

Colorectal Cancer Pathogenesis

Subjects: Allergy

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Colorectal cancer (CRC) is a predominant malignancy worldwide, being the fourth most common cause of mortality and morbidity. The CRC incidence in adolescents, young adults, and adult populations is increasing every year. In the pathogenesis of CRC, various factors are involved including diet, sedentary life, smoking, excessive alcohol consumption, obesity, gut microbiota, diabetes, and genetic mutations. The CRC tumor microenvironment (TME) involves the complex cooperation between tumoral cells with stroma, immune, and endothelial cells.

Keywords: colorectal cancer ; growth factors ; PI3K/AKT/mTOR ; MAPK

1. Introduction

If, in 1950, colorectal cancer (CRC) was a rare malignancy, today, it became a predominant form worldwide ^[1]. After breast, lung, and prostate cancer, CRC is the fourth most common cause of cancer ^[2] and aggressive malignancy ^[3]. In the United States, it is the second-leading cause of death ^[2]. Every year, more than 1.2 million patients are diagnosed with CRC, and more than 600,000 lose the battle with this disease ^[4]. Worldwide, CRC is the third most common cancer, and the incidence is increasing with age ^{[5][6][7]}. In Europe, around 11% of CRC cases are attributed to overweight and obesity, especially visceral fat or abdominal obesity. The epidemiologic studies reported an incidence of 30–70% increased risk of CRC in obese men ^[8]. The most common CRC subsets are colon, proximal colon, distal colon, and rectum ^[9]. Since 1994, the CRC incidence in adolescents and young adults under 45 years has been increasing every year ^{[10][11][12][13]}. The statistical data published in 2014 revealed that 26% of proximal colon cancers were diagnosed in women younger than 50 years, while 56% of the cases were registered in women aged 80 years and older ^[14]. Compared with older CRC patients, early-onset CRC is a heterogenous group that is distinct from the clinical, pathologic, and molecular points of view ^[15]. Therefore, an increased incidence was observed between 49 and 50 years ^[16]. Kim SE reported that women are more prone to developing right-sided (proximal) colon cancer compared with men. Proximal colon cancer is a more aggressive form versus the left-sided (distal) form ^[17]. Depending on the mutation origin, CRC carcinomas are classified as sporadic (70%), inherited (5%), and familial (25%). Unfortunately, metastatic CRC (mCRC) is often incurable in most cases, representing 13% of all diagnosed cancers ^{[18][19]}, with an overall survival rate of 13% ^{[18][20]}. Corroborating all the information received from genomic, epigenomic, transcriptomic, and microenvironment levels, CRC has molecular heterogeneity. Moreover, genomic events accumulated during carcinogenesis remain the leaders of cancer progression in the metastatic stage ^[21]. For early CRC, the 5-year survival rate is ~90%, but this rate decreases to 15% in the case of mCRC ^[22].

2. Risk Factors in CRC

Both environmental and genetic factors are involved in the etiology of CRC ^[23]. More than 80% of CRC cases are sporadic, as patients do not present a family history ^[23]. Therefore, the majority of the CRC cases (>90%) can be prevented if they are tested and screened early ^[24]. Several modifiable risk factors are involved in CRC pathogenesis such as diet, obesity, sedentary life, smoking, and moderate-to-heavy alcohol consumption ^[25]. Diet plays a pivotal role in CRC development ^{[26][27]}, the consumption of unhealthy food being a significant factor in CRC development ^[28]. Moreover, a diet rich in red meats, processed meats, saturated animal fats, spicy foods, refined carbohydrates are associated with increased CRC development ^[27]. The International Agency for Research on Cancer (WHO-IARC) classified the consumption of processed meat as “carcinogenic to humans”. Several compounds present in red (haem iron) and/or processed meat (nitrates and nitrites) as well as those formed during cooking will react with colorectal mucosa and promote carcinogenesis ^[29]. Experimental studies, performed on rodent models, reported that red meat haem iron induces lipid oxidation with the formation of 4-hydroxynonenal (HNE) from n-6 fatty acids. Aldehydes’ synthesis is correlated in rats with preneoplastic lesions. In vitro, it has been observed that haem iron and aldehydes can enhance cellular inflammatory processes and cellular permeability, as well as promoting cellular DNA damage ^[30]. The process of meat cooking can incorporate or develop mutagens and carcinogens, which have been shown to enhance

