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Review Article

Biochemistry Section

Role of Microbiota in Aetiopathogenesis of Colorectal Cancer

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ABSTRACT

Colorectal Cancer (CRC) accounts for sizeable disease burden globally. The symbiotic association between gut inhabitants and the digestive tract contributes to gut homeostasis. Studies suggest that altered microbiota composition or dysbiosis can contribute to colorectal carcinogenesis. This review outlines the complex interplay between the microbiome, diet and CRC with a special emphasis on microbial metabolites, gut barrier function, specific bacterial species which influence the micro environment by various mechanisms like oxidative stress, DNA damage, immune modulation and inflammation. This would help in establishing novel diagnostic, prognostic markers and newer therapeutics for CRC.

Keywords: Butyrate, Dysbiosis, Gut microbiota, Microbiome

INTRODUCTION

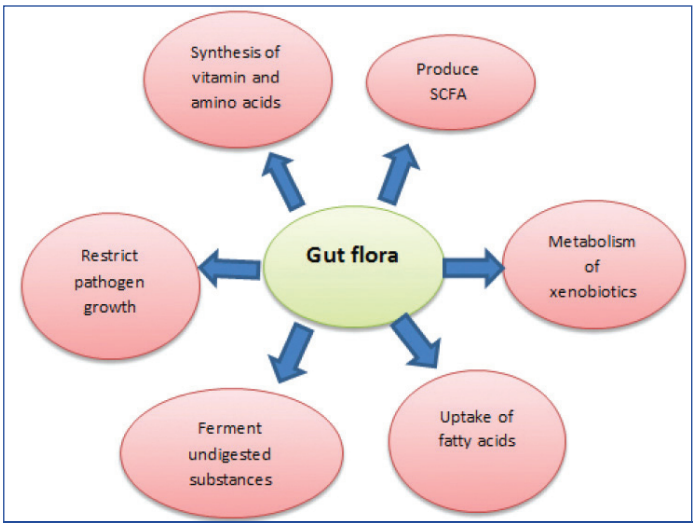
There have been great advances related to impact of microbiota on cancer immunology [1]. It is a well-known fact that cancer grows in close proximity to microbiota starting from primary lesion to metastasis to distant sites [2]. It has been postulated that composition of gut microflora influences anticancer immune surveillance by both cytoprotection and immunosuppression. In addition, the gut inhabitants also play a cardinal role in determining the therapeutic response of the anticancer treatment of the patient [3]. In a nutshell, microbiota research has revolutionised both the scientific and clinical aspect of cancer immunology unveiling fascinating insights into cancer therapy.

CRC is the fourth most common cause of cancer and second most common cause of mortality among cancer worldwide. The 5 year prevalence rate of CRC is about 4.7 million cases with 8.8 lakh deaths worldwide in the year 2018 [4]. Highest incidence rates are seen in Australia, New Zealand, Canada, the United States and parts of Europe whereas the lowest risk occurs in countries like China, India, parts of Africa and South America [5]. Diet and lifestyle are crucial factors that affect the pathogenesis of CRC [6]. As inflammation plays an important role in the aetiopathogenesis of CRC, in this review we will discuss the role of gut inhabitants in carcinogenesis with main emphasis on microbial metabolism and inflammation.

The collection of microorganisms that live in peaceful co-existence with their hosts are termed as the microbiota or microflora. The microbiota colonise all surfaces of the human body that are exposed to external environment including skin, genitourinary, gastrointestinal, and respiratory tracts [7]. The large intestine contains the densest microbial community containing over 70% of all the microbes in the human body [8]. Anerobic bacteria, the Bacteroidetes and the Firmicutes dominate the large colon, whereas Proteobacteria, Verrucomicrobia and Actinobacteria are present in minor proportions [9]. The gut microbes which appear at birth are similar to mother's vaginal microflora. The microflora undergo changes and start resembling the adult's flora after 1 year of age [10]. There are several factors like genetic makeup and dietary habits of the individual which influence the composition of gut flora [11,12]. There are two types of fecal microflora in the general population namely Low Gene Count (LGC) and High Gene Count (HGC). The LGC microflora shows less diversity and has more of bacteroides and less of Firmicutes [13]. On the other hand HGC are characterised by more diversity of gut flora and more of Firmicutes. In 2013, Cotillard A et al., postulated that individuals with obesity have LGC microbe community and weight loss diet improved microbial diversity, and which ultimately drifted towards HGC [14]. This result emphasises on the importance of diet on modulating the composition of gut flora.

