New Horizon on Gut Microbiome and Cancers: Recent Information on Pathogenesis and Treatment

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Abstract: An increasing number of studies have suggested that gut microbiota is closely related to tumor pathogenesis and their treatments. Among cancers, there have been many reports concerning gut microbiome and colon cancer (CRC), where microbial dysbiosis with depressing the population of "benign microbes" and increasing "harmful microbes" can lead to chronic enterocolitis and cancer development with progression. In addition, gut dysbiosis may change the metabolism of bile acids promoting CRC, which would offer a potential preventive therapeutic change in CRC by regulating gut microbiome and bile acid metabolism. Recently, SARS-CoV-2 impacts the gut microbiota, and the effects will have on CRC carcinogenesis. Obesity is estimated as an important factor that increases the risk of CRC. There has been accumulating evidence that the modulation of the gut microbiota composition by probiotics, prebiotics, and diets protects patients with CRC. Hepatocellular carcinoma (HCC) as the third leading cause of worldwide cancer mortality. Development of HCC in cirrhotic patients is related to changes in intestinal microbiome, including an escalation of dysbiosis and reduced bacterial richness. The species richness of fecal microbiota of hepatitis B-HCC patients was much high. The alterations of fecal microbiome may affect the process of *Helicobacter pylori (H. pylori)*-related progression of gastric lesion. Patients with gastric cancer have distinct microbiome in the stomach with lower biodiversity. Some bacteria from gastric microbiome are potentially carcinogenic as they are changed in gastric cancer. Patients with pancreas cancer and cholangiocarcinoma have also been related to gut dysbiosis. Other malignancies outside the gut like breast cancer (BC) might be related to gut microbiome as they might affect through metabolic, neural, and endocrine signal and immune function in the occurrence and progression of BC. Finally, cancer cachexia might be also associated with gut dysbiosis as it is closely related to bile acids (BA) metabolism regulation. The effects and side effects by variable cancer therapies such as chemotherapy, radiotherapy and also immunotherapy may be reconsidered from gut microbiome.

Keywords: Gut Microbiome (Microbiota), Dysbiosis, Colon Cancer, Hepatoma, Other Cancers and Cachexia, Treatments, Immunotherapy, Chemotherapy, Radiotherapy

1. Introduction

Gut dysbiosis is a risk factor for various human diseases including various inflammatory diseases and cancers. There have been tremendous recent studies on cancers and gut dysbiosis in subjects with pathological state for them. Fundamental microbial dysbiosis consists of depressing the population of "benign microbes" and increasing "harmful microbes" in the development and progression of various cancers. Most related cancers for this are those in the field of gastroenterology but some cancers outside the gut is also included. These non-gut diseases are associated with gut microbiome in metabolic and immunologic relations. Their pathogenesis is closely associated with gut dysbiosis. For treatment for cancers, we have experienced a remarkable progress in chemotherapy, radiation therapy and immunotherapy. However, the effect of these strategy should be based on the gut microbiome. Based on the profound knowledges in gut microbiome, various therapies should be reconsidered. The author considered that the pathogenesis and treatments of various cancers should be reconsidered on the fundamental bases of gut microbiome. As there have been no comprehensive review like this until now, I would like to summarize these topics in this mini review. I have

summarized important reviews and original articles on cancers for these 7 years. I have conducted Pubmed search using terms including "gut microbiome"," gut microbiota", "dysbiosis" and "cancers" between 2016 to 2022. Some very recent important manuscripts on cancers and microbiota were also included in the present manuscript.

2. Gut Microbiome Dysbiosis in Various Malignancies

We are now beginning to understand that the gut dysbiosis is a risk factor for various human diseases including various cancers.

