumor stage at diagnosis (Nawa et al., 2008).

LCRC is defined by tumor presence in areas of the splenic flexure, including the descending/sigmoid colon and the rectum. LCRC comes from the hindgut and although its gross morphology is diverse, frequently presents a polypoid morphology that grows towards the intestinal lumen. The tumoral process normally results in pain together with anal bleeding, making it sometimes easier to detect at earlier stages of cancer evolution (Yang and Pan, 2014).

This disparity in the body position provokes an additional plethora of differences in the molecular landscape. Left-sided and right-sided CRC are differentially represented in the different CMS, while RCC mainly correlates with CMS1 and CMS3, LCRC is most commonly associated to CMS2 and CMS4, which is consistent with the characteristic alterations discovered in each tumor location (Salem et al., 2017). However, CMS3 also skews toward left-sided (Lee et al., 2017). The fact that RCC has an altered metabolism away from oxidative phosphorylation could be another factor that increases its aggressiveness (Mukund et al., 2020).

RCCs are characterized by dMMR/MSI-H, CpG island methylator phenotypes (CIMP), high frequency of *BRAF/PIK3CA* mutations and Erythroblastic Leukemia Viral Oncogene Homolog/Mitogen-activated protein kinases/Transforming growth factor type II receptorv (ErbB/MAPK/*TGFβR2)* insulin signalling pathway dysregulation. This pattern occurs more often in genetic predisposition tumors, such as Lynch syndrome patients (Lynch et al., 2009). In contrast, LCRC tumors normally present chromosomal instable (CIN) phenotype, HER1/ERBB2 amplification, *KRAS/APC/p53* mutations and dysregulation of Wnt/EGFR signalling pathways (Hanna and Lenz, 2020).

The most common sites for LCRC metastases are liver and lung, whereas RCC tumors normally spread to the peritoneal cavity (Dong, 2019).

3. Differences in treatment response

Right-sided tumors have traditionally been more resistant to standard chemotherapy combinations, which is associated with worse prognosis and lower survival. However, with the development of clinically meaningful diagnostic biomarkers, new tailored agents have been developed. In this context, immunotherapy and targeted therapies have arisen (Golshani and Zhang, 2020). As RCC contains more T cell infiltrates, they have a better response to immunotherapy than LCRC (Chan et al., 2019). Specifically, inhibitors that block the immune checkpoint proteins, such as the pembrolizumab, which is the first anti-PD-1 drug approved by the Food and Drug Administration (FDA) for CRC patients with metastatic MSI-H/dMMR or previously untreated unresectable cancer.

In order to help the scientific community to evaluate the success of clinical trials results, data have been reanalyzed using the information about primary tumor sidedness (Table 2).

The use of pembrolizumab in the pivotal study KEYNOTE-177, enrolled a total number of 307 patients with dMMR or MSI-H CRC treatment-naive for metastatic disease. Around 70% of the recruited population was diagnosed with RCC. The trial demonstrated superiority of the treatment regimen containing pembrolizumab with an HR = 0.59 (0.45,0.79) over the placebo-controlled arm for Progression Free Survival (PFS) and HR= 0.74 (0.53, 1.03) for OS (André et al., 2020). Subgroup analysis of patients in KEYNOTE-177 can point out to a better response from RCC to pembrolizumab treatment versus LCRC. However, no segmentation between sides has been taken into consideration in the clinical development of other immune-checkpoint inhibitors as nivolumab and ipilimumab.

On the other hand, in the treatment of LCRC tumors, the use of EGFR blocking agents has proven to be beneficial for wild-type (wt) KRAS CRCs. KRAS mutations (mainly point mutations in exons 12 and 13) are critical biomarkers for the selection of potential responders to EGFR inhibitors (Lièvre et al., 2006; Misale et al., 2012; Meng et al., 2021).

In fact, cetuximab was the first targeted-agent approved by the FDA. CRYSTAL & PRIME clinical trials compared traditional chemotherapy regimens versus new anti-EGFR drugs, both concluding superiority of anti-EGFR-containing treatment schedules. CRYSTAL trial investigated the possible benefit of adding EGFR inhibitor, cetuximab, to FOLFIRI in an open-label phase III study on mCRC. With primary endpoint being PFS, 1198 patients were recruited, and risk of progression, by the addition of cetuximab to FOLFIRI, was reduced in 15%, being mPFS 8.9 months in the experimental arm and 8.0 months in the control group (HR 0.85, 0.72–0.99). PRIME study (phase III) evaluated PFS improvement for mCRC of another EGFR inhibitor, panitumumab, in combination with FOLFOX4 versus FOLFOX4 alone. The study demonstrated an improvement in mPFS in the wt-KRAS population, being mPFS in the

Table 1
Risk factors associated with CRC (CC; colon cancer, RC: rectum cancer).

Ref	Study Design	Population	Anatomic location	Sample size	RISK FACTOR									
					Age	Gender	Obesity/ Body mass index (BMI)	Ethnicity	Family history of CRC	Smoking status	Alcohol consumption	Physical activity level	Dietary factors	Diabetes	NSAIDs
Lewandowska et al., 2022	400 control group + 400 CRC patients	-	-	-	-	-	High BMI increase risk (P < .01). Obese risk 1.27 (AOR = 1.27; 95% CI, 1.06–1.53)	-	-	> 30 cigarettes daily increase the risk (P < .01). AOR = 2.12; 95% CI: 1.15, 3, 93	No association	Low activity increase risk (P < .001)	Higher fat and red meat consumption increase the risk (P < .01)	38% more risk	-
Colorectal Cancer Facts & Figures 2020–2022	-	-	CRC	-	Until 50 incidence rate doubles every 5 years. After 50, risk rises about	MEN 30% greater risk than WOMEN	-	Incidence in blacks: 20% higher NHWs and 50% higher	-	-	-	-	-	-	-
	-	-	Colon	-	30% (except for 50–54 years versus 55–59 years, for which there is	MEN 20% greater risk than WOMEN	-	than those in APIs / Mortality in blacks is 40% higher	-	-	-	-	-	-	-
	-	-	Rectum	-	only a 15% difference).	MEN 60% greater risk than WOMEN	-	than those in NHWs and 2X those in APIs.	-	-	-	-	-	-	-
Sawicki et al., 2021	-	-	-	-	> 65 years 30-fold than 25–49 y	MEN 30% greater risk than WOMEN	MEN: 50% greater risk WOMEN: 40% greater risk	NHB: 50% higher than in Asians/ Pacific Islanders 20% higher than in NHW	2–8% from hereditary syndromes	2–3 fold increase risk	2–3 drinks daily increases the risk 20% 3 alcoholic beverages increases this risk 40%	inactivity increases 50% risk	100 g daily Red meat increases 17% risk 50 g daily Processed meat increases 18% risk High fiber intake reduces 50% risk Dairy products reduces risk	2–3 times more risk to develop CRC	