IMPORTANCE OF MICROBIOTA IN THE INTESTINE

[Table/Fig-1] depicts the importance of microbiota in the intestine. The microbiota benefits the host's gut by restricting the pathogen's growth by colonising and occupying the attachment sites in the gut, and consuming the available nutrients [15]. It not only produces but also stimulates the host to produce antimicrobial substances (AMP-Antimicrobial peptides). These AMPs prevent overgrowth of commensals and prevent invasion from pathogens [16]. The gram positive bacteria such as *Lactobacillus* prevent *Listeria* infection in vitro through production of antimicrobial substances and modulation of immune responses of the epithelial cells [17]. The microbes help in maximising the caloric availability of ingested nutrients by extracting additional calories [18]. They help in fermenting the undigested dietary components (mucin, non-starch polysaccharides and resistant starch) into short chain fatty acids like acetate, propionate and butyrate in the ratio 3:1:1 [19]. In addition, the microbes also promote the uptake of fatty acids into adipocytes by suppressing the inhibition of lipoprotein lipase [20]. The metabolism of xenobiotics including pharmaceuticals is associated with contribution from both host and microbiota. Therefore, a new concept of pharmacometabonomics has now

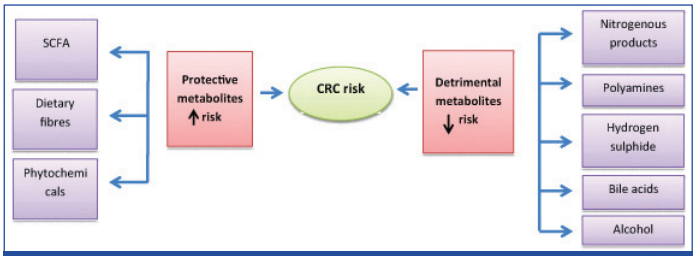


[Table/Fig-1]: Importance of microbiota.
SCFA: Short chain fatty acid

emerged. The gut inhabitants are associated with degradation of dietary oxalates that underlines their role in prophylactic treatment in calcium oxalate nephrolithiasis [21,22]. It also degrades hydrazine, a known industrial toxin and acts as a detoxifier [23].

ROLE OF MICROBIOTA IN AETIOPATHOGENESIS OF CRC

[Table/Fig-2] shows the role of microbial metabolism in the aetiopathogenesis of CRC. There are several models for microbial involvement in colorectal carcinogenesis. The first model states that single microbe causes disease aetiology, for example *Helicobacter pylori* causing gastritis. The second model says that initially host factors initiate disease pathology followed by change and alteration in microbiota leading to dysbiosis. The third model suggests that some gut inhabitants can aggravate or reduce the intensity of certain infections however clinical relevance remains debatable [24]. Accumulating evidence suggests that microbial metabolism influences CRC aetiopathogenesis [24]. These metabolites produced by gut flora impact carcinogenesis by various mechanisms.



[Table/Fig-2]: Role of microbial metabolism in the aetiopathogeneis of colorectal cancer.
SCFA: Short chain fatty acid; CRC: Colorectal cancer