At first, there have been many reports concerning gut microbiome and colon cancer. For colon carcinogenesis, microbial dysbiosis with decreasing the population of "benign microbes" (such as *L. acidophilus*, *L. rhamnosus*, *S. thermophilus*, *F. prausnitzii*, *A. muciniphila*, *B. breve* and *B. longum*) and increasing "harmful microbes" (such as *E. faecalis*, *H. pylori*, *A. spp*, *Genotoxic E. Coli*, *Genotoxic B. fragilis*, *S. bovis*, *F. nucleatum*, *S. spp* and *C. spp*) can induce chronic enterocolitis and cancer development [1]. There was another microbiome dysbiosis reported from Asia. *Parvimonas micra*, *Fusobacterium nucleatum*, *Peptostreptococcus stomatis* and *Akkermansia muciniphila* were increased in stool samples from patients in Kuala Lumpur, Malaysia [2]. Functional foods including probiotics, prebiotics and symbiotics may have a potentially good effect on health beyond basic foods and have anti-inflammatory effects [3]. Recent studies have identified carcinogenic bacteria like enterotoxigenic *Bacteroides fragilis* (ETBF) and *Streptococcus gallolyticus* (*S. gallolyticus*). Variable strategies including probiotics, prebiotics, postbiotics, antibiotics, and fecal microbiota transplantation (FMT) have been tried. Although these present promising investigations by correcting microbial dysbiosis, modulating innate immune system, enhancing gut barrier function, preventing pathogen transportation and exerting selective cytotoxicity against tumor cells, it should be noted that they are accompanied by risks that can potentially introduce clinical complications [4]. Gao et al have pointed at the same time protective bacterial like *Akkermansia muciniphila* (*A. muciniphila*). They have suggested these as potential targets of colon cancer (CRC) treatment [5]. Patients with inflammatory bowel disease is likely to have CRC, named as colitis-associated cancer. Investigations have revealed that the relation of gut dysbiosis to abnormal bile acid metabolism, and inflammation process [6]. In other words, gut dysbiosis may alter the metabolism of bile acids promoting CRC, which would provide a potential preventive strategy of CRC by regulating gut microbiota and bile acid metabolism [6]. Chew et al [7] found that *Fusobacterium nucleatum*, *Escherichia coli* and enterotoxigenic *Bacteroides fragilis* was to contribute to CRC development. *Fusobacterium nucleatum* has been found in colon tissue and stool in cancer patients and has been related to substantial clinical and molecular characters [8]. It was also

related to patient harmful therapy response [8]. The emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), led to a worldwide pandemic with over 170 million confirmed infections and over 3.5 million deaths [9]. They further considered that infection with SARS-CoV-2 impacts the gut microbiota and the effects will have on CRC carcinogenesis and progression [9]. Gut microbiome of patients with CRC disrupted intestinal barrier, induced low-grade inflammation and dysbiosis [10]. Challenges and remaining future unknown matters persisting now bear in mind the mechanisms by which the gut microbiota affects radiosensitivity, interactions between the gut microbiota and the above combination therapies [11]. Oral *Fusobacterium nucleatum* (Fn) and *Porphyromonas gingivalis* (Pg) can invade the gut epithelium, promoting tumor progression [12]. Pg was not detected in colon tissues but was related with the oral inflammation such as gingival and plaque indices. There was evidence that the oral concentration of Fn can affect colon tissue concentrations and predict the prognosis of CRC [12]. Fn raises the potential of antibiotic treatment for the prevention of CRC as a prognostic biomarker of this cancer risk, and therefore raises the potential of antibiotic treatment of Fn for the patients of CRC [13]. Previous studies of radiation enteropathy mainly focused on acute irradiation hazards. Their study provides new insight into the altered gut microbiome composition and their function in patients with hematochezia, implying the potential use of probiotics and prebiotics for assessment and treatment of CRC [14]. Treatment by mesenchymal stem cells (MSCs) has revealed promising results not only in inflammatory bowel disease but also in CRC because they prohibit chronic inflammation and regulate gut dysbiosis to suppress the occurrence of CRC [15]. The gut microbiome communicates closely with intestinal stem cells (ISCs). There is an evident crosstalk between host and microbiota at the ISC niche level. There is a possible key role of microbiota in the aberrant reprogramming of CSCs in the initiation of CRC. [16]. There is accumulating evidence which reveals that the activation of oncogenic pathways and the loss of tumor suppressor genes regulate the metabolic reprogramming mainly involved in glycolysis, glutaminolysis, one-carbon metabolism and lipid metabolism [17]. Several microbiome-mediated mechanisms of host immune signaling including short-chain fatty acid (SCFA) and bile acid metabolism, inflammasome activation, and cytokine regulation in developing CRC [18], Obesity is considered to play a cardinal factor that increases the risk of CRC. Patients with obesity and CRC display a specific gut microbiota profile characterized by a reduction in butyrate-producing bacteria and an increase of opportunistic pathogens, which could be responsible in part, for the increased proinflammatory cytokine IL-1beta, the deleterious bacterial metabolite TMAO, and gut enhanced permeability in these patients [19]. There has been increasing evidence that the modulation of the gut microbiome composition by probiotics, prebiotics together with diets protects patients with CRC from treatment-associated adverse effects [20]. There have been many reports concerning gut microbiome and CRC.