(*continued on next page*)

Table 1 (*continued*)

Ref	Study Design	Population	Anatomic location	Sample size	RISK FACTOR									
					Age	Gender	Obesity/ Body mass index (BMI)	Ethnicity	Family history of CRC	Smoking status	Alcohol consumption	Physical activity level	Dietary factors	Diabetes	NSAIDs
Murphy et al., 2019	Multicenter prospective cohort of 521,448 healthy participants, ≥ 35 years	10 European countries	general	6291	-	-	MEN: HR = 1.22 (95% CI, 1.16–1.29) per 5 kg/ m2 WOMEN: HR = 1.09 (95% CI, 1.04–1.13) per 5 kg/ m2	-	-	Current smokers vs never smokers: HR, 1.19; 95% CI, 1.11–1.28; P trend < 0.0001	Greater alcohol consumption: per 15-g/ d increment: HR, 1.05; 95% CI, 1.03–1.07	The physically active group: HR, 0.90; 95% CI, 0.82–0.98	-	Prevalent diabetes at baseline (yes vs no) was associated with a higher CRC risk (HR, 1.28; 95% CI, 1.12–1.47), with similar positive relation-ships found across anatomic sites (P heterogeneity >0.70), although the association for rectal cancer was not statistically significant.	Ever use of NSAIDs vs never use: HR, 0.85; 95% CI, 0.74–0.99
			proximal colon	1877	-	-	MEN: HR = 1.31 (95% CI, 1.18–1.47) per 5 kg/ m2 WOMEN: HR = 1.05 (95% CI, 0.97–1.13) per 5 kg/ m2	-	-			The physically active group: HR, 0.74; 95% CI, 0.63–0.87	-		
			distal colon	1743	-	-	MEN: HR = 1.32 (95% CI, 1.20–1.45) per 5 kg/ m2 WOMEN: HR = 1.13 (95% CI, 1.04–1.22) per 5 kg/ m2	-	-			-	-		
			rectum	2094	-	-	MEN: HR = 1.10 (95% CI, 1.01–1.20) per 5 kg/ m2 WOMEN: HR = 1.09 (95% CI, 1.01–1.18) per 5 kg/ m2	-	-	Former smoking (vs never smokers): HR, 1.27; 95% CI, 1.13–1.43		-	-		

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Table 1 (*continued*)

Ref	Study Design	Population	Anatomic location	Sample size	RISK FACTOR										
					Age	Gender	Obesity/ Body mass index (BMI)	Ethnicity	Family history of CRC	Smoking status	Alcohol consumption	Physical activity level	Dietary factors	Diabetes	NSAIDs
Diergaarde et al., 2007	Case-control study on environmental factors and HNPCC-associated CRC, carried out in the Netherlands. 1999– 2002	Individuals with family history of HNPCC		248 (145 cases + 103 controls)	OR (95% CI) for ≥ 45 years at last colonoscopy versus ≥ 35 years at last colonoscopy, 6.4 (3.0– 13.9)	-	No significant association with CRC was observed for BMI	-	-	Current cigarette smoking: OR = 2.4 (95% CI: 1.1–5.3) / Smoking less than 15 cigarettes: OR = 2.0 (95% CI: 1.0–3.9)	-	-	Fruit consumption: OR for highest vs lowest tertile, 0.4 (95%CI: 0.2–0.9)	-	-
Betés et al., 2003	Epidemiological registry study in Spain (1988–1998)	Individuals 40 y.o. or older who underwent full colonoscopy without previous cancer symptomatology or previous tumours		2210 total individuals (617 with andenomas or invasive cancer)	OR = 1.05 (95% CI 1.03–1.07)	MEN OR = 3.64 (95% CI 1.9– 7.1)	BMI > 30 kg/m2 OR = 1.78 (95% CI 1.00– 3.2)	-	-	-	-	-	-	-	-
Johns et al., 2001	Meta analysis of studies published investigating familial CRC	Heterogeneuous worldwide population which reported at least 1ST degree relative affected	general colon	Estimates from 26 different studies	-	-	- -	-	-	-	-	-	-	-	-
					-	-	- -	-	A 1ST -degree relative with CC, RR = 2.42 (95% CI: 2.20–2.65)	-	-	-	-	-	-
			rectal		-	-	- -	-	A 1ST -degree relative with RC RR = 1.89 (95% CI: 1.62–2.21)	-	-	-	-	-	-

Table 2
Clinical trials of CRC including a comparison between RCC and LCRC.

