

Review Article

Molecular aspects of Colorectal Carcinogenesis: A Review

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Abstract

Colon cancer is a common malignancy associated with significant mortality. Colon carcinogenesis generally occurs in a slow and stepwise process of accumulating mutations under the influence of genetic and environmental factors, the so-called adenoma-carcinoma sequence. The cellular origin of human cancer remains controversial and the mechanisms responsible for the complexity and heterogeneity of this condition remains undefined. Despite identification of genetic mutations and aberrant signaling pathways, little clinical benefit in terms of early diagnosis or treatment of advanced disease have been attained. Many reviews have analyzed genetic mutations and molecular signaling abnormalities, but the process of carcinogenesis is incompletely understood. Adenomatous polyposis coli (APC), a tumor suppressor gene, play a central role in colorectal carcinogenesis through the wnt/ β -catenin signaling pathway. Recent data suggests that peroxisome proliferator-activated receptor (PPAR) γ , a nuclear receptor, is important in cell differentiation protecting against carcinogenesis. COX-2 mRNA and protein are up-regulated in colorectal cancer, suggesting a possible role in the carcinogenic process. These three are the main known molecules involved in early colorectal carcinogenesis, although their respective interactions in this role have been poorly documented. In this review, we analyze the roles and relationships of these molecules and their interactions. We also evaluate the roles of genetic and epigenetic modifications on colorectal carcinogenesis, as well as the role of micro RNAs. Finally, we assess the impact of the gut microbiome and diet on this complex process.

Keywords

- Colorectal carcinogenesis
- β -catenin
- Peroxisome proliferator-activated receptor γ
- COX-2
- Gut microbiome

ABBREVIATIONS

APC: Adenomatous polyposis coli; BRCA1: Breast cancer susceptibility gene; CAC: Colitis-associated colorectal cancer; CD: Crohn's disease; CH₃: Methyl group; CIN: Chromosomal instability; CLA: Conjugated linoleic acid; COX-2: Cyclooxygenase-2; CRC: Colorectal cancer; CSC: Cancer stem cells; DNA: Deoxyribonucleic acid, DCC: Deleted in Colorectal Carcinoma; FAP: Familial adenomatous polyposis; GSK: Glycogen synthase Kinase; HATs: Histone acetyl transferases; HDACs: Histone deacetylases; HETE: Hydroxyeicosatetraenoic acid; HNPCC: Hereditary nonpolyposis colorectal cancer; IBD: Inflammatory bowel disease; Lef: Lymphoid enhancing Factor; LPS: Lipoprotein saccharide; miRNAs: MicroRNA; MMR: Mismatch repair; MSI: Microsatellite instability; NSAIDs: Non-steroidal anti-inflammatory drugs; PGE₂: Prostaglandin E2; PUFA: Polyunsaturated fatty acids; Rb: Retinoblastoma; RNA: Ribonucleic acid; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; SCFA: Short chain fatty acids; SEER: Surveillance, Epidemiology and End Result; SMAD4: Mothers against decapentaplegic homolog 4; Tcf: T Cell Factor; TP53: Tumour protein p53; UC: Ulcerative colitis; UTR: Untranslated region; VHL: Von-Hippel Lindau; wt: Wild-type

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer worldwide and is the second commonest cause of cancer-related mortality [1]. The life-time incidence of CRC in an average risk population is 5% and progressively increases after age 50. Both genetic and environmental factors play a role in colon cancer formation [2]. Despite better understanding of the molecular mechanisms involved in colorectal carcinogenesis, little progress has been made in the successful management of advanced CRC.

Data from the Surveillance, Epidemiology and End Result (SEER) program suggests that the 5 year survival rates have improved from 56.5% for patients diagnosed in the early 1980s to 64.9% for patients diagnosed in 2005. This trend is due mostly to early diagnosis and aggressive treatment. Cancer stage correlates well with survival/cure rates as outlined in Table 1. Sadly, the majority of patients diagnosed with CRC present with advanced disease. Although most CRC-related deaths are preventable through screening colonoscopy, it is estimated that less than 50% of eligible patients are screened for CRC [3].