For colon cancers, microbial dysbiosis with decreasing the gut "benign microbes" and increasing the "harmful microbes" can increase chronic enterocolitis and cancer development [1]. Functional foods including probiotics, prebiotics and symbiotics may have a potentially good effect on health beyond basic foods and have anti-inflammatory effects [3]. Recent studies have identified carcinogenic bacteria like enterotoxigenic *Bacteroides fragilis* (ETBF) and S*treptococcus gallolyticus (S. gallolyticus)*. Until now variable strategies including probiotics, prebiotics, postbiotics, antibiotics, and fecal microbiota transplantation (FMT) have been employed. Although these present promising results by correcting microbial dysbiosis, modulating innate immune system, enhancing gut barrier function, preventing pathogen transportation and exerting selective cytotoxicity against tumor cells, it should be noted that they are accompanied by risks that can potentially introduce clinical complications [4]. Gao et al have pointed out at the same time protective bacterial like *Akkermansia muciniphila* (*A. muciniphila*), They have suggested these as potential targets of CRC treatment [5]. Patients with long-lasting inflammatory bowel disease is likely to develop CRC, named as colitis-associated cancer (CAC). Research data have revealed that the relation of gut dysbiosis to abnormal bile acid metabolism with inflammatory reactions [6]. In other words, gut dysbiosis may change the metabolism of bile acids promoting CAC, which would give rise to a potential preventive therapy of CAC by regulating gut microbiome and bile acid metabolism [6]. Chew et al [7] found that *Fusobacterium nucleatum*, *Escherichia coli* and enterotoxigenic *Bacteroides fragilis* was to contribute to CRC development. *Fusobacterium nucleatum* as well has been detected in tissue and stool from patients with colon cancer and has been associated with substantial clinical and molecular features [8]. It was also related to therapy response in patients [8]. The development of a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induced to a worldwide pandemic with over 170 million confirmed infections with over 3.5 million deaths [9]. They further considered that infection with SARS-CoV-2 influences the gut microbiota, and the effects will have on CRC carcinogenesis with progression [9]. Gut microbiota of patients with colon cancer disrupts intestinal barrier, induces low-grade inflammation and dysbiosis [10]. Challenges and remained unknown future matters persisting now include the mechanisms by which the gut microbiome affects radiosensitivity, interactions between the gut microbiota and mixed treatments [11]. Oral *Fusobacterium nucleatum* (Fn) and *Porphyromonas gingivalis* (Pg) can invade the gut epithelium, promoting tumor progression [12]. Pg was not detected in colon tissues but was related with the oral inflammation including gingival and plaque indices. There has been evidence that the oral concentration of Fn is able to affect colon tissue concentrations and predicts the prognosis of colon cancer [12]. Fn increases the potential of antibiotic treatment for the prevention of colon cancer as a prognostic biomarker of this cancer risk, and therefore raises the potential of antibiotic treatment of Fn for the patients with CRC [13].

Previous investigations of radiation enteropathy mainly have been focused on acute irradiation hazards. Their study gives a new insight into the altered gut microbiome composition and their function in patients complaining hematochezia, which imply the potential use of probiotics and prebiotics for assessment and treatment of colon cancers [14]. Treatment by mesenchymal stem cells (MSCs) have shown promising results not only in inflammatory bowel disease but also in rectal cancers because they inhibit chronic inflammation and regulate gut microbial dysbiosis to suppress the development of colon cancer [15]. The gut microbiota relates closely to intestinal stem cells (ISCs). There is a significant crosstalk between host and microbiota at the ISC niche level. There is a possible key role of microbiome in the aberrant reprogramming of CSCs in the initiation of colon cancer. [16]. There is accumulating evidence which reveals that the activation of oncogenic pathways and the loss of tumor suppressor genes regulate the metabolic reprogramming chiefly involved in glycolysis, glutaminolysis, one-carbon metabolism and lipid metabolism [17]. Several microbiome-mediated mechanisms of host immune signaling including short-chain fatty acids (SCFAs) and bile acid metabolism, inflammasome activation, and cytokine regulation in developing colon cancer [18], Obesity is estimated as a cardinal factor increasing the risk of colorectal cancer. Patients with obesity and colon cancer show a specific gut microbiome profile characterized by a decrease in butyrate-producing bacteria and an increase of opportunistic pathogens, which could be responsible partly, for the increased proinflammatory cytokine IL-1beta, the harmful bacterial metabolite trimethylamine N-oxide (TMAO), and gut increased permeability in such kind of patients [19]. There has been increasing evidence that the modulation of the gut microbiota composition by probiotics, prebiotics, and diets protects patients with colon cancer from treatment-associated adverse effects [20].