Clinical Trial	Identification code	Phase	Treatment schedule	Results [months]		Cohort (N)	Reference
				Left-sided	Right-sided		
Bevacizumab							
TRIBE	NCT00719797	III	FOLFIRI + BV	PFS: 11 OS: 31.6	PFS: 9.4 OS: 20.2	358	(Lee et al., 2017)
			FOLFOXIRI + BV	PFS: 10.7 OS: 28.6	PFS: 11.2 OS: 26		
AVF2107g – retrospective analysis	NCT00012233	III	CTX	OS: 18.0 PFS: 8.0	OS: 13.6 PFS:5.4	144	(Loupakis et al., 2015)
			CTX + BV	OS: 24.2 PFS: 8.7	OS: 15.9 PFS:11.1	120	
NO16966 – retrospective analysis	NCT00069095	III	CTX	OS: 22.0 PFS: 8.3	OS: 17.0 PFS: 7.0	664	(Loupakis et al., 2015)
			CTX + BV	OS: 24.7 PFS: 10.0	OS: 20.6 PFS: 8.6	330	
PROVETTA – retrospective analysis	NCT01363739	Observational	FOLFIRI + BV	OS: 42 PFS: 12.1	OS: 24.8 PFS: 9.9	200	(Loupakis et al., 2015)
Cetuximab vs Bevacizumab							
FIRE-3	NCT00433927	III	FOLFIRI + Ctx	OS: 38.3 PFS: 10.7	OS: 18.3 PFS: 7.6	568	(Mukund et al., 2020)
			FOLFIRI + BV	OS: 28 PFS: 10.7	OS: 23 PFS: 9		
CALGB/SWOG80405	NCT00265850	III	FOLFIRI or FOLFOX + BV	OS: 32.6 PFS: 11.2	OS: 29.2 PFS: 10.2	2334	(Dong, 2019)
			FOLFIRI or FOLFOX + Ctx	OS: 39.3 PFS: 12.7	OS: 13.7 PFS: 7.5		
Cetuximab							
CRYSTAL	NCT00154102	III	FOLFIRI + Ctx	OS: 28.7 PFS: 12	OS: 18.5 PFS: 8.1	1221	(Mukund et al., 2020)
			FOLFIRI	OS: 21.7 PFS: 8.9	OS: 15 PFS: 7.1		
TAILOR	NCT01228734	III	FOLFOX4	PFS: 7.6 OS: 18.7	PFS: 4.5 OS: 9.3	393	(Qin et al., 2018)
			FOLFOX4 + cetuximab	PFS: 9.2 OS: 22.0	PFS: 7.4 OS: 11.3		
Panitumumab							
PRIME	NCT00364013	III	FOLFOX4	OS: 23.6 PFS: 9.2	OS: 15.4 PFS: 7	1183	(Lynch et al., 2009)
			FOLFOX4 + PN	OS: 30.3 PFS: 12.9	OS: 11.1 PFS: 7.5		
Panitumumab vs Bevacizumab							
PEAK	NCT00819780	II	FOLFOX 6 + BV	OS: 32.0 PFS: 11.5	OS: 21.04 PFS: 12.6	285	(Hanna and Lenz, 2020)
			FOLFOX6 + PN	OS: 43.4 PFS: 14.6	OS: 17.4 PFS: 8.7		
Others: Regorafenib, trifluridine/tipiracil							
CORRECT	NCT01103323	III	Regorafenib vs placebo/ BSC	HR 1 HR 1	HR 1.12 HR 1.21	555	(Chan et al., 2019; André et al., 2020)
CORRELATE	NCT02042144	observational	Regorafenib	OS: 7.4 PFS: 2.8	OS: 8.2 PFS: 2.7	975	(Golshani and Zhang, 2020)
PRECONNECT	NCT03306394	interventional	trifluridine/tipiracil	PFS: 2.8	PFS: 2.8	793	(Lièvre et al., 2006)

OS and PFS are provided in months. CTX: Chemotherapy; BV: Bevacizumab; PN: Panitumumab; Ctx: Cetuximab HR: Hazard ratio (95% CI). BSC: Best supportive care.

experimental group 10 months versus 8.6 months in the control arm (HR: 0.80, 0.67–0.95).

Anti-EGFR therapy in CRC has provided additional evidence on the notable differences between left and right CRC. LCRCs express EGFR to a greater extent than RCCs. In addition, response of RCC to EGFR inhibition is suboptimal (Xie et al., 2020), due to the presence of BRAF mutations (Ulivi et al., 2017) and its intrinsic nature (Merlano et al., 2017).

In the case of antiangiogenic drugs, both LCRC and RCC respond well. Bevacizumab clinical development included an extensive list of clinical trials that have demonstrated the superiority of adding bevacizumab to standard treatment regimen. Bevacizumab's clinical development did not include LCRC vs RCC segmentation and institutional approval for bevacizumab in CRC was consistent with this development, making the drug available for all comers population. Posterior studies have tried to investigate whether sideness could be a factor impacting response to anti-VEGF inhibitors in CRC. Early research seemed to indicate that sigmoid colon and rectum (part of LCRC) benefitted more of the anti-VEGF inhibitor addition to CAPEOX chemotherapy regimen in a retrospective cohort of 667 mCRC patients. However, more recent data [post hoc analysis of pivotal study AVF2107g, NO16966 and PROVETTA study, as well as prospective studies below-mentioned] suggests that both populations, L- and R- CRC, benefit of bevacizumab's addition to the treatment scheme. The two prospective studies that have been carried out reached the same conclusion. One of them studied 926 patients from an Australian prospective registry (Wong et al., 2016) and the other recruited 178 wtRAS patients in a single-center retrospective study (Fiala et al., 2019), both concluded that for bevacizumab therapy selection, the site of primary tumor origin is not a biomarker. Additionally, data from the TRIBE trial, a phase III clinical trial in which 358 patients had primary tumor location information available for analysis, suggested that RRC's optimal bevacizumab combination could be FOLFOXIRI chemotherapy triplet (Cremolini et al., 2018).

With different targeted therapy options for CRC patients, head-to-head comparison data has been of the highest value to design clinical strategies for patient management guidelines, especially in the RAS-wt population. The CALGB study (Venook et al., 2017), a phase III clinical trial comparing bevacizumab versus cetuximab in mFOLFOX6 or FOLFIRI chemotherapy regimens, reached to the conclusion that in the RAS wt population, no significant difference in OS was observed among the addition of the different biological drugs. However, one of the self-declared limitations of this study was that primary cancer site was only collected post hoc and no further analysis were done concerning this biological feature. Notwithstanding, posterior analysis demonstrated OS and PFS to be better with bevacizumab than with cetuximab in patients with right-sided primary tumors.

In FIRE-3, a phase III clinical trial comparing cetuximab versus bevacizumab in addition to FOLFIRI (n = 352), the cetuximab-containing regimen performed worse in RCC than the bevacizumab arm, both, in terms of PFS (7 vs. 9 months; HR: 1.56 (0.97–2.52)) and in terms of OS (19 vs 23 months; HR: 1.14 (0.71–1.84)). In a retrospective analysis of the FIRE-3 and CRYSTAL studies, it was further confirmed that cetuximab (Xie et al., 2020; Tejpar et al., 2017; Arnold et al., 2017) performed worse than bevacizumab in RCC (8.3 vs. 23 months, HR = 1.44, p = .28).