carcinogenesis. During high-temperature or open-flame meat cooking, heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are formed. In meat, the most common PAH compound is benzo(a)pyrene. Cytochrome P450 enzymes activate these pro-carcinogens, which will be further converted in several metabolic pathways [31]. Moreover, N-nitroso compounds (NOC) obtained by the interaction between nitrogen oxides or nitrite with secondary amines and N-alkylamides have CRC carcinogenic properties [32]. In addition, the consumption of red meat and other animal products is conducive to trimethylamine N-oxide (TMAO) synthesis, a gut microbiota-derived metabolite of choline and L-carnitine, associated with an increased risk of CRC, cardiovascular disease, and diabetes. The correlation between TMAO and cancer is performed via inflammation, OS, DNA damage, and protein folding disruption [33].

The results from the epidemiologic and experimental studies performed in the last few decades revealed that calcium, fibers, milk, and whole grains decrease the CRC incidence, while red and processed meat increase the risk [26]. While the Western society prefers to eat red and processed meat associated with an increased cancer incidence, the Mediterranean diet is correlated with a decreased cancer incidence [34]. Smoking and a sedentary lifestyle are major risk factors for early-onset CRC [35]. Smoking cigarettes generates more than 7000 toxic chemicals, with at least 70 known carcinogens that can affect the entire human body. Carcinogens from the cigarette smoke (nitrosamines, heterocyclic amines, benzene, and polycyclic aromatic hydrocarbons) directly interact with the colorectal mucosa in two ways—by direct ingestion or through the bloodstream. Overall, smoking has a direct oncogenic effect, being correlated with CRC adenoma [36]. Moreover, passive smoking is an independent risk factor for CRC neoplasia in non- and former smokers [37].

In addition, it seems that physical activity after CRC diagnosis may reduce the risk of mortality by 38% [38]. In 2015, Baena R and co-workers published the results of the epidemiologic studies from EMBASE and PubMed-NCBI, carried out since November 2014, and revealed that obesity increases the risk of CRC by 19%, while regular physical activity reduces this risk by 24%. In addition, fish, fibers, and milk consumption reduce the risk of colon cancer [39]. Among students, the most important factors for CRC development are smoking (90.5%), excessive alcohol consumption (87.4%), family history of cancer (84.2%), and obesity (82.6%) [40]. The results of a prospective study regarding the effect of diet on CRC development were published in 2020. The study was conducted over a period of 4 years (2006–2010) and included men and women aged 40–69 years. The study revealed that consumption of 76 g/d red and processed meat and alcohol consumption increase the risk of CRC, while fibers from bread and breakfast cereals were associated with a decreased risk [41]. Ethanol is metabolized to acetaldehyde by alcohol dehydrogenases (ADH), catalase, or cytochrome P450 2E1. Aldehyde dehydrogenase further oxidizes ethanal to acetate, a Group 1 carcinogen for humans. In the stomach and colon, the ethanal level is influenced by gastric colonization, by *Helicobacter pylori*, or by colonic enzymes. Furthermore, alcohol generates reactive oxygen species (ROS), leading to DNA damage and activating signaling pathways involved in inflammation, metastasis, and angiogenesis [42].

Diabetes is another risk factor for CRC [43]. An elevated body weight associated with a sedentary lifestyle plays an important role in CRC pathogenesis [43]. A link between insulin resistance (IR), hyperinsulinemia and cancer, and changes in the expression of insulin receptors and insulin growth factor (IGF) system, including IGF-I, IGF-II, has been observed. When insulin binds to IGF-1 receptor (IGF-1R) with low affinity, cell proliferation is stimulated via phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway [44]. Therefore, an IGF-I serum level within the upper part of the normal range has been associated with an increased risk of cancer development. In tumor cells, including in CRC and liver cancer, fetal isoforms of the IR have been observed to be increased. Leptin, a hormone produced by the adipose tissue stimulates cell growth, migration, and cytokines production by macrophages. Moreover, leptin activates proangiogenic factors, being also involved in tumor development [44]. Some cancer cells, such as those from human CRC, can locally produce IGF-II, triggering tumor proliferation and further metastatic effects [44].