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality in the world. Most of HCC exclusively develops in patients with chronic liver disease especially those with cirrhosis, enhanced by a vicious cycle. [21]. The mechanisms enhanced by the gut dysbiosis induing hepatoma, focusing on the leaky gut, microbe-associated molecular patterns and bacterial metabolites as important pathways driving cancer-promoting liver inflammation, fibrosis and genotoxicity [21]. Zhang et al showed that gut microbiome compositional and functional shifts, together with enhanced gut damage and microbial translocation, may promote the development of HCC by stimulating inflammatory response and suppressing T cell response in Chinese male patients [22]. Development of HCC in cirrhotic patients is related to changes in intestinal microbiome, including an enhancement of dysbiosis and reduced bacterial richness [23]. Overweight was associated with increased dysbiosis in patients with hepatoma compared to their normal-weight counterparts [23]. Fatty liver, taking artificial sweeteners, and high-sugar foods were related to alteration in microbial composition, including changed levels of *Akkamansia muciniphila* in cirrhotic

patients and hepatoma [23]. Increasing impact of gut dysbiosis is recognized with the progression of liver diseases from mild fatty liver to advanced liver cirrhosis, where the enterohepatic circulation is considered to strengthen a relation between gut microbiome and the liver [24]. They have determined that levels of alpha proteobacteria and the two genera CF231 and *Clostridium* are altered in cirrhotic patients with HCC, independently of cirrhosis severity and dietary habits. Gut dysbiosis is especially prominent in patties with HCC [23]. Liu et al [25] found that the species richness of fecal microbiota in patients with hepatitis B-HCC was much prominent. The feces of patients with NBNC-HCC have more potential pro-inflammatory bacteria (*Escherichia-Shigella, Enterococcus*) and reduced levels of *Faecalibacterium, Ruminococcus, Ruminoclostridium* resulting in decrease power of anti-inflammatory short-chain fatty acids [25]. Although local angiogenesis, tumor growth and Th17 cells were suppressed in an experimental study [26], the characteristic microbial changes and IL-*17* suppression were not treated by cisplatin [26]. Both diet and gut microbiome dysbiosis are related to NAFLD and accompanied HCC [27] In this situation, a high level of CXCR2(+) polymorphonuclear myeloid-derived suppressor cells (MDSCs) have been shown to be increased by tumors and to suppress antitumor immunity [28].

Gastric cancer is the most common malignancies in the world. Gastrectomy is still the only potentially curative treatment for this disease [29]. Gastric cancer is as well as esophageal cancer is one of the two major causes of cancer-related deaths in the world [30]. They are also related with the component of the gut microbiome, namely their homeostatic mechanisms and dysbiosis [30]. The key microbes in esophageal and gastric carcinogenesis were associated with delicate biology. The alterations of fecal microbiota, especially the predominant phyla of *Bacteroidetes*, *Firmicutes* and *Proteobacteria*, may influence the process of *Helicobacter pylori (H. pylori)*-related progression of gastric lesions and provide hints for evaluation of microbial changes after *H. pylori* eradication [31]. Further examination of these pathways and discovery of diagnostic and therapeutic targets could have wide impacts on subpopulations in the world. It is valuable to understand the nature of the gut microbiome and its potential risks for dysbiosis with an object to use its application to the individual patient and create a highly personalized, precision medicine [30]. *H. pylori* has been shown to be a pathogenic factor of gastric cancer in cohort studies and animal models [32]. Prospective studies showed that gastric cancer developed in 1–4% of *H. pylori*-infected subjects [32]. Patients with gastric cancer have distinct microbiome in the stomach [33]. It features with lowered biodiversity, discrete structure, and varied composition [33]. Some bacteria from gastric microbiome are potentially carcinogenic as they are increased or decreased in gastric cancer [33]. Distinct profile of microbial community in gastric cancer is possibly resulted from altered causes by pathophysiological and environmental factors. *H. pylori* is a carcinogen colonizing the human stomach [33]. Currently, it

