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The Human Microbiome and Cancer

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ABSTRACT

Since the turn of the century, the human microbiome has garnered significant interest from biologists, engineers, mathematicians, computer scientists, medical professionals, clinicians, the food industry, and the pharmaceutical industry. It is now widely understood that the human microbiome is far more diverse than we envisioned in the 17th century when microorganisms were isolated, viewed, and documented with a simple microscope. Recent seminal studies using next-generation molecular technologies and computation strategies have demonstrated a strong association between the human microbiome on human health and disease. This review explores the effects of the human microbiome on human cancers such as breast, colorectal, and liver cancer. Identification of localized microbiomes may serve as an early-warning biological detection system to aid in diagnosing human cancer. Tissue-specific microbiomes synthesize, secrete, and metabolize various host and microbial products that impact the growth or suppression of microorganisms and modify tumor development, cancer progression, immunological profiles, and responses to treatment strategies. Future review articles will survey the contribution of the human microbiome to other human carcinomas.

Keywords: Cancer; Microbiome; Diagnostics; Biomarker; Tumor

Introduction

The relationship between microorganisms and complex eukaryotic organisms has evolved for millions of years [1]. According to the endosymbiotic theory, bacteria with rudimentary bioenergetic systems occupied early eukaryotic animal and plant ancestors and, in turn, provided seminal eukaryotic cells with beneficial cellular machinery and an advantageous molecular arsenal that enhanced the viability and survival of unicellular and multicellular organisms [2,3]. Centuries of natural selection mechanisms at the microscopic level have produced a homeostatic balance between man and microbes that allows the perpetuation of the human species. As microbiology continues to advance and synergistic concomitant breakthroughs in closely related fields such as molecular biology and computational biology occur, our understanding of the diversity and functional attributes of microorganisms associated with human internal and external tissue also continues to grow exponentially each year. Data indicates a delicate balance of microbial symbiotic populations in humans. An imbalance in the numbers and types of microorganisms in an individual's normal microbiota at specific tissue sites can produce adverse or unhealthy outcomes. Dysbiosis drives human diseases such as cancer and modifies healthy immune profiles [4-6].

The human microbiome possesses thousands of microbial genes and proteins that modify normal human biological processes locally and systemically in ways that are not entirely understood. While the interaction between human molecules, metabolites, enzymes, biochemical reactions, and microbiome metabolic machinery may be beneficial to the host, it is worth noting that host-microbe molecular interactions are also capable of producing deleterious effects on specific human organs in incalculable ways, leading to human cancer [7,8]. Moreover, the effects on one individual may be different in another individual due to genetic factors, lifestyle, and environmental factors. Additionally, host-microbe molecular interactions are difficult to predict because it is known that individuals contain a unique set of microorganisms. The Human Microbiome Project funded by the National Institutes of Health and subsequent human microbiome projects that would soon follow demonstrated a strong and statistically significant correlation between microbial diversity and human morbidity and mortality [9,10]. It will take many more investigations and potentially novel molecular approaches to transition from correlation to causality. As previously mentioned, due to the complex nature of the microbiome, microbiome functions, and a staggering number of human factors that mediate health and disease, causality is an idealis-

tic goal that may differ from patient to patient. The following sections of this brief review article analyze previous work performed by other scientists interested in better understanding how microorganisms contribute to breast, colorectal, and liver cancer.

Microbiome: Breast Cancer

Parida and Sharma [11] provided strong support specifying how the human microbiome contributes to the development of breast cancer. Their review article documented many studies showing that human microbiomes employ various metabolic strategies to synthesize compounds analogous to estrogen. This steroid hormone plays a role in the development of female features and the development of breast cancer [12]. The previous article addressed how microbiome-mediated metabolic conversions facilitated by microorganisms located in the gastrointestinal tract affected breast cancer development. Many examples in the literature report on how the intracellular microbiome of various tumors, in which microbes symbiotically associate with specific tissues, can lead to abnormal tissue proliferation and enhanced metastatic potential [13]. In one such report, investigators employed the mouse breast cancer model MMTV-PyMT. They found that growth cessation of intratumor bacteria suppressed metastatic activity but had no discernible effect on the growth of the tumor itself [14]. Tzeng et al. [15] compared healthy human breast tissue microbiomes and breast cancer-related tissue samples using 16s rRNA gene sequencing and bioinformatics protocols. They noticed significant differences between the microbial populations of the experimental and control samples. Specifically, using the described protocols, Anaerococcus, Caulobacter, and Streptococcus were more prevalent in healthy than breast cancer tissue, indicating that these taxonomic groups may play critical roles in tumorigenesis.

