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Review Article

Promising role of Faecal Microbiota Transplantation in Cancer Management

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Abstract:

Cancer is not one disease; there may be more than 100 types, however, the causative factor that is mutation of gene is the common cause. Cancer Survives against all odds and develop strategies to evade body's immune system. Cancers can be effectively managed by treatments like chemotherapy, immunotherapy, radiotherapy, etc. However, side effects of such therapies are sometimes intolerable; more so, many a times cancers develop resistance to these therapies. Initial trails for Faecal Microbiota Transplant (FMT) therapy are promising one and suitable alternative for immunological, pharmacological and radiological therapies without any what so ever side effects.

Keywords: lipoidoproteinosis; urbach wiethe; pentoxifylline

Introduction

Cancer is a genetic disease caused by changes in the genes controlling the cell cycle due to mutation in oncogenes forcing cells grow uncontrollably and spread to other parts of the body. There are more than 100 types of cancer. Types of cancer are usually named for the organs or tissues where the cancers take its origin. Despite host immunity, tumour cells can escape antitumor immune cell responses by several different mechanisms, such as the loss of the antigen presentation capacity by some immune cells, which promotes tumour progression and resistance to immunotherapy [1; 2].

The human gut is home to a large and diverse microbial community, comprising about 1,000 bacterial species [3-7]. This group of microorganisms is a conglomeration of bacteria, fungi, protozoans and viruses; some of them are harmful and can cause infections. Many species of this group of organisms are supportive and beneficial to mankind and thus are essential for the body's well being and good health. Among these commensally residents that are expected to be present under normal circumstances do not cause disease. The gut microbes are indispensable for our survival; we wouldn't survive long without them [8]. Integrity of the gut barrier is maintained by the secretion of mucus from the goblet cells a good habitat for commensal bacteria and prevents bacterial infiltration and inflammation. In addition, these commensals aids digestion, helps with vitamin production and regulates physiological functions, including regulation of metabolism, blood production, immune enhancement, and protection against cancer [9]. These symbionts play a decisive role in the host's nutrition, immunity and metabolism. An experimental study with mouse models and brain imaging technology has given evidences for the role of intestinal microorganisms to influence the brain function and metabolism [10].

Pathogenic bacteria such as *Staphylococcus aureus*, *Escherichia coli* and *Mycobacterium tuberculosis* can cause serious infections in humans. Increasing antibiotic resistance poses a serious threat to public health inspite of these antibiotics creating a revolution in the treatment of bacterial infections. Susceptibility to infections depends on the immune system, health status; genetic factors, malnutrition, chronic diseases and age significantly impact public health, particularly through transmission in health care settings, which increases morbidity and mortality. Some people regularly take probiotics or during antibiotic treatment to support gut health. These supplements contain strains of beneficial bacteria, such as *Bifidobacteria* and *Lactobacillus.* Fermented pineapple whey protein (PWF) normalized the intestinal flora by increasing the populations of *Weissella, Lactococcus, Faecalibaculum* and *Bacteroides acidophilus* and reducing the numbers of *Akkermansia* and *Escherichia-Shigella* [11].

As long as the gut microbiota is functioning properly and maintaining a balance between pathogenic and beneficial organisms, the host physiology is maintained and protective effects are obtained. Imbalance in the gut microbiota is found to contribute to the progression of cancer by the production of harmful metabolites and cause immune dysfunction in the body.

Inflammation is a protective response essential for maintaining health and for fighting disease. The damaged cells due to inflammation release

chemicals such as, histamine, bradykinin, and prostaglandins causing blood vessels to leak fluid into the tissues, causing all the three subphases, namely, acute, subacute, and chronic (or proliferative). When living with chronic inflammation, body's inflammatory response can eventually start damaging healthy cells, tissues, and organs. Over time, this can lead to DNA damage, tissue death, and internal scarring [12]. Long-term metabolic disorders and inflammation also can lead to the development of tumours. For example, colon cancer may progress from chronic inflammation caused by dysbiosis [9].