appears in a disrupted homeostasis and inter-individual variations of gastric microbiota are involved in cancer development. Clarifying factors responsible for these changes would reveal how microbiota relates to carcinogenesis, benefiting the prevention of gastric cancer [33]. Although some earlier studies revealed high levels of macrolide resistance after triple therapy, recent studies showed that the increased antibiotic resistance rate may be restored 2–12 months after eradication therapy. These results collectively provide evidence of the long-term safety of *H. pylori* eradication [32]. The gastric carcinoma microbiota was characterized by decreased microbial diversity, by lowered abundance of *Helicobacte*r and by the increase of other bacterial genera, mostly represented by intestinal commensals [34]. Detailed analysis of the gastric microbiota showed that patients with gastric cancer show dysbiosis with genotoxic potential, which is clear from that of patients suffer from chronic gastritis [34]. Only 1-3% of patients with *H. pylori* develop gastric cancer. In gastric carcinogenesis, non-*H. pylori* bacteria in the stomach might interact with *H. pylori* [35]. Bacterial dysbiosis in the stomach can strengthen gastric neoplasia development via generating tumor-promoting metabolites, DNA damage, suppressing antitumor immunity, and activating oncogenic signaling pathways [35]. Dysbiosis after gastrectomy is characterized by increased microbiome consisting of typical oral cavity bacteria, characterized by increased aero-tolerant bacteria (aerobes/facultative anaerobes), and increased genera of bile acid-transforming bacteria [29]. Lower abundance of *Bifidobacteriaceae* was seen only in diffuse adenocarcinoma and of *Oscillibacter* in intestinal adenocarcinoma [36]. Their analysis revealed relation of higher *Enterobacteriaceae* genera to all types of gastric tumors [36]. It could be potentially useful as a marker of gastric malignancies [36]. Lower gut microbiome diversity may be indicative of poorly differentiated, invasive, and aggressive tumors and can probably be a prognostic marker for gastric cancers [36].

Recently, gut microbiota dysbiosis emerged as a key player that may directly and/or indirectly influence development, treatment, and prognosis of breast cancer (BC) through diverse biological processes: host cell proliferation and death, immune system function, chronic inflammation, oncogenic signaling, hormonal and detoxification pathways [37]. They discussed the origin, composition, and dynamic evolution of human microbiota, the links between gut/breast microbiota and BC, and explored the potential implications of metabolomics and pharmaco-macrobiotics that might impact BC development and treatment choices toward a more personalized medicine [37]. In BC the study by sequencing technologies for metagenomic analyses has admitted not only the description of the overall metagenomic figures but also the specific microbial alterations and their functional relations [38]. The microbiota influences in BC is in multi-factorial way, and the gut and breast tissue bacteria population might be valuable in regulating the local immune system, otherwise in tumor formation and progression and also in therapy response and/or resistance [38]. The

community of microorganisms inhabiting the gastrointestinal tract, the gut microbiota, affects human health through metabolic, neural, and endocrine signaling, and immune activity. It is through these mechanisms that the gut microbiota appears to influence BC risk, recurrence, and response to treatment. A disrupted gut microbiota or state of 'dysbiosis' can contribute to a biological environment associated with higher risk for cancer development as well as contribution to negative treatment side-effects [39]. The community of microorganisms inhabiting the gastrointestinal tract, the gut microbiota affects human health through metabolic, neural, and endocrine signaling, and immune activity. They strengthen potential strategies for adjustment of the gut microbiome inducing improved clinical outcomes and overall health in this population [39]. This is sometimes cited as a possible tool which links BC and high-fat, low-fiber diets as well as antibiotic exposure, relations previously detected in population-based studies [40]. Nowadays a distinct microbiome has been found within breast milk and tissue, but few studies have reported differences in the breast tissue microbiome of patients with and without cancer, and none have studied distant body-site microbiota other than the gut [40].

Pancreatic cancer (PC) remains a global health problem with high mortality [41]. Carriage of certain bacteria in the oral cavity (e.g., *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Streptococcus sp.*), gut (e.g., *Helicobacter pylori*, *Synergistetes*, *Proteobacteria*), and pancreas (e.g., *Fusobacterium sp.*, *Enterobacteriaceae*, *Pseudomonadaceae*) have been associated with an elevated risk of developing PC [41]. Additionally, the fungal genus *Malassezia* has been associated with PC development as well [41].

Cholangiocarcinoma (CCA) is the most common malignant tumor of the biliary system with a very poor prognosis [42]. Rao et al [42] aimed to summarize the recent evidence on dysbiosis in the human microbiome of CCA [42]. They generalized the effect of *Helicobacter pylori* on CCA. Additionally, the potential mechanism of human microbial dysbiosis promoted the progress of CCA, and its precancerous disease was also discussed [42]. Furthermore, the possibility of the human microbiome as a diagnostic and therapeutic target of CCA was discussed. [42].