This is further supported by the data trends observed in the PRIME and PEAK retrospective analysis; despite BRAF-mutated cases not being taken into consideration, very little benefit would be observed in RCC treated with anti-EGFR + FOLFOX. However, the number of patients with RCC recruited into the two trials is too small to draw significant conclusions (Boeckx et al., 2017). These evidences have ultimately led to the incorporation in the most recent ESMO clinical guidelines of sidedness as a key factor to consider for mCRC treatment selection (Cervantes et al., 2022) (Fig. 1).

4. Microbiota composition is dependent on its anatomical location

The human microbiota is composed of bacteria, archaea, fungi, viruses, and phages that associate symbiotically with barrier tissues of the body. Microbiota has an essential role in the balance of health and disease, being colon microbial community the most dense and active in the human body (Schroeder and Bäckhed, 2016). It is known that the gut's microbiome plays a key function in the colon performance by providing some vitamins, degrading certain nutrients, biotransforming bilic acids, eliminating some toxic substances and making functional interactions with the intestinal epithelium, immune and nervous systems (Margolis et al., 2022). As an essential part of intestinal homeostasis, microbial population distortions (dysbiosis) in colon are related with illness states as obesity, Crohn's disease and cancer. In the case of CRC, gut microbiome is involved in tumor initiation, progression, and chemotherapy efficacy. This knowledge is important in prevention, but also, for screening and positive modulations that could aid in the

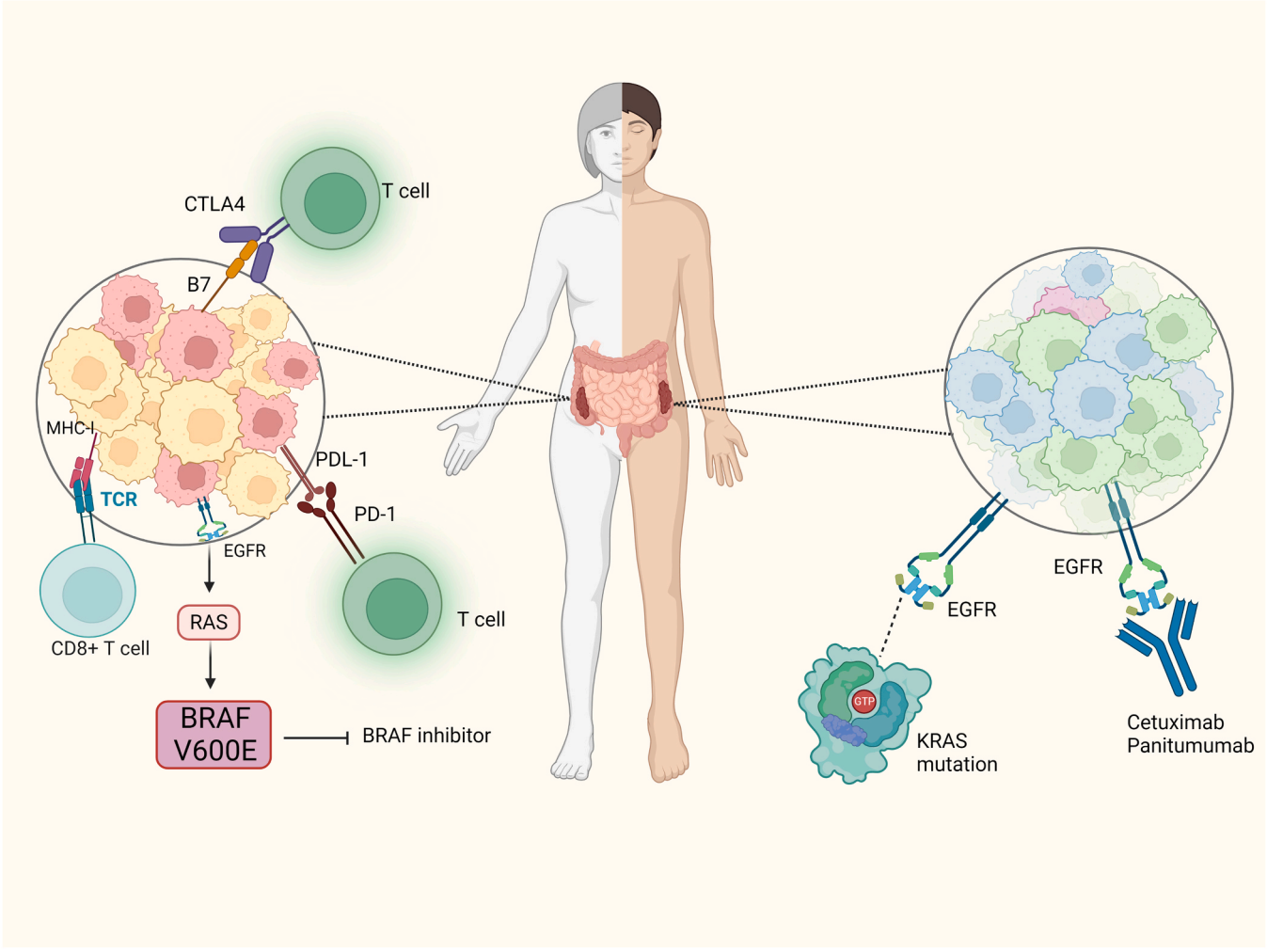

Fig. 1. Tumor immune environments. Right-sided tumors (more frequent in females) are enriched in immune cells and respond better to BRAF inhibitors. KRAS mutations are common in left-sided tumors. Preferred targeted therapies are antibodies that bind to the extracellular domain of EGFR, such as cetuximab and panitumumab.

treatment of cancer (Wong and Yu, 2019).

Most of the metagenomic studies carried out in colon are based on feces samples, as colon biopsies in healthy individuals are not usual, and technical variations, as well as medical treatments and regional and cultural environments hinder comparisons (He et al., 2018). But in general terms, fecal samples do not reflect the bacterial number and its organization in intestinal mucosa (Lyra et al., 2012).

Also, it is important to highlight that most studies show correlations, but they cannot distinguish if dysbiosis is a cause or a consequence of CRC development. After faecal analysis of healthy patients, gut bacteria include eight phyla, being the dominating ones the *Firmicutes* (especially *Clostridia*, *Bacteroidia* and *Bifidobacteriales*), *Actinobacteria* and *Bacteroidetes*. Usually, these data are obtained from solid biopsies, and it involves a bowel preparation that disturbs the real bacterial ecosystem.