Wealth of data gives strong evidence that gut dysbiosis or some special bacteria are the causal factors for the development of various cancers in humans. In the recent past the link between microorganisms and the development of several cancers has also been generally recognized. *Helicobacter pylori (H.pylori)*in gastric cancer, human *papillomavirus (HPV)* in cervical cancer, *hepatitis B and C viruses (HBV and HCV)* in hepatocellular carcinoma, *Enterotoxigenic Bacteroides fragilis, Streptococcus gallolyticus subsp. Gallolyticus (Sgg), Escherichia coli* (*E. coli*) *Fusobacterium nucleatum* are few examples to advocate that microbiota is not passenger or bystander [9].Their behaviour to act as our friend and foe drew the attention of the scientists in the recent past.

Special microbial pathogens in cancer

Twenty percent of total cancers worldwide are created by Human *papilloma virus, H. pylori* and *Hepatitis B virus* [13]. Tumour promoting mechanisms have been investigated mostly on cell and animal levels, including production of toxic metabolites, alteration of intestinal microenvironment and induction of tumorigenic signalling pathways. *H. Pylori* is responsible for chronic gastritis and gastric carcinogenesis by secreting virulence factors as well as activating various tumour-promoting signalling pathways [14-16]. *Enterotoxigenic Bacteroides fragilis* is observed to *induce* intestinal inflammation and DNA damage contributes to the pathogenesis of CRC by its toxin [17]. *Streptococcus gallolyticus subsp. Gallolyticus (Sgg),* a Gram-positive, opportunistic pathogen harbours in colon tumour tissue [18], pathogenic *Escherichia coli* (*E. coli*) induces tumorigenesis by its toxins including cyclomodulin [19], *Fusobacterium nucleatum* enriched in colon tumor tissues promoting proliferation and invasion ability of tumor cells in addition to cancer cell autophagy, thereby increasing chemotherapeutic drug resistance and tumor recurrence rate are few examples [20 - 22]. One very important recent finding indicates that patients with esophageal cancer also had dysbiosis of the gut microbiota (n = 10). Nevertheless, it is indispensible to maintain gut microbiome diversity for human health [23].

Collectively, a better understanding of how these special microbial pathogens elicit specific carcinogenesis may uncover valuable biomarkers for diagnosing and prognosticating cancer.

Specific metabolites produced by the gut bacteria from our diet either can promote or inhibit tumours. Short-chain fatty acid acetates, cadaverine, butyrate and propionate all inhibit inflammation and tumour development, while secondary bile acids can promote cancerous growths [9]. Animal proteins and saturated fats increases bile production, but the entry of bile into the intestine is caused by specific microbiota by producing secondary tumour-promoting bile acids [24]. On the contrary, *Clostridium perfringens*, has the capability to metabolize the dietary fibre to short-chain fatty acids and maintained normal physiological function of the intestine as well as maintain microbiota balance [25]. Butyrate, among the three most abundant short-chain fatty acids, as an energetic substance for colon cells participates in the prevention of colorectal cancer in murine model studies [26].

Our genetics and lifestyle influence the bacterial populations inhabiting the gut resulting in the differntial pattern that exists greatly between individuals. Many of our tissues and organs of the body, especially the digestive tract, are harboured with bacteria whose numbers and species are constantly changing as well. Host genetics, dietary components, drugs, chemicals, aging and stress have been shown to regulate the dynamic balance of the intra-host microbiome [27 -29]. Collectively, a better understanding of how these special microbial pathogens elicit specific carcinogenesis may uncover valuable biomarkers for diagnosing and prognosticating cancer. Despite the fact that some data have shown promising results regarding faecal microbiota transplantation (FMT) in Allogenic hematopoietic stem cell transplantation (allo-HSCT) though is still strongly limited, except for the treatment of Clostridium. *difficile* infection (CDI) prognosticating. Restoring gut microbiota diversity and maintaining its balance seem to be strongly needed in these cases which could be satisfied by fecal microbiota transplantation (FMT) [30].