Shi et al [43] reviewed recent reports that support a role for the gut microbiota in the occurrence of lymphoid neoplasms and pinpoint relevant molecular mechanisms. Accordingly, they proposed the microbiota-gut-lymphoma axis as a promising target for clinical translation, including auxiliary diagnosis, novel prevention, and treatment strategies [43]. They predicted clinical outcomes and treatment-related side effects of the disease in the future [43]. The gut microbiota has been shown to be an important determinant of the efficacy of immune checkpoint inhibitions (ICI) for patients with cancer [44]. Several lines of evidence reveal that antibiotic (ATB) usage prior to or within the first month of ICI initiation negatively impacts clinical outcomes [44]. They reported that ATB use within 30 days prior to ICI initiation in patients with advanced melanoma may adversely affect patient outcomes [44].

Gut microbiota is involved in the development and function of the brain as well through a bidirectional pathway named as the gut-brain axis [45]. Dehhaghi et al [45] reviewed the oncogenic and oncolytic effects of gut microbiota by classifying the modification mechanisms into amino acid deprivation (arginine and tryptophan), kynurenine pathway, microglia dysbiosis and myeloid-derived suppressor cells (MDSCs). By delineating the complexity of these gut-microbiota-brain-cancer axis, they summarized the research on the development of novel therapeutic strategies helping the efficient eradication of brain cancers [45].

Lu et al reported that gut and sputum microbiota showed that both were significantly disturbed in non-small cell lung cancer (NSCLC) and associated with distant metastasis while only the sputum microbiota was associated with non-distant metastasis NSCLC [46]. They added that the lung microbiota could have a stronger association with and may contribute more to disease development than the gut microbiota. [46].

Cancer cachexia is considered as a multifactorial metabolic syndrome in which bile acid (BA) metabolism may be involved [47]. Gut dysbiosis such as depression of *Lachnospiraceae* and enhancement of *Enterobacteriaceae* were recognized in the gut of mice with cancer cachexia, and microbial metabolism of BAs was decreed. Enhanced expression of FGF15 in intestinal tissue suggested the activation of FXR signal pathway inducing the regulation of BA synthesis enzymes, transporters together with metabolic enzymes [47]. Enhancement of BA conjugation was noted in the serum of mice with cancer cachexia. Studies in clinical patients revealed changes in BA metabolism, particularly the increase in BA conjugation and supposed compensatory mechanism in BA metabolism regulation [47].

3. Treatment

3.1. Immune Checkpoint Inhibitors

The important role of the gut microbiome determines the effect of anticancer therapy including immunogenic chemotherapy and immune checkpoint blocker [48]. Tumorigenesis is sometimes combined with immunosuppression which decreases the anticancer immunological defense activated in the host [49]. New anticancer therapies using immune checkpoint inhibitors (ICIs) may be very promising against both solid and hematological tumors [49]. Experimental study supports the cardinal role played by the gut microbiome activating the immune system against cancers [49]. This phenomenon indicates patient-tailored complementary therapies adjusting the gut microbiome, enabling the selective increase in microbial species, which improves the positive outcome of ICI-based immunotherapy [49]. The gut microbiome also influences the response of HCC patients to the new check-point inhibitor drugs which restore immunological responses of its host [50].

While immune checkpoint inhibitors have been effective for various cancers, getting over resistance has been an important area of ongoing research [51]. The gut microbiota and its role in cancer immunosurveillance have recently become a major field of study [51]. Gut microbiome has direct and systemic effects on cancer etiology together with hosts anti-tumor immune response [51]. Bouferraa et al reviewed on the role of microbiome in cancer etiology and immune system against it [51]. They have as well discussed preclinical and clinical investigations that have enhanced our understanding about the roles and the mechanisms through which microbiome influences the response to treatment with immune checkpoint inhibitors [51]. It seems that a variable gut microbiota supports therapeutic anticancer responses, while a microbiome composition that lacks immunostimulatory bacteria or contains excessive immunosuppressive species results in treatment failure [48]. T cell immunoglobulin together with mucin domain-containing protein-3 (Tim-3) are immune checkpoint molecules and targets for anti-cancer therapy [52]. Lee et al investigated if gut microbiota manipulation changed the anti-tumor efficacy of Tim-3 blockade [52]. Loss of microbiome diversity called as dysbiosis has been related to an unsatisfactory treatment response to ICPIs and unsatisfactory survival outcomes in patients with CRC [53]. In addition, the microbiome can affect the local immune response at the intestinal interface and act the trafficking of bacterial peptide primed T-cells distally, influencing the toxicity patterns to ICPI. Antibiotic and food induced changes in microbiota composition can also indirectly alter the production of certain bacterial metabolites including deoxycholate and short chain fatty acids that can act as the anti-tumor tolerance [53]. Gut microbiota is related to cancer and the effect of ICPIs, and supplement with specific bacterial species can restore or enhance the responses to the ICIs [54]. T cell immunoglobulin and mucin domain-containing protein-3 (Tim-3) are immune checkpoint molecules and targets for anti-cancer therapy [55]. These interactions show in various ways including signaling relay, metabolism, immunity, tumor development, genetic instability, and sensitivity to cancer chemotherapy and immunotherapy [55].