Li et al. [16] elucidated the effects of anti-PD-1, a monoclonal breast cancer immunotherapy technique, on the gut microbiome in combination with fucoidan, a complex carbohydrate found in algal species. They discovered that fucoidan altered the gut microbiome to promote higher efficacy of the anti-PD-1 breast cancer treatment. Fucoidan and anti-PD-1 increased the levels of short-chain fatty acids (SCFAs) and beneficial bacteria (e.g., Bifidobacterium, Faecalibaculum, and Lactobacillus) and T cell populations with anti-tumor properties. Their study reinforces the notion that gut microbiome can serve as a biomarker not only for breast cancer diagnosis and prognosis but also as a biomarker for the potential clinical outcome of specific breast cancer treatments. This study, coupled with nutrigenomics, a subdiscipline of genomics that explores how food sources impact human and microbial gene expression, will further expand how clinicians evaluate the efficacy of anti-cancer treatment strategies [17]. Terrisse et al. [18] conducted shotgun genomics on the fecal microbiome to demonstrate that the human microbiome diversity differs in breast cancer patients and that these differences produce adverse post-treatment side effects in breast cancer patients. These findings suggest that the identification of overabundant taxa could serve as an effective biomarker in breast cancer.

Microbiome: Colorectal Cancer

Colorectal cancer is also associated with detectable changes in the gut microbiome [19]. Consumption of nutrients has been shown in clinical studies to initiate the proliferation of bacterial populations that promote colorectal carcinoma [20]. These studies indicate that specific diets could be highly productive in dealing with colon cancer and other human carcinomas. Previous and ongoing studies are deciphering how intestinal microbes, immune cells, host cytokines, and microbe metabolites contribute to inflammation in the colon [21]. These findings suggest that future colon cancer treatment strategies may involve the suppression of specific microorganisms that produce or support the infusion of pro-inflammatory molecules in the colon. Alternatively, clinical methods to boost anti-inflammatory cytokines in the tumor microenvironment could reduce or eliminate colonic tissue degradation and avert tumor progression. Since the gut microbiome differs for different individuals and patients, it is unclear if some diets mentioned above, and molecular suppression strategies would be successful for each patient. It seems more likely that medical professionals and clinicians would succeed tremendously in pursuing personalized microbiome-based colon cancer amelioration strategies. Corroborating evidence that the gut flora and microbial products (e.g., metabolites, enzymes) are associated with the development and progression of colorectal cancer is provided by a recent experiment using metagenomic and metabolomic methods that showed that it is possible to establish a statistically valid classification scheme linking microtypes and microbial products to specific stages of colorectal cancer development (e.g., early-onset versus late-onset). Specifically, Kong et al. [22] showed that late-onset colorectal cancer is associated with increases in Fusobacterium nucleatum and decreases in SFAs and gamma-aminobutyric-acid (GABA) anabolism.

It was also demonstrated that early-onset colorectal cancer is associated with increases in Flavonifractor plauti, tryptophan, and choline metabolism. These types of studies have enormous value and are sure to change the way human cancers are diagnosed and treated. Yearly cancer statistics indicate that men are at higher risk of contracting and dying from colorectal cancer compared to women. A recent study implicated the male gut microbiome as a leading agent in the disparity in incidence and death rates between men and women. Wang et al. [23] used mouse models to show that sexual differences in colorectal cancer can be attributed to differences in microbial communities, and in particular higher levels of Akkermansia muciniphila and lower levels of Parabacteroides goldsteiniias, as well as differences in microbe tumor-promoting metabolites in men and women.

Microbiome: Liver Cancer

Liver cancer, also designated hepatocellular carcinoma (HCC), is a devasting disease that is the culprit for a substantial number of cancer-related deaths worldwide. Typically, individuals suffering from

this highly fatal disease are also afflicted with some persistent inflammatory liver disease. The latest information points to the human microbiome as a causative agent in the initiation and progression of liver cancer and liver disease [24].