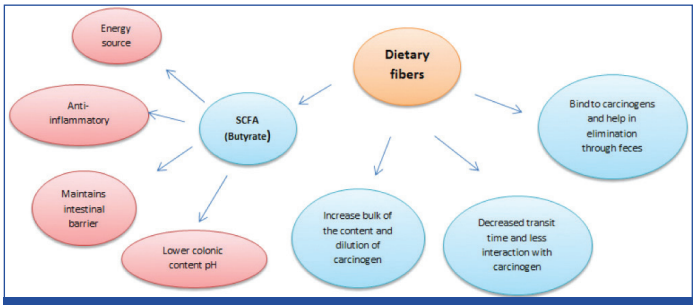
PROTECTIVE METABOLITES

1. Short Chain Fatty Acids (SCFAs)

The major bacterial fermentation products are the SCFAs namely butyrate, propionate and acetate. Butyrate is used as energy source by gut epithelium [25]. Butyrate and propionate when transported into host cells participate in epigenetic modification by directly inhibiting histone deacetylases in colonocytes and immune cells [26]. This leads to hyperacetylation of histones which further results in down regulation of pro-inflammatory cytokines (IL-6 and IL-12) in colonic macrophages which accounts for their anti-inflammatory effect [27]. Additionally, histone H3 acetylation in the promoter and enhancer region of Forkhead box P3 (FOXP3), leads to increased expression of FOXP3 and hence differentiation of regulatory T cells [28]. These SCFAs can also exert indirect effects by stimulating G protein-coupled receptors (GPCRs) on the surface of colonocytes and immune cells [28]. Hence, both Histone deacetylases (HDAC) inhibition and GPCR signaling results in an increase in total colonic regulatory T cell (cTReg) number and the production of anti-inflammatory Interleukin-10 (IL-10) and Transforming Growth Factor-β (TGFβ). In addition, HDAC inhibition is also thought to promote apoptosis of CRC cells [29]. Hence, butyrate is shown to prevent carcinogenesis by its anti-inflammatory and anti-apoptotic effect. Butyrate also assists the assembly of tight junctions by the activation of AMPK and thereby promotes the intestinal barrier function [30]. SCFAs lower the pH of colonic lumen resulting in various effects. This lower pH decreases the carcinogenic activity of secondary bile acids and the bacterial enzyme 7-α-dehydroxylase which converts primary to secondary bile acids. Since the solubility of calcium also increases at lower pH, higher concentration is available for binding with bile acids. As a result it has been seen that lower fecal pH is associated with lower risk of colon cancer [31].

2. Dietary Fibers

[Table/Fig-3] shows the role of dietary fibers in protection against CRC. The bacterial anaerobic fermentation of dietary fibers converts them into SCFAs, mainly acetate, propionate, butyrate and gases like hydrogen, carbon dioxide, methane, and hydrogen sulphide [32]. Most fermentation occurs in the proximal large bowel and the luminal environment where the pH turns acidic due to increased formation of SCFAs [33]. Apart from indirect benefit of generating SCFA, dietary fibers have many direct advantages. The undigested fibers bind to carcinogens and hence are eliminated through feces [34]. Dietary fibers increase the bulk of feces and results in shorter transit times with minimal interaction between carcinogens and mucosal cells [35]. As the bulk of the colon content increases, it also results in dilution of carcinogens which serves as another added benefit [36].



[Table/Fig-3]: Role of dietary fibers in protection against colorectal cancer.

3. Phytochemicals

Present as glycosides in the large intestine where it is transformed by gut microbiota. These newly formed metabolites inhibit pro-inflammatory mediators like TNF-α, NF-κβ and prostanoids and thereby contribute to healthy gut environment [37].

DETRIMENTAL METABOLITES

1. Nitrogenous Products

In high protein diets, nitrogenous products produced by fermentation of protein in colon can cause deleterious effects in the gut environment [38]. These compounds are formed endogenously via acid-driven nitrosation of amines in the stomach and microbial fermentation in the intestine [39]. It is suggested that the nitro reductases and nitrate reductases that catalyse nitrosation reactions are encoded by proteobacteria. The nitrogenous products which can be formed are branched-chain fatty acids, phenylacetic acid and N-nitroso compounds (NOCs) [40]. NOCs exert carcinogenic effects via DNA alkylation that causes mutations and leads to cancer [41].

2. Polyamines

Polyamines (putrescine, spermidine and spermine) synthesised by the gut bacteria and the host cells, are involved in the maintenance of the structural integrity of membranes and nucleic acids, gene regulation and translation [42,43]. Certain gut bacteria (such as enterotoxigenic *Bacteroides fragilis*) also upregulate polyamine production by host cells thus leading to high levels of polyamines [44]. The polyamine catabolism can lead to oxidative stress which is further associated development of cancer.

3. Hydrogen Sulphide

Studies suggest that by-products of metabolism of dietary proteins (suphur containing amino acids and taurine) such as hydrogen sulphide produced by sulfate reducing bacteria can be carcinogenic to the gut mucosa due to its cytotoxic effects [45,46]. Moreover, it has been reported that sulphide also prevents oxidation of butyrate, and is genotoxic due to ROS production [47,48]. Any modification of microbiota towards non-sulphate reducing bacteria (methanogenic bacteria) reduces the risk for colon carcinoma.

4. Bile Acids

High-fat diet lead to an increase in bile secretion, and increased fecal bile acid concentrations and are associated with the higher incidence of CRC [49]. When diet supplemented with deoxycholic acid is fed to rats, a decrease in the production of SCFAs along

with major changes in the composition of the gut microflora was observed [50].

The primary bile acids cholic acid and chenodeoxycholic acid are produced in the liver from cholesterol, are conjugated to glycine or taurine (which render the bile acids more hydrophilic) and are excreted into the duodenum to facilitate fat digestion. Majority of the primary bile acids are reabsorbed in the terminal ileum for enterohepatic circulation. However, the fraction of bile acid (approximately 5% of the total pool) which skips enterohepatic circulation undergoes extensive transformation by the microbiota in the large intestine [51]. Bacterial strains and the methanogenic archaea have bile salt hydrolases which cleave glycine and taurine residues from the primary bile acids along with dehydrogenation and dehydroxylations converting them into secondary bile acids (deoxycholic acid and lithocholic acid) [52].