3.2. Chemotherapy and Radiation Therapy

Microbiome has also substantial roles including effectiveness of chemotherapy, chemoresistance and in the related adverse effects [56]. Dysbiosis may have a pro-inflammatory state and the stimulation of a Th17 response with IL-17 and IL-22 secretions that have a pro-oncogenic activity, as demonstrated in *Fusobacterium nucleatum* [56]. Microbiota composition can induce marked effect on medical interventions including chemotherapy and radiation [57]. Ghanem et al discussed the character of the pathologic alterations in the gut microbiome resulting from antimicrobial use [58]. They explore the effect of these changes have on responses and outcomes to different cancer treatment modalities including chemotherapy and immunotherapy [58]. In addition to traditional chemoradiation, it places the patient at a higher risk of infection through a myelosuppressive effect [58]. High clinical suspicion and early use of antimicrobials play a major role in decreasing any associated morbidity and mortality [58]. Studies have also demonstrated that an intact gut microbiota is essential in the anticancer immune response [58]. Antimicrobial use can therefore modulate responses and outcomes [58]. Various cancer pathogenesis and recently developed treatment regimens should be investigated in the context of the gut microbiota [59]. These interactions show in close relay, metabolism, immunity, tumor development, genetic instability and sensitivity to cancer related to GI toxicities and have the potential to expect radiation/chemoradiation-induced adverse effects and quality of life in patients who has experienced these treatments [60]. Treated patients who enjoys clinical benefits from radiotherapy (responders, R) has higher microbial diversity and richness compared to non-responder patients (NR) [61]. The fecal microbiome of the R is enriched in butyrate-producing bacteria and have evidently higher levels of acetic, butyric, isobutyric, and hexanoic acids than NR. NR patients shows higher serum levels of spermine and acetyl polyamines (oncometabolites related to CRC) as well as zonulin (gut permeability marker), and their gut microbiome is abundant in pro-inflammatory species [61].

4. Conclusions

Gut dysbiosis has closely related to various cancers and their backgrounds in host. Conditions of gut microbiota has closely related to various cancers and its real impacts on cancer chemotherapy, immunotherapy, and radiotherapy. Even the efficacy of cutting-edge ICPIs appear to depend on the patient's gut microbiome. The direction indicated by the recent investigations on gut microbiome may open a new horizon in the discussions on cancer pathogenesis and therapies for the coming future.

Gut microbiomes locate throughout the entire gut. Large number of bacteria are found in intestines, but it locates in other part of gut from mouth to anus. Liver is a fundamental organ that get variable microbial metabolic substances and microbiome itself. Portal endotoxemia and IL-10 producing Treg cells show strong physiological effects. Liver is affected by non-alcoholic fat liver disease, steatohepatitis (NASH) which will progresses to cirrhosis and HCC.

The gut microbiota in the intestine is characterized by the decreasing beneficial microbes and the increasing harmful microbes. This dysbiosis together with endotoxemia and leaky gut due to increased intestinal permeability result in tissue injury and resultant cancers in various organs.