Epidemiology

In the United States, Black Americans have a higher incidence

Table 1: 5-year survival rates for colorectal cancer according to cancer stage.

Cancer classification	% 5 year survival
Dukes A	93
Dukes B	78
Dukes C	64
Dukes D	8

of CRC compared to Whites, with the disease developing at a younger age and at a higher tumour stage. Often, they develop proximal colon cancer (proximal to the splenic flexure). Although not exclusive, left sided and rectal cancer is more common in Whites. Men and women are equally affected with a proximal predominance in women and a distal predominance in men. In developing nations, the rate of CRC in non-Caucasians is low, although it is steadily increasing [4].

Colon cell turnover

The epithelial layer of the colon consists of a single sheet of columnar epithelial cells folded into finger-like invaginations, or crypts, surrounded by lamina propria. Stem cells located in or near the bottom of the crypt give rise to progenitor cells that differentiate into the various terminally differentiated, non-proliferative epithelial cell types through a process of upward migration (Figure 1). These epithelial cell types include colonocytes/enterocytes, goblet cells and endocrine cells, located in the upper third of the crypt [5].

Colon cancer stem cells

CRC, like most solid tumors, results from uncontrolled growth of a small subpopulation of undifferentiated cancer stem cells (CSC). The origin of CSCs is unclear but they are believed to develop from tumorigenic mutations in normal stem cells. The CSC has the capacity for indefinite self-renewal, as well as the ability to recreate the full repertoire of cancer cells exhibited by the parent tumor. This describes the bottom-up model. A top-down model has also been proposed. These models are not mutually exclusive and both result in CRC [6,7].

Considerable evidence exists for the role of wnt/ β -catenin pathway in the preservation of normal stem cell proliferation and pluripotency. Disruption of this pathway results in crypt death. Aberrant activation of this pathway, on the other hand, increases stem cell proliferation and crypt numbers, ultimately resulting in CRC [8].

Genetic models of colorectal carcinogenesis

Fearon and Vogelstein proposed the molecular pathogenesis of colorectal carcinogenesis with the emphasis on a sequence of events leading to colonic mucosal change, rather than a single event [9]. These events lead to a disturbed balance between cell growth and cell death in normal colonic epithelium. The end result of this neoplastic sequence is the development of adenocarcinoma with genetic mutations that include large chromosomal deletions or translocations, amplification of chromosomal segments and point mutations of certain genes [10].

In this adenoma-carcinoma sequence model, the adenomatous

polyp is the precursor lesion leading to colorectal adenocarcinoma. 90% of all sporadic CRC develops in this way and is associated with aberrations of the wnt/APC/ β -catenin signaling pathway. This pathway is the focus of discussion in this review. 10% of sporadic CRC develops through a recently identified 'serrated neoplasia pathway', where serrated adenomas progress via an alternate pathway to colorectal adenocarcinoma.

Serrated polyps are a heterogeneous group consisting of the hyperplastic polyp, the sessile serrated adenoma, the traditional serrated adenoma and the mixed polyp. Recently, Yamane *et al* discussed the molecular alterations in serrated colorectal carcinomas in detail and those include the *BRAF* or *KRAS* mutations and an enhanced CpG island methylation (CIMP) of multiple genes. Frequently, serrated adenomas carry a methylated *MIH1*, which is a DNA mismatch repair (MMR) gene. *BRAF* mutations lead to carcinogenesis through abnormal mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling. Microsatellite instability (MSI), initially identified in Lynch syndrome, is another molecular pathway associated with both the traditional adenoma-carcinoma pathway as well as the serrated neoplasia pathway [11,12]. This pathway is believed to have accelerated carcinogenic potential.

FAP

Familial adenomatous polyposis (FAP) has autosomal dominant inheritance pattern and accounts for 1% of all hereditary CRC. It is associated with a mutation in the adenomatous polyposis coli (APC) gene located on the long arm of chromosome 5q2. Clinically, it is characterized by the development of hundreds to thousands of adenomas in the colon and rectum in the second and third decades of life, predisposing to colorectal cancer [13].