In general, microbiota tumorigenic mechanisms in CRC may include bacterial toxins that influence host DNA damage (Contribution and Statement, 2021), stimulation of epithelial proliferation, mucosal barrier disruption with immune response activation (Gopalakrishnan et al., 2019), and butyrate production. Butyrate producing bacteria are overrepresented in CRC patients and, while butyrate effects are still under study, it may be involved in host cell senescence induction, a physiological state related to cancer initiation and progression (Salvi and Cowles, 2021).

Different studies have highlighted the role of oral microbiota in different diseases, including CRC (Zhang et al., 2020; Koliarakis et al., 2019). Through the saliva, oral microorganisms can enter the gastrointestinal tract and can disrupt the gut microbial communities (Zhang et al., 2020). 15 phyla have been detected in the oral cavity of healthy people, being the most predominant *Fusobacteria*, *Actinobacteria*, *Proteobacteria*, *Bacteroidetes*, and *Spirochaeta (*Le Bars et al., 2017*)*. Among these groups of bacteria, the most predominant genera are *Streptococcus*, *Haemophilus*, *Neisseria*, *Prevotella*, *Fusobacterium*, *Veionella, Leptotrichia, Porphyromonas, Parvimonas, Alloprevotella* and *Rothia (*Mo et al., 2022; Flemer et al., 2018). Although some bacterial genera are present naturally both in the oral cavity and gut, sequencing analyses have shown the presence of identical strains in both habitats of CRC patients. In fact, a study found that 40% of patients with CRC present the same strain of *Fusobacterium nucleatum* (*F. nucleatum subsp. vincetii*) (Komiya et al., 2019). Additionally, patients with CRC tumors showed an enrichment of *Fusobacterium* in the oral cavity (Zhang et al., 2020).

The analysis of fecal samples of patients with CRC have highlighted the presence of different oral bacteria, *Parviromonas micra, Fusobacerium nucleatum, Porphyromonas gingivalis, Peptostreptococcus stomatis, Streptococcus anginous, Streptococcus koreenis* and *Solobacterium moorei*. Moreover, *S. moorei* is present only in CRC patients in stage III and IV of the disease, and could be important in the tumor progression (Uchino et al., 2021; Yu et al., 2017). A comparation of mucosal microbiota from the tumor, the oral cavity and in pre-cancerous lesions is necessary to determine the role of the oral microbiota in the development of CRC. When the oral microbiota of healthy and precancerous lesion was compared, no differences were observed. However, a decrease of *Streptococcus, Parvimonas, Haemophilus, Neisseria, Prevotella* and *Alloprevotella* was found in CRC patients when they were compared with healthy controls (Flemer et al., 2018).

Additionally, the analysis of the microbiota adhered to tumors show 17 genera shared with the oral cavity which can be organized in two co-abundance groups (CAG): the oral pathogens, F*usobacterium nucleatum, Parvimonas micra, Peptostreptococcus stomatis* and *Dialister pneumonister*; and the dental biofilms group: *Actinomyces, Haemophilus, Rothia, Streptococcus* and *Veionella*. Both groups can form biofilm in the tumor and healthy intestinal tissue of CRC patients (Flemer et al., 2018; Wang et al., 2021). Furthermore, a negative correlation was found between the presence of these CAG groups and *Lachnospiraceae*, a healthy butyrate producer, necessary to maintain the mucous stability (Flemer et al., 2018).

Oral dysbiosis produces oral diseases, chronic periodontitis or gingivitis that increase the risk of CRC (Wang et al., 2021). In fact, patients with oral diseases present less diversity in gut microbiota composition. Furthermore, a decrease in *Bacteroidetes* and an increase in *Firmicutes*, *Euryarcheota*, *Proteobacteria* and *Verrucomicrobia* can be detected in oral microbiota (Arimatsu et al., 2014; Momen-Heravi et al., 2017). In parallel, diet factors associate with cancer development through gut microbiome modulation, for example, in mice, high fat diet induces dysbiosis, that is involved in higher CRC incidence by metabolomic changes and epithelial barrier dysfunction (Yang et al., 2022). Also, red meat or high alcohol intake are related to CRC through gut microbiota dysbiosis (Tuan and Chen, 2016). A decrease in *Lachnospiraceae,* an important maintainer of mucosal stability, has been related with western diet (Flemer et al., 2018). Instead, a high fiber diet or consumption of vegetable protein, correlates with abundance of *Bifidobacterium* and *Lactobacillus*, part of healthy microbiota. In addition, a high fiber intake and the associated microbiota modulation influence positively the chemotherapy efficacy (Song et al., 2020).

4.1. Spatial composition of microbiota in CRC

There is a significantly different microbial community associated with right and left sided CRC (Miyake et al., 2021). It has been described a correlation between certain bacteria and some tumor mutations, in a way that the microbiome profile could aid to predict the molecular mechanisms of tumorigenesis (Burns et al., 2018).

CRC dysbiosis depends on the location, in LCRC fecal samples, it has been described that *phylum Fusobacteriota* (usually *Fusobacterium*) is associated with L-lys fermentation to acetate and butyrate and cob(II) yrinate a,c-diamine biosynthesis (Dejea et al., 2014). But at the mucosal level, only 12%− 37% of these cancers show this bacterium forming biofilm (Drewes et al., 2017), and there is no correlation between *Fusobacteria* and poor prognosis. In tissues from left-sided tumors the *Proteobacteria* is overrepresented. In general, RCC cancer is defined by a biofilm architecture and a higher community richness compared with left-sided, while normal tissues do not show this difference (Jin et al., 2021). Some authors suggest that differences in tumor microbiota depending on the location can be a consequence of iron therapy, as right-sided tumors correlate with anemia and this fact is not considered in most studies (Phipps et al., 2021). Few evidence relates the oral microbiota and CRC site, De DecKer et al. have shown that sessile serrated polyp, a type of tumor frequent in the right side, presents more abundance of *Fusobacterium*, but also an increase of *P. micra, P. stomatis and P. gingivalis*. These bacteria form biofilms in the tumor and are frequently associated with other oral bacteria, *Treponema denticola* and *Tannerella forsythia* (Purcell et al., 2017). So, for the establishment of new biomarkers, more studies are necessary to compare the oral microbiota in different types of CRC tumors.