While it is not clear if liver disease causes bacterial dysbiosis or if bacterial dysbiosis causes liver disease, there is an evidence-based connection between the human microbiome and hepatocellular carcinoma. Critical bacterial species and microbial molecules influence HCC and tumor size [25]. Studies using animal models have shown that liver physiology improves following healthy adjustments to the gut microbiome. Chen et al. [26] conducted a research study to pinpoint better the relationship between the intestinal microbiome and liver cancer. Investigators devised a clever experiment involving a mouse model and used techniques to stimulate liver tumorigenesis in the experimental organism. Following the abrogation of the normal murine gut flora, it was demonstrated that mice in which the normal gut microbiome was disturbed enhanced tumorigenesis but had no significant effect on liver cancer progression.

Investigators showed that in addition to an increase in the tumor-promoting process in liver tissue, there was also an increase in SREBP2 (sterol regulatory element-binding protein 2) production and suppression of the tryptophan pathway in mice with diminished microbial populations, suggesting that at least SREBP2 and tryptophan intermediates play a role in liver cancer. Additionally, various techniques, such as fecal microbiota transplantation (FMT) [27], have been applied to murine models to assess the efficacy of FMT and other dietary modulation approaches to combat liver cancer. Sun et al. [28] performed fluorescent in situ hybridization experiments (FISH) experiments to decipher the relevance of microbial representation in the tumor microenvironment (TME). After comparing the intratumoral microbiome of liver cancer tissue with healthy tissue, it was determined that liver tumors have a higher percentage of the phyla Proteobacteria and Actinobacteria and that assessing the TME may serve as a biomarker and as an advantageous prognostic indicator of liver cancer following surgical procedures.

Conclusion

Microorganisms occupying the human body play known and yet unknown roles in the development and progression of human cancers. Based on the comprehension that microbes possess a unique and exciting enzymatic constituency that is not present in the human genome, there exists an unlimited number of strategies that microbes can employ to alter human molecules to produce molecular mediators of unregulated tissue growth. It is accepted that in healthy individuals, microbial partners protect humans from cancer development by resulting in the degradation of harmful oncogenic agents. Alternatively, it is known than certain microbial species contribute to cancer formation and progression following a drastic change in the microbial landscape that may follow antibiotic usage, alcohol consumption, unfavorable lifestyles, or pathogenic infection.

Data from numerous studies indicate that the microbiome can stimulate the environment for tumor development and cancer initiation by synthesizing cancer-promoting molecules, modulating the human immune system, degrading cancer-suppressing substances, modifying benign cellular products into harmful substances, and altering the human response to chemotherapy and other cancer drugs. Understanding how microbial metabolism, human metabolism, and subsequent metabolic products interact with human organ systems will expand our ability to protect humans from tumor formation by designing molecular activation and inhibition processes to restore or maintain a homeostatic environment. Future literature reviews will probe essential metabolic mechanisms, signaling pathways, and oncogenic tissue changes in more detail.

Successful therapeutic interventions may also include the development of phage-based therapies using genetic engineering approaches that target bacteria known to play a role in synthesizing or modifying cancer-initiating molecules. Moreover, identifying microbe-specific molecules with antimicrobial or antitumor properties may be helpful to slow or eliminate the growth of harmful microbes. Additionally, it will be essential to determine the positive and negative contributions of the gut microbiome and tissue microbiota to patient outcomes. Based on the overall importance of the human microbiome, it may be prudent to assess the composition of microbial populations in various tissues during routine yearly physicals. Regarding diagnostic potential, specific microbial fingerprints and molecular analyses of microbial substances and metabolites may be used as an early cancer biological detection system and may explain the efficacy of cancer-based therapeutic regimens.

Moreover, the contribution and interaction of the metabolome and proteome of human cells and microorganisms is a highly understudied area that may spearhead specific personalized nutritional strategies to prevent cancer. Deciphering the immeasurable complex crosstalk mechanisms between man and microbes will take several decades. Still, it may provide critical clues to elucidate diagnostics, prognostic indicators, and treatment strategies to combat human cancer.

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