APC is a tumor suppressor gene that plays a role in the wnt/ β -catenin signaling pathway (Figure 2). β -catenin is a component of cell-adhesion complexes where it binds to cadherins to link extracellular anchors to the cytoskeleton. In addition, β -catenin functions as a co-activator of T cell factor/lymphoid enhancer factor (Tcf/Lef) transcription factors and activates expression of specific genes regulated by the canonical wnt signaling pathway. Central to this signaling pathway, β -catenin exists

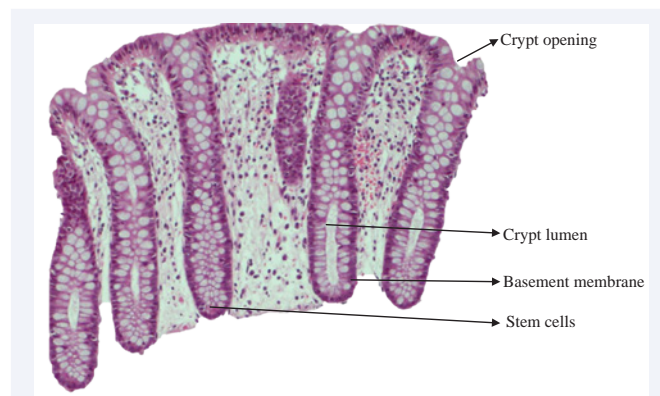


Figure 1 Microscopic image of colon crypts in the intestinal lumen with an illustration of the bottom-up maturation process resulting in differentiated colon epithelial cells.