Bile acids have strong antimicrobial activities due to their amphipathic properties. They can damage bacterial cell membranes and are likely to modify the composition of the gut microbiota. Owing to the production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) that causes DNA damage, bile acids have been implicated in carcinogenesis of the intestinal tract [53]. Secondary bile acids can promote carcinogenesis by various mechanisms. They are more hydrophobic and thus more potent at disrupting cell membranes. This leads to the generation of ROS via the activation of membrane-associated proteins such as NADPH oxidases and phospholipase A2 [54]. They can also induce NF-kB activation in intestinal epithelial cells and trigger proinflammatory cascade [55]. In-vitro studies indicate that their long term exposure can induce carcinogenesis by decreasing apoptosis and enhancing epithelial cell proliferation [49]. Thus, it can be postulated that both primary and secondary bile acids have potential as therapeutic targets for alleviating inflammation which promotes carcinogenesis.

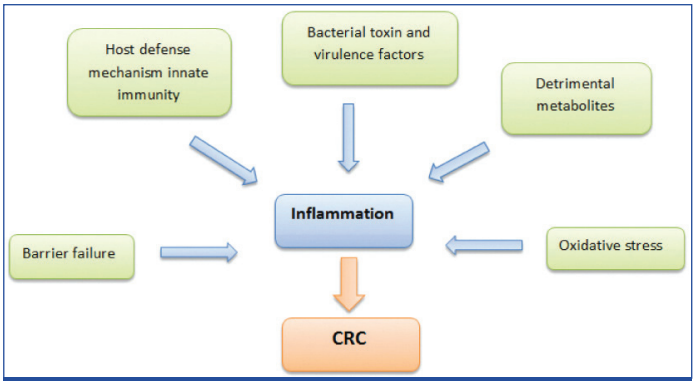
Various other factors have also been implicated in linking high fat diet to CRC. In 2012, Devkota S et al., reported that taurine conjugation of primary bile acids increases due to high fat diet [56]. This increases the growth of sulphur reducing bacterium *Bilophila wadsworthia* that further promotes inflammation [57]. Furthermore, it has been observed that *Clostridium, Ruminococcus* can convert chenodeoxycholic acid (primary bile acid) into ursodeoxycholic acid which can have beneficial effects in humans [58]. However, in the presence of 7b-dehydroxylase enzyme, the given strain can also convert ursodeoxycholic acid to the potentially toxic lithocholic acid. Further studies are required to validate microbe-based bile acid metabolism approach for CRC prophylaxis, and identifying the bacterium which can form ursodeoxycholic acid.

5. Ethanol (Alcohol)

Excessive consumption of ethanol is considered to be an important risk factor for several cancers [59]. Microbial metabolism may contribute to its toxicity, especially in the upper gastrointestinal tract. Acetaldehyde, a product of ethanol oxidation produced by microbial metabolism can cause DNA damage and degradation of the vitamin folate and is highly toxic and carcinogenic [60,61].

MICROBIOTA AND INFLAMMATION

[Table/Fig-4] shows the determinants of inflammation and their role in colorectal carcinogenesis. The colonic mucosa is constantly exposed to the gut microbiota and its metabolites with potential to cause chronic low-grade inflammation [62]. Therefore, the role of microbiota in aetiopathogenesis of CRC becomes important as chronic inflammation is a risk factor for CRC [63]. It is seen that germ-free *ApcMin* (mice having mutation in one copy of the tumour suppressor gene *Apc*) exhibit a two-fold reduction in small intestinal adenomas compared with *ApcMin* mice with normal microbiota composition [64]. This highlights the role of microbiota in triggering inflammation.



[Table/Fig-4]: Determinants of inflammation and its role in colorectal carcinogenesis.

The role of microbiota in inflammation is also underscored by the fact that altered Toll-Like Receptor-4 (TLR4) signaling is associated with CRC progression [65]. TLR4 is type of PRRs (Pattern Recognition Receptors) present in host that recognises Microorganism-Associated Molecular Patterns (MAMPs) such as Lipopolysaccharides (LPS), nucleic acids elicits an inflammatory response [66].