CDI is responsible for the high morbidity and mortality in cancer patients as well. Alterations in the gut microbiota due to chemotherapy, frequent use of broad-spectrum of antibiotics, prolonged hospitalization, immunodepression and other factors is a common feature in patients with cancer and recurrent CDI [31]. Already effectiveness of FMT for clinical cure of recurrent CDI approximately 90% and restoration of microbial diversity and bacterial metabolites, the regulation of bile acid metabolism through FMT for CDI has been acknowledged [32]. Hefazi *et al.* [33.] investigated the influence of FMT for recurrent CDI in 23 cancer patients (mainly hematologic cancer) receiving cancer chemotherapeutic agents and confirmed effective rate was 86% without serious adverse reactions or infectious complications [33]. Kelly *et al.* [34] found no infectious complications resulted from FMT in the 80 immuno-compromised patients who underwent FMT [34]. Neemann, et al. [35] reported the first case of successful application of FMT for severe CDI that was refractory to conventional treatment with antibiotics in an HSCT patient [35]. Later two simple case reports were published about FMT as the management of CDI refractory to conventional therapy [36] demonstrating the efficacy as well as the safety approaches in CDI after HSCT without infectious complications and other adverse effects which conventional therapy fails. The first case reported where FMT effectively solved the problem of pathogenic bacteria infection was reported in 2017 even before preparing for HSCT. A male patient suffered from Philadelphiapositive acute lymphoblastic leukemia and developed a severe infection (β-lactamase-producing *E. coli, C.difficile* and carbapenemase-producing *Enterobacteriaceae)* before preparing for HSCT. After receiving FMT, his infection symptoms improved [36].

Administration of antibiotics can suppress or kill pathogenic micro-organisms within the host but the unregulated use of broad-spectrum antibiotics may lead to antibiotic resistance, which in turn can lead to dysbiosis and even cancer development [37]. Though epidemiological evidence supports the opinion that long-term antibiotic exposures, known to change the composition and decrease the diversity of gut microbiota, increase the risk of colorectal cancer, pancreatic, lung, breast and prostate cancers, the conflicting data about the association between antibiotics and risk of cancer do exists. Further, investigations indispensible to elucidate the impact of antibiotic exposure in cancer patients, and its underlying mechanisms [32].

Microbiome-mediated cancers pathogenesis

It is worth noting that these mechanisms often co-exist in the course of tumour development. In the case of colorectal cancer (CRC) the disorder of intestinal flora leads to the progression of CRC through different signal pathways. *Clostridium nucleatum* is capable of encoding adhesin, FadA, which then activates β-linked protein signalling and modulates inflammatory and oncogenic responses differentially by binding to lectins and E-calciferin on the surface of host epithelial cells [38]. By triggering TLR4 dimerization and recruitment of MyD88 to the receptor, activation of the NF-κB signalling pathway caused by lipopolysaccharide (LPS) in *Fusobacterium nucleatum*,is

essential for the mediation of the innate vaccine response, consequently producing a proinflammatory microenvironment. JAK-STAT is the other signalling pathway that is activated in the development of tumours. Apart from different signalling pathways of CRC development, hepatobiliary cancer is also associated with the secretion of AvrA-activated b-linked protein by *Salmonella typhi* strains [9].

Cancer management by FMT

FMT is certainly an efficient means to modulate the host intestinal microbiota, which is considered to be a breakthrough in medical progress in recent years. Gut microbiota of cancer patients can influence whether the body responds to chemotherapy and immunotherapy when cancer is present. Growing evidence shows that the intestinal microbiota can improve the efficiency or reduce the toxicities of anti-neoplastic treatments (chemotherapy, immunotherapy and radiotherapy [9].

Manipulating the microbial populations with therapeutic intent has become a hot topic of cancer research, since, gut microbiota was observed to influence cancer therapy efficacy. Viaud *et al.* [39], reported that gut microbiota modulated the therapeutic effect of the anti-cancer immunomodulatory agent cyclophosphamide [39]. Two bacterial species, *Enterococcus hirae* and *Barnesiella intestinihominis*, were known to potentiate the antitumor efficacy of cyclophosphamide through engagement of immune responses [40]. Inturn *Bifidobacterium* helped in improving the effectiveness [41]. The relative abundance of *Akkermansia*, one of the most abundant bacteria was positively correlated with the survival time to anti-PD-1 monoclonal antibodies [42]. Transfer of the gut microbiome from cancer patients who responded to immunotherapy and oral supplementation of Akkermansia improved the efficacy of immunotherapy [32]. From all these observations we understand that gut bacteria can behave as friend and foe in humans.