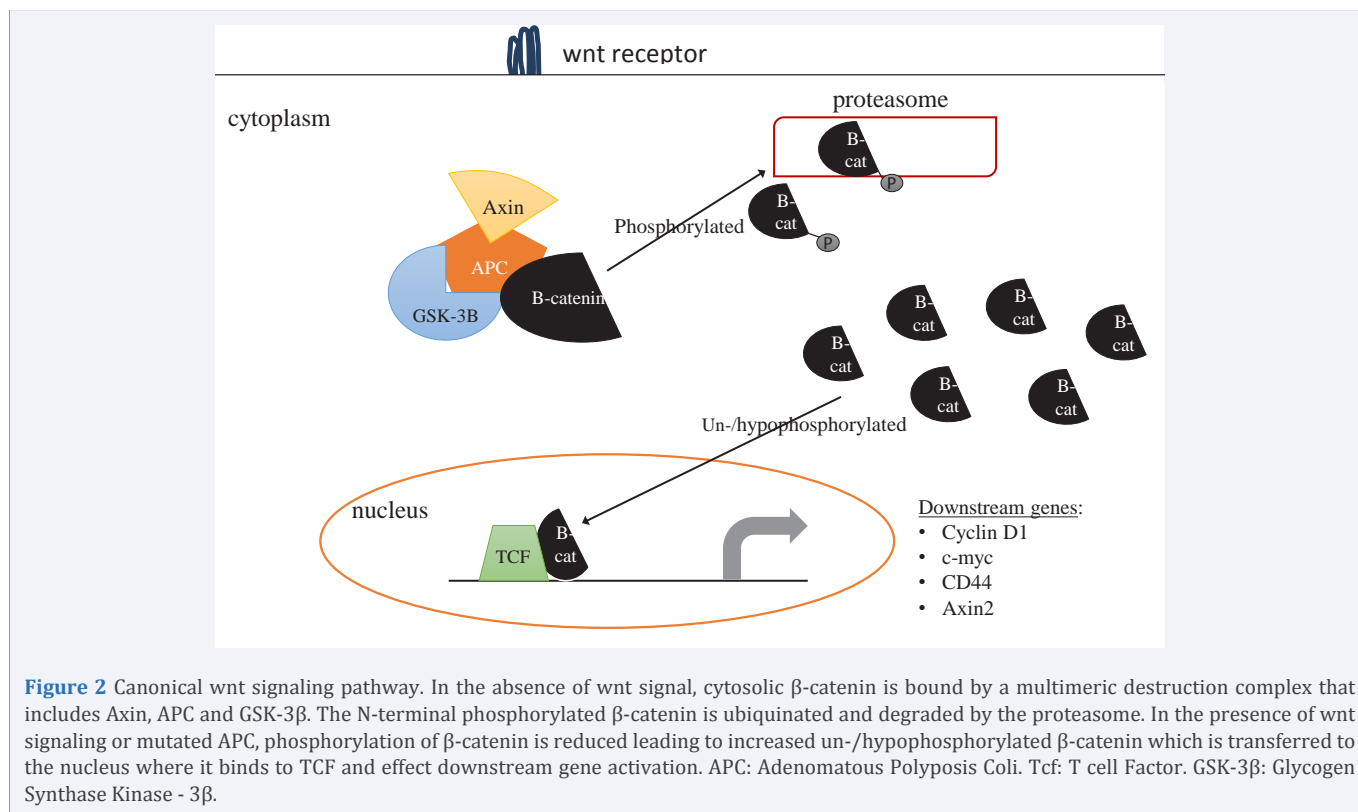


Figure 2 Canonical wnt signaling pathway. In the absence of wnt signal, cytosolic β -catenin is bound by a multimeric destruction complex that includes Axin, APC and GSK-3 β . The N-terminal phosphorylated β -catenin is ubiquitinated and degraded by the proteasome. In the presence of wnt signaling or mutated APC, phosphorylation of β -catenin is reduced leading to increased un-/hypophosphorylated β -catenin which is transferred to the nucleus where it binds to TCF and effect downstream gene activation. APC: Adenomatous Polyposis Coli. Tcf: T cell Factor. GSK-3 β : Glycogen Synthase Kinase - 3 β .

within a cytoplasmic complex (β -catenin destruction complex) along with APC, axin and glycogen synthase kinase - 3 β (GSK-3 β). In the absence of wnt signaling or the presence of wild-type (wt) APC, β -catenin levels are kept low through constitutive phosphorylation of GSK-3 β , which leads to the ubiquitination and proteasomal degradation of β -catenin [14].

In the presence of wnt signaling, GSK-3 β phosphorylation is reduced leading to inactivated GSK-3 β . This in turn leads to reduced β -catenin phosphorylation and a consequent reduction in its degradation, substantially increasing free cytoplasmic β -catenin. The unphosphorylated β -catenin is stabilized and translocated to the nucleus where it binds to Tcf/Lef family of transcription factors, leading to transcription of canonical wnt target genes [15].

In the instance of mutated APC, GSK-3 β is inactivated, so β -catenin remains unphosphorylated and enters the nucleus to activate Tcf/Lef associated gene transcription. The β -catenin pathway remains constitutively active leading to loss of normal cellular homeostatic and control mechanisms. The genes regulated by the β -catenin/Tcf/Lef complex play an important role in neoplastic transformation. They include *c-myc*, which controls neoplastic growth, *cyclin D1* which controls cell cycle progression and the *matrix metalloproteinase matrilysin*, which plays a role in tumour invasion [15].

Mutations in the APC gene are one of the initiating events in the development of sporadic and hereditary familial colorectal cancers. APC mutations are almost always insertions, deletions or nonsense mutations that lead to a stop codon and result in the production of a truncated protein with loss of APC function in the APC/Axin/GSK-3 β destruction complex. Mutations of

β -catenin have also been identified in colon cancer which lacks APC mutations, but to a lesser extent. The main pathogenic pathway in FAP is chromosomal instability (CIN). Cancers in FAP are located in the left colon (distal to the splenic flexure) in close to 100% of patients [16].

HNPCC

Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, accounts for 4-5% of all hereditary colorectal cancer [17]. It is inherited in an autosomal dominant fashion. The genetic defect in HNPCC is an error in MMR genes. Implicated genes include *MSH2*, *MLH1*, *PSM2* and *MSH6*. The affected DNA displays instability at microsatellite short tandem repeat sequences, resulting in genetic mutations. The instability impairs the ability of the cell to replicate or to repair microsatellite regions; hence it is called microsatellite instability (MSI). These acquired mutations eventually occur in oncogenes and tumor-suppressor genes, ultimately leading to cancer development. In HNPCC, patients develop colorectal cancer before the age of 50 and have predominantly proximal tumors in 60-70% of patients [16].