One of the most pertinent mechanisms for microbial tumourigenesis is loss of barrier function in the colonic epithelium leading to enhanced microbiota-host interactions. The initial activation of β-catenin and mutation of the *APC* gene in colorectal tumourigenesis may result in a loss of barrier function in the colonic epithelium leading to translocation of microbial products into the tumour microenvironment and colonisation of invasive-adherent bacteria at neoplastic sites [67]. Barrier failure can result from primary defects in genes that encode proteins that are essential to maintain a functional barrier, or from secondary defects owing to infection, inflammation and carcinogenesis. Ulcerative colitis is also associated with defects in intestinal barrier which predisposes the affected individuals to increased risk of cancer [68]. This underlines the importance of barrier permeability in carcinogenesis and inflammation.

Fusobacterium nucleatum

High incidence of gram negative anerobe in adenoma implicates its role in tumour growth initiation and aetiopathogenesis of CRC [69]. Studies suggest that its role in commencing carcinogenesis can be attributed to binding of its FadA antigen with the E-cadherin on colonocytes leading to activation of Wnt/β-catenin pathway [70,71]. This leads to uncontrolled cell division, loss of cell polarity and MSI tumour phenotype. It has also be known to bestow chemotherapeutic resistance by stimulating TLR-4 signaling and triggering autophagy by modulating regulatory microRNA [72]. *Fusobacterium nucleatum* is the most widespread strain associated with CRC and is associated with initiation, severity and modulating chemotherapeutic responses of the tumour [72].

Escherichia coli

E. coli is the most common cultivable, gram-negative, aero-anaerobic commensal gut bacteria. It has four different phylogroups depending on the presence of virulence factors. Out of them B2 and D are pathogenic and are involved in various diseases [73]. These strains synthesise several toxins called cyclomodulins such as Cytolethal Distending Toxins (CDT), Cytotoxic Necrotising Factor (CNF), cycle inhibiting factor, and colibactin [74]. Cyclomodulins are genotoxic and/or modulate cell-cycle progression, proliferation, cell differentiation, and apoptosis [75]. Colibactin, a hybrid polyketide nonribosomal peptide encoded by the pks genomic island can induce DNA double-strand breaks in the host cell and thereby activate DNA damage signalling cascades [76]. This can further lead to chronic mitotic and chromosomal aberrations as well as an increased frequency of gene mutation [77].

Enterotoxigenic *Bacteroides fragilis*

Enterotoxigenic Bacteroides fragilis is also implicated in intestinal carcinogenesis [78]. It is anerobic bacteria constituting 1% of gut microbiota [79]. It has two subtypes nontoxigenic and enterotoxigenic. The enterotoxigenic type is associated with production of BFT toxin that induces Spermine Oxidase (SPO) generating ROS which leads to DNA damage in intestinal epithelial cells [80,81].

Recent Updates

Li Shizhen gave the notion of using yellow soup (containing fecal matter) to treat abdominal diseases originated in China. Currently, Fecal Microbiota Transplantation (FMT) has become recognised and has shown promising results for treating patients with recurrent *Clostridium difficile* infection [82]. Few studies on patients with ulcerative colitis, have shown promising results, but its efficacy for treatment for Inflammatory Bowel Disease (IBD) remains unclear [83,84]. Although various studies have been conducted on investigating the role of FMT in patients with IBS, Hepatic Encephalopathy (HE), Metabolic syndrome, Autism, Graft Versus Host Disease (GVHD), no conclusive results have been obtained [85-88]. In 2017, Zhou YJ et al., showed that intestinal microflora belonging to phyla such as Actinobacteria, Proteobacteria and Firmicutes have anticarcinogenic effect against solid tumours and leukaemia [89]. In 2016, Hu Y et al., illustrated the role of resistant starch as protective agent against colitis associated with CRC in rodent model [90].

CONCLUSION

The role of the microbiota in CRC has become quite blatant and thereby delineates a new approach aimed at ameliorating the therapeutic management of patients with CRC. It is seen that the advancement to CRC is influenced by the metabolic output of the microbiota. These protective and detrimental metabolites can significantly influence gut microenvironment through the specific interactions at the mucosal level. Therefore, the diverse and healthy microbiota is essential in establishing stable and healthy gut microbiome and preventing dysbiosis characterised by a reduction in microbial diversity. The dietary manipulation has the ability to modify microbiome composition and offer desired benefits. Therefore, there is a need for identifying, analysing and assessing such strains for their long term effect on the health of the individual. There are many challenges which need to be addressed like the diagnostic efficacy of fecal microbiome is questionable as it mirrors the intraluminal microbiome and not mucosal microbiome. Moreover there are differences in the results of the numerous studies analysing the gut microbiome making standardisation of microbiota signature associated with colorectal carcinoma even more difficult. In addition to this, greater than 80% of our gut inhabitants are not cultivable. It thus becomes important to explore new molecular methods to characterise the microbial ecology, physiology and functional capacity.

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