



Role of Gut Microbiota in Colorectal Cancer

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Editorial

Colorectal cancer (CRC), an age-related malignancy whose incidence increases markedly after the age of 50 years, is the third most common cancer worldwide and shows significant variations in the distribution globally [1,2]. More than 1.2 million new cases of colorectal cancer (CRC) are reported each year, most of which (~85%) occur sporadically as a result of the accumulation of mutations and epigenetic modifications in several genes [3]. Incidence of CRC is found to vary markedly worldwide, with 4.1 cases per 100,000 males in India to 59.1 cases in Czech Republic. While among females, it ranges from 3.6 in India to 39.5 in New Zealand [1]. Some of the risk factors for colorectal cancers include obesity, a diet low in fruits and vegetables, physical inactivity and smoking [4]. There has been a decrease in the CRC mortality worldwide whereas the incidences are on the rise [1]. The decline in CRC deaths is attributed to an advanced diagnostic and prognostic technology, while, the “Westernized” life style in developing countries as well as improved longevity in developed countries, contributes to a greater incidence of CRC [1]. A better understanding of the environmental and other factor(s) that may be responsible for the increased incidence of CRC is crucial for developing preventive strategies.

CRC is a multi-step process resulting from accumulation of mutations during progression from normal epithelium to carcinoma. Genetic changes that occur at different stages of epithelial cell carcinoma have been extensively studied by Fearon and Vogelstein in human colon cancer [5], and have been reviewed by others. Briefly, two models have been proposed to explain the occurrence of CRC. One model states that the initial step begins with somatic mutations in adenomatous polyposis coli (APC) gene, which is considered as the initiating step of transforming the normal mucosa to an adenoma (class I) by hyper-proliferation [6]. The hyper-proliferation is brought about by accumulation of β -catenin that in turn enters the nucleus to trigger cell cycle [7]. The next step involved is the activation of K-ras, which is a proto-oncogene that results in the transformation of an early adenoma to an intermediate adenoma (class II adenoma) [6]. The third step is the loss of function gene- deleted in colorectal cancer (DCC) gene on chromosome 18q resulting in the formation of a class III adenoma [7]. The last step is the mutations in *p53* gene that finally transforms an adenoma into an invasive/early cancer [6]. It is predicted that the above 4 steps take approximately 10 years and hence a 10 years interval was selected as the screening interval for colonoscopies in people with normal colonic mucosa at initial colonoscopy [7]. The second CRC model is based on “Microsatellite Instability” that causes mutations in DNA mismatch repair genes leading to accumulation of uncorrected replication errors resulting in hyper proliferation and eventually carcinoma [7].

It is becoming increasingly evident that the human intestinal microbiota may contribute to the etiology of CRC [3]. The human colon harbors a complex microbial flora. Bacterial density in human colon is among the highest found in nature, approaching 10^{12} bacteria/gm wet weight of feces. Given the sheer vastness of our microflora and numerous arrays of species, interactions, and metabolites produced, bacteria are likely pivotal players in several gastrointestinal diseases including CRC [8-10]. Predominant bacterial phyla associated with adenomas and CRC are Bacteroidetes and Firmicutes (family *Lachnospiraceae* including *Clostridium*, *Ruminococcus* and *Butyrivibrio*) [11]. These two phyla also contribute to 95% of the total GI ecosystem [12]. One of the primary roles of gut bacteria is to participate in biotransformation of products in the gut, which among others include bile acids secreted from the liver, as depicted in Figure 1.

Primary bile acids are synthesized from cholesterol in hepatocytes via cholesterol 7- α -hydroxylase. In the large intestine, they are deconjugated by 7- α -dehydroxylation by enteric bacteria to form the secondary bile acids. Among the secondary bile acids deoxycholic acid (DCA) and lithocholic acid

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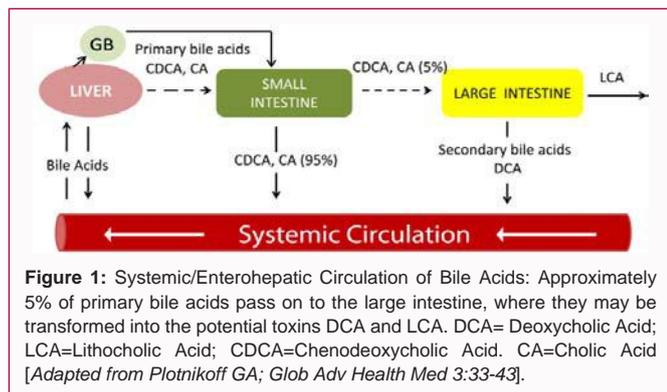
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(LCA), are thought to be most notorious for their co-carcinogenic activity [13-15] and considered to be most significant with respect to the development of CRC [16-18]. In support of this postulation, others have reported that cholecystectomy, which increases bile acids in the colon, leads to advanced colon adenomas and CRC [19-22]. Our published and unpublished observations also suggest a role for gut microbiome and their metabolites, the bile acids, specifically DCA and LCA in promoting colon carcinogenesis. We have observed that African Americans, who are known to have a higher incidence of CRC than Caucasian Americans [23,24], also show a significant increase in the number of adenomas [25]. These increases are associated with a concomitant rise in pro-inflammatory *Fusobacterium nucleatum*, *Enterobacterium* and *clostridium*, which are associated with CRC [26,27] and the levels of DCA and LCA as well as self-renewing, chemo-resistant, pluripotent cancer stem cells ([25] and unpublished observations). Latter are known to play a pivotal role in the development and progression of many malignancies, including CRC [28,29]. We also observed that both DCA and LCA enhanced cancer stem cells in colonic mucosal cells (unpublished observations).

Further support for DCA and LCA-induction of colon carcinogenesis comes from *in vitro* cell culture and *in vivo* animal experiments. Data from several *in vitro* and *in vivo* studies revealed that exposure of normal colonic epithelial cells to DCA caused mitotic aberrations that are known to be precursors of aneuploidy and are indicators of genome instability [16,17]. Studies with rats have demonstrated that administration of bile acids, specifically DCA greatly enhanced the incidence of tumors when a potent carcinogen was also administered [13], indicating tumor promoter activity of bile acids.

Clearly, these and other studies suggest that intestinal microbiota contributes to the etiology of colorectal cancer via the pro-carcinogenic activities of specific pathogens. Further studies are undoubtedly needed to determine the precise role of different microbiota in the colon in the development of progression of colorectal cancer.

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