Sporadic Colorectal Cancer

Sporadic colon cancer makes up 80-85% of all cases of CRC and occurs in average risk patients, age 50 and older without obvious predisposing risk factors (Figure 3). Only about 15-20% of all cases are familial and occurs in moderate risk patients with a family history of colorectal adenomas or cancer [17]. Understanding the molecular abnormalities in hereditary carcinogenesis has helped identify some of the molecular mechanisms involved in sporadic CRC. It is now established

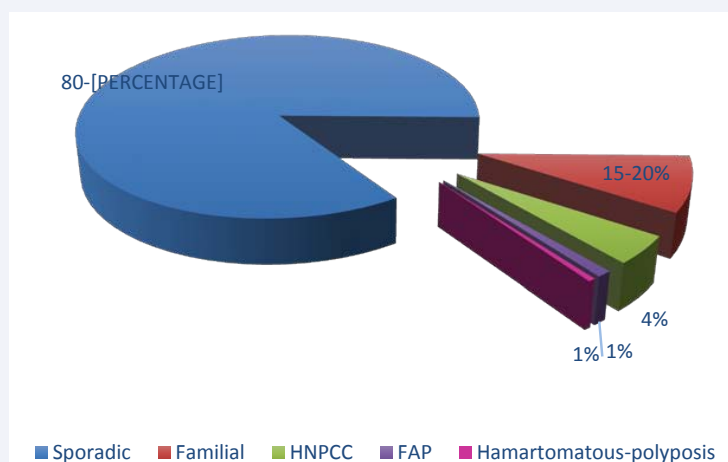


Figure 3 Colorectal cancer syndromes: Relative number of cases that are considered sporadic, familial and hereditary. FAP: Familial Adenomatous Polyposis, HNPCC: Hereditary Nonpolyposis Colorectal Cancer.

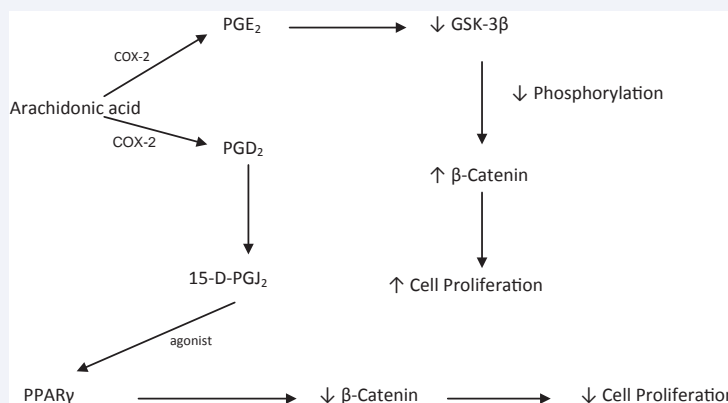


Figure 4 Schematic illustration of the relationship between COX-2/PGE2 and PPAR γ and its interaction with the APC/ β -catenin/TCF pathway.

that sporadic colorectal cancer is also associated with genetic abnormalities.

There is significant heterogeneity in the pathogenetic pathways leading to CRC and two major pathways have been proposed, CIN and MSI. CIN is the commonest genomic instability accounting for 80-85% of all cases. The earliest initiating event is mutation in the *APC* gene leading to a dysfunctional APC protein. Important tumour suppressor genes in CRC include *APC*, *Tumour protein p53* (TP53) and *Deleted in Colorectal Carcinoma* (DCC), also known as *SMAD4* (Mothers against decapentaplegic homolog 4). *K-RAS* is the most common oncogene affected, noted in 40% of CIN associated colorectal cancer [18]. Unfortunately, this alone is not sufficient to account for all the cases of CRC.