Applications FMT for Cancers

Carcinogenesis of gastric cancers is associated with *H. Pylori*, *Fusobacterium nucleatum* (Fn), *Parvimonas micra* and *Peptostreptococcus stomatis.* Significant enrichment of *Peptostreptococcus stomatis*, *Parvimonas micra*, *Streptococcus anginosus*, *Dialister pneumosintes*, *Slackia exigua*, *Clostridium colicanis* and *Fn* as well as the depletion of *Helicobacterium* was observed in gastric cancer.Clinical observations also support that eradication treatment for *H. pylori* could reduce the risk of gastric cancer[43;44].

Significant shifts in intestinal microbiota composition between healthy individuals and those afflicted with CRC demonstrate the involvement of CRC-specific bacterial signature. *Lactobacillus, Bifidobacterium*, etc. were reduced while Staphylococcaceae, *Fusobacteria*, *Peptostreptococcus anaerobius*, etc. were augmented in stool samples from patients with CRC vs. healthy individuals [32].

Several human studies have legitimate evidence for the differences in the gut microbial population in patients with non-alcoholic steatohepatitis or non-alcoholic fatty liver disease [45]. Gut-derived bacterial products or toxins such as lipopolysaccharide and deoxycholic acid takes the route of portal vein to reach liver since the existence of gut-liver axis has been extablished. There is a possibility that dysbiosis, could promote the development of chronic liver disease hepatocellular carcinoma HCC though this axis. FMT has already been used in human with chronic liver disease such as severe alcoholic hepatitis, persistent positive HBeAg, advanced liver cirrhosis and hepatic encephalopathy [32].

Recent pilot study involving patients with severe alcoholic hepatitis showed that FMT was associated with increased survival and resolved ascite [46]. These observations suggest the efficacy of FMT in managing in patients with HCC deserves attention.

Pancreatic cancer. The results of recent studies demonstrate the influence of gut bacteria in the development as well as treatment of pancreatic cancer [47]. In a recently published study, 76% of subjects were positive for intra tumour bacteria in 113 humans with pancreatic ductal adenocarcinoma (PDAC) [48]. In addition, earlier studies have given a clue for the variation of oral microbial composition between healthy and pancreatic cancer individuals as well. Some of these found in PDAC including *Gammaproteobacteria* could promote resistance to gemcitabine, a chemotherapeutic drug commonly used for PDAC, while antibiotic ciprofloxacin was able to abrogate the resistance.

Regarding the taxonomic population found in pancreatic cancer groups, significant increases were noted in *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, and significant decreases were observed in phylum Fusobacteria and genus *Leptotrichia.* These oral microbiotas may serve as a noninvasive and specific clinical diagnostic marker for pancreatic cancer. High abundance of *Fusobacterium* species in pancreatic cancer tissue was independently linked with a worse prognosis, suggesting that specifically this species may prove to be a promising prognostic parameter of pancreatic cancer. The outcome of these studies revealed that microbiota-based treatment might be useful to manage pancreatic cancer [32].

Breast cancer.

Similarity observed between colon and breast cancer in epidemiologic Characteristics, Hill *et al*. [49] first proposed a hypothesis about gut microbiota and the etiology of breast cancer, though evidences for the direct relationship between gut microbiota and breast cancer are rather limited. Later, Goedert *et al.* [50] analyzed differences between 48 pretreatment postmenopausal breast cancer patients and 48 healthy controls and found a significant reduction in alpha diversity and alterations in the composition of faecal microbiota in patients compared to the controls [50]. These observations led to the focus on studies to understand the mechanisms involved in estrogen metabolism, immune regulation, and obesity. [32]. Modulation of the gut microbiota by oral supplement with *Lactobacillus acidophilus* could delay the development of breast cancer by regulating antitumor immune response in murine model [51]. Further, in depth studies results are warranted to standardize the FMT regarding the management of breast cancer.

