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Review

The intricate connection between diet, microbiota, and cancer: A jigsaw puzzle

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ABSTRACT

The microbial community has a decisive role in determining our health and disease susceptibility. Presumably, this is closely associated with the complex community network of bacteria, fungi, archaea and viruses that reside our guts. This dynamic ecosystem exists in a symbiotic relationship with its host and plays a fundamental role in the hosts' physiological functions. The microbial community is highly personalized and therefore exhibits a high degree of inter-individual variability, which is dependent on host specifics such as genetic background, physiology and lifestyle. Although the gut microbiota is shaped early on during birth, there are several factors that affect the composition of microbiota during childhood and adulthood. Among them diet appears to be a consistent and prominent one. The metabolic activity of bacteria affects food digestion, absorption, energy production, and immunity. Thus, definition of the microbiota composition and functional profiles in response to a particular diet may lead to critical information on the direct and indirect role/use of the bacterial community during health and disease. In this review, I discuss gut microbiota and its potential link to cancer with specific emphasis on metabolism and diet.

1. Introduction

Due to improvements in high-throughput DNA sequencing and proteomic approaches, our current knowledge on taxonomical and functional role of bacterial community in the gut is exploding. From a quantitative point of view that gut metagenome exceeds the number of genes in host genome [1,2] to a functional view that microorganisms help develop/maintain mucosal immunity and regulate metabolism [3] microbiota certainly stand at the cross-roads of health and disease.

Initial colonization in newborns is shaped by the maternal microbiota [4]. This indeed plays a critical role in driving the early postnatal development of innate immunity [5]. Gestational colonization of mothers can increase intestinal group 3 innate lymphoid cells and F4/$80^{+}CD11c^{+}$ mononuclear cells in newborns, which provides an advantage against overt inflammatory responses to microbial molecules and invading bacteria [4]. Maturation of the infant's bacterial community takes place within the first 6 weeks of life, undergoing substantial changes primarily driven by the body sites but not the mode of delivery [6]. Further changes in microbiota include shift from lactate metabolism to short-chain fatty acid (SCFA) production and carbohydrate metabolism towards the later stages of life during aging [7].

Germ-free (GF) mice show deficits in both innate and adaptive components of the gut mucosal immune system. This underscores the pivotal role for colonisation of commensal bacteria in establishing a proper immune response [8,9]. Indeed, re-colonisation can partially correct some immune defects although a brief GF neonatal period can induce persistent immunological deficits [5]. This strongly suggests that establishment of a specific bacterial community within the early developmental stage is critical for development of a proper host immunity in adulthood.

In contrast to the strict stability of the host genome, the gut metagenome appears more prone to plasticity as it may have to acclimate and adapt in response to host physiology and environmental changes [10,11]. Among the environmental cues that can directly regulate the bacterial community in the gut, nutrition plays a pivotal role. Diet is vital but excess intake or imbalanced micro- and macronutrients can impose deleterious effects [12]. Indeed, interaction of genetic factors with environmental cues leads to extensive changes in the gut microbial community and the metagenomic plasticity [13]. Given the distinct shifts in climate, agriculture and changes in crops, food may have a decisive role in aggravating disease in the near future.

Microbiota seem to contain traits that can be transmitted. A good

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example for it is malnutrition, which impairs the development of gut microbiota in children. Indeed, the transfer of microbiota from healthy infants and children or undernourished donors to young GF mice fed with the specific relevant diet revealed that the immature microbiota transmit altered growth phenotypes [14,15]. Apparently, this is reversible and preclinical models show sialylated bovine milk oligosaccharides (S-BMO) can promote growth in a microbiota-dependent manner [16]. Although on one hand these studies imply that the maturity of microbiota is directly associated with nutrition and that phenotypic traits can be transferred, on the other hand they offer great potential for therapeutic interventions. Whether these traits are accomplished by direct contact with other strains to shape a specific colonization pattern or by direct release of bacterial products is of great interest [17,18].

While providing multiple functions, microbiota interact with the host organism via direct contact through surface antigens or via soluble molecules, which are produced by the microbial metabolism. Gut microbiota play a critical role in the production of active catecholamines [19], regulating serotonin biosynthesis, a brain neurotransmitter with potent functions on enterocytes, immune cells and enteric neurons [20], or butyrate biosynthesis, a SCFA that can act on histones [21]. These studies provide evidence that bacterial metabolites may indeed be the main hub for communication between the gut and extra-intestinal organs. Even though far from their site of production, bacterial metabolites can employ dramatic changes providing an important means of microbiome-host interactions [22]. This is in good agreement with the notion that dysbiotic microbiota is closely associated with a plethora of diseases. There is a significant link between autoimmune diseases such as multiple sclerosis, type I diabetes, and rheumatoid arthritis, respiratory diseases, allergies, and metabolic disorders with gut dysbiosis [23–29]. Alterations in gut microbiota are also implicated in the onset or progression of neurological diseases such as autism, pain, depression, anxiety, and stroke [30–35].