Fifteen to twenty percent of sporadic colorectal cancers arise through a mechanism involving MSI. Predominant genes affected in this setting are *MSH2* and *MLH1*. MSI occurs either in a high frequency (MSI-H) or a low frequency (MSI-L) form. MSI-L tumors are often grouped with microsatellite stable (MSS) tumors. MSI-H tumors have distinct clinical and pathologic features, including proximal colon predominance, diploid DNA content and poor differentiation [18]. Data suggest that

MSI-H tumors have a favorable prognosis compared to MSS/MSI-L tumors, but study designs have often been poor and data inconsistent.

Sinicrope *et al* showed that aneuploid/tetraploid DNA content was associated with higher tumor stage and poorer differentiation, distal tumor site and nuclear p53 expression than in diploid cells and tumors. The aneuploid/tetraploid tumors were generally MSS/MSI-L. Their study also confirmed that MSI-H tumors were frequently diploid, had a proximal tumor location and poor differentiation as expected. MSI-H tumors also expressed less p53 protein [19].

Further characterization of MSI tumors showed significant inverse correlation with cyclooxygenase-2 (COX-2) expression compared to MSI negative tumors. On the contrary however, studies indicate that COX-2 levels are increased in approximately 80% of human colorectal carcinomas, while COX-1 levels remain unchanged. Furthermore, both selective and non-selective COX-2 inhibition led to reduced incidence of colonic adenomas in patients with FAP and sporadic colorectal adenomas. The chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) confers an estimated 40% reduction in colorectal cancer incidence [20].

The clinical significance or etiological relevance of this remains unclear. However, it suggests that COX-2 plays a causal role in the early carcinogenic stages of CRC and this may prove to be a potential future therapeutic tool.

The role of chronic inflammation in carcinogenesis appears to be multifaceted. Patients with ulcerative colitis (UC) and Crohn's disease (CD), the two major forms of inflammatory bowel disease (IBD), are at increased risk of developing colitis-associated colorectal cancer (CAC). The risk of CAC in patients with UC is estimated at 2% after 10 years, 8% after 20 years and 18% after 30 years and most patients with UC are diagnosed before age 30. This calculates to an incidence rate ratio of 2.75 compared to the general population. The relationship between CD and CAC has been less clear because of the heterogeneous nature of CD, which can involve any part of the gastrointestinal tract in a non-continuous fashion, with many patients not having colonic involvement. Patients with exclusive colonic CD have recently been shown to have a relative risk of 5.6 to develop CAC. Several factors confer an increased risk of developing CAC in IBD patients. These are: (i) duration, (ii) extent and (iii) severity of disease. The molecular mechanisms underlying CAC development are still poorly understood. One of the possible mechanisms include the generation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) in the inflamed tissue, with subsequent DNA damage leading to activation of oncogenes and/or inactivation of tumor suppressor genes. Chronic inflammation contributes to carcinogenesis through a variety of possible mechanisms including: genomic instability, epigenetic alteration leading to inappropriate gene expression, resistance to apoptosis and/or increased proliferation and enhanced tumor neovascularization [21-23].

COX-2, an inducible form of cyclooxygenase, serves as an interface between inflammation and cancer. In response to various external stimuli, such as pro-inflammatory cytokines, bacterial LPS and ROS, COX-2 is transiently elevated in certain tissues. Abnormally elevated COX-2 causes promotion of cellular proliferation, suppression of apoptosis, enhancement of angiogenesis and tumour invasiveness, which accounts for its oncogenic potential. COX-2 expression and PGE₂ levels are up-regulated in gastrointestinal cancers. Cumulative evidence indicates that COX-2/PGE₂ promotes the growth of colon cancer cells. The molecular mechanism by which COX-2 promotes carcinogenesis remains unclear, but evidence suggests an interaction between COX 2/PGE₂ and the oncogenic APC/ β -catenin/TCF pathway in colorectal neoplasia. This transactivation is effected by inhibition of GSK-3 β [24, 25].