In fecal samples, the *Micrococcaceae* family is overrepresented in RCC tumors and is related with L-lys synthesis, also *Blautia*, *Eryspelotrichales*, *Holdemanella*, *Faecalibacterium*, *Subdoligranulum* and *Doreaga* are significantly present in this kind of tumor (Miyake et al., 2021). But if we look for differences at mucosal level after bowel preparation, a statistically higher incidence of *Escherichia coli* phylogroup B2 is found in RCC patients when compared with left sided ones, and this is related to a higher production of bacteriocins (Kohoutova et al., 2014). Tumors in the right colon side show a high abundance of *Bacteroides fragilis*, *E. coli* and oral pathogens forming invasive biofilms at the mucosal layer, and show a functional shift towards functions associated with this structural organization as peptidoglycan biosynthesis, cytoskeletal proteins increase, decrease in flagella biosynthesis, etc (Drewes et al., 2017). Specifically, genotoxic strains of *B. fragilis* and *E. coli* are found. Both produce toxins, the first one produces *B. fragilis* toxin (BFT), which cleaves E-cadherin, promoting proliferation through enhanced Wnt/β-catenin signaling and c-Myc pathway (Burns et al., 2018), and the second one produces colibactin, which makes double-strand breaks in DNA (Contribution and Statement, 2021; Tomkovich and Jobin,

2018). In the case of *B. fragilis*, also, an oxidase that promotes high reactive oxygen species (ROS) is expressed t (Goodwin et al., 2011). After these invasive bacteria started the pathogenesis and the environmental conditions have changed, other opportunistic bacteria like *Fusobacterium* and oral pathogens are able to displace them and colonize the mucosa (Tjalsma et al., 2012). *Fusobacterium* is a dominant bacterium in CRC gut microbiota compared to healthy individuals, and it can be used as a biomarker in fecal samples (Yu et al., 2017). In the case of RCC there is a trend in the correlation between the higher presence of this bacterium and shorter survival of the patient (Jin et al., 2021). *Peptostreptococcus anaerobius* is an oral pathogen usually found in polymicrobial biofilms with *Fusobacterium* in RCC and is able to promote carcinogenesis through activation of the PI3K-Akt pathway (Long et al., 2019). At mucosal level, the presence of the *phyla Bacteroidetes* and *Fusobacteria* with oral pathogens as *Porphyromonas* and *Peptostreptococcus,* is positively correlated with the presence of the cancer consensus molecular subtype CMS1, while in CMS2 there is a correlation with the genera *Selenomas* and *Prevotella (*Purcell et al., 2017*)*. Biofilms of *Fusobacterium* associated with *Peptostreptococus* and *Porphyromonas* can induce inflammation in the intestinal mucosa through interactions with immune cells, an initiating factor in tumorigenesis (Dejea et al., 2014). Also, *Fusobacterium* is able to make interactions between its adhesin FadA and E-cadherins promoting tumorigenesis through Wnt/β-catenin signaling (Zhou et al., 2018; Rubinstein et al., 2013), in the canonical CRC development linked to LCRC. This bacterium also promotes epithelial to mesenchymal transition (Yu et al., 2020) and inhibits antitumor adaptative immunity (Wu et al., 2019). If we consider the response to therapeutics, *Fusobacterium* promotes resistance to the drugs 5-FU and oxaliplatin through activation of autophagy and inhibition of apoptosis through the expression of Baculoviral IAP Repeat Containing 3(BIRC3) (Zhang et al., 2019), which could be related with the worse response to 5-FU in right-sided CRC patients compared to left-sided (Baran et al., 2018) (Fig. 2).

5. Nervous system in CRC: involvement in right and left sided tumoral process

5.1. Interaction between nervous system and CRC

Colon and rectum innervation is divided in two structures: an extrinsic innervation made of sympathetic and parasympathetic fibers coming from the brain and spinal cord, and an intrinsic innervation constituted by the enteric nervous system (ENS)(Fig. 3) (Rao and Gershon, 2018). Specifically, the superior mesenteric plexus provides sympathetic fibers to the ascending and transverse colon while parasympathetic innervation is brought by the vagus nerve. The inferior mesenteric plexus contributes with sympathetic innervation to descending colon and upper rectum and inferior hypogastric plexus (IHP) to lower rectum; parasympathetic input to these structures is provided by pelvic nerve (Alkatout et al., 2021).

The ENS is made up by the myenteric plexus (MP) and submucosal plexus (SP), responsible for autonomous gastrointestinal functions such as secretion and absorption, local blood flow or gut motility (Huang et al., 2015), and is believed to regulate intestinal immunity (Verheijden and Boeckxstaens, 2018). The developmental origin, in vertebrates, of enteric neurons and glia is neural crest cells from the neural tube that drift rostro caudally occupying the gastrointestinal tract. The ENS comprises neurons and enteric glial cells (EGC) with diverse transcriptomic, phenotypic, and functional characteristic (Gulbransen and Sharkey, 2012).

The nervous system plays a prevailing role in tumor propagation and progression in several cancer types, including CRC (Holland et al., 2021). Different scenarios have been reported for nervous system in the development of CRC. Morphologically, sympathetic nerves are found in