Melanoma. Research based evidence demonstrates that gut microbiota has an signature on the progression as well as treatment of melanoma. Frankel, *et al.* [52] did a pilot study to understand the effects of human gut microbiota and metabolites on immune checkpoint inhibitor (ICT) response in metastatic melanoma patients. 39 metastatic melanoma patients receiving immune checkpoint therapy also showed that there was a significant correlation between the content of microorganism and the response of immunotherapy [52]. They also observed that in the responders to cancer immunotherapy, *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii and Holdemania filiformis* were rich in their gut. The transfer of faeces harvested from responding melanoma patients into mice established that FMT could enhance the effectiveness of immunotherapy to optimize the current therapies [53]. Thus, FMT seems to be promising in enhancing antitumor immunity in melanoma patients by transferring a favourable gut microbiota.

FMT in Therapeutics

Intestinal microbes have a key role in radiation-induced intestinal damage. Small intestine epithelium has high sensitivity to radiation and is the major site of radiation induced injury due to frequent intestinal epithelial turnover. In a mouse model, gavage of intestinal microorganisms attenuated and

protected against radiation-induced injury. Specifically, FMT was able to improve irradiated mice recovery rate A major shift in intestinal microbiota composition after radiotherapy was observed in mice and interestingly, transplantation of fecal microbiota from healthy mice significantly alleviated radiation-induced gastrointestinal syndrome and improved the survival rate of irradiated mice [54]. Therefore, the dysbiosis due to radiation therapy could be managed with FMT approach to replenish the healthy gut microbiota [54]. Thus, the intensity of the radiation toxicity could be reduced by FMT to improve prognosis.

Microbiota and Chemotherapy

Microorganisms and chemotherapeutic agents such as 5-fluorouracil and cyclophosphamide can interact with each other in both directions. Alexander, et al. [55] suggested that chemotherapy alters the composition of the patient's microbial community, which may cause serious side effects in immunocompromised cancer patients. At the same time there is a possibility of the microbiota to metabolize drugs and modify anticancer drug efficacy. Improving drug efficacy, increasing antitumor effects, and reducing toxic effects are the three main challenges posed by the effects of intestinal microbes on chemotherapeutic drugs. Gram-negative bacilli increase the antitumor effect of cyclophosphamide by increasing T cells infiltration in tumour sites [56]. Microbiota may also have an influence on drug target to improve the side effects of many chemotherapeutic drugs on the gastrointestinal tract.

Though the underlying molecular and cellular mechanisms of FMT are unknown is an enigma, it may involve direct donor-intestinal microbiota-host interactions, resulting in in the observed effects on host physiology, the intestinal mucosal barrier, and the immune system [57]. Literature survey provides convincing evidences to emphasize the influence of FMT to improve the efficacy of chemotherapeutic agents and reduce related undesirable events.

FMT and recent past

Using the gut microbiota as an adjuvant to anti-cancer treatment has attracted the interest of researchers in recent years since, response to anticancer therapy and the incidence of adverse events is related to the gut microbiota. The combination of FMT with anti-PD-1(*immune checkpoint inhibitor)* for the treatment of refractory metastatic melanoma has recently been shown to be safe, practical, and potentially effective. Overall, FMT is a hopeful method to improve the therapeutic effect of immunotherapy and to reduce the side effects of chemotherapy [9].

Conclusion and future perspective

In future studies, it is necessary to explore the safe, duration, dosing, formulation, administration route, and combinations of FMT to determine the optimal regimen of it for cancer treatment. Wealth of knowledge from human, animal and *in vitro* studies implies that gut microbiota is critical to the development of personalized cancer treatment strategies and a need for a greater insight into prokaryotic co-metabolism of chemotherapeutic drugs is now required. The gut microbiota modulates the chemotherapeutic drugs through key mechanisms, structured as the 'TIMER' mechanistic framework: Translocation, immunomodulation, metabolism, enzymatic degradation, and reduced diversity and ecological variation Alexander, *et al.* [55]. High quality clinical data still want to further investigate whether FMT could be employed as a safe therapeutic intervention against cancer. Elucidating complex links between the gut microbiota and cancer could enable new novel therapies.

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