Another potential role player in colorectal carcinogenesis is peroxisome proliferator-activated receptor gamma (PPAR γ), although it's exact role in CRC development is still debated. PPAR γ , a member of the nuclear receptor superfamily, is involved in the regulation of growth, differentiation and metabolism of various cell types via transcriptional regulation of target genes. Most of the available data suggest an antitumor effect in CRC. PPAR γ activation is associated with the inhibition of cell growth in both human colon cancer cell lines as well as nude mice. Mice with a heterozygous deletion of PPAR γ (PPAR γ ^{+/-}) have an increased tendency to develop carcinogen-induced colon cancer.

Moreover, loss-of-function mutations in PPAR γ are associated with increased colon cancer development in humans. Recent results showed that increased PPAR γ expression in CRC is associated with a good prognosis [26-28].

Natural ligands of PPAR γ include: (i) certain polyunsaturated fatty acids (PUFA) e.g. arachidonic acid and eicosapentanoic acid; both are also substrates for COX-2. (ii) arachidonic acid metabolites derived from the cyclooxygenase and lipoxygenase pathways, e.g. 15-deoxy -D-12, 14-prostaglandin J₂ (15d-PGJ₂) and 15-HETE. Synthetic ligands include the thiazolidinedione (TZD) class of anti-diabetic drugs. Traditional and selective COX-2 inhibitors have also been shown to activate PPAR γ independent of their ability to inhibit COX-2 [29]. This demonstrates a biologically significant interaction between COX-2 and PPAR γ .

Conflicting data exists for PPAR γ expression in CRC. In some studies increased levels of PPAR γ expression have been demonstrated, while in others low levels of expression were shown. These results were documented in both animal and human studies, as well as cell lines. In a mouse model of CRC, PPAR γ inhibition promotes carcinogenesis through activation of the APC/ β -catenin/TCF pathway [30]. Figure 4 illustrates the relationship between COX-2 and PPAR γ and its interaction with the APC/ β -catenin/TCF pathway.

Epigenetic modification

Epigenetic modification has been identified as a potential contributor in colorectal carcinogenesis. Epigenetics is defined as heritable changes in gene expression not accompanied by changes in DNA sequence [31]. Three types of epigenetic modifications have been described:

DNA methylation: the covalent addition of a methyl group (CH₃) to the nucleotide cytosine. The most predominant aberrant DNA methylation is hypermethylation that typically occurs at the CpG islands located in the promoter region of tumour suppressor genes and other genes. Commonly affected genes include p16, von-Hippel Lindau (VHL), APC, breast cancer susceptibility gene (BRCA1), retinoblastoma (Rb) and E-cadherin. This methylation results in transcriptional silencing with loss of protein production, which can disrupt cell cycle control, DNA repair, cell adhesion and apoptosis [32]. These are critical elements in carcinogenesis.

Histone modification: involves chromatin remodeling by covalent modification of the histone protein. The acetylation/deacetylation is performed by histone acetyl transferases (HATs) and histone deacetylases (HDACs). The acetylation of lysine residues on the N-terminus of histones by HATs activates gene transcription. On the other hand, removal of an acetyl group from lysine residues in histone tails by HDACs results in transcriptional repression of genes. Inappropriate activation/inactivation of the HDACs and HATs has been implicated in carcinogenesis [10,33].

MicroRNA: miRNAs consist of short, single stranded, non-coding RNAs that regulate the translation of many genes by binding to their 3'- untranslated region (UTR) and degrading the mRNA or repressing translation. Evidence suggests that miRNA play a significant role in tumorigenesis. Epigenetic modifications like DNA methylation and histone acetylation, are able to affect miRNA expression and gene dysregulation. In addition, several

miRNAs behave like oncogenes or tumour suppressor genes [34]. The 3'-UTR of the COX-2 gene contains miRNA response elements, which, when bound by miRNAs, influences COX-2 stability and translational efficiency. This is an evolving field and new miRNAs are reported weekly. Currently, it only has prognostic significance, but hopefully in the near future, miRNA biomarkers will be developed aiding in still earlier intervention in this disease.