Immunogenic therapy due to immune checkpoint blockade and chemotherapy and radiation therapy through higher elevated levels of acetic, butyric, isobutyric, and hexanoic acids and higher microbial diversity with richness.
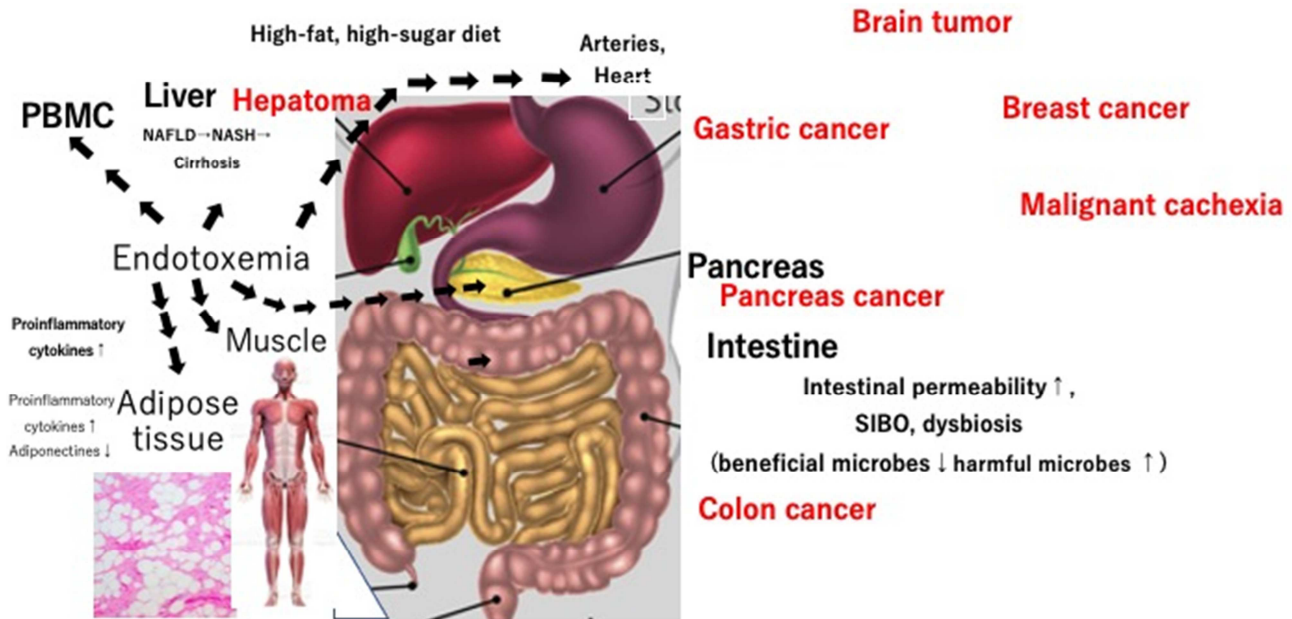
Figure 1. Various cancers and related physical states that are affected by gut microbiome.
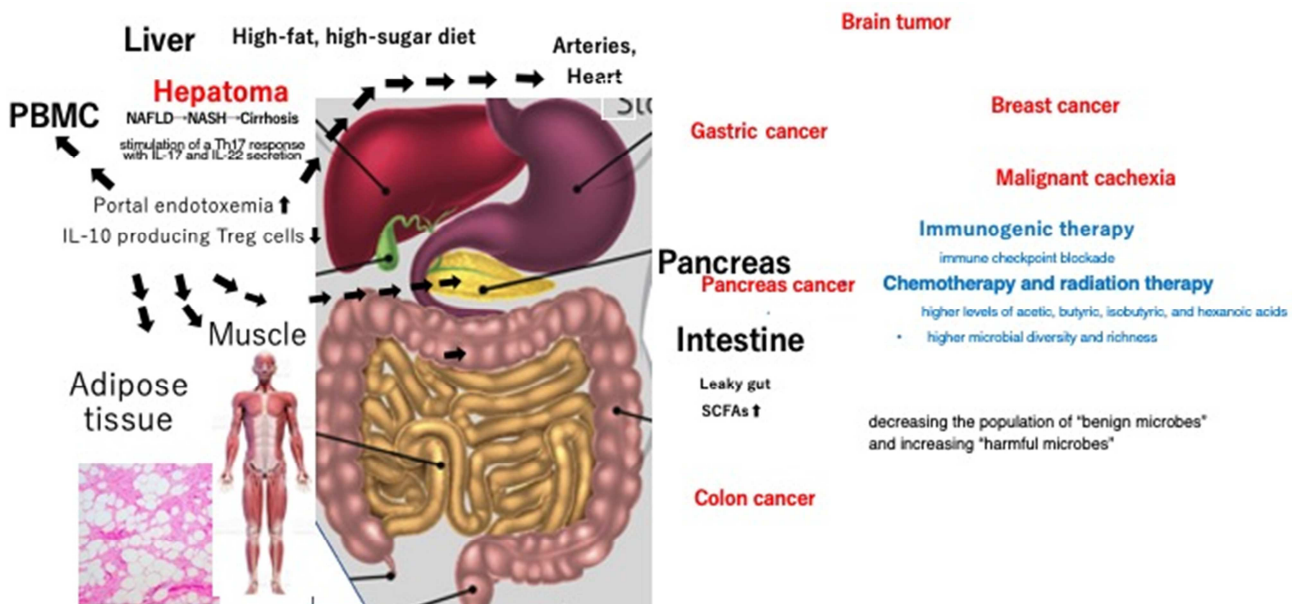

Figure 2. Treatment modalities for various cancers.

Conflict of Interest

The author does not have any possible conflicts of interest.

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