Under physiological conditions, intestinal microbiota cannot enter liver, spleen, brain, or other peripheral tissues. This line of defence is achieved through a gut-vascular barrier that controls translocation of antigens into circulation and inhibits the dissemination of bacteria [36]. Dysbiosis is often caused by antibiotic use, stress, or gastrointestinal dysfunction [9,37]. It can lead to bacterial translocation due to an impaired barrier function enabling bacteria to migrate from the intestinal lumen to extra-intestinal sites [9,37]. Strikingly, microbiota have been shown to play a causative role in NAFLD, Alzheimer's disease, cardio-vascular dysfunction or cancer of various tissues. This highlights the existence and great importance of communication circuits or messengers that act on the gut-liver, gut-brain or gut-muscle axis. Indeed, the critical need for keeping the barrier integrity is best described by those studies that show barrier dysfunction results in the invasion of body sites by the microbial products, which can lead to inflammation and trigger disease development [38–40]. Moreover, the important aspect of keeping the barrier intact is further hampered by the knowledge that both food restriction/deprivation and obesity can employ deleterious effects on the intestinal barrier function [41,42]. Future studies on the potential regulatory functions of food will delineate whether barrier defects play a causative role in disease development in extra-intestinal tissues and if they could be re-modulated to promote health.

2. Microbiota and the cancer link

Our current knowledge on the link between microbiota and cancer is mostly derived from intestinal tumor models in mice that suggest a causal role for bacterial diversity and community changes [43–45]. Consistent with these, studies on patients with colorectal cancer (CRC) and polyposis show dysbiosis or an altered diversity of microbiota [46–49], supporting the rationale to search for tumor-promoting and tumor-protective species.

Bacterial species with low abundance, such as enterotoxigenic *Bacteroides fragilis*, are suggested to exert unique virulence traits, which can confer pro-tumorigenic properties [50,51]. These can indeed alter the microbiome and thereby promote mucosal immune responses in the colonic epithelium. According to the driver-passenger model of CRC, intestinal bacteria (driver) may comprise the first hit that drive DNA damage contributing to CRC initiation [52]. Alternatively, tumorigenesis itself can induce alterations in the intestinal niche that may favour the proliferation of opportunistic bacteria (passenger) [53,54]. Importantly, CRC patients have an increased enrichment of opportunistic pathogens and Gram-negative anaerobic bacteria [55]. Patients with colonic adenomas demonstrate an increased bacterial diversity and richness with altered abundance of mucosal Proteobacteria and of Bacteroidetes when compared to healthy controls [56], which may be associated with changes in defensin expression [57].

Currently, the critical role of microbiota in CRC is based on analysis of only a small subset of patients, which is further hampered by heterogeneity in sampling and limited data on tumor phenotype, genetic background and lifestyle habits. Despite this, specific species such as *Streptococcus gallolyticus*, *Enterococcus faecalis* and *Bacteroides fragilis*, have been consistently and positively correlated with CRC [58]. Furthermore, *Escherichia coli* is also found to be overexpressed in the mucosa of CRC patients, which has a potential role in M cell translocation, angiogenesis and genotoxicity [59]. Moreover, *Fusobacterium nucleatum* is found abundantly in the stool of CRC patients. Through its FadA adhesin, *F. nucleatum* can invade human epithelial cells, thereby inducing an inflammatory response and targeting stem-progenitor cells [60]. Bacterial proteins such as AvrA, a pathogenic product of *Salmonella*, has been shown to activate β-catenin signaling in the colon and thereby impact tumorigenesis (R. [61].

In addition to the above-mentioned mechanisms, yet another mode of action of microbiota is achieved through its metabolic activity/functions. The interaction between diet (World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. http://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdfhttp://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf, 2007) and microbiota plays a significant role in the etiology of CRC [62,63]. Among the metabolites, the metabolism of fibres is a critical one. A significant reduction in butyrate levels has been closely associated with tumorigenesis in a mouse model with oncogenic K-ras activation [44]. This has been shown to be valid for CRC as metagenomic analyses show a consistent reduction of butyrate-producers in these patients [49,55]. Butyrate is a potent metabolite because it plays a critical role in regulatory T-cell homeostasis [64,65], regulates energy metabolism [66,67], and it can inhibit histone deacetylase [68]. However, the controversy over butyrate and its potential in cancer preventive intervention [21] still remains as there are studies that suggest it can expose pro-tumorigenic effects [69,70].

Similarly to the data in mouse models [44], there is now sufficient evidence to suggest that the host genotype interacts with diet to alter the diversity and function of the microbiota in the human gut [71]. Therefore, it is highly likely that individuals with a genetic predisposition to CRC may have an altered microbiome that is determined by their genetic makeup and dietary habits. This is quite evident in the African American population, whose colons are dominated by *Bacteroides*, meanwhile *Prevotella* appear to be more abundant in Africans [72]. African Americans who display a higher risk of CRC may have evolved a CRC-microbiota shaped by their dietary habits and environmental cues. Indeed, this study shows the rates of mucosal proliferation and colonic mucosal inflammation could be reduced within 2 weeks of a dietary intervention by switching the fat and fiber proportions. This leads to alterations in saccharolytic fermentation, butyrate production and suppression of secondary bile acid synthesis. An animal-source diet increases the abundance of bile-tolerant microorganisms (Alistipes, Bilophila and Bacteroides) and decreases the levels of Firmicutes that