Diet and colon cancer

The role of dietary constituents in the prevention of CRC has been the focus of research for many years. High fat diets generally increase CRC risk, while high fiber and vitamin-rich diets are protective [35]. Conjugated linoleic acid (CLA) is a natural compound present in meat, milk fat, cheese and other food products from ruminants. CLA exhibits anti-inflammatory and anti-carcinogenic properties. It also plays a role in proliferation and differentiation. CLA is now recognized as a promising dietary adjuvant for chemoprevention and chemotherapy for a variety of human cancers [36]. However, little information is available concerning the potential of CLA in influencing colon cancer risk. The anti-cancer effect of CLA is believed to be mediated by:

1 Lipid peroxidation: CLA-induced reduction in Bcl-2 expression might increase the sensitivity of cells to lipid peroxidation and programmed cell death.

2 Activation of PPAR γ .

CLA is an agonist of human PPAR γ and up-regulates PPAR γ in colon cancer cell lines [37]. Recent data indicates that CLA both up-regulates PPAR γ and decreases phosphorylation of Erk1/2 [38]. Bozzo *et al* showed that treatment with CLA increased wild type APC protein that binds β -catenin and reduced free cytosolic β -catenin, leading to the suppression of colon carcinogenesis. CLA treatment also decreased *c-myc* and *cyclin D*, both of which are downstream products of the APC/ β -catenin signaling pathway [39]. From this, it is clear that the principle mode of action of CLA is via the wnt/APC/ β -catenin pathway described above.

Microbiota and colon cancer risk

The human gut is home to a complex consortium of about 10^{11} microorganisms, collectively called microbiota [40]. Little is known about the complexity and dynamics of the human microflora, and its potential interactions with the human host, including the immune system. Identification of the microbiota present in the human digestive system is complicated. The composition of the microflora changes throughout the intestinal tract, with the majority of the microbes being found in the proximal colon. Changes in substrate availability, pH and reduction potential also affect the composition of the microflora [41].

The human colonic microbiota is largely composed of Bacteroidetes (Bacteroides species) and Firmicutes (Clostridium, Lactobacillus and Enterococcus), which together account for more than 90% of the gut bacterial phyla. The microbiota has the ability to process otherwise indigestible components of our diet, such as polysaccharides, through fermentation. The chief end products are short chain fatty acids (SCFA), gases and heat.

Population survey data show that faecal SCFA production is in the order of acetate>propionate> butyrate in a molar ratio of 60:20:20 respectively [42]. Acetate is absorbed and transported to the liver where it is involved with cholesterol synthesis. Propionate is a substrate for hepatic gluconeogenesis in the Krebs cycle.

Butyrate is the main source of energy for the colonocytes and has been implicated in the regulation of apoptosis, cellular proliferation and differentiation. It also has anti-inflammatory properties. The mechanism of action of butyrate in colon cancer is not clear, but three major possibilities exist. Butyrate can induce p21^{WAF1/Cip1} mRNA and protein levels, which causes G₁ cell cycle arrest and thus inhibits proliferation [43]. Alternatively, butyrate inhibits histone deacetylase activity, resulting in hyperacetylation of histones, and as a consequence induces apoptosis in colon cancer cells [44]. Furthermore, butyrate has also been shown to activate PPAR γ [45].

DISCUSSION AND CONCLUSION

From the above it is clear that colorectal carcinogenesis is a heterogeneous and complex multistep process involving progressive disruption of homeostatic mechanisms controlling intestinal epithelial cell proliferation, differentiation and programmed cell death. This disruption appears to be mediated by dietary and environmental factors that modulate intestinal epithelial cell signaling pathways, as well as genetic mutations of transforming oncogenes and deletion or mutation of DNA repair genes and tumor suppressor genes. Multiple genetic mutations are required over many years to finally produce aberrant growth resulting in colon cancer. The wnt/APC/ β -catenin is significant in both hereditary and sporadic colorectal carcinogenesis as shown. The roles of COX-2 and PPAR γ are less clear and need further elucidation. Future research must concentrate on molecular events preceding COX-2 and β -catenin up-regulation. In this way we may uncover the early genetic mutations and signaling aberrations in the initiation of colorectal carcinogenesis.

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