Leptin and adiponectin are involved in cancer cell proliferation, invasion, and metastasis by the activation of the Janus kinase (JAKs)/signal transducer and activator transcription proteins (STATs), mitogen-activated protein kinase (MAPK), PI3K, mTOR, and the AMP-activated protein kinase (5'AMPK) signaling pathways and induce multiple dysregulations, including those of Cyclooxygenase 2 (COX-2) and mRNA expression [45].

The adipose tissue can produce pro-inflammatory cytokines (Interleukins-ILs, IL-8, IL-6, and IL-2), enzymes (lactate dehydrogenase-LDH) and tumor necrosis factor alpha (TNF- α). The lipid peroxidation process leads to 4-hydroxynonenal (4-HNE) formation, an active compound that upregulates prostaglandin E2, which is directly correlated with an increased risk of CRC development. Furthermore, 4-HNE can dysregulate cell proliferation, cell survival, differentiation, autophagy, senescence, apoptosis, and necrosis via MAPK, PI3K/AKT, and protein kinase C signaling pathways [46].

Moreover, the adipose tissue of obese patients present M1 macrophage, which will secrete tumor-promoting molecules, such as TNF- α , IL-1 β , IL-6, IL-8, IL-18, IL-32, interferon (IFN)- γ , vascular endothelial growth factor (VEGF), osteopontin

(OPN), tenascin C (TNC), and monocyte chemoattractant protein (MCP)-1 [47]. During cancer development, TNF- α is involved in cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis [48].

Soltani G et al. conducted a study that included 693 patients who were evaluated for adenoma/adenocarcinoma and underwent colonoscopy. The study concluded that obese and diabetic patients present an increased risk of developing adenoma versus the control group. The research group did not detect any association between obesity, diabetes, and adenocarcinoma [49]. Another important risk factor for CRC may be considered the gut microbiota disruption [50]. Diet can influence the gut microbiota through production of metabolites. Butyric acid, an important source for colonocytes, protects the colonic epithelial cells from tumorigenesis, having anti-inflammatory and antineoplastic properties. Instead, protein fermentation and bile acid deconjugation will damage the colonic cells in proinflammatory and pro-neoplastic ways, leading to increased risk of developing CRC [51]. Moreover, the initial microflora plays a key role in maintaining the survival and health of the host organism, because it can activate antitumor cytokines and reduce the production of oxygen free radicals. In CRC patients, a significant intestinal decrease in intestinal microbiota diversity versus healthy people has been observed. Moreover, intestinal microbiome dysregulation can stimulate intestinal epithelial cells to activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway that will trigger an inflammation stage [52]. Dysbiosis or imbalance of gut microbiota may cause chronic inflammation, which is recognized as one of the prime causes of CRC. Therefore, gut microbiota-derived phytometabolites can eliminate gut pathogenic organisms and reduce DNA oxidative damage and pro-inflammatory mediators, regulating normal cell division and apoptosis [53].

Patients diagnosed with long-standing ulcerative colitis and Crohn's disease have an elevated risk of developing CRC [54]. Furthermore, gut microbiota has effects on the immune cells in the lamina propria, which further influence the inflammation process and subsequently CRC [55]. The fermented fibers produce butyrate, which further induces tumor cell and T-cell apoptosis, which represents the source of colonic inflammation [56]. Saturated fats or the Western diet negatively alter the gut microbiota. Instead, a diet rich in n-3 PUFA has a positive effect on gut microbiome, increasing the production of good probiotics such as *Lactobacillus* and *Bifidobacteria* and reducing *Helicobacter* and *Fusobacteria nucleatum* [56]. Smoking is another risk factor for CRC, especially in the case of individuals that have smoked for over 30 years [57]. Moreover, bile acid synthesis, such as cholic acid, may be strongly associated with colon cancer development [58].

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