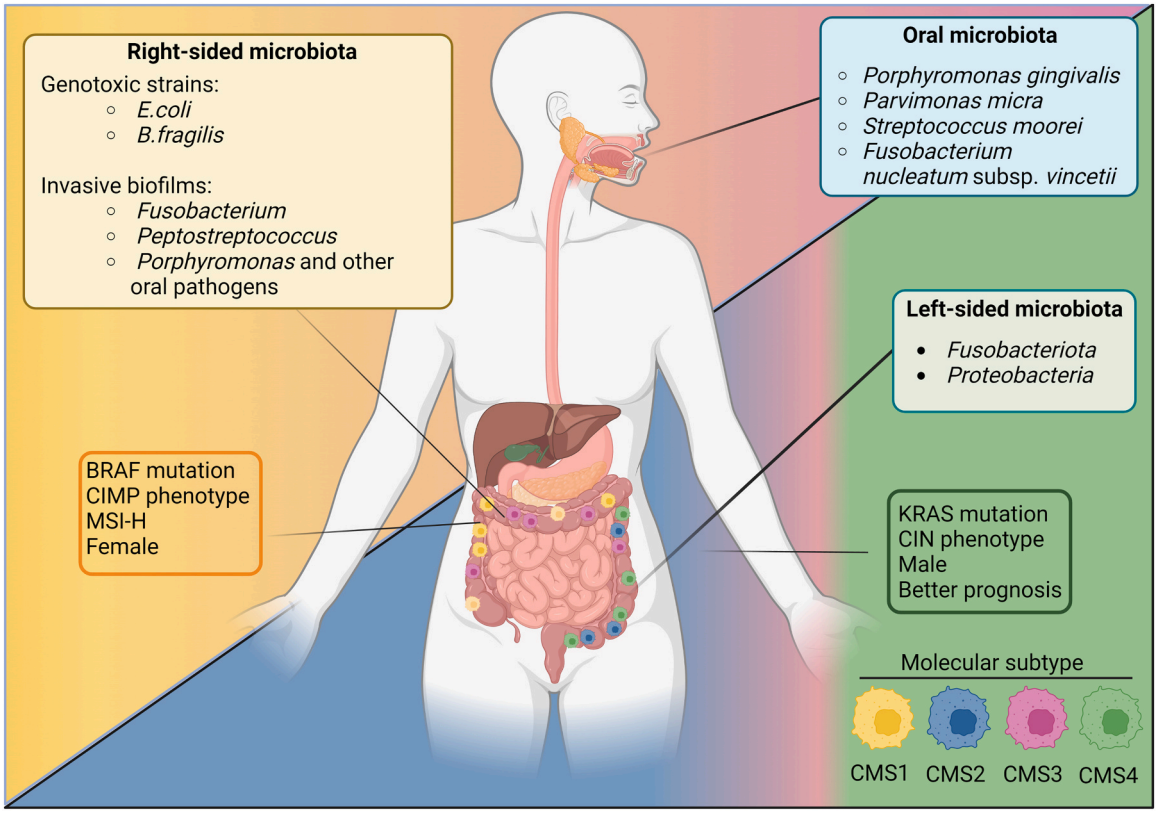

Fig. 2. Tumoral location influence in molecular and microbiota landscape. CMS1 is the predominant subtype in right-sided colon, whereas CMS2 and CMS4 are the characteristic subtypes that appear in LCRC. The CMS3 is enriched in RCC, although also appears in left-sided colon. Oral and right and left-sided microbiota are defined.

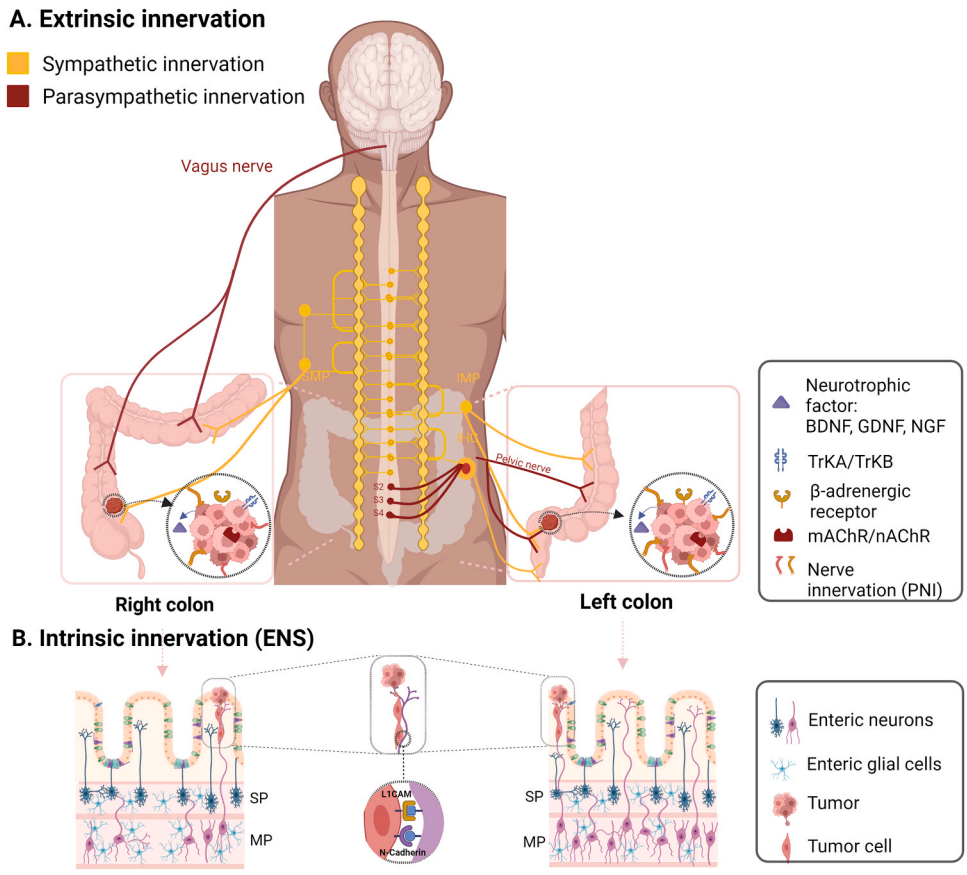

Fig. 3. Representation of right and left colon innervation in a physiological and in a CRC context. **A.** Extrinsic innervation is composed of sympathetic (yellow) and parasympathetic (red) systems. Preganglionic neurons of sympathetic division arise from the thoracolumbar region of the spinal cord and postganglionic fibers are localized in prevertebral or paravertebral ganglions formed by the superior mesenteric plexus (SMP), the inferior mesenteric plexus (IMP) and part of the inferior hypogastric plexus (IHP). The parasympathetic division comprises the vagus nerve (right) and the pelvic nerve (left). The magnified view of the tumor shows some of the proteins that CRC cells overexpress (neurotrophic factors and neurotransmitters receptors) and PNI in both sides. Note that PNI appears to be higher in rectal cancer than in right colon cancer. **B.** Intrinsic innervation consists of the enteric nervous system (ENS) which is made up of neurons organized in the myenteric plexus (MP) and the submucosal plexus (SP). Neurons/mm2 in myenteric plexus seem to be greater in left colon than in right colon. In magnified portion, migration of CRC cells along enteric neurons mediated by L1CAM and N-cadherin is shown.

the stroma closer to tumor site, while parasympathetic nerves are located away from tumor cells (Zahalka and Frenette, 2020). Another situation is perineural invasion (PNI), described as the migration of cancer cells along nerves of the peripheral nervous system (Liebig et al., 2009).

In this process, tumor cells use the nerve fibers as guidance pathways to migrate to other sites of the body, which allows tumor growth and metastasis. This circumstance can be used as a prognostic marker in high-grade CRCs and as an indicator of survival rate. Rectal cancers have a higher incidence of PNI with regard to colon cancer probably as a result of its denser extrinsic innervation compared to the colon (Knijn et al., 2016).

For cancer cell shifting communication between neoplastic, neuronal and glial cells through neurotrophic factors, neurotransmitters, adhesion molecules and matrix metalloproteinases is necessary. For example, brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) have been shown to induce tumor migration via upregulation of Vascular endothelial growth factor (VEGF) and activation of p38 and PI3K/Akt signaling pathway (Huang et al., 2015).

CRC tumor cells can also migrate along enteric neurons interacting with L1CAM and N-cadherin (Duchalais et al., 2018). Communication between cancer and neuronal cells not only has been reported in PNI but also related to tumor innervation (Battaglin et al., 2022). For example, BDNF, nerve growth factor (NGF), GDNF and receptors TRKA and TRKB are upregulated in CRC promoting the growth of nerves within the tumor (Ardini et al., 2014). Neurotransmitters may also play a role in tumor-nerve communication. An increase in adrenergic signaling and of beta-adrenergic receptors expression in the tumor stroma has been reported in CRC, which is accompanied by worse prognosis. On the contrary, an inhibitory effect on cancer growth has been attributed to dopamine receptors DRD1 and DRD5 expression, and gamma-aminobutyric acid (GABA) has been described as a CRC proliferation inhibitor and responsible of increasing sensitivity to chemotherapy in CRC cells (Song et al., 2016).

Cholinergic signaling is also involved in tumor-nerve dialogue: muscarinic and nicotinic acetylcholine receptors (mAChR and nAChR) are over-expressed in CRC lesions enhancing cell proliferation, inhibition of apoptosis, invasion and metastasis (Cheng et al., 2017). Serotonin or 5-hydroxytryptamine (5-HT) plays a dual role in cancer-nervous system signaling: it has been reported to protect against early carcinogenesis in the colonic mucosa, as a preventing agent of DNA damage, but might support CRC metastatic progression in advanced disease (Sakita et al., 2019).

Finally, neuropeptides might also be involved in CRC, including substance P and neurotensin as tumor-promoting signals (Qiu et al., 2017), somatostatin as a tumor-suppressing signal or galanin as a potential biomarker for CRC in sera and tissue (Kwiatkowski et al., 2016).

Next to enteric neurons, enteric glial cells (EGCs) could also play a role in the CRC tumor microenvironment, either by shifting towards a pro-tumorigenic phenotype or promoting a pro-malignant micro-environment, regulating various pro-inflammatory, angiogenic and anti-apoptotic factors (Valès et al., 2019).

In addition to intrinsic or extrinsic neural signaling in CRC, two other situations should be considered. On the one hand, it has been suggested that cancer cells may trans-differentiate into neural(-like) cells: cancer stem cells isolated from CRC patients were differentiated to neurons in vitro, being positive for synaptic markers (SV2A and synapsin) and for TH, indicating a sympathetic phenotype (Lu et al., 2017). Secondly, the previously explained microbiota could regulate ENS input, affecting CRC development and evolution. Therefore, signaling molecules would not be only secreted by enteric neurons or glial cells but can also be produced by gut microbiota (Obata et al., 2020).

5.2. Asymmetry in enteric nervous system

In a recent report, Graham et al. conduct a detailed analysis of human ENS describing differences between ascending and descending colon enteric innervation. Myenteric plexus area was similar in left and right colon, although myenteric ganglia occupied more area in left colon, with a two-fold difference in density between both regions. Neuron density within myenteric plexus ganglia was similar in left and right colon, but neurons/mm^2 colon was greater on left because ganglia occupy a larger percentage of bowel wall. Glial density was not statistically different in right versus left colon or within myenteric ganglia on a 2D analysis, but this parameter is upregulated in the right side after 3D imaging. It is worth noting that ratio of glia to neurons within myenteric ganglia was lower in left than right colon. No differences were found between left and right colon in percent of neuron subtypes in myenteric ganglia (Graham et al., 2020).

Studies carried out in mice show different results from those obtained in humans (Nestor-Kalinoski et al., 2022). Regarding size, both ganglionic area and the percentage of the colon occupied by the myenteric plexus decreased from proximal to distal colon and the same trend was observed in neuron per ganglion number. As for neuronal subtypes, there is a significant increase in the percentage of inhibitory motor neurons from proximal to distal colon, but there was not a significant difference in the percentage of excitatory motor neurons in colon regions. In addition, single-cell RNAseq studies in the mouse reported differences at the molecular level along the proximo-distal axis of the colon (Drokhlyansky et al., 2020): neurons were clustered in subsets according to their molecular profile and putative sensory neurons were enriched in the proximal colon whereas subsets of putative motor neurons were enriched proximally or distally.

Besides, the absence of ganglia in distal portions of the gut is the cause of the enteric neuropathy Hirschsprung disease. Among other genes, deficiencies along the signaling pathways of receptor tyrosine kinase (RET) and their family members or mutations in SOX10, PHOX2B and semaphorins, may result in failure of ENS progenitors to migrate, proliferate, differentiate within the distal intestine (Holland et al., 2021).

6. Perspectives and conclusion

Despite advances in molecular knowledge of CRC, we are still far away from translating our increasing anatomical understanding of tumor heterogeneity into clinical practice.

Herein, we discussed the differences between right and left-sided colorectal tumors. The development of more accurate and standardized methods to analyze the influence of microbiota in CRC evolution could guide basic and translational researchers in the development of novel therapies depending on the site of the primary tumor.

Although some asymmetry is observed in the nervous system, further studies are needed to understand the interaction with the tumor microenvironment.

Given the widely treatment options that are emerging, including biological agents, a correct patient stratification is required to improve survival rates.

CRediT authorship contribution statement

Sara Aljama, Estela P. Lago, Olga Zafra, Javier Sierra and Diana Simón performed a systematic review and wrote the manuscript. Jesus Rodriguez Pascual made the figures. Cruz Santos and Noemi Garcia-Romero reviewed and revised the manuscript accordingly.

Declaration of Competing Interest

All authors declare that there is no financial or other conflict of interest in the preparation of this article.

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